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Turkish Thoracic Journal (Turk Thorac J 2017; 18:) 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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Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	35	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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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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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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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.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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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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EDITORIAL

See article: Uzel FI, Karadağ P, Tural Önür S, et al. A Basic Question: Are Patients with COPD Aware of Their Disease? Turk Thorac J 2017:18:114-8.

If You Know the Enemy and Your Weapons, You Need not Fear the Management of Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by irreversible and progressive airflow limitations [1]. The prevalence of COPD is approximately 20%, and it is one of the most important causes of morbidity and mortality [1]. Morbidity and mortality rates due to COPD are gradually increasing, and COPD has been estimated to be third leading cause of death by the end of 2020 [2]. However, it is not yet appropriately diagnosed and treated.

Although it is a frequent and severe disease, the general population lacks awareness on COPD. In a study from Canada, the awareness rate of COPD was 17%, whereas the awareness rates of breast cancer, HIV/AIDS, and Alzheimer's disease were 95%, 95%, and 94%, respectively [3]. In a study from Turkey, which is part of the Global Alliance Against Respiratory Disorders project, 49.6% of the participants correctly stated that COPD mainly affected the lungs [4]. Among the participants, 47% declared that they did not know which organ was affected. Ersu et al. investigated the awareness rate of COPD among primary care doctors, and approximately half of the primary care physicians answered that they were aware about COPD [5].

This issue of the journal includes a research study that evaluated awareness on COPD in patients with COPD. In this study, Uzel et al. administered a questionnaire to 201 ambulatory COPD patients in a single center [6]. The questionnaire comprised 15 questions related to the symptoms of COPD, the status of smoking, the meaning of COPD, the organ primarily affected and the location of the organ in the body, and the treatment and etiology of COPD. The authors also asked whether the patients searched for information on COPD. While 78% knew that the acronym "COPD" stands for chronic obstructive pulmonary disease, only 3.5 could correctly write chronic obstructive lung disease in Turkish. Three of four knew the affected organ to be the lung and its location. Sixty-six percent did not search for information about their disease, and 59% mentioned cigarette smoking as the most important causal factor of the disease. Education level was related awareness on the disease, but age and, interestingly, the GOLD stage did not. The compliance of patients to the treatment is an integral part of COPD management. In the current study, 12% of the patients believed that inhaler drugs cause addiction and 4.5% stated that COPD is a contagious disease. The promising side was that at least 53% of the patients believed that COPD is a treatable disease.

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REVIEW

Immune Checkpoint Inhibitors in Advanced-Stage Non-small Cell Lung Cancer

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Abstract

More than half of non-small cell lung cancer (NSCLC) patients are at an advanced stage at the time of diagnosis, and they have a poor prognosis. Systemic treatment is the basic treatment approach for advanced-stage NSCLC, and chemotherapy and targeted treatments are commonly used based on the molecular characteristics. Although targeted therapies have led to a significant level of improvement in terms of survival, the results are still unsatisfactory. However, considerable attention has been focused to the immunotherapy with recent positive results reported by studies on this field. In this context, a certain portion of clinical studies have shown dramatic results, and these have involved inhibitors developed particularly against the immune checkpoint protein programmed death receptor-1 and its ligand (programmed death ligand-1). This review aims to present the significance of immune checkpoint inhibitors in NSCLC and to summarize the findings of relevant contemporary clinical studies.

KEYWORDS: Non-small cell lung cancer, immunotherapy, checkpoint inhibitors

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death for both genders worldwide and poses a serious public health problem [1,2]. Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancers. More than 50% of NSCLC patients are at an advanced stage at the time of diagnosis, and they are characterized by a poor prognosis. In addition, 40-70% of the early stage NSCLC patients develop distant metastases throughout the course of the disease, despite curative surgical intervention [3-5]. Systemic treatment is the basic treatment approach for advanced-stage NSCLC; some patients receive radiotherapy if needed, and other specific patients may undergo surgical intervention. With regard to the planning of systemic treatment, the decision is made by taking patient- and tumor-related factors into account. Primary patient-related factors include age, performance status, and comorbidity, and main tumor-related factors include classification of the histological type and molecular analysis of the tumor, which are of key importance [6,7]. Today, recommended molecular analyses are epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) fusion oncogene and C-ros oncogene 1 analyses. After performing these analyses, relevant patients receive targeted treatments (erlotinib, gefitinib, afatinib, or crizotinib), while others are treated with systemic chemotherapy. These approaches extend the survival time and increase the quality of life. In addition, there are recent studies available on the BRAF, RAS, and MET pathways, all of which have reported considerably positive findings [8-10]. The agents targeting these pathways may be used in this field in the near future.

Recently, we have witnessed a key development in the field of immunotherapy for the treatment of NSCLC. A better identification of the immune pathways playing a role in tumor progression and growth in lung cancer, which is known to have a relatively low immunogenicity, and inhibitor agents specifically developed for them have led to renewed attention to immunotherapy. Following various pre-clinical and clinical studies demonstrating that blocked immune checkpoints increase the immune response and cause tumor regression, agents blocking these points have received considerable attention. This review aims to present the significance of immune checkpoint inhibitors in NSCLC and to summarize the findings of relevant contemporary clinical studies.

Immune Response

The immune response against tumors consists of four main phases. These are tumor identification, presentation of tumor antigens to antigen-presenting cells (APCs), presentation of APCs to immune effector cells after being processed (priming

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phase), and direct attack on the tumor with T-cell activation (effector phase). At the beginning of immune recognition, APCs internalize tumor antigens and migrate to lymph nodes. In lymph nodes, APCs present tumor antigens to resting T cells. The antigen-specific T-cell receptor complex plays a fundamental role in this process, and the interaction between B7.1 or B7.2 and CD28 contributes to this presentation (priming phase). Once activated, the T cell carries out an attack on the tumor cell and causes lysis of the tumor cell by releasing cytolytic enzymes such as perforin and granzyme (effector phase) [11,12]. All aforementioned phases of the immune response are controlled by various immune checkpoints that prevent excessive inflammation and autoimmunity. In the presence of malignancy, cancerous cells further activate these checkpoints and thus gain immunological tolerance [13].

Two significant checkpoints have been identified, and specific inhibitors for them have been developed. The first is cytotoxic T-lymphocyte antigen 4 (CTLA-4), which inhibits T-cell activity by competing with CD28 to bind to B7.1 and B7.2. The second checkpoint is programmed death receptor-1 (PD-1), which mainly takes place by the interaction of tumor and T cells. When programmed death ligand-1 (PD-L1) on the tumor cell binds to the PD-1 receptor on T cells, the T cells are inactivated and are unable to carry out the immune response against the tumor [14,15]. PD-L1 release from the tumor cell is reported to take place in two forms: inflammation through interferon gamma within the tumor microenvironment and oncogene-dependent tumor PD-L1 expression [16,17].

CTLA-4 Inhibitors

Ipilimumab

Ipilimumab is a full-human, IgG1 monoclonal antibody against CTLA-4. A randomized phase II study including advanced NSCLC patients without a history of systemic treatment examined the effectiveness of its addition to a carboplatin/paclitaxel combination in two different ways (concurrently or subsequently). The study concluded that adding ipilimumab was beneficial; however, the benefit was more visible in the squamous histology [18]. This study's Phase III design (carboplatin/paclitaxel/ipilimumab) is in progress.

PD-1 and PD-L1 Inhibitors

Nivolumab

Nivolumab is a full-human, IgG4 monoclonal antibody against PD-1 [19]. A phase I study in which it was examined as monotherapy in advanced-stage NSCLC treatment obtained an objective response rate (ORR) of approximately 20%, which increased by up to 31% in PD-L1-positive tumors and remained at around 10% in PD-L1-negative tumors [20]. However, in a phase II study including advanced-stage NSCLC patients with a squamous histology (Check-Mate 063), PD-L1-positive cases in a group of patients who had received two or more lines of treatment had an ORR of 24%, while this rate was 14% in PD-L1-negative cases [21]. Both studies considered a cut-off limit as 5% for PD-L1 positivity. Having demonstrated the benefit in case of squamous histology in a phase II study, the Check-Mate 017 study was conducted on advanced-stage NSCLC patients with the same histology. The study included 272 patients, and the patients who had received a line of treatment were randomized into nivolumab (3 mg/kg biweekly) or docetaxel (75 mg/m^2 every three weeks) groups. It was concluded that nivolumab was superior to docetaxel in terms of ORR (20% vs. 9%), median overall survival (OS) (9.2 months vs. 6.0 months), and 1-year survival (42% vs. 24%). The study considered ≥1% as the cut-off value for PD-L1 positivity, and the findings were reported to be independent of the PD-L1 expression status (Table 1) [22]. After those studies, nivolumab was approved by the Food and Drug Administration (FDA) in March 2015 to be used for the treatment of advanced-stage NSCLC patients with a squamous histology and progression after platinum-based chemotherapy.

There are other available studies conducted on the effectiveness of nivolumab in patients with a non-squamous histology. Check-Mate 057, a phase III study, included a total of 582 advanced-stage and non-squamous NSCLC patients who had previously received a line of treatment. The patients were randomized into nivolumab (3 mg/kg biweekly) or docetaxel (75 mg/m^2 every three weeks) groups. This study concluded that nivolumab was more effective than docetaxel in patients with a non-squamous histology (ORR: 19% vs. 12%; median OS: 12.2 months vs. 9.4 months, and 1-year survival: 51% vs. 39%, in support of nivolumab). This study also reported an association between survival advantage and PD-L1 positivity (Table 1) [23]. Following this study, the FDA expanded its approval to include patients with a non-squamous histology as well.

Recently, the results of the Check-Mate 026 trial evaluating the efficacy of nivolumab in the first-line treatment in advanced-stage NSCLC patients have been published [24]. The study considered ≥1% as the cut-off value for PD-L1 positivity, and a total of 541 subjects were randomized 1:1 into nivolumab (3 mg/kg biweekly) or platinum-based chemotherapy groups. The primary endpoint was progression free survival (PFS) as assessed by the Independent Radiology Review Committee in patients with ≥5% PD-L1 tumor expression. It was concluded that there were no differences between the two arms in terms of PFS [4.2 months vs. 5.9 months, hazard ratio (HR): 1.15] or median OS (14.4 months vs. 13.2 months, HR: 1.02) (Table 1). However, the high rate of crossover to nivolumab on the chemotherapy arm, the higher overall survival rates in the chemotherapy arm than in historical controls, a greater proportion of Asian patients included in the study, and patients with a broad range of PD-L1 expression (≥1%) might have affected the results [24].

Pembrolizumab

Pembrolizumab is a humanized, type IgG4, monoclonal antibody against PD-1. A phase I study (KEYNOTE-001) was conducted with pembrolizumab on an advanced-stage NSCLC patient group, majority of whom had received prior treatment. Pembrolizumab was administered at varying doses, and the study found an ORR of 19.4%, a median duration of response time of 12.5 months, and a median OS of 12 months. The study reported similar responses for both histologies, but the response rate was higher (around 45%)

Table 1. Results of completed clinical studies on PD-1 and PD-L1 inhibitors

Study	Author	Design	Phase	Patient characteristics	Results
Check-Mate 063	Rizvi et al. [21]	Nivolumab 3 mg/kg, bi-weekly	II	Advanced-stage NSCLC patients with squamous cells who received >2 lines of treatment	ORR in the whole group: 20% ORR in PD-L1-positive group: 31% ORR in PD-L1-negative group: 10%
Check-Mate 017	Brahmer et al. [22]	Nivolumab 3 mg/kg, bi-weekly vs. Docetaxel 75 mg/m^2	III	Advanced-stage NSCLC patients who progressed after the platinum-based combination CT	ORR: 20% vs. 9% Median OS: 9.2 months vs. 6.0 months 1-year survival: 42% vs. 24%
Check-Mate 057	Borghaei et al. [23]	Nivolumab 3 mg/kg, bi-weekly vs. Docetaxel 75 mg/m^2	III	Advanced-stage NSCLC patients with non-squamous histology, progressed after the first line of CT	ORR: 19% vs. 12% Median OS: 12.2 months vs. 9.4 months 1-year survival: 51% vs. 39%
Check-Mate 026	Socinski et al. [24]	Nivolumab 3 mg/kg, bi-weekly vs. Platinum-based chemotherapy	III	Previously untreated, advanced-stage NSCLC patients	PFS: 4.2 months vs. 5.9 months, HR:1.15 OS: 14.4 months vs. 13.2 months, HR:1.02
KEYNOTE-001	Garon et al. [25], Rizvi et al. [26]	Pembrolizumab 2 mg/kg, bi-weekly	I	Advanced-stage NSCLC patients with squamous cells who received >2 lines of treatment	ORR: 45% in the group with PD-L1 positivity of ≥50%
KEYNOTE-010	Herbst et al. [27]	Pembrolizumab 2 mg/kg, bi-weekly; 3 mg/kg, bi-weekly vs. Docetaxel 75 mg/m^2	II/III	Advanced-stage NSCLC patients with squamous cells who received >1 line of treatment	ORR: 18%, 18%, and 9% in patients with PD-L1≥1% 30%, 29%, and 8% in patients with PD-L1≥50% Median OS: 10.4 months, 12.7 months, and 8.5 months in patients with PD-L1≥1% 14.9 months, 17.3 months, and 8.2 months in patients with PD-L1≥50%
KEYNOTE-024	Reck et al. [28]	Pembrolizumab 200 mg, every three weeks vs. Platinum-based chemotherapy	III	Previously untreated, advanced-stage NSCLC patients	ORR: 45% vs. 28%, p<0.001 Median PFS: 10.3 months vs. 6.0 months, p<0.001 Median OS not reached in both arms
POPLAR	Fehrenba-cher et al. [30]	Atezolizumab 1200 mg, every three weeks vs. Docetaxel 75 mg/m^2	II	Advanced-stage NSCLC patients who progressed after the CT, platinum-based combination	ORR: 15% vs. 15% Response duration time: 14.3 months vs. 7.2 months Median OS: 11.4 months vs. 9.5 months
OAK	Rittmeyer A et al. [31]	Atezolizumab 1200 mg, every three weeks vs. Docetaxel 75 mg/m^2	III	Advanced-stage NSCLC patients who progressed after the platinum-based combination CT (2./3.line)	Median PFS: 4.0 months vs. 2.8 months Median OS: 13.8 months vs. 9.6 months Efficacy is correlated with PD-L1 expression
BIRCH	Besse et al. [32]	Atezolizumab 1200 mg, every three weeks	II	Advanced-stage NSCLC patients who had received/not received treatment	ORR in the whole group: Received treatment: 17% Not received treatment: 19% PD-L1 expression: ORR in TC≥50% or IC≥10%: Received treatment: 25% Not received treatment: 25%
Durvalumab study	Higgs et al. [33]	Durvalumab 10 mg/kg, bi-weekly	I	Advanced-stage NSCLC patients who received multiple lines of treatment in the past	ORR: Whole group: 16% Squamous group: 21% Non-squamous group: 13% PD-L1-positive group: 27% PD-L1-negative group: 5%
Avelumab study	Gulley et al. [34]	Avelumab 10 mg/kg, bi-weekly	Ib	184 advanced-stage patients who progressed after platinum-based chemotherapy	ORR: 12%, SD: 38%, and median PFS: 11.6 weeks

NSCLC: non-small cell lung cancer; CT: chemotherapy; ORR: objective response rate; SD: stable disease; PFS: progression-free survival; OS: overall survival; PD-1: programmed death receptor-1; PD-L1: programmed death ligand-1; TC: tumor cell; IC: immune cell

among those who had not received prior treatment and among those with PD-L1 expression higher than 50% (Table 1) [25,26]. Following this study, pembrolizumab was approved by the FDA in October 2014 to be administered to NSCLC patients who progress after platinum-based chemotherapy, who have a negative EGFR mutation and ALK rearrangement, and who express PD-L1.

A recent phase II/III study investigated the effectiveness of pembrolizumab on advanced-stage and progressive NSCLC patients who had received chemotherapy at least once. Including a total of 1,034 patients with PD-L1 expression of ≥%1, this study (KEYNOTE-10) randomized the patients into a pembrolizumab group at two different doses (2 mg/kg or 10 mg/kg every three weeks) or a docetaxel group (75 mg/m^2 every three weeks). The study concluded that pembrolizumab was superior to docetaxel in terms of ORR and survival, with no significant difference between the two doses of pembrolizumab. The study analyzed the results under two categories (PD-L1 positivity≥1% and ≥50%) and reported that both groups benefited from the drug, which was in support of the use of pembrolizumab. The patients with PD-L1≥1% presented ORR of 18%, 18%, and 9% for 2 mg/kg and 10 mg/kg pembrolizumab and 75 mg/m^2 docetaxel, respectively, while the corresponding rates were 30%, 29%, and 8% for those with PD-L1≥50%. Similarly, the patients with PD-L1≥1% presented median survival times of 10.4 months, 12.7 months, and 8.5 months for 2 mg/kg and 10 mg/kg pembrolizumab and 75 mg/m^2 docetaxel, respectively, while the corresponding rates were 14.9 months, 17.3 months, and 8.2 months for those with PD-L1≥50%. This study demonstrated that pembrolizumab was beneficial for the PD-L1≥1% group and the PD-L1≥50% group (Table 1) [27]. There are ongoing studies investigating the role of pembrolizumab as monotherapy or combination therapy in various lines of treatment. Those studies include PD-L1-positive patients.

The effectiveness of pembrolizumab was recently evaluated in a phase III study (KEYNOTE-024) in a first-line setting in advanced-stage NSCLC patients. A total of 305 patients with PD-L1 expression of ≥50% were randomized into pembrolizumab (200 mg/every three weeks) or platinum-based chemotherapy groups. This study showed that pembrolizumab was more effective than chemotherapy in terms of ORR (45% vs. 28%, p<0.001), median PFS (10.3 months vs. 6.0 months, p<0.001), and median OS (not reached in both arms, p=0.005). Further, less frequent grade 3/4 toxicities were reported in the pembrolizumab arm (26% vs. 51%) (Table 1) [28].

Atezolizumab

Atexolizumab is a humanized, type IgG1, monoclonal antibody against PD-L1. It was created through a special process to prevent the antibody-dependent cellular cytotoxicity that might be caused by active T cells. The phase I study reported an ORR of around 23% and a median survival of 16 months for the advanced-stage NSCLC patients who had received multiple lines of treatment [29]. This study evaluated PD-L1 expression in both tumor cells and immune cells infiltrating the tumor, and it reported a correlation between increased PD-L1 expression and increased response rates and survival times in those cells. The patients with a PD-L1 expression of ≥50% in tumor cells or ≥10% in immune cells had an ORR of 48% and a median OS of 18 months. The subsequent phase II POPLAR study randomized a total of 287 advanced-stage NSCLC patients who had received at least one line of systemic treatment into atezolizumab (1200 mg fixed dose, every three weeks) or docetaxel (75 mg/m^2 every three weeks). The study obtained a similar response rate (15%) in both arms, and the results supported atezolizumab in terms of response duration time (14.3 months vs. 7.2 months) and median survival (11.4 months vs. 9.5 months) (Table 1). This study evaluated PD-L1 expression in both tumor cells and immune cells infiltrating the tumor, and it reported a positive correlation between increased PD-L1 expression and survival time in those cells [30].

In a phase III trial (OAK trial), a total of 1,225 patients who had received a previous line of treatment were randomized into atezolizumab (1200 mg fixed dose, every three weeks) or docetaxel (75 mg/m^2 every three weeks). It was concluded that atezolizumab was superior in terms of median PFS (4.0 months vs. 2.8 months) and median OS (13.8 months vs. 9.6 months). Also, a positive correlation was reported between PD-L1 expression and response [31]. Based on these results, atezolizumab was approved by the FDA in October 2016 to be used for the treatment of advanced-stage NSCLC patients who had progressed after platinum-based chemotherapy (Table 1).

Recently, a phase II BIRCH study examined atezolizumab in a PD-L1-positive patient group, including patients with and without a history of treatment [32]. The study included a total of 659 patients, and PD-L1 positivity was defined as membranous staining in at least 5% of the tumor cells and/or immune cells in the tumorous area. The patient groups with and without a history of prior treatment had response rates of 17% and 19%, respectively. The findings were correlated with PD-L1 expression, and the group with a higher PD-L1 expression (≥50% in tumor cells or ≥10% in immune cells) displayed a response rate of 25%, which was more or less the same for both groups (Table 1) [32]. The studies on atezolizumab are ongoing for both first and later lines of treatment, including its application both as monotherapy and combined with chemotherapy.

Durvalumab

Durvalumab is a full-human, type IgG1, monoclonal antibody against PD-L1. It was subjected to a special process to prevent the antibody-dependent cellular cytotoxicity that might be caused by active T cells. As part of the phase I study, 200 advanced-stage NSCLC patients with a history of multiple lines of treatment received durvalumab (10 mg/kg biweekly) with a 16% response rate. In terms of histological sub-types, the squamous group had a higher response rate than the non-squamous group (21% vs. 13%). This study defined PD-L1 positivity as ≥25% membranous staining in tumor cells. The total response rate was 27% in the PD-L1-positive group, while it remained around 5% in the PD-L1-negative group (Table 1) [33]. There are ongoing studies on the administration of durvalumab both as part of the first line treatment and combined with curative chemoradiotherapy in advanced-stage local diseases.

Avelumab

Avelumab is a full-human, type IgG1, monoclonal antibody against PD-L1. As part of a phase Ib study including 184 advanced-stage NSCLC patients who progressed after platinum-based chemotherapy, avelumab was administered biweekly at a dose of 10 mg/kg and the ORR, stable disease (SD), and median PFS were 12%, 38%, and 11.6 weeks, respectively. The study considered ≥1% staining in the tumor cell to indicate PD-L1 positivity, and the ORR and median PFS were 14.4% and 11.7 weeks in the PD-L1 positive group, respectively, and 10.0% and 5.9 weeks, respectively, in the PD-L1-negative group [34]. As part of a phase Ib study including 145 metastatic NSCLC patients without a history of prior treatment, avelumab was administered biweekly at a dose of 10 mg/kg, and the ORR, SD, disease control rate, and median PFS were 18.7%, 45.3%, 64.0%, and 11.6 weeks, respectively. The study considered ≥1% staining in the tumor cell to indicate PD-L1 positivity, and the ORR was 20% in the PD-L1-positive group and 0.0% in the PD-L1-negative group (Table 1) [35]. There are other ongoing studies concerning different lines of treatment, especially Javelin Lung 200 that compares avelumab to docetaxel as second-line treatment.

Toxicity

Alongside their distinctive mechanisms of action, immune checkpoint inhibitors have demonstrated specific characteristics of toxicity. These toxicities are generally associated with the activation of the immune system and manifest themselves as skin rash, colitis, hepatitis, pneumonitis, endocrinopathies, and infusion reactions. These toxicities also exhibit a different pattern in terms of their time of occurrence; skin toxicities appear earlier, while endocrinopathies may occur relatively later. In an evaluation of basic grade 3/4 toxicities, the Check-Mate 063 study [21] reported 17% toxicity with nivolumab and diarrhea and pneumonitis were both observed at rates of 3%. The Check-Mate 017 [22] study reported total grade 3/4 toxicity rates of 7% and 55% for nivolumab and docetaxel, respectively. The KEYNOTE-010 [27] study reported rates of 13% and 35% for pembrolizumab and docetaxel, respectively. Alongside the monitoring of effectiveness, it is very important to thoroughly monitor and manage these specific toxicities through the follow-up and treatment processes of patients treated with checkpoint inhibitors.

Biomarker Status

Because the response rate obtained through immunotherapy has remained at around 15-20% and results depend on a series of factors associated with patients and tumors, researchers have felt it necessary to identify biomarkers [22,23,29,30]. Two biomarkers have gained prominence thus far: PD-L1 expression and mutational load status.

PD-L1 Expression Status

The PD-L1 positivity rate is reported to be approximately 50-60% in NSCLC. Regarding studies concerning the role of PD-L1 expression as a biomarker, some report that results obtained with immunotherapy are not related to PD-L1 expression, while others suggest a relation and a correlation with the positivity rate [22,23,27,30,31]. However, there are some issues concerning the consideration of PD-L1 expression as a biomarker. The first problem is the variable character of PD-L1 expression; a significant variability is reported between the biopsy material and resection material as well as between the primary tumor and metastasis. The second problem concerns the non-uniform character of the evaluation methods. The examination of PD-L1 expression in various studies with different methods and in the context of different cell groups [in the tumor cell (TC) or in both the TC and immune cell (IC)] leads to further heterogeneity [36-39]. The third problem pertains to the difference of cut-off limits assumed by studies. For instance, nivolumab studies take cut-off limits as ≥1%, 5%, 10%, 25%, and 50%, whereas pembrolizumab studies assume those limits to be <1% (low), 1%-49% (medium), and ≥50% (high). In atezolizumab studies, these values are scored as 0: <1% (TC/IC), 1: ≥1-<5% (TC/IC), 2: ≥5%-<50% (TC), ≥5%-<10% (IC), and 3: ≥50% (TC), ≥10% (IC) [29-32]. The International Association for the Study of Lung Cancer performs standardization studies in order to minimize all problems brought about by the heterogeneity of the evaluation methods for PD-L1 expression.

Regarding the role of PD-L1 expression as a biomarker, some studies (Check-Mate 063 and Check-Mate 017) report results independent of PD-L1 expression, while others (Check-Mate 057, KEYNOTE-001, KEYNOTE-010, and POPLAR) report results related to PD-L1 expression and even report a correlation with higher levels of PD-L1 expression (KEYNOTE-010, POPLAR). Two recent meta-analyses [17,40] and the aforementioned studies suggest that the effectiveness of PD-1/PD-L1 inhibitors is related to PD-L1 expression; while there was no benefit to PD-L1-negative cases, PD-L1-positive cases exhibited a significant level of benefit, which was observable beginning from ≥1%.

Mutational Load

Rizvi et al. [41] investigated the relationship between the mutational load and effectiveness in advanced-stage NSCLC patients receiving PD-1 inhibitor treatment and demonstrated that those with a non-synonymous mutational load had better rates of objective response, clinical benefit, and survival compared with those without non-synonymous mutational load. Likewise, they have also reported a correlation between a molecular smoking signature, higher neoantigen burden and DNA repair pathway mutations.

In conclusion, highly positive results consistent with immunotherapy-checkpoint inhibitors in particular-have been obtained in the treatment of advanced-stage NSCLC. Although the beneficial effect appears to be independent of PD-L1 expression, both clinical studies and meta-analyses indicate a significant level of benefits for PD-L1-positive cases and a positive correlation between the PD-L1 expression rate and response. However, further standardized examinations are required in order for PD-L1 expression to be utilized as a biomarker. Due to the high cost of immunotherapy drugs, biomarker studies are highly important for determining which groups of patients are likely to receive more benefits from such treatments. There are ongoing studies investigating the effectiveness of immunotherapy agents

utilized as monotherapy in different lines of treatment and combined with other treatment methods, particularly targeted agents. The findings of such studies are anxiously awaited.

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ORIGINAL ARTICLE

Results of Polysomnographies and Treatment Strategies in Elderly Patients with Symptoms of Obstructive Sleep Apnea Syndrome

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Abstract

OBJECTIVES: In this study, we evaluated data regarding the management of geriatric patients with symptoms of obstructive sleep apnea syndrome (age, >65 years) who were admitted to our sleep clinic.

MATERIAL AND METHODS: Symptoms and sleep data of the patients were retrospectively evaluated, and the patients were reevaluated after treatment.

RESULTS: A total of 85 patients with a median age of 69 years were included. Snoring and fatigue were the most common symptoms. Cardiovascular diseases were the most frequently listed comorbidity. The median Epworth sleepiness scale was 10, and based on Berlin sleep questionnaire findings, 63.5% of the participants were in the high-risk group. Eighty-seven percent were diagnosed with obstructive sleep apnea (2/3 of them were positional), and moderate-to-severe obstructive sleep apnea was observed more in women than in men. Only one patient was diagnosed with central sleep apnea. There were positive and linear correlations between increased age and the apnea-hypopnea index, arousal index, Epworth sleepiness scale, and being in a high-risk group according to the Berlin sleep scale; however, there was no correlation between increased age and the number of hypopnea and apnea events. There were also positive and linear correlations between the apnea-hypopnea index and the Epworth sleepiness scale, being in a high-risk group according to the Berlin sleep questionnaire, an increased number of known medical conditions, and increased body mass index. We were able to contact 72 of the 85 patients via phone calls. Patients who adjusted to treatment had positive feedbacks.

CONCLUSION: Sleep disorders are observed more in the elderly, and an increasing age is an independent factor for sleep disorders. Besides the usual signs and symptoms of sleep disorders, it should be considered in elderly who have cognitive dysfunction and dementia.

KEYWORDS: Elderly, polysomnography, obstructive sleep apnea

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INTRODUCTION

The proportion of elderly people (age, >65 years) has been increasing, particularly in developing countries. The World Health Organization has estimated that the population of people aged >65 years will be 1.5 billion by 2050 [1]. Although some people age without having any serious illnesses, some elderly might have "pathological aging" with significant comorbidities that lead to functional impairment [2]. One way or another, the elderly may complain of changes in sleep habits such as difficulty falling asleep and maintaining sleep, with frequent nocturnal awakenings and early morning awakening; thus, sleep gets more fragmented and consequently lighter [3]. Because of the changes in sleep architecture or physiological and/or pathological changes owing to aging, elderly people may report increased daytime sleepiness and fatigue as well as concentration and memory problems [4]. These symptoms can also occur because of obstructive sleep apnea syndrome (OSAS), which is characterized by nocturnal episodes of upper airway obstruction, sleep fragmentations, and hypoxemia [5]. These symptoms might be under-recognized in elderly patients because the presence of the symptoms might be accepted by patients, caregivers, or even by doctors as a "natural" occurrence of aging.

Obstructive sleep apnea defined as anapnea-hypopnea index (AHI) of >5/h is commonly observed in elderly (age >65 years), with a large range of incidence (5%-75%). Prevalence of OSAS ncreases with age, with a conservative estimation of double the prevalence in younger age groups [6]. There are several mechanisms associated with this age-related increase, including reduction in pharyngeal muscle function, age-related differences in pharyngeal morphology (including a decrease in the size of the upper airway lumen), increase in arousal frequency that leads to periodic breathing, and increase in the prevalence of obesity andcomorbidities [including congestive heart failure and neurocognitive impairment (such as dementia and stroke)] [7].

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Symptoms of sleep disorders are similarly observed in both younger and older populations [5]. However, there might be a great variability in the level of sleepiness with the same degree of OSAS. Obesity is main risk factor of OSAS and is reported to be less important in the elderly who usually have a lower body mass index (BMI) and neck circumference than in younger OSAS patients [3]. Polysomnography (PSG) is the gold standard diagnostic tool for evaluating OSAS, but only a small percentage of people at risk for OSAS have access to PSG, and using PSG in elderly populations with multiple comorbidities may be difficult [8]. Treatment options are similar for younger and older patients, as recommended by the American Academy of Sleep Medicine (AASM) [9].

In this study, we evaluated data regarding the management of geriatric patients with OSAS symptoms (age,>65 years) who were admitted to our sleep clinic. We assessed the correlation between age and sleep parameters, including the severity of the sleep disorder, and attempted to clarify the characteristics of sleep problems among elderly people. Moreover, the patients were re-evaluated and adherencerates to suggested treatment options were also assessed.

MATERIAL AND METHODS

Subjects

Eighty-five patients with a suspected diagnosis of OSAS and who were aged >65 years and were admitted to the sleep clinic at Baskent University Istanbul Hospital between January 2013 and December 2015 were enrolled in the study. After 6 months, these patients were contacted by telephone, and informed consent was obtained from the patients. Of 85 patients, 72 could be contacted, and their symptoms of OSAS and their adherence to treatment were assessed. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of Baskent University.

Demographic Data and Clinical Conditions

Baseline demographic characteristics, symptoms, and comorbidities were recorded on the basis of the responses given in the questionnaires filled at the outpatient clinic. The Epworth sleepiness scale (ESS) and Berlin sleep questionnaire (BSQ) scores, which predict the level of daytime somnolence and likelihood of OSAS, were recorded.

Sleep Study

All subjects underwent nocturnal PSG testing with the same polygraphic device (Grass Comet) at our sleep laboratory following the protocol of AASM [9]. Sleep studies were scored and analyzed according to the AASM recommendations by a medical doctor certified in sleep medicine. Other sleep disturbances such as central sleep apnea were excluded according to the PSG results. AHI, computed as the ratio of apneas and hypopneas per hour, was used to define the presence (i.e., AHİ of ≥5/h) and severity of OSAS (5-15 as mild, 15-30 as moderate, and >30 as severe) [9]. Titration studies with noninvasive ventilation (Resmed, S9, autocpap), as described by AASM, were performed in selected OSAS patients.

Statistical Analysis

IBM Statistical Package for the Social Sciences 21.0 (IBM Corp.; Armonk, NY, USA) and MedCalc statistical software were used in the statistical analysis. Descriptive statistics (frequency, percentage, mean (±), median [min-max]) were used to evaluate the numerical data in the study. The independent-sample *t*-test was used to compare parameters between the evaluated groups. For the analysis of difference between groups, non-parametric Mann-Whitney U tests and Kruskal-Wallis tests were used. Spearmen's correlation analysis was used to evaluate the relationship between age and AHI, arousal index, and number of apneas and hypopneas. Moreover, the relation between AHI and BMI, ESS, and BSQ scores was evaluated. Results were determined with 95% confidence intervals, and a p value <0.05 was considered statistically significant.

RESULTS

A total of 85 patients with a median age of 69 years (range, 65-88 years) were enrolled. Demographic data, symptoms, and comorbidities are summarized in Table 1. Snoring and fatigue were the most common symptoms. Cardiovascular disease (including hypertension and other heart diseases) was the most frequently listed comorbidity. As expected with aging, comorbidities were quite common. Comorbidities, such as chronic obstructive pulmonary disease (COPD) and cardiovascular diseases, or symptoms, such as memory problems, were assessed using standard procedures by specialists. Our patients were sleepy during the daytime, with a median ESS score of 10 (range, 1-24). On the basis of BSQ findings, 63.5% of patients were in the high-risk group.

Table 1. Demographic data, symptoms, and comorbidities of patients

Variables	n
Age (IQR), years	69.0 (67-74)
Sex (male/female)	52/33
BMI (IQR)	29.1 (25.7-36.9)
Symptoms (n, %)	
Snoring	81 (95.3)
Fatigue	75 (88.2)
Apnea	55 (64.7)
Daytime sleepiness	51 (60.0)
Waking up with a feeling of being drowned	41 (48.2)
Memory problems	37 (43.5)
Headache	21 (24.7)
Comorbidities (n, %)	
Hypertension	65 (76.4)
Heart disease*	37 (43.5)
Diabetes	36 (42.3)
COPD, asthma, and other lung diseases	14 (16.4)
Others	29 (34.1)
Number of comorbidities (IQR)	2.52 (1.25-3.0)

IQR: interquartile range; COPD: chronic obstructive pulmonary disease
*Coronary arterial disease, congestive heart failure, arrhythmias

Seven patients were administered alprozalam because of difficulty in falling asleep. Sleep efficiency and other PSG data are shown in Table 2. Twelve percent of patients (n=10) were diagnosed with simple snoring. Eighty-seven percent of the enrolled patients (n=74) were diagnosed with OSAS, with 16.4% (n=14) being mild, 30.5% (n=26) being moderate, and 40% (n=34) being severe OSAS. Nearly two-thirds of them were positional(in supine position AHI> 5, and in non-supine AHI <5) (n=46). Moderate-to-severe OSAS was observed more in women than in men [39 women vs. 21 men ($p<0.05$)]. Only one patient was diagnosed with central sleep apnea.

Rhinolaryngeal examination, positional therapy, and PAP treatment were the treatment options planned for the patients. Positional therapy and rhinolaryngeal examination were planned for 17 mild OSAS patients, and based on the rhinolaryngological examination findings, the severity of OSAS, and patients' preferences, two patients underwent a nasalseptum operation and one was treated with an oral appliance. For 61 patients, PAP treatment was planned; one of them had central sleep apnea and 60 patients had moderate-to-severe OSAS. Nine of the 60patients with moderate-to-severe OSAS refused to undergo titration. Finally, PAP treatment wasinitiated for the one central apnea patient and other 51 moderate-to-severe OSAS patients. Treatment options are summarized in Table 3. After 6 months wereevaluated the patients via phone calls, and their adherence to treatment, outcomes, and symptoms were assessed. We were able to contact 72 of 85 patients via phone calls. We couldnot reach three of nine patients who refused to undergo titration, and among the remaining six patients, only one got better with lifestyle modifications (BMI decreased from 33 to 24), whereasthe other five patients continued to have sleep disturbances. Forty-five patients who regularly used their devices (6.2±1.8 h/day for 6.3±0.7 days/week) had positive feedbacks, and most of their symptoms got better and their sleep disturbances reduced. We recommended all patients to change the mask each year, but only 37.8% of them renewed their mask yearly. Besides PAP treatment, 30 patients were recommended for other treatment options. We were able to contact 90% of the patients in this group, and 81% of them had positive feedbacks. People whose symptoms did not improve were the ones who did not comply with our suggestions.

We also performed a correlation analysis and evaluated if there was an association between age and the number of apnea-hypopnea events, AHI, arousal index, BSQ score, ESS score, and periodic limb movement index (PLMI). We observed a positive and linear correlation between increased age and AHI, arousal index, being in a high-risk group according to BSQ scores, and ESS scores; however, there was no correlation between increased age and the number of apnea-hypopnea events or PLMI (Figure 1, Table 4). We also performed a correlation analysis between AHI and ESS scores, being in a high-risk group according to BSQ scores, increased number of known medical condition, and increased BMI value, and there was a positive and linear correlation between AHI and all these parameters (Table 4).

Table 2. Polysomnography results

Variables (IQR)	
Sleep efficiency, % of TRT	77.9 (68.8-88.6)
Arousal index, /h	31.8 (18.5-49.4)
Total number of hypopnea events	63.0 (26.0-123.0)
Total number of apnea events	35.0 (8.5-79.5)
AHI, /h	24.2 (11.7-43.1)
Minimum oxygen saturation, %	82.0 (76.0-86.75)
Duration of oxygen desaturation (<88%), % of TST	2.7 (0.15-19.5)
PLMI	2.45 (0-14.1)

IQR: interquartile range; AHI: apnea-hypopnea index; NREM: non-rapid eye movement; TST: total sleep time; TRT: total recording time; PLMI: periodic limb movement index

Table 3. Treatment choices planned for the sleep apnea patients

Treatment option	n/%
PAP treatment	52 (69.3)
CPAP	35 (46.6)
BIPAP	10 (13.3)
BIPAP-ST	4 (5.0)
AUTO-CPAP	2 (2.6)
ASV	1 (1.3)
Nasal septum operation	2 (2.6)
Oral appliance	1 (1.4)
Positional therapy	14 (16.4)

PAP: positive airway pressure; CPAP: continuous positive airway pressure; BIPAP-ST: bilevel positive airway pressure; ASV: adaptive servoventilation

Table 4. Results of correlation analyses between evaluated parameters

	Variables	Correlation coefficient	p
	AHI	0.223	0.038
AGE	ESS score	0.253	0.022
	Arousal index	0.246	0.038
	High risk in BSQ score	0.329	0.016
	ESS score	0.457	0.001
AHI	High risk in BSQ score	0.620	0.001
	Number of medical conditions	0.215	0.031
	BMI	0.351	0.019

AHI: apnea-hypopnea index; ESS: Epworth sleepiness scale; BSQ: Berlin sleep quality; BMI: body mass index

DISCUSSION

This study was a summary of the data of an elderly population who were admitted to our sleep clinic. Snoring was the

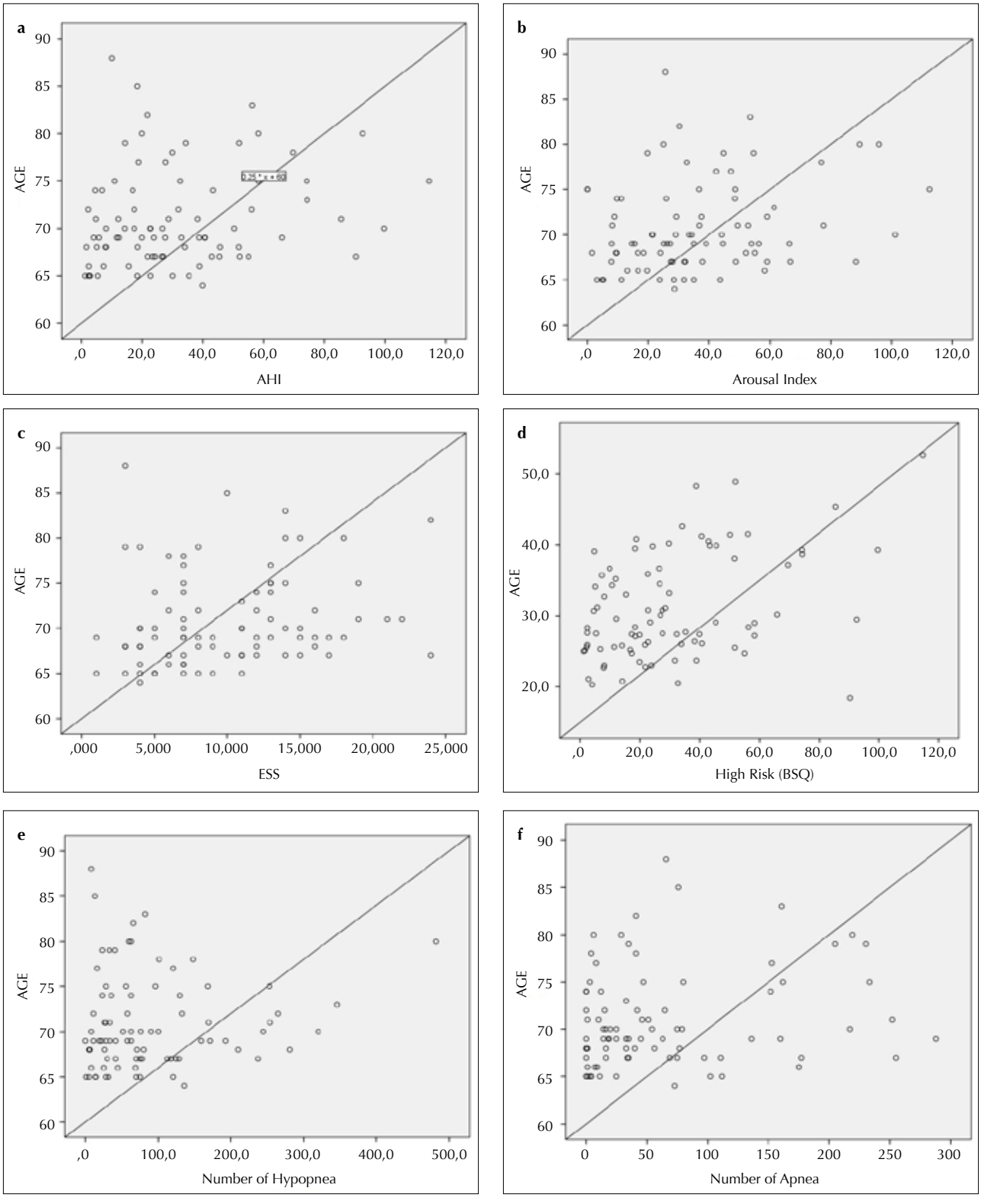

Figure 1. a-f. Correlation between age and sleep parameters. (a) Correlation between age and AHI. (b) Correlation between age and arousal index. (c) Correlation between age and ESS scores. (d) Correlation between age and being high risk in BSQ scores. (e) Correlation between age and the number of hypopnea events. (f) Correlation between age and the number of apnea events.

AHI: Apnea-hypopnea index; BSQ: Berlin sleep questionnaire; ESS: Epworth sleep scale

most observed symptom, and the patients mostly complained of fatigue. Most patients (60%) had moderate-to-severe OSAS, and we preferred PAP (mostly CPAP) treatment for such patients. No treatment was offered to people with AHI of <5. We first planned rhinolaryngological examination for people with AHI of 5-15, and if necessary, surgery was offered. The main aim of the study was to determine the risk of increasing age on sleep parameters, and we observed that increased age was a risk factor for increased AHI, arousal index, ESS score, and being in a high-risk group according to

BSQ scores. There was a positive and linear association between AHI and BMI, increased ESS scores, being in a high-risk group according to BSQ scores, and an increased number of known medical conditions. Most patients who adjusted to the PAP treatment and tried other treatment options had positive feedbacks.

Increased age, polypharmacy, and obesity are known risk factors for sleep disturbances [10]. In our study, the probability of observing OSAS was more in elderly people with more medical conditions and whose BMI was high. There was no difference in OSAS between men and women in our population (87% of men and 86% of women had AHI of >5); however, moderate-to-severe OSAS was observed more in women. Duran et al. [11] suggested similar results (80% of women and 81% of men had AHI of >5). The prevalence of OSAS is 2-3-fold lower in pre-menopausal women than in males, and with respect to post-menopausal women, the prevalence is equal [12]. Protective function of estrogen is lost in elderly in women because of menopause. At younger ages the prevalence of OSAS is more in men, however in elderly the prevalence of OSAS is more in women, and it may be related to loss of protective function of estrogen at that age group. Therefore hormone replacement therapy has been suggested as a therapeutic intervention for elderly women with OSAS [13]. In our study group, the most important risk factor for OSAS was obesity, andthe probability of having OSAS was 35.5% greater among obese patients than among those with normal BMI. In the current literature, it is estimated that overall, 50%-60% of obese people have OSAS [14], and obesity is a major risk factor for OSAS. Obesity promotes the enlargement of soft tissue structures within and surrounding the airway, contributing to pharyngeal airway narrowing. In contrast, impaired glucose metabolism in OSAS might be the reason for metabolic syndrome and obesity [15].

Snoring, fatigue, daytime sleepiness, and cessation of breath during sleep were the most common signs and symptoms we observed, and these symptoms can be observed in both young and elderly people with sleep disorders [5]. We also observed dementia and headache in our population. Dementia observed more in elderly people, and it may be directly related to OSAS. Day-time somnolence and sleep fragmentations may be the reason of cognitive dysfunction and also dementia. Therefore all the symptoms of dementia should not be associated with natural mechanism of getting older, moreover OSAS should also be considered in patients with symptoms of dementia. [16]. Such findings could simply occur because of the comorbidities in elderly people, but chronic hypoxia during sleep can cause neural injury, and this may be another reason for cognitive dysfunction and headache [17]. The overexpression of the apolipoprotein E (APOE) gene is observed in both Alzheimer disease and OSAS, and this may be another reason for the observed dementia in people with sleep disorders [18].

In elderly populations, age-related differences in pharyngeal morphology and reduction in pharyngeal muscle function are observed [19], and these are the basic mechanisms of OSAS in elderly people. In our study group, there was a positive and a linear association between age and AHI. As the age of our patients increased, the probability of a high arousal index increased, and it was previously shown that arousal frequency increases with age [20]. Our clinic is a sleep center in an university hospital, and most of our patients were referred from other clinics such as cardiology, endocrine and metabolism, and nephrology; therefore, these patients tended to have multiple comorbidities. We observed that the diagnosis of OSAS was more probable as the number of medical conditions increased. An increased number of comorbidities or polypharmacy can be the reason for sleep disturbances in elderly populations [21]. Diuretic therapy or diseases such as benign prostate hyperplasia might cause nocturia, or people with chronic renal or heart failure may have ortopnea or PND; and all of these may affect the sleep quality [22]. Being high risk in BSQ and having high ESS scores are positively and linearly correlated with both increased age and high AHI score, similar to that reported in previous studies [5,7,23]. In contrast, there have been studies in which ESS and BSQ scores had low accuracies for discriminating subjects with or without OSAS. Sforza et al. [8] showed that the third item of BSQ hypertension is not appropriate for discriminating OSAS because many people in this age group have hypertension; therefore, this item should only comprise obesity. Because of the decrease in symptom awareness in elderly people, ESS and BSQ scores might have limited use as indicators of sleep disorders [8,24]. Higher values of PLMI have been observed in elderly populations [25,26]; however, the median value of PLMI in our study group was 2.45, and there was no association between PLMI values and increased age.

Treatment options depend on the severity of sleep disease and the patient's symptoms. All patients were encouraged to pursue lifestyle modifications, including weight loss, cessation of smoking, increased exercise, and reduced consumption of alcohol and caffeine. Oral appliances and positional measures were preferred for people with symptomatic mild and moderate sleep disorders. PAP treatment is the mainstay therapy choice for moderate-to-severe sleep disorders [27]. Nearly 70% of our patients who followed our suggested treatment option got better, and 80% of them had positive feedbacks about symptom-related outcomes and quality of life. There have been a few prospective cohort studies in which outcomes of symptoms of sleep apnea patients were observed after CPAP treatment. Similar to our results, in these studies, improvement in sleep quality, cognitive functions, and quality of life were observed [28,29]. It was observed both in our study and previous studies that people who use PAP treatment regularly have perfect outcomes [30,31].

This study has some limitations. We could have had more exact results if the study was prospectively designed, and the measurements of the records of sleep data in the PAP devices would have been better than phone calls.

In conclusion, sleep disorders are observed more in the elderly, and increasing age is an independent risk factor for sleep disorders. Besides the usual signs and symptoms of SDB such as snoring, daytime somnolence, and fatigue, OSAS should be considered in the elderly who have cognitive dysfunction or dementia.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University School of Medicine.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.O.U.; Design - B.B., A.Ö.U.; Supervision - A.Ö.U.; Resources - B.B., A.Ö.U.; Materials - A.Ö.U.; Data Collection and/or Processing - B.B.; Analysis and/or Interpretation - A.Ö.U.; Literature Search - B.B.; Writing Manuscript - B.B.; Critical Review - A.Ö.U.

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ORIGINAL ARTICLE

A Basic Question: Are Patients with Chronic Obstructive Pulmonary Disease Aware of Their Disease?

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Abstract

OBJECTIVES: Increased awareness and understanding of chronic obstructive pulmonary disease (COPD) is important for its management, but there are limited data regarding the basic knowledge among patients with COPD. This study aimed to evaluate the basic information and knowledge of patients who were specifically provided with a medical exemption certificate for COPD.

MATERIAL AND METHODS: This cross-sectional, observational, single-center study was conducted at an outpatient clinic of our hospital and included 201 consecutive ambulatory patients who visited the outpatient clinic between January 01, 2015 and June 30, 2015. Data regarding sex, age, educational level, symptoms, smoking history, years since diagnosis, years since obtaining the exemption certificate, and COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease-GOLD) stage were obtained. A questionnaire comprising 15 questions was used.

RESULTS: The question regarding the organ primarily affected by COPD was correctly answered as "lung" by 145 (72%) of patients. In addition, 152 (76%) patients declared that they knew the localization of the affected organ; only 44 (22%) patients correctly located the organ on an image. Only seven (3.5% of the total) patients could correctly write "chronic obstructive pulmonary disease."

CONCLUSION: The lack of awareness among patients with COPD emphasizes the lack in the field of patient education. Simple questionnaires can be used to determine and also to improve the awareness and basic knowledge among patients with chronic diseases.

KEYWORDS: Chronic Obstructive Pulmonary Disease, awareness of disease, patient education

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INTRODUCTION

Chronic respiratory diseases are a major cause of morbidity and mortality. According to the World Health Organization (WHO) fact sheet that was updated in January 2017, chronic obstructive pulmonary disease (COPD) claimed 3.2 million lives in 2015 and is projected to rank third in 2030, with 8.6% in burden of disease caused worldwidewhich is a modelling technique that combines multiple data sources to count and compare the total fatal and nonfatal health loss from diseases and injuries in a population [1]. In 2013, a survey regarding chronic diseases and risk factors conducted in Turkey reported that COPD prevalence based on self-reporting of a doctor's diagnosis or spirometry was 5.0% (4.9% in males and 5.1% in females). In addition, 46.1% of patients with COPD regularly used medication [2]. Many attempts are being made to mitigate the negative effects of COPD on the general health worldwide. Increasing the awareness level regarding the disease is one of the key components of these attempts. WHO established the Global Alliance Against Respiratory Disorders (GARD) project with the aim to reduce the global burden of chronic respiratory diseases. [3]. As a participant of GARD project, Turkey conducted studies to evaluate the knowledge and awareness regarding asthma and COPD in the general population [4]. Increased awareness and understanding of COPD is an important part of disease management, but there are limited data about the basic knowledge of the disease among patients with COPD. We often forget to ask the simple questions regarding the organ that is the main target of a specific disease.

This study aimed to evaluate the basic information and knowledge of patients with COPD with regard to the educational level and GOLD stages; these patients were specifically provided with a medical exemption certificate for COPD.

MATERIAL AND METHODS

Study Design

This was a cross-sectional, observational, single-center study that was conducted at an outpatient clinic of our hospital.

This study was presented at the 19th Annual Congress of Turkish Thoracic Society, 6-10 April 2016, Antalya, Turkey.
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Patients

A total of 201 consecutive ambulatory patients who visited the outpatient clinic between January 01, 2015 and June 30, 2015 and who were provided with a medical exemption certificate for COPD were included. This certificate is given to patients with chronic diseases with the approval of the relevant specialists in Turkey. In case of COPD, these specialist are either Internal Medicine or Pulmology specialists. This is a kind of proof that the patient suffers from this disease and needs lifelong treatment.

Participants were excluded if they were diagnosed with dementia or mental illness or if they were illiterate because that would prevent them from answering the questionnaire. The participating physicians were trained to standardize the application of the questionnaire. The patients filled the forms themselves, and only simple objective answers were given to them. All patients gave written informed consent to participate in the study. This study was approved by the ethical committee of our hospital (registration number 2015/38).

Measurements

Data regarding sex, age, educational level, COPD-related symptoms, smoking history, years since diagnosis, years since obtaining exemption certificate, and COPD GOLD stage were obtained. A questionnaire comprising 15 questions regarding COPD diagnosis, as well as the basic knowledge regarding the human body and health literacy, was used (Figure 1). The questionnaire required an average of 20 min for completion. Although the questionnaire is not validated, it includes questions about the main symptomatology of the disease, the beliefs related to the cause of COPD and its treatment, the location of lungs, and the meaning of COPD.

1- When did you get the diagnosis of COPD?
a) 0-1 years b) 2-5 years c) 6-10 years d) more than 10 years

2- When did you get the medical exemption certificate for COPD?
a) 0-1 years b) 2-5 years c) 6-10 years d) more than 10 years

3- Do you cough on most days of the week?
Yes No

4- Do you have sputum on most days of the week?
Yes No

5- Do you have more shortness of breath when compared to persons of your age?
Yes No

6- Did you smoke before or are you still smoking?
Yes No

7- Do you know what COPD means? Can you write, what the acronym stands for?
Yes No

8- Which organ is primarily affected by COPD?

9- Do you know the localization of this organ? If yes, please sign:

10- Do COPD drugs cause addiction?
Yes No I do not know

11- Do COPD drugs cause weight gain?
Yes No I do not know

12- Is COPD a contagious disease?
Yes No I do not know

13- Is COPD a treatable disease?
Yes No I do not know

14- What is the most important causal factor of COPD?

15- Did you make any information search for COPD (book/leaflet/internet)?
Yes No

Figure 1. The questionnaire

Table 1. Characteristics of the study patients

	n	%
Male:Female	179:22	89:11
Age group, yr		
40-49	12	6.3
50-59	57	29.8
60-69	81	42.4
≥70	51	21.5
Education		
Uneducated	24	12
Primary school	135	67.2
Secondary school	26	13
High school	13	4.5
University	3	1.5
Smoking status		
Current or ex-smoker	130	65
Never smoked	81	35
COPD history, yr		
<1	42	21
2-5	71	35
6-10	56	28
>10	30	15
Medical exemption certificate history, yr		
<1	52	26
2-5	80	40
6-10	57	28
>10	12	6
GOLD stage		
A	74	37
B	41	20
C	26	13
D	60	30

The educational level was categorized as follows: a) completed primary school (duration of 5 years), b) completed secondary school (duration of 8 years), c) completed high school (duration of 11 years), d) completed university, or e) uneducated (not attended any level of education). COPD stage was determined as combined assessment using symptoms, breathlessness, and risk for exacerbations according to the GOLD update 2016 [5]. The patients were first staged according to dyspnea using the modified Medical Research Council dyspnea scale, followed by risk assessments of exacerbations using spirometry for determining the GOLD grade of airflow limitation, the number of exacerbations the patient experienced in the previous 1 year, or if the patient had one or more hospitalizations owing to COPD exacerbation within 1 year, whichever was available. All the patients were classified as GOLD stage A, B, C, or D.

Statistical Analysis

Data was analyzed using Statistical Package for the Social Sciences version 20.0 (SPSS Inc.; Chicago, IL, USA).The study findings were expressed as categorical variables. The values were presented as percentages for qualitative data. Descriptive statistics (counts and frequencies in percent) was used. The sample size was calculated for α=5% and β=20%. The sample size required for detecting a 10% difference of proportion according to the knowledge of COPD was calculated as 194 patients, with a focus on previous data of nearly 50% awareness that COPD patients have regarding their disease. Fisher's exact test was used to compare the educational level, GOLD stages, and awareness levels among the patients.

RESULTS

Characteristics of COPD Patients

Five pulmonologists provided data of 201 patients who visited the outpatient clinic of our hospital. The characteristics of the patients are described in Table 1.

Regarding symptoms, dyspnea was more prevalent than cough and sputum production (60% vs. 36% vs. 38%).

Knowledge of and Beliefs Regarding COPD and Lungs

The first part of question 7, i.e., "Do you know what COPD means? Can you write what the acronym stands for?" was answered as "no" by 156 (78%) patients. Of the remaining 45 patients, only seven (3.5% of the total) could correctly write "chronic obstructive pulmonary disease." There was no statistically significant association between the GOLD stages and the lack of knowledge (p=0.678). Patients in all COPD stages were equally unaware of the meaning of COPD. Conversely, having graduated from primary school and the lack of knowledge were statistically significantly associated (p=0.002).

The question regarding the organ that was primarily affected by COPD was correctly answered correctly as "lung" by 145 (72%) patients. Forty (20%) patients did not know the correct answer and did not mention another organ. Of 40 patients, 22 (55%) belonged to the GOLD stage A. The difference between the "knowing" and "not knowing" groups with regard to the GOLD stages was statistically significant (p=0.052). When the answer to the same question was compared between two age groups, namely ≤60 and ≥60 years, the difference was not statistically significant (p=0.098). Hence, age did not a play a role in the awareness about the affected organ.

Of all patients, 152 (76%) declared that they knew the location of the affected organ; only 44 (22%) patients correctly located the organ on an image. The location was decided to be correct if both lung fields were marked in the thoracic region. Sixty-three (31%) patients indicated the thoracic region but did not fulfill this criterion.

Twenty-four (12%) patients believed that the drugs used for treating COPD caused addiction, whereas 101 (50%) patients had no idea regarding this issue.

With respect to the question about the causal association between COPD drugs and obesity, 40 (20%) patients gave a positive response, whereas 98 (49%) gave a negative response ("no"); 63 (31%) patients did not have an answer.

Only nine of 201 (4.5%) patients considered COPD to be a contagious disease; 132 (66%) patients answered that COPD was not contagious, whereas 46 (23%) patients had no idea regarding the same.

More than half of the patients (n=106; 53%) responded that COPD was a treatable disease.

Cigarette smoking was mentioned as the most important causal factor of the disease by 118 (59%) patients; 41% of patients with COPD did not mention cigarette smoking as a causal factor.

Furthermore, 132 (66%) patients did not research regarding their disease, thus reflecting the health literacy in this population.

DISCUSSION

Our study population only comprised specialist-diagnosed patients with COPD. Being unable to correctly write down the name of the disease, not knowing the main target organ, and being unaware of cigarette-COPD association were considered to be thought provoking. This lack of awareness and basic knowledge among patients who visit a reference hospital in the biggest city of our country was the most striking result of our study.

While there was no statistically significant association between GOLD stages and the lack of knowledge (p=0.678), having graduated from primary school and a lack of knowledge were statistically significantly associated (p=0.002).

Awareness and basic knowledge regarding the disease, in the general population and in patients with the specific disease, are important factors in the management of the chronic disease. Many studies in Turkey and worldwide have been designed to identify and fill the gap regarding the awareness of COPD.

A study, designed and performed as the GARD project in Turkey, revealed that 49.6% of the population of subjects aged >15 years was aware that COPD was a lung disease and that the most important causal factor was cigarette smoking [4]. Only 25.2% of the population accepted COPD to be a treatable disease. Ersu et al. [6] investigated the awareness regarding COPD among primary care doctors in Turkey who were not previously provided any education. More than half of them correctly responded to the questions regarding the awareness and 83.4% of them considered spirometry to be a diagnostic tool.

There are many studies attempting to investigate the awareness about COPD in the general population or doctors. On the other hand, studies that shed a light on the awareness of patients with COPD themselves are scarce [7-9].

Some questionnaires have been developed to evaluate the level of knowledge of patients with COPD, and one of them is the Bristol COPD Knowledge Questionnaire [10], which examines the level of knowledge and the effects of education. We developed a simple questionnaire comprising 15 questions, because there is no validated tool for generally assessing COPD knowledge in our country, we developed a simple questionnaire comprising 15 questions.

The international BREATHE study was conducted among the populations of 10 countries in the Middle East and North Africa [7]. It identified subjects aged ≥40 years who fulfilled the epidemiological definition of COPD and examined their perceptions regarding the disease, as well as their attitudes and beliefs. It was found that 19.3% of patients had a university degree and 31.6% had a high school degree, whereas in our study, the population had a much lower education level, with only 1.5% having a university degree and 3.5% being high school graduates. Overall, 50.3% of patients identified smoking to be the underlying cause, which was in concordance with our result of 59% of patients. The educational level of our patients was not high; thus, their intellectual ability was not good. Compared with the general Turkish population according to the 2013 data of Turkish Statistical Institute, our study population had a lower education level, with 80% of our patients having less than a high school education level compared with 54% of the general population. This can be attributed to the fact that COPD affects people with lower socioeconomic status and that these patients frequently visit state hospitals.

Another study that examined comorbidities, patients' knowledge, and disease management of patients with COPD in a national sample in USA showed that patients with COPD had a much better recall of their blood pressure and cholesterol levels than their FEV_1. This was considered interesting as lung function is a stronger independent predictor of survival than blood pressure or cholesterol levels [8]. This again underlines the need for a more public education of COPD.

In Korea, with a COPD prevalence of 17.2%, a nationwide survey was developed to explore the behavior of patients with COPD [9]. The proportion of well-educated respondents among the 300 subjects was low, similar to our study population. Furthermore, 42 % of the subjects did not know the exact diagnosis of their condition, with the percentage decreasing to 30% among very severe patients. Low awareness appears to be a global problem with regard to such an important disease.

A striking fact is that 41% of our patients were unaware about the association between cigarette smoking and COPD. After evidence was found that tobacco package health warnings increased the consumers' knowledge about the health consequences of tobacco use, Turkey was one of the countries that transferred this into practice in 2010. There is actually no package warning mentioning COPD in our country and this could explain the basic lack of knowledge regarding this association. Adding warnings about COPD on cigarette packages could be a simple method of increasing attention to this disease.

Many programs have been developed worldwide to improve patients' education and awareness regarding chronic diseases. The International COPD Coalition was organized in 2001 to improve awareness regarding COPD.

A survey completed in 41 countries showed that there was a global increase in awareness since 2001, with almost 37% of the countries reporting a public awareness of ≥20% [11].

Health literacy is defined as the degree to which individuals can obtain, process, and understand basic health information and use this information to make appropriate health decisions. A study that investigated the health literacy among patients with cardiac disorders using the Short Test of Functional Health Literacy in Adults found out that inadequate or marginal health literacy was a risk factor for re-hospitalization owing to heart failure or all-cause mortality among rural patients with heart failure [12]. Although we did not use a specific tool to determine the health literacy level of our study population, 132 (66%) patients did not research regarding their disease, reflecting the lack of health literacy in this population.

This study has some limitations. Because the study was a single-center study, its generalizability was limited. The awareness level of patients visiting a teaching and reference hospital should be a reference point for other facilities, emphasizing the importance of general education for patients with COPD. The questionnaire that we used in this study was not a validated one. Furthermore, we did not perform a pilot study to evaluate its appropriateness. The majority (80%) of our patients were either uneducated or only completed primary school. Hence, a comparison regarding awareness among different educational levels was not possible. We did not assess the financial burden of medications or hospital admissions, which increase the costs of the healthcare system.

There is a lack of awareness and knowledge regarding the disease among patients with COPD regardless of the disease stage. Being unable to write down the name of the disease may be attributed to the general low educational level of the patients, but the ability to name the target organ and the awareness of the association between cigarette and COPD should be achieved for these patients. An educational program should be developed, which can be extended to the majority of patients with COPD, and further studies should be designed with a large number of patients, which evaluate the status before and after educational intervention.

Practice Implications

Simple questionnaires can be used to improve the awareness and basic knowledge of patients, particularly those with chronic diseases. This may be very helpful in directing our efforts to improve disease management.

Ethics Committee Approval: Ethic committee approval was received for this study from the Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Decision No: 2015/38).

Informed Consent: Written informed consent was obtained from the participants for this study.

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

Characterization of Chronic Obstructive Pulmonary Disease Patients with a Long Length of Stay: A Retrospective Observational Cohort Study

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Abstract

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) exacerbation is one of the most common reasons for hospital admission. Patients with COPD with a long length of stay (LoS) occupy a disproportionately high fraction of hospital bed-days. The objective of this study was to identify associations of long LoS in patients admitted with COPD exacerbation.

MATERIAL AND METHODS: From December 2012 until June 2013, 499 patients were admitted to Queens Hospital, Romford, UK, with COPD exacerbation. Mean LoS was 7 days, with a median of 5 days, and a 90th percentile of 14 days. In this retrospective observational cohort study, 64 patients with a short LoS were compared with 62 patients with a long LoS.

RESULTS: Relative to the short LoS, patients with long LoS had significantly lower arterial blood pH, higher arterial PaCO2 and HCO3, higher white cell count, higher globulin and more frequent chest X-ray changes, lower albumin levels, and lower Barthel and Braden scores. They were less likely to have seen the hospital COPD specialist nurse, more likely to require escalation of social care on discharge, and more likely to die during admission. Nearly 66% of the long LoS patients remained in hospital beyond the time of being medically fit for discharge. Commonly cited reasons for delayed discharge were the wait for therapy and social services assessments and the wait for commencement of community social care.

CONCLUSION: Meticulous targeting of features peculiar to long LoS patients has the potential to reduce future hospital bed-days for patients with COPD in our and other hospitals.

KEYWORDS: Chronic obstructive pulmonary diseases, length of stay

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common chronic disease in the UK with a likely prevalence of 3 million people or 4% of the population [1]. Episodic exacerbations are usual and often require hospital admission. COPD exacerbation is the second most common reason for emergency admission to hospital behind circulatory disease and is associated with considerable risks of re-admission, death, and expense. Each COPD hospital admission is estimated to cost NHS commissioners £1960 [2].

Estimates of typical length of stay (LoS) vary in the published literature. A British Thoracic Society study found a mean value of 7.1 days, whereas in Norway, it was 8.9 days, and a study in Blackpool reported 9.8 days [3-5]. Importantly, there is significant variation across England and Wales between many aspects of service provision and clinical outcomes for patients with respiratory disease. The NHS Atlas of Variation in Healthcare 2010 highlighted a four-fold variation in hospital bed-days occupied by COPD patients [6]. In London, there is a variation in LoS between hospitals by nearly 5 days [7]. Those patients with long LoS also occupy disproportionately more bed-days, and 50% of bed-days have been shown to be occupied by the minority of patients who stay at least 11 days [8]. Previously described associations of long LoS in COPD include poor organization of care, lack of early discharge schemes, advancing age, poor performance status, extensive co-morbidity (in particular, heart failure), being female, being admitted at the weekend, low albumin, hyperglycemia, infection, hypoxia, hypercapnia, and being managed by a general medical rather than by a respiratory team [4-5,9-11].

As well as being an important national issue, COPD is also very much a local one. Queens Hospital, Romford, is a busy Acute District General Hospital, which together with its smaller sister hospital King George's serves a large population of

This study was presented at the European Respiratory Society International Congress, 8 September 2014, Munich, Germany.
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around 700,000 people. High levels of socioeconomic deprivation are common: The majority of COPD patients admitted to Queens Hospital, during the period of data collection for the Royal College of Physicians COPD national audit in 2014, belonged to the lowest two quintiles of national deprivation [12]. COPD prevalence in Barking & Dagenham and in Havering, the two main boroughs whose patients are served by Queens Hospital, is among the highest of any in Greater London and is increasing [13]. The COPD emergency admission rate for Havering is the same as that of London overall, but for Barking & Dagenham is more than 1.8 times that of England overall [14]. In addition, the standardized mortality ratio for COPD for Barking & Dagenham is close to twice the London rate [14].

MATERIAL AND METHODS

The aims of this study were to characterize patients who had a prolonged LoS and to identify any associations which might be potentially targetable to reduce LoS in subsequent episodes of COPD inpatient care. Full requisite approval was granted by the trust Clinical Governance department as an audit-related project prior to it being undertaken. The study was conducted according to the Helsinki Declaration.

Patients who had a hospital admission at Queens Hospital with COPD as the primary admitting diagnosis between December 1, 2012, and May 31, 2013, were identified from our Trust Information Services monthly COPD report. This captures hospital admissions with International Statistical Classification of Disease- (ICD-10) codes J43.9, J44.0, J44.1, J44.8, J44.9, or J47X. The mean LoS for the 499 patients admitted during this period was 6.96 days with a median of 5 days and a 90th percentile of 14 days. Two cohorts of patients were derived corresponding to "short" LoS and "long" LoS. The short LoS group was derived by identifying consecutive cases with a LoS close to median of 5 days (range between 4 and 7 days). The long LoS group was derived by identifying consecutive cases with a LoS equal to or above the 90th percentile of 14 days. Where a patient had been admitted more than once during the study period, only their first admission was included. The intention was to compare two groups of around 70 patients each, although case notes or other pivotal data were missing for a small number of patients in each group. The final dataset comprised 64 short LoS patients and 62 long LoS patients.

For each patient, data were collected pertaining to patient demographics, co-morbidities, pre-existing community support and social care, initial laboratory tests, admission arterial blood gas, last recorded FEV_1, admission chest radiograph, input from hospital respiratory specialists, nutrition, measure of performance in activities of daily living (Barthel scale), pressure score risk (Braden scale), and requirement for escalation of social care or placement on discharge. Data sources comprised patient case notes; pathology, radiology, and cardiac investigation systems; and records from the hospital COPD nursing and social services teams. Data was statistically analyzed by a statistician, Paul Bassett, from Statsconsultancy Ltd., Amersham, Buckinghamshire, United Kingdom, using Stata version 12.1 software (StataCorp LLC, Texas, USA). The distribution of continuous variables was inspected using histograms. Continuous variables that were found to be normally distributed were compared between groups using the unpaired t-test. The Mann-Whitney test was used for those continuous variables that were not found to be normally distributed. The chi-squared test was used to compare categorical variables between the two groups. The significance of the group comparisons was determined by the size of the p-values resulting from all analysis methods. A p-value of less than 0.05 was regarded as representing evidence of a statistically significant difference.

Table 1. Patient demographics, prevailing disease severity, and pre-admission levels of social care

Variable	Short LoS (n=64)	Long LoS (n=62)	p
Age (years)	76 (10.7)	77.6 (11.4)	0.44
Male gender	32 (51%)	24 (39%)	0.17
Last recorded FEV1 (liters)	1.15 (0.44)	0.98 (0.71)	0.34
Atrial fibrillation	17 (27%)	18 (29%)	0.80
Oxygen at home	18 (29%)	23 (37%)	0.31
Diuretics used pre/during admission	29 (46%)	28 (45%)	0.92
Nebulizers at home	22 (35%)	30 (48%)	0.13
Carers at home	18 (29%)	26 (42%)	0.12
Lives in care home	5 (8%)	6 (10%)	0.76
Heart failure	21 (46%)	28 (61%)	0.14
Previous admissions	1 [0, 4]	1.5 [1, 3]	0.55
Known to respiratory consultant	26 (41%)	22 (35%)	0.51

LoS: length of stay; FEV1: forced expiratory volume in 1 second

Figures reported for continuous variables are the mean (standard deviation) for normally distributed variables; and median [interquartile range] for non-normally distributed variables. For categorical variables the number of patients and (percentage) are reported.

For a subset (around 50%) of the patients in the long LoS group, the comparison of the date the patient was deemed medically fit for discharge in the hospital case notes with actual date of hospital discharge was examined to determine whether delay in the hospital discharge process contributed to the prolonged hospital stay.

RESULTS

Age and sex distribution did not differ between the two groups as shown in Table 1. Atrial fibrillation, diuretic usage, and heart failure were common in both groups with no difference in prevalence. In this study, heart failure was defined as either a listed diagnosis of heart failure in the case notes or echocardiographic evidence of left-sided heart dysfunction. There was also no difference in the incidence of right heart dysfunction on echocardiogram between the groups (data not shown). Mean FEV_1 (last value in case notes) was low and close to 1 liter in both groups. Use of home nebulizers and home oxygen was common in both groups. No significant differences were observed for either FEV_1, use of nebu-

Table 2. Inpatient investigations

Variable	Short LoS (n=64)	Long LoS (n=62)	p
pH	7.43 [7.39, 7.34]	7.38 [7.34, 7.44]	0.02
pCO_2 (kPa)	5.4 [4.6, 6.6]	6.4 [5.3, 8.1]	0.001
HCO3- (mmol/L)	26.6 (5.1)	28.9 (6.8)	0.004
CO (%)	0.60 [0.30, 1.25]	0.55 [0.30, 0.90]	0.57
WCC ($x10^9$/L)	10.7 [8.9, 13.6]	12.5 [9.9, 16.1]	0.04
Urea (mmol/L)	7.1 [5.4, 9.9]	7.8 [5.6, 9.4]	0.49
Hb (g/L)	13.5 (2.8)	13.3 (1.9)	0.75
CRP (mg/L)	28 [9, 63]	36 [15, 118]	0.13
Globulin (g/L)	32.0 (4.1)	34.4 (5.6)	0.008
Albumin (g/L)	38.0 (5.2)	36.3 (4.5)	0.04
Creatinine (umol/L)	92 [74, 107]	93 [72, 108]	0.67
CXR changes	15 (24%)	30 (48%)	0.004
Braden score	21 [19, 22]	18 [16, 20]	<0.001
Barthel score	17 [15, 19]	16 [14, 18]	0.04
MUST score	0 [0, 0]	0 [0, 0]	0.25
Weight (kg)	63.4 [50.5, 77.6]	63.3 [52.8, 80.1]	0.43
Known to hospital COPD nurse	33 (52%)	19 (31%)	0.01
Discharged/ managed by Respiratory Team	26 (41%)	28 (45%)	0.66

LoS: length of stay; pCO_2: partial pressure of carbon dioxide: HCO_3: bicarbonate; CO: carbon monoxide; WCC: white cell count; Hb: hameoglobin; CRP: C-reactive protein; CXR: chest x-ray; MUST: malnutrition universal screening tool; COPD: chronic obstructive pulmonary disease

Figures reported for continuous variables are the mean (standard deviation) for normally distributed variables; and median [inter-quartile range] for non-normally distributed variables. For categorical variables the number of patients and (percentage) are reported.

Table 3. Discharge outcomes: Social care provision and in-hospital mortality

Variable	Short LoS (n=64)	Long LoS (n=62)	p
Extension of POC: No	52 (84%)	52 (87%)	0.008
Restart	10 (16%)	3 (5%)	
Yes	0 (0%)	5 (8%)	
New POC	3 (5%)	8 (13%)	0.10
Placement at discharge: No	57 (92%)	43 (73%)	0.02
Yes	3 (5%)	8 (14%)	
Died	2 (3%)	8 (14%)	
Death as Inpatient	2 (3%)	11 (18%)	0.009
New POC and/or Placement at discharge in patients surviving to discharge	6/60 (10%)	15/51 (29%)	0.009

LoS: length of stay; POC: package of care

Figures reported for continuous variables are the mean (standard deviation) for normally distributed variables; and median [inter-quartile range] for non-normally distributed variables. For categorical variables the number of patients and (percentage) are reported.

lizers, or use of oxygen at home. Similar numbers of patients in each group were known to a respiratory consultant within the trust. There was no significant difference in the number of previous hospital admissions. A substantial proportion of our patients in both groups had either carers at home or lived in a care home prior to admission, although the proportions did not differ significantly between groups.

In comparison to short LoS, long LoS was associated with significantly lower pH, higher pCO_2, and higher HCO_3 on admission arterial blood gas (Table 2). Long LoS was also associated with elevated admission white cell count (WCC), elevated serum globulin, and more frequent admission chest X-ray (CXR) changes. The proportion of patients with previous isolates of *Pseudomonas aeruginosa* or other specific pathogens did not differ between the two groups (data not shown). Long LoS was associated with lower serum albumin levels and lower Braden and Barthel scores. Being managed by a specialist respiratory team rather than a general medical team did not obviously influence LoS, as the proportion discharged by a specialist respiratory team did not significantly differ between the two groups. However, patients in the long LoS group were significantly less likely to have seen the hospital COPD specialist nurse.

Important discharge outcomes are described in Table 3. There was a significant association of in-hospital mortality with long LoS. Death was around six times more common in the long LoS group. Relative to the short LoS group, patients in the long LoS group who survived to hospital discharge were also almost three times more likely to require extension of a pre-existing package of care (POC) or require a new POC or community placement at discharge.

Thirty-two case notes of the 62 long LoS patients were evaluated for entries pertaining to the time of the patient being medically fit for discharge and for any documentation as to reasons for delayed hospital discharge beyond this point. In 21 of 32 (66%) cases, there was evidence of a delay beyond this time. Documentation about specific reasons for delay was, in some cases, limited, but where documented, chiefly related to the discharge process itself including waits for social services and multidisciplinary assessment, wait for provision of equipment or carers, wait for a care home bed, or family or patient wishes.

DISCUSSION

There was no age difference between the groups in this study, although the average age overall is slightly higher than that reported for our trust in the COPD national audit of secondary care [12]. An explanation for this could be that COPD patients identified retrospectively from hospital coding data (as in this study) include a number of elderly patients where COPD is one of several co-morbidities which precipitate hospital admission. They may therefore represent a subtly distinct population than those COPD patients presenting to the acute medical take and identified prospectively by specialist COPD nurses (as for the COPD national audit of secondary care). In reality, both methods are likely to be imperfect.

The significantly lower Barthel score in our long LoS group is consistent with these patients having poorer performance in activities of daily living. Indeed, lower physical activity is a predictor of prolonged stay in another study [15]. The lower Barthel score in our patients might also indicate greater frailty; and increased frailty is known to promote prolonged hospital stay [16]. In addition, there was a trend for home carers to be required more frequently in our long LoS group, although this trend failed to reach statistical significance (p=0.12).

The majority of patients in both groups probably had severe COPD, as evidenced by low FEV_1, and high prevalence of the use of home oxygen and nebulizers. Co-morbidities were common in both groups, particularly heart failure, but also ischemic heart disease and other vascular disease (data not shown). Heart failure has been shown to be a strong independent predictor for a long LoS after a COPD exacerbation [4], and a high degree of co-morbidity, as shown by the Charlson Index, correlates with LoS [5,17] in other studies. There was a trend for heart failure being slightly more prevalent in the long LoS group in this study, although this did not reach statistical significance (p=0.14). Nonetheless, it is possible that a real association does exist, but that this was not able to be appreciated because of our small sample sizes.

Admission arterial blood gas pH was lower, and pCO_2 and HCO_3 were significantly higher in the long LoS group. Our data are consistent with another report in the literature showing that pCO_2 independently predicts prolonged hospital stay [4]. This suggests that respiratory failure is more common in the long LoS group. This could be explained by more advanced respiratory disease, greater frailty, or reduced physiological reserve in these patients.

The demonstration of elevation of WCC and globulin and more frequent CXR changes in our long LoS group suggests that respiratory infection may promote prolonged hospital stay. Indeed COPD patients with infection as identified by coding data, by those needing antibiotics, or by those having pneumonic CXR changes, have all previously been shown to stay longer in hospital in other studies [5,15,18]. While some patients with COPD exacerbation in the context of recent *Pseudomonas* isolation are treated as inpatients with prolonged intravenous antibiotics in our institution, we did not find any difference in the prevalence of previous *Pseudomonas* isolation between our two groups (data not shown). Consistent with this, no association of LoS was found with any particular sputum pathogen in a six-month study of 329 patients admitted with COPD exacerbation in Hong Kong [19].

A number of indices of poor nutritional status predict prolonged LoS in adult patients [20]. Patients with advanced COPD often have nutritional deficiency and low body mass index; and long LoS in these patients can be significantly reduced by oral nutrition supplementation [21]. In our LoS patients, we found reduced serum albumin and an increased pressure sore risk as shown by reduced Braden score. Albumin is an imperfect marker of nutrition that correlates with body cell mass but is also greatly affected by systemic disease [22]. Malnutrition is an important risk factor for the development of pressure sores; and the Braden score is significantly influenced by nutritional status. Our findings suggest that malnutrition may well be a feature in our long LoS group, although significant differences in the Malnutrition Universal Screening Tool (MUST) score were not seen.

In contrast to other authors who found that being managed by a respiratory physician was associated with a shorter hospital stay, the proportion of patients discharged by a respiratory physician did not differ significantly between the groups in the current study [5]. However, being reviewed by the hospital COPD respiratory nurse was significantly less common in the long LoS group. In our trust, the COPD nurses have an instrumental role involving liaison with community respiratory teams and facilitating early supported discharge and hospital at home schemes. These reduce LoS, re-admissions, and mortality for selected patients [23,24]. Failure to ensure review of some patients by the hospital COPD nurse may have limited opportunities for post-discharge integrated care with community COPD services. This could have contributed to delays and avoidable bed-days in those patients requiring complex discharge planning. Thus, it is plausible that the care and LoS of some of the patients in our long LoS group could be improved if we made greater efforts to involve our expert specialist COPD nurses in their care.

In our study, there was a significantly increased rate of death by six-fold in those patients with a long LoS. This effect was also seen in a large cross-sectional U.S. study where the LoS was nearly twice as long in those patients who died, and LoS itself was an independent predictor of in-hospital mortality [25]. Requirement for social services assessment has previously been shown to independently predict prolonged length of stay in patients admitted with COPD exacerbation in a Canadian study [26]. Escalation of social care provision was also significantly more common in the long LoS group in the current study. Furthermore, many of our COPD long LoS group would be expected to require complex discharge planning based on their age, advanced disease, multiple co-morbidities, limited functional status, and pre-existing social care needs. Complex discharge involving multiple stakeholders has the potential to be delayed by a number of process problems. A London teaching hospital reported that discharge process delays accounted for 21% of medical inpatient bed-days, and in 77% of cases were due to assessment for, or provision of social care [27]. Our study highlights a similar problem in our institution since 66% of the long LoS patient group remained in hospital beyond the time that they were medically fit for discharge. Hospitals such as ours will undoubtedly face increasing challenges discharging many COPD patients in the future as the population ages, and the investment in social care provision is reduced year-on-year [28]. The best way for hospitals to mitigate against such discharge difficulties may be to ensure their workforce is intimately familiar with the local and national discharge process but also to strive for timely discharge-related decision making and ever more effective communication with community services, patients, and next-of-kin [29]. Current evidence is that being admitted over a weekend predicts prolonged hospital stay [4]. This is probably due to a number of factors including reduced weekend clinical decision making and reduced

assessments for and provision of social care. In an effort to achieve effective inpatient care and discharge-related decision making every day of the week, our hospital has recently commenced a 7-day consultant-led respiratory service. This practice is, in fact, a recommendation of the Royal College of Physicians national COPD audit report [12].

Our study has a number of limitations. LoS is a continuous variable that we have categorized into somewhat arbitrary short and long LoS groups. Given our limited dataset of small patient numbers, this was a pragmatic solution to highlight *potentially* real differences between patients with long LoS and a more usual LoS. In addition, many of the variables we studied, such as pH, HCO3, and CO2, would be expected to be related and not therefore independent. The best way to accurately identify independent predictors of long LoS would likely be by stepwise logistic regression analysis of a much larger sample of patients with all possible LoS, but unfortunately this was beyond the scope of our study. A number of the variables we have reported, for example, blood gas values may simply be a marker of severity of respiratory illness, and it is possible that it is disease severity which predominantly influences LoS. Unfortunately, data in the medical case notes were not sufficient for us to evaluate differences in a severity measure such as BODE (Body Mass Index, airflow Obstruction, Dyspnea, Exercise Capacity) index between the two groups. Similarly, incomplete information regarding co-morbidities in the medical case notes hindered our derivation and evaluation of differences in an established co-morbidity index such as the Charlson Co-morbidity index. Rather we focused on individual co-morbidities, in particular heart failure, for which we also had supportive echocardiographic data.

Despite the limitations of our study, it is likely to have value as a real-world observational study to highlight that features such as infection, respiratory failure, malnutrition, frailty, and requirements for social care are associations of prolonged LoS in COPD patients. It is tempting to speculate that, by meticulously targeting these features both during and after hospital stay, we might reduce future hospital bed-days for some of our COPD patients. Certainly, the existence of significant variability in LoS across hospitals in London supports the notion that LoS may be to some extent modifiable [7]. The key to reducing LoS may lie in adopting an integrated COPD service involving multiple specialties in primary and secondary care including physicians, respiratory nurses, therapists, social services, and community teams. Such a strategy in Salford which focused on smoking cessation, improving COPD early diagnosis and treatment, and improving access to pulmonary rehabilitation reduced their LoS from 8.3 to 7.7 days in a single year [30].

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

The Reliability and Validation of the Turkish Version of the Asthma Self-Management Knowledge Questionnaire

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Abstract

OBJECTIVES: There is no validated questionnaire in Turkish to assess asthma knowledge. In this study, we aimed to evaluate the reliability and validity of the Turkish version of the Asthma Self-Management Knowledge Questionnaire (AKQ) among asthmatic adults.

MATERIAL AND METHODS: The AKQ was translated into Turkish by two medical-text translators, followed by back translation and final review by two clinicians with experience in asthma management. The Turkish Asthma Self-Management Questionnaire was then applied to 202 adult asthma patients, and additional demographic and clinical features of the patients were collected for analysis.

RESULTS: The internal reliability of the 24-item AKQ was not high (Cronbach's alpha=0.55). Tukey's test of additivity was significant ($p<0.001$). This result revealed that all questions are consistent and measure the same concepts. Factor analysis demonstrated a probable structure of 10 factors that together explained 63.7% of total variance in results. Intra-class reliability of the AKQ was quite high.

CONCLUSION: This study shows that AKQ seems to be a suitable instrument to evaluate the effect of different components of asthma knowledge - such as triggers, medications, asthma exacerbations, and avoidance measures - in adult asthmatics.

KEYWORDS: Asthma, adult asthma knowledge, asthma knowledge questionnaire, validity, reliability

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INTRODUCTION

Effective asthma management necessitates the development of a partnership between the patient and the health care provider [1]. A possible barrier for this partnership, and thus a risk for inadequate asthma control, might be insufficient understanding of asthma and its management by the patients. The improvement of asthma knowledge is one of the main objectives of asthma management, and asthma education has been found to be effective in adult asthmatics [1,2]. Many asthma education programs use validated asthma knowledge questionnaires to measure the effectiveness of the program [3,4]. Through a recent study from Turkey, we have learned that the percentage of controlled adult asthmatics ranges between 3%-39% [5]. The control level was lower in the eastern-southeastern part of the country where asthma patients tend to have lower socioeconomic status and education level compared to the western parts of the country. Because of the low asthma control levels in Turkey, we need to evaluate the level of asthma knowledge in different regions of Turkey to improve the national asthma management program. However, there are no convenient tools for evaluating such knowledge.

Schaffer and Yarandi [6] developed a questionnaire measuring asthma knowledge among asthmatics in 2007, referred to as the Asthma Self-Management Knowledge Questionnaire (AKQ) (Appendix 1). This questionnaire includes 24 items about general asthma knowledge, asthma medications, asthma exacerbations, and environmental triggers, with responses of "true" or "false". A score of one point is given for each correct answer, and the total score indicates the patient's knowledge of asthma. Even it is a useful questionnaire, it has not been previously validated in a language other than English. In this study, we aimed to establish the reliability and the validity of the AKQ when applied to Turkish adults. Additionally, we expected that by developing a suitable questionnaire adapted to the Turkish language it would be possible to more

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accurately determine the low health literacy among Turkish asthma patients, which is one of the main barriers to better asthma control in Turkey.

MATERIAL AND METHODS

Study Design and Population

The study was approved by Medeniyet University and Göztepe Training and Research Hospital's medical ethics committee, and written informed consent was obtained from the participants. Informed consent of illiterate patients was obtained in the form of a fingerprint signature after providing oral information. Illiteracy was defined as the inability to read and write due to the lack of a formal education.

The study was conducted in the Adult Allergy Department of Medeniyet University. Adults were eligible if they had been diagnosed with asthma by a physician at least 6 months prior to the study. Asthma was diagnosed according to the criteria of the Global Strategy for Asthma Management and Prevention by the Global Initiative for Asthma [1]. Patients were excluded if they had a diagnosis of a psychiatric disorder or any severe uncontrolled comorbidity such as heart failure, dementia, hemiplegia, malignant diseases, or liver or renal failure. We consecutively enrolled adult asthma patients (18 years or older) to the study. At baseline, self-reported data including demographic (age, gender, occupation) and clinical characteristics (symptoms, the onset of asthma, smoking history, the history of atopy and familial atopy, the medications used for asthma, asthma severity, Asthma Control Test (ACT) scores, comorbidities, and additional allergic disease) were recorded [1,6].

AKQ and the Translation into Turkish

The AKQ was originally developed to assess patient knowledge of asthma [4]. The questionnaire provides information about the patient's general knowledge of asthma, environmental factors, asthma medications, triggering factors, exacerbating factors, symptom frequency, nighttime awakenings, and activity limitation due to respiratory symptoms in the last four weeks. [4] Permission was obtained from the authors of the original questionnaire for the Turkish validation.

This questionnaire included 24 questions to determine asthma knowledge, and each was answered as "true" or "false" [Appendix]. The option of "I don't know" was added to rate the lack of knowledge. A correct answer was scored as 1, and an "I don't know" response or a wrong answer was scored as 0. The sum of these items gives the total score, which ranges from 0 to 24. The higher scores indicate better asthma knowledge, and there is no specific cut-off for defining a low level of asthma knowledge. All questionnaire data were collected by the same physician through face-to-face interviews, and the total scores were recorded. After receiving permission from the authors of the AKQ, two independent certified translators translated the questionnaire from English to Turkish. During the process, they were blinded to each other's work. Two allergists examined the Turkish translations and selected one of the translated texts. That text was compared with the original text by another independent observer, and back translation was carried out by a third translator with no previous knowledge of the original document.

Table 1. Demographic characteristics and clinical features of the patients

Variables	n (%) or Mean±SD
Age (years)	52±15
Female	173 (85)
Education	
Illiterate	13 (6.7)
Elementary school	99 (51.3)
High school	39 (20.2)
University, master's degree, or PhD	42 (21.7)
Smoking	
Active smoker	2 (1.4)
Never smoker	109 (74.1)
Ex-smoker	24 (16.3)
Asthma severity	
Mild	61 (41.5)
Moderate	59 (40.1)
Severe	23 (15.6)
Asthma Control Test	
Uncontrolled (<20)	101 (50.8)
Partly or well-controlled	98 (49.2)
BMI (kg/m^2)	29.6±5.9
FEV_1 (L)	2±0.7
FEV_1 / FVC (%)	79±9.1

SD: standard deviation; BMI: Body Mass Index; FEV1: force expiratory volume in 1 second; FVC: forced vital capacity

Sample Size

Use of factor analysis requires 5-10 participants for each item of the questionnaire [7]. Therefore, we ended the study after enrolling 202 participants.

Statistical Analysis

Descriptive analysis (mean, median, standard deviation, minimum, maximum) was used for evaluating continuous data. To describe categorical variables, frequencies (n) and percentages (%) were used. We used the split-half method and calculated Cronbach's alpha coefficient to assess the reliability of the questionnaire. In the validation study, an identical factor analysis was performed to ensure the stability of the AKQ domain structure. The preliminary tests for factor analysis included the Kaiser-Meyer-Olkin test (for the adequacy of the sample size) and Bartlett's test (for sphericity). Factor analysis was based on principal component analysis. Rotation was done with the varimax method. Statistical calculations were performed with Statistical Package for Social Sciences version 18.0 (IBM Corp.; Armonk, NY, USA). In our analyses, $p<0.05$ indicated statistical significance.

RESULTS

Study Population

A total of 202 adults (85% female) with a mean age of 52±15 years were included in the study. Six percent of those enrolled were illiterate. Forty-nine percent of them were partly or well controlled according to the ACT results. The demographic characteristics and clinical features of the patients are presented in Table 1. For the allergic comorbidities, our patients

Table 1. Demographic characteristics and clinical features of the patients

Factors										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Question 1	0.266	0.468	-0.342	0.027	-0.228	-0.099	-0.047	0.286	0.047	-0.080
Question 2	-0.095	0.723	-0.110	0.234	0.077	0.076	-0.038	-0.233	0.027	-0.044
Question 3	-0.060	0.696	0.164	-0.084	-0.012	0.022	0.283	0.143	0.098	-0.024
Question 4	-0.018	0.025	0.724	0.160	-0.083	0.040	0.137	0.037	0.043	-0.077
Question 5	0.078	-0.042	0.146	0.721	-0.097	0.010	0.155	0.091	-0.092	0.031
Question 6	-0.150	-0.087	-0.563	0.300	0.102	0.019	0.135	0.033	0.509	0.014
Question 7	-0.232	0.275	-0.182	0.169	0.010	0.179	0.537	0.173	-0.042	0.208
Question 8	0.028	0.251	0.059	0.645	0.280	-0.042	-0.092	0.139	0.131	-0.013
Question 9	-0.110	0.345	-0.093	-0.201	0.295	0.430	-0.031	-0.049	0.152	0.370
Question 10	-0.317	0.206	-0.321	0.056	0.002	-0.449	0.243	-0.039	0.277	0.267
Question 11	-0.100	0.084	0.045	-0.006	0.034	0.775	0.033	0.100	0.084	0.077
Question 12	-0.001	0.036	0.059	0.024	0.092	-0.070	0.822	-0.027	0.066	-0.057
Question 13	-0.115	0.222	0.009	-0.260	0.413	-0.426	0.000	0.348	-0.019	0.166
Question 14	0.057	0.137	-0.036	0.154	0.764	-0.046	0.087	-0.155	0.025	0.058
Question 15	0.000	-0.269	-0.092	-0.055	0.628	0.154	0.036	0.122	-0.092	-0.237
Question 16	-0.134	-0.050	-0.029	0.120	-0.110	0.224	0.142	0.745	-0.025	-0.001
Question 17	-0.737	0.018	0.064	-0.130	-0.046	0.176	0.109	0.002	0.117	0.102
Question 18	0.742	0.003	0.086	0.081	-0.027	0.000	-0.103	-0.105	-0.008	0.003
Question 19	0.536	-0.104	0.009	-0.223	0.060	0.123	0.226	0.257	0.146	-0.072
Question 20	0.419	-0.095	-0.219	-0.047	-0.155	0.187	0.199	0.066	0.390	0.422
Question 21	0.011	-0.133	0.600	0.235	0.004	0.027	-0.248	0.062	0.305	0.228
Question 22	-0.002	0.162	0.147	-0.060	-0.042	0.059	0.014	0.053	0.787	-0.109
Question 23	0.285	0.055	0.154	0.227	0.121	-0.217	-0.172	0.604	0.199	0.038
Question 24	-0.108	-0.069	0.053	0.039	-0.053	0.014	-0.013	0.019	-0.122	0.841

Method: Principal Component Analysis

Rotation: Varimax with Kaiser Normalization using 45 iterations.

reported having allergic rhinitis (77.7%), drug hypersensitivity (16.3%), urticaria (5.4%), bee venom allergy (3.5%), and atopic dermatitis (2%). The majority of our patients (86%) were reported to have late-onset asthma.

Statistical Analysis

Reliability

Internal consistency

Cronbach's alpha of the Turkish version of the AKQ was calculated as 0.555. Tukey's test of additivity was significant ($p<0.001$). This result revealed that all questions are consistent and measure the same concepts.

Intra-class consistency

The use of the test-retest method to assess intra-class consistency might bias the results. To avoid this bias, the split-half method was used, and the Spearman-Brown coefficient between the first 12 questions and the last 12 questions was calculated. The coefficient was 0.795, and this shows that the intra-class reliability of the Turkish version of the AKQ is quite high.

Validity

Content validity

Each question of the Turkish version the AKQ was scored by three pulmonologists between 1 and 4 for content validity.

4: The item is efficient in explaining the content of the questionnaire.

3: The item is efficient in explaining the content of the questionnaire, but it needs minor changes.

2: The item is confusing and should be revised.

1: The item is irrelevant to the content of the questionnaire.

The mean score was 3.61±0.3.

Construct validity

Based on the patient's preference, a "true" response was scored as 1; an "I don't know" response was scored as -2; and a "false" response was scored as 0. The construct validity of the questionnaire was evaluated using this coding system. The score for the Kaiser-Meyer-Olkin test was 0.577, and the

Table 3. Components of the Asthma Self-Management Knowledge Questionnaire

Components	Name	Question Number
Component 1	Environment	17;18;19
Component 2	General knowledge of asthma	1; 2; 3
Component 3	Triggers and treatment	4; 6; 21
Component 4	Asthma exacerbation	5; 8
Component 5	Usage of inhalers	14; 15
Component 6	Medications	9; 10; 11; 13
Component 7	Other	7; 12
Component 8	Knowledge about inhalers	16; 23
Component 9	Sleep hygiene	22
Component 10	Avoiding exacerbation, treatment for exacerbation	20; 24

diagonal values of the anti-image correlation matrix were between 0.427 and 0.683 (Table 2). These results showed that the sample size of this study was adequate for factor analysis. Bartlett's test was used to assess sphericity ($p<0.001$).

Construct validity of the questionnaire was determined by exploratory factor analysis, and principal component analysis was used to determine the structure of the components. A structure with 10 components was found, and this structure explained 63.7% of the total variance (Table 3).

Results of the AKQ

The mean score on the Turkish version of the AKQ was 13.5±3.9. The minimum score was 0 and the maximum score was 20 out of 24. Three questions (Question 8, 13, 23) were answered correctly by less than 20% of the patients, and all three questions were related to knowledge about inhaled steroids. There were no associations between asthma knowledge and asthma control, education level, or gender ($p=0.4$, $p=0.26$, and $p=0.37$, respectively).

DISCUSSION

In this study, the Turkish version of the 24-item AKQ was found to be acceptable as a reliable and valid tool for evaluating asthma knowledge in adult asthmatics. This is the first study validating this questionnaire in a foreign language. The questionnaire addresses the knowledge of environmental factors, proper use of inhalers, asthma exacerbations, sleep hygiene, triggers, and treatments.

Numerous standardized tools for assessing asthma knowledge exist, but most evaluate patient self-management capacities, which is distinct from general asthma knowledge [8-11]. Both components are useful for comprehensive asthma care, but general knowledge is particularly important because it objectively measures components that can accurately determine gaps in asthma understanding and can provide targets for additional training. The validation of this simple AKQ, originally developed by Drs. Schaffer and Yarandi [6], specifically focuses on general knowledge of asthma, which is appropriate to accurately understand the correlation between asthma control and general asthma knowledge in different cultures. Overall, the content of the AKQ considers the essential aspects that asthma patients have to cope with in their daily lives. These issues constitute important objectives for healthcare providers in terms of enhancing the knowledge about identified factors.

In our study, patient characteristics were similar to other studies, with greater participation of women than men [6,12]. However, the education level of our population was lower. Six percent of the study population were illiterate. All questionnaire data were collected by the physician through face-to-face interviews. Collecting data by physicians usually takes a significant amount of effort, but the 24-item AKQ is a short test and takes only 8 to 10 minutes when administered during an interview.

We found that administering the questionnaire through interviews increased the response rate and decreased poor understanding of the questions, especially in less-educated patients, compared to self-administration of the questionnaire. We added the option of "I don't know" to rate the lack of knowledge. When we collected data from the patients, we encouraged them to choose this option where applicable because it was helpful in identifying the main topics we needed to focus on. In this study, asthma knowledge was average in a cohort of 202 asthmatic patients under the established care of asthma specialists. Of interest, the areas in which knowledge was lowest were related to the role of inhaled steroids for the control of asthma. The following three questions on this topic were answered incorrectly by more than 80% of the patient cohort:

- The purpose of steroid medication inhalers is to stop an asthma attack when it occurs
- It is okay to take inhaled steroid medication only when you notice yourself wheezing
- Steroid inhalers will relieve an asthma attack within 20 minutes

This might related with poor understanding of questions about the role of inhaler steroid use, and the contents of these questions might need to be restructured for the Turkish population.

There are no reliable general questionnaires in Turkish that measure various aspects of asthma knowledge and can be compared with the AKQ. Therefore, we used the ACT test for assessment. In our population, we found that total AKQ score was not correlated with asthma control nor with asthma severity. This fact can be due to the relatively higher level of asthma control and education in our population compared to the other parts of Turkey and a lower percentage of severe asthmatics, which might be considered as limitations of our study [3]. Another limitation is the fact that this study was performed in a single institution, thus generalization of the findings is restricted. The application of the Turkish version of the AKQ to a cohort of asthmatics from different centers in Turkey will increase the validity, reliability, and generalizability of the findings of this research. Finally, the reasons for knowledge questionnaires not being translated into other

languages and not being used sufficiently are not well understood. These may be due to a lack of attention to the issue of disease-specific knowledge or to inadequacy of the questionnaire itself.

Cronbach's alpha (the reliability coefficient) normally ranges between 0 and 1. The closer Cronbach's alpha coefficient is to 1.0 means greater internal consistency of the items in the scale. It is acceptable to have a Cronbach's alpha of 0.70 or higher [13]. In our study, Cronbach's alpha of the Turkish version of the AKQ was 0.555. It was acceptable in the original study [6]. This limitation could mean that some questions in the Turkish context might decrease the coefficient. This might be related to the questions about inhaler steroid use. Increasing the test length, restructuring of the contents of questions, and improving item quality can increase reliability. Likert-type scales can be used instead of "true", "false", and "I don't know" options. Further validation would be needed to extend the use of the Turkish version of the AKQ in clinical practice.

In summary, we have reported the validation of the first Turkish-language knowledge questionnaire of asthma. This study shows that the Turkish version of the AKQ seems to be a suitable instrument to evaluate the effect of different components of asthma knowledge, such as triggers, medications, asthma exacerbations, and avoidance measures, in adult asthmatics. Using this questionnaire might allow physicians dealing with asthma to determine whether their patients are aware of the main features of this chronic disease. This might help to identify and fill the gaps in knowledge. Further studies investigating the impact of different methods of asthma education on patients' knowledge levels will be needed.

Ethics Committee Approval: Ethics committee approval was received for this study from Medeniyet University Ethical Committee.

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.B.O., L.P.O., A.B.; Design - A.B.O., L.P.O., A.B.; Supervision - G.K., F.K., M.Ş.Ş.; Resource - A.B.O, H.K.; Materials - A.B.O, H.K.; Data Collection and/or Processing - A.B.O, H.K.; Analysis and/or Interpretation - A.B., M.Ş.Ş.; Literature Search - A.B.O., L.P.O.; Writing - A.B.O., L.P.O.; Critical Reviews - G.K., F.K., M.Ş.Ş.

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Appendix

Appendix 1. Asthma Self-Management Knowledge Questionnaire

Please circle "true" for statements that are correct and "false" for statements that are not correct.

1.	Frequent coughing can be a symptom of asthma	**True**	False
2.	People with asthma have swollen and inflamed airways even when they feel normal	**True**	False
3.	Asthma may cause wheezing when you exercise	**True**	False
4.	People with asthma can usually control their symptoms by taking medicine and avoiding things that make their asthma worse	**True**	False
5.	Untreated asthma can cause death	**True**	False
6.	Asthma can be completely cured	True	**False**
7.	People with asthma should avoid exercise	True	**False**
8.	The purpose of steroid medication inhalers is to stop an asthma attack when it occurs	True	**False**
9.	People with asthma do not need to take medicine if they feel normal	True	**False**
10.	Quick relief medication such as Ventolin (albuterol) should always be taken every day	True	**False**
11.	You should wait until your symptoms are really bad before you use a quick relief medication such as Ventolin (albuterol)	True	**False**
12.	It may take 1-4 weeks to notice improvement in your breathing when you start using inhaled steroid medication	**True**	False
13.	It is okay to take inhaled steroid medication only when you notice yourself wheezing	True	**False**
14.	To use an asthma inhaler correctly, you need to breathe in as you press down on the inhaler	**True**	False
15.	You should hold your breath for 10 seconds after each puff of your inhaler	**True**	False
16.	You should wait about one minute between puffs of your quick relief medication (Ventolin/albuterol)	**True**	False
17.	It does not bother your asthma when people smoke cigarettes around you	True	**False**
18.	Your bedroom is the most important room to keep free of dust and animal fur or feathers	**True**	False
19.	Getting rid of cockroaches in your house may help your asthma	**True**	False
20.	Keeping your bedroom windows open at night will help prevent asthma symptoms	True	**False**
21.	Carpets that smell moldy can trigger asthma	**True**	False
22.	Covering pillows and mattresses with plastic covers can help asthma	**True**	False
23.	Steroid inhalers will relieve an asthma attack within 20 minutes	True	**False**
24.	Taking an antibiotic such as penicillin will help most bad asthma attacks	True	**False**

Correct answers are in boldface

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CASE REPORT

A Rare Cause of Hemoptysis in Childhood: Tracheal Capillary Hemangioma

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Abstract

Hemangiomas are benign tumors most frequently seen in childhood and are mostly associated with cutaneous and mucosal surfaces. Tracheal capillary hemangiomas are extremely rare. The most common presenting symptom is hemoptysis, ranging from minor to major and chronic cough. We present the case of a 12-year-old boy with recurrent hemoptysis due to tracheal capillary hemangioma, who was treated with interventional bronchoscopy.

KEYWORDS: Hemoptysis, capillary hemangioma, trachea

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INTRODUCTION

Primary tumors of the trachea are extremely rare, with an estimated incidence of approximately 2.7 new cases per million per year, and usually malignant in adults [1]. Lobular capillary hemangioma (LCH) is a benign tumor, more commonly seen in children, with a distinctive lobular arrangement of capillaries in edematous and fibroblastic stroma [2]. The usual sites of tumor are the lips, nose, oral cavity, and tongue. It typically presents with nonspecific clinical symptoms, such as cough and hemoptysis. Stridor is observed with subglottic localization of the tumor. Radiologic studies and bronchoscopy are usually sufficient for diagnosis. Interventional bronchoscopic techniques can treat these lesions and avoid aggressive surgical approaches. Mills et al.[3] reviewed 639 cases of vascular lesions of the oral cavity and upper respiratory tract. They found only 73 cases with LCH and no case with localization in or below the larynx. There is very limited literature on tracheal LCH [1]. We present here the diagnosis and management of a rare case of tracheal LCH that was successfully treated with interventional bronchoscopy.

CASE PRESENTATION

A 12-year-old boy was admitted to our clinic due to recurrent hemoptysis. His symptoms started 2 years ago with approximately 100 mL of hemorrhage in a day after coughing. He also mentioned that a small amount of hemoptysis recurred whenever he had a respiratory tract infection. There was nothing in his history to indicate causes of hemoptysis, such as tuberculosis, recurrent lower respiratory tract infections, intravenous or oral drug use, or antibiotic therapy. He had no pets. Physical examination showed no abnormalities. His hematologic parameters were as follows: activated partial thromboplastin time: 24.7 sc; prothrombin time:15.2 s-58.2%, INR: 1.22; within normal limits). Other chemical laboratory test results were normal, as were chest radiography findings (Figure 1). Sputum acid-fast bacilli and Löwenstein-Jensen cultures were negative. Thorax computed tomography showed a polypoid lesion on the left lateral wall of the proximal trachea (Figure 2). Rigid bronchoscopy revealed a reddish polypoid lesion with a smooth surface on the left lateral wall localized in the proximal one-third of the trachea. The lesion was attached to the tracheal wall with a short pedicle (Figure 3a). The lesion was excised with electrocautery snare and was taken using biopsy forceps. The tracheal wall was coagulated with argon plasma coagulation (APC) (Figure 3b). Histologic examination revealed a subepithelial lobular arrangement of proliferating capillary vessels, dilatation, and congestion; thus, the diagnosis of LCH was confirmed (Figure 4a, b). Upon follow-up, the patient had no hemoptysis episodes. On bronchoscopic examination at the 6-month follow-up, no relapse or other abnormality was observed except for a small scar on the previous biopsy site (Figure 3c). Written informed consent was obtained from the parents of the patient for this case presentation.

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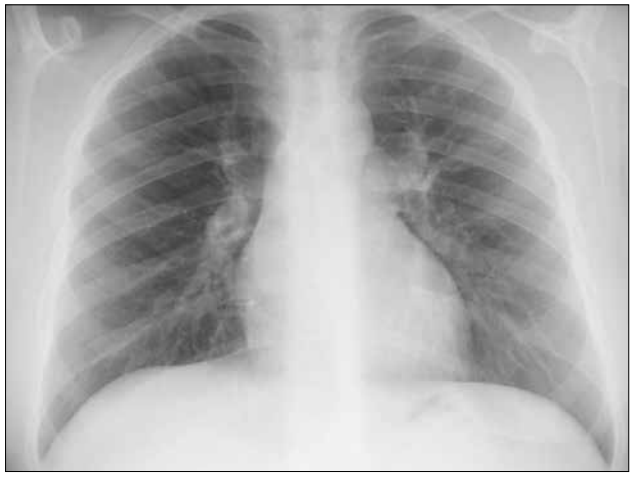

Figure 1. Normal chest X-ray of patient

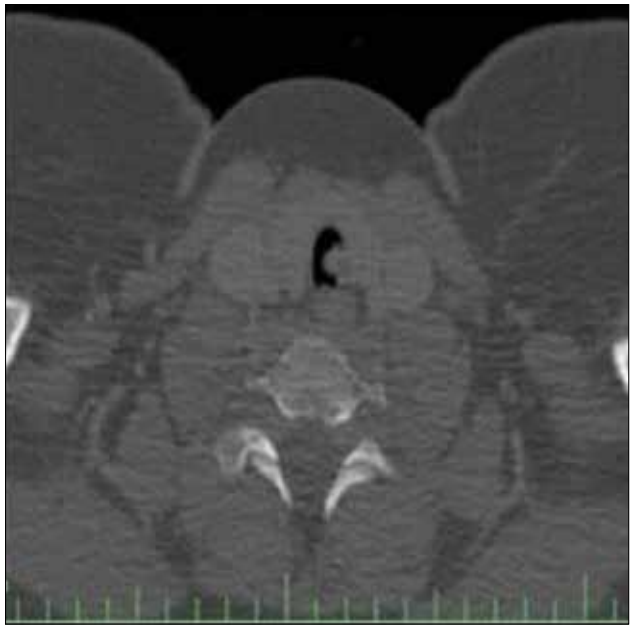

Figure 2. Tracheal lesion was observed on thorax computed tomography

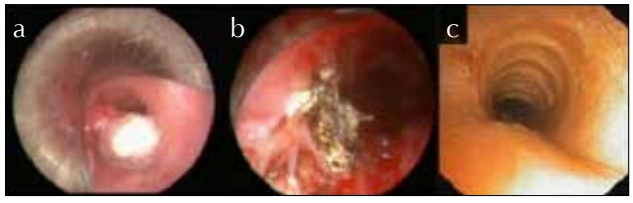

Figure 3. a-c. Tracheal polypoid lesion (a), appearance of lesion after bronchoscopic treatment (b), appearance of trachea after 6 months of treatment (c)

DISCUSSION

The most frequent causes of hemoptysis are infectious diseases, malignant tumors, cardiovascular diseases, and other inflammatory disorders in adults. LCH has seldom been reported in the English literature [4]. Chest X-ray findings are generally normal. LCH is frequently diagnosed while researching etiology of cough and hemoptysis with thorax CT and bronchoscopy [5]. Bronchoscopic appearance is also nonspecific and mimics adenoid cystic carcinoma, tracheal adenoma, and carcinoid tumors [6]. Definitive diagnosis is made with bronchoscopic biopsy. Our patient was an adolescent whose chest X-ray findings were normal, but he had tracheal lesion on thorax CT, that was taken to determine the etiology of hemoptysis.

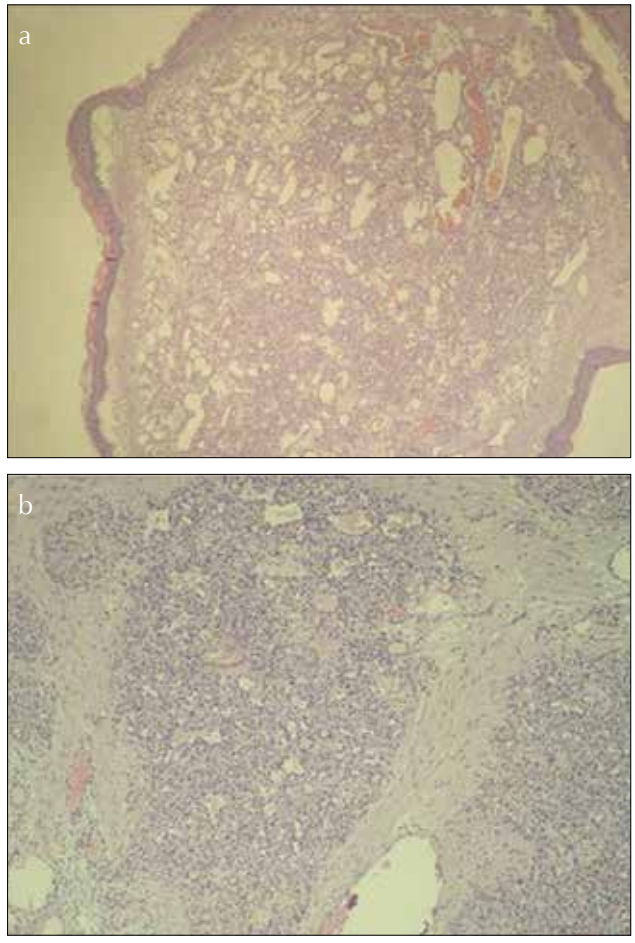

Figure 4. a,b. Respiratory epithelial surface showing squamous metaplasia, proliferating and dilated capillary structures in stroma (H&E ×40)

Pathogenesis of capillary hemangiomas (CH) is unknown. Bartonella infections are implicated in CHs of the skin. Minor trauma, such as endotracheal intubation and tracheostomy, has been reported to play a role in the etiology, but it is not clear because of the small number of cases in the literature [7]. There is no trauma history in our case. CHs can be successfully treated with various methods such as cryotherapy, yttrium aluminium garnet (YAG) laser, topical or intralesional steroids or neoplastic agents (vincristine), oral propranolol, and surgical excision. However, these treatments are mostly used for cutaneous, oral, and subglottic hemangiomas [8,9]. Although case reports are limited in number, successful results with different bronchoscopic techniques were obtained in the treatment of tracheal CHs.

Rameau et al.[10] successfully treated children presenting with symptomatic large tracheal hemangioma using K-potassium titanyl phosphate laser ablation, and they suggested this method for tracheal lesions. Excision of tumor with bronchoscopic forceps has also been reported as a successful method [2,4,5,7]. In our case, after the tracheal lesion was excised with electrocautery snare, excised tumor was taken with forceps and tracheal wall of the lesion was cauter-

ized using APC. After six months, control bronchoscopy revealed minimal scarring with no sign of recurrence.

In conclusion, we would like to remind that tracheal CH is an extremely rare cause of hemoptysis and radiological findings may be normal. So, it should be kept in mind for differential diagnosis. These exceptionally rare tumors also can successfully treated with interventional bronchoscopic methods.

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.A.O., E.T., E.Ç.; Design - M.A.O., E.T., E.Ç.; Supervision - E.Ç.; Materials - E.T., Ş.G.; Data Collection and/or Processing - E.T., Ş.G., Z.Y.A., N.A.F.; Analysis and/or Interpretation - E.T., Z.Y.A.; Literature Review - E.T., M.A., K.A.; Writer - M.A.O., E.T., Ş.G.; Critical Review - M.A.O., E.Ç.; Other - M.A., K.A., N.A.F.

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CASE REPORT

A Case of Pulmonary Alveolar Microlithiasis Diagnosed by Transbronchial Biopsy

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Abstract

Pulmonary alveolar microlithiasis is a rare infiltrative pulmonary disease, in which intraalveolar accumulation of small stones (microliths) consisting of calcium phosphatite occurs. It is an autosomal recessive disorder. The disease occurs as a result of the disruption of type IIb sodium phosphate cotransporter in type II alveolar cells after the mutation of *SLC34A2*. Majority of patients are diagnosed between age 20 and 40. Here, we present a case of alveolar microlithiasis that was diagnosed with transbronchial biopsy.

KEYWORDS: Microliths, pulmonary alveolar microlitiasis, transbronchial biopsy

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INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is an exremely rare interstitial lung disease, which is characterized by intraalveolar accumulation of microliths. It is an autosomal recessive disorder [1]. Clinical presentation varies from asymptomatic to life-threating respiratory failure [2]. The typical radiological image is a bilaterally dense diffuse micronodular view called snowstorm. White lung pattern may be seen in advanced disease [3]. Clinicoradiologic findings, genetic studies, and histopathological confirmation are used to diagnose PAM. The definitive treatment of PAM is only lung transplantation [4]. Here we present a case of PAM that was diagnosed with transbronchial biopsy.

CASE PRESENTATION

A 31-year-old non-smoker female was admitted to our clinic with non-productive cough, chest pain, and dyspnea symptoms. She had no remarkable diseases in her past history. End-inspiratory fine crackles were detected on thorax auscultation. Posteroanterior chest X-ray showed intense reticulonodular pattern in bilateral lung fields. Thorax computed tomograpy revealed a bilateral diffuse dense reticulonodular appearance with no mediastinal lymphadenopathy (Figure 1). There was restrictive pattern on pulmonary function testing (forced vital capacity: 71%, forced expiratory volume: 72%: Tiffeneau index: 88%) and mild hypoxia on arterial blood gas analysis. Hemogram, biochemistry, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests were normal. After the patient and her relatives signed informed consent forms, diagnostic fiberoptic bronchoscopy was performed and endobronchial lesion was not observed. Transbronchial biopsy and bronchoalveolar lavage were performed. Results of AFB tests and tuberculosis culture (Löwenstein-Jensen medium) from bronchial lavage samples were negative. Transbronchial pathology was reported as alveolar lamellar calcification (Figure 2). Increased uptake of Tc-99m was observed in the middle and lower parts of the bilateral lungs on whole body bone scan and patient diagnosed as alveolar microlithiasis (Figure 3). Family screening was performed with chest X-ray, and no abnormality was found in other family members and it was considered sporadic PAM.

DISCUSSION

Pulmonary alveolar microlithiasis is an autosomal recessive disease characterized by the deposition of stones called microliths in the intraalveolar space. *SLC34A2* mutation results in a disruption in the sodium phosphate transport in type II alveolar cells and calcium phospate stones called microliths begin to accumulate in the interstitium [5,6].

Until now, a total of 1022 cases of PAM have been reported worldwide, with the most number of reports being from Turkey with 139 patients. While sex differences varies with region, male sex has been reported more frequently in Turkey (67% male and 33% female). Although it can be seen in almost all age groups, it is often diagnosed in the second and third decades [1].

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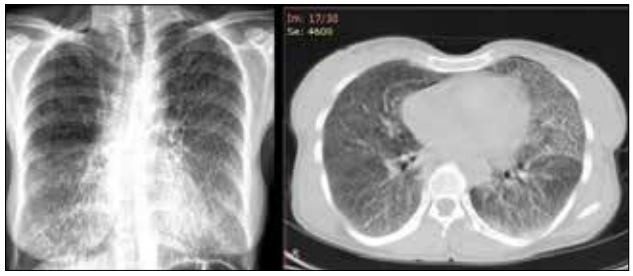

Figure 1. Bilateraly diffuse dense multiple micronodules

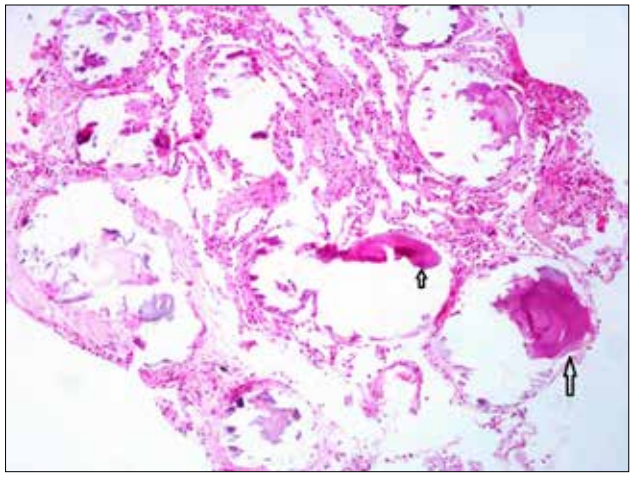

Figure 2. Calcified lamellar bodies (arrows) are viewed in the alveolar lumens
(Hematoxylin & Eosin,100× magnification)

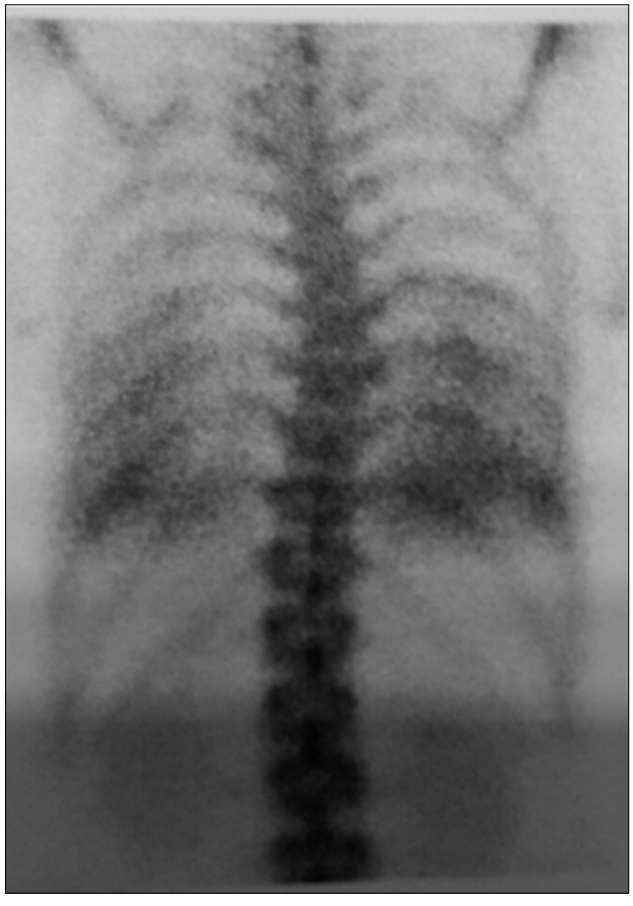

Figure 3. Increased uptake of Tc-99m is observed in the bilateral lungs field

We reached the following conclusions when we examined previous articles on the Turkish population. Ucan et al.[7] published a review article that included 52 cases of PAM, and they stated that the female/male ratio was approximately 1/2, mean age was 27.3, and the most common symptoms were cough and dyspnea. Usually restrictive pattern was detected on pulmonary function test, and family history was reported in almost half of the cases. Tanrıkulu et al.[8] said that in a case series of eight patients with PAM in Turkey, PAM was more common in males. Although the majority of patients were asymptomatic, the most common symptoms were cough and shortness of breath. Restrictive pattern was determined in pulmonary function test of patients. The incidence of PAM per million of population was 1.85 for Turkey and male predominance was reported by Castellena et al. [9].

Clinical presentation varies from asymptomatic to pneumothorax, even life-threating respiratory failure [2]. Our patient had exertional dyspnea, non-productive cough, and chest pain complaints. The characteristic radiological finding is a bilaterally dense diffuse micronodular changes called sandy or snowstorm. White lung phenomenon can be seen in advanced cases [3]. There was a snowstorm view in radiologic images of our patient, and increased uptake of radiopharmaceutical substance was observed in the bilateral lungs area on bone scan. Similar radiological appearances can also be seen in pneumoconiosis, sarcoidosis, tuberculosis, hemosiderosis, and amyloidosis.

Diagnosis and differential diagnosis are made by bronchoalveolar lavage, transbronchial biopsy, and open lung biopsy [9,10]. Our patient was diagnosed with bronchoscopy and transbronchial biopsy. Genetically autosomal recessive transition and mutation in *SLC34A2* gene are defined in this entity [5]. We could not perform genetic studies on our patient. Approximately 32% of cases are familial [1]. Our case was considered a sporadic PAM as there was no familial feature.

Histopathologically PAM chararacterized by intraalveolar microliths accumulation which staining with periodic acid-Schiff and microliths consist of calcareous concentric lamellae around a central nucleus with an amorphous or granular aspect. Calcifications are located in interstitial or vascular compartments [3,6]. Histopathologic examination of our case revealed that calcified lamellar bodies exist in the alveolar lumens.

Therapeutic options are limited and the only definitive treatment is lung transplantation. Calcium sequestrants, serial bronchoalveolar lavage, and corticosteroid treatment have been shown to be effective in preventing disease progression and are thought to have a palliative role. Although bisphosphonates are recommended in the treatment of PAM, efficacy data are limited. Therefore, although there is no prognostic data to identify the same indications, lung transplantation remains the only current teratment option [1-4].

Pulmonary alveolar microlithiasis is a rare interstitial lung disease that can persist with mild symptoms, and it should be kept in mind in the differential diagnosis of interstitial lung

disease, and transbronchial biopsy can be used for diagnosis at centers where genetic mutations cannot be studied.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.A., M.S., N.A., F.B., A.Y.B., H.K., M.T.; Design - H.A., M.S., M.A., F.B., A.Y.B., H.K., M.T.; Supervision - H.A., M.S., M.A., F.B., A.Y.B., H.K., M.T.; Resources - H.A., M.S., N.A.; Materials - H.A., M.S., F.B.; Data Collection and/or Processing - H.A., M.S., H.K.; Analysis and/or Interpretation - H.A., M.S., M.T.; Literature Search - H.A., M.S., M.T.; Writing Manuscript - H.A., M.S., A.Y.B.; Critical Review - H.A., M.S., N.A.; Other - H.A., M.S., M.T.

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