

To cite this article: Ozcibik Isik G, Turna A, Aydin BS, Polat B, Kilic B, Ersen E, Kara HV, Kaynak MK. Prognostic factors for recurrence after surgical resection in early-stage non-small cell lung cancer. *Curr Thorac Surg* 2026;11(1):37-44.

## Original Article

# Prognostic factors for recurrence after surgical resection in early-stage non-small cell lung cancer

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## ABSTRACT

**Background:** Non-small cell lung cancer (NSCLC) constitutes the majority of lung cancer cases, with surgical resection being the main treatment for stages 1 and 2. Despite advances, postoperative recurrence remains a major cause of mortality. Identifying recurrence risk factors could allow individualized follow-up strategies.

**Materials and Methods:** We retrospectively analyzed 246 patients with stage 1-2 NSCLC who underwent surgery between 2005-2022. Stage 3 disease and neoadjuvant-treated cases were excluded. Clinical, laboratory, radiological, and surgical data were collected. Recurrences (locoregional or distant) within at least two years of follow-up were recorded. Comparisons were made using Student's t-test or Chi-square test; survival was analyzed with Kaplan-Meier and Cox regression.

**Results:** VATS (Video-assisted thoracoscopic surgery) was more frequent in non-recurrence cases ( $p=0.017$ ), while pneumonectomy was more common in recurrence cases ( $p=0.017$ ). Advanced T and TNM stages, lymphatic and vascular invasion were significantly associated with recurrence. Cox regression identified N1 disease, pleural invasion, and lymphatic invasion as independent predictors of poor survival. Pneumonectomy and lymphatic invasion were significantly associated with reduced recurrence-free survival.

**Conclusions:** Recurrence after early-stage NSCLC surgery is linked to worse survival. Pneumonectomy and lymphatic invasion may predispose to recurrence, warranting closer follow-up and consideration of adjuvant therapy.

**Keywords:** non-small cell lung cancer, early stage, recurrence, prognosis

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Doi: 10.26663/cts.2026.005

Received 26.01.2026 accepted 30.03.2026

## Introduction

Non-small cell lung cancers (NSCLC) constitute the majority of newly diagnosed lung cancers [1]. Correct staging is very important to determine the appropriate treatment strategy and the 8th TNM staging system is used [2]. Treatment for non-small cell lung cancer (NSCLC) varies depending on the stage. For stage 1 and stage 2 NSCLC, surgical resection is the primary treatment modality, provided there are no contraindications. If surgery is contraindicated, patients are typically considered for conventional radiotherapy or stereotactic body radiotherapy (SBRT) [3].

In stage 3 patients and some stage 2 patients' cisplatin based combination regimens are indicated as adjuvant therapy. Furthermore, in recent years, immunotherapy has also been introduced in these patient groups [3].

Today, a uniform approach is recommended for all patients for postoperative follow-up [4]. It is recommended to conduct surveillance every six months for the first 2-3 years, which should include a review of the patient's medical history, a physical examination, and ideally a contrast-enhanced spiral chest Computed Tomography (CT) scan at the 12- and 24-month marks. After this period, annual follow-ups are advised, comprising a medical history review, physical examination, and chest CT to monitor for second primary tumors. Routine follow-up with PET-CT (positron emission tomography-computed tomography) is not advised [5].

Despite all advances, high recurrence rates are a serious problem in the treatment of lung cancer. Recurrence rates after complete resection in early stage lung cancer ranging from %20 to %41 [6,7]. The differences reported in the literature can be attributed to the examination of different stages of disease, the separate evaluation or exclusion of either local and distant metastases, and the variability in follow-up durations [8].

The majority of mortality in the post-resection period in non-small cell lung cancer is related to the development of recurrence [9]. Furthermore, the healthcare resource utilization is much higher in the recurrence group [10].

Overall recurrence is more likely in patients with a PET-CT maximum standard uptake value (SUVmax) over 5, advanced stage disease, or those who received preoperative radiation therapy. Local recurrence is more

common in patients with specific risk factors including larger tumor size and lymphovascular invasion, which facilitate cancer spread and metastasis [8].

The factors related recurrence risk for early stage lung cancers are poorly defined, and the available data cannot clearly distinguish these factors based on time periods and relapse sites [11]. Our main aim in our study is to identify predisposing factors for recurrence and then to highlight which cases need more aggressive treatment methods and to create patient-specific follow-up options in the light of these factors.

## Materials and Methods

Patients who were operated on for non-small cell lung carcinoma in our clinic between 2005 and 2022 were included in the study.

A total of 272 patients with stage 1-2 disease were included in our study. Twenty-six patients were excluded due to a history of neoadjuvant treatment. 246 patients with stages 1 and 2 were identified.

The patient's clinical, laboratory and respiratory data, radiological features of the tumor and surgical features were recorded retrospectively. Patients were further stratified by histological subgroups, resection types, stages, comorbidities and operation method (VATS/Thoracotomy). Patients were followed for a minimum of 2 years, with a median follow-up duration of 59.5 months for recurrence evaluation. Recurrence was defined as the appearance of locoregional or distant relapses, with sites and timing categorized according to the disease stage. Locoregional recurrence was defined as the development of tumors within the surgical field or adjacent lymph node stations, including bronchial stump recurrence, hilar or mediastinal lymph node involvement, and recurrence within the ipsilateral lung parenchyma. Distant recurrence was classified as the presence of lesions in the contralateral lung parenchyma or involvement of extrathoracic organs.

Recurrence was verified through radiological imaging and/or histopathological examination. In our clinical practice, asymptomatic patients were followed postoperatively with thoracic computed tomography every three months for the first two years, and every six months for the subsequent three years. In the presence

of additional clinical symptoms, Magnetic Resonance Imaging (MRI) and PET-CT were utilized for further investigation. All recurrences were histopathologically verified, except in cases where the anatomical location was not amenable to biopsy.

The study was approved by the Institutional Ethics Review Board of Istanbul University-Cerrahpasa (Number and Date: E-83045809-604.01.01-712053; 15/06/2023). Informed consent received. All patient data were anonymized and confidentiality was maintained.

### Statistical Analysis

Patients were divided into two groups: those with recurrence (Group 1) and those without (Group 2). Groups were analyzed for parametric data with the Student-t test, and non-parametric data with the Chi-square test. Kaplan-Meier test was used for survival analysis, and multivariate analysis was performed for survival with Cox regression analysis. SPSS 27.00 was used.  $p < 0.05$  was considered statistically significant.

### Results

This study includes 246 patients, comprising 73 women and 173 men. Among all patients, 87 (35.3%) experienced recurrence. The recurrence rate in male and female patients were 66 (75.8%) and 21 (24.1%), respectively. The mean age of patients without recurrence was  $60.9 \pm 10.4$  years, while those with recurrence had a mean age of  $62.1 \pm 9.3$  years ( $p=0.348$ ) (Table 1).

	No Recurrence n=159	Recurrence n=87	p
Gender			
-Male	107 (67.2%)	66(75.8%)	0.160
-Female	52 (32.7%)	21(24.1%)	
Age	$60.9 \pm 10.4$	$62.1 \pm 9.3$	0.348

In terms of smoking, patients without recurrence had a mean smoking duration of  $41.4 \pm 37.6$  years, whereas those with recurrence had a mean duration of  $43.6 \pm 29.3$  years ( $p=0.093$ ). Furthermore, regarding postoperative hospital stay, patients without recurrence had an average stay of  $6.0 \pm 3.0$  days, in contrast to those with recurrence, who had a significantly longer stay of  $7.0 \pm 5.0$  days ( $p < 0.001$ ) (Table 2).

**Table 2.** Table containing parametric data of the groups.

	No Recurrence n=159	Recurrence n=87	p
Smoking (Pack Year)	$41.1 \pm 37.6$	$43.6 \pm 29.3$	0.093
Postoperative Hospital Stay (Days)	$6.0 \pm 3.0$	$7.0 \pm 5.0$	<0.001

In stage 1, local relapses were the most frequent, occurring in 25.4% of total cases, followed by distant relapses at 23.7%, and combined local and distant relapses at 6.8%. For stage 2, local relapses were observed in 18% of total cases, distant relapses in 22.7%, and combined relapses in only 3.4% (Table 3).

Regarding the Cardiac Risk Index, the majority of patients with recurrence (79, or 90.8%) had a score of 1, compared to 136 (85.5%) of patients without recurrence. 15 (9.4%) patients with Cardiac Risk Index Score 2 were without recurrence whereas, 8 (9.1%) patients were with recurrence. For scores of 3 and 5, recurrence was less common, with no patients in the recurrence group having a score of 3, and only one patient with a score of 5 in the no recurrence group. The difference of Cardiac Index scores between two groups was not statistically significant ( $p=0.079$ ) (Table 3).

As for the Pulmonary Risk Index, 56 (35.2%) patients with recurrence had a score of 0, in contrast to 15 (7.2%) of patients without recurrence. 70 (44%) patients with score 1 experienced recurrence, same as without a recurrence. A score of 2 was seen in 25 patients (15.7%) with recurrence and 21 patients (24.1%) without recurrence. Moreover, 8 (5%) patients had a score of 3, compared to 2 (2.2%) patients without recurrence. The distinction between recurrence and without recurrence in terms of Pulmonary Risk Index was not statistically substantial (Table 3).

Five different surgical resection methods were utilized; lobectomy, bilobectomy, pneumonectomy, wedge resection and segmentectomy. These procedures were performed using video-assisted thoracoscopic surgery (VATS) or thoracotomy.

Most of the patients had stage 1 cancer (n:171 69.5%), whereas only %30.5 (n:75) had stage 2 cancer. The recurrence rate was 35.3%, with 87 out of 246 patients experiencing relapse. Among stage 1 patients, the recurrence rate was 30% (n=52), whereas it was significantly higher in stage 2 patients at 46.6% (n=35,  $p=0.014$ ) (Table 3).

**Table 3.** Table containing non-parametric data of the groups.

	No Recurrence n=159	Recurrence n=87	p
Diabetes	33 (20.7%)	10 (11.4%)	0.067
Cardiac Risk Index			0.079
1	136 (85.5%)	79 (90.8%)	
2	15 (9.4%)	8 (9.1%)	
3	7 (4.4%)	0	
5	1 (0.6%)	0	
Pulmonary Risk Index			0.066
0	56 (35.2%)	15(17.2%)	
1	70 (44%)	49(56.3%)	
2	25 (15.7%)	21(24.1%)	
3	8 (5%)	2(2.2%)	
Charlson Comorbidity Index			0.128
2	117 (73.5%)	72(82.7%)	
3	42 (26.4%)	14(16.09%)	
5	0	1(1.1%)	
Vats	91 (57.2%)	36 (41.4%)	0.017
Thoracotomy	68 (42.7%)	51(58.6%)	
Resection Method			0.017
-Lobectomy	132 (83.0%)	71 (81.6%)	
-Bilobectomy	4 (2.5%)	1 (1.2%)	
-Pneumonectomy	2 (1.3%)	8 (9.2%)	
-Wedge	12 (7.5%)	6 (6.9%)	
-Segmentectomy	9 (5.7%)	1 (1.1%)	
Pathologic Diagnosis			0.464
-Adenocarcinoma	88 (55.4%)	54 (62.1%)	
-Squamous Cell Carcinoma	50 (31.5%)	21 (24.1%)	
-Other	21 (13.1%)	12 (13.8%)	
N0	143 (89.9%)	72 (82.7%)	0.107
N1	16 (10.1%)	15 (17.2%)	0.184
T Staging			0.021
-1A	19 (11.9%)	9 (10.3%)	
-1B	47 (28.5%)	12 (13.8%)	
-1C	24 (15.2%)	13 (14.9%)	
-2A	46 (28.9%)	31 (35.6%)	
-2B	16 (10.1%)	10 (11.5%)	
-3	7 (4.4%)	12 (13.8%)	
TNM Staging			0.035 for Stage 1 and 2, p=0.014
-1A1	18 (11.3%)	8 (9.2%)	
-1A2	44 (27.6%)	11 (12.6%)	
-1A3	17 (10.6%)	13 (14.9%)	
-1B	40 (25.1%)	20 (22.1%)	
-2A	13 (8.1%)	8 (9.2%)	
-2B	27 (16.9%)	27 (31%)	
Pleural Invasion	58 (36.4%)	40 (45.9%)	0.135
Perineural Invasion	44 (27.6%)	33 (37.9%)	0.199
Lymphatic Invasion	102 (64.2%)	74 (85.1%)	0.001
Vascular Invasion	70 (44.0%)	54 (62.1%)	0.008

**Table 4.** Survival of the patients.

	5-Year Survival Rate (%)	Median Survival (Months)	95 % Confidence Interval
No recurrence	83.6	164.7 ± 6.9	151.2-178.2
Recurrence	59.8	131.3 ± 9.9	111.9-150.7
Overall	75.2	154.2 ± 6.3	141.9-166.5

The VATS surgery rate was statistically significantly higher in the group without recurrence ( $p=0.017$ ). There were statistically significantly more pneumonectomies performed in the relapse group ( $p=0.017$ ). Regarding histopathological distribution, the non-recurrence group comprised 55.4% adenocarcinoma and 31.5% squamous cell carcinoma, whereas the recurrence group showed 62.1% and 24.1%, respectively. There was no statistically significant difference in histopathological types between the two groups ( $p=0.464$ ).

The relapse group had statistically significantly more advanced T stage and TNM stage ( $p=0.021$ ,  $p=0.035$ , respectively). Statistically significant lymphatic invasion and vascular invasion were observed more frequently in the relapse group ( $p=0.001$ ,  $p=0.008$ , respectively). Smoking history and number of postoperative hospital stay days were higher in the recurrence group ( $p=0.093$ ,  $p<0.001$ , respectively) (Table 3).

For the non-recurrence group with operated stage 1 and stage 2 cancers, it was 164.7 months ( $\pm 6.9$ ; 95% CI: 151.2 - 178.2). In contrast, the recurrence group had a mean survival time of 131.3 months ( $\pm 9.9$ ; 95% CI: 111.9 - 150.7) (Table 4). The group in which relapse was monitored was statistically significantly worse in terms of survival data ( $p=0.002$ ) (Figure 1).

In Cox regression analysis, the group with recurrence had a statistically significantly worse survival ( $p<0.001$ ). In Cox regression analysis, the presence of N1, pleural invasion and lymphatic invasion were associated with poor survival as independent risk factors ( $p=0.019$ ,  $p=0.005$ ,  $p=0.004$ , respectively). The presence of N1 and pleural invasion were not statistically significant on relapse-free survival ( $p=0.125$ ,  $p=0.111$ , respectively) (Figure 2,3). Pneumonectomy and the presence of lymphatic invasion were statistically significant on recurrence-free survival ( $p=0.023$ ,  $p=0.001$ , respectively) (Table 5) (Figure 4,5).

Table 5. Multivariate Cox regression analysis of survival.			
	Hazard Ratio	p Value	95 % Confidence Interval
N1	16.4	0.019	1.6-167.9
Pleural Invasion	6.25	0.005	0.04-0.56
Lymphatic Invasion	6.25	0.004	0.05-0.57

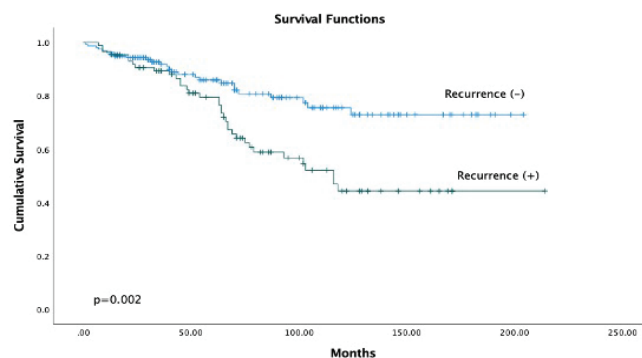


Figure 1. Survival graph of recurrence and non-recurrence groups in early stage non-small cell lung cancer patients.

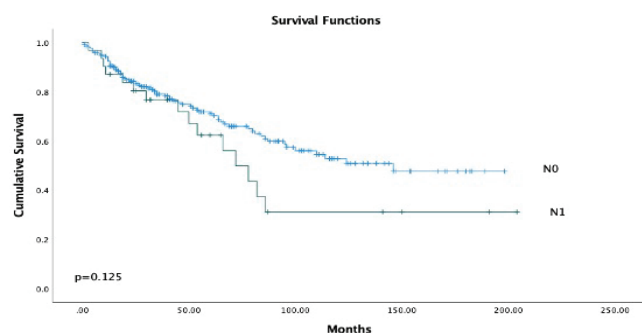


Figure 2. Survival graph showing the effect of the N factor on recurrence-free survival.

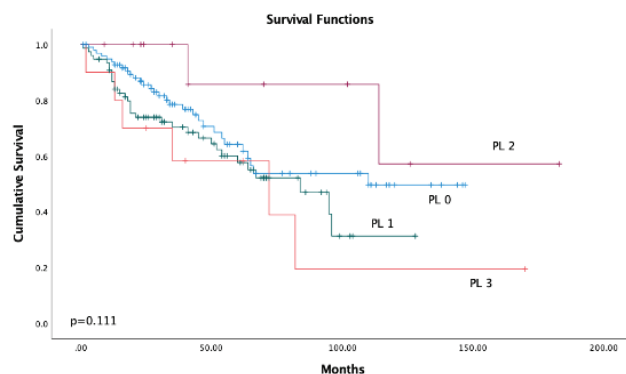


Figure 3. Survival graph showing the effect of the pleural invasion on recurrence-free survival.

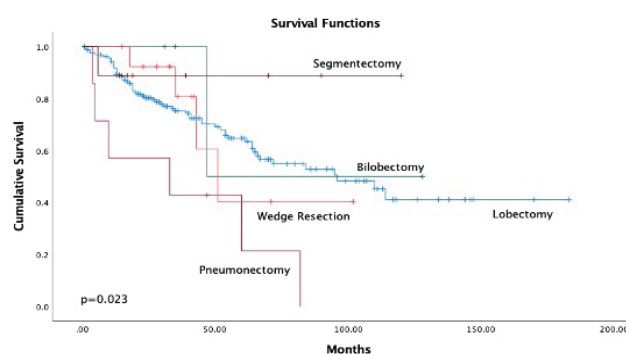
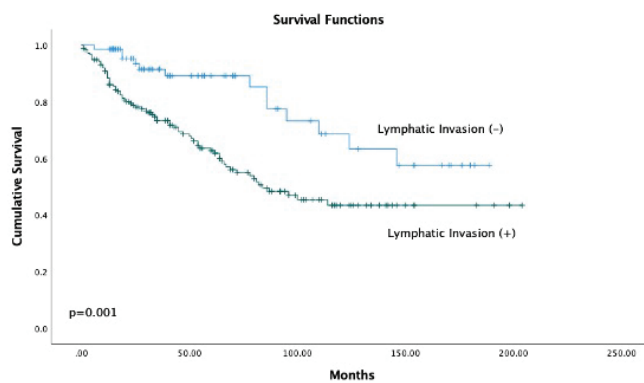


Figure 4. Survival graph showing the effect of the resection types on recurrence-free survival.



**Figure 5.** Survival graph showing the effect of the lymphatic invasion on recurrence-free survival.

### Discussion

In this study, we retrospectively analyzed factors affecting recurrence in primary early stage lung cancer patients who were treated in our hospital between 2005 and 2022. Higher T and TNM stages, positive lymphatic and vascular invasion were significantly more common in the recurrence group. In contrast, the non-recurrence group showed a significantly higher rate of VATS surgery.

The Cox regression analysis confirmed recurrence as an independent predictor of poor survival ( $p < 0.001$ ). Additionally, the presence of N1, pleural invasion and lymphatic invasion were identified as significant risk factors for reduced survival ( $p = 0.019$ ,  $p = 0.005$ ,  $p = 0.004$ , respectively). These findings highlight the importance of closely monitoring patients with these high-risk features and providing targeted interventions to help improve their outcomes [12].

Studies showed a strong association between locoregional recurrence and both visceral pleural invasion and N1 lymph node involvement [13,14]. Various studies have frequently discussed visceral pleural invasion concerning the prediction of postoperative recurrence. However, its prognostic significance is mostly confirmed through univariate analysis or found to be affected by tumor size [15,16]. However, a randomized controlled trial by Altorki et al. reported an increased recurrence rate and decreased disease-free survival in the presence of visceral pleural invasion [13]. In our study, the presence of pleural invasion was found to be an independent risk factor for survival, which is consistent with the literature, and it should be considered that additional treatment or close follow-up may be required in this patient group.

The presence of lymph node metastases (N1, N2) has been shown in multiple previous studies to significantly increase the risk of recurrence [17,18]. Furthermore, advanced N Stage (N1 compared to N0) and T stage (T3-T4 compared to T1-T2) have been found associated with loco-regional failure [19]. Similar to the literature, the presence of N1 was found to be an independent poor prognostic factor for survival. This highlights the importance of perioperative lymph node sampling.

In our study, the VATS surgery group had significantly lower recurrence rates compared to the Thoracotomy group. While other studies have also reported lower recurrence rates with VATS, even in larger tumors, the reasons for this remain unclear, particularly when considering the criteria used to determine the choice between VATS and thoracotomy [20,21]. Li et al., in their study presenting long-term outcomes after surgery for stage 1-3 NSCLC, demonstrated the advantage of VATS over thoracotomy in terms of overall and disease-free survival. However, when performing propensity score matching according to TNM stage, they found that VATS superiority in disease-free survival was observed only in stage 2 [22]. In our study, T stage was higher in the group that experienced recurrence. The lower recurrence observed in VATS patients may be due to the higher likelihood of performing thoracotomy in patients with larger tumors and more advanced T stage. However, this bias in incision selection should not be interpreted as recurrence caused by the type of incision [22].

Pneumonectomies were performed more frequently in the relapse group, and the number of postoperative hospital stay days was higher among the recurrence group. This may reflect the inclusion of patients with more advanced disease or worse overall health conditions in the relapse group, which could contribute to poorer survival outcomes and an increased likelihood of recurrence. In addition to advanced-stage disease, the necessity of a central pneumonectomy may also influence recurrence rates. Furthermore, pneumonectomy carries inherent risks of increased morbidity and mortality, which often result in prolonged hospitalizations and diminished overall health. Consequently, extended hospital stays likely reflect a more complex postoperative recovery driven by the patient’s compromised health status or the presence of advanced-stage disease.

## Limitations of the Study

Being a retrospective study conducted at a single institute, there are several limitations. First of all the study was conducted at a single center, which may limit the findings to broader population and variability in outcomes. Moreover, time-related bias was unavoidable due to our 17-year time interval. In order to mitigate this bias, we excluded the majority of patients (n = 506, 69%) with inconsistent, missing, or unexplainable data. Additionally, patients with advanced-stage disease were also excluded from the analysis. Although the study focused on stage I and II patients, these early-stage cases still exhibit significant heterogeneity and the variability within these groups may affect the interpretation of prognostic factors and outcomes. Despite these limitations, the strict exclusion of incomplete data and the long follow-up period enhance the reliability of our findings.

The TNM staging as well as the presence of lymphatic and vascular invasion were significantly linked to higher recurrence rates. Moreover, recurrence was more frequent in individuals with a smoking background and an extended hospital stay post-surgery. According to Cox regression analysis, lymphatic invasion was recognized as an independent factor associated with both lower survival rates and higher recurrence risk. Additionally, patients with pleural invasion, N1 involvement, advanced tumor stage, and those who underwent pneumonectomy also demonstrated a higher risk of recurrence and lower survival rate. Therefore, we recommend closer monitoring of these patient groups and a thorough assessment of adjuvant therapy strategies to enhance their prognosis.

In conclusion, recurrence in patients operated on for early-stage non-small cell lung carcinoma is important as it is associated with worse survival. In our study, the presence of N1, pleural invasion and lymphatic invasion were independently associated with poor survival in patients with early stage non-small cell lung carcinoma, indicating their effects as poor prognostic factors. The fact that pneumonectomy and the presence of lymphatic invasion have an impact on relapse-free survival shows that they are predisposing factors for relapse. In patients who underwent pneumonectomy and observed lymphatic invasion, more careful and close patient fol-

low-up can be applied in terms of recurrence. Adjuvant treatment options may be considered. Moreover, recurrences occurring after five years may be more common than previously recognized, highlighting the need for stricter and longer surveillance programs for lung cancer patients. Consequently, high-risk patients require closer clinical surveillance. Incorporating adjuvant immunotherapy and chemotherapy into the treatment plan allows for personalized management strategies, optimizing patient outcomes.

## 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.

## Ethics approval

The study was approved by the institutional ethics review board of Istanbul University-Cerrahpasa (Number and Date: E-83045809-604.01.01-712053; 15/06/2023).

## Authors' contribution

GOI: contributed to the study's concept, design, data collection or processing, analysis or interpretation, literature search, and writing. AT: played a key role in the concept, design, analysis or interpretation, and writing of the manuscript. BSA: was involved in the design, data collection or processing, analysis or interpretation, and writing. BP, BK, EE, and HVK: focused on data collection or processing and conducted the literature search. MKK: contributed to the study's concept, analysis or interpretation, and final writing. All authors have read and approved the final version of the manuscript.

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