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Original Article

The Role of Pulmonary Genetic Variations in the Pathogenesis of Pediatric Postinfectious Bronchiolitis Obliterans

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Abstract

OBJECTIVE: Postinfectious bronchiolitis obliterans (PIBO) is a chronic airway disease. The severity of the damage and the subsequent obstructive and inflammatory processes varies from one individual to another. The objective was to identify genetic variations that may be associated with pulmonary diseases in patients with PIBO.

MATERIAL AND METHODS: This retrospective descriptive study was carried out to define potential genetic changes that may be associated with PIBO. Medical records were used to obtain sociodemographic characteristics. Neutrophil, lymphocyte, platelet counts, immunoglobulins and C-reactive protein values, thoracic computed tomography (CT) findings and genetic analysis results for pulmonary panel using next-generation sequencing technology were recorded.

RESULTS: Sixteen patients were enrolled. Median age at diagnosis was 27.5 months (range: 7-195 months). Wheezing was the most common presenting symptom. The most prevalent finding on thoracic CT was a mosaic pattern. In all but one, a wide range of variations genes related to both pulmonary structure and function were identified. The genes identified included those related to primary ciliary dyskinesia (DNAH genes), surfactant metabolism disorder (ABCA3, CSF2RB), pulmonary fibrosis (MUC5B, SFTP), and bronchiectasis (SCNN1B).

CONCLUSION: Heterozygous variations associated with pulmonary diseases, including the *MUC5B* and *DNAH* genes, and CSF2RB, were identified in most patients diagnosed with PIBO, which may have clinical significance. These data are valuable in hypothesis formation that may lead to the evaluation of these three genes in the pathogenesis of PIBO in children.

KEYWORDS: Postinfectious bronchiolitis obliterans, next generation sequencing, whole exon study, genetics

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INTRODUCTION

Postinfectious bronchiolitis obliterans (PIBO) is a rare, chronic obstructive lung disease that is characterized by injury to the bronchiolar epithelium, followed by an inflammatory response and non-uniform luminal obliteration of the small airways. The fundamental mechanism is the injury of the airway epithelium, followed by the proliferation of fibroblasts and peribronchiolar fibrosis. Although PIBO frequently develops in children following adenovirus, influenza, measles, or respiratory syncytial virus infections, it may also occur following other lower respiratory tract infections.[1-3]

Although the role of an increased inflammatory response and peribronchial inflammation that occur with infection in the pathogenesis of BO is well-established, there are still some unresolved questions regarding its emergence. Some children infected with the same virus develop BO, while others recover without sequelae. However, a subset of these children develops severe structural and functional lung disease. This discrepancy may be attributable to a combination of genetic predisposition, the nature of the viral infection, and environmental factors. It is important to consider the role of primary structural, immunological, and functional genetic substructure in that affect the pulmonary immune response and fibrotic process. As is the case with many diseases, genetic predisposition may influence the individual's response

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to infection. Previous research has shown an association between the genetic variants of dynein axonemal heavy chain 1 (DNAH1) and mannose binding lectin.[4,5] Moreover, epigenetic changes associated with the disease were reported, such as the presence of dysfunctional miRNAs that have a role in cytokine-cytokine receptor interaction, transforming growth factor-beta (TGF-β) signaling, and FoxO signaling pathway.[6]

The identification of specific genetic variants associated with the development of PIBO, and the elucidation of their impact may help establish evidence-based diagnostic strategies. Additionally, it may aid in the development of individualized medical therapies to improve the quality of life of patients with certain rare lung diseases with which they may be associated. Therefore, the objective of this study was to identify genetic variations that may be associated with pulmonary diseases in patients with PIBO.

MATERIAL AND METHODS

Research Design and Ethical Approval

This retrospective descriptive study was approved by the Institutional Review Board of Manisa Celal Bayar University Ethics Committee (no: 20.478.486/1521, date: 21.09.2022).

Study Population

A total of 16 children aged 0-18 years who were diagnosed with PIBO based on history, clinical and radiological findings between January 2017 and December 2022 in our Pediatric Pulmonology clinic were included in the study. Genetic screening for lung-related diseases was performed in these patients.

The diagnosis of PIBO can be made on the basis of a history of acute severe respiratory tract infection in childhood, particularly in the early years. It requires the presence of clinical findings such as persistent or recurrent wheezing and airway obstruction that persists after findings revealed by lung function tests, if available. The lack of an expected response to systemic steroids and bronchodilators, along with the presence of a mosaic pattern, air trapping, and/or bronchiectasis, or atelectasis on thoracic CT also supports the diagnosis, as well as the exclusion of other diseases that may cause chronic lung disease.[7,8] The diagnosis of PIBO was made on the basis of clinical features, chest X-ray, and thorax CT findings, after excluding other causes of chronic lung disease as suggested by Teper et al.[8]

Informed consent was obtained from the parents of all patients.

Data Collection

The complaint at presentation to our center, presence of bacterial co-infection in the history requiring the first hospitalization, antibiotic use, glucocorticoid use, mechanical ventilation, duration of hospital stay, and treatments received were recorded from the files. Sociodemographic characteristics and previous medical history, including age, gender, mode of delivery, birth week, presence of postnatal respiratory distress, and whether there was neonatal intensive care unit hospitalization, were also noted. Family history was documented regarding the smoking habits of the mother and father, the mother's smoking during pregnancy, the quantity of cigarettes smoked, and the presence of chronic lung diseases in the family. Moreover, physical examination findings, such as the severity of respiratory distress and the auscultation findings, were recorded.

The genetic results of the pulmonary panel were evaluated.

Thorax CT images were evaluated, and the findings reported by the pediatric radiology specialist of our institution, as well as echocardiography findings routinely performed by the pediatric cardiology specialist at our institution, were recorded.

Moreover, the results of the spirometry, which is routinely performed by the lung function test nurse according to the ATS and ERS guidelines, were obtained.[9]

Genetic Screening for Lung Diseases

In our clinic, all patients with chronic lung symptoms who are followed up with a pre-diagnosis of interstitial lung disease, cystic fibrosis, primary ciliary dyskinesia (PCD), and PIBO are screened for genes that may be associated with lung diseases. Next-generation sequencing technology is used for genetic analysis with the Illumina MiSeq system and compatible reagent kits, and the variants detected are classified according to American College of Medical Genetics and Genomics 2015 criteria.

NGS DNA Extraction

Genomic DNA was extracted from peripheral venous blood using the QIAamp® DNA Mini Kit (QIAGEN, Ankara, Türkiye).

Sequencing for Pulmonary Panel

Virtual panel analysis containing 60 genes (*ACVRL1, BLOC1S6, BMPR2, CAV1, CCDC39, CCDC40, CFTR, CHRNA3, CHRNA5, DNAAF1, DNAAF2, DNAH11, DNAH5, DNAI1, DNAI2, DNAL1, DOCK8, DSP, DTNBP1, EDN3, EFEMP2, ELMOD2, ELN, ENG, FBLN5, FLCN, FOXF1, GDNF, GSTP1, HPS1, HPS4, IL10, IL13, IL2RA, IL4, IL4R, KCNK3, LTBP2, LTBP4, MFAP4, MUC5B, NME8, PHOX2B, RPGR, RSPH4A, RSPH9, SCNN1A, SCNN1B, SCNN1G, SERPINA1, SFTPA1, SFTPA2, SFTPD, SMAD9, SOD3, STAT3, TERT, TGFβ1, TSC1, TSC2*) associated with pulmonary diseases was performed on the patients. Clinical Exome Solution V2 (CES v2) by Sophia Genetics was used for the exome enrichment. All procedures were carried out according to the manufacturer's protocols. Paired-end sequencing was performed on an Illumina NextSeq 500 system with a read length of 150 by 2. Base calling and image analysis were performed using Illumina's Real-Time Analysis software. The BCL (base calls) binary file was converted to FASTQ using the Illumina bcl2fastq package.

Bioinformatics Analysis

All bioinformatics analyses were performed on Sophia DDM™ platform, which includes algorithms for alignment, calling SNPs and small indels (Pepper®), calling copy number variations (Muskat®) and functional annotation (Moka®). Raw reads were aligned to the human reference genome (GRCh37/hg19). Variant filtering was performed on Sophia DDM™. Variant interpretation was evaluated according to American College of Medical Genetics criteria. Integrative Genomics Viewer was used for Bam file visualization.

Whole Exome Sequencing

Whole-exome sequencing was applied to the genomic DNA extracted from peripheral blood lymphocytes. Sequencing libraries were generated using the MGIEasy Exome Capture V4 Probe Set, and the samples of the patients were sequenced on a MGISEQ-2000 sequencing platform (MGI Tech Co. Ltd., Shenzhen). "Variant Annotation and Filter Tool (VarAFT)" and "SEQ Platform (Genomize Inc.)" were used for annotating the the variant-calling file and filtering the variants. According to the lung disease phenotype of the patients, the gene list titled "abnormal respiratory system physiology (HP: 0002795)" in the Human Phenotype Ontology database was used for analysis. Variant interpretation was evaluated according to American College of Medical Genetics criteria.

Sanger Sequencing

Familial segregation analyses of the variants were performed using the Sanger sequencing method.

Statistical Analysis

The Jamovi program was used for data analysis. We described categorical data as number and percentage, and continuous data as means, median, and standard deviation.

RESULTS

Sociodemographic and Background Characteristics

A total of 16 patients diagnosed with PIBO were included in the study. The study included 12 male patients (75%) and 4 female patients (25%). No parents or siblings of the patients had been diagnosed with PIBO. The median age at diagnosis was 27.5 months (minimum-maximum range: 7-195 months). Two patients (12.5%) were born prematurely at 34 and 36 weeks' gestation, while six patients (37.5%) were delivered via normal delivery. Three patients (18.8%) were admitted to the hospital due to respiratory distress during the neonatal period. Two patients (12.5%) had a mother who smoked one to two cigarettes per day during pregnancy. However, these two patients did not experience respiratory distress in the neonatal period. Following birth, 10 patients (62.5%) were exposed to domestic cigarette smoke.

Clinical and Treatment Characteristics

Main Points

- Postinfectious bronchiolitis obliterans (BO) is a chronic airway disease that occurs after severe damage to the lower airways in childhood.
- The severity of this damage and the subsequent obstructive and inflammatory process varies individually.
- It should be taken into account that this difference may be related to the character of the viral infection and the environment, as well as genetic predisposition.
- In our study, a wide range of genetic variations in molecular structural or functional genes in the lung were demonstrated in patients with BO.
- These data suggest that BO is not a random process and that one or more primary molecular causes should be sought.

A total of three patients (18.8%) presented to our clinic with cough, eight patients (50%) with wheeze, four patients (25%) with cough and wheeze, and one patient (6.3%) with cough and dyspnea. Six (37.5%) of the PIBO patients exhibited no history of recurrent respiratory tract infection and no findings indicative of disease before the first severe infection occurred. According to the anamnesis obtained from the families, 15 patients (93.8%) were hospitalized during the period of severe respiratory symptoms. The median duration of hospitalization was 6.5 days (minimum 0 days, maximum 30 days). Antibiotics were administered to 14 patients (87.5%), and steroids were given to 8 patients (50%) during hospitalization. Five patients required oxygen support. One patient was intubated and subsequently monitored.

Laboratory Investigations

Four patients (25%) had positive respiratory viral panel results, and all were positive for adenovirus.

The sweat test was found to be within normal limits in all cases in the examinations performed until the time of diagnosis.

Imaging Results

The echocardiography of three patients included in the study revealed pathological findings. One patient exhibited a right arcus aorta, one patient had atrial and ventricular septal defects, and one patient had increased left ventricular thickness. Flexible bronchoscopy revealed no anatomical abnormalities in any of the patients. The most prevalent finding in patients whose contrast-enhanced thoracic CT scans were evaluated, was the mosaic pattern, observed in 10 patients (62.5%). Additionally, air trapping was observed in 10 patients (62.5%). In the remaining patients, in addition to the mosaic pattern, two patients (12.5%) exhibited atelectasis, another two (12.5%) bronchiectasis, and two more (12.5%) both atelectasis and bronchiectasis. The computed tomography (CT) specimens of the patients who were followed up are available for sharing (Figures 1-4).

Pulmonary Function Test Evaluations

At the time of admission, 6 patients (cases 2, 4, 6, 7, 9, 14) underwent spirometry, the others were younger than 6 years or

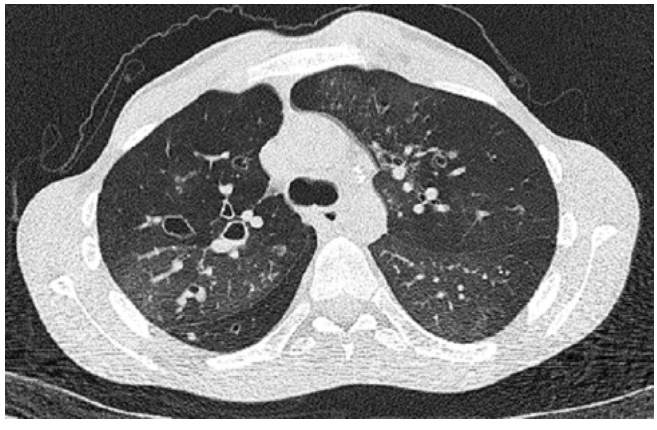

Figure 1. Fourteen years old, bronchiectatic segments with localized secretion-air leveling and bilateral ventilation asymmetries

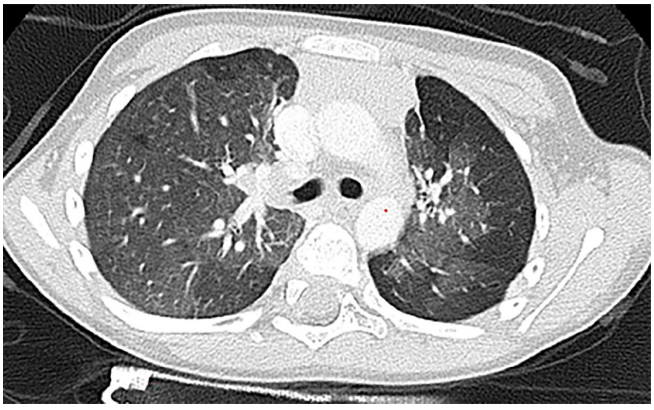

Figure 2. One year of age, diffuse patchy ground-glass areas and ventilation asymmetries from both apices to the lower lobes

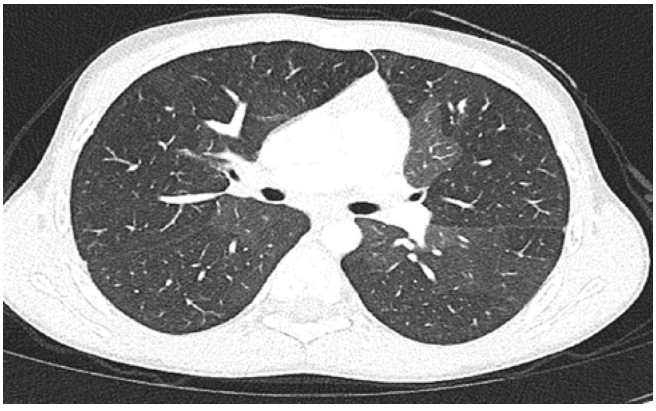

Figure 3. Nine years of age, peribronchial thickening and bilateral ventilation asymmetries

did not comply with the test. The results showed that one (case 2) had restrictive lung dysfunction; the others were normal.

Genetic Panel Results

As the cases had recurrent or prolonged respiratory symptoms and developed chronic lung disease process, the pulmonary panel was studied and 99% of all exons and exon-intron junctions (up to 20 bases) encoded by the studied genes were sequenced and analyzed. This study was performed with next-generation sequencing technology using the Illumina NextSeq® system and compatible reagent kits. In total, 17 different variations were detected. The results of the pulmonary panel were evaluated by the department of medical genetics in accordance with the individual characteristics of each patient and reported in the table (Table 1).

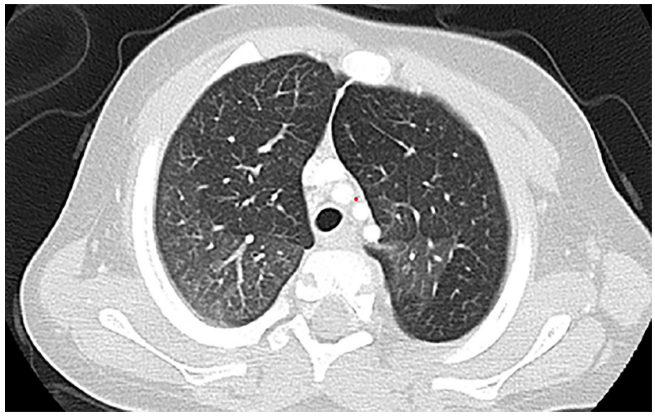

Figure 4. Two years old, bilateral mosaic perfusion appearance, more prominent in the right lung

Table 1. Gender and age distribution of patients with bronchiolitis obliterans and genetic results

Age (in years)	Gender	Genetic result
2	Girl	Normal
14	Boy	*CSF2RB, DNAAF4, DNAH1, DNAH 5, DNAH9, MUC5B* heterozygous
1	Boy	*CCDC40* heterozygous
8	Boy	*DNAI2* heterozygous
1	Boy	*CSF2RB, DNAH9* heterozygous
9	Boy	*MUC5B* heterozygous
6	Girl	*NLRP12* heterozygous
1	Boy	*MUC5B, SCNN1B* heterozygous
16	Boy	*DOCK8* heterozygous, *FLNA* hemizygous
1	Boy	*CSF2RB, DNAH5, MUC5B* heterozygous
3	Girl	*FLNA* heterozygous
4	Boy	*HYDIN, SCNN1G* heterozygous
2	Boy	*DNAH11* heterozygous
16	Boy	*MUC5B* heterozygous
1	Boy	*CCDC40, DNAH11, DNAH5* heterozygous
4	Girl	*ABCA3, CARMIL2* heterozygous

ABCA3: ATP binding cassette subfamily A member 3, *CARMIL2*: Capping protein regulator and myosin 1 linker 2, *CDC40*: Coiled-coil domain 40 molecular ruler complex subunit, *CSF2RB:* Colony stimulating factor 2 receptor subunit beta, *DNAAF4:* Dynein axonemal assembly factor 4, *DNAH1*: Dynein axonemal heavy chain 1, *DNAH5:* Dynein axonemal heavy chain 5, *DNAH9*: Dynein axonemal heavy chain 9, *DNAH11*: Dynein axonemal heavy chain 11, *DNAI2*: Dynein axonemal intermediate chain 2, *DOCK8*: Dedicator of cytokinesis 8, *FLNA*: Filamin A, *HYDIN:* Axonemal central pair apparatus protein, *MUC5B*: Mucin 5B, oligomeric mucus/gel-forming, *NLRP12*: NLR family pyrin domain containing 12, *SCNN1B*: Sodium channel epithelial 1 subunit beta, *SCNN1G:* Sodium channel epithelial 1 subunit gamma

DISCUSSION

The findings of our study indicated that there is a considerable diversity of genetic variations in structural or functional genes, that have been shown to be associated with distinct lung diseases in patients diagnosed with PIBO. This explains the patient-specific risk factors for the development of PIBO following a respiratory tract infection.

BO describes a common pathological change in the small airways that occurs following a variety of diseases with different etiologies and characteristics. PIBO is frequently linked to a range of viruses and bacteria, including adenovirus, influenza, respiratory syncytial virus, and *Mycoplasma pneumoniae*. In our study, as most patients presented to our center weeks or months after the acute infection period, it was not possible to determine the presence of an associated pathogen in 75% of cases. Clinically, the condition is characterized by tachypnoea, rales, wheezing, and hypoxemia, which persists for a long time after the onset of symptoms or recurrent episodes.[10-12] Cough and wheezing were the most prevalent symptoms observed in our patient cohort. No hematological or biochemical pathology was identified in the blood tests conducted at the initial presentation, and there was no apparent immunoglobulin deficiency.

The diagnosis of bronchiolitis is typically based on typical clinical findings, fixed airway obstruction on pulmonary function tests, and radiological findings, especially a mosaic pattern on CT.[8,12,13] Although atelectasis, peribronchial thickening, air trapping, and bronchiectasis form the other CT changes, only the mosaic pattern was included in the PIBO score by Teper et al.[1,8,14] Consistent with this information, all the subjects enrolled had a mosaic pattern among lung CT findings.

Differential diagnosis of PIBO has been reported to include asthma in previous research. Onay et al. have reported that about one third of their PIBO patients had been diagnosed with asthma before presenting to their clinic.[15] Moreover, if PIBO is associated with bronchiectasis, then other etiologies related to bronchiectasis need to be considered, such as cystic fibrosis, PCD, and tuberculosis. Lee et al. have demonstrated that PIBO was the underlying reason in 14% of the subjects with bronchiectasis in their Korean population.[16] All subjects enrolled had sweat chloride testing, immunoglobulin levels, and tuberculin skin tests performed to rule out these diagnoses.

The most crucial step is to forecast the progression of PIBO, in a select group of children with respiratory tract infections, as well as the specific children who are most susceptible to developing severe complications. Although the pathogenesis of PIBO remains incompletely understood, it is becoming increasingly clear that the microbiological factors thought to be effective in the development of the disease are associated with genetic predisposition in affected individuals. An example of this is the development of PIBO in PCD patients with DNAH1 mutation more commonly than in those with a CCDC39 mutation.[17-19] Although we had subjects with DNAH mutations, none of them were diagnosed with PCD. Therefore, mutations that would lead to PCD if present as compound heterozygous or homozygous may be associated with the development of PIBO if present as a heterozygous mutation. However, this interpretation needs to be tested in a larger cohort.

Previous research identified genetic disorders related to surfactant dysfunction as causes of severe respiratory distress and childhood interstitial lung disease in infants.[20] Genetic surfactant dysfunction is the result of variations in genes encoding proteins that are crucial for surfactant production and function. Four proteins that are highly expressed in the lung are designated (SP)-A, -B, -C and -D. SP-B and SP-C reduce surface tension and are encoded by the *SFTPB* and *SFTPC* genes, respectively. One of the principal causes is associated with pathogenic variants, such as ABCA3 (ATP-binding cassette, subfamily A, member 3) and CSF2RB (granulocyte-macrophage colony-stimulating factor receptor, beta). ABCA3 is responsible for transporting phospholipids, which are essential for surfactant function, to the lamellar body. This process is encoded by a single *ABCA3* gene. The *NKX2.1* gene, which encodes the thyroid transcription factor 1 protein, has been demonstrated to affect the expression of the surfactant genes SFTPB, SFTPC, and ABCA3.[21] However, although many of these genes lead to severe clinical findings or respiratory distress when homozygous, the clinical outcome is not known for heterozygous or partially inactive genes. The genetic screening in our study population revealed a heterozygous mutation in the *ABCA3* gene. Surfactant protein mutations may be associated with PIBO due to the immunoprotective effects of these proteins.

Similarly, MUC5B (MUCIN 5, subtype B, tracheobronchial) has been linked to pulmonary fibrosis, while pathogenic variants of SCNN1B (sodium channel, non-voltage-gated 1, beta subunit) have been associated with small airway disease, which can lead to bronchiectasis.[20,21] We have detected MUC5B mutations in four of the subjects with PIBO enrolled in our study population. This may be related to the mucous quality changes in these children; therefore, further physiological studies on its quality are required.

Study Limitations

The most significant limitation of this study is its descriptive nature. Nevertheless, the objective of this study is to provide a foundation for future observational studies. The most significant strength of this study is that it is one of the few to examine genetic variations in cases of BO. This study will contribute to the elucidation of the pathogenesis of this condition.

CONCLUSION

In conclusion, the data indicate that PIBO is not a random process, and genetic variations in genes related to dynein, mucous quality, and surfactant metabolism may be associated with increased risk. The objective of this descriptive study is to develop a hypothesis. The potential role of these genes in the development of PIBO needs to be elucidated with further research linking genetic analysis with protein function analysis.

Ethics

Ethics Committee Approval: This retrospective descriptive study was approved by the Institutional Review Board of Manisa Celal Bayar University Ethics Committee (no: 20.478.486/1521, date: 21.09.2022).

Informed Consent: Informed consent was obtained from the parents of all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.N.T., G.K., Ö.Y., M.Ö., H.Y., Concept: S.N.T., Ö.Y., H.Y., Design: S.N.T., Ö.Y., H.Y., Data Collection or Processing: S.N.T., G.K., Ö.Y., M.Ö., H.Y., Analysis or Interpretation: S.N.T., G.K., Ö.Y., M.Ö., H.Y., Literature Search: S.N.T., Ö.Y., H.Y., Writing: S.N.T., G.K., Ö.Y., M.Ö., H.Y.

Conflict of Interest: The author of this article, Özge Yılmaz, is a member of the Editorial Board of the Thoracic Research and Practice. However, she did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

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