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Özgün Araştırma / *Research Article*

Prognostic Effects of Neutrophil-Lymphocyte Rates in Serum and Pleural Fluids in Malignant Pleural Fluids

Malign Plevral Sıvılarda Plevral Sıvı ve Serum Nötrofil-Lenfosit Oranının Prognostik Etkisi

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ABSTRACT

Objective: Various studies have reported that the neutrophil-to-lymphocyte ratio in the serum (sNLR) may serve as a cost-effective and useful prognostic factor in patients with various cancer types. We investigated the clinical impact of NLR as a prognostic factor in malign pleural effusion (MPE) and sNLR on prognosis in MPE.
Method: We retrospectively reviewed all of the patients who were diagnosed MPE. The relationship between sNLR and neutrophil-to-lymphocyte ratio in the malign pleural effusion (mNLR) value, age, Eastern Cooperative Oncology Group (ECOG), histopathologic type, serum albumin and lactate dehydrogenase (LDH) with survival were investigated.
Results: A total of 222 patients with a mean age of 65.7±11.5 were included in the study. Patients with a mNLR value ≥0.42 and a serum NLR value ≥4.75 had a shorter survival (p: 0.000). Multivariate analysis, which showed that survival was significantly related mNLR value > 0.42 and/or sNLR value > 4.75 (Odds Ratio (OR): 2.66, %95 CI, 1,65-4,3 p: 0.001), serum LDH > 210 (OR = 1.8, %95 CI, 1,33-2,46 p: 0.001) and age > 65 (OR = 1.9, %95 CI, 1,41-2,55 p = 0.001).
Conclusion: sNLR and mNLR may act as a simple, useful, and cost-effective prognostic factor in patients with MPE. Furthermore, these results may serve as the cornerstone of further research into the mNLR in the future. Although further studies are required to generalize our results, this information will benefit clinicians and patients in determining the most appropriate therapy for patients with MPE.

Keywords: malignant pleural effusion, neutrophil-to-lymphocyte ratio, prognostic factor, serum

ÖZ

Amaç: Çeşitli araştırmalarda serum nötrofil-lenfosit oranının (sNLR) çeşitli kanser tiplerine sahip hastalarda uygun maliyetli ve yararlı bir prognostik faktör olarak kullanılabileceği bildirilmiştir. Malign plevral efüzyonda (MPE) NLR'nin prognoz üzerindeki klinik etkisini araştırdık.
Yöntem: MPE tanısı alan tüm hastalar retrospektif olarak incelendi. sNLR ve malign plevra sıvısı NLR (mNLR) değeri, yaş, Eastern Cooperative Oncology Group (ECOG), histopatolojik tip, serum albümin ve laktat dehidrogenaz (LDH) ile sağkalım arasındaki ilişki araştırıldı.
Bulgular: Çalışmaya toplam 222 hasta dahil edildi ve ortalama yaş 65,7 ± 11,5 idi. mNLR değeri ≥0,42 ve sNLR değeri ≥4,75 olan hastalarda sağkalımın daha kısa olduğu saptandı (p: 0,001). Çok değişkenli analizde mNLR değeri 0,42 ve / veya sNLR değeri ≥4,75 (Odds oranı (OR): 2,66, p: 0,001), serum LDH> 210 (OR = 1,8, p: 0,001) ve yaş> 65 (OR = 1.9, P = 0,001) olmasının sağkalımla ilişkili olduğu görüldü.
Sonuç: sNLR ve mNLR, MPE'li hastalarda basit, kullanışlı ve uygun maliyetli bir prognostik faktör olarak kullanılabilir. Ayrıca, bu sonuçlar gelecekte mNLR ile ilgili daha fazla araştırmanın temel taşı olarak hizmet edebilir. Sonuçlarımızı genelleştirmek için daha fazla çalışmaya ihtiyaç duyulmasına rağmen, bu bilgiler MPE'li hastalar için en uygun tedaviyi belirlemede klinisyenlere ve hastalara fayda sağlayacaktır.

Anahtar kelimeler: malign plevral efüzyon, nötrofil-lenfosit oranı, prognostik faktör, serum

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INTRODUCTION

Often, Malignant Pleural Effusion (MPE) is the first sign of cancer as a prognostic factor in patients who have advanced pulmonary disease. MPE can be the complication of any malignancy. MPE frequency ranges between 7% and 23% in lung cancer patients [1]. MPE is an indicator of an advanced stage of disease and current research shows that median survival periods range between 3 and 12 months [2]. Lung cancer patients with MPE have the shortest survival times. For this reason, the diagnosis/prognosis stage category for lung cancer with MPE was upgraded from category T4 to M1a [3]. In lung cancer and metastatic carcinoma, MPE is an indicator for advanced-stage disease, and usually shows that mortality will likely occur in a few months after pleural fluid is first identified [4,5]. Many treatment modalities might relieve MPE's respiratory symptoms. If expected survival level is shorter, less-invasive procedures are performed in MPE [4-7].

Some factors might be useful in predicting survival in patients who have malignant pleural disease, including tumor characteristics, disease extent, comorbidity, and the composition of the effusion. Many previous reports used clinical data such as the patient's Performance Status (PS), cancer histology and primary site, and biochemical parameters from pleural fluid examinations, such as, pH, lactate dehydrogenase (LDH), and glucose, as tools in estimating patient survival periods [8,10]. Recently, a meta-analysis consisting of an analysis of 100 studies showed that elevated serum neutrophil-to lymphocyte ratios (sNLR), are associated with adverse Overall Survival (OS) for many solid tumor types as a several systemic inflammatory indicator. Therefore, the sNLR may be used as a beneficial and cost-effective survival time prognostic factor.[11] Also, Lee et al. examined clinical effects of NLR as a predictive tool in MPE (mNLR) and developed a new scoring system in lung cancer patients that uses sNLRs and mNLR, known as the smNLR score [12], which suggest that the mNLR (also the sNLR) may serve as a new predictive factor of survival times in MPE patients. Therefore, the purpose of the present study was to investigate the contribution of mNLR and sNLR on estimating survival times in patients presenting with an MPE.

MATERIALS and METHODS

The study had a retrospective design, local ethical approval was received and ethical approval date and number 07/11/2017-7549; and study protocol was approved by İzmir Dr. Suat Seren Chest Diseases and Surgery Training Hospital.

Statics

Statistical analysis was performed using SPSS [18]. The compliance of continuous variables to normal distribution was tested. Receiver Operating Characteristic (ROC) analysis was performed for independent variables affecting survival, and the most appropriate cut-off value was determined according to the Youden index. Overall survival (OS) curves were produced using Kaplan-Meier methods and survival difference between groups was assessed by the log-rank test. Cox regression analysis was used to develop the multivariate models describing the association of the independent variables with OS.

$p<0.05$ was considered to have statistical significance; and 95% Confidence Interval was identified for parameters.

Study Population

The medical records of all past patients who presented with pleural effusion during the period January 2016 - November 2018 were reviewed. Only patients who had malignant cells that were confirmed with pleural fluid or pleural biopsy were included. Patients who had not hemogram parameters of the fluid, that had not malignant cells identified in effusion fluid and/or pleural biopsy tissue, and who had not sufficient clinical data in their patient files were also excluded

A total of 302 patients with malignant pleural fluid were detected. 21 patients were excluded

from the study because of the lack of pleural fluid hemogram value in the hospital information system, and 59 patients were exluded from the study because of the paramalign pleural fluid. As a result, 222 patients were analyzed in the study.

Data Collection

Clinical and laboratory data (baseline & prognostic) were collected from the system of the hospital, which included age, gender, smoking status, Eastern Cooperative Oncology Group Performance Status (ECOG PS) at diagnosis. ECOG Performance scale shown that 0 means normal health and 5 means death. Low scores indicate good general condition, while high scores indicate poor prognosis. Tumor-related variables consisted of histology and tumor state, and NLRs were achieved by dividing absolute neutrophil count by lymphocyte count in complete blood count at diagnosis and in total cell count of MPE during diagnostic thoracentesis. Survival times were collected from the hospital medical records system. The last check was made on March 31, 2021.

RESULTS

Patient Characteristics

A total of 222 patients were included in the study. Table 1 shows the characteristics of the 222 patients in the study population and the causes of MPE. The mean age of the patients was 65.7 + 11.5 years. Of the 222 patients, 162 (72.5%) were male. The majority of patients were lung cancer patients; 43.2% had an ECOG PS of 2; and 38.3% exhibited an adenocarcinoma histology. The survival analysis according to the type of primary tumor is given in Figure 3.

Types of NLRs and Overall Survival

The optimal cut off values for sNLR and mNLR were identified with Receiver Operating Curve (ROC) analysis. The cut off values used for the sNLR was > 4.75 and the mNLR was > 0.42.

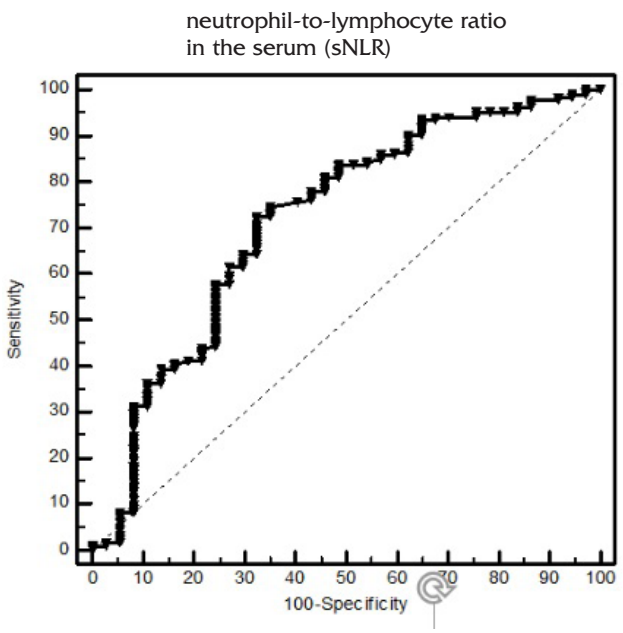


Figure 1. Receiver operating characteristic curve analysis showing the cut off value of serum neutrophil lymphocyte ratio (sNLR) as a prognostic factor in malignant pleural effusion. An area-under-the-curve (AUC) value of 0.716 was obtained using the serum NLR as a prognostic factor for malign pleural effusion, and the sensitivity, specificity, were, respectively, 72,4 %, 67,6%, at a cut-off level of ≥4,75.

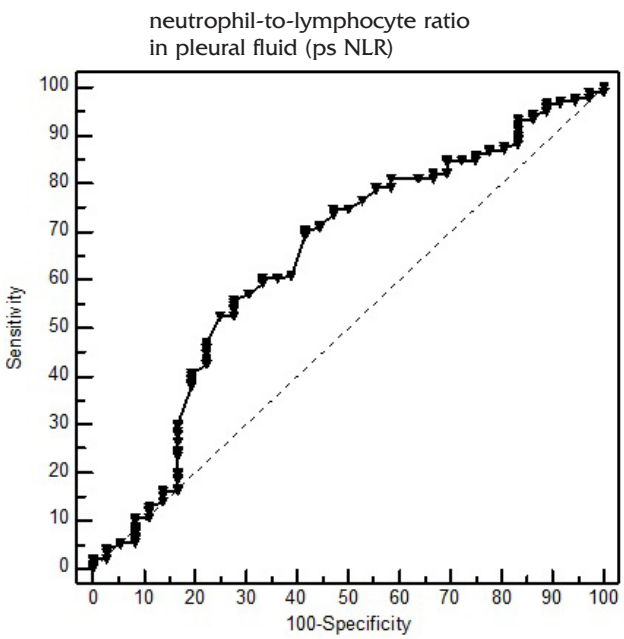
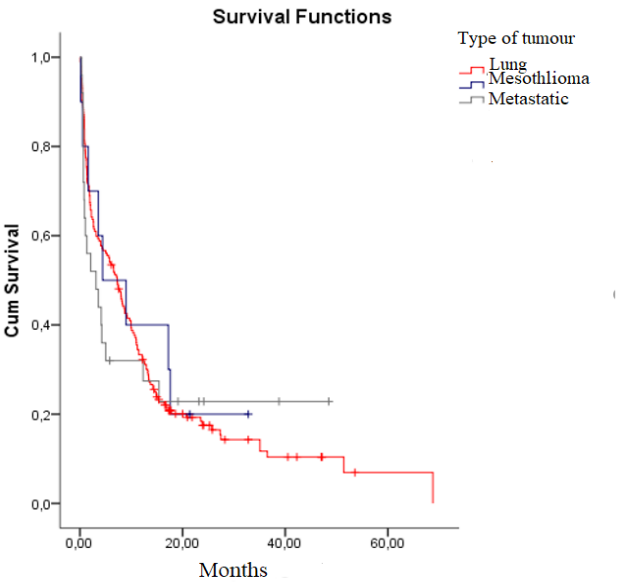


Figure 2. Receiver operating characteristics curve analysis showing the cut off value of pleural fluid neutrophil lymphocyte ratio as a prognostic factor in malignant pleural effusion. An area-under-the-curve (AUC) value of 0.644 was obtained using the pleural fluid NLR as a prognostic factor for malign pleural effusion, and the sensitivity, specificity, were, respectively, 70,4%, 58,3%, at a cut-off level of ≥ 0,428.

Table 1. The characteristics of the patients.

Characteristics	N	%
Age (mean)	65,7±11,5	
Gender (Male/Female)	162/60	72,5/27,5
Histopathology		
Adenocarcinoma	85	38,3
Squamous	22	9,9
Non small	41	18,5
Small cell carcinoma	37	16,7
Mesothelioma	10	4,5
Metastatic carcinoma	25	11,3
Radıological lung cancer	2	0,9
ECOG		
ECOG 0	14	6,3
ECOG 1	51	23,0
ECOG 2	97	43,7
ECOG 3	58	26,1
Survival		
Dead	185	83,3
Alive	37	16,7

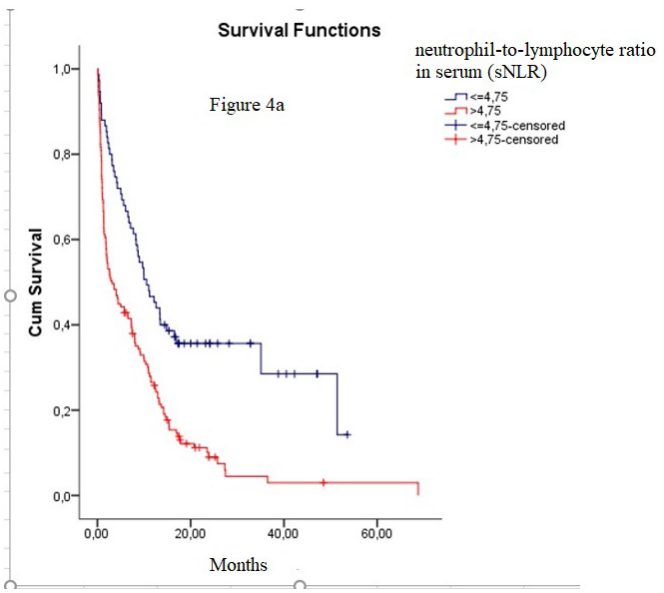
ECOG: Eastern Cooperative Oncology Group



Type of primary tumour	Number of patients	Median survival time ± SD
Lung	187	7,27 ± 0,93 6
Mesothelioma	10	4,41 ± 4,26
Metastatic carcinoma	25	3,12 ± 1,88

Figure 3. The Survival analysis according to primary tumor types.

When the sNLR is > 4.75 the sensitivity is 72.4% and the specificity is 67.6%. When the mNLR is > 0.4, the sensitivity is 70.4% and the specificity 58.3% (Figure 1 and 2).



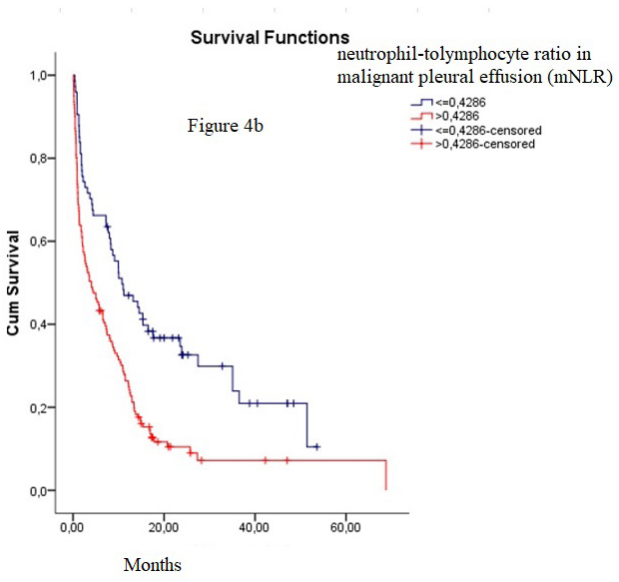


Figure 4a,b. Overall survival of the total study population according to (a) the neutrophil-to-lymphocyte ratio in serum (sNLR), and (b) the neutrophil-tolymphocyte ratio in malignant pleural effusion (mNLR).

Table 2. Survival analysis according to primary type.

Type of primary tumour	Number of patients	Median survival time ± SD
Lung	187	7,27 ± 0,93 6
Mesothelioma	10	4,41 ± 4,26
Metastatic carcinoma	25	3,12 ± 1,88

Table 3. Multivariate analyses of the factors that are predictive of overall survival in all patient.

	Odds Ratıo	P
NLR (PS >0,4286 and/or S>4,75)	2,66	0,001
LDH (S)	1,81	0,001
Yaş	1,90	0,001
NLR (PS >0,4286 and S>4,75)	2,12	0,001

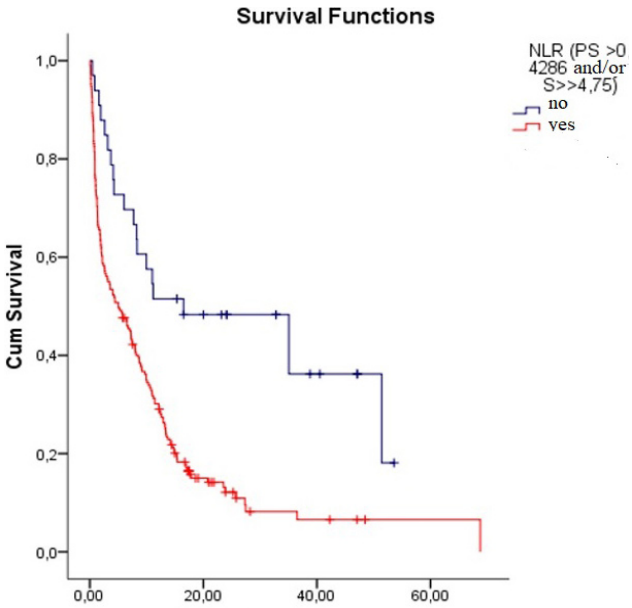


Figure 5. Survival analysis according to neutrophil-to lymphocyte ratio mNLR≥ 0,428 and/or sNLR ≥ 4,75.

Figure 4a and 4b show survival analysis based on NLR types. Patients with a mNLR value > 0.42 and a serum NLR value > 4.75 had shorter survival times (p: 0.001) (Figure 4a and 4b).

The median survival time was 5 months when pleural fluid NLR and/or serum NLR values were above cut-off values. The median survival time was longer (16.5 + 10.2 months) when sNLR and mNLR were less than cut-off values (Figure 5). Table 2 shows the multivariate analysis showing that the survival that was related to mNLR values at significant levels > 0.42 and/or sNLR value>4.75 (Odds Ratio (OR): 2.66, %95 CI, 1,65-4,3 p: 0.001), serum LDH >210 (OR=1.8, %95 CI, 1,33-2,46 p: 0.001) and age >65 (OR=1.9, %95 CI, 1,41-2,55 p=0.001). The remaining potential independent diagnostic factors, which were evaluated did not affect survival periods.

DISCUSSION

In the present study, it was found that sNLR and mNLR are significant predictive factors for OS times in MPE patients. Therefore, evaluation of both the sNLR and mNLR values together or assessing only the mNLR value, are useful and cost-effective OS estimating strategies for physicians having patients with MPE. The sNLR and mNLR values made up a more accurate prognostic tool than mere sNLR, which had first been reported as a prognostic factor in various cancer patients [11,13,17].

Isolated and small-size MPE was associated with significantly worse survival times in lung cancer patients[18], but it depends on the state and histopathological classification of malignancy. In this study, all MPE and lung cancer patients had adenocarcinoma non-small-cell lung cancer. In the study of Jimenez et al., patients with massive MPEs experienced shorter survival periods, independent of age and histological group [19]. In our study, lung cancer and MPE patients had longer survival times compared to those with cancers in other primary sites. Contrary to our study, Zamboni et al. found that ovarian cancer and MPE patients had longer survival times compared to those with cancers in other primary sites [20]. Due to the fact that our study was performed by analyzing patient records from a thoracic disease and surgery hospital, most of the study population consisted of patients with lung cancer. This may explain the different survival

expectancies between this analysis and the Zamboni et al. study.

Recent research examined the most commonly used measures of inflammatory response and their potential prognostic effects in cancer patients; e.g, C-Reactive Protein (CRP), the Glasgow Prognostic Score, cytokines, and leucocytes [21-25]. Also, leucocyte subtypes, especially neutrophil and lymphocyte count, are objective parameters and can evaluate systemic inflammatory response severity in cancer patients [11,13,15]. These studies reported that elevated sNLR levels make up a consistent predictor of shorter OS times in solid tumor patients of various stages. A recent study showed that the sNLR is a significant prognostic factor to predict survival in MPE patients. To use LENT Score (pleural fluid LDH, ECOG PS, the sNLR, and Tumor type) clinically, they selected four variables, which are readily available in clinical practice. The multivariable analysis showed these had highly significant associations with survival times. They also showed that LENT score is effective to identify patients with worst prognosis, and it is better compared to ECOG PS alone in identifying such patients.[23] This is critical to assist patients and clinicians to select an optimal disease and therapy management strategy. Patients who have particularly poor prognosis might wish to minimize time spent at hospital by preferring an Indwelling Pleural Catheter (IPC) vs. more invasive procedures to manage their effusion such as therapeutic pleural aspiration or pleurodesis. For this reason, the sNLR show great potential as a readily-available and inexpensive predictor to assist both patient and doctor in decision making, as shown by the multivariate analysis in our study. The prognostic value of using the sNLR in estimating survival times in MPE patients was consistent with the results reported by previous studies. The mNLR might have potential prognostic effects in MPE patients. However, when the reason of MPE is not clear, its effects may be associated with hematogenous direct spread of tumor cells in the pleura. In this study, it was found that higher mNLR levels were associated with shorter survival times in MPE patients. Another recent study showed the sNLR, mNLR and smNLR scores as important predictors for shorter OS times patients with MPE. In our study, Cox Model regression analysis showed that the following are associated with shorter survival times:

1. mNLR> 0.42 and/or sNLR > 4.75,
2. sLDH > 210, and,
3. age > 65.

Previous studies reported that ECOG PS is a prognostic factor in cancer [18-28]. However, in our analysis, ECOG did not affect survival in MPE patients. Anevlavis et al. reported that prognostic factors that affected survival in MPE patients were ECOG PS, primary tumor histology, and NLR (28). Bielsa et al. showed that tumor type and some biochemical characteristics in pleural effusion (e.g. pH, concentrations of protein, and LDH) affect survival in MPE patients [29].

Study Limitations

The limitations of this study are as follows:

1. this data were collected from one single facility;
2. the study had a retrospective design;
3. the number of patients was small in several categories (e.g., mesothelioma and metastatic carcinoma);
4. NLR is a non-specific variable that can be affected by concurrent conditions (e.g. infection, inflammation, and medication), which is found in most studies on the sNLR.11; and,
5. Some other general prognostic factors about cancer were not considered in detail because of the retrospective design of the analyses.

In order to mitigate these limitations and maximize the validity of the analysis, only patients in whom malignant cells were identified in pleural fluid or in pleural biopsy were included. Secondly, none of the cases had identifiable infection reasons e.g. bacteria, tuberculosis, or viruses in blood, sputum, or MPE. Thirdly, the optimal cut-off values of sNLR and mNLR were determined

with maximally-selected statistics to ensure the objective status of the study.

In conclusion, sNLR and mNLR can act as simple, useful, and cost-effective prognostic factors in MPE patients. These results might also be considered as the milestone for further studies on mNLR in the future. Although more studies are needed to generalize our results, our results will be useful for clinicians and MPE patients to determine the most appropriate treatment.

Ethical Approval: The present study had a retrospective design, local ethical approval was received and ethical approval date and number 13/11/2017- 49109414-806.02.02. The study protocol was approved by Izmir Dr. Suat Seren Chest Diseases and Surgery Training Hospital. All procedures performed in studies that involve human subjects were in line with ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest: The authors declare there are no potential conflicts of interest. This article is protected by copyright. All rights reserved.

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