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Original Articles

Invited Review

Review

Case Reports

Letters to the Editor

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Turkish Thoracic Journal (Turk Thorac J) is the double-blind, peer-reviewed, open access, international publication organ of Turkish Thoracic Society. The journal is a quarterly publication, published on January, April, July, and October and its publication language is English.

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The aim of the journal is to convey scientific developments and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

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Letter to the Editor	500	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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CONTENTS

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Turk Thorac J 2018; 19(4): 159-64 DOI: 10.5152/TurkThoracJ.2018.17081

Original Article

Evaluation of Noncystic Fibrosis Bronchiectasis Using Clinical and Radiological Scorings in Children

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Abstract

OBJECTIVES: The aim of this study was to evaluate radiological, clinical, and demographic data of patients with noncystic fibrosis bronchiectasis and to compare high-resolution computed tomography (HRCT) scores based on the demographic and clinical characteristics.

MATERIALS AND METHODS: A total of 34 patients (18 male, 16 female) were assessed in terms of age at symptom onset, age at diagnosis, annual attack frequency, cough severity score, physical examination findings, and pulmonary function test results. Modified Bhalla scoring system (B total) and anatomical prevalence degree score (D total) were used for HRCT examination.

RESULTS: There was a strong negative correlation between forced expiratory volume at first second (FEV_1) and bronchial dilatation degree (SBRDIL). There was a moderate negative correlation of FEV_1, forced vital capacity (FVC), and maximum mid-expiratory flow rate (MEF; 25-75) with bronchiectasis degree (EXBRNC), bronchial wall thickness degree (SBWTHICK), and mucus accumulation in the major airways (PMPLA). The B total, D total, EXBRNC, and SBRDIL scores were significantly higher in patients with hemoptysis and sputum. In comparing B and D total scoring systems, B total provided better results in terms of rale, annual exacerbation frequency (AEF), cough severity score (CSS), and FEV_1 values.

CONCLUSION: As it is proved using HRCT, pulmonary function impairment, sputum production, hemoptysis, and increase in AEF strongly correlating with objective HRCT scoring can be accepted as markers for pathological changes due to bronchiectasis.

KEYWORDS: Bronchiectasis, modified Bhalla scoring system, high-resolution computed tomography

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INTRODUCTION

Bronchiectasis is a chronic inflammatory lung disease, characterized by abnormal permanent enlargement of the bronchi with phlegmy cough and recurrent pulmonary infections [1]. It is a common result of many pulmonary diseases and is typically irreversible, unless detected in the prebronchiectasis stage [2]. It is still a significant problem in developing countries and low socio-economic regions of developed countries. However, while there are approximately 10-50 patients with bronchiectasis per 10,000 individuals in developing countries, there is no reliable information about its incidence and prevalence [3, 4]. The appropriate use of high-resolution computed tomography (HRCT) can result in improved diagnostic capabilities in patients. The severity of disease shows a wide spectrum. While some patients report only intermittent cough and infrequent lower respiratory tract infections, many others exhibit daily productive cough, odiferous green phlegm, frequent lower respiratory tract infections, and frequent presentation to the hospital due to hemoptysis [5]. All these situations negatively affect such children's quality of life, growth, and development and result in frequent hospital admission and need for medication.

Currently, the severity of bronchiectasis is initially determined noninvasively using physical examination, sputum culture, hospitalization incidence and duration, pulmonary function tests, and radiological evaluation [6]. Diagnosis of patients at an early stage before the development of irreversible lung damage is crucial.

There are many respiratory function impairments in bronchiectasis due to numerous morphological abnormalities [7]. Significant lung damage can develop before pulmonary function tests are able to detect these changes [8]. Children under school age and some patients with growth retardation cannot undergo standard spirometry. This exemplifies the need for new tools to evaluate bronchiectasis. Early diagnosis of the disease and significant improvement of prognosis can be achieved with the development of CT techniques. The evidence obtained from studies conducted on children with cystic fibrosis showed that

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HRCT can detect early lung injury before a decrease in FEV_1 and emergence of FVC are detected on pulmonary function tests [9]. Similar to bronchiectasis due to cystic fibrosis, these clinical clues obtained via HRCT will be instrumental in evaluating both diagnostic changes and their correlations during the follow-up of patients with noncystic fibrosis bronchiectasis. To date, there have been a limited number of detailed studies investigating children with noncystic fibrosis bronchiectasis in terms of the clinical and radiological features.

Cystic fibrosis is separately assessed among diseases causing bronchiectasis because of its different clinical and pathological features. The aim of this study was to evaluate the radiological, clinical, and demographic data of patients with noncystic fibrosis bronchiectasis and to compare HRCT (Modified Bhalla and anatomical prevalence) degree scores with demographic and clinical characteristics [10-13].

MATERIALS AND METHODS

Study Subjects and Design

A total of 34 patients aged 6 months to 20 years who were admitted to the Pediatric Allergy-Immunology and Pediatric Pulmonology polyclinics in Akdeniz University between 2003 and 2015 and diagnosed with bronchiectasis based on clinical and HRCT findings were included in the study. Children with cystic fibrosis were excluded based on sweat test and/or genetic mutation analysis results. Children with a previous history of lobectomy or pneumonectomy were also excluded. Ethics Committee approval for the study was obtained from Akdeniz University Clinical Research Ethics Committee, and written informed consent was obtained from the participants.

Patients' age, sex, age at diagnosis, age at symptom onset, family history, cough severity score (CSS), annual exacerbation frequency (AEF), cough, sputum, hemoptysis, and physical examination findings (clubbing, chest deformity, hypoxia, rale, and rhonchi) were assessed by a pediatric pulmonologist. Sputum culture results were recorded, and the underlying etiologies of bronchiectasis were investigated. For adaptable children aged >5 years, spirometry (ZAN 100 Spiromed, Germany) was performed within a week of HRCT during a nonacute state. All HRCTs were interpreted by a radiologist with 25 years of experience in thoracic radiology (A.G.) who was blinded to the children's clinical status. In each patient, exacerbation frequency was calculated as the number of exacerbations that occurred in the preceding 12 months and was determined based on patient history and review of clinical charts. Acute exacerbation of bronchiectasis was assessed by an increase in cough and sputum amount/purulency, chest pain, shortness of breath as described by family members or the child, rale, rhonchi, wheezing, hypoxia symptoms, increases CRP levels, increased neutrophil proportion, and impairement in respiratory function tests [14]. Patients' CSSs were obtained by scoring daytime cough symptoms from 0 to 5 (0=no cough; 1=1 or 2 short coughing episodes in a day; 2=> 2 short coughing episodes in a day; 3=frequent coughing but does not affect school or other activities; 4=frequent cough affecting school or other activities; and 5=severe cough inhibiting most activities) [15].

Radiological Evaluation

High-resolution computed tomography was performed using a Toshiba Aquilion (Tokyo, Japan) scanner. After a scout view, 1-mm collimation sections were obtained at intervals of 7 or 10 mm as appropriate for the child's size. The protocol for HRCT required an exposure time of 0.4 s, with scans at 100-200 mA and 120 kV. Scans were performed in the supine position. Children aged <5 years and older children who were unable to cooperate with the breath-holding maneuver were scanned under general anesthesia, with images captured during a suspended inspiration. Older cooperative children were asked to hold their breath during a maximal inspiration. Expiratory scans were not used.

Bronchiectasis was confirmed if the inside bronchial diameter was greater than that of the adjacent (apparently normal) artery (ratio >1) according to Webb et al. [16]. Bronchiectasis severity, bronchial dilation degree, bronchial wall thickness degree, mucus accumulation in major and small airways, and reduction in parenchymal attenuation were scored separately for each lung lobe (total of 6 lobes considering lingula as a separate lobe) according to the modified Bhalla system [10-12]. The scores of each lobe were added and total scores according to the Bhalla system were identified as B total in this study. A second scoring was conducted by the same radiologist evaluating anatomical prevalence of bronchiectasis separately for each of the six lobes as following: degree 0=no bronchiectasis; 1=mild (<25% of the lobe); 2=moderate (25%-50% of the lobe); and 3=severe (>50% of the lobe) [13]. The scores of each lobe were added, and a general score for anatomical prevalence degree of bronchiectasis was obtained, which was called as D total in this study.

Statistical Analysis

Analysis was conducted using SPSS (Statistical Package for Social Sciences) version 21.0 (IBM Corp.; Armonk, NY, USA) software. Descriptive statistics were presented by percentage, mean, and standard deviation, median, minimum, and maximum values. The normality assumption was controlled using the Shapiro-Wilk test in the analysis of difference between the measures of both the groups. The Mann-Whitney U test was used for evaluating non-normally distributed data, and the Student's t test was used for normally distributed data. The Kruskal-Wallis test was used in nonparametric comparison of three stage group; the Bonferroni-Dunn test was used for significant cases as the post hoc test. The Spearman correlation test was used for determining the relationships among nonnormally distributed continuous variables, whereas the Pearson correlation test was used for normally distributed continuous variables. A significance level of 95% (or error margin of α=0.05) was used for determining the differences in analyses. For the Spearman correlation coefficient (r), 0.90-1.00 was accepted as a very strong correlation, 0.70-0.89 as strong correlation, 0.50-0.69 as moderately strong correlation, 0.30-0.49 as weak correlation, 0-0.29 as no correlation, and negative values as an inverse correlation. The post hoc power analysis showed that when the correlation between B total and FEV_1 was used (r=-0.56, α=0.05) and the total number of samples was 29, the power of the study was 0.94.

RESULTS

Patients

The mean age of the 34 patients (18 male, 16 female) included in this study was 13.69±4.67 years (range: 5-20 years). The mean age at the onset of symptoms was 3.78±4.06 years (0.5-16 years), and the mean age at diagnosis was 9.61±4.84 years (1-18 years). The mean difference between the age at the onset of symptoms and at diagnosis was 5.84±3.96 years. The most frequent complaint at diagnosis was cough (98.3%). A total of 26 patients (76.5%) had a complaint of sputum at presentation. Hemoptysis was noted in 5 patients (14.7%), clubbing in 5 (14.7%), and oxygen dependency in 1 (2.9%). There was a family history of bronchiectasis in 3 (8.8%) patients. There was no etiology of bronchiectasis in 10 patients (29%); however, immunodeficiency was detected in 7 (20.6%), PSD in 5 (14.7%), previous infection in 5 (14.7%), asthma in 4 (11.8%), and other causes in 3 (bronchiolitis obliterans, rheumatic disease, and foreign body aspiration in 1 patient each). The mean frequency of annual exacerbation was 2.00±1.41, and the mean CSS was 2.00±1.26. Five patients could not undergo SFT as their young age prevented successful testing. In patients undergoing SFT, the mean FEV_1 was 72.51%±22.31%, mean FVC was 67.35%±21.32%, and mean maximum mid-expiratory flow rate (MEF; 25-75) was 72.90%±30.44%. There was no bacterial isolation in sputum culture in 30.7% of patients (8/26), whereas *Haemophilus influenzae* was isolated from 12 (46.1%), *Streptococcus pneumoniae* from 3 (11.5%), *Staphylococcus aureus* from 1 (3.8%), *Moraxella catarrhalis* from 1 (3.8%), and *Klebsiella pneumoniae* from 1 (3.8%) patient.

Radiological Scores

There was a positive and significant correlation of age of patients with B and D total scores (r=0.379, p=0.032 and r=0.371, p=0.037, respectively), but there was no correlation with CSS. There was a positive and weak correlation between age at diagnosis and B total (r=0.351, p=0.049). There was no correlation of age at the onset of symptoms with D total CSS, B total, or sub parameters.

The CSS, B total, SBRDIL, and EXDECAT values were higher in patients with rales than those in patients without rales (p=0.048, p=0.015, p=0.030, p=0.017, respectively) on physical examination. The B total, D total, EXBRNC, and SBRDIL values were significantly higher in patients with hemoptysis and sputum than in those without hemoptysis and sputum (Table 1).

There was a statistically significant negative strong correlation of FEV_1 with SBRDIL; negative and moderate correlation with B Total, EXBRNC, SWTHICK, and PMPLA; and statistically significant negative weak correlation with EXDECAT and D total. There was a statistically significant negative moderate correlation of FVC with D total, B total, EXBRNC, SBRDIL, SWTHICK, and PMPLA. There was a statistically significant negative moderate correlation of MEF 25-75 with EXBRNC, SBRDIL, SWTHICK, and PMPLA (Table 2).

Table 1. Comparison of hemoptysis, sputum, and HRCT scores*

	Hemoptysis Present Mean+SD	Hemoptysis Absent Mean+SD	p	Sputum Present Mean±SD	Sputum Absent Mean±SD	p
D total	8.83±3.48	5.00±3.40	0.044	6.82±3.43	3.30±3.16	0.010
B total	40.83±6.27	24.04±12.43	0.002	31.95±12.37	16.70±8.30	0.001
EXBRNC	9.50±3.88	5.58±3.83	0.022	7.64±3.73	3.40±3.37	0.005
SBRDIL	7.50±2.81	3.81±2.94	0.018	5.64±3.01	2.00±2.10	0.003
SBWTHICK	6.67±3.50	4.85±2.34	0.196	5.95±2.59	3.50±1.90	0.008
PMPLA	3.00±1.78	1.58±1.44	0.063	1.30±1.49	1.30±1.49	0.150
PMPSA	3.33±1.21	2.38±2.00	0.194	3.00±1.82	1.60±1.77	0.052
EXDECAT	7.33±1.75	5.92±3.47	0.451	6.68±3.52	5.10±2.33	0.146

EXBRNC: bronchiectasis degree; SBRDIL: bronchial dilatation degree; SBWTHICK: bronchial wall thickness degree; PMPLA: obstruction in major airways by mucus; PMPSA: obstruction in small airways by mucus; EXDECAT: reduced attenuation degree; *: Bold, p≤0.05; Bold italic, p≤0.01

Table 2. Comparison of pulmonary function test findings with HRCT scores*

	FEV_1 (%)	FVC (%)	MEF (25-75) (%)
D TOTAL	-0.462 (p=0.012)	-0.522 (p=0.004)	-0.380 (p=0.042)
B TOTAL	-0.560 (p=0.002)	-0.590 (p=0,001)	-0.475 (p=0.009)
EXBRNC	-0.658 (p=0.000)	-0.615 (p=0.000)	-0.537 (p=0.003)
SBRDIL	-0.713 (p=0.000)	-0.667 (p=0.000)	-0.557 (p=0.002)
SBWTHICK	-0.575 (p=0.001)	-0.575 (p=0.001)	-0.595 (p=0.001)
PMPLA	-0.562 (p=0.002)	-0.555 (p=0.002)	-0.441 (p=0.017)
PMPSA	-0.280 (p=0.141)	-0.310 (p=0.102)	-0.012 (p=0.950)
EXDECAT	-0.463 (p=0.011)	-0.428 (p=0.020)	-0.488 (p=0.007)

EXBRNC: bronchiectasis degree; SBRDIL: Bronchial dilatation degree; SBWTHICK: bronchial wall thickness degree; PMPLA: obstruction in major airways by mucus; PMPSA: obstruction in small airways by mucus; EXDECAT: reduced attenuation degree; *: Bold, p≤0.05; Bold italic, p≤0.01

Table 3. Comparison of HRCT scores with cough severity score and annual exacerbation frequency*

	Cough severity score	Annual exacerbation frequency
D TOTAL	0.483 (p=0.006)	0.483 (p=0.005)
B TOTAL	0.533 (p=0.002)	0.621 (p=0.000)
EXBRNC	0.593 (p=0.000)	0.501 (p=0.003)
SBRDIL	0.602 (p<0.001)	0.591 (p=0.000)
SBWTHICK	0.653 (p<0.001)	0.511 (p=0.003)
PMPLA	0.369 (p=0.041)	0.325 (p=0.069)
PMPSA	0.350 (p=0.054)	0.289 (p=0.108)
EXDECAT	0.383(p=0.034)	0.275 (p=0.128)

EXBRNC: Bronchiectasis degree; SBRDIL: Bronchial dilatation degree; SBWTHICK: Bronchial wall thickness degree; PMPLA: Obstruction in major airways by mucus; PMPSA: Obstruction in small airways by mucus; EXDECAT: Reduced attenuation degree; *: Bold, p≤0.05; Bold italic, p≤0.01

There was a statistically significant negative weak correlation of CSS with FEV_1, FVC, and MEF (25-75) (r=-0.434; p=0.006, r=-0.439, p=0.005; r=-0.489, p=0.002, respectively). CSS had a statistically significant positive moderate correlation with B total, EXBRNC, SBRDIL, and SBWTHICK and a statistically significant positive weak correlation with D total, PMPLA, and EXDECAT. There was a statistically significant positive moderate correlation of annual exacerbation with B total, EXBRNC, SBRDIL, and SBWTHICK (Table 3).

DISCUSSION

High-resolution computed tomography remains the gold standard for the definitive diagnosis of bronchiectasis. There have been few studies in the literature investigating the advantages of HRCT in the diagnosis of bronchiectasis and correlation of HRCT with the clinical findings of patients [13, 17]. We compared HRCT findings and clinical characteristics of patients with noncystic fibrosis bronchiectasis in this study.

Consistent with the literature, the proportion of male patients was slightly higher than that of female patients (52.9% male, 47.1% female) in this study [18]. The mean age at diagnosis in this study (13.69±4.67 years) was higher than those in previously published studies [2,19-21]. The age at symptom onset in this study was found to be consistent with that in the literature [5]. It was noteworthy that most patients presented to the hospital due to very longstanding complaints. The difference between the age at symptom onset and at diagnosis was 5.84±3.96 years. Because patients presented from both rural and urban areas, there was a possibility of some late admissions. These findings suggested that the disease should be suspected in patients with findings, such as chronic productive cough and persisting rales, and an examination for bronchiectasis should be promptly conducted.

The most frequent complaint upon presentation is cough in patients with bronchiectasis. A diagnosis of bronchiectasis should be considered in cases with chronic, persistent, and productive cough [18]. In developing countries, such as Turkey, if the long-term complaint history cannot be realized, crucial diagnosis may be delayed [20]. The most frequent complaint was cough in our patients (98.3%), followed by sputum production (76.5%).

The incidence of hemoptysis in pediatric patients has been reported to be between 4% and 10% [5,22,23]. Hemoptysis was detected in 14.7% of the patients in our study; this proportion was slightly higher than that in the literature, which may have been caused due to the progression of bronchiectasis because of late diagnosis.

The majority of patients with bronchiectasis in the literature were idiopathic cases (33.3%-49%). In our study, 29% of patients with bronchiectasis were idiopathic cases [5,24,25]. We suspected that the reason for fewer idiopathic bronchiectasis cases in our study could be that our patients underwent a detailed etiological examination in a comprehensive university hospital, which is better equipped to make such a diagnosis.

High-resolution computed tomography is the most reliable objective imaging method for the diagnosis of bronchiectasis and to assess its severity. Eastham et al. [2] reported a ten-fold increase in the diagnosis of noncystic fibrosis bronchiectasis using HRCT. HRCT provides detailed information about the airway size and wall thickness. Because this method provides information about hyperinflation due to air involvement, edema, and fibrosis, it is considered to be a very sensitive investigational tool to detect structural changes in the lungs. Evaluation of bronchiectasis using HRCT is also important in terms of scoring radiological findings, comparing data associated with bronchiectasis, and providing information about its prevalence and severity.

Similar to the literature, HRCT scores were also found to be associated with SFT results. There was a negative correlation of total HRCT score with FEV_1, FVC, and MEF (25-75) in our patients.

Similar to our study, Habesoğlu et al. [12] used a modified Bhalla score in HRCT scoring of adult patients with noncystic fibrosis bronchiectasis and found a negative strong correlation of FEV_1 and FVC with the degree of bronchiectasis, bronchial dilatation severity, bronchial wall thickening severity, and parenchymal attenuation reduction. They found no relationship between mucus accumulation in airways and SFT values in patients with bronchiectasis. Therefore, mucus accumulation in the airways was not found to be a primary reason for impairment in SFT. They reported the degree of bronchiectasis prevalence and reduction of attenuation in the lung parenchyma to be the primary determinants for the decrease in FEV_1 and FVC. In our study, there was a negative strong correlation between FEV_1 and the degree of bronchial dilatation. There was a negative moderate correlation of FEV_1, FVC, and MEF (25-75) with bronchiectasis severity, bronchial wall thickness degree, and mucus accumulation in major airways. These findings showed that pathological changes in the bronchial morphology of patients with bronchiectasis cause both obstructive and restrictive disorders of respiratory functions.

Sheehan et al. [26] correlated HRCT data obtained at two different times from 48 adult patients with bronchiectasis with SFT using the same modified Bhalla scoring system. They stated that the variation in the mucus load over time in the small airways may be responsible for changes in SFT. There have been no pediatric studies in the literature that have investigated the relationship between mucus load and SFT. In our study, there was no correlation between mucus accumulation in small airways and SFT values in children with bronchiectasis.

In a study by Ooi et al. [13] conducted on 60 adult patients in China, there was a negative moderate correlation of anatomical prevalence of bronchiectasis with FEV_1 and MEF (25-75) based on the D total scoring system, as in our study. D total was found to be associated with FEV_1, FVC, and MEF (25-75) in our study. There was a statistically significant negative weak correlation of D total with FEV_1 and MEF (25-75) and statistically significant negative moderate correlation of D total with FVC.

B total, D total, EXBRNC, and SBRDIL scores of patients with hemoptysis and sputum were found to be significantly higher than those of patients without hemoptysis and sputum. In addition, SWTHICK scores of patients with sputum were higher than those of patients without sputum. These scores indicated the prevalence of the disease, due to which they were probably higher in patients with hemoptysis and sputum.

The B total, EXDECAT, and SBRDIL scores were higher in patients with rale than in those without rale in physical examination. This finding was indicative of disease severity; therefore, it is important to utilize HRCT for the diagnosis of bronchiectasis in patients with rale observed during follow-up examinations.

There was a statistically significant positive moderate correlation of AEF with B total, SBRDIL, SBWTHICK, and EXBRNC. There was a statistically significant positive moderate correlation of CSS with B total, SBRDIL, SBWTHICK, and EXBRNC. These comparisons have not been performed in the literature. These results demonstrated the effectiveness of HRCT in indicating disease severity.

Comparing D total with B total, with the latter including more parameters and more complex scoring, B total scoring showed better correlation with clinical and pulmonary function test parameters, such as rale, AEF, CSS, and FEV_1, in pediatric patients with bronchiectasis. Therefore, the B total scoring system is significantly superior for HRCT scoring.

High-resolution computed tomography is an objective and gold standard method for the evaluation of disease severity in bronchiectasis follow-ups. The correlation of clinical findings with HRCT findings is good. As it is proved using HRCT, pulmonary function impairment, sputum production, hemoptysis, and increase in AEF strongly correlating with objective HRCT scoring can be accepted as markers for pathological changes due to bronchiectasis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Akdeniz University (Approval Date: December 11, 2013; Approval No: 303).

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

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Original Article

Causes of Dyspnea after Cardiac Surgery

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Abstract

OBJECTIVES: Postoperative dyspnea is common after cardiac surgery, even in low-risk patients. Cardiac surgeons and anesthesiologists are familiar with patients suffering from dyspnea in the early postoperative period, but in some cases, conventional treatment strategies may be ineffective, and a consultation with a pulmonologist may be required. The aim of this study is to investigate the causes of dyspnea after cardiac surgery in this particular patient group.

MATERIALS AND METHODS: The hospital database was searched for non-emergency cardiac surgery for the period January 2014–October 2015. Individuals with an impaired spirometry result and a history of any pulmonic disease were excluded. Only patients for whom a pulmonary consultation was needed because of dyspnea in the postoperative course were enrolled in the study. Causes of dyspnea were analyzed according to consultation reports and computed tomography findings.

RESULTS: One hundred and three patients were enrolled in the study. Of those, 67 (65%) were male, and the mean age was 61.50±9.43. The most common procedure was the coronary artery bypass grafting. Atelectasis (n=57, 42%) was the most common cause of dyspnea. The length of the intensive care unit (ICU) stay was significantly longer in the pneumonia group (p=0.012). Hospital mortality in the pneumonia group was significantly higher compared with other subgroups (p<0.001).

CONCLUSION: After cardiac surgery, atelectasis was the most common cause of dyspnea, followed by pleural effusion and pneumonia. Patients who experienced dyspnea due to pneumonia had a longer ICU stay. Developing the treatment strategies with consideration of these causes may help reduce the length of stay, morbidity, and mortality in this patient group.

KEYWORDS: Pulmonary rehabilitation and chronic care, respiratory intensive care, thoracic surgery, clinical problems, respiratory infections

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INTRODUCTION

As a result of advances in the cardiac surgical and anesthetic techniques, more patients have been recently referred to cardiac surgery [1,2]. Patients undergoing a cardiac surgical procedure tend to be older and sicker because of the aging population nowadays [1,2]. Dyspnea in the early postoperative period is a major complaint, and postoperative pulmonary complications (PPCs) still remain one of the major causes of morbidity, mortality, increased cost, and prolonged hospital stay after cardiac surgery, particularly in this patient group [1,3–9]. Predicting the high-risk patients for PPCs causing dyspnea and developing a plan to reduce the risk is worthwhile [1,6,9]. Several studies were conducted to investigate the incidence of the PPCs following cardiac surgery [8]. These studies reported diverse results, because of the different patient groups and the variability of the signs and symptoms in a spectrum ranging from dyspnea, cough, and fever to respiratory failure requiring reintubation [8,9]. The success of the surgery is to some extent associated with the effective prevention and management of the PPCs [2]. After general anesthesia, some patients may suffer from dyspnea. However, causes of dyspnea may differ because of the incision, operation site, cardiopulmonary bypass, and internal thoracic artery harvesting, which are unique to cardiac surgery. Although cardiac surgeons are familiar with the patients suffering from dyspnea in the early postoperative period, occasionally, a consultation with a pulmonologist is required to overcome the issue in some patients. The aim of this study is to investigate the incidence, causes, and the risk factors of PPCs causing dyspnea in the early postoperative period after cardiac surgery in this particular patient group.

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MATERIALS AND METHODS

Patients who underwent a non-emergency cardiac surgery in from January 2014 to October 2015 were searched in the hospital database. Individuals with an impaired spirometry result preoperatively and a history of any pulmonary disease, such as asthma and chronic obstructive pulmonary disease, were excluded by reviewing the routine preoperative assessment data to obtain a more homogeneous patient group. Among remaining patients, those for whom a pulmonary consultation was needed because of dyspnea in the postoperative course, were enrolled in the study (Figure 1). Spirometries including a ratio of forced expiratory volume in 1 second to forced vital capacity greater than 0.7, a forced vital capacity greater than 80% of the predicted, and no artifacts in spirogram and flow-volume loop were accepted as normal.

Because dyspnea is a relatively subjective symptom reported by patients, we defined dyspnea according to clinical signs and physical examination as well as patient complaints. The presence of one or more findings such as shortness of breath at rest or with minimal effort, tachypnea (the frequency greater than 20 breaths per minute), oxygen inhalation requirement, and oxygen desaturation (lower than 94%) measured by the arterial blood gas analysis or pulse oximetry were accepted as dyspnea in a patient. Dyspnea was assessed first in the intensive care unit (ICU) after extubation and in daily rounds in both the ICU and ward. In the ICU, anesthesiologists and surgeons cooperatively, and in the ward, surgeons on their own, decided to consultation according to clinical status of the patients. Data of the patients including age, sex, spirometry results, ejection fraction (EF), And the ICU and ward progress were collected.

The same anesthetic medications and routine postoperative care of the hospital applied to each patient. Patients were provided with an incentive spirometer after extubation and were encouraged to cough. A postoperative pulmonary toilet regimen included chest physiotherapy and walking on the first postoperative day. All operations were performed through a median sternotomy with mild hypothermic cardiopulmonary bypass. Warm blood cardioplegia and topical cold saline were used for myocardial protection. Valvular procedures included valve replacements with biological or mechanical prosthesis, ring implantations, and De Vega annuloplasty for the tricuspid valve. Thoracic aorta procedures included valve-sparing aortic procedures, supracoronary replacement of the ascending aorta, Bentall procedure, hemiarch, and total aortic arch replacements. Procedures related to a descending thoracic aorta and thoracoabdominal aorta carried out via a thoracotomy incision were excluded. The use of an intra-aortic balloon pump and inotropic agents were noted.

Table 1. Surgical procedures

CABG	63 (61.2%)
Valvular	16 (15.6%)
CABG+valvular	13 (12.6%)
CABG+thoracic aorta	7 (6.8%)
Thoracic aorta+valvular	2 (1.9%)
Thoracic aorta	2 (1.9%)
Total	103 (100%)

CABG: coronary artery bypass grafting

All patients consulted with the same pulmonologist who was unaware of the study. Plain radiographs were obtained on the operation day and on the first postoperative day routinely, and on the following days when needed. The pulmonologist decided to carry out a computed tomography (CT) of the thorax to ascertain the diagnosis, because plain radiographs were not able to provide adequate information in some patients. Diagnoses were made with plain radiographs in only 21 (20%) individuals, in whom the pulmonologist was able to define the pathology without the need of further investigation. The same radiology team, unaware of the study, interpreted all CT scans. The clinical diagnoses of the pulmonologist were compared with the radiological diagnoses derived from CT scans. In the case of co-occurrence of two or more pathologies in a patient, or a mismatch between the clinical and the radiological diagnoses, the pulmonologist was requested to reassess the case and elucidate the major pathology causing dyspnea.

Diagnosis of pneumonia was made when a new lung infiltrate was observed radiologically accompanied by fever, purulent sputum, leukocytosis, and a decline in oxygenation.

Informed consents were obtained from all patients. The local ethic committee of the Dr. Siyami Ersek Cardiothoracic and Vascular Surgery Training and Research Hospital approved the study on 16/12/2015, document number 9342.

Statistical Analyses

The normal distribution of continuous data was checked by the Kolmogorov-Smirnov test. Normally distributed data were presented as the mean±standard deviation, whereas a median (25^{th} quantile-75^{th} quantile) was used to express non-normal distribution. Continuous data between the groups were analyzed by the Student's t test, or by nonparametric tests for small subgroups. The Mann-Whitney U test was used for the evaluation of differences in non-normally distributed data. Differences in categorical outcome measures were analyzed by the Fisher's exact test and Yates' correction of continuity test. Data were analyzed using the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software. A $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 103 patients were enrolled in the study. Of those, 67 (65%) were male, and the mean age was 61.50±9.43. The mean body mass index (BMI) was 29.35±5.70, and the median preoperative EF was 55% (40–60). A CT scan of the thorax was conducted in 82 (80%) patients. The most common surgical procedure was the coronary artery bypass grafting (CABG), followed by isolated valvular procedures and a combination of valvular procedures with CABG. Table 1 demonstrates the surgical procedures carried out on the patients.

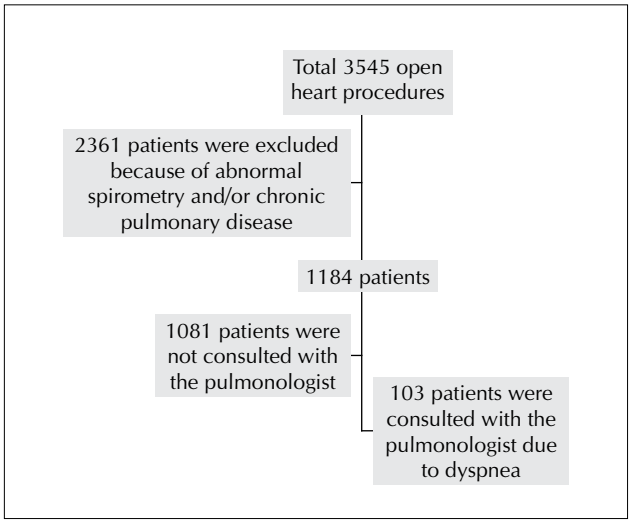

Figure 1. Patient flow in the study

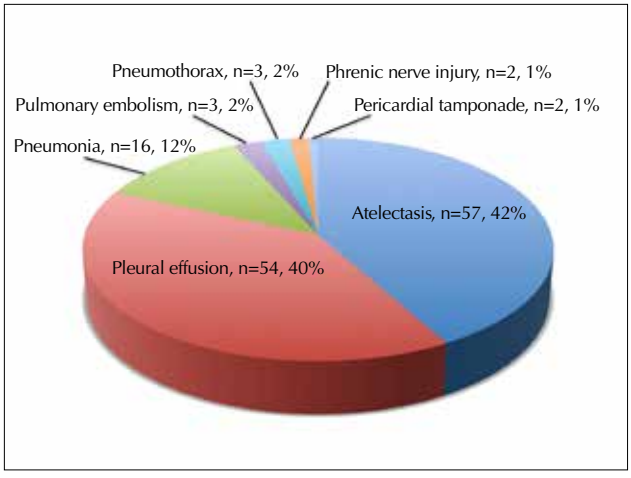

Figure 2. Distribution of dyspnea causes

Table 2. Data related to postoperative course

Length of the ICU stay (median day)	2 (1-4)
Length of hospital stay (median day)	12 (8-19)
Prolonged ICU stay, n(%)	53 (51.5%)
Use of inotropic agents, n(%)	19 (18.4%)
Use of IABP, n(%)	9 (8.7%)
Hospital mortality, n(%)	8 (7.8%)

IABP: intra-aortic balloon pump; ICU: intensive care unit

The median length of the ICU and hospital stay were 2 (1-4) and 12 (8-19) days, respectively. Other parameters observed in the postoperative course are shown in Table 2.

The most common cause of dyspnea was atelectasis, which was reported in 57 (55%) patients. The left lower lobe was the most frequently affected segment (n=34, 60%). Pleural effusion (n=54, 52%) and pneumonia (n=16, 16%) were the second and third most common causes of dyspnea, respectively. Figure 2 shows the distribution of the dyspnea causes. The atelectasis, pneumonia, and pleural effusion rates did not differ among the groups of surgical procedures (p=0.60, p=0.29, p=0.42).

In 57 patients in whom atelectasis was the major cause of dyspnea, accompanying minor findings were pleural effusion and pneumonia, which were seen in 39 (68%) and 7 (12%) individuals, respectively. On the other hand, pleural effusion was accompanied by atelectasis in 39 (72%) of 54 patients. In the pneumonia subgroup, accompanying pathologies were atelectasis and minor pulmonary embolus in 7 (44%) and 1 (6%) patients, respectively. Comparisons of the observed parameters within the groups are demonstrated in Table 3. Age, sex, the BMI, and preoperative left ventricular EF did not differ between groups. The length of the ICU stay in patients with pneumonia was longer than that in patients in who dyspnea was attributed to other causes, significantly (p=0.012). The length of hospital stay in patients with pneumonia and the length of the ICU stay in patients with atelectasis were longer than those in who dyspnea was attributed to other causes, but the differences were not statistically significant (p=0.249 and p=0.902, respectively). Pleural effusion did not affect the length of the ICU or hospital stay. Hospital mortality in the pneumonia group was significantly higher compared with other subgroups (p<0.001).

DISCUSSION

Among cardiovascular, thromboembolic, and infectious complications, PPCs require a considerably longer hospital stay as well as higher health care costs [6,7,9]. Whereas dyspnea causes in high-risk patients with a history of lung disease such as asthma or chronic obstructive pulmonary disease may be anticipated, in patients without a pulmonary disease, as in our group, dyspnea causes are unpredictable [1,3,8-10]. In addition, conventional strategies including oxygen inhalation or bronchodilator medications in the postoperative period may be sometimes insufficient in the treat-

Table 3. Parameters observed within groups

	Atelectasis			Pleural effusion			Pneumonia		
	Yes	No	p	Yes	No	p	Yes	No	p
n	57 (55%)	46 (45%)		54 (52%)	49 (48%)		16 (16%)	87 (84%)	
Age (mean±SD year)	60.23±8.80	63.07±10.04	0.13	61.67±9.31	61.31±9.66	0.848	60.81±11.01	61.62±9.18	0.755
Sex (male)	33 (58%)	34 (74%)	0.09	37 (69%)	30 (61%)	0.438	13 (81%)	54 (62%)	0.139
Preoperative EF (median)	60 (45-60)	50 (40-60)	0.117	55 (45-60)	57.5 (40-60)	0.930	57.5 (35-60)	55 (40-60)	0.627
ICU stay (median day)	2 (1-4)	1 (1-5)	0.902	1 (1-3)	3 (1-5)	0.259	5 (1-7)	1 (1-4)	0.012
Hospital stay (median day)	12 (8-18)	12 (8-20)	0.883	12 (8-20)	12 (8-18)	0.766	14 (10-28)	12 (8-19)	0.249

EF: ejection fraction; ICU: intensive care unit

ment of dyspnea, and a consultation with a pulmonologist is required. Determining the causes and dyspnea risk factors in this patient group may help reduce the length of the ICU and hospital stay, morbidity, and mortality after cardiac surgery.

In our patient group, atelectasis was the most common cause of dyspnea consistent with the literature [8,9]. Lower lobe segments of the left lung were the most frequently affected segments, according to the CT scan findings. A direct trauma to the lungs, pleurotomy for internal thoracic artery (ITA) harvesting, diaphragmatic dysfunction secondary to phrenic nerve injury, and a high oxygen concentration may cause atelectasis and explain the predominance of atelectasis development in the left lower lobe [1,4,8-10]. After beginning the cardiopulmonary bypass, ventilation is stopped, and the lungs collapse. A reduced alveolar distention results in and impaired surfactant production, which increases the alveolar collapse [1,9]. Stagnation of the microcirculation, shearing forces, and increased pulmonary capillary permeability owing to exposure of the blood to the foreign mechanical surfaces lead to the closure of small airways [1]. Thus, atelectasis is an unsurprising consequence of cardiac surgery, even in patients without a history of preoperative lung disease.

Pleural effusion was the second most common cause of dyspnea in our patient group. Several factors such as heart failure, electrolyte imbalance and pericardial inflammation after surgery, hypoalbuminemia, ITA harvesting and pleural dissection, atelectasis, pneumonia, and pulmonary embolism may contribute to the development of pleural effusion [1,3,8,9,11,12]. The effects of administration of anticoagulant drugs on pleural effusion occurrence after valvular procedures may be questionable [1,11,12]. Pleural effusion incidence did not differ among the groups of surgical procedures in our study.

Some studies reported that pleural effusions were the most common PPC following cardiac surgery, and atelectasis was found to be associated with preoperative EF and BMI contrary to our results [1,8,10,11,13]. This may be due to patient selection criteria or the definition method of the major pathology in the patients. We, therefore, confirmed the clinical diagnosis with the findings of the CT scan and obtained more accurate diagnoses.

The incidence of pneumonia reported after cardiac surgery ranges from 2% to 22% [1,9]. Accompanying atelectasis and pleural effusion, which are common pulmonary complications after cardiac surgery, may hinder diagnosing pneumonia by physical examination and chest radiographs in this patient group (9). In our patient group, CT scans, which enhanced the diagnosis, were available in 15 out of 16 patients with pneumonia. Nosocomial pneumonia increases the length of the ICU and hospital stay, as well as morbidity and mortality after cardiac surgery [9,14]. Carrel and colleagues reported preoperative smoking, preoperative positive tracheal aspirate, postoperative low cardiac output, and transfusion of more than 4 units of concentrated erythrocyte as independent predictors for the development of early postoperative pneumonia in their prospective study investigating pneumonia after CABG [14]. These factors were not found to be associated with postoperative pneumonia in our patient group. This may be due to absence of a control group which consists of patients with an uneventful postoperative period. However, the length of the ICU stay of patients with pneumonia was longer than that of patients in whom dyspnea was attributed to other causes significantly. The length of hospital stay was also longer in this group, but the difference was not significant, most probably because of a small patient group.

The reported incidence of pulmonary embolism and deep venous thrombosis (DVT) after cardiac surgery are 0.4%–9.5% and 23%, respectively [9,15]. Edema, tenderness, swelling, and pain are generally acceptable symptoms in the leg from which the saphenous vein was harvested. In addition, the usual symptoms of pulmonary embolism, including chest pain, dyspnea, tachycardia, rales, and cough, may be widely seen in patients after cardiac surgery [15]. Thus, the diagnosis of the pulmonary embolism after cardiac surgery mostly depends on the suspicion of the physician. Relatively uncommon occurrence of DVT and pulmonary embolism after cardiac surgery compared with other major surgical subspecialties may be a result of a routine use of heparin during the cardiopulmonary bypass and antiplatelet drugs after surgery [15]. Furthermore, the incidence of pulmonary embolism may be lower after valve surgery compared with coronary bypass grafting because of administration of anticoagulant drugs in the early postoperative period [9]. In our study, the incidence of pulmonary embolism did not differ among groups of surgical procedures, and DVT was not detected in patients with pulmonary embolism.

Pneumothorax is a rare complication after cardiac surgery with an incidence of 0.7%–1.7% [1,9,13]. However, this incidence may reach 5.3% in patients with an ITA graft [9]. Pneumothorax caused by air leaks results in tension pneumothorax in intubated patients in the ICU. Other causes of pneumothorax in the early postoperative period are air accumulation in an intact pleura, misplacement of chest tubes, and blockage caused by coagulum or kinking [9]. Surgeons or anesthesiologists may easily diagnose pneumothorax in the early postoperative period, and counseling of pulmonologist may not be required. However, pneumothoraxes in our patient group were challenging cases in whom pneumothorax developed in the ward and was diagnosed in the thoracic CT scan. This may be an additional cause for the low incidence of this complication in our patient group.

Phrenic nerve dysfunction results in diaphragmatic paralysis and alterations in pulmonary mechanics, thereby impairment in lung capacity after cardiac surgery [1]. Myocardial cooling techniques were implicated in the hypothermic injury to the left phrenic nerve and the left-sided predominance of the atelectasis after coronary bypass surgery [16]. Topical cooling with ice slush rather than applying cold saline for only a few minutes may be responsible for the phrenic nerve paralysis [1,5,9]. The ice slush was not used in our patient group, and the phrenic nerve injury was relatively rare.

Postoperative cardiac dysfunction is one of the major causes of poor pulmonary outcome after cardiac surgery [9]. A low cardiac output state may result in pulmonary edema, acute

respiratory distress syndrome (ARDS), as well as atelectasis and pneumonia, which are consequences of fatigue, weak coughing, and lack of deep breathing related to heart failure. Although a low cardiac output state was evident in some of the patients in our group, neither pulmonary edema nor ARDS was the major cause of dyspnea. The rationale underlying this result may be the successful management of pulmonary edema and ARDS by anesthesiologists and surgeons without counseling of the pulmonologist in the early postoperative period.

There are several limitations to this study. A small patient group might have a negative effect on some results that were not statistically significant. In this study, dyspnea causes were investigated in patients for whom a consultation with a pulmonologist was needed. The results were compared with other subgroups, in which dyspnea was attributed to other causes, instead of a control group which consisted of patients with an uneventful postoperative period. Thus, some results, which may be otherwise statistically significant, need further studies. However, more accurate diagnoses were made with the aid of CT scan of the thorax, which was available in high proportion of the patients (n=82, 80%) in this study.

In conclusion, after cardiac surgery, atelectasis was the most common cause of dyspnea followed by pleural effusion and pneumonia in patients for whom a consultation with a pulmonologist was required in the early postoperative period. Patients who experienced dyspnea due to pneumonia had a longer ICU stay than those in whom dyspnea was related to other pulmonary complications. Developing the treatment strategies with consideration of these causes may help reduce the length of stay, morbidity, and mortality in patients with postoperative dyspnea after cardiac surgery. The phrenic nerve dysfunction, pulmonary embolism, and pneumothorax were relatively rare causes of dyspnea. Randomized controlled trials should be conducted with large groups to detail the causes of dyspnea, preventive strategies, and their effects on the ICU and hospital stays, morbidity, and mortality in the early postoperative period after cardiac surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethic committee of the Dr. Siyami Ersek Cardiothoracic and Vascular Surgery Training and Research Hospital (Approval Date: 16.12.2015, document number 9342).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – A.B., S.İ., R.G., İ.K.; Design - A.B., S.İ., R.G., İ.K.; Supervision - A.B., S.İ., İ.K.; Resource – A.B.; Materials – A.B., A.C.T.; Data Collection and/or Processing - A.B., S.İ., A.C.T., R.G.; Analysis and/or Interpretation - A.B., S.İ., A.C.T., R.G.; Literature Search – A.B., R.G.; Writing – A.B., A.C.T.; Critical Reviews – A.B., R.G., S.İ., A.C.T., İ.K.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Article

Pulmonary Rehabilitation Reduces Emergency Admission and Hospitalization Rates of Patients with Chronic Respiratory Diseases

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Abstract

OBJECTIVES: Chronic respiratory diseases exert a global health burden with high health care costs, morbidity, and mortality. The aim of the present study was to investigate the effect of pulmonary rehabilitation (PR) on emergency admission and hospitalization rates of patients with chronic respiratory disease.

MATERIALS AND METHODS: In this retrospective cohort study, hospitalization rates and emergency admissions of patients before (December 2014-December 2015) and after PR (January 2015-December 2016) were investigated. Patients with chronic respiratory diseases were included. Chronic obstructive pulmonary disease (COPD) patients were classified based on the Global Initiative Chronic Obstructive Pulmonary Disease assessment scheme. PR was applied by three physiotherapists over 8 weeks (2 days/week). Data on patient demographics, clinical and anthropometric data, spirometry, exercise capacity, and quality of life before and after PR were acquired.

RESULTS: This study evaluated 51 patients, of whom 76% were men. A total of 37 (73%) COPD patients and 14 (27%) non-COPD patients (7 bronchiectasis, 4 interstitial lung disease, and 3 kyphoscoliosis) were included. The patients exhibited significantly improved incremental shuttle walk test (ISWT) and endurance test scores ($p<0.05$) after PR. Similar to exercise capacity, the patients exhibited significantly improved Modified Medical Research Council (mMRC) score, St. George's Respiratory Questionnaire (SGRQ), anxiety and depression scores ($p<0.05$) after PR. In COPD patients, differences in pre- and post-PR ISWT, COPD assessment test, mMRC, and SGRQ scores were statistically significant ($p=0.001$). The number of emergency admissions and hospitalizations significantly decreased after PR ($p=0.001$; $p=0.001$). The post-PR FEV_1% of COPD significantly increased ($p=0.029$).

CONCLUSION: Pulmonary rehabilitation leads to an increase in exercise capacity as well as improved quality of life, resulting in a decrease in emergency admissions and hospitalization rates. Considering the cost of hospitalization, it is important to add PR to the management of patients with chronic respiratory diseases, in addition to medical therapy.

KEYWORDS: Pulmonary rehabilitation, exercise treatment, quality of life, emergency application, hospitalization

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INTRODUCTION

Chronic respiratory diseases exert considerable global health burden and are associated with high health care costs, mortality, and morbidity [1,2]. Despite receiving optimal medical care, limited daily life activity, social isolation, and depression result in reduced quality of life (QoL) [3]. Moreover, frequent emergency and hospital admissions for chronic respiratory diseases result not only from exacerbation of the disease but also due to anxiety, lack of knowledge regarding the disease, and care problems [4,5].

Pulmonary rehabilitation (PR) is a non-pharmacological, extensive interdisciplinary program for patients with reduced daily life activity. The primary goal of PR is to restore the patient's optimal functional level and QoL [3]. PR programs are evidence-based and are individualized for each patient [6,7]. Nevertheless, data on the effects of PR on emergency admission and hospitalization rates in Turkey are limited [8].

The object of this study was to investigate the effect of PR on emergency admission and hospitalization rates of patients with chronic respiratory diseases.

MATERIALS AND METHODS

The study was planned as a retrospective cohort study and was conducted in the PR unit of a tertiary training hospital for chest diseases. Patients with hospital and emergency admissions before PR (December 2014-December 2015) and

The study was presented in 20th Annual congress of the Turkish Thoracic Society, April 5-9, 2017, Antalya, Turkey.
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whose emergency and hospital admission information were available after PR (January 2015-December 2016) were recruited.

The study was approved by the ethics committee of Health Sciences University Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (protocol code: 116.2017.022). The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients

Patients with chronic respiratory diseases were included in the PR program in a day-hospital setting. Patients with unstable cardiac disorders, cognitive disorders, neurological disorders, or orthopedic diseases were excluded from the program. Before PR, cardiological evaluation was performed for all patients.

Patients with chronic obstructive pulmonary disease (COPD) were diagnosed in accordance with the Global Initiative Chronic Obstructive Pulmonary Disease (GOLD) assessment scheme. All recruited patients were >40 years old, with a forced expiratory volume in the first minute (FEV_1) of <80% of the predicted value and a ratio of FEV_1 to forced vital capacity of ≤0.7 [9].

Patients with COPD were evaluated on the basis of the refined GOLD assessment scheme and COPD assessment test (CAT) [10]. Dyspnea was assessed in accordance with the Modified Medical Research Council (mMRC) [11]. The GOLD system has four grades, which are based on the assessment of symptoms/risk of exacerbations. Highly symptomatic (mMRC ≥2, CAT ≥10) patients were classified into grades D and B [12].

Patients with diseases other than COPD, such as bronchiectasis, kyphoscoliosis, and interstitial lung disease, were referred for PR.

This study included patients who completed the 8-week PR program between December 2014 and December 2015. The recruited patients had chronic respiratory diseases, were >18 years old, and had at least one emergency and/or hospital admission 1 year before the PR program.

Patients were excluded if their emergency application and hospital admission data were missing, if they were candidates for surgery due to malignancy or other causes, if they were candidates for surgery and had undergone short-term PR program before surgery, or if they could not perform a walking test because they were bed-bound.

Measurements

Spirometry was performed before and after PR with ZAN 300. Body mass index and fat-free mass index were calculated with a bioelectrical impedance analyzer (Tanita Body Composition Analyzer, Model TBF-300).

Exercise capacity was evaluated through the incremental shuttle walk test (ISWT). Patients with low exercise capacity and high disease burden were evaluated through the 6-min walk test (6MWT).

Incremental shuttle walk test was conducted according to the guidelines set by the European Respiratory Society/American Thoracic Society [13]. Modified Borg dyspnea score and blood pressure were recorded before and after the walking test [14]. The patients were informed about the test; the test was performed in a corridor between two cue cones (the distance between the two cones was set at 10 m) with guidance of voice signals in time to a set of beeps on a CD in. The walking speed was increased at 1-min intervals. The test was discontinued if the patient felt too breathless to continue the test or when the patient failed to walk 10 m in the allowed time. Heart rate and oxygen saturation were also monitored during the entire walking test. The total walking distance was recorded in meters [15]. ISWT was used to measure the sub-maximal exercise capacity of the patient.

Similar to ISWT, the endurance shuttle walk test (ESWT) was developed to evaluate the sub-maximal exercise capacity of a patient. First, ISWT was performed before ESWT. Then, walking speed was calculated as 85% of peak VO_2 sustained in ISWT. ESWT included a "warm-up" period to allow the patient to adapt to the test. The patient then walked at a constant speed. The test was discontinued if the patient felt too breathless to continue or if the test time of 20 minutes had elapsed. The primary measurement of the test was the duration of walking expressed in seconds [15,16].

6MWT was performed in accordance with the guidelines of the American Thoracic Society. The patients were guided to walk back and forth in a 30-m-long corridor. Modified Borg dyspnea score and arterial blood pressure were also recorded before and after the walking test. The total walking distance at the end of 6 min was recorded. The test was repeated, and the best results were recorded [17,18].

Health-related QoL was assessed through the St. George's Respiratory Questionnaire (SGRQ). The total score was calculated from subcategory scores (symptoms, activity, and impact).The scores ranged from 0 (no impairment) to 100 (maximum impairment). A change of four units was considered as minimally clinically significant [19,20]. Anxiety and depression were evaluated using the hospital anxiety and depression questionnaire (HADS), which has 14 items and scores between 0 and 21 for either anxiety or depression [21].

The outpatient PR program was delivered by three physiotherapists in 8 weeks (2 days/week). Exercise programs and workload intensity were targeted at 60%-85% of the maximal workload information gathered from 6MWT and ISWT results. The PR sessions included upper and lower limb strengthening and breathing exercises (0.5-1 kg dumbbell/Cosfer dumbbell sets) and cycle ergometer and treadmill training for 30 min. Workload intensity was increased in accordance with each patient's improvement. The program also included bronchial clearance techniques and energy conservation methods depending on the patients' needs [22].

During the sessions, patients receiving long-term oxygen therapy (LTOT) at home also received O_2. The rest of the patients received O_2 if SpO_2 decreased below 90%.

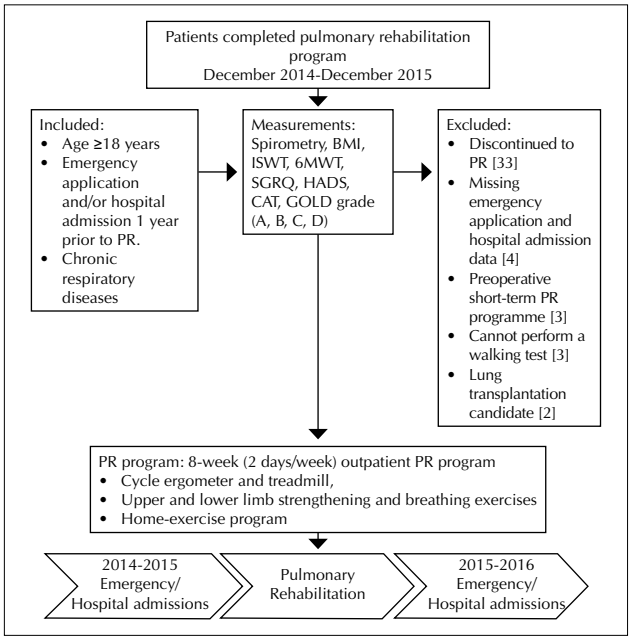

Figure 1. The flowchart of the study
COPD: Chronic obstructive pulmonary disease; mMRC: modified medical research council; COPD assessment test; GOLD: Global Initiative Chronic Obstructive Pulmonary Disease; ISWT: incremental shuttle walk test; 6MWT: six-minute walk test; SGRQ: St. Georg's Respiratory Questionnaire; HADS: hospital anexiety and depression questionnaire; BMI: body mass index; FFMI: fat-free mass index

Table 1. Demographics of pulmonary rehabilitation patients (n=51)

Age (mean±SD)	60±8
Sex, n (%)	
Female	12 (24)
Male	39 (76)
Chronic pulmonary disease, n (%)	
COPD	37 (73)
Non-COPD	14 (27)
Bronchiectasis	7 (14)
Interstitial lung disease	4 (8)
Kyphoscoliosis	3 (6)
Smoking history, n (%)	42 (82)
Smoking (pack-year), median (IQR)	35 (10-50)
LTOT, n (%)	23 (45)
NIV, n (%)	11 (22)
BMI (kg/m^2)*	26±6
FFMI (kg/m^2)	20±3
mMRC, median (IQR)	2.5 (2-3)
FEV_1 %*	40±17

*: mean±SD; LTOT: long-term oxygen therapy; NIV: noninvasive ventilation; FFMI: fat-free mass index; BMI: body mass index

The patients were encouraged to exercise at home apart from the designated session days; for this purpose, a written home-exercise program diary, including exercise figures, were given to all patients. Besides the exercise program, patients' medical therapies were also optimized, and disease-related educational sessions were held and inhaler medication techniques were taught to the patients and their relatives. Educational sessions were repeated at the beginning of the PR program and weekly between the sessions by the training nurse. Psychological and nutritional support was provided to the patients when needed.

The study is summarized in the flowchart (Figure 1).

Data Collection

Patient demographics, clinical and anthropometric data, exercise capacity, and spirometry and QoL data were obtained before and after PR. Data on emergency and hospital admissions were collected by accessing the hospital registration system and medication records and by calling the patients by telephone.

Outcomes

The primary outcome was hospital admissions and the secondary outcome was emergency admissions.

Statistical Analysis

The SPSS (Statistical Packege for Social Sciences) portable 20.0 package program (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. The median with interquartile range was employed for non-parametric continuous variables, and mean ± standard deviation was used for parametric continuous variables. The non-parametric changes within the groups were analyzed through the Wilcoxon test, and the parametric changes within the groups were analyzed through the t-test. Count and percentage were used when applicable. A $p<0.05$ was accepted as statistically significant.

RESULTS

This study evaluated 51 patients, of whom 39 (76%) were men and 12 (24%) were women. The patients had a mean age of 60±8 years. A total of 37 (73%) COPD patients and 14 (27%) non-COPD patients (7 bronchiectasis, 4 interstitial lung disease, and 3 kyphoscoliosis) were included. Out of all recruited patients, 23 (45%) received *LTOT* and 11 (22%) received noninvasive ventilation (NIV) at home. Table 1 summarizes patients' demographics.

The exercise capacity and QoL of patients before and after PR are shown in Table 2. The patients exhibited significant improvement in walking distance in ISWT and endurance time test scores (p=0.001, p=0.037) after PR. Eight patients were subjected to 6MWT, given that they were unable to carry on to ISWT as they had reduced effort capacity. The improvement in 6MWT after PR was not statistically significant (p=0.08), whereas minimal clinically important difference (MCID) (30 m) was established.

Similar to exercise capacity, the patients exhibited significantly improved mMRC, SGRQ, and anxiety and depression scores (p=0.001, p=0.001, p=0.003, and p=0.022, respectively) after PR.

Changes in exercise capacity, QoL, emergency and hospitalization characteristics before and after completion of the PR program of 37 COPD patients are defined in Table 3 in accordance with the GOLD grade.

Table 2. Exercise capacity and quality of life of patients before and after pulmonary rehabilitation (n=51)

	Before PR	After PR	p
ISWT (m),*	296±114	366±106	0.001
Endurance time,(min)*	6.9±5.3	10.2±7.3	0.037
6MWT (m),*	234±50	310±81	0.08
BMI (kg/m^2),*	26±6	26±6	0.13
FFMI (kg/m^2),*	20±3	20±2	0.39
mMRC, median IQR	2.5(2-3)	2(1-2)	0.001
SGRQ score,*			
Symptom	65±17	56±18	0.001
Activity	73±19	64±19	0.001
Impact	53±24	39±23	0.001
Total	61±19	49±18	0.001
HADS,*			
Anxiety	10±5	7±5	0.003
Depression	9±5	7±4	0.022

*: mean±SD; HADS: hospital anxiety and depression questionnaire; SGRQ: St. George's Respiratory Questionnaire; FFMI: fat-free mass index; BMI: body mass index; ISWT: incremental shuttle walk test; 6MWT: 6-min walk test was performed in 8 patients; IQR: interquartile range

Table 3. Exercise capacity and quality of life characteristics before and after the pulmonary rehabilitation program of COPD patients n=37

	Before PR	After PR	p
ISWT (m),*	302±118	373±111	0.001
Endurance time (min), median IQR	5.5(3.5-9.2)	6.6(4.2-20)	0.050
6MWT (m),*	227±72	302±114	0.47
BMI (kg/m^2),*	26±6	27±6	0.46
FFMI (kg/m^2),*	20±3	20±3	0.88
mMRC, median IQR	2(2-3)	2(1-2)	0.001
CAT, median IQR	17(15-24)	11(8-17)	0.001
FEV_1%*	38±15	46±16	0.029
SGRQ score,*			
Symptom	63±18	52±19	0.001
Activity	71±19	59±19	0.001
Impact	53±20	35±24	0.001
Total	50±21	44±20	0.001
HADS,*			
Anxiety	9±5	7±4	0.014
Depression	9±6	7±3	0.027
COPD GOLD grade, n (%)			
GOLD B	20 (54)	26(70)	0.11
GOLD C	0	5(14)	0.025
GOLD D	17(46)	6(16)	0.001

*: mean±SD; GOLD: global initiative for obstructive lung disease grade; HADS: hospital anxiety and depression questionnaire; CAT: COPD assessment test; BMI: body mass index; FFMI: fat-free mass index; ISWT: Incremental shuttle walk test; 6MWT: 6-min walk test was performed in 4 patients; IQR: interquartile range

Table 4. Changes in emergency admissions and hospitalization rates in 1 year: before and after pulmonary rehabilitation

	Before PR	After PR	p
Emergency applications*			
All patients, (n=51)	2(1-4)	0(0-1)	0.001
COPD patients, (n=37)	2(1-5)	0(0-1)	0.001
Hospitalizations*			
All patients, (n=51)	1(0-2)	0(0-1)	0.001
COPD patients, (n=37)	1(0-2)	0(0-1)	0.001

*: median; IQR: interquartile range

The differences in pre and post-PR ISWT, CAT, mMRC, and SGRQ scores were statistically significant (p=0.001). The post-PR FEV_1% of COPD significantly increased (p=0.029). The depression and anxiety scores of COPD patients significantly improved after PR (p=0.014, p=0.027).

Before PR, COPD patients were more likely to be in the GOLD grade B (n=20, 54%) and D (n=17.46%). After PR, however, the number of patients in the GOLD grade D significantly decreased (p=0.001), whereas those in grades B and C significantly increased (p=0.11, p=0.001).

Changes in emergency admissions and hospitalization rates before and after PR are shown in Table 4. The number of emergency admissions and hospitalization rates significantly decreased after PR (2 vs 0.1 vs 0; p=0.001, p=0.001, respectively). Similarly, the emergency admissions and hospitalization rates of patients with COPD post-PR significantly decreased (p=0.001).

DISCUSSION

The present study demonstrates that PR decreases emergency and hospital admissions of patients with chronic respiratory diseases. In addition, PR improves the exercise capacity and QoL of the studied patient group.

Gas exchange restriction, cardiac restriction, ventilatory limitation, malnutrition, hypoxia, systemic inflammation, and lower extremity and respiratory muscle dysfunctions are the major reasons for shortness of breath and movement restrictions experienced by patients with chronic respiratory disease [6,23]. O_2 and NIV support, although sometimes necessary, restrict the patient's mobility, consequently causing the patient to stay at home frequently, to become withdrawn and socially isolated. These social effects create a vicious circle that must be broken through PR. On the basis of GOLD guidelines, PR has been approved as a non-pharmacological comprehensive treatment in addition to medical therapy [10]. Recent studies have shown that PR has positive effects on older patients with COPD [20,21]. The present study included patients with COPD, as well as those with chronic respiratory diseases other than COPD. The results suggested that PR is suitable not only for COPD but also for other chronic lung diseases. Thus, patients with early-stage interstitial lung disease should undergo PR [24].

The walking distance in ISWT and endurance time in ESWT significantly improved. Although pre- and post-PR results of 6MWT, which was performed by only six patients, were not statistically different, they exhibited minimal clinical significance. An increase in the walking distance of 47.5 m in ISWT in the whole study group and in the COPD sub-group was established [25,26]. There is no MCID value for endurance time obtained with ESWT for PR yet [27]. The difference in walking distance obtained by 6MWT between pre- and post-PR exceeded the proposed 30 m, which is the MCID value suggested for all chronic respiratory diseases [18]. A score of 1.5 for HADS, 4 for SGRQ, and 2 for CAT are all clinically important values [16,19,21,26].

Dyspnea, the need for medication and care, social isolation, emergency admissions, and hospital admissions often result in depression and anxiety among patients with chronic respiratory disease [28,29]. The patients' relatives and caregivers also exhibit emotional disorders. In this study, the anxiety and depression scores of patients significantly improved after PR (p=0.003, p=0.022). The anxiety and depression scores and exercise capacity of patients who can cope with illness-related complaints, such as frequent coughing and increased sputum production, significantly improved after PR. Inadequate medical treatments and the fear of the disease often create anxiety and even panic in patients with interstitial lung diseases. Depression should not be ignored while following up with these patients, and psychological support should be recommended if necessary.

The significant improvements in SGRQ score indicated that PR achieved its main objective of ensuring that patients with chronic respiratory disease become active and independent. In addition to the 8-week (2 days/week) PR program provided at the hospital, patients were encouraged to apply and practice PR at home using a printed home-exercise program diary including exercise figures. Patients who exercise regularly are convinced that exercise should be a permanent behavioral change when they witness their gains.

Patients with COPD and bronchiectasis are often housebound, especially during autumn and winter, due to frequent attacks of their illness. The implementation of PR increases the awareness and ability of patients to control their disease as well as improves relationship between patients and their physicians. These effects collectively decrease the number of hospital and emergency appointments [30]. Man et al. [29] reported the importance of early PR after exacerbations; moreover, they reported that hospitalization rates decreased within the first 3 months after the implementation of PR. Although PR is an effective procedure, adherence to the program is still below expectations [9,31,32]. Golmohammadi et al. [33] mentioned the cost effectiveness of PR for patients with COPD and for those who had frequent emergency and hospital admissions. However, the duration and components of PR should be developed and optimized to enable its application in real clinical practice [34].

Educational sessions on inhaler drug techniques, O_2 therapy, and energy conservation methods were provided as a component of rehabilitation to the patients and their caregivers. These sessions applied at first days in the PR program and repeated weekly between sessions by the training nurse. The sessions positively affected patients' compliance. Spencer et al. [31] emphasized the importance of education as a PR component in decreasing healthcare costs [4,35]. In this study, the FEV_1% of COPD patients significantly increased (p=0.029) after PR. Although it has not been reported that PR increases respiratory function, in this study, we observed improvement in FEV_1% values. This result can be attributed to an increase in compliance with treatment as a result of educational sessions on inhaler drug techniques and O_2 therapy and the positive effect of exercise on hyperinflation [13,36].

The present study has some limitations. This is a retrospective study conducted at one center. In addition, the small sample size of this study may limit the identification of small but potentially significant associations; the number of interstitial lung disease is inadequate; and there is no control group. The strength of this study based on its collected data, which indicated the importance of PR among patients with chronic respiratory diseases.

In conclusion, PR increases the exercise capacity and QoL of patients with chronic respiratory diseases. These positive effects will collectively decrease the emergency admission and hospitalization rates of this patient population. Therefore, PR should be added to the management of patients with chronic respiratory diseases in conjunction with medical therapy to decrease hospitalization costs. Furthermore, PR should be promoted among pulmonologists to facilitate its use in real-life settings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Health Sciences University Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval No: 116.2017.022)

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

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Original Article

Abstinence-Related Motivational Engagement Scale: Validity and Reliability in Turkish People

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Abstract

OBJECTIVES: This research aimed to conduct a validity and reliability study of the Turkish version of the abstinence-related motivational engagement (ARME) scale.

MATERIALS AND METHODS: This study included 122 people and was administered in a smoking cessation clinic. The sociodemographic-smoking status characteristics questionnaire and the ARME scale were used for data collection. A psycholinguistic language adaptation was performed. In the validity, analyses, content, construct, and criterion-related validities were used. For content validity, expert evaluation was performed. For construct validity, principal component analyses (exploratory factor analyses) were performed. Orthogonal (Varimax) rotation was used to explore multiple factors. The Kaiser-Meyer-Olkin test was used to assess the adequacy of the sample size. For criterion-related validity, we compared the ARME scale points of people who were abstinent and had relapse for smoking at the end of the sixth month. In the reliability analysis, standard deviation (SD) and item analysis, internal consistency, and test-retest methods were used.

RESULTS: The four factors explain 58% of the total variance. Items have factor loading between 0.409 and 0.805. When the factor structure of the scale was assessed, the items in each factor group have a factor load of at least "0.40." Due to one-dimensional use of the original scale, it has been decided to maintain this scale in its original form. The ARME scale points of people who quit smoking were statistically higher than the points of people who had relapse at the end of the sixth month. Cronbach's alpha coefficients were between 0.846 and 0.763. Significant and positive correlation was found between the test-retest scale scores.

CONCLUSION: The Turkish adaptation of the ARME scale, which was developed for adults who quitted smoking, is an adequately valid and reliable measurement instrument. It is considered that the scale might be used reliably in different cultures as well.

KEYWORDS: Abstinence-related motivational engagement scale, validity, reliability, quit smoking, motivational engagement

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INTRODUCTION

Smoking is a complicated habitual form of behavior, and it has different types of behavioral components, such as beginning, quitting, maintaining, interruptedly smoking, and relapsing. In contrast, the process of smoking cessation requires a behavioral change [1]. One of the biggest problems with those who quitted smoking is the relapsing period [2-4]. Most current smokers are interested in smoking cessation, and each year approximately two out of every three smokers attempt to quit. Many quit attempts are unplanned without any systemic support or program and do not utilize evidence-based treatments. For these reasons, successfully quitting smoking and achieving long-term abstinence is very difficult for smokers [5-8]. The proportion of successful quit attempts and prolonged abstinence achievement for these smokers is estimated at only 3% to 5% [3,6,9]. Therefore, identifying factors that are related to relapse and planning preventive interventions are crucial [4,8,10].

Motivational engagement has been successfully applied to smoking cessation [11]. Motivation is expressed as a critical factor for increasing the intention to quit smoking, facilitating cessation attempts, and maintaining successful abstinence in both the Relapse Prevention Theory and the Transtheoretical models [8]. The motivation level of quitting smoking is one of the important indicators to determine the success of short- and long-term abstinence or relapse [8,9]. Measuring the temporary changes in the motivation after the cessation seems to be helpful in comprehending and analyzing the role of abstinence motivation on smoking relapse. Simmons et al. [9] clinically monitored that smokers are inclined to be immensely involved in the quitting process in the early stage and maybe even weeks after the cessation, but that motivational involvement mostly decreases in time. Lesser motivational involvement might be due to the high rates of smoking relapse. After the smoking cessation, having a relapse in an early period is related to withdrawal symptoms, and it may associate with psychosocial reasons in the long term [9,12,13].

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There have been numerous researches on the evaluation of being prepared for quitting smoking and has received considerable clinical attention. The measures of being prepared to quit smoking, such as contemplation ladder and the stages of change algorithm, have predicted the quit attempts in the future. However, very few researches have been carried out to date for achieving gross motivational changes after a smoker has attempted to quit smoking. The abstinence-related motivational engagement (ARME) scale is a tool that is specifically designed for the people who are ex-smokers or quitted smoking. The study by Simmons et al. [9] supported the ARME construct at first and offers two versions of a reliable instrument to evaluate this construct. ARME has been shown to be a valid tool in measuring the level of abstinence-related motivational engagement.

This study aimed to conduct a validity and reliability study of the Turkish version of the ARME scale for the people who quitted smoking.

MATERIAL AND METHODS

Participants and Setting

This study was administered in a smoking cessation clinic of Etlik Cancer Early Diagnosis, Screening and Training Centre (CEDSTC). Ethical approval was received from the Institutional Ethics Committee (1491-193-14/1648-461). To use the ARME scale, we obtained permission from Thomas Brandon by e-mail. The participants were informed about the study; participants provided written informed consent.

Sample

In scale studies, it is suggested to reach sample size in number of 5-10 times of the scale items [14,15]. The ARME scale includes 16 items and is a 7-point Likert scale scored from 1 to 7. The sample size was calculated according to 16 items and 7 points. We determined the sample size for this study as at least 112. All the individuals who applied to this center to quit smoking, who met the research criteria, and who agreed to participate in the study, were included in the study until the sample size reached. The study included 122 people.

The inclusion criteria were as follows:

- ≥18 years of age
- Having quit smoking for at least 1 week and no longer than 1 year
- Previously smoked ≥10 cigarettes/day for ≥1 year

Study Instruments

The sociodemographic and smoking status characteristics

The sociodemographic and smoking status characteristics were collected using a questionnaire prepared by the researchers.

The ARME Scale

The scale was designed by Simmons et al. [9]. It evaluates the degree of ongoing engagement in the cessation and maintenance process. Abstinence motivation is reflected by an ex-smoker's daily experience in areas that include cognitive effort, priority, vigilance, and excitement. Simmons et al. [9] did not conceptualize these themes as separate factors or subscales; they conceptualized ARME as a one-dimensional construct. The ARME scale consists of 16 items and designed in 7-point Likert-type in an order from the weakest "completely disagree: 1" to the strongest "completely agree: 7". Items 4, 6, 12, and 13 are reverse encoded. A higher score indicates higher abstinence motivation. The Cronbach's alpha value was determined as 0.89 [9]. In our study, the Cronbach's alpha value was 0.84. The English and Turkish versions of scale items are shown in Table 1.

Translation process

Psycholinguistic Language Adaptation of the ARME Scale

The ARME scale was translated into Turkish by a researcher and three academicians who had a good command of English. Then, the ARME scale was reviewed by two researchers. The reviewed scale was translated from Turkish to English by an academician who did not know the original copy of the scale; the translated scale was compared with the original scale by another academician and researcher. Since there was no major difference in meaning, the scale was applied to 5 ex-smokers. There were not scale items that misunderstood or inconsistent. Thereafter, the study was started [16].

Psychometric Features of the ARME Scale

The reliability and validity study was administered to 122 ex-smokers at Etlik CEDSTC. After 2 weeks, the test-retest reliability was administered to 30 participants who were randomized.

Statistical Analysis

In this study, the data were analyzed using SPSS (Statistical Package for the Social Sciences) version 15.0 (SPSS Inc.; Chicago, IL, USA) for Windows Evaluation Version. The results were assessed at 95% confidence interval and significance at a $p<0.05$. To assess the validity and reliability of the Turkish version of ARME scale, several analyses were conducted:

Validity

1. Content validity: Expert evaluation
2. Construct validity: Factor analyses
3. Criterion-related validity: ARME scale points of people who quit smoking and relapse

Content validity

Content validity was conducted by five experts to validate the given scale in the frame of purpose, clarity, and conformity to the Turkish Culture. Regulations were made in line with the recommendations and critics of the experts.

Construct validity

Principal component analyses (exploratory factor analyses) were performed. Orthogonal (Varimax) rotation was used to explore multiple factors (sub-dimensions). To assess the adequacy of the sample size, the Kaiser-Meyer-Olkin (KMO) test was used [17].

Criterion-related validity

We compared the ARME scale points of people who quit smoking and relapse at the end of the sixth month.

Reliability

1. Standard deviation and item analysis
2. Internal consistency analysis
3. Test-retest reliability

Table 1. The Abstinence-Related Motivational Engagement (ARME) Scale (English Version and Turkish Version)

	Items (English/Turkish)
Item 1	Being smoke-free is my highest priority at this time.
	"Şu anda en önemli önceliğim sigarayı bırakmak."
Item 2	I try to anticipate and prepare for any challenges to being smoke-free.
	"Sigarayı bırakmayla nasıl mücadele edebileceğimi öngörmeye ve hazırlanmaya çalışıyorum."
Item 3	The thought of being a nonsmoker still excites me.
	"Sigara içmeyen biri olma düşüncesi beni hala heyecanlandırır."
Item 4	I spend little time thinking about becoming or staying smoke free.
	"Sigara içmeyen biri olma veya bırakmış olarak kalma üzerinde az düşünürüm."
Item 5	I am doing whatever I can to avoid smoking.
	"Sigara içmekten kaçınmak için elimden gelen her şeyi yapıyorum."
Item 6	I am no longer all that excited about being smoke-free.
	"Sigara içmeyen biri olma düşüncesi artık beni heyecanlandırmıyor."
Item 7	I think about quitting smoking, or staying off cigarettes every single day.
	"Sigarayı bırakma ya da sigara içmeden durma hakkında her gün düşünürüm."
Item 8	Nothing is more important to me right now than being tobacco free.
	"Benim için hiçbir şey şu anda sigara içmiyor olmaktan daha önemli değil."
Item 9	I am willing to make sacrifices in other areas in order to be free of cigarettes.
	"Sigarayı bırakmak için hayatımın diğer alanlarında fedakarlık yapmaya razıyım."
Item 10	At this time, I am still very excited by the idea of being smoke-free.
	"Şu anda, sigarayı bırakma fikri hala beni heyecanlandırıyor."
Item 11	I spend a great deal of time thinking about becoming or staying smoke-free.
	"Sigarayı bırakma veya sigara içmeden durma düşüncesine çok zaman harcıyorum."
Item 12	I spend very little time preparing myself for any challenges to being smoke-free.
	"Sigarayı bırakma mücadelesine hazırlanmak için çok az zaman harcıyorum."
Item 13	Compared with other things in my life, fighting the urge to smoke is not the top priority for me right now.
	"Hayatımdaki diğer şeylerle karşılaştırıldığında, sigara içme isteği ile mücadele etmek, benim için şu anda en öncelikli konu değil."
Item 14	I am willing to spend a lot of mental energy on being smoking free.
	"Sigarayı bırakmış olmak için; çok fazla kafa yormaya razıyım."
Item 15	I feel energized just thinking about being smoke-free.
	"Sigarayı bırakmış olduğumu düşününce dahi kendimi enerjik hissediyorum."
Item 16	I am carefully watching out for things that might put me at risk for smoking.
	"Beni sigara içme riskiyle karşı karşıya getirebilecek şeylere dikkat ederim."

1: completely disagree "kesinlikle katılmıyorum"; 4: neither disagree or nor agree "kararsızım"; 7: completely agree "tamamen katılıyorum"

The scale must reliable and an indicator of consistency or accuracy of measurement values and validity. A higher value indicates that the measuring instrument is more reliable [18,19]. In this study, in the reliability analyses, the internal consistency of the ARME scale was measured by the Cronbach α-coefficient.

Retest should be applied to the same study group on the same conditions. The time interval must be sufficiently long to prevent significant reminders, but short enough not to allow significant changes in the measured characteristic. In the literature, for reliability, it is stated that 25-50% of the participants in the first measurement are sufficient to participate in retest [14,16,18-20]. Our sample size was 122. Twenty-five percent of our sample was approximately 30. For this reason, retest measurements of 30 randomly selected samples were applied after 2 weeks. Scores of the two measures were analyzed using paired samples t-test and Pearson's correlation analyses for test-retest reliability.

RESULTS

Sample Description

The total number of participants was 122 in the final sample of the study. Of the participants, 59% were men, 41% were women, 81.1% were married, 63.9% were university graduates, and the average age was 44.7 years (SD=1.2; min: 25, max: 71). Furthermore, 42.6% of individuals were workers. Before the smoking cessation, addicts had been smoking approximately 22.9±11.4 cigarettes per day, and they had been smoking for up to 25.8±12.1 years. Participants had started smoking at the age of 18.4±4.8 years and 26.5% of those ad-

Table 2. Demographic and smoking status characteristics

Characteristics		n	%
Age (years)	≤45	55	45.1
min=25, max=71, $\overline{X}$ =44.7±1.17	>45	67	54.9
Gender	Women	50	41.0
	Men	72	59.0
Marital status	Married	99	81.1
	Single / Widowed	23	18.9
Educational status	Primary education or lower	31	25.4
	Secondary education	13	10.7
	University	67	54.9
	Postgraduate	11	9.0
Working status	Working	52	42.6
	Not working	34	27.9
	Retired	36	29.5
Characteristics (before quit smoking)			
Age to start smoking (n=122)	≤17	59	48.4
min=6, max=36, $\overline{X}$ =18.43±4.84	>17	63	51.6
The reason for starting the cigarette (n=147*)	Wonder	18	12.2
	Emulation	33	22.4
	Environment / Other smokers	62	42.2
	Stress	25	17.0
	Other reasons	9	6.1
Cigarettes per day (n=122)	≤1 pack (20 pieces)	75	61.5
min=10, max=60, $\overline{X}$ =22.94±11.38	>1 pack (20 pieces)	47	38.5
Years smoked (n=122)	1-9	11	9.0
	10-19	35	28.7
min=2, max=56,	20-29	15	12.3
$\overline{X}$ =25.84±12.13	30-39	40	32.8
	≥ 40	21	17.2
The reason for quitting smoking (n=143*)	Family request	20	14.0
	Public request/ALO 171	8	5.6
	Economic reasons	17	11.9
	Current disease/doctor's recommendation	25	17.5
	Fear of being sick in the future	35	24.5
	Beliefs	6	4.2
	Want to have children	7	4.9
	Physical effects/discomforts	16	11.2
	Own wish	9	6.3

*: multiple answers were given; min: minimum; max: maximum; $\overline{X}$: arithmetic mean

dicts had started smoking due to psychological pressures in their social environments. The participants who quit smoking had approximately smoked for 25.8±12.1 years (Table 2).

Validity

Construct validity

According to the KMO test, the coefficient was 0.802 and the sample size was adequate. According to the Bartlett's test, the ARME scale items were suitable for factor analysis (χ^2=648.751, df=120, p<0.01).

A principal factor analysis was conducted to assess the factor structure of the ARME scale. Dataset yielded five eigenvalues >1.0; 64% variance percentages were explained by the factors and a scree plot, which visually suggested a five-factor solution. However, when we analyzed the five factors according to the initial principal-components analysis and performed Varimax rotations to standardize the loadings, we found that items in the second and third factors came together to form a consistent meaning, but factors 4 and 5 consisted of only two variables with high factor loadings. Therefore, we decided that the most appropriate solution was the four-factor structure.

According to the Varimax rotations, a second principal-component analysis with the 16 ARME scale items was used to determine structure validity. In the exploratory factor analysis, four factors with an eigenvalue above 1 were found; these factors explained 58% variance percentages. Distribution of items to factors and conceptual structure of the scale were appropriate. Finally, a four-factor structure was acceptable. Factor eigenvalues and variances, Cronbach Alpha values, and factor loadings are presented in Table 3.

The four factors explain 57.5% of the total variance (first factor 17%, second factor 16%, third factor 14%, and fourth factor 10%). Items have factor loading between 0.409 and 0.805. When the factor structure of the scale was assessed, the items in each factor group have a factor load of at least "0.40" (Table 3). Due to one-dimensional use of the original scale, it has been decided to keep this scale in its original form.

According to the factor analysis, the Cronbach Alpha values were 0.846 for total scale, 0.737 for first factor, 0.814 for second factor, 0.653 for third factor, and 0.514 for fourth factor (Table 3).

Criterion-related validity

The ARME scale points of people who quit smoking (85.78±13.04) were statistically higher than the points of people who relapse (74.59±15.60) at the end of the sixth month (t=2.907; p<0.05).

Reliability

Standard deviation and item analysis

There is no item with a corrected item-total score correlation of less than 0.20. If fourth and twelfth items are removed from the scale, the Cronbach alpha value rises from 0.846 to 0.849 and 0,850. However, since this is not a significant increase, it was decided to remain on the scale (Table 4).

Internal consistency analysis

The internal consistency analysis of the ARME scale with 16 items showed that the Cronbach's alpha coefficients were between 0.846 and 0.763 (p<0.01).

Test-retest reliability

For the 30 participants, the average test scale scores were 83.67±13.79, and average retest scale scores were 80.50±14.47. No significant difference was found between the test-retest scores (t=1.738; p=0.093). Significant and positive correlation was found between the test-retest scale scores (r=0.752; p<0.01).

Table 3. Factor structure

Factors	Theme	Items	Factor loadings	Variances %	Eigenvalue	Cronbach alpha
Factor 1	Priority	Item 1	0.646	17.111	2.738	0.737
	Vigilance	Item 2	0.582			
	Priority	Item 8	0.461			
	Priority	Item 9	0.552			
	Excitement	Item 15	0.695			
	Vigilance	Item 16	0.543			
Factor 2	Excitement	Item 3	0.757	15.964	2.554	0.814
	Excitement	Item 6	0.805			
	Excitement	Item 10	0.740			
Factor 3	Cognitive effort	Item 4	0.519	13.981	2.237	0.653
	Effort	Item 7	0.675			
	Cognitive effort	Item 11	0.764			
	Cognitive effort	Item 14	0.595			
Factor 4	Vigilance	Item 5	0.409	10.399	1.664	0.514
	Vigilance	Item 12	0.703			
	Priority	Item 13	0.672			
Total		16 items		57.455		0.846

Table 4. Items total points correlations

	Scale items	Average of scale points when item is deleted	Scale variance when item is deleted	Corrected item total score correlation	Scale Cronbach alpha when item is deleted
n=122	Item 1	72.541	252.548	0.502	0.835
	Item 2	72.738	255.303	0.472	0.836
	Item 3	72.492	247.905	0.600	0.830
	Item 4	74.467	267.623	0.213	0.850
Item=16	Item 5	72.812	245.840	0.605	0.829
	Item 6	72.828	256.045	0.401	0.840
Cronbach alpha=0.846	Item 7	73.566	244.198	0.517	0.834
	Item 8	73.812	249.129	0.497	0.835
	Item 9	73.057	251.509	0.496	0.835
	Item 10	72.680	241.657	0.702	0.824
$\overline{X}$ ±SD	Item 11	74.730	250.282	0.522	0.834
78.17±16.90	Item 12	74.500	267.012	0.233	0.849
	Item 13	74.279	252.517	0.427	0.839
Variance= 285.582	Item 14	72.959	253.147	0.485	0.836
	Item 15	72.230	263.385	0.389	0.841
	Item 16	72.893	259.253	0.389	0.841

$\overline{X}$: arithmetic mean; SD: standard deviation

DISCUSSION

In this study, the validity and reliability of the ARME scale in Turkish ex-smokers were assessed. It is concluded that the scale is an adequately valid and reliable measurement instrument. The results were compared with the study of Simmons et al. [9]. Since no other study using this scale in the literature has been found, we could not make a comparison.

Simmons et al. [9] used the four themes to assess the domain of interest. However, they preferred a one-factor solution because of factor analysis and decided that the instrument was sampling a unitary construct. In scale adaptation studies, various results may be obtained depending on the countries and the characteristics of the individuals participated in the study. In our study, 5 factors, which explain 64% of the total variation, were determined because of the first factor analysis. Since the fourth and fifth factors consisted of only two vari-

ables, four factor solutions were preferred. It is considered that the four factors that were presented in our study comply with the conceptual construct determined for the scale.

The fact that scale reliability coefficient is approximately "1" indicates that the scale is similar to the standard test, and the fact that it is approximately "0" indicates that similarity is weak. Coefficients higher than 0.70 are often considered satisfactory, but coefficients higher than 0.80 are preferable [14,19]. In the original validity study of the scale, the Cronbach's alpha coefficient was 0.89, and in our study, the Cronbach's alpha coefficient was 0.85 [9]. A general evaluation showed that in the present study and the original study, the overall internal consistency of the ARME scale was high, and the scale structure represented the whole well.

In general, the time between two measurements in attitude scales varies according to the features of the measured instrument and it varies between 2-3 and 4-5 weeks; it is considered adequate that the test is repeated on 25-50% of the population [14,16,18-20]. Simmons et al. [9] argues that the instinctive commitment to quit smoking will decline over time. As predicted, ARME was negatively associated with length of abstinence, and this suggested that it is more sensitive to the dynamic aspects of continuing abstinence motivation. Hence, in our study, the test was administered after 2 weeks. Even after 2 weeks, there was a decrease in scores. In our study, when we looked at the test-retest correlations for the ARME scale, significant and positive correlations were found between the ARME scale scores. In conclusion, we found that the reliability of the Turkish version of the ARME scale was adequate.

The items were scored by the interview method when we were not able to observe the task directly. Discussion could be made just with original study. The study had recruited only one type of ex-smoker participants, which is considered a limitation.

In conclusion, findings obtained from validity and reliability studies have shown that the Turkish adaptation of the ARME scale, which was developed for adults who quit smoking, is an adequately valid and reliable measurement instrument. Hence, it is considered that the scale might be used reliably in different cultures as well. We suggest that further studies could be conducted longitudinally with different cultures samples.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Ethics Committee (1491-193-14/1648-461).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - T.Y., A.G., H.B.; Design - T.Y., A.G., H.B.; Supervision - T.Y., A.G., H.B.; Resource - T.Y., A.G., H.B.; Materials - T.Y., A.G., H.B.; Data Collection and/or Processing - T.Y., A.G., H.B.; Analysis and/or Interpretation - T.Y., A.G., H.B.; Literature Search - T.Y., A.G., H.B.; Writing - T.Y., A.G., H.B.; Critical Reviews - T.Y., A.G., H.B.

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Original Article

Duration of Stay of Patients with Community-Acquired Pneumonia in Influenza Season

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Abstract

OBJECTIVES: There is a seasonal variation in the incidence of some infectious diseases. We analyzed the impact of influenza season (IS) on duration of stay (DOS) and some other characteristics of patients with community-acquired pneumonia (CAP).

MATERIALS AND METHODS: In our retrospective cohort study, we analyzed data of 369 patients with CAP.

RESULTS: The mean patient age was 65.5±16.69 years, and 267 (72.4%) patients were male. There was no difference between patients with CAP admitted to hospital and intensive care unit during IS and non-influenza season (NIS) with respect to age, mortality, and DOS. There was no difference in leukocyte and neutrophil counts, C-reactive protein level, and erythrocyte sedimentation rate in different seasons. Although most comorbid disease rates were similar, only cancer, especially lung cancer, was more prevalent in NIS. Bilateral CAP confirmed using thorax computed tomography was more frequent in IS.

CONCLUSION: Although more patients with bilateral pneumonias were hospitalized in IS, DOS was not different between IS and NIS.

KEYWORDS: Influenza, community-acquired pneumonia, hospitalization duration, season

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INTRODUCTION

Seasonal variation in occurrence is a common feature of many infectious diseases. Studies on seasonal variation contribute to healthcare planning and analysis of infections.

Seasonal variation in occurrence of community-acquired pneumonia (CAP) has epidemiological significance. Bacterial, viral, or other pathogens may cause CAP. Some of these pathogens, especially respiratory viruses, exhibit seasonal variation, resulting in a higher incidence of CAP in winter and spring and a lower incidence in summer and autumn [1]. Hence, incidences of and mortality associated with sepsis and severe sepsis are seasonal and highest during winter, owing to respiratory sepsis [2].

Influenza is one of the most significant seasonal diseases [3]. It is a public health problem that affects 5%-20% of the world population. Annual epidemics result in approximately 3-5 million cases of severe illness and approximately 250,000-500,000 deaths worldwide. Diagnosis and treatment of patients with CAP are crucial during influenza epidemics. Hospitalization and death mainly occur among high-risk groups [4]. Elderly people, those with comorbidities, and pregnant women are high-risk patients. Influenza epidemics occur annually during autumn and winter in temperate regions [5]. Typical and atypical bacteria and viruses are the cause of primary CAP. However, it may be difficult to distinguish seasonal influenza pneumonia from bacterial pneumonia [6].

Outbreak of influenza increases hospital admissions due to pneumonia. Longer duration of stay (DOS) in hospital may lead to problems in the allocation of beds in health care institutions and result in higher health care costs. Determining DOS in hospital for patients with CAP in influenza season (IS) will help in efficient management of resources. Although it is difficult to precisely document primary influenza infection, some characteristics of CAP may be different in IS. The aim of our study was to determine the duration of hospital stay for patients with CAP admitted during "IS" and to compare it with the remaining period in which influenza infection is rare.

This study was presented in the "Turkish Thoracic Society 16th Annual congress" April 3- 7, 2013, Antalya, Turkey, and "European Respiratory Society Annual Congress" September 7-11, 2013, Barcelona, Spain
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MATERIALS AND METHODS

This is a retrospective cohort study on DOS of patients with CAP hospitalized in the pulmonary diseases ward of a tertiary chest diseases and surgery training hospital. We retrospectively examined all computer-based data of patients with CAP from January 2010 to March 2015 for study variables. Ethics committee approval was not required for this retrospective study, and patient's confidentiality was maintained.

Variables

Age, gender, comorbid diseases, age ≥65 years, duration of hospital and intensive care unit (ICU) stays, blood leukocyte and neutrophil counts, C-reactive protein levels, sputum cultures, chest radiographs, and mortality were analyzed.

We compare these variables with respect to the "season" in which patients were hospitalized. Each year is divided into "IS" and "non-influenza season" (NIS). IS is defined as the period between December 1 and April 30, and NIS is defined as period between May 1 and November 30. We derived these time intervals from data from a study by Puig-Barbera [4] and an influenza surveillance report in Turkey [7].

Patients

CAP was defined using the following:

Pneumonic infiltration in chest X-rays and one major criteria: cough, sputum expectoration, and fever or two minor criteria: dyspnea, pleuritic chest pain, physical examination findings compatible with consolidation, and white blood cell count >12000/mm^3

Table 1. Demographic features of patients with CAP (n=369)

Age (years) [mean±SD (min-max)]	65.5±16.69 (16-102)
Duration of stay in hospital (days) [mean±SD (min-max)]	11.96±8.57 (1-82)
Duration of stay in ICU (days) [mean±SD (min-max)]	8.15±8.56 (1-40)
Leukocyte count (×10^3/μL) [mean±SD (min-max)]	13307.1±7917.9 (1690-85200)
Neutrophil count (×10^3/μL) [mean±SD (min-max)]	97555.4±5928.4 (650-40100)
CRP (mg/dL) [mean±SD (min-max)]	15.7±12.4 (0.32-55.3)
Erythrocyte sedimentation rate (mm/h) [mean±SD (min-max)]	59.87±30.4 (2-140)
Number of patients aged ≥65 years [n (%)]	205 (56)
Males [n (%)]	267 (72)
ICU admission [n (%)]	20 (5)
Mortality [n (%)]	28 (8)
Comorbid diseases [n (%)]	307 (83)
Availability of thorax CT [n (%)]	275 (75)
Availability of sputum culture [n (%)]	180 (49)
Availability of hemoculture [n (%)]	79 (21)

CAP: community-acquired pneumonia; ICU: intensive care unit; CRP: C-reactive protein; CT: computed tomography

The authors reviewed the files from the patient data system of the hospital and recorded the patients with a diagnosis of pneumonia (ICD code J18). One pulmonologist reviewed chest X-rays for the diagnosis. Patients aged <16 years, cases with bronchiectasis, patients discharged from hospital on their own will, immunosuppressed patients, patients with hospital-acquired pneumonia, and patients with healthcare-related pneumonia were excluded.

Data Analysis

Data were recorded and analyzed using the SPSS (Statistical Packagefor Social Sciences) version 18.0 (IBM Corp.; Armonk, NY, USA) program. Continuous variables (mean, standard deviation, median, and minimum and maximum values) and categorical variables (frequencies and percentages) were presented. Independent variables with normal distributions were analyzed using independent samples t-test; independent variables with non-normal distributions are analyzed using Mann-Whitney U test. Categorical variables were presented as frequencies and percentages in cross tables, and group differences for categorical values were analyzed using X^2 test. Type 1 error is α=0.05, and it was tested in two ways. A $p<0.05$ was considered to indicate significance.

RESULTS

A total of 1170 patients were hospitalized at our clinic during the study period; 427 patients were diagnosed with pneumonia. We excluded 44 patients with hospital-acquired pneumonia, 10 patients with immunosuppression, and 4 patients with healthcare-related pneumonia. Overall, 369 patients with CAP were enrolled in the study. Table 1 shows their demographic and clinical characteristics.

In total, 247 (66.9%) patients showed pneumonic infiltration, 10 (2.7%) showed empyema findings, and 17 (4.6%) showed lung abscess in their thorax computed tomography (CT). Overall, 109 (29.5%) cases were bilateral and 260 (70.5%) were unilateral.

We obtained sputum cultures of 180 (48.8%) patients, and growth was observed in 166 (91.7%) cultures; 163 (90.1%) and 3 (1.7%) cultures showed the growth of a single and two agents, respectively. No growth was observed in 15 (8.3%) cultures. Figure 1 shows the growing microorganisms in sputum cultures. We collected samples for hemoculture from 79 (21.4%) patients, and growth was observed in 15 (19%) of them. *Staphylococcus* spp. grew in 11 hemocultures, and *Bacillus*, *Corynebacterium*, diphtheroid bacilli, and *Streptococcus pneumoniae* grew in each of the remaining four hemocultures.

Overall, 197 (53.4%) patients were hospitalized during IS and 172 (46.6%) were hospitalized during NIS. Table 2 shows their features. DOS in hospital or ICU did not differ among the patients in IS. Furthermore, there were no differences regarding age, age≥65 years, gender, and mortality. No association was observed between season and blood test or sputum culture results.

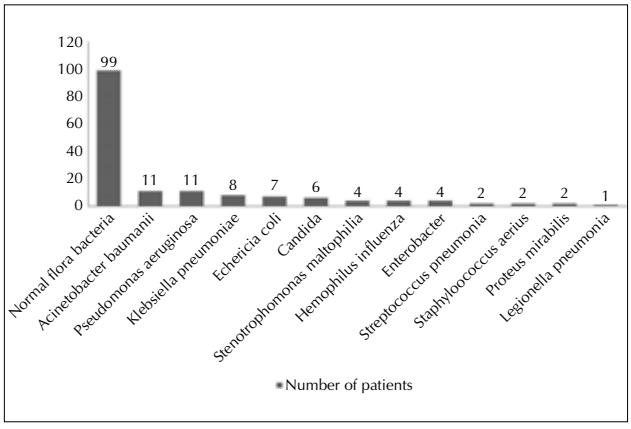

Figure 1. Microorganisms detected in sputum cultures

A thorax CT of patients with CAP in IS showed mostly bilateral lesions (p=0.044). Comorbid disease frequency was similar in both seasons (p=0.387). The frequency of cancer (p=0.027), especially that of lung cancer (p=0.007), was high in NIS. Table 3 lists the comorbid diseases.

DISCUSSION

Hospital admissions due to pneumonia increase during influenza outbreaks. Longer DOS may lead to problems in the allocation of beds. No study has so far examined DOS of patients with CAP during IS and NIS The aim of our study was to determine the duration of hospital stay for patients admitted with CAP during IS. We found no difference in DOS between IS and NIS.

Table 2. Variables according to the season

	IS	NIS	p
Mean age±SD	66.79±16.01	64.04±17.37	0.114
Number of patients aged ≥65 years [n (%)]	118 (59.9)	87 (50.6)	0.072
Gender (male) [n (%)]	138 (70.1)	129 (75)	0.289
Mortality [n (%)]	14 (7.1)	14 (7.1)	0.86
Median duration of hospitalization (days)	10.0 (1-50)	9.0 (1-82)	0.676
Median duration of ICU stay (days)	5.0 (1-10)	6.0 (2-40)	0.206
Median leukocyte count (×10³/μL)	11400 (1690-56100)	11900 (1900-85200)	0.755
Median neutrophil count (×10³/μL)	8360 (850-37100)	8410 (650-40100)	0.868
Mean CRP (mg/dL)	15.59±12.31	15.79±12.5	0.895
Mean ESR±SD (mm/h)	57±30	63±30	0.068
Sputum culture positivity [n (%)]	82 (49.9)	84 (50.6)	0.83
Blood culture availability [n (%)]	30 (15.2)	49 (28.5)	0.002*
Blood culture positivity [n (%)]	7 (23.3)	8 (16.3)	0.63
Pneumonia in thorax CT [n (%)]	130 (66)	117 (68)	0.679
Bilateral localization in thorax CT [n (%)]	67 (34)	42 (24.4)	0.044*
Empyema [n (%)]	4 (2)	6 (3.5)	0.524
Lung abscess [n (%)]	6 (3)	11 (6.4)	0.200

(Significance: p<0.05) CU: intensive care unit; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CT: computed tomography; IS: influenza season; NIS: non-influenza season

Table 3. Comorbidities according to the season

	IS [n (%)]	NIS [n (%)]	p
COPD	81 (41.1)	59 (34.3)	0.178
Diabetes mellitus	36 (18.3)	22 (12.8)	0.149
Chronic renal failure	9 (4)	12 (7)	0.441
Congestive heart failure	28 (14.2)	21 (12.2)	0.680
Neurological disorders	27 (13.7)	26 (15.1)	0.813
Hypertension	37 (18.8)	29 (16.9)	0.631
Asthma	8 (4.1)	2 (1.2)	0.113
Carcinoma	18 (9.1)	30 (17.4)	0.027*
Lung carcinoma	8 (4.1)	21 (12.2)	0.007*
Prostate carcinoma	4 (2)	2 (1.2)	0.689
Larynx carcinoma	2 (1)	6 (3.5)	0.153

(Significance: p<0.05) COPD: chronic obstructive pulmonary disease; IS: influenza season; NIS: non-influenza season

The appropriate duration of treatment for patients with CAP varies. This duration is 10.8-16 days in Turkey [8]. Mean DOS of our patients was consistent with that reported in previous studies. It is recommended to determine the responsible pathogen for CAP treatment [9,10]. However, diagnostic tests are optional for hospitalized patients without severe CAP. Most hospitalized patients with CAP are treated empirically with no etiological diagnosis. Diagnostic yield of microbiological tests is low, and pathogen detection rates vary [11]. In addition, identifying the etiological agent is confounded by limitations in diagnostic tests and by poor-quality specimens contaminated with bacteria colonizing the upper airway [6].

Influenza surveillance studies are performed to determine the circulating influenza virus type. However, viruses other than influenza virus (respiratory syncytial virus, human metapneumovirus, human parainfluenza virus, and coronavirus) as well as typical and atypical bacteria are the responsible pathogens during influenza season. In addition, laboratory facilities are mostly inefficient, and pathogens may not be determined. Consequently, influenza tests are not performed in 25%-60% of patients hospitalized for influenza, even in the United States. Furthermore, low-sensitivity tests lead to false-negative results [12]. Influenza either remains undiagnosed or under coded in a substantial proportion of critical illnesses [13]. In the Netherlands, only 40% of patients admitted to ICU for CAP were tested for influenza [14]. It is difficult to detect some pathogens using laboratory tests [6]. In addition, influenza virus acts synergistically with certain bacteria to increase the infectivity, and influenza is often complicated by bacterial superinfection. The rate of mixed viral-bacterial infection is 20%, and CAP caused by mixed infections is associated with more severe symptoms and longer hospitalization than that caused by bacterial infection alone [15].

In as much as one-third of pneumococcal pneumonia cases, atypical bacterial pathogens coinfect patients with CAP. New polymerase chain reaction tests are now available for detecting *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* as well as 14 respiratory tract viruses. These tests are rapid, sensitive, and specific [16]. Use of such tests can aid in the rapid diagnosis of viral pneumonia and reduce the unnecessary use of antibacterial agents, but they are not available in most centers. Therefore, it is usually not possible to distinguish whether the patient had influenza infection or any other infection before CAP in daily practice. Clinicians usually treat patients with CAP empirically with no etiological diagnosis.

Blood cultures are positive in only 3%-14% of patients hospitalized with CAP [6]. In our daily practice, we collect blood samples for cultures from patients with high fever. In our study, more samples for blood cultures were obtained in NIS than in IS. There might be more patients with pneumonia with high fever in NIS and more cases of atypical clinical presentation during IS. However, blood culture positivity did not differ between both the seasons.

Community-acquired pneumonia is more prevalent in elderly patients and risk of its occurrence increases with age [6]. Similarly, influenza affects older age groups more frequently. In a study conducted in Germany, children aged <18 years and people aged >60 years had the highest rate of influenza-related hospitalizations [17]. Relative frequency of influenza-related hospitalizations was highest among patients aged >60 years (5.5%). Patients aged >60 years stayed in hospital for a mean of 13.1 days, whereas children aged 2-6 years stayed in hospital for a mean of 6.6 days for influenza-related hospitalization. That study was performed based on a population database including 4 million people. Our study included 55.6% patients aged >65 years, and we did not observe any increase in the number of older patients in IS. However, our study was conducted including limited number of patients and was based on the data of a tertiary hospital.

Chest X-ray is generally adequate for clinical care of patients with CAP. If the clinical presentation favors pneumonia but X-ray is negative, a CT scan can be performed as it has a higher sensitivity and accuracy than chest X-rays [18]. Chest X-rays were performed for all of our study patients. There were more thorax CT-confirmed patients with pneumonia in IS than in NIS, and these thorax CTs showed mostly bilateral lesions. During IS, there were more incidences of primary influenza pneumonia or atypical pneumonia; they appear as a ground-glass attenuation on X-ray and may be difficult to identify using only chest X-rays. Atypical pneumonia incidence was more predominant and the main radiological findings were ground-glass opacities during IS. For these reasons chest x-ray is insufficient diagnostic tool. In addition, influenza might complicate and facilitate severe bilateral pneumonia.

Although chronic obstructive pulmonary disease (COPD) is an important risk factor for adverse outcomes with influenza infection, COPD rate was not higher in IS than in NIS in our study. This might be because COPD exacerbations were often associated with bacterial agents. Furthermore, patients might be externalized after their pneumonia resolves, and malignancies might be diagnosed in the follow-up period as an outpatient. Only carcinoma rate, especially lung cancer rate, was higher in NIS. This may be due to the relative increase in hospitalization of patients with pneumonia in IS. Furthermore, our hospital is a tertiary chest disease center, and patients with other malignancies are less frequently hospitalized.

Annual surveillance studies show that the timeline of IS changes every year. This minimal change occurs in terms of weeks. We analyzed data from previous studies and defined "IS" in Turkey as the common period in all years: December 1-April 30 [4,7]. It would be more precise to define IS on a weekly basis and perform analysis in terms of the weeks during which the patients were hospitalized

Our study has several limitations. As it is a retrospective study, data collection may be defective. We could not perform tests for viral and atypical agents. We could not precisely distinguish primary influenza pneumonia from secondary bacterial pneumonia. Thus, it was not clear whether our bacterial pneumonia cases were secondary to influenza. Since information regarding serologic diagnoses was limited and because of our focus on culture results, we likely underestimated the incidence of atypical pathogens. However, the aim was to de-

termine whether DOS and other parameters changed in IS irrespective of the etiological agent. DOS in hospital might be affected by multiple factors, such as socioeconomical factors. Varying discharge practices of physicians during the study period might also affect the length of hospital stay. Another confounding factor is air pollution. Air pollution rate is higher during IS. Further studies may enlighten the relationship between hospital admissions in IS and air pollution. Our study was conducted in a single tertiary hospital, and there might be difficulties in generalizing our results to other centers.

In conclusion, an influenza outbreak takes place every year, causing an increase in hospital admissions and hospitalizations. Also, it is difficult to determine the pathogen. There was no difference in DOS of patients with CAP between IS and NIS. The length of stay did not increase in older patients. Furthermore, bilateral pneumonia was more prevalent in IS, whereas lung cancer was more frequent in NIS.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: N/A.

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Original Article

Omalizumab Treatment for Atopic Severe Persistant Asthma: A Single-Center, Long-Term, Real-Life Experience with 38 Patients

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Abstract

OBJECTIVES: Omalizumab is a monoclonal antibody that is used as add-on therapy for treating moderate-to-severe persistant atopic asthma in patients with persistant symptoms and frequent exacerbations, despite step 4 treatment according to GINA guidelines. Real-life studies on omalizumab treatment are limited in Turkey. Thus, the present study aims to assess the clinical efficacy and treatment outcomes of omalizumab in patients with atopic severe persistant asthma.

MATERIALS AND METHODS: Patients with atopic severe persistant asthma who were treated with omalizumab between 2009 and 2017 were retrospectively evaluated. Baseline and last results of the following variables were compared: symptom scores (GINA categorical), controller medications, blood eosinophil counts, forced expiratory volume in 1 second (FEV_1) values, and the number of exacerbations that were treated with systemic corticosteroids for at least 3 days within the last 1 year. The effect of coexisting aspirin-exacerbated respiratory disease (AERD) on these parameters was also analyzed. Step-down of other asthma medications was attempted in patients with symptom control and in those without an exacerbation history within the last 6 months.

RESULTS: Thirty-eight patients (mean age, 50 years; females, 30) were included in this study, of whom four showed AERD. After treating with a mean time of 30±22.1 (min: 6, max: 92) months, 26 (68%) patients showed complete controlled disease and 12 (32%) showed partly controlled disease, of whom all had uncontrolled disease before. Mean exacerbation rates within the last 1 year decreased by approximately 76% (9.4±8.4 vs. 1.8±1.5; p<0.001) and FEV_1 values increased by approximately 14% (2075±729 vs. 2321±800 cc; p=0.001) compared with baseline levels. Although the reduction in eosinophil count was not significant in all patients (503.8±524.8 vs. 370.8±314.5; p=0.134), repeated measures analysis of variance revealed a more prominent reduction in eosinophil count in the AERD group than in the non-AERD group, independent from the treatment period (F: 4.23, p=0.049). The mean inhaled corticosteroid dose (budesonide eq., 1063±397 vs. 958±439 mcg; p=0.084), the number of other controller medications, and the number of patients with long-term systemic steroid use decreased after omalizumab treatment. No serious adverse events were recorded during the follow-up period.

CONCLUSION: Our results confirm that omalizumab significantly improves disease control and is a safe add-on therapy. In addition, in suitable patients with controlled disease over time, the step-down of other asthma medications will be appropriate.

KEYWORDS: Severe asthma, allergic asthma, therapy management, anti-IgE, omalizumab

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INTRODUCTION

Asthma is a chronic respiratory disease characterized by variable symptoms and airflow limitation; it is usually associated with chronic airway inflammation and hyperresponsiveness [1]. A subgroup within the asthmatic population is at a high risk for complications, uncontrolled disease, and exacerbations. The patients in this subgroup are classified as having severe asthma, and it is estimated that severe asthma accounts for approximately 3.6% of individuals with asthma [2].

Severe asthma is defined as a disease that remains uncontrolled despite high-dose (>800 mcg budesonide) inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA) or leukotriene modifier/theophylline treatments in the previous year or systemic corticosteroid treatment for at least half of the past year, or asthma that can only be controlled with these treatments [3]. Some phenotype-based add-on treatments are available for treating severe asthma. Omalizumab (Xolair; Novartis, Switzerland) is a humanized anti-IgE monoclonal antibody (mAb) approved as an add-on treatment to ICS/LABA for patients with atopic moderate or severe asthma that is uncontrolled with step 4 treatment [1]. The efficacy of omalizumab in patients with atopic severe persistant asthma has been shown in many randomized clinical trials and real-life data stud-

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ies [4-6]. Previous studies have reported a positive effect of omalizumab on symptom control, lung function, and quality of life, and omalizumab has been found to reduce ICS use, systemic corticosteroid (SCS) use, and the number of severe exacerbations. It has been shown that patients with a positive therapeutic effect are likely to exhibit a sustained response that may extend up to 2-4 years after discontinuation [5].

Although omalizumab is approved in our country since 2008, studies on treatment outcomes in the Turkish patient population are limited [7-10]. Hence, the present study aims to evaluate the clinical efficacy of omalizumab in a real-life setting. In addition, the reduction or withdrawal of ICS and/or other asthma medications during omalizumab therapy, was also investigated.

MATERIALS AND METHODS

The records of adult (>18 years) patients with atopic severe persistant asthma who were treated with omalizumab for >6 months in 2009-2017 at a referral university hospital were retrospectively analyzed. Adherence, inhaler technique, and coexisting conditions that may intervene with disease control were investigated in all the patients. All the patients showed serum IgE levels within the recommended range for omalizumab treatment and positive test results demonstrating at least one perennial allergen sensitization.

Data on demographics, baseline serum total IgE levels, and allergen sensitization status of the patients were collected from the charts. In addition, for each patient, we noted baseline and last results for the following variables: all asthma medications, symptom control measures, blood eosinophil counts, forced expiratory volume in 1 second (FEV_1) values, and the number of exacerbations that required SCS for at least 3 days (either ER admission, outpatient clinic visit, or hospitalization) within the last 1 year (only for the patients who were treated for more than 1 year with omalizumab). ICS and SCS were presented as their budesonide and methyl-prednisolone equivalents, respectively. Symptom control was assessed by the GINA symptom control tool wherein the frequency of daytime symptoms, night waking, reliever treatment use, and activity limitation in the past 4 weeks was questioned at each follow-up [1]. For these four questions, three or four positive answers was accepted as uncontrolled, one or two positive answers as partially controlled, and all negative as well controlled. To establish the effect of omalizumab on disease prognosis more efficiently, basal and last measures of symptom scores, laboratory and FEV_1 parameters were obtained from the patients' exacerbation-free periods. An exacerbation was defined as the acute worsening of symptoms and lung functions from the usual status of the patient that requires unscheduled medical care and increase in daily medications [1].

Patients received appropriate dosage and intervals based on an omalizumab dosing chart that used the serum total IgE levels and body weight. All injections were performed by nurses with experience in the allergy clinic. Omalizumab was continued in patients who were considered to benefit from the treatment at the end of 16 weeks. Omalizumab was discontinued at the end of 5 years and reinitiated if the patient was still symptomatic despite other therapies on their follow-up. While calculating the total treatment period, these omalizumab-free periods were subtracted. Reactions that may have been associated with the drug were recorded.

In well-controlled and exacerbation-free patients over 3-6 months, first, SCS withdrawal was attempted, which was followed by long-acting muscarinic antagonist, montelukast, and theophylline according to the GINA counter-stepwise approach. Further, stepping down to the lowest ICS/LABA dose was attempted if the patient was still well controlled for every 3-6 months. LABA discontinuation was attempted only if the patient was constantly well controlled and exacerbation-free for at least 6 months. The last stabilizing treatment dose was re-established when patients became symptomatic. Complete ICS withdrawal was not attempted in any patient. Patients whose inhaler steroid dose could (ICS dose could be permanently reduced from baseline for at least 6 months) and could not be reduced permanently were also compared. Due to the retrospective design of this study, written informed consent was not obtained. This retrospective study fully conformed to the principles of the Declaration of Helsinki and does not require ethics approval [11].

Statistical Analysis

Data recording and statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 17.0 (SPSS Inc.; Chicago, IL, USA). Distribution of the data was established using the Kolmogorov-Smirnov test. Numerical data were expressed as mean±standard deviation (SD) or median (25^{th}-75^{th} percentile) according to the distribution of the variable. Paired sample t-test was performed to test the differences between pre- and post-treatment. Between-group comparisons were performed using independent sample t-test, Mann-Whitney U-test, or chi-square test, as appropriate. Repeated measures analysis of variance was used to demonstrate the effect of aspirin-exacerbated respiratory disease (AERD) on the change in peripheral eosinophilia. A $p<0.05$ was considered significant.

RESULTS

Of the 38 patients included in the present study, 30 were female. Mean age was 50±10.8 years. All the patients had at least one perennial allergen sensitization. Median basal serum IgE level was 173 IU/mL (101.8-410), and mean blood eosinophil count was 503.8±524.8 cells/mL (Table 1). Four patients showed AERD.

The baseline mean inhaler steroid dose was 1063±397 mcg. Patients' treatments are summarized in Table 2. The patients who had uncontrolled asthma (mean categorical scores, 3.6±0.5) despite these therapies were administered omalizumab for a mean of 30±22.1 months (min: 6, max: 92; <1 year=6 patients, 1-3 years=20 patients, and 3-5 years=12 patients). The last symptom scores decreased by 87% (Table 3). In total, 68% of patients who had uncontrolled disease prior to omalizumab treatment had well-controlled disease in their last visit. The mean number of systemic steroid-requiring exacerbations per year decreased from 9.4±8.4 to 1.8±1.5, and FEV_1 values increased from 2075±729 to 2321±800 cc ($p<0.001$ and $p=0.001$, respectively). Blood eosinophil count decreased by 13%, but the difference was not significant. Repeated measures analysis of variance showed a more prominent reduction in eosinophil count in the AERD group than in the non-AERD group, independent from the treatment duration (F: 4.23, $p=0.049$) (Figure 1).

Table 1. Patient characteristics and clinical findings at baseline

	N=38
Age, years±SD	50±10.8
Female gender, n (%)	30 (79)
Median serum total IgE, IU/mL±SD	173 (101.8 - 410)
Serum eosinophil count, cells/mL±SD	503.8±524.8
Upper respiratory tract involvement, n (%)	
None	5 (13)
Chronic rhinitis	29 (76)
AERD	4 (11)
Treatment duration, months±SD	30±22.1
Allergen sensitization status, n (%)	
Mite	31 (82)
Pollen	11 (29)
Dander	2 (5)
Mold	15 (40)
Single allergen sensitization	17 (45)

SD: standard deviation; AERD: aspirin-exacerbated respiratory disease

While seven patients were receiving long-term systemic steroid treatment before omalizumab (sum of daily SCS need for seven patients was 57 mg; mean, 8.1 mg per patient), the number decreased to two at the last visit (sum of daily SCS need for two patients was 8 mg; mean, 4 mg per patient). Budenoside-equivalent inhaler steroid doses also decreased

Table 2. All baseline and last controller medications

	Baseline	Last	p
ICS dose*, mcg±SD	1063±397	958±439	0.084
Other controller medications, n (%)			
LABA	38 (100)	37 (97)	>0.05
Montelukast	34 (90)	30 (79)	
Theophylline	8 (21)	3 (8)	
LAMA	9 (24)	7 (18)	
Total dose of long-term SCSs, mg/day**	57 (n=7)	8 (n=2)	-

ICS: inhaled corticosteroid; SD: standard deviation; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; SCS: systemic corticosteroid

*: Budesonide equivalent; **: Represented as the sum of all the patients' daily SCS dosage as methyl-prednisolone equivalent

Table 3. Comparison of the baseline and last symptom scores, exacerbation rates, FEV_1 values, and eosinophil counts

	Baseline	Last	Mean change from baseline	p
Symptom scores (GINA)	3.6±0.5	0.5±0.7	-87%	<0.001
Complete control, n (%)	0	26 (68)		
Partial control, n (%)	0	12 (32)		
Uncontrolled, n (%)	38 (100)	0		
The number of exacerbations that required SCS for at least 3 days within the last 1 year±SD (n=32)	9.4±8.4	1.8±1.5	-76 %	<0.001
FEV_1, % predicted±SD	77±18.9	86.9±21.2	15%	0.001
FEV_1, cc±SD	2075±729	2321±800	14%	0.001
Serum eosinophil count, cells/mL±SD	503.8±524.8	370.8±314.5	-13%	0.134

SCS: systemic corticosteroid; FEV_1: forced expiratory volume in 1 second; SD: standard deviation

Table 4. Comparison of patients that inhaled corticosteroids could and couldn't be reduced permanently

	ICS dose permanently reduced (n=10)	No reduction in ICS dose (n=28)	p
Female gender, n (%)	7 (70)	23 (82)	0.4
Age, years±SD	54±9.8	48.6±11	0.2
Treatment duration, months±SD	28±21.7	31.9±25.6	0.67
Baseline median serum total IgE, IU/mL±SD	163 (102-230)	173 (95-467)	0.42
Baseline FEV_1 values, cc±SD	1997±733	2104±740	0.7
Change in FEV_1, cc±SD	301±234.7	212.6±470	0.57
Baseline serum eosinophil count, cells/mL±SD	525±340	497.3±575.3	0.9
Change in serum eosinophil count, cells/mL±SD	-71.3±398	-229.2±534	0.45
Last ICS dose, mcg±SD	600 (350-800)	800 (800-1600)	0.002
The number of exacerbations that required SCS for at least 3 days within the last 1 year±SD	0.78±1.1	1.93±1.5	0.04

ICS: inhaled corticosteroid; SD: standard deviation; FEV_1: forced expiratory volume in 1 second; SCS: systemic corticosteroid

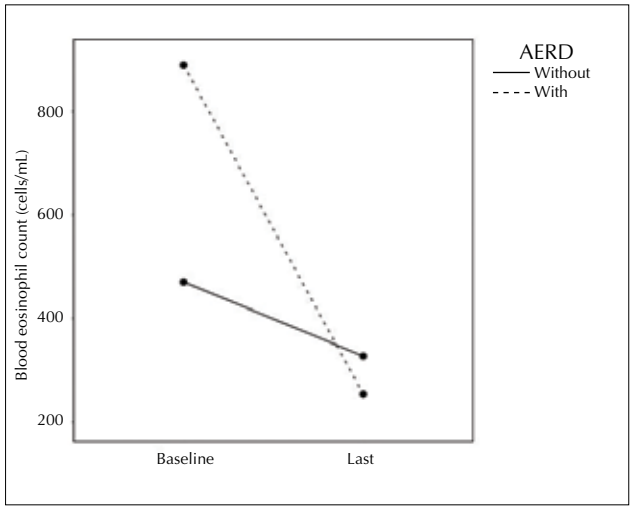

Figure 1. The aspirin-exacerbated respiratory disease (AERD) group showed a more prominent reduction in the eosinophil count [median, -600 (-850-460) vs. -10 (-240-130)]. This reduction was independent of the duration of treatment (F: 4.23, p=0.049). However, symptom scores, exacerbation rates, and the number of ICS-reduced patients were not different between the AERD and non-AERD groups

compared with baseline (1063±397 vs. 958±439 mcg, respectively; p=0.084). In 10 patients, besides other controller medications, inhaler steroid doses could be reduced permanently. The number of systemic steroid-requiring exacerbations in the last year was significantly lower in these patients (0.8±1.1 vs. 1.9±1.5; p=0.04) (Table 4). However, there was no significant difference between these groups in terms of demographic, clinical, physiological, or laboratory parameters. All other controller medications, except inhaler steroids, could be discontinued in only one patient who was well controlled and exacerbation-free for 1 year. ICS doses could not be reduced in any patient with AERD.

Omalizumab treatment was terminated at the fifth year in three patients. Because they were again symptomatic after 12 and 18 months, omalizumab was reinitiated in two of these patients. Omalizumab was well tolerated in all patients throughout the therapy, and no systemic reactions or serious adverse events were recorded during the follow-up period.

DISCUSSION

Our results show that omalizumab add-on therapy for 30 months is an efficient therapy in patients with atopic severe persistant asthma in real-life settings. With omalizumab, the systemic corticosteroid-requiring exacerbation rate decreased by 76%, and basal FEV_1 values increased by 14%. Of all the patients who had uncontrolled disease prior to omalizumab treatment, 68% and 32% showed well controlled and partly controlled disease, respectively, after the treatment. In addition, step-down therapy from ICS and other controller medications was managed in some patients.

The effect of omalizumab in patients with severe persistant allergic asthma has been shown in many randomized clinical trials and real-life data studies [4-6]. Similar to our study, these studies also reported symptom control, improved lung function, and improved quality of life, as well as reduced ICS and SCS use and the number of severe exacerbations. In a study by Alfarroba et al. [12], which also used GINA categorical symptom control classification, 54% of all patients with uncontrolled disease improved to well-controlled disease at the end of a 24 month-therapy. In their cross-sectional, national observational study on patients receiving omalizumab therapy in Italy, Novelli et al. [13] evaluated the level of control according to the GINA classification and reported 25.2% of patients with well-controlled disease and 47.1% of patients with partially controlled disease at the end of a 32 month-therapy (median). Similar to GINA scores, 66% of patients had asthma control test (ACT) scores ≥20. Another study that used ACT scores for evaluation demonstrated a 65% improvement with omalizumab therapy at the end of 3 years [14]. A real-life observational study also reported an increase in ACT scores from 10.4 to 20.4 with omalizumab treatment in Turkey [7].

Besides symptom control, omalizumab also has an effect on exacerbation and hospital admission rates and improves the quality of life. Our study showed a 76% decrease in mean steroid-requiring exacerbation per year from 9.4±8.4 to 1.8±1.5. Our baseline mean exacerbation rates were higher than those reported in the literature; this is because our values included all exacerbations-hospitalization, ER admission, or outpatient clinic visit-that require at least 3 days of SCS treatment. In a meta-analysis of real-life studies, a decrease in exacerbation rates after 1 year of treatment with omalizumab was reported, which was 46%-80% [5]. López-Tiro et al. [14] reported a 95% decrease in hospitalization and an 80% decrease in ER admissions after 1 year of treatment as well. Another important result of our study is the 14% (approximately 250 cc) increase in FEV_1 values with the treatment. FEV_1 increase was not correlated with the duration of treatment (min: 6, max: 92 months). Previous real-life data studies have also shown an 8%-33% increase in FEV_1 values after 1 year of omalizumab treatment [5]. More importantly, Özgür et al. [10] noted a 24.5% increase in FEV_1 values at the first year, which persisted beyond 3 years (20.4% at the last visit beyond 36 months).

Previous studies have shown that peripheral blood eosinophilia may be an important marker for the clinical response to omalizumab [15]. In their placebo-controlled study, Hanania et al. [16] reported that following omalizumab treatment, the mean reduction in the exacerbation rate was only higher in patients with a higher baseline peripheral eosinophil count (>260/µl). Another study showed that a peripheral eosinophil count of >300/µL can predict a better treatment response [17]. Apart from this relationship between baseline eosinophil count and treatment response, decreased peripheral eosinophil count was also noted with omalizumab treatment. In a pooled analysis of data from five randomized controlled trials, Massanari et al. [18] found that post-treatment eosinophil counts were significantly reduced in the treatment group. They also found similar results in patients with pre-treatment SCS use. Although the eosinophil count dropped with omalizumab treatment in our study, the difference was not statistically significant. This could be due to our small sample size and the higher baseline eosinophil levels of our patients compared with previous studies. Interestingly, despite our small

sample size, the eosinophil count drop was significantly higher in patients in the AERD group than in those in the non-AERD group. However, the ICS dose was not reduced in any of these patients; symptomatic scores and decrease in the exacerbation rates were also similar to the other patients. Although omalizumab markedly decreased the eosinophil counts in these patients, these findings suggest that clinical effects occur via mechanisms other than eosinophil count decrease. In addition, even though the blood eosinophil count decreases, it is still unclear how it affects tissue eosinophilia; therefore, it would be speculative to comment on the clinical effects of this decrease.

First-line controller therapy involves ICS, and up-dosing is recommended, up to long-term systemic steroids, if the disease cannot be controlled otherwise. The primary advantage of mAbs, which act through the Th-2 pathway, is their steroid-sparing effects, and the disease can be controlled without any possible steroid-related side effects [19]. It has been proposed that long-term omalizumab treatment has disease-modifying effects, but this is still arguable [20, 21]. Therefore, despite several previous studies, we do not completely discontinue ICS in any patient with atopic severe persistant asthma who receives omalizumab therapy. However, we try to use the controller medications in the lowest dose possible as long as the patient is under control with omalizumab. As expected, patients whose ICS dose could be reduced also had lower exacerbation rates at the last year, but no other difference was found between the patients whose ICS dose could be and could not be reduced. There are controversial data on ICS and SCS dose reduction/withdrawal in the literature. A Cochrane meta-analysis reported no significant difference between omalizumab and placebo groups in terms of the median reduction of daily SCS and also the number of participants that were able to withdraw SCS. Interestingly, ICS reduction or withdrawal was significantly more likely in patients who received omalizumab treatment [4]. In another meta-analysis based on real-life data, ICS reduction rates in 1 year were 10%-28% [5]. Bavbek et al. [7] also reported a significant decrease in SCS and other asthma drug dosages but no difference in ICS doses at the end of 15 months (median). It should be noted that a marked heterogeneity exists in both patient characteristics and methodology in these studies. However, based on our findings, we suggest that for patients who are asymptomatic and exacerbation-free under omalizumab treatment, asthma medications other than ICS should be decreased and withdrawn, if possible, starting with SCS, as a counter-stepwise approach. If the patient is still stable, the ICS dose should also be reduced.

In conclusion, this study presents our 8-year experience of omalizumab treatment in patients with atopic severe asthma. Our results show a significant decrease in symptom scores, the number of exacerbations that required SCS for at least 3 days, and systemic steroid requirement, as well as improved FEV_1 values, after omalizumab treatment. In addition, step-down was possible in a quarter of the patients, and ICS could be permanently reduced under omalizumab treatment. Our study may also contribute to the method of step-down of asthma treatments in patients under omalizumab treatment.

Ethics Committee Approval: This retrospective study fully conformed to the principles of the Declaration of Helsinki and does not require ethics approval.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

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Original Article

A Revised Treatment Approach for Hospitalized Patients with Eosinophilic and Neutrophilic Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVES: The choice of treatment according to the inflammation type in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has been of recent interest. This study investigated the role of novel biomarkers, hospital outcomes, and readmission rates in the first month in patients with eosinophilic or neutrophilic AECOPD.

MATERIALS AND METHODS: We conducted a retrospective observational cohort study in a Chest Teaching Hospital with hospitalized AECOPD patients. Subjects' characteristics, hemogram results, C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet/mean platelet volume (PLT/MPV), length of hospital stay, mortality, and steroid use were recorded. Eosinophilic AECOPD defined as peripheral blood eosinophilia (PBE) was >2% and neutrophilic AECOPD as PBE ≤2%. Readmission within 28 days of discharge was recorded.

RESULTS: Of 2727(31.5% females) patients, eosinophilic AECOPD was found in 510 (18.7%) patients. Leucocytes, CRP, NLR, and PLR were significantly higher in neutrophilic AECOPD than in eosinophilic AECOPD (p<0.001). Steroid use and mortality rate were 45% and 0.6% in eosinophilic AECOPD and 71%, and 1.4% in neutrophilic AECOPD, respectively (p=0.001, p=0.19). Age >75 years, albumin <2.5 g/dL, CRP >50 mg/dL, and PLT/MPV <20×103 were found to be risks factors for hospital mortality (p<0.05 each). Readmission rates within 28 days of discharge were 5% (n=136), and this rate was higher in eosinophilic AECOPD patients not taking steroids (p<0.001).

CONCLUSION: NLR, PLR, and CRP levels were higher in neutrophilic AECOPD compared with eosinophilic AECOPD. These markers decreased with treatment in neutrophilic AECOPD. A PLT/MPV ratio of <20×103 resulted in an increased mortality rate. Thus, appropriate steroid therapy may reduce readmission rates in the first 28 days after discharge in eosinophilic AECOPD.

KEYWORDS: Chronic obstructive pulmonary diseases, exacerbation, peripheral eosinophilia, neutrophil to lymphocyte ratio, steroid treatment

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INTRODUCTION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) requiring hospitalization is a significant cause of morbidity and mortality [1]. Different cumulative environmental exposures (air pollution, cigarette smoking, feeding habits, allergens, and infections) lead to pathobiological changes in the airway, and these changes can be addressed as endotypes in patients with chronic obstructive pulmonary disease (COPD) [2]. During AECOPD, these multi pathobiological changes are determined by some biomarkers, which are easily obtained (peripheral blood eosinophil) or require high-end technology (exhaled nitric oxide) [3,4]. The clinical presentations of COPD, such as no symptom or with very severe symptoms and having muscle wasting or obesity, are defined as COPD phenotypes [2]. The awareness of endotypes can lead to a mechanistic approach to COPD stratification and treatment. Determining the nature of AECOPD according to the endotype of inflammation may be important for treatment options in the future. Predominantly neutrophilic and to a lesser extent, eosinophilic inflammation, is observed with COPD, although recent studies have shown that the eosinophilic inflammation rate may reach up to 45% [5-8]. Some studies have shown that corticosteroid treatment of AECOPD may be less effective if it is not the eosinophilic endotype [3,7,9]. A number of studies have investigated sputum and bronchial biopsy eosinophilia, steroid response, and frequency of attacks [7,10,11]. Very recently studies have focused on peripheral blood eosinophilia (PBE) as a biomarker, which reflects sputum eosinophilia, increasing in patients with AECOPD [3,12]. The eosinophilic and neutrophilic endotype of AECOPD can be easily identified using peripheral blood analysis.

Making a decision regarding corticosteroid and/or antibiotic treatment is important for the length of stay (LOS) in the hospital, morbidity, and mortality in patients with hospitalized AECOPD. The results of sputum culture C-reactive protein

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(CRP), which is a well-known inflammatory biomarker, or any other biomarker are not helpful to physicians when deciding the avenue of treatment with antibiotics in patients with AECOPD [13,14]. The AECOPD endotypes can however provide clues for accurate treatment, thus shortening the LOS in the hospital [15]. In addition to peripheral blood eosinophil percentage, other novel biomarkers have recently been investigated to define the endotype of AECOPD, namely neutrophil/lymphocyte ratio (NLR), platelet/mean platelet volume (PLT/MPV), and platelet/lymphocyte ratio (PLR) [16-18]. The studies have assessed these biomarkers in light of defining the attack severity and managing the treatment approach to shorten hospital stay and decrease hospital mortality, together with reducing readmission rates to hospital. In previous studies, we evaluated outcomes with respect to eosinophilic and noneosinophilic COPD exacerbation and identified a new biomarker (NLR) for predicting the long-term survival (6 months). However, this previous study did not analyze the patient data with respect to hospital stay and readmission rates within the first 28-days post discharge [19].

In the current study, we retrospectively assessed the real-life treatment approach and outcomes of hospitalized eosinophilic and neutrophilic AECOPD patients. We also investigated the LOS in the hospital, mortality risk factors, and the effect of steroid treatment in these AECOPD patients hospitalized with eosinophilic and neutrophilic endotypes.

METHODS

Study Design

A retrospective observational cohort study was performed in a chest disease training and research hospital between January 2014 and December 2014. This study was approved by the Süreyyapaşa Chest Disease and Thoracic Surgery Training and Research Hospital local ethics committee (2015/06/22). Ethical approval was in accordance with the Declaration of Helsinki. All data were collected retrospectively from the hospital database. As informed consent was not obtained due to the retrospective nature of the study, the patient data were de-identified.

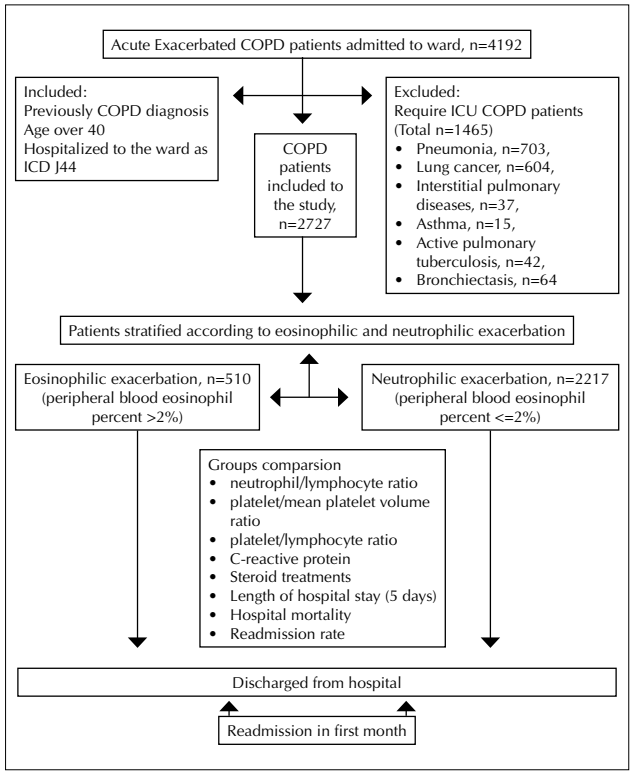

Figure 1. Flow chart showing study enrollment of patients with AECOPD

Patients

Hospitalized patients recorded as J44.0-J44.9 according to the International Classification of Diseases (ICD) 10 coding system and previously diagnosed with COPD by a pulmonology specialist using spirometry test results according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 American Thoracic Society, European Respiratory Society (ATS/ERS) criteria**,** were included in the study [1]. The diagnosis of COPD was also controlled by a chest training center, and the diagnosis of COPD was checked at least four times in our center. Each patient was to be followed only in the study center and not in other center and city.

Study patients were divided into two groups according to the level of PBE. PBE >2% defined the eosinophilic COPD exacerbation group and PBE ≤2% defined the noneosinophilic COPD exacerbation group (Figure 1).

Patients were further divided into subgroups according to LOS in the hospital. An LOS of <7 days defined the "short stay" group and an LOS ≥7 days defined the "long stay" group. These subgroups were evaluated according to the presence eosinophil predominance, steroid use, and hospital mortality.

Definitions

Chronic obstructive pulmonary disease diagnosis was established by a pulmonologist who evaluated airflow obstruction on spirometry, forced expiratory volume in 1 second (FEV_1) of 70% predicted or less, and FEV_1 to forced vital capacity ratio of 70% or less [1].

AECOPD was defined as an acute change in a patient's respiratory symptoms, such as dyspnea, sputum production, volume, and alteration in color, resulting in a change in current therapy [1]. The reasons for COPD exacerbations according to the ICD 10 coding system were as follows: infections, arrhythmia, heart failure, pleurisy, pneumothorax, and pulmonary embolism.

Exclusion criteria were patients diagnosed with pneumonia, lung cancer, interstitial pulmonary diseases, asthma, bronchiectasis, or active pulmonary tuberculosis. We accepted peripheral blood eosinophil percent as a biomarker of airway inflammation, which reflects sputum eosinophil in patients with AECOPD [3].

Neutrophilic endotype was defined as an inflammation of noneosinophilic airway in patients with AECOPD, and a PBE of <2% was the biomarker [2,3]. PBE, which reflects sputum eosinophilia, increases in patients with AECOPD [3,12].

Eosinophilic endotype was defined as an inflammation of eosinophilic airway in patients with AECOPD, and a PBE of >2% was the biomarker [2,3].

Table 1. Demographics and laboratory findings of COPD patients at admission for eosinophilic and neutrophilic acute exacerbation

	Eosinophilic Exacerbation	Neutrophilic Exacerbation	p
Number of patients, n	510	2217	
Male, %	68.8	68.4	0.85
Age, year, mean± SD	69 ±11	70 ±10	0.67
Steroid use, n (%)	340 (67)	1452 (66)	0.62
LOS, days,	6.6 (4.6-8.0)	7.0 (5.0-9.0)	0.001
Hospital mortality, n (%)	3 (0.6)	32 (1.5)	0.19
LTOT, n (%)	176 (34.5)	845 (38.1)	0.13
Comorbidities n (%)			
Diabetes mellitus	54 (10.5)	182 (8.2)	0.9
Hypertension	77 (15.0)	328 (14.7)	0.86
Congestive heart failure	71 (13.9)	355 (16.0)	0.24
Coronary artery disease	17 (3.3)	72 (3.2)	0.92
Arrhythmias	13 (2.5)	45 (2.0)	0.46
Chronic renal failure	8 (1.5)	35 (1.5)	0.99
Anemia	3 (0.5)	10 (0.4)	0.66
Anxiety/Depression	10 (1.9)	30 (1.3)	0.48
Hemogram values			
Leucocyte count, 10^9 L	8.02 (6.40-9.81)	10.110.001 (7.67-13.11)	
Eosinophil count above 0.34x10^9 L	147 (28.8)	9 (0.4)	0.001
Eosinophil count 10^9 L	0.26 (0.20-0.36)	0.05 (0.01-0.10)	0.001
Neutrophil, %	67.9 (61.6-73.6)	82.4 (74.4-89)	0.001
Monocyte, %	7.5 (5.8-9.3)	5.4 (3.1-7.7)	0.001
Lymphocyte, %	19.2 (14.9-24.4)	10.2 (6.3-16.5)	0.001
Basophil, %	0.50 (0.30-0.90)	0.30 (0.10-0.61)	0.001
Erythrocyte count, 10^{12}L	4.34 (3.90-4.77)	4.35 (3.92-7.79)	0.39
Hemoglobin, g/dL	12.1 (10.8-13.6)	12.3 (10.9-13.6)	0.16
Hematocrit, %	36.7 (32.8-41.4)	37.2 (33.4-41.3)	0.31
MCV, fL	86 (82-90)	86 (82-90)	0.87
Platelet count, 10^9 L	249 (197-313)	250 (198-315)	0.97
Mean Platelet Volume, fL	8.43 (7.80-9.20)	8.54 (7.85-9.22)	0.35
Biochemistry values			
Blood glucose mg/dL	111 (93-144)	135 (102-182)	0.001
Blood urea nitrogen, mg/dL	25 (16-39)	30 (20-48)	0.001
Serum creatinine, mg/dL	0.80 (0.68-1.05)	0.82 (0.68-1.06)	0.82
Sodium, mmol/L	139(137-141)	139 (137-141)	0.005
Potassium, mmol/L	4.2(3.9-4.7)	4.3 (3.9-4.7)	0.43
SGOT, U/L	20 (14-27)	18 (14-26)	0.12
SGPT, U/L	16(10-25)	17 (11-26)	0.07
Albumin, g/dL	3.1 (2.7-3.5)	3.2 (2.8-3.6)	0.50

IQR: interquartile range (25%-75%), Values median (IQR). Mann Whitney U Test used; LOS: length of hospital stay; LTOT: long-term oxygen therapy; MCV: mean corpuscular volume; SGOT: serum glutamic-oxalacetic transaminase; SGPT: serum glutamic-pyruvic transaminase

Neutrophil/lymphocyte ratio as a marker of systemic inflammation was defined as the absolute neutrophil count divided by the absolute lymphocyte count [20]. An NLR of 2-20 was assessed for an effect on LOS. PLT/MPV ratio as a marker of systemic inflammation was calculated as the ratio of platelet count to the MPV.

Platelet/lymphocyte ratio as a marker of systemic inflammation was defined as the absolute platelet count divided by the absolute lymphocyte count [18]. Hospital readmission was defined as rehospitalization within the first 28 days after discharge from the hospital.

Comorbidities were recorded as diabetes mellitus, hypertension, congestive heart failure, coronary artery diseases, arrhythmia, renal failure, anemia, and anxiety/depression.

Recorded Data

The following patient information from the hospital database was recorded: age, gender, hemogram values, blood biochemistry and laboratory results on admission and discharge from the hospital, and mortality in the hospital. As inflammatory markers, peripheral blood eosinophil count, neutrophil count, and CRP were recorded, and NLR, PLR, and PLT/MPV ratio were calculated. Pulmonary function tests results could not be obtained due to the absence of an electronic database of spirometry values. The LOS at hospital and cases of rehospitalization within 28 days of hospital discharge were also recorded.

The total leukocyte, neutrophil, eosinophil, lymphocyte, and platelet counts and MPV were determined using a Coulter LH 780 Hematology Analyzer (Beckman Coulter, USA). The CRP was checked by the nephelometry method using a BN II System (Siemens, Germany). The normal range of CRP is 0-5 mg/L.

Management of COPD exacerbation

COPD exacerbation treatment was managed by an academic pulmonology specialist using protocol-based treatment in accordance with national and international guidelines [1,21].

Anti-inflammatory and bronchodilator treatment

Steroid treatment was used if the COPD exacerbation was believed to have a noninfectious origin, and the steroid protocol was 40-60 mg/day of oral methylprednisolone, if there were no gastrointestinal (GI) symptoms. If GI symptoms were present, intravenous steroid was administered. The duration of steroid use was 5-7 days. Discontinuation of steroid treatment was done abruptly.

Theophylline was administered orally (100/200/300 mg) or intravenously (200 mg/100 mL or 400 mg/500 mL) every 12 hours.

Bronchodilator

A short-acting ß2 agonist (salbutamol, 100 µg per puff) and ipratropium bromide (100 µg/20 µg per puff) were given every 4-6 hours (one puff per use) via a metered dose inhaler chamber (Aerovent, Altech®, Altera Firm, İzmir, Turkey). A nebular form of salbutamol (2.5 mg/2.5 mL per nebule) was given every 4-6 hours, or ipratropium bromide/salbutamol (0.5 mg/3.01 mg/2.5 mL per nebule) was given every 4-6 hours.

Table 2. The inflammatory biomarkers on admission and discharge from the hospital of eosinophilic and neutrophilic COPD exacerbation groups

	Eosinophilic Exacerbation		Neutrophilic Exacerbation		
	N	Variables	N	Variables	p
NLR (baseline)	510	3.60 (2.56-4.91)	2217	8.09 (4.50-13.94)	0.001
NLR (on discharge)	489	3.67 (2.60-5.17)	2117	6.19 (3.75-11.00)	0.001
PLR (baseline)	510	166.69 (121.51-228.47)	2217	247.62 (156.43-388.30)	0.001
PLR (on discharge)	489	166.19 (122.55-231.34)	2121	213.59 (139.79-341.05)	0.001
PLT/MPVx10^3(baseline)	510	30 (22-39)	2217	29 (22-38)	0.58
PLT/MPVx10^3(on discharge)	489	31 (23-40)	2116	30 (23-41)	0.97
CRP, mg/dL (baseline)	484	22.4 (7.7-62.4)	2120	34.9 (11.5-96.7)	0.001
CRP, mg/dL (on discharge)	478	12.8 (5.5-30.5)	2093	12.5 (4.6-32.0)	0.95
ESR mm/h (baseline)	223	42 (26-65)	1060	48 (26-70)	0.23
ESR mm/h (on discharge)	226	40 (23-65)	1064	44 (22-66)	0.64

Baseline: Day of admission to the hospital; Discharge: the day of discharge from hospital; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet volume; CRP: C reactive protein; ESR: erythrocyte sedimentation rate

Table 3. A comparison of acute exacerbation COPD patients' characteristics and inflammatory biomarkers on admission to hospital, and length of hospital stay relative to mortality

	Survival, n=2692	Non-survival, n=35	p
Age, above 75 year, n (%)	899 (33)	22 (63)	0.001
Gender, Male %	1144 (69)	23 (66)	0.72
Co-morbidities, n (%)			
• Diabetes mellitus	232 (9)	4 (11)	0.56
• Hypertension	401 (15)	4 (11)	0.57
• Congestive heart failure	417 (16)	9 (26)	0.10
• Coronary artery disease	88 (3)	1 (3)	0.89
LTOT, n (%)	1005 (37)	16 (46)	0.31
Steroid use in hospital, n (%)	1777 (66)	13 (41)	0.001
Eosinophil > 2%, n (%)	507 (19)	3 (9)	0.001
NLR, median (IQR)	6.60 (3.82-12.28)	9.59 (4.11-18.85)	0.07
NLR >7, n (%)	1287 (48)	23 (66)	0.035
NLR >15, n (%)	487 (18)	11 (31)	0.042
PLR, median (IQR)	224.64 (146.75-353.66)	224.14 (122.54-391.17)	0.75
PLR >182, n (%)	1682 (63)	19 (54)	0.32
PLT/MPV <20x10^3, n (%)	496 (18)	16 (46)	0.001
CRP, mg/dL, median (IQR)	31.7 (10.6-89.5)	91.9 (18.1-149.0)	0.045
CRP > 50 mg/dL, n (%)	411 (16)	15 (43)	0.001
Albumin <2.5mg/dL, n (%)	279 (12)	13 (41)	0.001
Length of stay, days, median (IQR)	7 (5-9)	4 (2-7)	0.001

LTOT: long term oxygen therapy; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PLT/MPV: platelet to mean platelet volume; CRP: C reactive protein; IQR: inter quartile range

A combined form of long-acting ß2 agonists and inhaler steroid as formoterol plus budesonide (4.5/160 µg, 9/320 µg, 12/200 µg, 12/400 µg) or salmeterol plus fluticasone (50/250 µg, 50/500 µg) were used in COPD patients.

Statistical Analysis

A descriptive analysis was used to investigate the subject demographics and hospital data. Groups were compared using the Mann-Whitney U-test for nonparametric continuous variables or Student's t-test for parametric continuous variables. The chi-square test was employed for dichotomous variables. If n was <5, the Fisher's exact test was used. The median with interquartile range was employed for nonparametric continuous variables, and mean ± standard deviation was used for parametric continuous variables. Count and percentage were used when applicable. A logistic regression analysis of hospital mortality was performed. In the hospital mortality model, we included NLR >15, LOS >7 days, age >75 years, serum albumin <2.5 g/dL, CRP >50 mg/dL, PLT/MPV <20, and steroid use. A $p<0.05$ was accepted as statistically significant. Hospital readmission within 28 days relative to the use of steroids in the two the groups were compared using the chi-square test.

RESULTS

During the study period, 4192 patients were hospitalized with AECOPD. In total, 2727 eligible patients with AECOPD were included into the study. There were 510 (18.7%) in the eosinophilic AECOPD group. Patient enrollment is summarized in Figure 1.

Table 1 shows a comparison of the eosinophilic and neutrophilic AECOPD study groups. The study groups were compared according to the patients' demographic characteristics, comorbidities, steroid use, hospital stay, mortality rates, and biochemistry on admission. The male/female ratio, average age, rate of steroid use, and serum biochemistry values (except blood glucose) were very similar between the two groups. The eosinophilic group had a significantly shorter LOS in hospital ($p<0.001$), a significantly lower leucocyte

Table 4. Logistic regression analysis of mortality risk factors in acute exacerbation of COPD requiring hospitalization

Variables	Odds ratio	95% CI, lower-upper	p
C-reactive protein >50 mg/dL on admission	3.82	1.69-8.62	0.001
Serum albumin <2.5 mg on admission	2.60	1.12-6.04	0.026
PLT to MPV <20x10^3	3.52	1.62-7.63	0.001
Age >75 years	2.51	1.15-5.49	0.021
NLR >15	1.13	0.46-2.78	0.79
Steroid use	0.50	0.22-1.10	0.09
Hospital days longer than 7 days	0.72	0.33-1.55	0.37
Eosinophilic AECOPD	0.49	0.14-1.72	0.27

CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio; PLT to MPV: platelet to mean platelet volume ratio

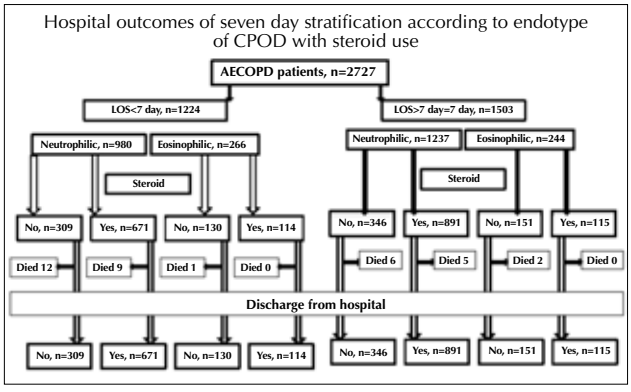

Figure 2. Hospital outcomes of study groups according to eosinophilia and steroid use

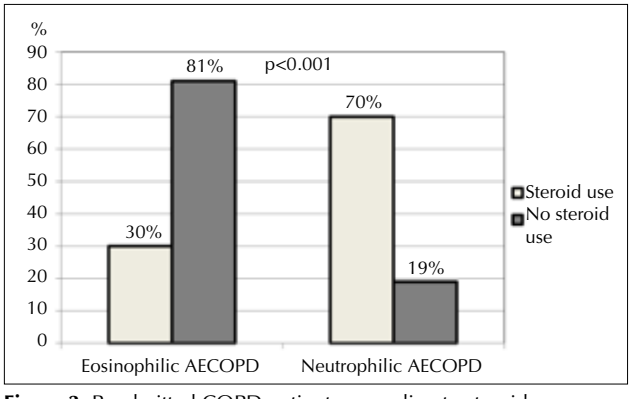

Figure 3. Readmitted COPD patients according to steroid use

and neutrophil count, and a significantly higher percentage of monocytes, basophils, and lymphocytes (p<0.001).

Table 2 shows a comparison of the novel inflammatory biomarkers NLR, PLR, PLT/MPV, and CRP and the sedimentation rate in the eosinophilic and neutrophilic AECOPD groups on the day of admission to the hospital (baseline) and the day of discharge from the hospital. The neutrophilic AECOPD group had a significantly higher level of NLR and PLR on the first and last day of hospitalization. CRP was significantly higher in the neutrophilic group on admission, but not at the time of discharge. Both groups had similar PLT/MPV ratios and erythrocyte sedimentation rate on the first and last days of hospitalization.

Table 3 shows the patients' demographics, comorbid diseases, eosinophilic endotype, steroid use, and biomarkers in the survival and nonsurvival groups. Nonsurvival patients with AECOPD had very similar demographics to the survival group. All the inflammatory biomarkers besides PLR were significantly different in the nonsurvival group compared with the survival group. The nonsurvival group had a shorter LOS than the survival group.

Figure 2 summarizes the outcomes of hospital stay, which was stratified over 7 days according to eosinophilic and neutrophilic endotype and whether steroid therapy was received in the hospital. There was no mortality in eosinophilic AECOPD patients who received steroid in the hospital independent from LOS at the hospital. Mortality in the shorter (3.8%) and longer (2%) stay groups was higher in the neutrophilic AECOPD patients who did not receive steroid therapy in hospital.

Among the 2217 neutrophilic AECOP patients, 32 died in hospital and 18 (56.3%) of these did not receive steroid therapy.

Table 4 shows the multivariate logistic regression analysis results. NLR>15, LOS>7 days, age>75 years, serum albumin <2.5 g/dL, CRP >50 mg/dL, PLT/MPV <20, and steroid use were included in the model. Mortality was observed in 35 patients. Age >75 years, serum albumin <2.5 g/dL, CRP >50 mg/dL, and PLT/MPV <20 were all found to be risks factors for hospital mortality in AECOPD patients.

Readmission within 28 days of discharge from hospital was observed in 130 patients (5%). Of these, 20 (15%) were eosinophilic AECOPD patients and 116 (85%) were neutrophilic AECOPD patients. In the eosinophilic group, six patients had received steroid therapy, while in the neutrophilic group, 94 patients had received steroids. Readmission rates were significantly higher in those patients who had not received steroids in the eosinophilic group, while readmission rates were significantly higher in those patients who had received steroids in the neutrophilic group (p<0.001; Figure 3).

DISCUSSION

This study revealed that in AECOPD patients requiring hospitalization, the eosinophilic (peripheral blood eosinophils >2%) and neutrophilic (peripheral blood eosinophils ≤2%) endotypes demonstrated significantly different inflammatory biomarkers. We also found that eosinophilic to neutrophilic endotype rate was 1:4. The level of inflammatory biomarkers in the neutrophilic endotype was much greater than that in the eosinophilic AECOPD group. During the hospital stay, NLR, PLR, and CRP values decreased and PLT/MPV values increased with treatment. A CRP level >50 mg/dL, age >75 years, serum albumin <2.5 g/dL, and a PLT/MPV ratio <20×10^3 were found to be mortality risk factors for AECOPD. Eosinophilic AECOPD patients had a shorter LOS and better outcome with steroid therapy in the hospital and decreased readmission rates compared with the neutrophilic group.

Endotypes of AECOPD: Eosinophilic versus Neutrophilic

Bafadhel et al. [3] and Pascoe et al. [22] showed that the peripheral blood eosinophil count is a valid biomarker of COPD exacerbation, and they also showed that the 2% threshold value is a sensitive marker for the presence of an eosinophilic attack that can be responsive to corticosteroids. The evaluation of COPD longitudinally to identify predictive surrogate end-points (Eclipse) cohort study accepted the cut-off value of ≥2% eosinophils in peripheral blood and sputum in COPD patients, and persistent eosinophilia was detected in 37% of patients [23]. Vedel-Krogh and colleagues recently published a similar study, but instead of a blood eosinophil percent, they showed that an eosinophil cell count >0.34×10^9/L can be associated with an increased risk of AECOPD requiring hospitalization in patients with COPD [12]. In the present study, a PBE rate >2% was observed in nearly one-fifth of the hospitalized patients with COPD exacerbations. However, eosinophilic AECOPD (eosinophils >2%) revealed a cell count of eosinophils (0.26×10^9/L) lower than that defined in the Vedel-Krogh's study (0.34×10^9). The classification of patients with eosinophilic inflammation suggests a change in the treatment plan and management of the disease. Identifying this inflammation with peripheral blood samples, which is cheap and easily accessible, will provide more practical solutions for the management of these patients.

The Behavior of CRP and Novel Biomarkers (NLR, PLR, and PLT/MPV) in Eosinophilic and Neutrophilic AECOPD

C-reactive protein levels higher than 8 mg/mL and the Anthonisen's criteria were reported to support the diagnosis of AECOPD [19,24]. In our previous study that evaluated factors affecting long-term (6month) survival in AECOPD, CRP values greater than 19 indicated a high risk for mortality in a noneosinophilic attack [19]. In another prior study, Salturk and coworkers evaluated AECOPD outcomes, and patients were grouped as eosinophilic and noneosinophilic; CRP values were significantly lower in the eosinophilic group compared to the noneosinophilic group (39.3 and 52.7, respectively), and AECOPD patients with CRP values >50 had a 1.7 times increased risk of intensive care unit (ICU) mortality [25]. The AECOPD patients requiring ICU care in their study had higher CRP values compared to the patients presented in this study. CRP values can also indicate the severity of AECOPD. In the present study, long-term mortality was not investigated; however, CRP values >50 were associated with a nearly four times increased risk of hospital mortality. Gunay et al. [16] reported that NLR values of COPD patients were higher than the control group in stable COPD and AECOPD (AECOPD, 4.28; stable COPD, 2.59; and control group, 1.71; $p<0.001$). Gunay and coworkers made no distinction between the AECOPD endotypes in their analysis. In the present study, we found almost two-fold greater NLR values in the neutrophilic AECOPD group than the values reported by Gunay and coworkers, while NLR values in the eosinophilic AECOPD subgroup were lower than those reported by Gunay and coworkers. Salturk and coworkers evaluated patients with very severe AECOPD requiring intensive care admission, and they reported NLR values nearly 2.8 times lower in the eosinophilic group compared to the noneosinophilic group (NLR=4.6 versus NLR=13.0, respectively) [25]. However, the NLR values of their patients requiring ICU admission were higher than the NLR values of the patients presented in the current study. The NLR values have been reported to increase as the severity of attack increases [16,25]. Kurtipek and coworkers published a study on 94 COPD patients; 46 of the 94 patients had AECOPD, and 48 of them had stable COPD. They reported that an NLR >3.3 and a PLR >150 could be used for the diagnosis of AECOPD [26]. Our study group had a larger sample size than the Kurtipek study, and all the patients had severe AECOPD. In addition, Kurtipek et al. [26] did not categorize the AECOPD patients into subgroups with respect to endotypes. NLR values in our eosinophilic AECOPD subgroup were similar to those reported by Kurtipek et al. [26]; however, the neutrophilic AECOPD subgroup presented here had NLR values nearly two times higher than those of the eosinophilic group.

The relationship between MPV and COPD is controversial. MPV is reported to be higher in stable COPD patients compared with healthy individuals (stable COPD, 10.6 and smoker control group, 9.9) [27]. In contrast, Wang et al. [17] reported that MPV was lower in the stable period and during the exacerbation of COPD compared with healthy individuals (COPD exacerbation, 9.5; stable COPD, 9.8; and control group, 10.4). They found that a reduced MPV was positively related to white blood cell count and CRP levels in exacerbated COPD patients. In the present study, PLT/MPV rate was found to be significantly higher in the longer stay group, but it is difficult to make a clinical interpretation solely on this result. PLT/MPV values were similar in the eosinophilic and noneosinophilic groups at both hospital admission and discharge. However, a PLT/MPV ratio of <20 was found to indicate a nearly 3.5 times higher risk of hospital mortality in the logistic regression model.

Steroid Therapy and Readmission in Eosinophilic and Neutrophilic AECOPD

Studies have shown the presence of sputum eosinophilia with good response to steroids in COPD [28,29]. Bafadhel et al. [3] reported that a steroid regimen determined by the presence of peripheral blood eosinophils greater than 2% did not result in treatment failure or deterioration of symptoms compared with the standard treatment regimen. In another study, treatment failure was 11% for patients receiving steroids and 66% for patients not receiving steroids in the group with peripheral blood eosinophils ≥2% [8]. Steroid use did not affect the success of treatment in the group with peripheral blood eosinophils <2% [8]. In the present study, the shorter- and longer stay group with eosinophilic AECOPD patients who received steroid therapy, had no incidence of hospital mortality (Figure 2). In this study, hospital readmission within the first 28 days after hospital discharge was found to be higher in the eosinophilic patients who did not receive steroid therapy and higher in the noneosinophilic patients who received steroid therapy. These findings may suggest that steroid usage in an eosinophilic attack of COPD is important; however, in noneosinophilic exacerbations, steroids may not be the first choice of treatment. The COPD guidelines suggest the use of steroid as "consider" in patients with AECOPD [1]. However, there are no detail definitions for the criteria of considering steroids and also for antibiotics. The unnecessary use of steroid or not to use antibiotic can lead to undesired

complications, such as progress the infections and prolonged hospitalization. However, the logic that "consider steroid if peripheral blood eosinophil >2%" appears relevant. Further well-designed studies will support this approach.

Length of Hospital Stay and Mortality

The LOS in the hospital and mortality is reported to be longer and higher as the severity of the disease increases [30]. In different studies, the length of hospitalization was found to be 8.4-9 days, and hospital mortality was found to be 5.9-7.4% [30-32]. Advanced age, poor performance status, low albumin, and pulse oxygen saturation levels have been identified as independent risk factors for prolonged hospitalization. Age, blood urea, serum albumin, arterial pH, arterial oxygen saturation levels, and performance status were independent factors that increased mortality [32]. In a previous study, the 6-month mortality was found to be similar in the eosinophilic and noneosinophilic groups (14.2% and 15.2%, respectively) [19]. In the present study, CRP values >50 mg/dL, age >75 years, serum albumin <2.5 g/dL, and PLT/MPV <20 were associated with an increased risk of hospital mortality. Some studies have investigated an association between COPD severity and mortality and eosinophilia. In the study of Holland and coworkers comparing COPD exacerbations with eosinopenia and COPD exacerbations with a normal eosinophil count, the days of hospitalization were 8 and 5 days, respectively, and mortality rates were reported to be 17% and 2%, respectively [33]. In the present study, the shorter- and longer stay group had lower mortality rates, both in the eosinophilic and noneosinophilic groups, compared with those in the Holland's study. Salturk and coworkers showed that the LOS in hospital and mortality in eosinophilic and noneosinophilic patients with COPD exacerbation were 4 days and 6 days and 12.9% and 24.9%, respectively [25]. Recently Yao and colleagues conducted a study on 303 AECOPD patients to evaluate NLR and PLR as potential prognostic biomarkers for hospital mortality (n=37, 12.2%) [18]. They defined an NLR >6.24, PLR >182.68, and CRP >16.45 as high risk for increased mortality. Thus, increased NLR and PLR may be useful prognostic biomarkers in AECOPD for hospital mortality. In their study, both survivors and nonsurvivors had a mean LOS in the hospital of 15 days. In the present study, the mortality rate of patients with AECOPD was nearly one-eighth less than that reported by Yao et al. [18]. Also, LOS was shorter in the nonsurvivors (a fourth less) and survivors (half), respectively, in our study.

In the present study, the PLR (182.68) was evaluated for an association with mortality in a binary logistic regression model; however, there was no significant difference between the groups.

There were some limitations in this study. Firstly, it was a retrospective study; however, we believe that it provides valuable clinical information for hospital-assessed outcomes of patients with eosinophilic and noneosinophilic exacerbations of COPD. Secondly, the COPD severity and spirometry results were not recorded. However, all patients were previously diagnosed using spirometry results by a pulmonologist in a teaching hospital for chest diseases. All study patients were chronic followed-up patients, and patients were not included from other center and city. Lastly, this study was carried out at a single center. The study center is however the biggest chest teaching hospital in the country (503 beds), and patient numbers could be high enough for an acceptable valuable support to future studies.

In conclusion, this study showed the inflammatory indicators of eosinophilic and neutrophilic AECOPD. If AECOPD has an eosinophilic endotype (i.e., peripheral blood eosinophils>2%), the novel inflammatory markers NLR and PLR are not helpful for follow-up treatment response due to nonsignificant changes during the hospital stay. However, NLR and PLR can be used to follow-up treatment and clinical response in the neutrophilic endotype (i.e., peripheral blood eosinophil ≤2%) of AECOPD. In routine clinical assessment, the treatment choice for AECOPD is made without focusing on the endotype of AECOPD. For patients hospitalized with COPD exacerbation and grouped according to their endotype, i.e., noneosinophilic (eosinophils≤2%) and eosinophilic (eosinophils>2%), clinicians can more effectively plan their treatment regimen. Blood count values can guide the clinician when deciding on antibiotics (infectious attack) or steroids (noninfectious attack). We found a longer LOS in the hospital when steroid therapy was received in cases of infectious exacerbation and when antibiotics were used for inflammatory COPD exacerbations. Distinguishing an infectious or inflammatory exacerbation of COPD can be very simply achieved by checking peripheral blood eosinophil levels, NLR, and even PLR. If the appropriate treatment regimen for COPD exacerbations is carried out, LOS in the hospital may be shorter than 7 days and readmission rates may be decreased.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: The study designed as a retrospective study, hospital electronic database was used, patients' identity information is confidential.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Article

Cryptogenic and Secondary Organizing Pneumonia: Clinical Presentation, Radiological and Laboratory Findings, Treatment, and Prognosis in 56 Cases

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Abstract

OBJECTIVES: Organizing pneumonia is an important disease that is associated with non-specific clinical findings and radiographic appearance. Our aim was to examine the clinical and radiological features, laboratory findings, diagnostic approach, and response to therapy in subjects with cryptogenic (COP) and secondary organizing pneumonia (SOP).

MATERIALS AND METHODS: Patients' medical records were retrospectively reviewed between 2010 and 2016 in our hospital. We analyzed the symptoms, radiological features, pulmonary function tests, laboratory data, bronchoalveolar lavage findings, treatment, and prognosis.

RESULTS: Thirty-seven patients were diagnosed with COP and 19 patients with SOP. The most common causes of SOP were determined as rheumatologic diseases. The most common symptoms were cough (71.4%) and dyspnea (66.1%). Bilateral symmetrical consolidations were the most prominent radiological appearance in both COP and SOP. The general radiographic findings were not different in COP and SOP. However, pulmonary lesions were located rather in the central (p=0.023) and middle (p=0.001) zones in patients with SOP. Corticosteroid (CS) therapy was administered to 34 (60.7%) patients. Two patients showed deterioration despite CS therapy.

CONCLUSION: The clinical and radiographic findings, treatment response, prognosis were similar in patients with COP and SOP.

KEYWORDS: Cryptogenic organizing pneumonia, secondary organizing pneumonia, clinical radiological laboratory features, prognosis

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INTRODUCTION

Organizing pneumonia (OP) is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue. This condition can be cryptogenic OP (COP) or secondary OP (SOP) to other known causes [1].

The bronchiolitis obliterans with OP (BOOP) terminology was abandoned because the main event is OP, and bronchiolitis obliterans is only a minor finding [1]. The presenting symptoms, radiographic findings, and laboratory data are usually non-specific [2]. SOP has a characteristic pathological pattern, but it is associated with known diseases or situations. Some of these entities include connective tissue diseases, infections, malignancies, drugs, radiation, transplantation, and aspiration. COP is diagnosed in the appropriate clinical, radiographic, and pathological setting after excluding situations associated with SOP [3].

The aim of the present study was to examine the etiological factors; clinical, laboratory, and radiological features; treatment response; and prognosis in patients with COP and SOP.

MATERIALS AND METHODS

The medical records of the patients from 2010 to 2016 were retrospectively reviewed. Demographic characteristics, radiological examinations, laboratory data, pulmonary function tests (PFTs), and follow-up data were collected retrospectively through the hospital information management system.

The diagnosis of OP was based on the following criteria:

1. Abnormal chest radiograph and/or thorax high-resolution computed tomography (HRCT) ranging from multiple acinar/nodular shadows,

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2. Histopathologically, the presence of intraluminal fibrotic buds within the alveoli and alveolar ducts with or without bronchiolar involvement and infiltration of chronic inflammatory cells in the alveolar septa with preservation of the alveolar structure,
3. Negative microbiological analysis on bronchoalveolar lavage (BAL) fluid, and
4. A well-documented improvement that was either spontaneous or after exclusive corticosteroid (CS) treatment.

Multidisciplinary approach was used in the diagnosis, treatment, and follow-up of the patients. Patients who were not diagnosed histopathologically were diagnosed according to clinical and radiological features. The diagnosis of OP was supported by the response to CS treatment in these patients. No pathogen was detected in the BAL examination of patients.

PFTs (SensorMedics Vmax Series 20C Respiratory Analyzer; SensorMedics Corp., Yorba Linda, CA, USA) were performed according to the American Thoracic Society guidelines. Arterial blood gases were measured at rest (Radiometer ABL 735 blood gas analyzer; Radiometer, Copenhagen, Denmark).

Fiberoptic bronchoscopy (FOB) (Olympus EVIS LUCERA CV-260; Olympus, Tokyo, Japan) was performed to obtain BAL and transbronchial biopsy (TBB). BAL was applied according to the guidelines. HRCT was used to detect the most affected area. The right middle lobe or lingula was used in the presence of diffuse involvement. At least three aliquots of 40 mL sterile saline at room temperature were instilled through FOB and gently retrieved by mechanical suction. Only the second aliquot was used for BAL analysis [4]. The following technique was used for biopsy. With the bronchoscope in the appropriate segmental bronchus, the forceps, with a biopsy cup of 2×4 mm, is passed into the bronchus and advanced until resistance is met. It is withdrawn at 2 cm, opened, and again advanced until resistance is met. The patient breathes out, and the forceps is closed and withdrawn with the biopsy specimen. After fixation in formol saline, the tissue is prepared by the Millipore filter technique and processed by conventional methods [5].

Table 1. Clinical variants of OP in the study population (n=56)

	Patients	
OP variants	**n**	**%**
COP	37	66.1
SOP	19	33.9
Rheumatoid arthritis	4	7.1
SLE	1	3.6
Sjogren syndrome	3	5.4
Lymphoma	2	3.6
Ovary cancer	1	1.8
Lung cancer	2	3.6
Nasopharynx cancer	1	1.8
Psoriasis	1	1.8
HBV	1	1.8
Stevens-Johnson syndrome	1	1.8
POEMS	1	1.8

OP: organizing pneumonia; COP: cryptogenic organizing pneumonia; SOP: secondary organizing pneumonia; SLE: systemic lupus erythematosus; HBV: hepatitis B virus; POEMS: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes

Patients were evaluated at 1, 3, and 6 months and 1 year of diagnosis and examined in four categories according to their follow-up status: stable, remission, progression, and exitus.

Stable patient was defined as a patient whose symptoms, functional status, and radiological findings remain unchanged. Remission was defined as a patient whose symptoms, functional status, and radiological findings remain recovered. Progression was defined as a patient whose symptoms, functional status, and radiological findings remain worsened.

Approval of the ethics committee was not obtained because the study was designed retrospectively. The authors declare that there is no conflict of interests regarding the publication of this paper.

Statistical Analysis

The SPSS (Statistical Packege for Social Sciences) version 21.0 (IBM Corp.; Armonk, NY, USA) software was used for statistical analysis. Continuous data for normal distribution are expressed as mean±standard deviation (SD). A $p<0.05$ was considered as significant. In descriptive statistics, frequency and percentage were used for discrete data, and mean±SD were used for continuous variables. The normality test was performed by the Kolmogorov-Smirnov and Shapiro-Wilk methods. The Mann-Whitney U test and t-test were used to compare the differences between the groups.

RESULTS

Table 1 shows the clinical types of OP and the associated diseases of SOP. The most common causes of SOP were determined as rheumatologic diseases and malignant diseases, respectively.

Table 2 shows the demographic features and symptoms. The most common symptoms were cough (71.4%), dyspnea (66.1%), and malaise (64.3%). Cough was usually non-productive. Dyspnea lasted from 10 days to 2 years. Both COP and SOP did not differ with regard to demographic findings and symptoms.

X-ray findings included consolidation in 29 (51.8%) patients that was bilateral in 68.0% and unilateral in 32.0% of the patients. Migratory alveolar infiltrates were observed in 8 (14.3%) patients. A diffuse reticulonodular pattern was present in 15 (26.8%) patients and mass-like lesions in 13 (23.2%) patients. There was no difference between the groups in consolidation, migratory infiltration, reticulonodular pattern, and mass-like lesion. The SOP group had more middle zone infiltration ($p=0.025$) and central localization ($p=0.049$) in chest X-ray.

On HRCT scan, a reverse halo sign was not detected in patients. None had honeycomb changes. The distribution of the infiltrates was more frequent in the lower and peripheral

Table 2. Clinical characteristics of patients with COP and SOP

Variable		OP n=56	COP n=37	SOP n=19	p
Age, mean±SD, years		57.09±12.68	57.38±12.04	56.53±14.15	0.789
Age, range, years		28-83	35-83	28-75	-
Male		29 (51.8%)	20 (54.1%)	12 (63.2%)	0.267
Female		27 (48.2%)	17 (45.9%)	7 (36.8%)	
Smoking					
Smokers		33 (58.9%)	22 (59.5%)	11 (57.9%)	0.775
Non-smokers		21 (37.5%)	13 (35.1%)	8 (42.1%)	
Missing data		2 (3.6%)	2 (5.4%)	0 (0%)	
Antibiotic use	Yes	31 (55.4%)	20 (54.1%)	11 (57.9%)	0.948
Before diagnosis	No	22 (44.6%)	14 (37.8%)	8 (42.1%)	
Cough	Yes	40 (71.4%)	25 (67.6%)	15 (78.9%)	0.747
	No	14 (25.0%)	10 (27%)	4 (21.1%)	
Sputum	Yes	20 (35.7%)	12 (32.4%)	8 (42.1%)	0.769
	No	34 (60.7%)	23 (62.2%)	11 (57.9%)	
Hemoptysis	Yes	4 (7.1%)	3 (8.1%)	1 (5.3%)	0.657
	No	47 (83.9%)	20 (81.1%)	17 (89.5%)	
Dyspnea	Yes	37 (66.1%)	23 (62.2%)	14 (73.7%)	0.760
	No	17 (30.4%)	12 (32.4%)	5 (26.3%)	
Fever	Yes	24 (42.9%)	16 (43.2%)	8 (42.1%)	0.775
	No	28 (50.0%)	17 (45.9%)	11 (57.9%)	
Chest pain	Yes	7 (12.5%)	5 (13.5%)	2 (10.5%)	1.000
	No	46 (82.1%)	30 (81.1%)	16 (84.2%)	
Loss of appetite	Yes	25 (44.6%)	16 (43.2%)	9 (47.4%)	0.939
	No	27 (48.2%)	17 (45.9%)	10 (52.6%)	
Malaise	Yes	36 (64.3%)	24 (64.9%)	12 (63.2%)	0.541
	No	16 (28.6%)	9 (24.3%)	7 (36.8%)	
Weight loss	Yes	14 (25.0%)	8 (21.6%)	6 (31.6%)	0.515
	No	39 (69.6%)	27 (73.0%)	12 (63.2%)	
Crackles	Yes	31 (55.4%)	20 (54.1%)	11 (57.9%)	0.869
	No	24 (42.9%)	16 (43.2%)	8 (42.1%)	
Wheezing	Yes	2 (3.6%)	2 (5.4%)	0 (0%)	0.539
	No	53 (94.6%)	34 (91.9%)	19 (100%)	
Clubbing	Yes	1 (1.8%)	0 (0%)	1 (5.3%)	0.333
	No	53 (94.6%)	37 (100%)	17 (89.5%)	
Cyanosis	Yes	5 (8.9%)	2 (5.4%)	3 (15.8%)	0.327
	No	50 (89.3%)	34 (91.9%)	16 (84.2%)	
Bronchial breath sounds	Yes	2 (3.6%)	2 (5.4%)	0 (0%)	0.539
	No	53 (94.6%)	34 (91.9%)	19 (100%)	
NPEF	Yes	23 (41.1%)	15 (40.5%)	8 (42.1%)	0.975
	No	32 (57.1%)	21 (56.8%)	11 (57.9%)	

COP: cryptogenic organizing pneumonia; SOP: secondary organizing pneumonia; NPEF: normal physical examination findings

zones. Middle zone involvement (p=0.001) and central localization (p=0.023) in the SOP group were significantly higher than those in the COP group (Table 3).

Erythrocyte sedimentation rate (ESR) was >20 mm/h in 38 (67.8%) patients. The mean C-reactive protein (CRP) level in the total patient population was 34.5±32.6 mg/L. There was no difference between the groups in CRP levels (p=0.868). The leukocyte count was >10,000/mm^3 in 18 (32.1%) patients. A slight eosinophilia was observed in 18 (32.1%) patients. There was no difference between the groups with regard to laboratory parameters (Table 4).

Table 3. CT scan and HRCT findings in 56 patients with COP and SOP

Variable		OP n=56	COP n=37	SOP n=19	p
Distribution					
Upper zone	Yes	16 (28.6)	12 (32.4)	4 (21.1)	0.365
	No	38 (67.9)	23 (62.2)	15 (78.9)	
Middle zone	Yes	23 (41.1)	9 (24.3)	14 (73.7)	0.001
	No	31 (55.4)	26 (70.3)	5 (26.3)	
Lower zone	Yes	38 (67.9)	26 (70.3)	12 (63.2)	0.534
	No	16 (28.6)	9 (24.3)	7 (36.8)	
Peripheral distribution	Yes	35 (62.5)	22 (59.5)	13 (68.4)	0.771
	No	19 (33.9)	13 (35.1)	6 (31.6)	
Central distribution	Yes	25 (44.6)	12 (32.4)	13 (68.4)	0.023
	No	29 (51.8)	23 (62.2)	6 (31.6)	
Bilateral alveolar	Yes	31 (55.4)	20 (54.1)	11 (57.9)	0.958
	No	23 (41.1)	15 (40.5)	8 (42.1)	
Reticular	Yes	15 (26.8)	8 (21.6)	7 (36.8)	0.345
	No	39 (69.6)	27 (73.0)	12 (63.2)	
Mass-like lesion	Yes	13 (23.2)	9 (24.3)	4 (21.1)	0.705
	No	41 (73.2)	26 (70.3)	15 (78.9)	
Cavitation	Yes	2 (3.6)	0 (0)	2 (10.5)	0.053
	No	52 (92.9)	35 (94.6)	17 (89.5)	
Migratory lesions	Yes	8 (14.3)	4 (10.8)	4 (21.1)	0.431
	No	46 (82.1)	31 (83.8)	15 (78.9)	

Table 4. Laboratory data in patients with COP and SOP

Variable (no. of COP/SOP)	OP±SD	COP±SD	SOP±SD	p
WBC, 10^3/mL (26/14)	7.960±2.631	6.959±4.449	6.959±4.449	0.207
Hb, g/dL (26/14)	12.8±1.86	12.61±1.91	13.16±1.76	0.309
Plt, 10^3/mL (26/14)	270.0±1.48	295.45±1.39	223.00±1.57	0.089
ESR, mm/h (26/14)	48.97±37.71	50.56±40.05	45.95±33.65	0.666
CRP, mg/dL (26/14)	34.57±24.56	35.32±23.24	33.20±28.40	0.868
Eosinophilia, % (26/14)	2.8±1.4	3.38±2.48	1.75±1.70	0.178
ANA	3/56	0/37	3/19	-
Anti-dsDNA	2/39	0/37	2/19	-
RA	2/39	0/37	2/19	-
ANCA	1/39	0/37	1/19	-
Anti-Ro	3/39	0/37	3/19	-
Anti-La	2/39	0/37	2/19	-
Viral hepatitis markers	3/40	1/37	2/19	-

SD: standard deviation; WBC: white blood cell; Hb: hemoglobin; Plt: platelet; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibody; RA: rheumatoid arthritis; ANCA: antineutrophil cytoplasmic antibody

PFT was available for 49 patients, and diffusion capacity for carbon monoxide (DLCO) test was available for 43 patients (Table 5). Eleven (22.4%) patients had pure-restrictive defect, and 7 (14.3%) patients had obstructive defects. DLCO was reduced (<60%) in 15 (34.9%) of 43 patients. Normal PFT was determined in 30 (61.2%) of 49 patients (Table 5).

BAL analysis was completed in 38 (67.8%) patients. Neutrophilia >5% in BAL fluid was observed in 20 (52.6%) patients. The BAL neutrophil count was higher in the SOP group than in the COP group (16.85±5.35% vs 5.71±5.01) (p=0.044). Lymphocytes were 28.6% of the total cells. A lymphocytosis of >25% was identified in 12 (31.6%) patients. There was no difference between the groups in terms of spirometric mea-

Table 5. PFTs and BAL findings in patients with COP and SOP

Variable (no. of COP/SOP)	OP±SD	COP±SD	SOP±SD	p
FEV_1, % (32/17)	82.77±19.32	81.50±20.21	85.18±17.88	0.526
FVC, % (32/17)	86.11±18.59	83.76±19.55	90.12±16.63	0.263
FEV_1/FVC, % (32/17)	77.81±9.06	76.65±8.97	80.06±9.07	0.220
DLCO, % (26/17)	67.73±13.98	68.11±13.29	67.06±15.56	0.817
DL ADJ, % (26/17)	68.79±14.84	69.24±13.76	68.00±17.13	0.802
DLCO/VA, % (26/17)	80.18±13.60	77.44±13.34	85.07±13.12	0.093
DL/ADJ/VA, % (26/17)	80.31±14.57	78.28±14.36	84.23±14.73	0.232
Lymphocytes (mean±SD) (24/14)	17.52±16.42	16.58±14.85	19.15±19.03	0.643
Lymphocytes (>20% of total BAL cells, n) (24/14)	16 (28.6%)	10 (41.67%)	6 (42.86%)	1.000
Neutrophils (mean±SD) (25/14)	9.52±6.16	5.71±5.01	16.85±5.35	0.044
Neutrophils (>5% of total BAL cells) (25/14)	19 (33.91%)	12 (50%)	7 (50%)	1.000
Eosinophils (mean±SD) (25/14)	4.68±4.63	5.48±4.18	3.15±2.35	0.305
Eosinophils (>2% of total BAL cells) (25/14)	14 (25%)	10 (41.67%)	4 (28.57%)	1.000
Macrophages, % (25/14)	51.68±26.66	57.24±26.05	41.00±25.41	0.075

DLCO: diffusion capacity for carbon monoxide; DL ADJ, DLCO adjusted for hemoglobin; DLCO/VA, DL (CO) to alveolar ventilation (DLCO/VA)

surement and eosinophil and lymphocyte counts. Table 5 shows the other BAL findings.

Thirteen (23.2%) patients were diagnosed with OP (COP: 8 (14.3%) patients and SOP: 5 (8.9%) patients) clinically and radiologically, after exclusion of all other possible etiologies. Clinical and radiological improvement in patients using corticosteroid (CS) treatment with OP pre-diagnosis supported the diagnosis of OP. Twenty-four (42.9%) patients were diagnosed with OP (COP: 17 (30.4%) patients and SOP: 7 (12.5%) patients) using TBB. Seventeen (30.4%) patients were diagnosed with OP (COP: 10 patients and SOP: 7 patients) using video-assisted thoracoscopy (VATS). Two (3.6%) patients were diagnosed with COP using CT-guided percutaneous transthoracic needle biopsy (PTNB).

Oral CS was administered to 37.5% (n=21) of the patients with COP and 23.2% (n=13) of the patients with SOP. Eight (14.3%) patients were not treated because of the lack of specific symptoms or functional and physical limitations. In addition, 6 (10.7%) patients (4 (7.1%) with COP and 2 (3.6%) with SOP) underwent surgery for removal of a solitary pulmonary nodule due to suspected carcinoma. Treatment of patients with COP and SOP was similar.

In-hospital mortality and a 1-year mortality in patients with OP were 2.5% and 0%, respectively. One patient (who had SOP-Hodgkin lymphoma) who used CS treatment had a rapidly progressive respiratory failure requiring mechanical ventilation; the patient died.

Overall, 34 patients underwent CS therapy. Table 6 shows the information about the prognosis of the disease at 1, 3, and 6 months and 1 year of follow-up of the patients. Eight patients were followed up without any treatment, and 5 patients were treated surgically. Table 6 shows the features of these patients.

The response to CS treatment was not different between those with lymphocyte dominance and those with neutrophil dominance (p=0.6). However, the response to CS treatment was different between those with ground glass opacity and those without ground glass opacity patterns in high resolution computed tomography (HRCT) (p=0.002). In the ground glass opacity group, 9 of the patients with CS therapy at 3 months were in remission, and 12 at 6 months were in remission. However, none of the patients without ground glass opacity in HRCT were in remission at 3 months of CS treatment, and 3 were in remission at 6 months.

DISCUSSION

The classification of OP is very important because the treatment and follow-up of patients with SOP include not only the treatment of OP but also the management of underlying diseases. The most common causes of SOP include drugs, infections, rheumatologic diseases, malignancies, and their treatments [6]. In our study, 37 patients were COP, and 19 were SOP. Rheumatologic diseases and malignancies were the most common causes of SOP.

OP is most common in the 5-6 decades of life [7,8]. In our study, patients were between 28 and 83 (mean age: 57.09±12.68) years. Studies that examined the distribution of patients with COP and SOP according to gender have shown no significant difference between the two groups [6,8]. Our results were similar to previous studies.

The association of smoking with OP has been controversial [9]. In our study, 58.9% of all patients had a smoking background, and there was no statistically significant difference between COP and SOP (p=0.775). These results were similar to studies by Sveinsson [6] and Drakopanagiotakis [2]. In the study by Lazor et al. [9], 71% of the patients were non-smokers, and most of the patients who were non-smokers were women. Researchers thought that smoking could be protective against COP development in women [9].

Table 6. Prognosis for patients

	Values (no. of treatment/total patients)	n	%
Prognosis for patient on corticosteroid treatment	1 month (27/34) (missing data=7)		
	Stable	27	79.4
	3 months (26/34) (missing data=1)		
	Stable	17	65.4
	Remission	8	30.8
	Progression	1	3.8
	6 months (21/34) (missing data=5)		
	Stable	6	28.6
	Remission	13	61.8
	Progression	1	4.8
	Exitus	1	4.8
	1 year (19/34) (missing data=2)		
	Stable	2	10.5
	Remission	17	89.5
	Progression	-	-
Prognosis for patient on no treatment	1 month (8/56)		
	Stable	8	100
	3 months (8/56)		
	Stable	7	87.5
	Remission	1	12.5
	6 months (8/56)		
	Stable	2	25
	Remission	6	75
	1 year (8/56)		
	Remission	8	100
Prognosis for patient on surgical treatment	1 month (6/56)		
	Remission	5	83.3
	Missing data	1	16.7
	3 months (5/56)		
	Remission	4	83.3
	Missing data	1	16.7
	6 months (4/56)		
	Remission	4	100
	1 year (4/56)		
	Remission	4	100

OP is characterized by non-specific symptoms, such as flu-like illness [10-13]. Most of our patients had flu-like symptoms. Non-specific symptoms of malaise, cough, fever, and dyspnea occurred in more than two-thirds of the patients [9,14]. Hemoptysis was previously described to be uncommon in many studies. The hemoptysis rate in our patients was 7.1%. Our results were similar to previous studies [8,15,16]. Hemoptysis could occur as a result of underlying diseases, such as malignancies but not OP.

The most common radiological findings in patients with OP are consolidation and ground glass opacities, and these are usually bilateral-peripheral [1]. Our findings were consistent with the literature; however, centrally located lesions were more frequent in SOP than in COP (p=0.023). A previous study showed a predominance of lesions in the lower lung areas in 55% of the patients [1]. Another study showed a predominance of lesions in the middle zone in 91.7% of the patients [7]. We detected involvement in the lower lobes in the general patient population, but the most common middle lobe was affected in SOP (p=0.001). Only 14.3% of the cases had migratory infiltrates. This number is significantly lower than previous reports [13,17]. Although a solitary opacity is an uncommon presentation in OP that is known as focal OP, and 10%-15% of the patients are focal OP [15]. We found 23.4% of mass-like lesions.

An elevated ESR was common in patients. This was similar to previous studies [1,14,18,19]. The majority of cases have been reported to have elevated CRP [20]. The cause of elevated acute phase reactants (APRs; such as CRP and ESR) in patients with OP is not well known. Elevated APRs have been defined in several studies. However, no explanation was given as reason [6,20]. APRs are synthesized from liver cells during inflammation, most often with the effect of cytokines (especially interleukin 6). They are elevated in acute infections and autoimmune, rheumatologic, and granulomatous diseases and are used in the course of active disease [21,22]. Previous studies have shown increased inflammatory cytokines in OP [23,24]. APRs may be elevated by the increase of cytokine in OP. In addition, most of the known causes of SOP are associated with acute inflammation. It is thought that elevated APRs may develop secondary to these diseases.

OP normally presents a restrictive pattern on PFT [25]. However, our results and the study by Kavakli et al. [26] differed from previous studies. In the study by Kavakli et al. [26], normal PFT was detected in 58% of the patients, and we observed normal PFT in 33 (58.9%) patients. Nine (16.1%) of our cases had isolated restrictive defects. The mechanism of the restrictive pattern in OP is not well established yet.

BAL examination usually shows expansion of all cell lines [27]. In the study by Drakopanagiotakis et al. [2], BAL was performed in 32 of 61 patients. In 43% of the 32 patients, BAL lymphocyte was found >20%. However, in the present study, there were 21 patients in the SOP group, and only 5 had BAL lymphocyte. Of these 5 patients, 4 (80%) had a BAL lymphocyte level >20%. Possibly, the rates could have changed if there were more patients whose BAL lymphocyte levels were examined in the SOP group. In our study, a significant part of patients with SOP had BAL neutrophilia, and this was statistically significant (p=0.044). These findings were inconsistent with previous studies [1,6]. Costabel et al. [27] analyzed BAL findings in 10 patients with BOOP syndrome. All 10 of them had lymphocytosis >20%, 8 (80%) exhibited neutrophilia (>5%), and 5 (50%) exhibited eosinophilia (>5%). There have been almost no explanation about the cause of the cellular distribution in previous studies.

Open lung biopsy, VATS, and CT-guided PTNB are preferred in the diagnosis of OP, whereas TBB often fails to obtain a large and adequate piece of lung tissue [28]. However, by the proper clinical and radiographic findings, TBB and BAL may be diagnosed with OP [1,27]. Moreover, OP can be diagnosed by clinical findings and compatible imaging (especially in patients who are too frail) [1]. Cazzato et al. [29] investigated the clinical and radiological features at onset, outcome, and diagnostic approach in subjects with OP. They found that although clinical and radiological findings usually suggest the diagnosis, a definitive confirmation requires TBB and BAL. In our study, 13 (23%) patients were diagnosed with OP by clinical and radiological findings. Of these patients, 10 were >65 years old, and the patients did not accept TBB or VATS. TBB has been used for diagnosis in many studies [1,14,29,30]. According to Cazzato et al. [29], from a diagnostic perspective, TBB (together with BAL) should be the first diagnostic step. They diagnosed 74% of the patients with TBB and determined that although the sensitivity of BAL was found to be lower than that of TBB, the combination of the two procedures improved the diagnostic yield (sensitivity 86%) [29]. In our study, approximately 43% of the patients had pathological diagnosis by TBB.

VATS allow biopsy of the lung in well conditions of security. Currently, VATS is a safe procedure that may be used in many patients [30]. Seventeen (30%) patients were diagnosed by VATS.

Two patients were diagnosed by CT-guided PTNB. These patients had peripheral located consolidation in thorax CT. PTNB is a rare diagnostic method in the literature [26].

There are no sufficient studies available to make recommendation CS, and length of treatment is not known [6]. In accordance with previous studies, we applied CS treatment to most of our patients (34 of 56 patients) [1,7]. Of the patients who were followed up for 1 year, 89% were fully recovered with CS therapy. Only one patient relapsed, and one patient died. All patients with focal lesions underwent surgery for both diagnosis and treatment, and there was no relapse in any patient. Relapses were frequently reported in the literature, but in our patients, it was negligible. However, approximately half of our patients were lost during follow-up.

The response to CS treatment has not been evaluated in subgroups, such as neutrophil predominance group and lymphocyte predominance group, in HRCT pattern in previous studies [6,7]. These subgroups were evaluated in our study. We found that in patients with ground glass opacity in HRCT, the response to CS treatment is better. Ground glass opacities also respond better to CS treatment in other interstitial lung diseases. However, we do not know how to respond to CS treatment in nodular OP because these patients are usually patients with surgical resection with malignancy pre-diagnosis and did not use CS therapy.

In conclusion, the clinical and radiological findings in patients with both COP and SOP are similar. The most common complaints were cough and dyspnea. The most common radiological appearance was peripheral consolidation area. Lesions tended to predilect the central part of the middle zone in SOP. COP and SOP have similar treatment response and prognosis.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

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Original Article

Current Statement of Intensive Care Units in Turkey: Data obtained from 67 Centers

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Abstract

OBJECTIVES: We aimed to obtain information about the characteristics of the ICUs in our country via a point prevalence study.

MATERIAL AND METHODS: This cross-sectional study was planned by the Respiratory Failure and Intensive Care Assembly of Turkish Thoracic Society. A questionnaire was prepared and invitations were sent from the association's communication channels to reach the whole country. Data were collected through all participating intensivists between the October 26, 2016 at 08:00 and October 27, 2016 at 08:00.

RESULTS: Data were collected from the 67 centers. Overall, 76.1% of the ICUs were managed with a closed system. In total, 35.8% (n=24) of ICUs were levels of care (LOC) 2 and 64.2% (n=43) were LOC 3. The median total numbers of ICU beds, LOC 2, and LOC 3 beds were 12 (8-23), 14 (10-25), and 12 (8-20), respectively. The median number of ventilators was 12 (7-21) and that of ventilators with non-invasive ventilation mode was 11 (6-20). The median numbers of patients per physician during day and night were 3.9 (2.3-8) and 13 (9-23), respectively. The median number of patients per nurse was 2.5 (2-3.1); 88.1% of the nurses were certified by national certification corporation.

CONCLUSION: In terms of the number of staff, there is a need for specialist physicians, especially during the night and nurses in our country. It was thought that the number of ICU-certified nurses was comparatively sufficient, yet the target was supposed to be 100% for this rate.

KEYWORDS: Intensive care unit, point prevalence, survey

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INTRODUCTION

The intensive care unit (ICU) is a special and separately staffed and equipped self-contained area of a hospital dedicated to the management of patients with life-threatening illnesses, injuries, and complications and monitoring of potentially life-threatening conditions. Critical care is provided in these specialized units with sophisticated equipment and educated staff and for this reason staff to patient ratio is very important for the care of these kind of patients with multiple organ failure [1-4]. The aims of an ICU are both to monitor and support the impaired and failed vital functions in critically ill patients with illnesses exhibiting a potential threat to life to perform adequate diagnostic measures and medical or surgical therapies to improve the outcome [2]. The characteristics of ICUs show variability at different centers worldwide. This variability is influenced by factors such as hospital characteristics, levels of staff training, and economic and political factors [5]. Although we have strict quality criteria as determined by the Ministry of Health for all types of care [4], structural, technical, and personal differences still occur. There are various types of hospitals in Turkey such as university, training, and research, and state or private hospitals. In some centers, there are multiple ICUs in the same or different locations of the hospital. Therefore, as the Respiratory Failure and Intensive Care Assembly of the Turkish Thoracic Society (TTS), we planned a 1-day point prevalence study to obtain information about the characteristics of different types of ICUs in our country.

METHODS

The study was cross-sectional. Data were obtained by a survey that was shared with several communication channels (e-mail/social interaction platforms) with the members of the TTS who were actually working in an ICU. The survey included

61 questions (Figure 1) about the unit's physical infrastructures, technical possibilities, applicable interventional procedures, properties of staff, and working conditions of the unit. The type of the ICU, the levels of care (LOC), the number of hospital and ICU beds, the ICU working system, and the total number of ventilator and transport ventilators were asked in the survey. In addition, information about the number of physicians and nurses during the day and night (total and per patient) was obtained. The diagnostic and therapeutic facilities of the units including hemodialysis, echocardiography, and fiberoptic bronchoscopy (FOB) were recorded. The study was performed between October 26, 2016 at 08:00 and October 27, 2016 at 08:00. Data were collected via post or online from each center. Ethics Committee Approval was obtained from the Ethics Committee for Non-invasive Researches of Çukurova University School of Medicine on October 7, 2016 (number 57). Each participant was informed by e-mail and there was no need informed consent.

Statistical Analysis

Descriptive analysis was used to define the characteristics of the centers. The statistical analyses were conducted using the SPSS (Statistical Package for the Social Sciences) version 21.0 (IBM Corp.; Armonk, NY, USA). Continuous data were expressed as medians with 25^{th}-75^{th} percentiles and compared with data from the Mann-Whitney U test. Categorical data were expressed as numbers with percentages and compared with data from the Fisher's exact test. A $p<0.05$ was considered as statistically significant.

Table 1. General physical characteristics of ICUs

	Median	25%-75%
No. of hospital beds, n	600	400-1000
No. of ICU beds, n	12	8-23
No. of active ICU beds	11	6-21
No. of ventilators	12	7-21
No. of NIV mode (+)	11	6-20

ICU: intensive care unit; NIV: non-invasive ventilation

Table 2. Characteristics of ICUs according to the levels of care

	Level 2 ICU n=24	Level 3 ICU n=43	p
No. of hospital beds	488 (350-600)	750 (460-1009)	0.009
No. of ICU beds	14 (10-25)	12 (8-20)	0.31
No. of full beds	12 (8-21)	11 (7-20)	0.53
No. of doctors	3 (1-4)	4 (2-7)	0.018
No. of patients per doctor during the day	8 (3.2-11.7)	3.1 (2-6)	0.002
No. of patients per doctor during the night	14 (8-25)	13 (9-19)	0.72
No. of certified nurses	6 (2-10)	5 (2-8)	0.641
No. of patients per nurse during the day	3 (2.5-3)	2.5 (2-3.1)	0.206
No. of patients per nurse during the night	3 (3-3.3)	3 (2.5-3.3)	0.488
No. of allied health personnel during the day	3 (2-4)	4 (2-6)	0.044
No. of allied health personnel during the night	2 (1-3)	2 (1-3)	0.59

ICU: intensive care unit

RESULTS

In total, 77 centers replied to the invitation of the study. However, ten of them were excluded because of their unavailability on the study day. Overall, data were collected from 67 centers. Most of the ICUs were located in the university hospitals and training and research hospitals (n=29, 43% and n=22, 33%, respectively) (Figure 2). General (n=21, 31.3%), medical (n=18, 26.9%), and respiratory ICUs (n=15, 22%) were the main units that participated in the study (Figure 3). Most of the units were managed in a closed system (76.1% vs. 23.9%). Intensive care specialists existed in 23 out of the 67 (34.3%) centers, mostly in training hospitals. There was at least one specialist on duty in 47 out of the 67 (70.1%) centers.

Table 1 shows the general physical conditions in the ICUs. The median numbers of hospital beds and ICU beds were 600 (400-1000) and 12 (8-23), respectively. According to the LOC, 35.8% (n=24) of the centers were LOC 2 and 64.2% (n=43) were LOC 3. The median numbers of beds in LOC 2 and LOC 3 were 14 (10-25) and 12 (8-20), respectively. At the relevant date, the bed occupancy rate was 88%. The median numbers of ventilators and non-invasive ventilation modes were 12 (7-21) and 11 (6-20), respectively. Transport ventilator was present in 58 centers (86.6%). A total of 80.6% of the units had at least one isolation room with a median number of 2 (1-4), and 26.9% had a room with negative pressure. Hemodialysis was the most commonly available therapeutic technique (85.1%) followed by FOB (71.6%) (Figure 4).

Figure 5 shows the distribution of physicians in different hospitals. Other physicians such as those practicing internal medicine and chest physicians were present in other hospitals, whereas only an anesthesiologist existed in private hospitals.

There was no significant difference between LOC 2 and LOC 3 ICUs in terms of the median number of physicians (n=3 (1-4) vs. n=4 (2-7), p=0.018). Among LOC, there was a significant difference in the number of patients per doctor during the day (8 (3.5-11.7) vs. 3.1 (2-6), p=0.003), whereas there was no difference during the night (14 (8-25) vs. 13 (9-19), p=0.63) between LOC 2 and LOC 3.

The National Certification Corporation (NCC) certificated nurse rate was 88.1%, and there was no statistical difference between LOC 2 and LOC 3 ICUs (n=6 (2-10) vs. n=5 (2-8), p=0.641). The number of patients per nurse during the day and night in both the levels of ICUs was insignificant (n=3 (2.5-3) and n=2.5 (2-3.1), p=0.206 vs. n=3 (3-3.3) and n=3 (2.5-3.3), p=0.488). There was a statistical difference between LOC 2 and LOC 3 ICUs in the median number of patients per allied health personnel during the day (n=3 (2-4) vs.

1. Institution / Hospital name:
2. ICU type: General Internal Surgical Respiratory Anesthesia and reanimation Other :
3. Total number of beds in your hospital:
4. Total number of beds in your ICU and level:
5. Number of active beds used in your ICU:
6. Number of inpatient in your ICU at the time of the study:
7. Number of patients discharged from ICU at the relevant date:
8. Number of died patients in your ICU at the relevant date:
9. ICU working system: OPEN ☐ CLOSED ☐
10. Number of full bed at the time of the study:
11. Number of isolation room:
12. Is there negative pressure room? YES ☐ NO ☐
13. Number of negative pressure room:
14. Total number of active ventilator in your ICU:
15. If there is number of ventilator with NIV mod:
16. Is there transport ventilator? YES ☐ NO ☐
17. Number of doctor in your ICU during working hours:
18. The number and type of physicians involved:
19. Are the doctors a specialist or an intensive care specialist?
20. Do you have a specialist doctor on duty? YES ☐ NO ☐
21. What is the number the specialist doctor on duty ?
22. Is there an on call guard in your ICU?
23. Total number of physicians per bed in working hours in your ICU:
24. Total number of physicians per bed in during night in your ICU:
25. Total number of nurses per bed during day in your ICU:
26. Total number of nurses per bed during night in your ICU:
27. Number of certified nurse in your ICU:
28. Total number of assistant health staff during day in your ICU:
29. Total number of assistant health staff during night in your ICU:
30. Do you use hemodialysis in your ICU? YES ☐ NO ☐
31. If applicable, number of hemodialysis at the relevant date:
32. Do you have continue veno-venous hemodiafiltration in your ICU? YES ☐ NO ☐
33. If applicable, the number of venous venous hemodiafiltration:
34. Is plasmapheresis applied to your intensive care unit? YES ☐ NO ☐
35. If applicable, the number of plasmapheresis:
36. Do you have ECMO in your ICU? YES ☐ NO ☐
37. If applicable, the number of ECMO:
38. Do you have echocardiography in your ICU? YES ☐ NO ☐
39. If there is, the number of case that performed echocardiography:
40. Do you have ultrasound in your ICU? YES ☐ NO ☐
41. Do you have bronchoscopy? YES ☐ NO ☐
42. If applicable, the number of bronchoscopy:
43. What are the reasons for bronchoscopy;
44. The number of tracheotomy in your ICU:
45. Which method was used for tracheotomy PERCUTANOUS ☐ SURGICAL ☐
46. The branch of the physician who opens the tracheostomy: INTENSIVE CARE SPECIALIST/FELLOW ☐ OTHER ☐
47. The reason for the opening of the tracheostomy:
48. Number of patients who underwent weaning test on the day of your ICU:
49. Number of successful weaning patients in your ICU on the study day:
50. Number of extubated patients in your ICU on the study day:
51. Is PICCO applied in your intensive care unit? YES ☐ NO ☐
52. Number of cases applied to PICCO at the relevant date:
53. Is hypothermia applied in your ICU? YES ☐ NO ☐
54. Number of cases and reasons for hypothermia on the study day:
55. Are the liver support systems avaliable in your ICU? YES ☐ NO ☐
56. Number of cases in which the liver support system was applied at the relevant date:
57. Is physiotheraphy applied in your ICU? YES ☐ NO ☐
58. Number of physiotherapist:
59. Number of cases under physiotherapy on the study day:
60. Is high-flow oxygen therapy applied in your intensive care unit?
61. If yes, the number of cases applied at the relevant date:

Figure 1. Survey form

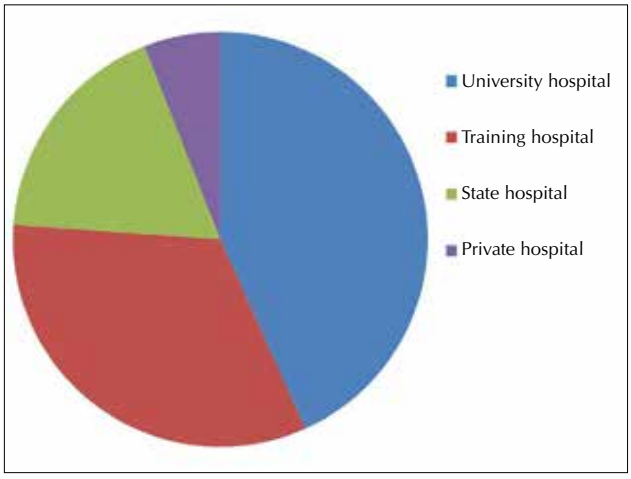

Figure 2. Types of hospitals

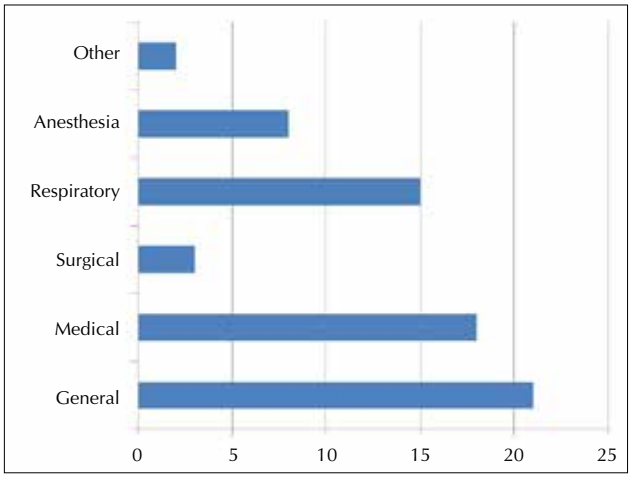

Figure 3. Types of ICU

n=4 (2-6), p=0.044), whereas there was no difference during the night (n=2 (1-3) vs. n=2 (1-3), p=0.59) (Table 2). Overall, 77.6% of the ICUs had a physiotherapist, and there was no statistical difference in the median number of physiotherapists in both levels of ICUs (n=1 (1-2) vs. n=1 (1-2), p=0.83).

DISCUSSION

This is the first national survey to evaluate the characteristics of ICUs in Turkey. We have shown that ICUs in Turkey have a great variability in terms of physical, technical, and staffing conditions. A significant number of ICUs still require technical and staff support to improve health care services. The bed occupancy rate was relatively high compared with that in the literature (70%-75%) [6].

In our study, most of the centers (76.1%) were managed in a closed system according to the modern literature, indicating favorable outcomes [5]. In a closed system ICU, patients are believed to have better care, and this is associated with improved outcomes and a more efficient use of ICU resources [7].

The number of staff required was quite variable in our survey. The number of staff could be calculated by taking into account several factors including the number of beds, occupancy rate, LOC, and clinical, research, and teaching workload.

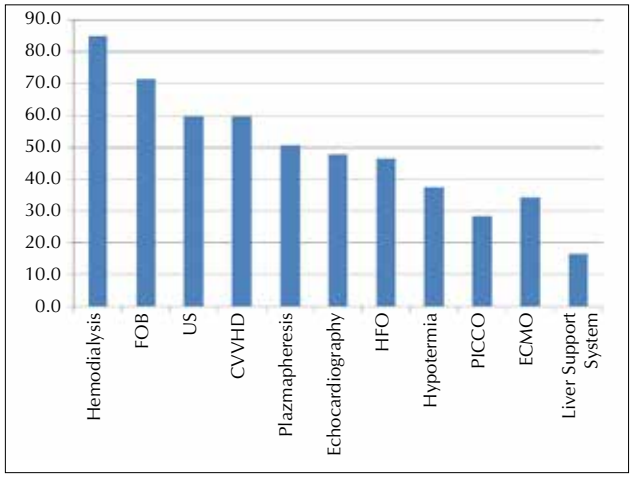

Figure 4. Technical opportunities and implemented interventional procedures in ICUs
FOB: fiberoptic bronchoscopy; US: ultrasound; HFO: high flow oxygen; CVVHD: continuous venovenous hemodialysis; ECMO: extracorporeal membrane oxygenation

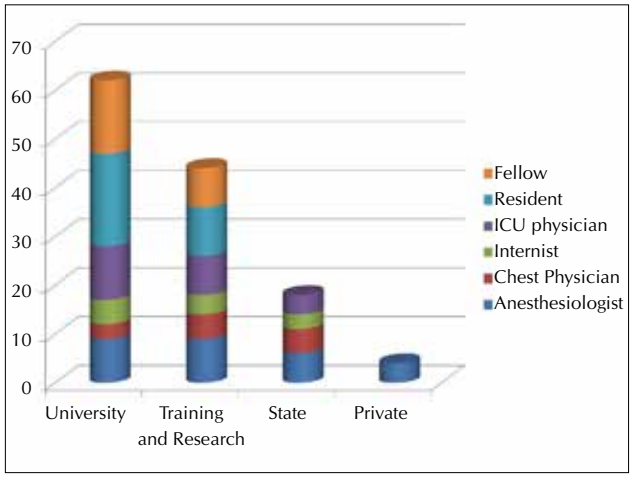

Figure 5. Characteristics of physicians in different hospitals

However, it should be emphasized that an ICU is a 24-hour and 7-day continuous working unit with high LOC. According to several studies, an ICU should accommodate a minimum of at least six beds with 8-12 beds considered as the maximum number [2,8-11]. The Ministry of Health of Turkey recommends at least four beds for LOC 2 and 6 beds for LOC 3 in our country [4]. In the present study, the median numbers of ICU beds were 12 (8-23) in all ICUs, 14 (10-25) in LOC 2, and 12 (8-20) in LOC 3. Over the years, critical care medicine has evolved in terms of structure, process, and outcome in many countries. During that time, unlike a decrease in the total number of hospital beds, the number of ICU beds has increased [9,12]. For every 100 hospital beds, 1-4 ICU beds are recommended [1]. As a matter of fact, the ratio of the number of ICU beds to hospital beds was suggested as 5%-10% [2,8,10,11,13]. In this study group, this ratio was found to be 2%, which is lower than recommended. LOC 2 represents patients requiring monitoring and pharmacological and/or device-related support for only one acutely failing vital organ system with a life-threatening character. LOC 3 represents patients with multiple (two or more) acute vital organ failure with an immediate life-threatening character. These patients depend on pharmacological and device-related organ sup-

port such as hemodynamic support, respiratory assistance, or renal replacement therapy [14-16]. In the present study, most of the ICUs (n=43, 64.2%) were LOC 3, and the bed occupancy rate was 88% at the time of the study.

In many studies, there is paucity of conclusive data about ICU physician staffing. Although most people agree on the idea that intensivists should provide care for critically ill patients, the optimal intensivist/patient ratio is unknown [17]. The intensivist/patient ratio is likely to be influenced by several factors such as the patients' acute severity of illness and comorbidity, case mix, available human support, and non-human resources. In a study conducted, the impact of intensivist/bed ratio (1 to 7.5, 9.5, 12, and 15) was evaluated, and there was no statistically significant difference in mortality among the four groups. However, a 1/15 intensivist/bed ratio was associated with a longer ICU length of stay. Although no specific ratio was stated, a higher numbers of patients per intensivist may have some negative impacts on patient care and should be avoided [18]. In the present study, the number of patients per physician was compatible in LOC 2 ICUs, whereas the same was incompatible in LOC 3 ICUs during the day and night, showing heterogeneity between the units.

The number of ICU nurses necessary to provide appropriate care and observation is calculated according to the LOC in the ICU [2,6,19]. Many aspects of staffing may differ across ICUs and are fundamental to the definition of an ICU bed in some regions. One of the standards for critical care nursing concerns the nurse to patient ratio [3,20]. It is notable that adverse patient outcomes have been associated with more patients per nurse, including complication rates, length of stay, and even risk-adjusted mortality [21]. Some studies suggested that there is an association between nurse staffing and hospital-acquired pneumonia, sepsis, shock, cardiac arrest, longer than expected length of stay, and mortality [22,23]. The literature documents the nurse to patient ratios as ranging from 1/1 to 1/4 for care of critically ill patients [3]. According to the standards of the Australian College of Critical Care Nurses and the British Association of Critical Care Nurses, a 1/1 ratio is recommended for patients receiving mechanical ventilation [24,25]. Recent comprehensive literature reviews have further validated the relationship between ICU nurse staffing and patient outcomes, confirming that a higher level of registered nursing staff to patient ratio (1/1 or 1/2) relates to the improved safety and better outcomes for patients [26]. The Ministry of Health of Turkey sets the standard nurse to patient ratio as 1/3 for LOC 2 and 1/2 for LOC 3 [4]. In the present study, this ratio was not found to be compatible in LOC 3 ICUs for the day and night. Although the NCC certified nurse rate was relatively high in the study, the ideal number should be 100%; therefore, the certification programs and education of the nurses should be continued.

The present study has several limitations. First, this was a cross-sectional study that only shows the results of one day. Although it can be concluded that some of the results including the bed occupancy rate may differ day by day, most of the results including the number of beds, staff, or equipment will be the same. In addition, our results may also be interpreted as a real representation of the ICUs in Turkey. Second, owing to the multicenter nature of the study, some of the data collection was not performed uniformly. However, being a large multicenter report including units from 33 cities from all regions of the country, we believe that it represents the whole country. To the best of our knowledge, this is the widest study that evaluates the conditions of the ICUs in Turkey. Our results may reflect the ICU profile in Turkey with significant heterogeneity in terms of both infrastructural and staffing conditions. This could also be considered as strengthening the communication between ICUs, determining the common shortcomings, and making it possible for more multicenter researches to be conducted together in the future.

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Informed Consent: N/A

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Invited Review

What Does the TOVITO Programme Tell Us about How We Can Manage COPD?

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Abstract

Chronic obstructive pulmonary disease (COPD) patients suffer from a significant burden of disease which impairs their quality of life, exercise capacity and lung function. They also suffer from acute worsening of disease, called exacerbations. The role of drug treatment in the management of COPD is aimed at improving lung function, quality of life and reducing the risk of exacerbations. Bronchodilator drugs are the mainstay of therapy and the tow classes, long acting beta2 agonists and long acting anti-muscarinics, are being combined together. The TOVITO programme of clinical research is a comprehensive and consistent set of studies investigating the role of Tiotropium and Olodaterol (Spiolto) on lung function, quality of life, exercise capacity and exacerbation frequency. The programme has included over 16 000 patients who have received the benefits of these two compounds when given together in a suitable inhaler. Safety data was collected with a focus on cardiovascular morbidity and mortality. The use of tiotropium/olodaterol combination resulted in significant gains in lung function, quality of life and exercise endurance. There was no difference between the arms in the Dynagito study which was designed to compare tiotropium/olodaterol combination with its constituent compounds. In all studies no safety concerns were raised. Tiotropium/Olodaterol (Spiolto) is an effective treatment for COPD with benefits to lung function, quality of life and exercise tolerance.

KEYWORDS: Tiotropium, olodaterol, COPD, exacerbations, quality of life

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INTRODUCTION

The TOVITO programme is a series of clinical trials investigating the efficacy of the dual bronchodilators Olodaterol and Tiotropium (Spiolto). The studies investigated all aspects of efficacy including: lung function, exercise tolerance, quality of life and effect on exacerbations. They varied in sample size, length of study and comparators in accordance with the primary end point of the individual study. The programme has included over 16 000 participants.

Olodaterol is one of the super long acting beta agonists with a true sustained action allowing it to be used once a day. On its own it has a fast onset of action and a prolonged (24) duration of bronchodilation. In its registration studies Olodaterol demonstrated at both 5 and 10 microgram does a significant improvement in FEV_1 area under the curve (AUC) of 140 mls which was sustained after 48 weeks of therapy when compared to placebo. When trough FEV_1 was measured there was a clear 80 mL improvement versus placebo which was sustained for 48 weeks. This makes Olodaterol a good choice of partner for Tiotropium [1–6].

Tiotropium was the first once daily long acting anti-muscarinic (LAMA) drug to be used in chronic obstructive pulmonary disease (COPD). It has a huge heritage of trials behind it and has been shown to provide sustained improvements in lung function, exercise capacity, quality of life and also impact exacerbation rates in COPD. The studies of tiotropium have varied in duration (up to 4 years) and in comparator. Tiotropium is generally used as the standard comparator for all new long acting bronchodilators in COPD trials [7–12].

We need better treatments for COPD. Patients present late in the course of the disease and by the time we treat them significant declines in lung function have already occurred [13,14]. Of great significance is the loss of function that has happened with the COPD patient developing increasing breathlessness with activity, which leads them adapting what they do. They often reduce activity and this in turn leads to deconditioning and so a rapid progressive downward spiral occurs [15]. For an individual by the time of presentation this process may already be established leading to a loss of quality of life. This needs to be addressed urgently and we need to give our patients the best evidence-based treatment

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we can to improve lung function, increase exercise capacity, reverse the deconditioning and improve quality of life. This requires effective bronchodilation coupled with behavioral change and pulmonary rehabilitation.

The TOVITO development programme was designed to address each aspect of this downward spiral and demonstrate that rapid, sustained bronchodilation could impact on each dimension of COPD. Each study also collected safety and side effect data.

Effect on Lung Function

The VIVACITO study was performed to measure the lung function effects of Spiolto measured for a 24-hour period for 6 weeks. Two hundred nineteen participants were enrolled in the study. The study demonstrated a 339 mL improvement in FEV_1 AUC (0-3 hr) and a 207 mL improvement in trough FEV_1 for Spiolto versus placebo and the monocomponents. The study also measured FVC and again demonstrated a clear superiority for the dual bronchodilator. Of great interest and perhaps significance is the full lung function data set that was also collected on a subgroup of participants. This demonstrated a large reduction in both functional residual capacity and residual volume. This reduction in gas trapping is a likely mechanism of possible improvements in exercise capacity and much of the quality of life benefits of these drugs [16,17].

The TONADO study was a long term clinical trial which focused on lung function [18,19]. The trial lasted for one year and enrolled participants with GOLD stage 2, 3 and 4 COPD. There were also measurements of quality of life using the St George's Respiratory Questionnaire (SGRQ) as well as a high level of safety monitoring. The study really asked the questions: does Spiolto improve lung function in the longer term and do patients feel better because of it? Over the 52 weeks of the study there were significant improvements in spirometry as measured by trough fev1 and FEV_1 AUC versus the monocomponents. This was real-world patient population and the study also demonstrated improvements in quality of life. There were reductions in SGRQ score for those on Spiolto versus the mono-components and a 32% increase in the proportion of participant achieving the clinically significant 4-point reduction in SGRQ scope (44.8% vs 57.5%, Olodaterol versus Spiolto). The TONADO study also revealed a trend towards a difference in exacerbation rate between the dual therapy and the mono-components. The study was not designed or powered for this outcome.

The loss of lung function in COPD is not linear and recent studies have shown that patients with milder disease lose more lung function annually than those with more severe disease as measured by GOLD stage [20]. So, it is important to see how those with earlier stage disease (GOLD stage 2) respond to the dual bronchodilators. In the TONADO study the GOLD2 participants actually achieved greater improvements in lung function than the more sever, GOLD 3 and 4, participants and this difference was seen irrespective of prior long acting bronchodilator treatment.

Chronic obstructive pulmonary disease patients use prn rescue medication when they get breathless. This is a marker of subjective control of disease and a reduction in rescue medication use implies that the patient is feeling less breathless. The TONADO study demonstrated that the participants treated with Spiolto used less rescue medication throughout the year of the study. The study also measured breathlessness using the transitional dyspnea index. The results consistently demonstrated a reduction in breathlessness if taking Spiolto with an increase in the proportion of patients achieving the minimal clinically important difference (48% vs 54.9%, Olodaterol vs Spiolto).

The ENERGITO study compared Spiolto delivered in a Respimat with Salmeterol/Fluticasone delivered in an Accuhaler (Seretide) [17]. The doses given were 5/5 micrograms once a day and 50/500micrograms twice a day respectively. Two hundred and twenty-nine patients were studied for 6 weeks using a cross-over design. The primary outcome was lung function. The patient population contained GOLD stage 2 and 3 COPD patients. After 6 weeks of treatment the participants on Spiolto had a rapid, significant and sustained improvements in FEV_1 when measured over a continuous 24-hour period. The largest difference was seen in FEV_1 AUC for 0-12 hours 317 mL versus 192 mls, Spiolto and Seretide respectively. This result is to be expected given that the comparison is one bronchodilator against two with a lung function end point.

Effect on Quality of Life

The OTEMPTO studies were a pair of 12-week studies which studied the effects of Spiolto on quality of life in a very detailed manner [21,22]. 1621 subjects were studied, lung function changes were also measured with two comparators; placebo and tiotropium alone. The results show a significant improvement of 4.7 units in SGRQ versus placebo and 2.1 units against tiotropium. There was a striking increase in the SGRQ responder rate (those who achieved a 4 unit change) with this occurring in 52.4% for Spiolto, 41.4% for Tiotropium and 31.9% for placebo. As a physician having over 50% of patients on a treatment reporting that they feel significantly better is a very positively reinforcing factor. Breathlessness as measured by the TDI score was significantly reduced for the participants taking Spiolto versus tiotropium and placebo (1.73 vs 1.14 vs 0.11 respectively) with again a significant increase in responder rate (those who achieve the MCID od 1 point) 53.9% versus 41% versus 26.2% respectively. These changes were seen in subjects with both GOLD stage 2 and 3 disease. These studies give us confidence that the changes seen in lung function are then translated into changes in breathlessness and quality of life.

The TOVITO programme also looked at exercise capacity in the PHYSACTO, TORRACTO and MORACTO studies [23,24]. A variety of assessments were used including endurance shuttle walk tests (ESWT) in the PHYSACTO study. This demonstrated significant increases in endurance time for those on Spiolto versus tiotropium and placebo at both 8 weeks and 12 weeks.

Every study in the TOVITO programme included a safety analysis with a particular focus on cardiovascular events. In all assessments there were no significant signals by any measure [25].

Effect on Exacerbations

Exacerbations of COPD are important. They lead to morbidity, mortality and consume enormous amounts of healthcare resource world-wide [26]. They are classed into mild, moderate and severe depending upon which treatment is given and where they are given as a surrogate for physiological and systemic severity [27]. The final study of the TOVITO programme was the DYNAGITO study. This was the final piece in the puzzle designed to assess the effect of Spiolto on the exacerbation rate in a 1-year study in 7800 participants with the comparator of tiotropium alone. The study background and design are important. Previous studies had demonstrated the potential for Tiotropium to reduce exacerbation rate and the TONADO studies had demonstrated a trend towards a reduction in exacerbations in those taking Spiolto [10,18]. The DYNAGITO study is the largest of the TOVITO programme as required by the power calculation which set a significance rate of 1% (as this was single study and not a paired study) as required by regulators, with an anticipated reduction in exacerbation rate of 10% [28]. DYNAGITO was a double blind randomised study with a primary endpoint of rate of moderate or severe exacerbation, with secondary endpoints of time to first moderate-to-severe exacerbation, annualized rate and time to first exacerbation leading to hospitalization, and time to all-cause mortality. Given the size and duration of the study a large amount of safety data was collected. The inclusion criteria included those with a FEV_1 less than 60% and a history of one or more moderate or severe exacerbation in the year prior to study entry. It was designed to be as real world as possible and there was no pre-planned statistical adjustment for relevant co-variates. If a participant was taking inhaled cortico-steroids (ICS) at entry, then they stayed on the steroid throughout. 70% of the participants were taking ICS throughout the study. 50% of the participants were GOLD stage 3 COPD patients with 48% being in the GOLD category B and 39% being GOLD category D. Patients were 27% less likely to drop out of the study if taking the dual bronchodilator suggesting that they were more stable on this therapy. This study did not reach the pre-set level of statistical significance and demonstrated a 7% reduction in exacerbation rate for Spiolto versus Tiotropium (p=0.0498). When analysed considering baseline therapy it was clear that there was a significant effect of dual therapy versus tiotropium alone (relative rate of exacerbation 0.91 (95% CO 0.84-0.99). There was a significant reduction (20%) in those exacerbations needing treatment with oral corticosteroids in those receiving Spiolto. The meaning of this finding for clinical practice is unclear and deserves further study. This may help our understanding of the nature of exacerbations and why physicians choose treatments. When a post-hoc analysis of the DYNAGITO data included adjustment for co-variates which may affect the baseline exacerbation rate (sex, disease severity, baseline therapy, smoking status or baseline exacerbation rate) the exacerbation rate ratio was significantly different between Spiolto and tiotropium at the 1% level (0.89, 95% CI 0.84-0.96, p=0.001). The health status of the participants, as measured by CAT (COPD assessment test), was significantly better for those taking Spiolto versus those taking Tiotropium. There was no difference in adverse event rate between either of the treatment arms. And a detailed assessment of major cardiovascular events showed no difference for the duration of the DYNAGITO study.

The DYNAGITO study was an attempt to take a very real-life approach to treatment aimed at reducing exacerbations of COPD. It was well designed and appropriately powered to achieve an answer based upon the predicted effect rate. Perhaps the effectiveness of Tiotropium on exacerbation rate was unexpectedly good. In taking a very clear and statistically clean approach and not including any adjustments for co-variates was brave but potentially wakened the ability of the study to demonstrate the effect of dual therapy on exacerbation rate. It will be interesting to see more data as it emerges especially with regard to the effect of blood eosinophils in this study and, given the number of participants, duration of the study and level of data collected, much more will come out of the DYNAGITO study which will enhance our understanding of the nature of COPD exacerbations.

CONCLUSION

Taking the TOVITO programme as a whole there is no doubt that treatment using a dual bronchodilator approach has consistent and significant effects on COPD patients of all disease severity. There are improvements in lung function, with a particular benefit on measures of gas trapping. Exercise capacity is improved, and patients feel less breathless and have an improved quality of life. In my opinion, there is adequate evidence to recommend that the optimal baseline therapy for our patients with COPD should be the use of dual bronchodilators given in an effective device designed specifically for patients with COPD.

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Review

Biologic Agents in the Treatment of Multicentric Castleman Disease

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Abstract

Multicentric Castleman disease (MCD) causes an extensive range of systematic symptoms and can be life-threatening if not treated promptly and appropriately. The pathophysiology of the disease remains unclear; however, interleukin 6 (IL-6) pathway and human herpesvirus 8 infection appear to play an important role. As a result, the treatment of MCD remains complex and often insufficient, although a plethora of therapeutic approaches have been used. Between these, biological agents in the form of monoclonal antibodies against specific pathogenic processes of the disease have improved survival rates significantly. In the present study, we review the clinical results of rituximab, which targets B lymphocytes, siltuximab and tocilizumab, which target the IL-6 pathway, bortezomib, which is a selective proteasome inhibitor, and anakinra, which is an interleukin 1 receptor antagonist. The introduction of these biological agents in the treatment of MCD appears to be promising in the first studies performed. However, more clinical trials are required to assess the efficacy and safety of each agent and to form therapeutic strategies that will be widely accepted.

KEYWORDS: Castleman disease, multicentric castleman disease, biological agents, human herpesvirus 8, human immunodeficiency virus

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INTRODUCTION

Castleman disease, alternatively known as angiofollicular lymph node hyperplasia, consists of a heterogeneous group of reactive lymphoproliferative disorders, which share some basic histopathological features but vary greatly in clinical manifestations, severity, treatment, and prognosis [1]. The first case of the disease was reported in 1954 by Benjamin Castleman [2] who identified a new histopathologic entity in a surgically resected mediastinal mass. Castleman et al. reported a series of similar cases over the next 2 years, confirming the diagnosis of the new disease.

Nowadays, the disease is clinically divided into two distinct subtypes: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD). The former, which is usually asymptomatic, is effectively treated by surgical excision of the enlarged lymph node. The latter can cause a wide range of systematic symptoms, such as fever, night sweats, weight loss, peripheral edema, ascites, pleural effusion, lymphadenopathy, and organomegaly [1,3,4]. Laboratory hallmarks include anemia, leukocytosis, thrombocytosis or thrombocytopenia, increased C-reactive protein (CRP) and fibrinogen, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, and hypoalbuminemia [3]. Moreover, it has been associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome, paraneoplastic pemphigus, and an increased risk of hematologic malignancies, especially B-cell lymphomas [5]. MCD can be life-threatening if not treated promptly and appropriately, or it can be refractory to treatment. It requires combined systematic treatment, and despite recent advances in therapies that target the pathophysiology of the disease, its prognosis remains relatively poor [6,7].

Castleman disease is divided into at least four histopathological subtypes. All of these are characterized by excessive intrafollicular vascular proliferation. Most of the UCD cases belong to the hyaline vascular subtype, whereas most of the MCD cases belong to the plasma cell subtype. However, each histopathological subtype, as well as mixed variants, can be found in both UCD and MCD. The recently described plasmablastic subtype has been associated with aggressive forms of MCD, usually in the setting of human immunodeficiency virus (HIV) infection [1,3]. Castleman disease is usually a diagnosis of exclusion, as many benign and malignant diseases present with similar reactive lymph node histopathology [8].

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Etiology and Pathophysiology

The etiology of MCD still remains unclear. However, there is good evidence to support the critical role of interleukin 6 (IL-6) pathway and human herpesvirus 8 (HHV-8) infection in the pathogenesis of at least a number of cases [9-11]. MCD is more frequent among patients infected by HIV, and its incidence is constantly increasing, especially after the introduction of highly active antiretroviral therapy [12]. Almost all HIV-positive MCD cases present with an HHV-8 coinfection, whereas the frequency of HHV-8 in patients with HIV-negative MCD varies in association with the prevalence of the infection in each population [9,10]. The World Health Organization proposed a classification of MCD depending on the HHV-8 infection status, characterizing MCD as either HHV-8-associated or idiopathic MCD.

IL-6 Signaling Pathway

Several studies suggest that the lymph node enlargement, the specific histopathological alterations, and the systematic symptoms reported in MCD are all secondary to proinflammatory hypercytokinemia. Among many cytokines that have been proposed to play a role in MCD, overproduction of IL-6 appears to be the critical point in the pathogenesis of the disease [10,11,13]. IL-6 is produced by a wide range of immunocompetent cells, including lymphocytes, monocytes/macrophages, endothelial cells, and fibroblasts, and performs multiple immunoregulating activities. The most important of these include: (1) induction of B lymphocyte proliferation and differentiation, leading to diffuse lymph node enlargement, (2) synthesis and release of hepatic acute phase factors responsible for the systematic symptoms of MCD, (3) induction of hepcidin production in the liver, which mediates anemia of chronic disease, and (4) stimulation of vascular endothelial growth factor (VEGF) expression, which causes the characteristic excessive intrafollicular angiogenesis [14]. Both experimental models and clinical studies provide strong evidence for the important role of the IL-6 pathway in MCD. Yoshizaki et al. [11] reported that IL-6 is mainly produced by the germinal centers of hyperplastic lymph nodes, whereas lymph node hyperplasia, plasma levels of acute phase proteins, and clinical symptoms were correlated to serum IL-6 concentration. Moreover, van Gameren et al. [13] conducted a phase I and II study to examine the safety of recombinant human IL-6 when administered to patients with cancer. The main side effects reported were identical to an MCD-like syndrome, and most of the clinical and laboratory abnormalities were dose dependent. Similar results were obtained by Brandt et al. [10] who used a genetically modified mouse model that overproduced IL-6. Shortly after the genetic modification, mice presented with symptoms and histopathological changes typical of MCD. The exact etiology of IL-6 pathway dysregulation remains indistinct. In patients positive with HHV-8, viral infection appears to play the most significant role. In patients with idiopathic MCD, multiple factors have been suggested to contribute, including viral infections other than HHV-8, genetic aberrations in the IL-6 pathway, autoimmune phenomena, and ectopic IL-6 production by malignant cells [9].

HHV-8 Infection

HHV-8, alternatively known as Kaposi sarcoma-associated herpes virus, was first isolated from an HIV-associated Kaposi sarcoma biopsy sample in 1994 [10]. Since then, its involvement in the pathogenesis of various diseases, including Kaposi sarcoma, primary effusion lymphoma, and a proportion of MCD cases, has been well documented [9,12,15]. HHV-8 primarily infects CD20+/IgM+ B lymphocytes in the mantle zone of the affected lymph node. Soulier et al. [9] were the first to investigate HHV-8 prevalence in excised lymph nodes from patients with MCD, using polymerase chain reaction and Southern blot analysis. All patients positive with HIV were HHV-8-positive as well, whereas HHV-8 frequency among patients negative with HIV was estimated at 41%. Subsequent studies confirmed the strong association between HIV and HHV-8 in MCD. However, the HIV-negative group was more heterogeneous when examined for HHV-8 infection [16,17]. Furthermore, Stebbing et al. [14] reported that there is a correlation between HHV-8 plasma levels and disease activity in patients positive with HIV. Therefore, they proposed HHV-8 plasma levels as a potential biomarker for disease exacerbations. Consistent with the previous study, Casper et al. [18] reported three patients who improved clinically after having antiviral treatment with ganciclovir. HHV-8 encodes a viral form of IL-6 (vIL-6), mostly during the lytic phase of the viral proliferation. It remains controversial whether vIL-6 alone can cause MCD. However, vIL-6 also induces human IL-6 expression, which is potent enough to cause MCD, alone or synergistically with vIL-6 [19]. Finally, vIL-6 upregulates VEGF expression as well, contributing to the intranodular capillary proliferation reported in the disease [20].

Targeted Therapies

Surgical resection of the enlarged mass provides radical treatment to the majority of patients with UCD. Radiotherapy is an important alternative when surgical resection is contraindicated or technically challenging [21]. The treatment of MCD still remains complex and often insufficient as the diagnosis of the disease can sometimes be delayed, and the pathogenetic onset of each case is usually different among patients [4,8]. Moreover, MCD is a rare clinical entity, and therefore, there is a lack of randomized controlled trials (RCTs) to support clinical practice. Only one RCT has been published to date, evaluating siltuximab (anti-IL-6 monoclonal antibody) safety and efficacy in patients with idiopathic MCD [6]. The rest of the knowledge that constitutes the basis of our clinical practice lies mostly upon case series, case reports, and expert opinions. As a result, multiple therapeutic approaches have been used, including conventional cytotoxic chemotherapy (single-agent or combined), antiviral treatment, glucocorticoids, thalidomide, interferon-alpha, and molecular targeted therapies. Determination of HHV-8 status is very important for the selection of the appropriate therapeutic strategy [9]. Below, we summarize current clinical data regarding the use of biological agents (monoclonal antibodies) in the treatment of MCD.

Targeting B Lymphocytes

Rituximab

Rituximab is a chimeric monoclonal antibody that was initially (approximately 20 years ago) approved for use in low-grade non-Hodgkin's follicular lymphoma. It targets CD20 antigens on the surface of B lymphocytes, leading to their destruction mostly via complement activation and antibody-

dependent cell mediated cytotoxicity [22]. It has now been used for many B-cell mediated and autoimmune diseases, such as non-Hodgkin lymphomas (NHLs), chronic lymphocytic leukemia, rheumatoid arthritis, and Wegener's granulomatosis [23]. Moreover, it has been used off-label as first-line treatment in HIV-positive/HHV-8-positive MCD, alone or in combination with conventional chemotherapeutics (e.g., etoposide) and antiviral treatment (e.g., ganciclovir) [24]. In addition, it has been used as second-line treatment, along with combined conventional chemotherapeutics (e.g., CHOP) in HIV-negative/HHV-8-negative MCD, when the disease is refractory to anti-IL-6 treatment [25].

Most of the clinical evidence regarding rituximab use in MCD comes from both prospective and retrospective studies in patients positive with HIV/HHV-8. Bower et al. [24] conducted a single-group, phase II trial in which 21 patients with HIV-positive/HHV-8-positive MCD participated. Each patient received 4 doses of 375 mg/m^2 of body surface area at weekly intervals, without having any other treatment prior to this. Twenty patients showed clinical response to the treatment, with resolution of symptoms. Fourteen patients had partial radiological response (assessed by the Response Evaluation Criteria in Solid Tumors), and most of the patients presented with improvement in a number of hematological and viral markers, including hemoglobin, platelet count, and HHV-8 viral load. In addition, after 2 years, the overall survival rate was 95%, and the relapse-free survival rate was 79%. Similarly, Gerard et al. [7] published a prospective, phase II trial in which 24 patients were treated with the same dose of rituximab as in the study described above. Participants had been effectively treated with conventional chemotherapy in the past, but they became chemotherapy-dependent, with at least one exacerbation of the disease when chemotherapy was withdrawn. All patients received at least one dose of rituximab. Twenty-two of them exhibited sustained remission of the disease off chemotherapy at day 60 after the first dose (primary endpoint), and 17 participants showed sustained remission of the disease off chemotherapy at day 365 after the first dose (secondary endpoint). The estimated 1-year overall survival, event-free survival, and disease-free survival rates were 92%, 71%, and 77%, respectively. Moreover, rituximab has been found to reduce significantly the incidence of NHL, a potentially fatal complication occurring frequently in the setting of HIV-positive/HHV-8-positive MCD [26].

Two retrospective studies aimed to assess the effect of rituximab-based therapies on overall survival. Hoffmann et al. [27] examined 52 patients with HIV-positive MCD, some of whom received rituximab (alone or in combination with conventional chemotherapeutics), and some others did not. A predominance in sustained complete remission rate (91% vs 41% after 1 year) and overall survival rate was reported in the rituximab-treated group compared with the group of patients who received conventional chemotherapy (with or without antiviral agents). In a similar study of 61 HIV-positive MCD cases by Bower et al. [28], the overall survival rates reached 94% at 2 years and 90% at 5 years in the rituximab-treated group compared with 42% and 33%, respectively, in the group of patients who did not receive rituximab. Moreover, the investigators reported 24 patients with Kaposi sarcoma at the time of MCD diagnosis. Nine of them suffered progression of Kaposi sarcoma after 3 months of rituximab therapy, and all of them except for one required systemic liposomal anthracycline chemotherapy. In conclusion, despite their limitations, both studies suggest that rituximab has dramatically improved survival rates in HIV-positive MCD.

Treatment of HIV-positive MCD with rituximab-based therapies has significantly improved survival; however, the potential benefit of maintenance therapy is low. In a prospective cohort study, 84 patients with HIV-positive MCD were treated with risk-stratified rituximab-based therapy [28]. Four patients died of refractory HIV-positive MCD, while the rest achieved clinical remission. The median follow-up for these patients was 6.9 years. The 5-year overall survival for the 80 patients was 92%. Eighteen patients relapsed, including five with concomitant HHV8-associated lymphoma at relapse, with a median time to first relapse of 30 months (maximum 10 years). Moreover, all patients were successfully retreated with rituximab-based therapy. Therefore, the high risk of developing HHV8-associated lymphoma, the relatively low relapse rate and the high salvage rates at relapse, reduce the potential benefit of maintenance therapy.

Targeting IL-6 Pathway

IL-6 plays a critical role in the pathogenesis of both idiopathic and HHV-8-associated MCD, as described above. Therefore, the investigators tried to target the IL-6 signaling pathway, IL-6 or IL-6 receptor (IL-6R), in order to provide an etiologic therapy for MCD. Beck et al. [29] were the first to administer a murine anti-IL-6 antibody (BE-8) in a case of MCD. Symptoms improved within 24 h after administration and improvement of laboratory markers followed after a few weeks. However, symptoms and laboratory abnormalities recurred within a few days after therapy cessation. Since then, two more monoclonal antibodies targeting IL-6 pathway have been used in the treatment of MCD, siltuximab (anti-IL-6) and tocilizumab (anti-IL-6R), which are discussed in more detail below.

Siltuximab

Siltuximab is a chimeric monoclonal antibody that binds to IL-6 with high affinity and, therefore, prevents IL-6 binding to its receptor (IL-6R). It has been the only drug approved for the treatment of idiopathic MCD in the United States and Europe so far. The first clinical data regarding siltuximab use in MCD were published in 2010 by van Rhee et al. [30] who examined 23 patients negative with HIV/HHV-8 with symptomatic MCD or unresectable UCD. The interim results of this phase I clinical trial showed that 18 (78%) patients exhibited clinical benefit response (CBR, a combination of certain clinical and laboratory indicators, as defined by the investigators of the study) after siltuximab administration. The CBR rate was 100% (11 patients) in the group who received a higher dose of siltuximab (12 mg/kg). Moreover, 11 (52%) patients experienced radiologic tumor response (complete or partial), as defined by the modified Cheson criteria, whereas hemoglobin increase (0.2-4.7 g/dL) was reported in 19 patients. Finally, neither dose-limiting toxicities nor treatment-related deaths were reported, whereas only three patients experienced grade 3 or higher adverse events.

The final results of this study, mainly focusing on the evaluation of siltuximab safety, were published by Kurzrock et al. [31] in 2013. Sixty-seven patients with NHL, multiple myeloma, or symptomatic Castleman disease were enrolled in this cohort study and received siltuximab at a dose of 3, 6, 9, or 12 mg/kg weekly, every 2 or 3 weeks for a median of 8.5 (maximum 60.5) months. No dose-related toxicities associated with siltuximab administration were reported, whereas the most frequent all-grade adverse events possibly linked to siltuximab administration were thrombocytopenia (25%), neutropenia (19%), hypertriglyceridemia (19%), leukopenia (18%), hypercholesterolemia (15%), and anemia (10%). Grade 3 or greater adverse events reasonably related to siltuximab included neutropenia (11 patients), thrombocytopenia (3 patients), sepsis (1 patient), and hyperlipidemia (1 patient). An extension of the initial phase I trial, including 19 patients, was published by van Rhee et al. [32] in 2015. The median duration of treatment for all patients was 5.1 (range 3.4-7.2) years. Neither evidence of cumulative toxicities nor treatment discontinuations were reported. In addition, all patients were alive at the time of the publication. Grade 3 or greater adverse events reasonably attributed to siltuximab were leukopenia, lymphopenia, and a serious case of polycythemia (1 patient in each event).

Van Rhee et al. [6] also conducted a randomized, double-blind, placebo-controlled trial in which siltuximab efficacy was compared with best supportive care in patients with HIV-negative/HHV-8-negative MCD. Siltuximab was administered intravenously at a dose of 11 mg/kg every 3 weeks. Eighteen (34%) out of 53 patients who received siltuximab had durable radiologic tumor response (according to the Cheson criteria) and symptomatic response (as defined by the authors in the study), with a median response duration of 383 (range 232-676) days. One patient experienced complete response, whereas the other 17 patients had only partial response. None of the 26 patients in the placebo group showed radiologic tumor response or symptomatic response. Furthermore, similar incidence of grade 3 or greater adverse events was reported in each group, but specific adverse events, such as pruritus, maculopapular rash, weight gain, upper respiratory tract infection, and localized edema, were reported more frequently in the siltuximab group. Three (6%) patients experienced adverse events reasonably attributed to siltuximab administration (lower respiratory tract infection, anaphylactic reaction, and sepsis). In conclusion, siltuximab has been proven to be a potent and considerably safe drug, which improved significantly life expectancy in patients with idiopathic MCD.

In a study conducted by Yu et al. [33], siltuximab was shown to have a greater proportion of complete responses and longer progression-free survival for HIV-negative/HHV-8-negative MCD compared to rituximab. Twenty-one patients received siltuximab intravenously at a dose of 11 mg/kg every three or six weeks. A dose of 375 mg/m^2 of rituximab was administered intravenously to 25 patients once a week for four weeks. Siltuximab was associated with a significantly higher rate of complete response than rituximab or rituximab-based therapies (p=0.034). Moreover, it controlled and improved the clinical manifestations and progression-free survival in cases where rituximab failed. However, patients treated with siltuximab might need lifelong administration of the medication, as relapse has been reported on cessation of IL-6 receptor therapy with tocilizumab.

Tocilizumab

Tocilizumab is a humanized IL-6R antagonist, which blocks the IL-6 signaling pathway very effectively. It has been approved for the treatment of idiopathic MCD in Japan and moderately to severely active rheumatoid arthritis in adults worldwide. The first data regarding tocilizumab use in MCD were published by Nishimoto et al. [33] in 2000. The investigators administered tocilizumab in seven patients with HIV-negative/HHV-8-negative MCD at a dose of 50-100 mg either once or twice weekly. Fever and fatigue resolved immediately after tocilizumab administration, whereas laboratory markers, such as hemoglobin, CRP, and albumin, started to improve within a few days. After 3 months of treatment, hypergammaglobulinemia, lymphadenopathy, and renal dysfunction in the setting of secondary amyloidosis improved significantly. However, recurrence of the disease was reported 2 weeks after therapy cessation. No severe adverse events were reported, except for self-limited, transient neutropenia in two patients.

Thereafter, Nishimoto et al. [34] published an open-label phase II trial to evaluate the safety and efficacy of tocilizumab in 28 patients with MCD (26 with idiopathic MCD and 2 with HIV-negative/HHV-8-positive MCD). The investigators administered eight tocilizumab infusions at a dose of 8 mg/kg every 2 weeks, and afterwards, dose and treatment intervals were adjusted to each patient individually for the next 16 weeks. Within the initial phase of administration (16 weeks), lymphadenopathy was markedly improved, recorded as a reduction of the mean short-axis from 10 mm to 9.1 mm. After 1 year of treatment, this was further reduced to 8.6 mm. In addition to lymphadenopathy alleviation, inflammatory markers, hemoglobin level, and nutritional status (total and high-density lipoprotein cholesterol levels and body mass index) were also improved significantly after treatment with tocilizumab. Regarding the safety of the drug, no severe adverse events were reported. The most common adverse events possibly attributed to tocilizumab treatment were flu-like symptoms, such as cough, rhinorrhea, and pharyngitis. Moreover, no patients developed malignancies, and only one patient who suffered from chronic myelomonocytic leukemia experienced exacerbation of secondary disease. In 2007, Nishimoto et al. [35] published an extension of the prospective trial, in which they examined the efficacy and safety of tocilizumab in a long-term, >5 years, follow-up. Tocilizumab was initially administered to 35 patients, from whom 30 (86%) continued to have tocilizumab for >5 years at doses and intervals as stated above. The effect of tocilizumab on lymphadenopathy, constitutional symptoms, and laboratory markers was sustained. In addition, pulmonary diffuse lymphoid hyperplasia, identified in 31 patients initially, improved dramatically over the 5-year period, as examined by two independent radiologists in high-resolution computed tomography scans. Finally, the most frequent adverse events were similar to those reported in the initial phase of the study, with the majority of them classified as not severe. Several case reports and case series published thereafter described similar effects of tocilizumab on symptoms and laboratory markers. In addition to this, some studies supported the efficacy of tocilizumab when used as treatment for complications attributed to MCD, such as renal failure, myelofibrosis, pulmonary hypertension, glomerulonephritis, cardiomyopathy, and autoimmune hemolytic anemia [36-42].

Targeting Other Signaling Pathways

Bortezomib

Bortezomib is a selective proteasome inhibitor, which is believed to reduce IL-6 production possibly via inhibition of nuclear factor-κB. It has been approved for treatment of relapsing multiple myeloma and mantle cell lymphoma in the USA and Europe. A limited number of case reports regarding bortezomib use in MCD have been published so far. Hess et al. [43] reported a case of a 48-year-old female patient with recurrent, treatment-refractory HIV-negative/HHV-8-negative MCD. After bortezomib administration, the patient exhibited significant alleviation of symptoms, improvement of general performance status (as defined by the Eastern Cooperative Oncology Group), improvement of inflammatory markers, and loss of transfusion dependency for >1 year. Furthermore, no severe adverse events were reported during the treatment period. In addition, Wang et al. [44] and Sobas et al. [45] treated two cases of Castleman disease associated to POEMS syndrome using bortezomib in combination with thalidomide and dexamethasone, respectively. Both patients experienced disease remission, which lasted for 2 and >4, respectively, without any severe adverse events during this period. Finally, Yuan et al. [46] and Khan et al. [47] published two cases of MCD in the setting of multiple myeloma, which were treated with bortezomib and dexamethasone (followed by maintenance treatment with thalidomide in the second case). Both patients remained in partial disease remission when examined after 18 and 24 months, respectively.

Anakinra

Anakinra is an interleukin 1 (IL-1) receptor antagonist. IL-1 is an IL-6 up-regulator via activation of the nuclear factor-κB pathway. Therefore, it has been used in the treatment of several IL-6-mediated diseases. Officially, it has been approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndromes in the USA and Europe. Similar to bortezomib, only a small number of case reports regarding anakinra use in MCD have been published thus far. Galeotti et al. [48] reported a case of a 13-year-old boy who suffered from treatment-refractory MCD. Initially, the patient received a combination of conventional chemotherapy (cyclophosphamide and vinblastine) with rituximab, which proved to be inefficient. Thereafter, he received anakinra and responded immediately, experiencing a rapid resolution of symptoms and improvement of laboratory markers. Similarly, El-Osta et al. [49] reported a case of a 61-year-old woman with MCD refractory to previous therapies (cladribine, rituximab, steroids, etanercept, and anti-IL-6 monoclonal antibody) who experienced both clinical and laboratory remission of the disease after anakinra administration for 1 week.

CONCLUSION

Multicentric Castleman disease is a rare systematic disorder, which was characterized by aggressive development and poor prognosis during the past decades. The introduction of biological agents targeting the pathophysiology of the disease improved survival rates significantly. Rituximab, mainly used in HHV-8-positive MCD cases, and IL-6/IL-6R antagonists, mainly used in idiopathic MCD cases, have geared the disease course toward a relapsing-remitting pattern. However, further studies, especially RCTs, are required to assess the efficacy and safety of each agent and implement a therapeutic strategy that will be widely accepted. Moreover, targeting new mechanisms in the pathophysiology of the disease may benefit patients with MCD refractory to current therapies. For example, abnormally high levels of IL-10 and VEGF have been reported in many MCD cases, rendering these two molecules rather appealing therapeutic candidates in the future [50]. Finally, combinational approaches may minimize the proportion of non-responding patients and, therefore, improve therapeutic outcomes.

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Case Report

Unexpected Pregnancy during Treatment of Multidrug-resistant Tuberculosis

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Abstract

Several drugs used in the treatment of multidrug-resistant tuberculosis (MDR-TB) have been reported as teratogenic. Treatment of such cases during gestation is disputable. Some experts favor the termination of pregnancy, whereas others suggest reducing the dose of teratogenic drugs or even suspending the regimen during pregnancy. There have been no clinical trials on the subject, but case reports and case series show excellent outcomes for children exposed during pregnancy to second-line agents, indicating that aggressive management of gestational MDR-TB may benefit not only the mother but also the fetus. We present a case of pregnancy in a teenager while she was under treatment for MDR-TB and continued with full treatment and nevertheless delivered a healthy child.

KEYWORDS: Multidrug-resistant, tuberculosis, treatment, teratogenicity, pregnancy

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) mainly affects young adults, including women of childbearing age. Several drugs used in the treatment of MDR-TB (ethionamide, fluoroquinolones, and aminoglycosides) have been reported as teratogenic. The management of MDR-TB during pregnancy is disputable [1]. Although some experts favor the termination of pregnancy, others suggest reducing the dose of teratogenic drugs or even suspending the regimen during pregnancy [2]. We present a case of pregnancy in a teenager who was under treatment for drug-resistant tuberculosis.

CASE PRESENTATION

During contact investigation, the 15-year-old daughter of an MDR-TB case (her mother) was diagnosed with active pulmonary tuberculosis resistant to isoniazid, rifampin, and ethambutol and classified as a new MDR-TB case; HIV rapid testing was negative. A chest radiograph at the outset showed airspace infiltrates in the lingula region (Figure 1).

Treatment was initiated in November 2015, and her regimen included levofloxacin, prothionamide, amikacin, cycloserine, and pyrazinamide. She responded rapidly and had converted her culture by mid-January 2016. After 8 months of treatment and 6 months with consecutive negative sputum cultures, she reported the start of sexual relations. When referred for contraceptive measures, the pregnancy test was already positive, and an obstetric ultrasound revealed an 8-week pregnancy. Although amikacin had been stopped before pregnancy started, the patient was still receiving levofloxacin and prothionamide, two potentially teratogenic drugs. The case was evaluated by the hospital bioethics committee, and the patient was informed of the risk of congenital malformations and the option of undergoing a therapeutic abortion owing to the risk of relapse if treatment was stopped; besides, the fetus had been already exposed to the drugs for at least 2months. Nonetheless, she decided to continue with the pregnancy. In March 2017, she delivered a healthy male child (weighing 2.9 kg) with no congenital defects. The patient was discharged as asymptomatic and with a normal chest radiograph, and declared as cured of MDR-TB in June 2017.

DISCUSSION

Ethionamide and fluoroquinolones are classified as pregnancy category C drugs and amikacin as category D (category C drugs: animal reproduction studies have shown adverse effects to the fetus and there are no adequate and well-controlled human clinical trials; category D drugs: there is evidence in clinical trials in humans of teratogenic risk). The loss of auditory acuity associated with the use of amikacin is usually severe and irreversible and may occur even after its use for just a few days; its effect is usually associated with the cumulative dose of the drug. Other aminoglycosides (streptomycin,

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kanamycin, tobramycin, and gentamicin) and capreomycin (a polyene) are also associated with auditory toxicity [3].The use of ethionamide during the first trimester of pregnancy has been associated with defects of the central nervous system [4]. Animal studies with fluoroquinolones have suggested that there are risks of damage to the articular cartilages of the fetus and, consequently, of joint lesions [5].

There are not many management options for pregnant women with MDR-TB; the available options include interruption of pregnancy, interruption of the mother's MDR-TB treatment, or continuation of the regimen with potentially teratogenic drugs despite pregnancy [6]. Therapeutic abortion has been proposed in these cases, since discontinuation of treatment puts the mother at grave risk and favors the possible transmission of a resistant strain in the community [7].

Our patient had stopped the aminoglycoside treatment before getting pregnant but was still receiving both prothionamide and levofloxacin. Human studies yield conflicting data regarding the teratogenicity of ethionamide/protionamide. In general, thioamides are considered as potentially teratogenic, and it is recommended to avoid pregnancy while under treatment with this class of drugs [8].

On the contrary, experiences from Peru and India reveal excellent outcomes for children exposed to second-line drugs during pregnancy, suggesting that aggressive management of gestational MDR-TB may benefit both the mother and the fetus [6-8]. Long-term follow-up (>5 years) in 6 children exposed to multiple potentially teratogenic antituberculosis drugs showed a virtually normal psychomotor development [9].

Patients should have the right to choose once they have been thoroughly informed of their options. On the basis of available evidence, it appears that the demonstrated and hypothetical benefits of continued MDR-TB treatment despite pregnancy are greater than the theoretical risks for the mother and fetus [6, 10, 11]. Finally, all women of childbearing age (even the very young, as we have learned from this case) should be screened for pregnancy before initiation of treatment. In addition, family planning that does not require perfect adherence (e.g. birth control implant or an intrauterine birth control device) should be made a strong recommendation for the duration of therapy.

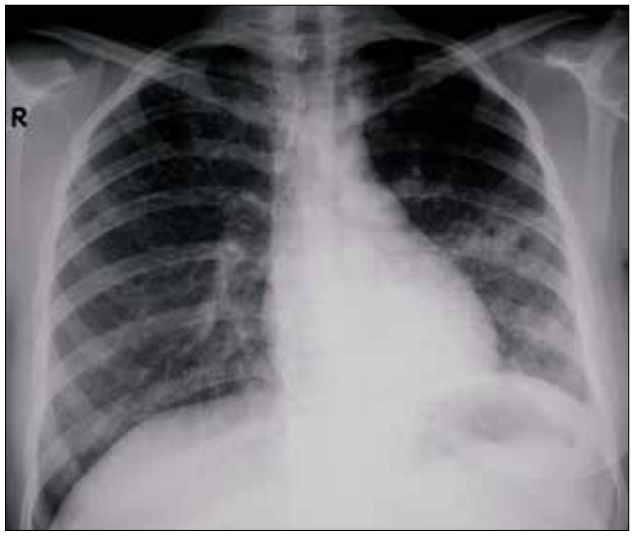

Figure 1. Chest radiograph at the time of diagnosis showing an airspace infiltrate in the lingula

Informed Consent: Informed consent was obtained from the parents of the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - R.L.L., K.C.L., A.H.P.; Supervision - R.L.L.; Resource - R.L.L.; Materials - R.L.L.; Data Collection and/or Processing - K.C.L., A.H.P.; Analysis and/or Interpretation - R.L.L., K.C.L., A.H.P.; Literature Search - K.C.L., A.H.P.; Writing - R.L.L.; Critical Reviews - K.C.L., A.H.P.

Conflict of Interest: Authors have no conflicts of interest to declare.

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Case Report

Squamous Cell Carcinoma Arising in Zenker's Diverticulum: A Case Report and Review of the Literature

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Abstract

The occurrence of squamous cell carcinoma (SCC) arising in a Zenker's diverticulum is a very rare incident. Complete excision of the diverticulum is considered as the procedure of choice for SCC in the pharyngeal pouch. Histopathological assessment of the pouch is the only modality to rule out SCC. Here, we report a case of a 71-year-old male with 20 years of history of Zenker's diverticulum, who recently presented with a history of weight and appetite loss. A barium swallow confirmed Zenker's pouch, the patient underwent diverticulectomy and cricopharyngeal myotomy; a histopathological examination of the specimen revealed a fungating mass of SCC within the pouch. This report highlights the suggestion of considering SCC not only in patients with a long history of Zenker's diverticulum but also when there is a clinical suspicion with new symptoms for a more aggressive management for diagnosis and complete excision of the pouch.

KEYWORDS: Zenker's diverticulum, squamous cell carcinoma, pharyngeal pouches

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INTRODUCTION

Pharyngeal pouches were first described by Ludlow in 1769, and after more than a century, Zenker published a full clinical pathological description in 1877 [1,2]. The occurrence of squamous cell carcinoma (SCC) arising in Zenker's diverticulum is a very rare entity. However, the published incidence rates fall between 0.3% and 7% among occasional reports in the literature [3]. SCC in the pouch is diagnosed mainly after obtaining full histopathologic examination of the specimen following surgical resection [4]. For this reason, the procedure of choice for suspected SCC in the pouch is by complete surgical excision of the pouch. We report a rare case of recurrent Zenker's diverticulum and SCC development in the pouch.

CASE PRESENTATION

A 71-year-old British male patient presented to our institute with a history of dysphagia and regurgitation for the past 20 years. Endoscopy was done earlier, and he was diagnosed with Zenker's diverticulum. He underwent endoscopic stapling of the diverticulum in the years 2006, 2009, and 2011 without any symptomatic improvement. At that time, he denied any history of weight or appetite changes. He complained of new symptoms such as dysphagia and regurgitation mostly to soft food and liquids, which aggravate with coughing, and also of a decrease in weight and appetite. The patient is a smoker and an occasional alcohol consumer.

On physical examination, it was found that he was healthy, and all systems exam were unremarkable. All laboratory investigations were normal.

Barium swallow showed pharyngeal pouch as Zenker's diverticulum (Figures 1, 2). A written consent was obtained from the patient for surgery and publications.

The patient underwent left neck incision, diverticulectomy, and cricopharyngeal myotomy under general anesthesia. Postoperative recovery was uneventful. He was discharged home after few days in a good stable condition. Histology results showed an esophageal pouch consisting of a cyst-like lesion measuring 4.0×3.5×1.0 cm^3 (Figure 3). The cyst wall was thickened. The inner mucosal surface showed fungating mass lesion measuring 1.5×1.0×0.5 cm^3, tan white in color, and friable in consistency. The resection margins were free of the lesion and were marked with staples. Microscopic results showed moderately differentiated SCC (Figures 4a, b).

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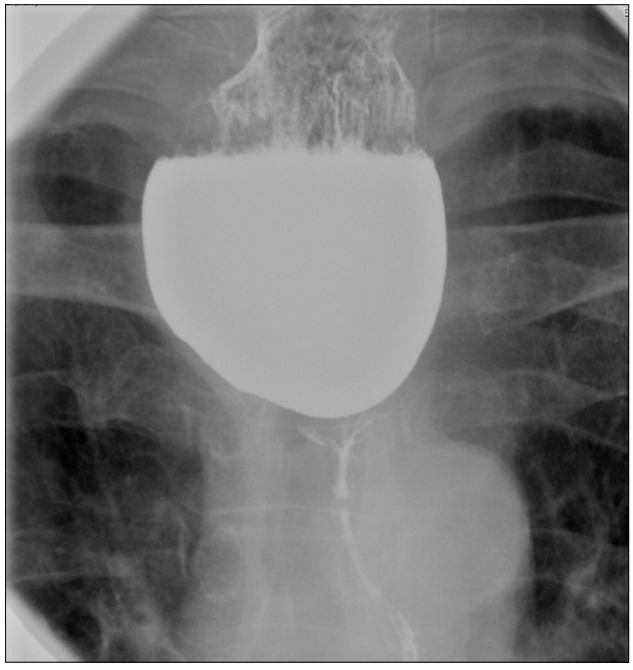

Figure 1. Barium swallow, anteroposterior view showing club-like diverticulum demonstrating large Zenker's diverticulum

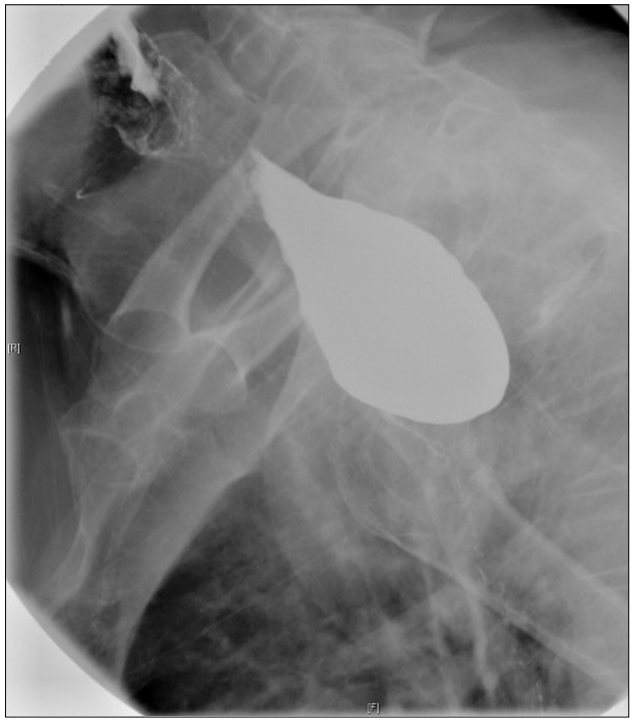

Figure 2. Barium swallow, lateral view showing the Zenker's diverticulum

DISCUSSION

The occurrence of SCC in a Zenker's diverticulum was first described by Halstead [5] in 1904 and subsequently reported in the literature as a very rare entity [3]. However, SCC in the pouch was usually diagnosed mainly after obtaining full histopathologic examination of the specimen following complete surgical resection [4,6]. Malignancy of the esophageal diverticula was mostly reported to be in the cervical esophagus, and the common locations of the malignancy in the pouch usually include the fundus or the lateral wall of the

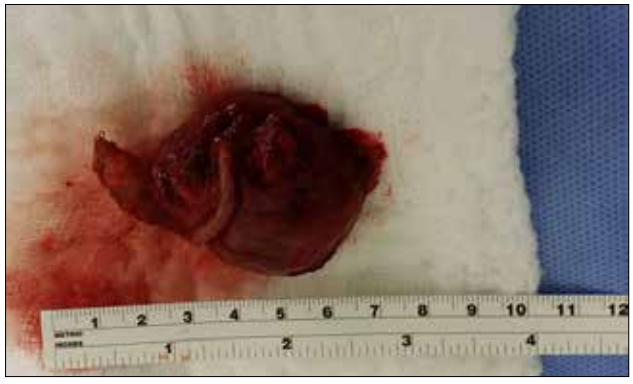

Figure 3. The resected Zenker's diverticulum specimen "pouch" consisted of a cyst-like lesion measuring 4.0×3.5×1.0 cm3

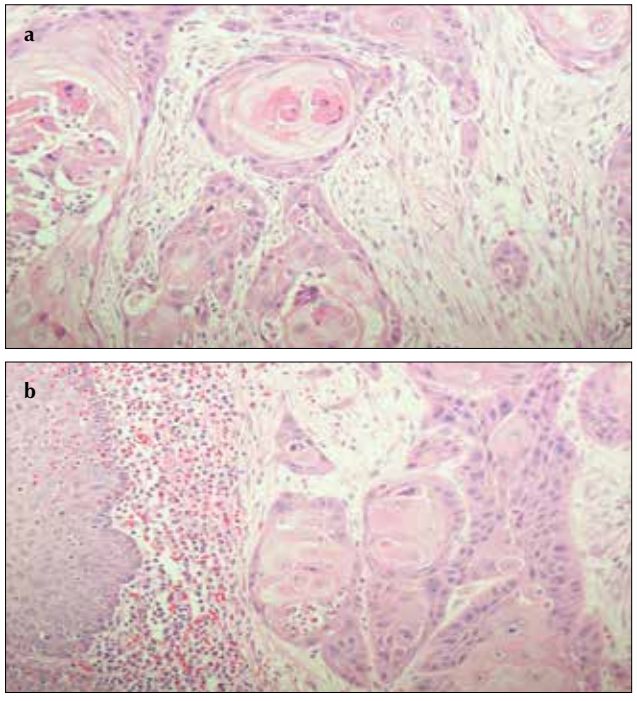

Figure 4. a, b. Microscopic appearance of the mass revealed an invasive, moderately differentiated squamous cell carcinoma. All resection margins were free, and there was no evidence of lymph vascular invasion (a); another view Figure 4a, the mass revealed an invasive, moderately differentiated squamous cell carcinoma (b)

distal two thirds of the pouch [4,7]. The risk factors for developing cancer of the pouch are the patient's old age, large pouch size, and long pouch life duration; a high frequency of food retention and manual emptying of the pouch by digital pressure increases cancer risk from the prolonged and direct irritation and inflammation [4-8]. Signs and symptoms suggesting malignancy of the pouch according to frequency, are changes in the character of dysphagia, rapid dysphagia progression, and less frequently weight loss, pain, blood in the regurgitated materials, and pouch recurrence after treatment [4].

Some reported cases of early SCC of the pouch showed normal morphology on endoscopic observation and did not present any alerting clinical symptoms or signs [6-8]. Contrast imaging and endoscopic observations are used to diagnose most of the cases of Zenker's Diverticulum but it could miss carcinoma in situ because the detection rate usu-

ally is less than 10%, where histopathological assessment of the complete resected pouch is the definitive modality of diagnosis [4]. However, Acar et al. recently reported that FDG-PET/CT could contribute to the diagnosis of SCC arising from a Zenker's diverticulum [9].

Siddiq and Sood [6] reported that the most common modality for treating Zenker's diverticulum is by endoscopic stapling or by diverticulectomy.

In our case, the patient had Zenker's diverticulum for 20 years and received multiple treatments endoscopically with recurrence. Recently, he complained of dysphagia, regurgitation, and weight loss, all of which support the literature review of the risk factors of SCC arising in Zenker's diverticulum.

In conclusion, the discrepancies in the reported cases suggest that SCC arising in Zenker's diverticulum is underreported in the English literature. The occurrence of SCC in the pouch is very rare. Clinical suspicion must be sought in patients with progressive dysphagia, weight loss, loss of appetite, blood in the regurgitated materials, and recurrence of the pouch. Carcinoma in situ within the Zenker's pouch has a high failure rate of detection, which is an area of concern. We advise complete surgical excision of the pouch for all patients with clinical suspicion regardless of their diagnosis with SCC or carcinoma in situ or not, to relieve the symptoms, prevent the complications of delayed recognition, and to maximize the therapeutic intervention.

Informed Consent: Written inform consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Design - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Supervision - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Materials - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Data Collection and/or Processing - W.M.H., O.T.A., M.A.J., S.A.A.; Analysis and/or Interpretation - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Literature Search - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Writing - W.M.H., O.T.A., M.A.J., S.A.A., E.R.; Critical Reviews - W.M.H., O.T.A., M.A.J., S.A.A., E.R.

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Letter to Editor

Reliability and Validity of the Turkish Translation of the Beliefs about Medicines Questionnaire (BMQ-T) in Patients with Behçet's Disease

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Dear Editor,

We have read with great interest the article entitled "Cross-cultural Adaptation and Validation of Beliefs about Medicines Questionnaire on Asthma and Chronic Obstructive Pulmonary Disease Patients" by Arıkan et al. [1], which appeared in the January 2018 issue of Turkish Thoracic Journal. In this article, the authors have stated that they evaluated the reliability and validity of the Beliefs about Medicines Questionnaire (BMQ) Turkish translation (BMQ-T) in patients with asthma and chronic obstructive pulmonary disease. However, it is not the first study assessing the validity and reliability of the BMQ-T, since my colleagues and I have published our study in 2016, wherein we assessed the reliability and validity of the BMQ-T for patients with Behçet's disease (BD) [2].

In the study by Arıkan et al. [1], in terms of reliability, the internal consistency of BMQ-T Specific Necessity, BMQ-T Specific Concern, BMQ-T-General Harm, and BMQ-T-General Overuse were 0.83, 0.72, 0.79, and 0.68, respectively. The original Cronbach's α values were 0.86, 0.65, 0.60, and 0.51, respectively [3]. Although the Cronbach's α values in our study was slightly lower than those of this study, the Cronbach's α values of our study (0.81, 0.67, 0.68, and 0.66, respectively) were consistent with those of the original version [2]. In addition, we calculated the intraclass correlation coefficient to assess test–retest reliability. An adequate statistically significant and positive correlation was observed between the first test and the retest scores ($p<0.05$) in our study. Additionally, we performed the paired samples t test and demonstrated that there was no difference between test and retest scores of the whole scales of BMQ-T ($p>0.05$) [2].

In both studies, the construct validity of the scale was evaluated using factor analysis. In our study, the total explained variance was 54.73%, and the lowest item load was 0.46 (2); in the study by Arıkan et al. [1], the total explained variance is 58.3%, and the lowest item load is 0.42 (2). In the study of Arıkan et al. [1], they found that the "natural remedies are safer than medicines", which is on the subscale of General Harm, has a lower factor load than the other items. They have reported that natural remedies that are being used for a long time are replacing conventional medicine. However, in our study, we found that the factor structure obtained is consistent with the original scale structure. We think that this is because patient groups with chronic diseases chosen in our studies were different [2].

The BMQ-T is a reliable and valid scale for evaluating patients' attitudes and beliefs about drug therapy in patients with chronic illness. Furthermore, it is valid and reliable in different disease groups, as shown in both studies. Our study is the first study in this context and our findings emphasize the utility of BMQ-T for assessing the beliefs of BD patients regarding their medicines.

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Author's Reply

We thank Çınar et al. [1] for their knowledgeable comments on our study. Their main concern is that their study published on May 2016 is the first study of Beliefs about Medicines Questionnaire (BMQ) in Turkish. This is indeed true. As we mentioned in acknowledgments, our study is a product of MECOR 2015 which took place in November. We did our literature search at that time. So, we did not come across for mentioned study and proceed as usual.

In our study, like Çınar et al. [1], we used factor analysis to show construct validity. But apart from that we provided confirmatory factor analysis and indices like comparative fit index, normed fit index and root mean square of error of approximation. These indices provide more insight to construct validity.

Unlike from Çınar et al. [1] we found that item G4 of BMQ which is "natural remedies are safer than medicines" has a lower factor load than original study. We speculated that natural remedies have been in the Turkish tradition for a long time and are regarded as a substitute for conventional medicine. As for chronic obstructive pulmonary disease and asthma although there is little data and that cannot be generalized we know that use of natural remedies like herbs or herbal teas is 46.7% [2]. Interestingly although we could not find any study regarding complementary and alternative medicine (CAM) use in Behçet's disease a study on rheumatoid arthritis revealed that 46.9% of patients used CAM [3]. This could be an interesting research topic and may provide us more insight regarding natural remedies.

In summary, although they may have diversity among results, we believe that both studies revealed that cross cultural adaptation of BMQ is valid and reliable in different patient populations.

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Letter to Editor

Behçet's Disease and Hemoptysis

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Behçet's disease (BD) is a very uncommon inflammatory and autoimmune condition that was first described in 1937 by the Turkish physician Hulusi Behçet. It is characterized by recurrent oral ulcers; genital, ocular, cutaneous, and vascular changes; and a positive pathergy test result [1-4]. Venous vessels are more often affected than arteries (aorta, femoral, lower extremity, mesenteric, coronary, renal, subclavian, and pulmonary). Importantly, the rupture of the pulmonary artery or aneurysms are factors of a poor outcome and the main cause of death in BD [1]. Pleural and parenchymal involvement, including infarcts, atelectasis, alveolar infiltrates, and ground-glass areas, and a tree-in-bud pattern may be found in less than 10% of the cases; pleural involvement in BD may cause nodules and effusions and reactive lymphadenopathies. Chest computed tomography is the best tool to diagnose and follow the course of these manifestations of BD [1]. Pericarditis, endomyocardial fibrosis, and coronary artery involvement have rarely been reported [2].

In a very interesting editorial recently published in this journal, Çağırıcı and Kılınç [5] briefly commented on key learning points associated with massive hemoptysis. They highlighted the lack of consensus on the definition of this severe condition, with published values ranging from 200 mL to 1000 mL of blood expectoration during a 24-h period. Moreover, they emphasized the life-threatening cardiopulmonary hemodynamic instability due to hemoptysis, which must be considered "massive," regardless of the blood loss amount. Hemoptysis may be caused by conditions such as arteriovenous malformation, pseudoaneurysm, bronchiectasis, tuberculosis, mycoses, abscess, polyangiitis, and pulmonary malignancy [5]. Additional comments were on the best timing of a surgical procedure in cases of hemoptysis from arterial (after embolization and clinical stabilization) or venous (immediate) vessels [5].

Abarca et al. [1] described the case of two male patients with BD and massive hemoptysis due to aneurysms in the pulmonary segmental and interlobar arteries, which were successfully controlled. The authors commented that in up to 29% of the cases, aneurysms may be an initial manifestation. The patients were 14- and 42-year-old males and presented with pulmonary thrombosis. The younger patient underwent total resection of the right lower lobe and received prednisone 20 mg daily, whereas the older patient had a good clinical outcome after receiving corticosteroids and cyclophosphamide.

The purpose of the comments included is to broaden the clinical awareness of non-specialists about uncommon entities that may also be the etiology of massive hemoptysis. In Brazil, although ethnic groups are not well characterized in relation to the risk of BD, this issue would be of primary interest for primary healthcare workers in the Mediterranean area, considering the high prevalence (71 per 100,000 people per year) in Turkish descendants [3]. Didactic editorials and case reports may enhance the suspicion index about rare conditions.

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Letter to Editor

Confusing Terminology: Difficult Asthma, Difficult-to-Treat Asthma, Difficult-to-Control Asthma, Therapy-Resistant Asthma, Severe Asthma, and Refractory Asthma. Which One is Truly Severe Asthma?

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Dear Editor,

Clear definitions of "difficult asthma" and "severe asthma" are very important in terms of using a common language in our daily practice. If a patient is diagnosed with severe asthma, determination of phenotypic patterns and assessing targeted treatments according to these phenotypes should be the next step. However, physicians often use the terms "severe asthma" and "difficult asthma" interchangeably and disagreeably. The term "difficult asthma" (also known as difficult-to-treat asthma or difficult-to-control asthma) is used for patients whose condition is uncontrolled despite GINA step 4 or 5 treatment. This uncontrolled asthma may be difficult to treat owing to inadequate or inappropriate treatment, comorbidities such as obesity, gastroesophageal reflux disease, chronic rhinosinusitis, poor adherence, and allergen exposure. Asthma may also be misdiagnosed. It is recommended that patients presenting with "difficult asthma" have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for longer than three months [1]. The most commonly accepted terminology for "severe asthma" (also known as refractory severe asthma, therapy-resistant asthma, or difficult-to-treat asthma), defined by the Task Force and supported by the European Respiratory Society and American Thoracic Society is, "The disease that remains uncontrolled despite GINA step 4 or 5 treatment (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year, or treatment with systemic corticosteroids for at least half of the past year, or if the disease can only be controlled with these treatments." [1]. In other words, "severe asthma" is a subset of "difficult asthma". The most significant point in these terminologies is that all difficult asthma should not need to be severe asthma. Difficult asthma can be defined as severe asthma only if all the factors have been excluded (Figure 1). GINA's definition of severe asthma is the same as the ATS/ERS consensus definition of severe asthma, and it has been reported that the definition of severe asthma should only be reserved for patients with truly severe asthma (refractory severe asthma or therapy-resistant asthma) [2].

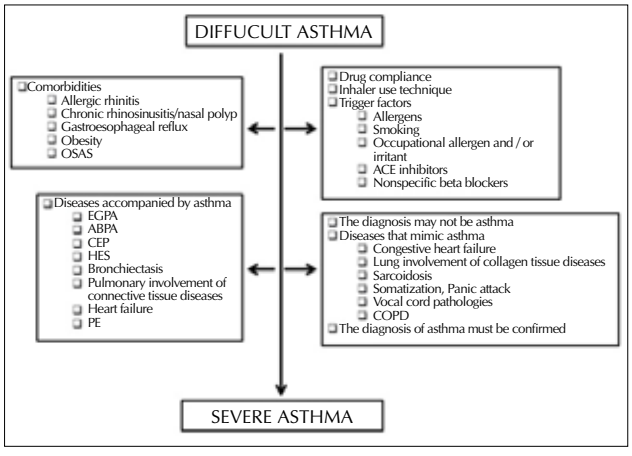

Figure 1. Differentiation between difficult asthma and severe asthma
OSAS: obstructive sleep apnea syndrome; EGPA: eosinophilic granulomatosis with polyangiitis; ABPA: allergic bronchopulmonary aspergillosis; CEP: chronic eosinophilic pneumonia; HES: Hypereosinophilic Syndrome; PE: pulmonary embolism; ACE: angiotensin-converting enzyme; COPD: chronic obstructive pulmonary disease

We believe that "difficult asthma" should be defined as the disease that is uncontrollable despite GINA step 4 or 5 treatment under all circumstances, and "severe asthma" should be defined as asthma that is controllable using GINA step 4 or 5 treatment or that which remains ''uncontrolled" despite this therapy after all the other factors (drug compliance, technique, differential diagnosis, and diseases accompanying asthma) have been excluded. In this way, the definitions of "difficult asthma" and "severe asthma" would become clearer. The use of just two clear definitions would eliminate the confusion surrounding terminologies such as difficult asthma, difficult-to-treat

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asthma, difficult-to-control asthma, therapy-resistant asthma, severe asthma, and refractory asthma. We also believe that patients with uncontrolled asthma should be referred to a clinic specialized in asthma as having "difficult asthma." In such cases, an asthma specialist should decide whether or not the patient has "severe asthma" and can further be treated using the most suitable phenotype-based options including monoclonal antibodies, long-term systemic steroids, or macrolides, or severe asthma may be excluded.

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Letter to Editor

Reporting Adverse Drug Reactions in a Tertiary Care Hospital in İstanbul

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Dear Editor,

The World Health Organization (WHO) defines adverse drug reactions (ADR) as "response to a drug that is noxious and unintended and occurs at doses normally used in men for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [1]. Reactions can be caused by any therapeutic agent, such as antibiotics, analgesics, blood products, vaccines or radiographic contrast media [2]. The reaction may be a well-known side effect of the drug or an undefined new reaction. Initially, many ADRs are unpredictable; they are mostly described after the post-marketing widespread usage [2]. Age, polypharmacy and additional diseases are the main risk factors for ADRs [3]. A study by Pirmohamed et al. [4] showed that patients admitted with ADRs were significantly older than patients without ADRs (76 versus 66 years). Therefore, ADRs pose a considerable burden among hospitalized patients who are more likely to be older and taking multiple medicines. ADRs are more common than expected among hospitalized patients; they may occur in up to 16.8% of patients during hospitalization, and 16% of these reactions may be fatal [5,6].

Spontaneous ADR reporting systems are used for surveillance of drug associated risks, and in many countries, the adverse drug reporting form is the standard of care for detecting the annual rate of ADRs in inpatient or outpatient settings. Additionally, a computer software and database for case report management have been designed for monitoring ADRs at some centers in Europe [2]. Questionnaires are an inexpensive and simple method for identifying new ADRs occurring in hospitals. The adverse drug reporting form can be filled by pharmacists, hospital doctors, nurses, and other healthcare professionals. However, many physicians are not aware of this form and are not reporting ADRs. According to the results of a survey, only 26% of physicians know which ADRs to report, 36% think that reporting is too bureaucratic, 22% do not know how to report and 18% are unaware of the need to report ADRs [7]. Doctors and other healthcare professionals also declare that they do not have enough time to report ADRs [7]. Nevertheless, in recent years, an increase in the proportion of reports, filled and sent by nurses and pharmacists, has been noticed [2].

At our institutions, we systematically monitor ADRs occurred during inpatient care. The ADR reporting forms are completed by our inpatient nurses immediately after an unwanted drug reaction has been detected. These forms include patients' demographic details, culprit drug, details of the reaction and the management of ADR (Figure 1) [8]. The ADR team at our hospital, which comprises a pharmacist, an allergist, a pulmonologist, and a nurse, is responsible for collecting data from the forms and organizing educational activities for improving ADR management. The allergist arranges training activities according to the needs of the staff and the pharmacist submits data to our national pharmacovigilance data system. Two training sessions are organized each year for inpatient nurses; these trains consist of updated education about drug interactions, ADRs, allergic drug reactions, and methods for appropriately filling out the ADR reporting form. Our reporting system provides valuable information to our healthcare professionals and helps them to be aware of the factors related to ADRs and prevention strategies to reduce the occurrence of unwanted drug reactions, accurate diagnosis, and effective management of ADRs, such as adrenaline use in anaphylaxis. Our computer based data collecting system will also be available in the near future and will help improve the service we provide.

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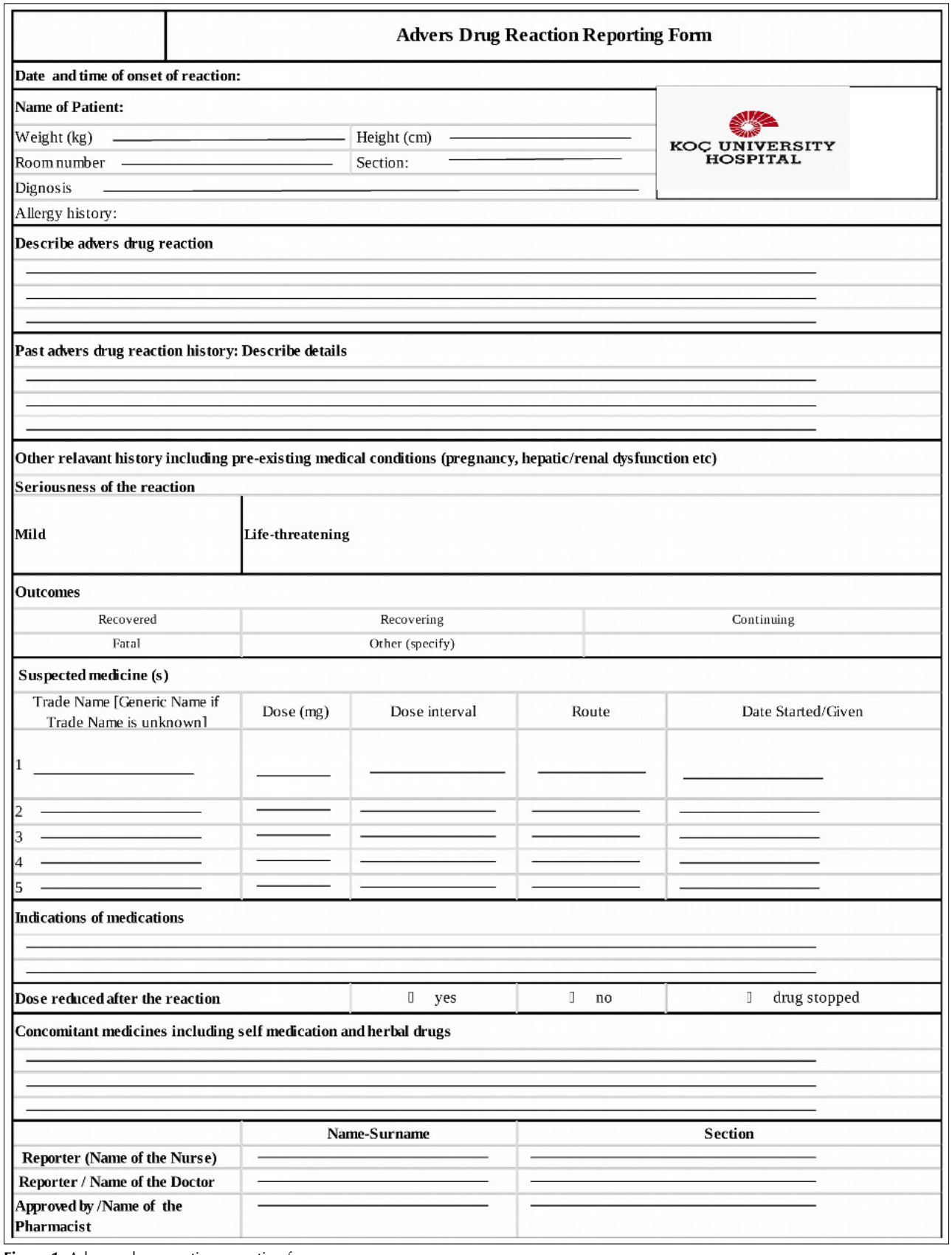

Advers Drug Reaction Reporting Form

Date and time of onset of reaction:

Name of Patient:

KOÇ UNIVERSITY HOSPITAL

Weight (kg) _____ Height (cm) _____

Room number _____ Section: _____

Dignosis _____

Allergy history:

Describe advers drug reaction

_____

_____

_____

Past advers drug reaction history: Describe details

_____

_____

_____

Other relavant history including pre-existing medical conditions (pregnancy, hepatic/renal dysfunction etc)

Seriousness of the reaction

Mild	**Life-threatening**

Outcomes

Recovered	Recovering	Continuing
Fatal	Other (specify)	

Suspected medicine (s)

Trade Name [Generic Name if Trade Name is unknown]	Dose (mg)	Dose interval	Route	Date Started/Given
1 _____	_____	_____	_____	_____
2 _____	_____	_____	_____	_____
3 _____	_____	_____	_____	_____
4 _____	_____	_____	_____	_____
5 _____	_____	_____	_____	_____

Indications of medications

_____

_____

Dose reduced after the reaction	☐ yes	☐ no	☐ drug stopped

Concomitant medicines including self medication and herbal drugs

_____

_____

_____

	Name-Surname	**Section**
Reporter (Name of the Nurse)	_____	_____
Reporter / Name of the Doctor	_____	_____
Approved by /Name of the Pharmacist	_____	_____

Figure 1. Adverse drug reaction reporting form

Adverse drug reactions are regularly recorded at our inpatient settings using ADR reporting forms, which are filled by nurses. The rate of ADR reporting has nearly quadrupled over eight years (Figure 2). Between 2016 and 2017, ADRs were observed in 65 of 14,347 hospitalized patients. The mean age of the patients was 49.2±19.4 years; 69% of all patients were female. Four of these patients were children, whereas the others were adults. There were no ADR-related deaths.

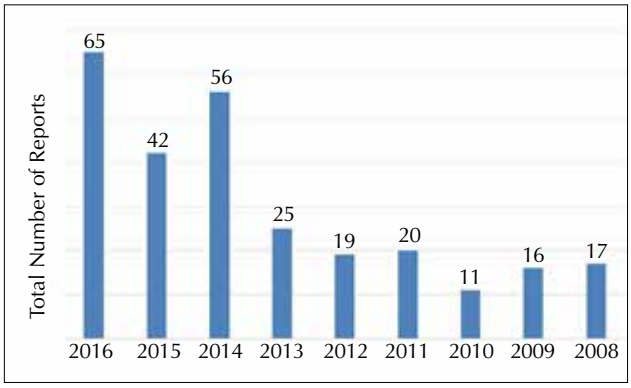

Figure 2. Total number of adverse drug reactions (ADRs) reported by inpatient nurses between 2008 and 2016

At our hospital, the ADR rate was particularly high in the elderly and patients receiving cancer treatment. The mean age of patients receiving cancer treatments was 56.1±14.6 years. Forty-seven reports were received from the adult oncology department. Seventeen of them had hematologic, 10 had urogenital, and 7 had gastrointestinal system malignancies. Eight patients had breast cancer, 3 had lung cancer, and 2 had other diseases. Nine patients had drug allergy and 2 had respiratory allergy history who reported ADRs. Chemotherapeutic and biologic administrations were mostly related to ADRs. Taxol and platinum salts were the most commonly used chemotherapeutic drugs; Rituximab was the most common among biologics. All reactions were allergic ranging from mild to severe. Five of these patients had tryptase results. After discussing the annual results of 2016–2017 at the ADR team meeting, we planned and realized two additional anaphylaxis management educations for nurses and healthcare professionals. We also discussed our results with the oncology team to provide effective management after chemotherapy and biological agent allergy, such as desensitization.

The routine use of ADR reporting forms increased the chemotherapeutic and biological drug allergy awareness at our hospital. Our inpatient nurses are now more aware of their responsibility to report ADRs and how to report them. Clinicians are now more aware of both the common occurrence of ADRs and their responsibility to manage them. We require greater use of such documentation in hospitals in Turkey. Therefore, improving reporting rates of ADRs would decrease the ADR-related mortality rates in hospitalized patients, particularly in the elderly population. This reporting system can only be successful if used more widely in hospitals. We should discover the potentials gaps for reporting ADRs in hospitals and find answers to improve the awareness of ADRs in hospital settings.

In conclusion, ADRs are common among hospitalized patients and may be severe. Older patients and the ones taking chemotherapeutic and biological drugs are more prone to ADRs. Additionally, allergic reactions occupy a significant place among all ADRs. The contribution of nurses and clinicians is essential to increase good pharmacovigilance practices. The routine use of the ADR reporting system is easy and inexpensive and may largely impact the safety and quality of patient-centered health care delivery.

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