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ABOUT

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Thoracic Research and Practice is a bimonthly journal that is published in English in January, March, May, July, September, and November.

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Thoracic Research and Practice aims to publish studies of the highest scientific and clinical value, and encourages the submission of high-quality research that advances the understanding and treatment of pulmonary diseases.

Thoracic Research and Practice covers a wide range of topics related to adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery, including diagnostic methods, treatment techniques, and prevention strategies. The journal is interested in publishing original research that addresses important clinical questions and advances the understanding and treatment of these conditions. This may include studies on the effectiveness of different treatments, new diagnostic tools or techniques, and novel approaches to preventing or managing pulmonary diseases.

Thoracic Research and Practice publishes clinical and basic research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, systematic reviews and meta-analyses, letters to the editor and editorials. Conference proceedings may also be considered for publication.

The target audience of the journal includes healthcare professionals and researchers who are interested in or working in the pulmonary diseases field, and related disciplines.

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Thoracic Research & Practice
Official Journal of the Turkish Thoracic Society

CONTENTS

ORIGINAL ARTICLES

117 **Validity and Reliability of the Vietnamese Version of the Inhaler Use Scale for Chronic Obstructive Pulmonary Disease Patients**
Nguyen Thi Thu Trieu, Döndü Şanlıtürk, Michele Upvall, Pham Thi Thuy, Tran Van Long, Nguyen Thi Anh Phuong

123 **The Profiling of Apoptosis-Associated MicroRNA Expressions of the Lung Adenocarcinoma**
Füsun Fakılı, Ahmet Feridun Işık, Demet Kahraman, Seval Kul, Ömer Eronat, Sedat İlhan, Cansu Bağcı

131 **Short-Term Pulmonary Rehabilitation Among Post-Pulmonary Tuberculosis Patients During Coronavirus Disease 2019 Pandemic**
Munazzah Orooj, Ajay Pant, Aqsa Mujaddadi, Moli Jain, Irshad Ahmed

137 **Breathlessness Beliefs and Related Factors in Male Patients with Chronic Obstructive Pulmonary Disease**
Deniz Bayraktar, Elvan Felekoğlu, Aylin Özgen Alpaydın, Sevgi Özalevli

143 **Investigation of the Prevalence of Oral Mucositis and Associated Risk Factors in Chronic Obstructive Pulmonary Disease Patients: A Prospective Cross-Sectional Study**
Öznur Gürlek Kısacık, Azize Özdaş, İbrahim Güven Coşğun

151 **Factors Affecting Smoking Cessation After Acute Myocardial Infarction**
Ajar Koçak, Onur Yıldırım, Ayhan Coşgun, Mustafa Hamidullah Türkkanı

157 **Facing Pandemic: Burnout in Nurses in Turkey**
Gökçen Ömeroğlu Şimşek, Eyüp Sabri Uçan, Aynur Türeyen, Neşe Direk Tecirli, Nezihe Uyar, Emre Yıldız, Merve Demirci Atik, Bahriye Oya İtil

165 **Does Pneumococcal Vaccination Have an Effect on Hospital Costs?**
Nurdan Şimşek Veske, Özgür Uslu, Özlem Oruç, Sedat Altın, Enver Yalnız, Zuhal Karakurt, Erkut Bolat, Seval Kul, Oğuz Kılınç, Abdullah Sayıner

REVIEW

170 **Home-Based Physiotherapy and Rehabilitation in Patients with Idiopathic Pulmonary Fibrosis: A Review**
Meltem Çelik, Esra Pehlivan

CASE REPORT

177 **A Postpartum Immigrant with Pulmonary, Pleural, and Intestinal Tuberculosis**
Pelin Pınar Deniz, Pelin Duru Çetinkaya, Filiz Aydoğan

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Original Article

Validity and Reliability of the Vietnamese Version of the Inhaler Use Scale for Chronic Obstructive Pulmonary Disease Patients

Nguyen Thi Thu Trieu[1,2], Döndü Şanlıtürk[3], Michele Upvall[4], Pham Thi Thuy[2], Tran Van Long[5], Nguyen Thi Anh Phuong[6]

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Abstract

OBJECTIVE: The purpose of this study was to establish and evaluate the validity and reliability of the Vietnamese version of the inhaler use scale for chronic obstructive pulmonary disease patients.

MATERIAL AND METHODS: This study was conducted with 150 participants who were admitted to the Outpatient Department of Pulmonary Diseases in Vietnam, using a face-to-face interview technique. The Kaiser-Meyer-Olkin test, Bartlett's test, and exploratory factor analysis were used to assess construct validity. Cronbach's alpha coefficient and intraclass correlation coefficient were used to evaluate the reliability of the scale.

RESULTS: In the results of exploratory factor analysis with eigenvalues > 1.00, 3 factors of scale appeared. The total variance of the questionnaire was 78.78%, where variances of each component were 34.16%, 26.88%, and 17.73%, respectively. Cronbach's alpha coefficients of scale in the first test and re-test after 4 weeks were 0.913 and 0.901, respectively. The intraclass correlation coefficient was 0.826.

CONCLUSION: The validity and reliability of the Vietnamese version of the inhaler use scale study were found to be equivalent to the original author-developed scale and it can be applied to measure the factors affecting behavioral intention in Vietnamese chronic obstructive pulmonary disease patients.

KEYWORDS: Validity, reliability, COPD, Vietnamese
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease. Characterized by persistent symptoms and airway or alveolar limitation, COPD often occurs from exposure to toxic particles and gases. Comorbidities will also increase disability and mortality.[1]

As of 2020, nearly 3 million deaths can be attributed to COPD globally every year, and the frequency is increasing due to smoking in developing countries, aging populations, and the environment. Chronic obstructive pulmonary disease frequency increases by 2060, with about 5.4 million projected COPD-related deaths.[1] In Vietnam, the prevalence of COPD is estimated to be 6.7%, the highest in Southeast Asia. More than half of these cases have experienced at least 1 episode of the severity of the disease.[2]

Early treatment and adherence to the doctor's instructions can reduce symptoms, slow down lung damage, and improve patients' quality of life.[1] Inhaled medications are becoming increasingly popular in the treatment of COPD. On the contrary, improper use of the technique will reduce the drug's effectiveness. Unlike oral medications, inhaled drugs require the patient to perform the correct inhalation technique to achieve the optimal therapeutic effect.[3]

Poor inhaler technique can significantly reduce the effective delivery of the respirable fraction of the emitted dose that reaches the lungs.[4] In clinical studies, up to 94% of patients demonstrated incorrect inhalation with metered-dose inhalers (MDI) or dry powder inhalers (DPI),[5] but only 22% of patients reported that they were completely confident in using their inhaler correctly.[6] Ngo et al[7] demonstrated that the proportion of patients with good inhalation technique was 22.7% for an MDI, 30.4% for a DPI, and 31.8% for a soft mist inhaler. The whole exhalation technique was the most common mistake in COPD patients observed in the study.

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Proper use of inhalation devices is one of the most important aspects to be taken into account when assessing the treatment progress of patients with COPD, and the instructions emphasize the importance of assessing inhalation techniques to improve the effectiveness of drug delivery. However, not all patients will perform properly because of cognitive or physical reasons, or both (Jardim & Nascimento, 2019).

The inhaler use scale (IUS) developed by Sanlıturk and Ayaz[8] consists of 13 questions to measure the degree of intention changing behavior of people with COPD toward the use of inhalation devices in the treatment of the disease. The IUS was developed based on the Theory of Planned Behavior (TPB) to measure the factors affecting the intention changing behavior, including 3 subscales: attitude toward behavior (ATB), subjective norm (SN), and perceived behavioral control (PBC).

The IUS has been tested for validity and reliability on 130 asthmatics with Cronbach's alpha coefficient of 0.72. Calculating the value of the scale by factor analysis results in Kaiser-Meyer-Olkin (KMO) coefficient of 0.763, eigenvalues > 1.00 (the eigenvalues of ATB, SN, and PBC are 3.790, 1.793, 1.789, respectively), and total variance of 52.087% (29.151%, 13.790%, and 9.145% respectively).[8] However, there were no publications and versions of the IUS for the Vietnamese population. Thus, in this study, we have established and evaluated the validity and reliability of the Vietnamese version of the IUS (V-IUS) for COPD patients.

MATERIALS AND METHODS

Study Designs and Participants

This study was conducted using a face-to-face interview technique on patients who were admitted to the Outpatient Department of Pulmonary Diseases at Da Nang C Hospital Vietnam from October 2021 to February 2022. Simple random sampling was used to recruit patients with the following criteria: FEV1/FVC < 0.70 in respiratory function test, aged 40 years and over, patients who were able to establish healthy communication including reading literacy, and who did not have hearing and/or speech disorder.

Hair (2019) suggested that the sample size be determined based on determining a ratio of 5 or 10 participants per sale item. The IUS questionnaire consists of 13 items; the sample size was then determined to be 13 × 10 = 130. The expected rate was 10%; therefore, the final sample size was 150.

MAIN POINTS

- The study evaluates many attributes of the inhaler use scale questionnaire in Vietnamese version, including internal reliability, surface validity, content validity, and structural validity.
- Vietnamese version of the inhaler use scale has good content value, high structural value, and high internal reliability.
- Vietnamese version of the inhaler use scale can be applied to measure the factors affecting behavioral intention in Vietnamese chronic obstructive pulmonary disease patients.

This study was approved by ethical review committee of Nam Dinh University of Nursing (No. 1681/GCN-HĐĐD) and permissions for data collection from the authorities of Da Nang C Hospital. All participants agreed to sign an informed consent to participate in this study after received a full explanation about the study from the researcher.

Data Collection Instruments

Both the questionnaire developed by Sanlıturk and Ayaz[8] and the subsequent translated version, V-IUS, were used in collecting study data.

Inhalers Use Scale

The IUS includes 13 questions to measure the degree of intention to change behavior of people with asthma with respect to target behaviors desired to be changed. The IUS was developed according to the TPB. This theory was used to measure the factors affecting behavioral intention including 3 subscales: ATB, SN, and PBC. Each item was rated on a 5-point Likert-type scale (strongly agree: 5, agree: 4, undecided: 3, disagree: 2, and strongly disagree: 1) Of the 13 items included in IUS, the first item represented the general intent; items 3, 7, and 9 represented ATB; items 2, 4, 6, 8, 11, and 13 represented SN; and items 5, 10, and 12 represented PBC.[8]

The scores for each group were calculated separately, with the behavior intention scores ranging from 1 to 5 points. Scores of the group ATB, SN, and PBC were calculated by adding the scores of all questionnaire items divided by the number of questions in the group. Only question 7 (ATB) was written as negative, requiring this item to be reversed-scored. While evaluating the scales, we determined the impact of the factors affecting the behavioral intentions of the patients. Accordingly, the higher the ATB score, the more aware the patient is of the behavior. The higher the score on the SN, the more environmental pressure the patient experienced to perform the target behavior. The higher the score on the SN, the more environmental pressure the patient experienced to perform the target behavior.[8]

Translation of the Inhalers Use Scale

The researchers received permission to use the IUS after agreeing to allow each question to be translated from English to Vietnamese. According to the World Health Organization, 2009 procedure, the translation process is best carried out using a clearly defined approach. In the study, the following steps were implemented: first, the original IUS was translated from English into Vietnamese by 2 English lecturers at the University of Foreign Languages, Hue University (the lecturers are Vietnamese who are proficient in English). Second, some inconsistencies between the translations were discussed and agreed upon by the researcher and another interpreter. This translation from Vietnamese into English was done by a Vietnamese who again was proficient in the English language. Finally, this version was compared to the original IUS.[10]

The V-IUS was sent to 5 experts to assess the validity of the content by giving a score from 1 to 4, corresponding to the level of "1 not relevant" to "4 very suitable" of each item in the questionnaire compared to the research objective. The members of this assessment expertise council who met

the criteria included 2 doctors (master-degree qualified) specializing in respiratory internal medicine with experience in treating people with COPD; 2 nurses with doctorates with experience in teaching and guiding students at the Department of Respiratory Internal Medicine; and 1 PhD prepared employee working in the Department of Public Health with experience in building and developing toolkits.[10,11] All experts were proficient in English and have worked in their respective fields for more than 10 years.

The validity score derived from the experts was then used to calculate the content validity index for Items Content Validity Index (I-CVI) items. The I-CVI is calculated based on the number of experts giving a score of 3 or 4 on a 4-point Likert scale for an item divided by the total number of experts and has a value from 0 to 1. The I-CVI was compared with thresholds equivalent to the clarity of the questions: >0.79 (clear), 0.70-0.79 (should revise), and <0.70 (so cannot use). When there are 5 or less experts, the consensus of all experts is required to prove that the item has content validity (I-CVI = 1).[12]

The content validity of the IUS was determined based on the quantitative assessment scores of the experts. Independent assessors, all comments, criticisms, and recommendations for adjusting the questionnaire were recorded on the assessment minutes and verbally explained to graduate students at the time of receiving the assessment form. The time for experts to review the questionnaire was 7 days. After receiving the assessment form, the researcher summarized the results and opinions of the experts.[11]

Finally, a pilot study was conducted with 30 COPD patients. Out of a total of 30 persons surveyed by questionnaire, 26 said the questionnaire was "easy to understand" and 4 persons said it was "very easy to understand." The surveyed persons did not have any difficulty in reading, understanding, and grasping the content of the questionnaire, and there was no question making them uncomfortable when answering. All respondents believed that the questionnaire could survey aspects of inhaled medication use in COPD patients. The average response time was 7.8 minutes.

Data Analysis

This study used Statistical Package for the Social Sciences software version 23 to analyze the data. Descriptive statistics were used to describe the sample characteristics. An exploratory factor analysis (EFA) was performed to determine the main factor. Correlation matrix, Bartlett's test, and KMO test were performed to test the conditions for conducting factor analysis. The factors have an eigenvalue greater than 1, and the variation rate is explained by factors of 50% or more and the distribution of elements on the scree plot. Then, the rotated factor matrix, Vartimax, was used to determine the subitems of each component, with a condition that these subcategories have a factor loading greater than 0.5. In order to analyze the reliability of the Vietnamese version, Cronbach's alpha and total item correlation were performed to calculate the internal consistency of the scale, with Cronbach's alpha of 0.70 or higher considered acceptable. If the coefficient of correlation of the variable - total (Corrected Item-Total Correlation) ≥ 0.30 then the variable meets the requirements. The intraclass correlation coefficient (ICC) was used to assess the reproducibility of tests and retests between 2-time clinic visits (4 weeks apart) of 30 participants.

RESULTS

Characteristics of Research Subjects

Table 1 presents the characteristics of the study participants.

Validity and Reliability of the Inhaler Use Scale

Validity of the Inhaler Use Scale

To check the conditions for performing factor analysis of the questionnaire, the KMO study and Bartlett's tests were

Table 1. Characteristics of Participants (n = 150)

Characteristics	n	%
Age	Mean 60.48 (SD = ±8.33)	
Gender		
Male	117	78.0
Female	33	22.0
Education level		
Illiterate	1	0.7
Primary school	10	6.7
Junior high school	12	8.0
High school	19	12.7
Vocational school	43	28.7
College, University	65	43.3
Occupation		
Farmer	7	4.7
Worker	24	16.0
Public servants	46	30.7
Retired	51	34.0
Trader	21	14.0
Other	1	0.7
Living with family		
Yes	121	80.7
No	29	19.3
Comorbidity		
Yes	90	60.0
No	60	40.0
Using metered-dose inhaler		
Yes	102	68.0
No	48	32.0
Using turbuhaler		
Yes	10	6.7
No	140	93.3
Using accuhaler		
Yes	45	30.0
No	105	70.0
Number of year living with disease	11.6 (±5.8)	
Number of year using medicine	4.5 (±2.9)	

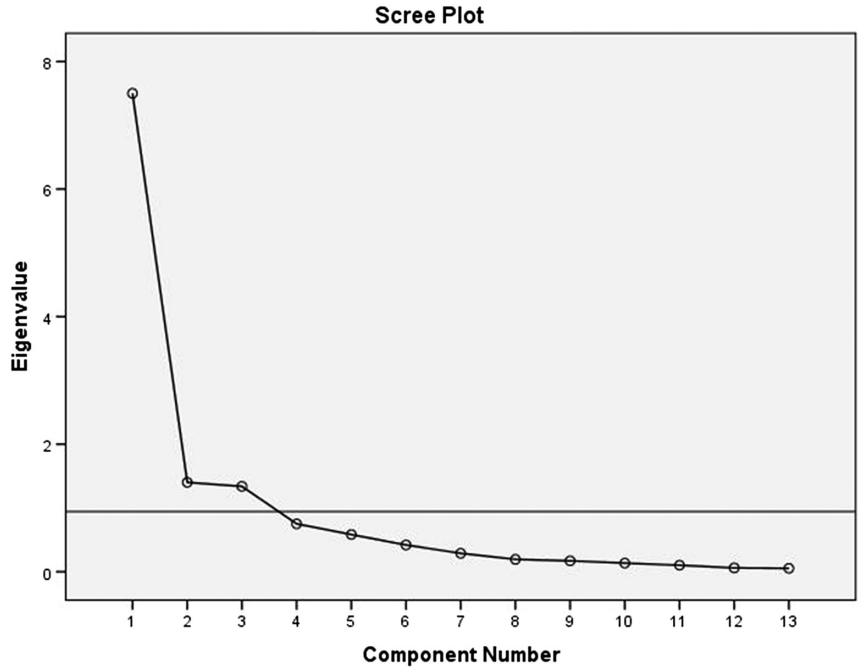


Figure 1. Scree Plot.

used. With the found KMO index of 0.864 (<0.5), it demonstrates that the sample size is sufficient for factor analysis. The Bartlett's test value with $P < .001$ indicated that there was enough correlation among the research variables to perform the factor analysis (Table 2).

In the results of EFA with eigenvalues > 1.00, 3 factors of scale appeared in the scree plot (Figure 1). The total variance of the questionnaire was 78.78%, where variances of each component were 34.16 %, 26,88%, and 17.73%, respectively. According to the results of rotation factor analysis using the principal component analysis, items 6, 8, and 11 represented for ATB subgroup were found in factor 3, items 5, 12, and 10 represented for PBC subgroup were found in factor 2, items 3 and 9 represented for SN subgroup were found in factor 1, and the general intent (item 1) was found in factor 1 (Table 3).

Reliability of the Inhaler Use Scale

The Cronbach's alpha coefficient was used to assess the internal consistency of the questionnaire. In this study, Cronbach's alpha coefficients of scale in the first-time survey with 150 samples (test) and the second-time survey with 30 samples (retest) were 0.913 and 0.901, respectively (Table 4).

Table 2. Kaiser-Meyer-Olkin (KMO) and Bartlett's Test Result of Inhaler Use Scale

KMO measure of sampling adequacy		**0.864**
Bartlett's test of sphericity	Approx. chi-square	1972,930
	df	78
	Significance	.000

The test–retest reliability of the questionnaire was evaluated 4 weeks after the first survey of the questionnaire. The intraclass correlation was used to measure the similarity between values from the same group in 2 times response. The ICC was 0.826. These values indicate that the V-IUS is a highly valid tool (Table 4).

DISCUSSION

The V-IUS is the Vietnamese version of the inhaled drug use scale to measure inhaled drug use in COPD patients, using

Table 3. Factor Analysis of Vietnamese Version of the Inhaler Use Scale

	Components		
	Factor 1	**Factor 2**	**Factor 3**
Item 3	0.861		
Item 9	0.844		
Item 2	0.843		
Item 13	0.829		
Item 1	0.557		
Item 5		0.866	
Item 10		0.863	
Item 4		0.797	
Item 12		0.751	
Item 7			0.804
Item 11			0.792
Item 8			0.650
Item 6			0.510

Factor 1, attitude toward behavior; Factor 2, perceived behavioral control; Factor 3, subjective norm.

Table 4. Test–Retest Reliability of V-IUS

	Cronbach's Alpha Coefficient Test	Cronbach's Alpha Coefficient Retest	ICC
V-IUS	0.913	0.901	0.826

ICC, intraclass correlation coefficient; V-IUS, Vietnamese version of the inhaler use scale.

EFA to assess the validity of the structure and reliability of the scale.

Comparing the validity and reliability of original IUS of authors named Sanlıturk and Ayaz[8] that developed and tested on asthma patients the translated version of IUS performed on Vietnamese people with COPD also showed the same finding with a good validity, and high reliability.

Results indicate that the V-IUS is very easy to use and, in the opinion of experts and patients, all questions are easy to understand. High internal consistency was observed (Cronbach's alpha = 0.913). The Cronbach's alpha coefficient reassessed after 4 weeks was 0.901 (Table 4), which is in the acceptable range of 0.7-0.95, demonstrating that the V-IUS questionnaire has good internal reliability and good reproducibility (ICC = 0.826).

Although the IUS was originally designed to measure the factors affecting behavioral intention in asthma patients, the V-IUS seems to work equally well in COPD patients possibly because both asthma and COPD patients use inhaled medication for the treatment of diseases. The patient's understanding of the questionnaire items may indicate that the patient has received clear information about the disease from the health workers. All of these are considered positive evidence that the V-IUS can be applied to measure the factors affecting behavioral intention in COPD patients.

Exploratory factor analysis reveals the concordance between the variables. The KMO and Bartlett's sphericity tests were used to evaluate the fitness of the study sample. The KMO must be higher than 0.60 and *P* must be less than .05 in Bartlett's test to analyze the data to be adequate in the factor analysis.[13] Kaiser-Meyer-Olkin sampling adequacy coefficient was found to be 0.864, and χ^2 value in Bartlett's sphericity test was found to be $P < .001$). According to these results, evaluated data were found to be adequate for factor analysis original questionnaire developed by Sanlıturk and Ayaz[8] comprised 3 subgroups, number of subgroups in the present study was limited to 3. The scale was composed of 13 items and 3 subgroups. The analysis revealed that the number of items in the subgroups was different from the number of items in the subgroups of the original form. Total variance of the questionnaire in EFA was 78.78% where variables of subscales were 34.16% for ATB, 26.88% for PBC, and 17.73% for SN.

According to the results of rotation factor analysis using principal component analysis, items 5, 12, and 10 represent the PBC group found in factor 2. This factor is completely similar to the factor of the original questionnaire and similar to the test results of the author on subjects with asthma. This result means that individuals' beliefs about the ease or difficulty of behavior remain the same regardless of country.[8]

The results show that item 1 is a question of general intention. According to Ajzen,[14] intention determines behavior, when the patient intends to perform a certain positive behavior they will strive to achieve. The results (Table 3) show that items 3 and 9 represent ATB in V-IUS for factor 1 and items 6, 8, and 11 represent SN for factor 3. This result is equivalent to the scale originally developed by the author based on the TPB theory. However, this result differs in the order of occurrence of factors compared with the test results of the author on subjects who are asthma patients.[8] All of this is acceptable because this study was conducted in COPD patients while the original questionnaire was experimentally performed on asthma patients. The results of the study demonstrate that the subtypes of ATB, SN, PBC, and general intention to measure factors affecting behavioral intention in asthma patients are suitable for measuring behavioral intention in Vietnamese patients with COPD.

Strengths and Limitations of the Study

The study evaluates many attributes of the V-IUS questionnaire, including internal reliability, surface validity, content validity, and structural validity. The findings show that the IUS questionnaire in Vietnamese version has good content value, high structural value, and high internal reliability. From the various validity and reliability tests, it appears that V-IUS could be a valid and reliable instrument to measure the factors affecting behavioral intention in COPD patients.

However, there was no involvement of native English speakers in the reverse translation phase. The study managed this limitation by inviting interpreters who were proficient in English and have lived and worked in English-speaking countries.

In summary, the V-IUS is a valid instrument that is useful and reliable for measuring the factors affecting behavioral intention in COPD patients in Vietnam.

CONCLUSION

Given the validity and reliability reported by V-IUS and its ease of use in COPD patients, this self-report measure could serve as a screening tool in clinical settings to measure the factors affecting behavioral intention in COPD patients in Vietnam.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Nam Dinh University (Approval No: 1681, Date: 02/8/2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Original Article

The Profiling of Apoptosis-Associated MicroRNA Expressions of the Lung Adenocarcinoma

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Abstract

OBJECTIVE: The most common histopathological subtype of lung cancer is adenocarcinoma. MicroRNAs are a class of non-coding RNAs that play roles in the regulation of gene expression. MicroRNAs affecting apoptosis may have different roles in lung adenocarcinoma development, progression, and differentiation. The objective of this study is to profile all known microRNAs linked to apoptosis in normal and lung cancer tissue using real-time polymerase chain reaction.

MATERIAL AND METHODS: Tissues with adenocarcinoma and healthy tissues were taken from the same lung. The degree of differentiation of all tumors was determined. Expressions of 84 apoptosis-associated microRNAs in both tissues were analyzed by real-time polymerase chain reaction array.

RESULTS: Eleven patients and 22 samples were included in the study. In the comparison of expression levels of apoptosis-associated microRNAs in normal and adenocarcinoma tissue, miR-134, miR-183-5p, miR-192-5p, miR-193b-3, miR-194-5p, miR-200c-3, miR-212-3p, miR-25-3p, miR-449a, and miR-9-5p showed significant difference in downregulation. Receiver operating characteristic curve analysis of 10 identified microRNAs was performed, and cut-off values, sensitivity, and specificity were determined. No significant difference was found between microRNA expression levels in adenocarcinoma tissues classified as moderate-well to poorly differentiated.

CONCLUSION: Differently, downregulated expressed apoptosis-associated microRNAs were detected in lung adenocarcinoma tissues. MicroRNAs can be used as biomarkers in the diagnosis in lung adenocarcinoma. The expression of microRNAs linked to apoptosis should be investigated in different lung cancer histological subtypes in order to identify potential biomarkers.

KEYWORDS: Apoptosis pathway, lung adenocarcinoma, miRNA expression profiles, tumor biomarker, experimental researches
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INTRODUCTION

Lung cancer is the most common cancer in men and has the highest mortality rate. The most common histopathological subtype of lung cancer is adenocarcinoma.[1,2] According to the World Health Organization's 2021 report, there were 2.21 million new cases and 1.80 million deaths in 2020 due to lung cancer.[3]

MicroRNAs (miRNAs) are a class of small, non-coding RNAs, with a length of 20-24 nucleotides, which play important roles in the regulation of gene expression. Increased and decreased expression of miRNAs may affect the behaviors of oncogenes and tumor-suppressor genes in lung cancers. MicroRNAs regulate the gene expression through post-transcriptional regulation of mRNA. MicroRNAs contribute to the process of carcinogenesis by regulating the cell cycle, metastasis, angiogenesis, metabolism, and apoptosis.[4] Abnormal expression of miRNAs occurs in many types of cancer, and many miRNAs function in tumor-suppressor genes or oncogene activations.[5] Recently, circulating extracellular miRNAs have been identified as non-invasive biomarkers for cancer diagnosis, prognosis, and the prediction of treatment response.[6,7] MicroRNAs can directly target pro- or anti-apoptotic mRNAs or their functional regulators to exert both anti- and pro-apoptotic effects.[8] Apoptosis-associated miRNAs may offer novel insights into lung adenocarcinoma prognosis and targeted therapeutics at the time of diagnosis.

The histological classification of the tumor is one of the critical parts of evaluating the prognosis of lung cancer.[9] The link between early diagnosis, treatment response, and the prognosis for various histological subgroups of lung cancer has been studied. A similar situation does not exist for adenocarcinoma subtypes and miRNAs.[10,11] MicroRNA expression patterns may differ among tissues with pathologically distinct lung adenocarcinoma differentiation.

The primary aim of this study is to compare all discovered miRNAs linked to the apoptotic pathway in healthy lung tissues with lung tumor tissues from the same lung using real-time (RT) polymerase chain reaction (PCR). In this way, we planned

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to determine the changing apoptosis-miRNA expressions between lung adenocarcinoma tissues and healthy tissues. One of the secondary goals of the study was to investigate the degree of histological differentiation and distinctions of miRNA expressions in lung adenocarcinomas.

MATERIAL AND METHODS

Sampling

This cross-sectional study included 11 patients who were newly diagnosed with lung adenocarcinoma, accepted to participate in the study, and had surgery for lung cancer between February 2020 and July 2021. The resection specimens were promptly sent to the pathology unit following the procedure without the addition of any fixative solutions. Pathologists collected fresh lung parenchyma samples and non-neoplastic lung tissues from neoplastic tissues for the PCR analysis. Following the removal of fresh tissue samples, formaldehyde was added to the resection materials to allow for routine macroscopic and micromorphological analysis. For cross-checking purposes, the preoperative and final pathology diagnoses were compared. This study used healthy and malignant tissues from the same lungs of 11 patients.

All participants did not receive any adjuvant therapies before the surgery. All patients were staged according to the International Association for the Study of Lung Cancer (IASLC) 8th Edition, and the grade of adenocarcinoma differentiation was made according to the IASLC, American Thoracic Society, and European Respiratory Society's classifications. According to these classifications, the lepidic pattern was well-differentiated, the acinar and papillary patterns were intermediate, and the solid or micropapillary patterns were poorly differentiated.

This study was conducted with permission numbered 2020/75 from the Gaziantep University's ethics committee, and informed consent forms were received from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Acquisition of the Lung Tissues

Following a diagnosis of adenocarcinoma lung cancer, the researchers weighed 100 mg of tumors and healthy tissue components from the same lung samples that would otherwise be thrown away. The tissues were maintained in a special liquid (RNA later) at –80°C to ensure that the RNA in the tissues was stable and undamaged until the isolation.

MAIN POINTS

- Detection of the differentially expressed apoptosis-associated microRNAs (miRNAs) between lung adenocarcinoma and healthy tissues was done. All of the apoptosis-associated miRNAs were downregulated in lung adenocarcinoma tissues.
- No significant difference was found between the levels of apoptosis-related miRNA expressions in adenocarcinoma tissues pathologically classified as moderately well differentiated to poorly differentiated.
- For biomarker determination, the expression of apoptosis-associated miRNAs in other histopathological subtypes of lung cancer should be examined.

Isolation of the MicroRNA

The tissues that were withdrawn from the RNA were treated with the solution and remained on the ice block, and then, they were treated with QIAzol® Lysis Reagent. Tissues were homogenized quickly using Tissue Ruptor II, which smashed them at the greatest speed possible (Qiagen, Hilden, Germany). Filtering and removing of the homogenized tissue particles from the medium were executed before adding chloroform to the remaining liquid and starting the miRNA isolation procedure. The miRNA simple Mini Kit (cat. No. 217004; Qiagen) procedure was followed to the letter, and the quality and concentration of the miRNAs collected were determined using a micro-drop plate reader. Good-quality RNAs were defined with an absorbance value of 260/280, 1.8, or higher.

cDNA Synthesis From the MicroRNA

Before converting mature miRNAs to cDNA, all samples were exposed to 50 ng concentration to ensure standardization between the samples. MyScript II reverse-transcriptase RT-kit (cat. No. 218161; Qiagen) was used for cDNA synthesis from samples with a working concentration of 50 ng. The reaction content and experimental stages in the cDNA synthesis were carried out according to the manufacturer's instructions. MicroRNA samples were converted to cDNA by incubating in a PCR device at 37ºC for 60 minutes and at 95ºC for 5 minutes with the kit mix.

Measuring and Evaluating the Expressions of MicroRNAs

Variations between human apoptosis miRNA expression profiles were discovered using the miScript miRNA PCR Array (cat. No. MIHS-1 14Z; Qiagen). Prepared PCR buffer, SYBR Green, and master mix containing 50 ng cDNA were added to qPCR plates containing 84 specific microRNA primers and 12 internal controls. Quantitative PCR procedure was performed for 40 cycles of 94°C for 15 s, 55 s, and 70 s. Real-time polymerase chain reaction array plates were made using 84 miRNAs whose functions are known to be associated with apoptosis.

Statistical Analysis

The conformity of the data to the normal distribution was tested with the Shapiro–Wilk test, and the Wilcoxon test was used to compare the non-normally distributed data on miRNAs in 2 dependent groups. Relationships between numerical variables were evaluated with Spearman's correlation coefficient. Threshold values for significant miRNAs were determined by using the receiver operating characteristic (ROC) curve analysis; sensitivity, specificity, and 95% CIs were calculated. As for descriptive statistics, mean ± SD for numerical variables, median (25%-75%), and number and percent values for categorical variables were presented. Statistical Package for Social Sciences (SPSS) for Windows version 24.0 package program (IBM Corp.; Armonk, NY, USA) was used for statistical analysis, and the *P*-value of <.05 was regarded as statistically significant.

RESULTS

Characteristics of the Participants

The study included 11 patients with lung adenocarcinoma, of which 72.7% of them were men, with a mean age of 63.7 ± 7.9 years. Except for one, all of the patients were smokers. In the study, 45.4% (n = 5) of them were in stage I, 27.3% (n = 3) of them were in stage II, 27.3% (n = 3) of them were in stage III, and 18.2% (n = 2) of them were in stage IV lung cancer and 1 had single brain metastasis. Pathological examinations of tumor differentiations revealed that 9.1% (n = 1) of them had well-differentiated tissues, 45.4% (n = 5) of them had moderately differentiated tissues, and 45.4% (n = 5) of them had poorly differentiated adenocarcinoma (Table 1).

Table 1. Demographic and Main Clinical Characteristics

Lung Adenocarcinoma Patients		n	%
Gender	Female	3	27.3
	Male	8	72.7
Smoker (package/year)	0	1	9.1
	30	2	18.2
	40	1	9.1
	50	2	18.2
	55	1	9.1
	60	2	18.2
	80	2	18.2
T	1a	1	9.1
	1b	1	9.1
	1c	1	9.1
	2	1	9.1
	2a	1	9.1
	3	4	36.4
	4	2	18.2
N	0	7	63.6
	1	2	18.2
	2	2	18.2
M	0	9	81.8
	1	2	18.2
Metastasis	0	10	90.9
	Brain	1	9.1
Pathology	Well-differentiated	1	9.1
	Intermediate-differentiated	5	45.4
	Poorly differentiated	5	45.4
TNM	Stage I	5	45.4
	Stage II	3	27.3
	Stage III	3	27.3
	Stage IV	2	18.2
Survey	Alive	11	100

TNM, tumor node metastasis.

Adenocarcinoma and Normal Lung Tissue's MicroRNA Real-Time-Polymerase Chain Reaction Expressions

In the comparison of miRNA expression levels by RT-PCR of normal and lung adenocarcinoma tissues, significant differences were observed in the expression of miR-134 ($P < .017$), miR-183-5p ($P < .016$), miR-192-5p ($P < .050$), miR-193b-3 ($P < .012$), miR-194-5p ($P < .050$), miR-200c-3p ($P < .021$), miR-212-3p ($P < .041$), miR-25-3p ($P < .050$), miR-449a ($P < .028$), and miR-9-5p ($P < .05$). All apoptosis-associated miRNAs which were differentially expressed were downregulated in adenocarcinoma tissue versus healthy tissues. Although not statistically significant, all apoptosis-associated miRNAs were less expressed in adenocarcinoma tissues (Table 2).

Cutoff values, sensitivity (95% CI), and specificity (95% CI) were calculated using ROC curve analysis of 10 discovered miRNAs. The correlation coefficients of 10 miRNAs that were calculated were strongly or very strongly correlated (Table 3, Figure 1).

MICRORNA EXPRESSIONS IN LUNG ADENOCARCINOMA'S TUMOR DIFFERENTIATIONS

In the present study, there was no statistically significant difference between miRNA expression levels by RT-PCR of adenocarcinoma tissues, which were pathologically classified as well-moderately and poorly differentiated.

DISCUSSION

In the current study, it was determined that 10 apoptosis-associated miRNAs were significantly downregulated in lung adenocarcinoma tissues versus healthy tissues. The expressions of miRNAs were altered in adenocarcinoma tumor tissues compared to healthy tissues. This leads us to think that decreased tumor miRNA expression can have a significant positive impact on adenocarcinoma patient identification. The fact that miRNAs acting on the apoptotic pathway are less expressed in lung adenocarcinoma tissues suggests that these miRNAs act more on tumor-suppressor genes. The link between apoptotic pathways and miRNAs requires more research.

miR-134 and miR-449a are involved in the epidermal growth factor receptor (EGFR) of p53/p73/p63 and Kirsten rat sarcoma virus (KRAS) pathways.[12] In addition to apoptosis, miR-134 is known to contribute to carcinogenesis, cancer cell proliferation, invasion, treatment resistance, and metastases. miR-134 promotes non-small cell lung cancer (NSCLC) cell apoptosis by increasing caspase-3 and caspase-7 and decreasing the expression of Bcl2 protein.[13] miR-134 expression was associated with the invasive potential and epithelial–mesenchymal transition (EMT) phenotype of the NSCLC cells. miR-134 has been shown to inhibit EMT by targeting Forkhead Box M1 in the NSCLC cells.[14] In the present study, miR-134 and miR-449a were downregulated in adenocarcinoma tissues versus healthy tissues. The effects of miR-134 on prognosis in the NSCLC should also be investigated.

Overexpression of the miR-183-5p reduces cell proliferation, tumor growth, migration, and invasion, and the miR-183-5p

Table 2. Comparison of miRNA Expressions in Normal and Lung Adenocarcinoma Tissue

		Normal	Adenocarcinoma	
miRNA	**n**	**Median (25%-75%)**	**Median (25%-75%)**	***P***
hsa-let-7a-5p	11	21.26 (19.27-22.94)	19.02 (18.29-23.07)	.657
hsa-let-7c	11	22.13 (20.3-23.72)	20.12 (19.37-23.47)	.594
hsa-let-7e-5p	11	24.09 (22.2-25.71)	21.81 (21.12-25.75)	.477
hsa-let-7g-5p	11	21.75 (20.13-23.64)	19.32 (18.52-23.34)	.424
hsa-miR-1	11	27.4 (26.04-30.62)	27.21 (26.15-27.91)	.594
hsa-miR-101-3p	11	19.54 (19.03-24.85)	19.39 (18.48-23.29)	.722
hsa-miR-106b-5p	11	22.88 (21.64-25.88)	20.26 (18.9-23.45)	.131
hsa-miR-122-5p	2	32.02 (31.87-32.08)	33.11 (32.83-33.71)	.655
hsa-miR-125a-5	11	19.9 (19.24-21.87)	18.82 (18.14-22.03)	.424
hsa-miR-125b-5	11	19.59 (18.39-21.14)	18.43 (17.64-21.64)	.534
hsa-miR-128	8	29 (28.82-31.25)	27.27 (25.35-32.04)	.161
hsa-miR-1285-3p	9	31.79 (31.27-32.53)	28.46 (28.27-30.26)	.110
hsa-miR-133a	10	27.02 (26.29-30.63)	26.59 (25.95-27.49)	.241
hsa-miR-133b	10	27.99 (27.25-32.02)	27.3 (26.5-27.61)	.333
hsa-miR-134	10	28.1 (27.53-32.02)	26.92 (26.04-27.93)	.017*
hsa-miR-141-3p	11	20.41 (19.22-25.03)	19.15 (16.25-22.38)	.248
hsa-miR-143-3p	11	19.41 (19.12-22.3)	19.32 (18.1-21.81)	.657
hsa-miR-144-3p	9	25.06 (22.82-29.66)	23.27 (22.84-23.68)	.110
hsa-miR-145-5p	11	18.68 (18.24-20.02)	18.55 (18.05-20.05)	1.000
hsa-miR-146a-5p	11	22.62 (21.53-25.47)	21.31 (19.35-22.56)	.075
hsa-miR-149-3p	4	32.62 (32.42-33.52)	32.27 (31.98-33.45)	1.000
hsa-miR-153	8	29.25 (29.07-31.11)	28.64 (26.34-30.89)	.263
hsa-miR-15a-5p	11	21.09 (20.65-25.12)	20.52 (18.89-23.1)	.248
hsa-miR-15b-5p	11	23.33 (22.45-25.8)	21.85 (20.89-26.02)	.374
hsa-miR-16-5p	11	18.26 (17.09-20.27)	16.84 (15.59-21.66)	.477
hsa-miR-17-5p	11	26.49 (25.17-29.22)	23.91 (22.64-29.52)	.286
hsa-miR-181a-5	11	21.75 (20.92-22.89)	19.92 (19.25-22)	.131
hsa-miR-181b-5	11	22.75 (21.7-23.91)	20.54 (19.9-23.05)	.182
hsa-miR-181c-5	10	28.39 (26.77-31.42)	26.2 (25.14-27.02)	.059
hsa-miR-181d	11	27.17 (26.26-29.62)	25.36 (23.92-28.06)	.213
hsa-miR-183-5p	11	26.78 (26.03-28.57)	24.1 (20.27-26.28)	.016*
hsa-miR-185-5p	11	22.3 (22.02-26.31)	21.48 (20.55-23.27)	.131
hsa-miR-186-3p	4	32.44 (31.2-32.59)	29.96 (28.77-31.96)	.068
hsa-miR-192-5p	11	25.45 (25.08-27.14)	22.64 (21.82-26.22)	.050*
hsa-miR-193a-5	11	25.18 (24.99-27.91)	24.41 (23.64-27.19)	.248
hsa-miR-193b-3	10	26.39 (25.31-28.78)	23.92 (22.59-24.36)	.012*
hsa-miR-194-5p	11	24.51 (23.68-26.05)	21.67 (21.11-25.38)	.050*
hsa-miR-195-5p	11	20.11 (19.8-21.38)	19.91 (19.12-22.15)	.929
hsa-miR-200c-3p	11	20.67 (19.52-21.49)	17.8 (16.47-20.29)	.021*
hsa-miR-203a	11	24.04 (22.58-24.99)	23.15 (21.33-24.68)	.182
hsa-miR-204-5p	11	26.61 (26.1-28.55)	27.88 (25.98-29.11)	.722
hsa-miR-205-5p	11	27.37 (25.14-28.8)	24.49 (20.62-26.36)	.155
hsa-miR-206	8	32.36 (31.22-32.95)	33.12 (31.36-33.27)	.401

(*Continued*)

Table 2. Comparison of miRNA Expressions in Normal and Lung Adenocarcinoma Tissue (*Continued*)

		Normal	Adenocarcinoma	
miRNA	**n**	**Median (25%-75%)**	**Median (25%-75%)**	***P***
hsa-miR-20a-5p	11	21.98 (20.07-24.23)	18.52 (17.46-24.22)	.248
hsa-miR-21-5p	11	16.1 (15.51-19.11)	13.39 (12.08-18.25)	.091
hsa-miR-210	8	27.32 (24.13-28.58)	23.36 (19.42-25.36)	.327
hsa-miR-212-3p	11	29.1 (28.83-31.01)	26.34 (26.14-28.62)	.041*
hsa-miR-214-3p	11	24.7 (23.17-25.16)	22.64 (21.62-23.45)	.286
hsa-miR-218-5p	11	22.24 (21.14-22.95)	21.55 (20.67-23.81)	.929
hsa-miR-221-3p	8	25,72 (24.05-27.68)	23.06 (21.06-25.95)	.263
hsa-miR-222-3p	9	22.97 (21.44-24.44)	20.82 (18.23-26.29)	.594
hsa-miR-23a-3p	11	18.21 (17.72-19.38)	17.45 (16.54-19.48)	.477
hsa-miR-24-3p	11	17.51 (16.65-19.07)	16.16 (15.68-18.6)	.248
hsa-miR-25-3p	11	21.28 (20.91-22.49)	19.07 (18.31-21.35)	.050*
hsa-miR-26a-5p	11	19.5 (18.35-20.86)	18.18 (17.32-22.08)	.657
hsa-miR-26b-5p	11	21.62 (20.43-23.22)	19.94 (19.37-24.29)	.722
hsa-miR-27a-3p	11	18.77 (18.12-20.95)	17.75 (16.9-21.02)	.424
hsa-miR-29a-3p	11	21.33 (20.44-24.04)	20.06 (18.84-22.77)	.110
hsa-miR-29b-3p	11	22.13 (20.92-24.25)	20.91 (18.75-21.17)	.155
hsa-miR-29c-3p	11	20.56 (20.09-23.43)	19.46 (18.12-22.01)	.131
hsa-miR-30a-5p	11	19.99 (19.36-21.04)	20.04 (19.04-22.42)	.424
hsa-miR-30b-5p	11	19.53 (18.91-22.54)	18.87 (17.58-20.86)	.424
hsa-miR-30c-5p	11	20.04 (19.3-22)	18.95 (18.38-20.86)	.477
hsa-miR-30d-5p	11	20.21 (19.21-21.53)	19.32 (18.43-20,27)	.155
hsa-miR-30e-5p	11	21.21 (20.29-24.61)	20.6 (18.54-24.69)	.533
hsa-miR-31-5p	11	26.43 (25.53-31.17)	23.76 (19.13-26.03)	.062
hsa-miR-32-5p	10	26.84 (25.36-29.28)	24.19 (22.6-25.66)	.262
hsa-miR-338-3p	8	25.15 (22.98-26.99)	24.75 (22.3-25.96)	1.000
hsa-miR-34a-5p	10	23.77 (22.26-30.1)	22.06 (19.95-23.59)	.074
hsa-miR-34c-5p	8	28.29 (27.1-29.31)	25.14 (24.49-31.17)	.327
hsa-miR-365a-3p	10	26.42 (25.64-30.78)	24.3 (22.58-27.09)	.093
hsa-miR-378a-3	11	22.82 (21.95-27.06)	21.79 (21.01-25.49)	.213
hsa-miR-409-3p	11	28.28 (27.65-31.17)	26.32 (25.41-28.61)	.075
hsa-miR-449a	7	28.91 (28.35-31.28)	25.29 (24.55-26.4)	.028*
hsa-miR-451a	11	20.16 (19.08-24.54)	20.14 (19.39-20.79)	.657
hsa-miR-491-5p	11	28.05 (27.63-34.66)	26.15 (25.34-30.05)	.062
hsa-miR-497-5p	8	24.3 (23.79-26.85)	23.55 (21.84-24.7)	.263
hsa-miR-512-5p	0		34.68 (33.3-36.06)	N/A
hsa-miR-542-3p	11	27.24 (27.08-29.13)	25.01 (24.06-28.28)	.155
hsa-miR-7-5p	9	27.05 (26.79-29.94)	24.68 (21.15-28.01)	.173
hsa-miR-708-5p	11	26.08 (25.73-29.09)	23.47 (21.68-28.63)	.110
hsa-miR-9-5p	11	28.42 (27.35-30.37)	24.03 (21.94-31.56)	.050*
hsa-miR-92a-3p	11	21.59 (21.12-24.08)	20.1 (19.07-22.74)	.131
hsa-miR-98-5p	9	25.83 (25.71-28.56)	25.24 (23.37-28.61)	.515

*Significant at .05 level, Wilcoxon test.
miRNA, microRNA; N/A, not applicable.

Table 3. miRNAs ROC Curve Analysis

miRNA	AUC ± SE	*P*	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
hsa-miR-134	0.805 ± 0.10	.003	≤27.34	70 (34.8-93.3)	90.91 (58.7-99.8)
hsa-miR-183-5p	0.843 ± 0.09	.001	≤24.51	72.33 (39.0-94.0)	90.91 (58.7-99.8)
hsa-miR-192-5p	0.793 ± 0.11	.010	≤24.19	72.73 (39.0-94.0)	100.00 (71.5-100)
hsa-miR-193b-3	0.882 ± 0.08	.001	≤24.36	80 (44.4-97.5)	90.91 (58.7-99.8)
hsa-miR-194-5p	0.777 ± 0.120	.021	≤23.44	72.73 (39.0-94.0)	100 (71.5-100)
hsa-miR-200c-3p	0.826 ± 0.09	.001	≤19.15	72.73 (39.0- 94.0)	90.91 (58.7-99.8)
hsa-miR-212-3p	0.835 ± 0.095	.001	≤28.62	81.82 (48.2- 97.7)	81.81(48.2-97.7)
hsa-miR-25-3p	0.785 ± 0.109	.009	≤19.12	63.64 (30.8- 89.1)	100 (71.5-100.0)
hsa-miR-449a	0.903 ± 0.09	.001	≤26.95	87.50 (47.3- 99.7)	88.89 (51.8-99.7)
hsa-miR-9-5p	0.760 ± 0.119	.029	≤25.37	63.64 (30.8- 89.1)	100.00 (71.5-100.0)

AUC, area under the ROC curve; miRNA, microRNA; ROC, receiver operating characteristic; SE, sedimentation equilibrium.

induces cell cycle arrest and increases apoptosis.[15] It has been presented that miR-183-5p can suppress p53 and activate protein kinase B signaling through phosphorylation. miR-183 is effective in DNA damage, cell metabolism, and apoptosis pathway.[16] In the current study, miR-183-5p expression was decreased in adenocarcinoma tissues. Interventions that increase the miR-183-5p expression may be involved in the treatment of lung adenocarcinoma.

The miR-192-5p overexpression plays a potential role in suppressing tumorigenesis and metastases through different mechanisms. Overexpression of the miR-192-5p in the studies was thought to suppress tumor growth in vivo.[17] Exosomal miR-192-5p has been found as a potential prognostic marker for lung adenocarcinoma.[18] In the present study, the miR-192-5p is downregulated in the lung adenocarcinoma tissues. However, in this study, no comparison was made between serum and healthy controls.

The miR-193 is involved in suppressing cell proliferation, cell cycle progression, cell migration, and invasion in lung cancer.[19] It has been shown that the nuclear factor kappa B (NF-κB) signaling contributes to cancer progression by controlling the EMT and metastasis.[20] miR-193b-3p has been previously identified as a diagnostic biomarker for the NSCLC.[21] The NF-κB can bind to the promoter region of the miR-194-5p and regulate the miR-194-5p expression in ovarian cancer cells.[22] Lung cancer's cell viability and proliferation are inhibited by the miR-194-5p. CircCHST15 in the cytoplasm has been presented to promote tumor growth by the programmed death ligand-1-mediated escape from the immune system, downregulating the expression of miR-194-5p.[23] Therefore, low expression of the miR-194-5p could be a risk factor for cancer prognosis.

miR-200c-3p is involved in the EGFR–tyrosine kinase inhibitor (TKI) resistance by regulating the EMT modulations. miR-200c-3p was downregulated in the EGFR–TKI-resistant cell lines. Patients with high miR-200c-3p expression had a higher progression-free survival with EGFR–TKI treatment. The miR-200c-3p overexpression promoted cell death by inhibiting the EMT process in the EGFR–TKI-resistant cell lines.[24] Increased expression of the miR-200c-3p appears to be an increasing factor for apoptosis. In the present study, the miR-200c-3p expression was downregulated in the tissues with adenocarcinoma.

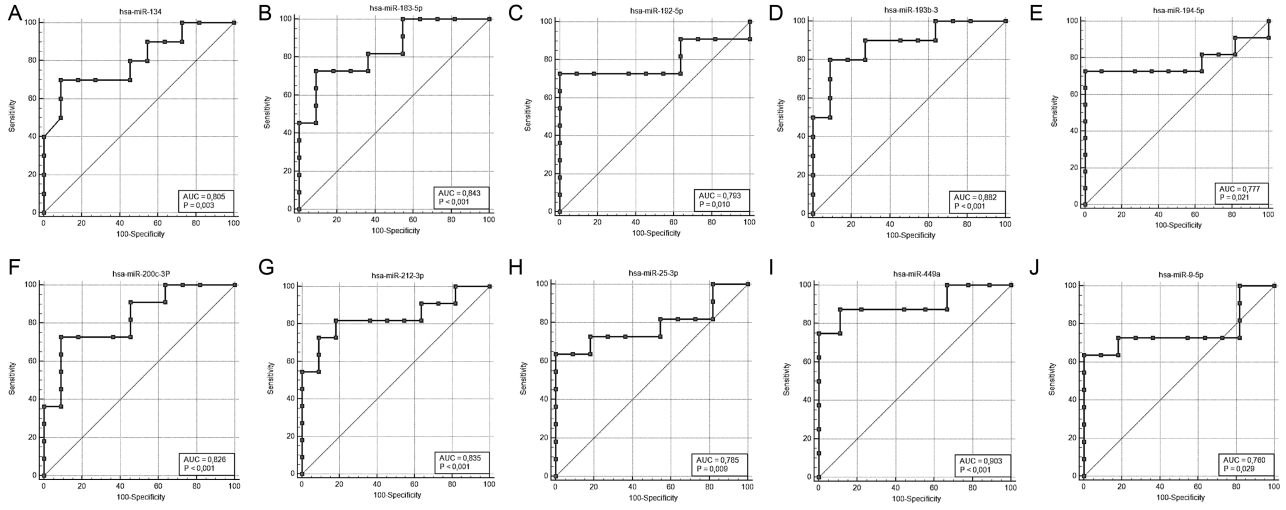


Figure 1. MicroRNA receiver operating characteristic curve analysis results [(A) miR-134, (B) miR-183-5p, (C) miR-192-5p, (D) miR-193b-3, (E) miR-194-5p (F) miR-200c-3p, (G) miR-212-3p, (H) miR-25-3p, (I) miR-449a, (J) miR-9-5p]. AUC, area under the curve.

miR-212-3p plays a suppressive role in the malignant invasion by targeting the disintegrin and metalloproteinase 10 (ADAM10) in the NSCLC.[25] Non-small cell lung carcinoma is involved with the miR-212-3p, X-inactive specific transcript, and Casitas B-lineage proto-oncogene like 1. X-inactive specific transcript knockdown has been shown to suppress the NSCLC cell proliferation, migration, invasion, and EMT in vitro, and it reduces tumor growth in vivo.[26] As in our study, the miR-212-3p was downregulated in the NSCLC tissues in previous studies, as well. The expression levels of miR-212-3p should be investigated for the determination of lung adenocarcinoma prognosis.

miR-25-3p is associated with cell proliferation, migration, and invasion in the NSCLC primary tumors and cell lines. High miR-25-3p expression levels were positively correlated with lung cancer patients' survival.[27] miR-25-3p affects the NSCLC progression by targeting the Forkhead Box P2.[28]

miR-449a has been downregulated in the NSCLC tissues and cell lines in the studies. When miRNA-449a was upregulated in the NSCLC cells, the ability of the cells to invade and migrate was weakened, and the ADAM10 expression was presented to be decreased.[29] There are promising studies on the use of exosome engineering for the treatment of cancer.[30] miR-25-3p and miR-449a could be used in lung adenocarcinoma in line with the targeted drug therapies. The upregulation of miR-9-5p in the NSCLC promotes the growth, invasion, and metastasis of cancer cells by suppressing the expression of transforming growth factor-β receptor 2.[31] However, miR-9-5p was downregulated in adenocarcinoma tissues in the present study. Different NSCLC histological subtypes might express the miR-9-5p differently.

The insufficient number of samples prevented us from obtaining any useful information about the relationship between the histological grades and microRNA expressions. However, although there are not enough studies on this subject in the literature, we believe that the relationship between pathological grading and miRNA expression levels might be crucial for early diagnosis, treatment response, and prognosis follow-up.

The current study has a number of limitations. Although the characteristics of gender and stage of the patients reflect society, the findings need to be supported by a larger number of cases. Larger sampling and demographic diversity are needed to examine the difference between the degree of differentiation and miRNA expressions of lung adenocarcinoma. Another limitation of the study is that the miRNA expressions linked to apoptosis of the tissues were not investigated in serum. Serum and tissue miRNA correlations could not be demonstrated. In addition, serum miRNA levels should be compared with completely healthy volunteers.

CONCLUSION

The detection of apoptosis-associated miRNAs, which were expressed differently in lung adenocarcinoma, was presented. The identification of these miRNAs that may be associated with the activation of tumor-suppressor genes could inspire new research and target therapeutics in this area. The histological subtype of lung adenocarcinoma's apoptosis-associated miRNAs can be employed as biomarkers for prognosis and targeted treatments. To fully understand the function of miRNAs in cancer biology, further studies on different histological subtypes of lung cancer are needed, and these studies should be conducted with more patients.

Ethics Committee Approval: This cross-sectional study was conducted with permission numbered 2020/75 from the Gaziantep University Ethics Committee.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.F., A.F.I., D.K.; Design – F.F., A.F.I., D.K.; Data Collection and/or Processing – F.F., A.F.I., O.E., C.B., D.K.; Analysis and/or Interpretation – F.F., D.K, S.I, C.B., K.M., O.E., S.K.; Writing Manuscript – F.F., S.K., D.K.; Critical Review – F.F., S.K., D.K.

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Original Article

Short-Term Pulmonary Rehabilitation Among Post-Pulmonary Tuberculosis Patients During Coronavirus Disease 2019 Pandemic

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Abstract

OBJECTIVE: Coronavirus disease 2019 is expected to have a widespread and significant impact on pulmonary tuberculosis services. This study aims to investigate the effect of comprehensive short-term, outpatient pulmonary rehabilitation program among treated pulmonary tuberculosis patients during the coronavirus disease 2019 pandemic.

MATERIAL AND METHODS: Forty-five pulmonary tuberculosis patients who completed their tuberculosis treatment were randomly allocated to the outpatient pulmonary rehabilitation group and the other 45 were allocated to the control group for 4 weeks. The pulmonary rehabilitation program comprised supervised endurance and resistance training, breathing techniques, self-management strategies, and patient education. The outcome measures evaluated in both groups were functional capacity assessed by a 6-minute walk test, health-related quality of life (short-form 36 questionnaire), pulmonary function (forced expiratory volume in 1 second/forced vital capacity, forced vital capacity, and forced expiratory volume in 1 second), and dyspnea by modified Medical Research Council dyspnea scale. All measurements were performed at enrolment and after completion of 4 weeks protocol in both the groups.

RESULTS: There was a significant improvement in 6-minute walk distance in meters ($P = .001$) and percentage predicted ($P = .014$) in the pulmonary rehabilitation group compared to the control group. All domains of the short-form 36 questionnaire showed significant improvement post-pulmonary rehabilitation ($P < 0.05$), and modified Medical Research Council dyspnea scale also significantly improved in the pulmonary rehabilitation group ($P < .001$). However, no significant differences were observed in any of the pulmonary function measures ($P > .05$) between the groups after 4 weeks.

CONCLUSION: Short-term pulmonary rehabilitation program in pulmonary tuberculosis demonstrated improvement in functional capacity, quality of life, and dyspnea. However, it failed to register changes in pulmonary function. The study results provide motivation to consider the implementation of a short-term pulmonary rehabilitation program after pulmonary tuberculosis treatment to reduce the impairment the patient may suffer even after microbiological cure.

KEYWORDS: COVID-19 pandemic, exercise tolerance, lung function impairment, pulmonary rehabilitation, pulmonary tuberculosis, quality of life

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INTRODUCTION

By distorting the healthcare system at several levels, the coronavirus disease 2019 (COVID-19) pandemic has impacted pulmonary tuberculosis (PTB) control strategies and the occurrence of catastrophic expenses. The prioritization has also resulted in a drastic shift in healthcare personnel's role toward COVID-19-related services which has led to a reduction in the number of consultation services and the delivery of PTB-related programs at both hospitals and community levels. Due to the allocation of numerous PTB-related resources to COVID-19 programs, there is also a reduction in the availability of healthcare services for efficient PTB management strategies.[1] Between 2020 and 2025, the globe might see an additional 6.3 million cases of PTB, and 1.4 million PTB deaths are suspected.[2] Social distancing measures established in several countries to restrict COVID-19 transmission had an immediate and substantial impact on the delivery of pulmonary rehabilitation (PR) programs.[3]

In most impacted nations, PR programs included a minimum of 6-7 weeks duration (24 supervised sessions) followed by 3 months of maintenance phase.[4,5] Pulmonary rehabilitation setups were discontinued to protect vulnerable population from contracting the virus. However, the dire need for PR cannot be neglected; therefore, formal discussions were conducted among healthcare professionals on how to continue delivering PR services in the midst of the crisis.[6]

Short-term PR programs can be considered as an efficient and effective treatment strategy at the time of the crisis where delivering long-term PR can be challenging. Short-term PR programs have shown immediate benefits in patients with

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various chronic respiratory conditions.[7] However, there have been no published evaluations on the efficacy of short-term PR during the COVID-19 pandemic on post-PTB pharmacologically treated patients. Therefore, the aim of the present study is to evaluate the effect of short-term PR on functional capacity, pulmonary function, health-related quality of life (HRQoL), and dyspnea during the COVID-19 pandemic on post-PTB-treated patients.

MATERIAL AND METHODS

The present randomized control trial was conducted after obtaining ethical clearance from the Institutional Ethics Committee of Sharda University, Greater Noida, India, with ethical approval number SU/SMS&R/76-A/2022/01. The study was designed according to the Consolidated Standard of Reporting Trials (CONSORT) guidelines designed for reporting Randomized control trials. Potential participants were educated about the protocol based on eligibility criteria, signed informed consent was acquired from all participants, and research methods were followed based on the Declaration of Helsinki, 1964.

Inclusion criteria for both groups were patients with PTB 18 years of age and older, who exhibit shortness of breath on exertion, who have limitations in the activities of daily living, and who have a documented history of smear-positive PTB with pharmacological treatment completed more than 6 months prior to the study enrolment.[8] Subjects who have not participated in any physical activity or rehabilitation program during the previous 6 months were included. Subjects with a previous history of other respiratory diseases such as chronic obstructive pulmonary disease, asthma, and interstitial lung disease as well as cardiovascular diseases such as myocardial infarction, angina, and congestive heart failure were excluded. Patients over the age of 80 and those with orthopedic or cognitive impairments who would be unable to participate in the rehabilitation program on a regular basis were also excluded from the present study.

MAIN POINTS

- The burden of pulmonary tuberculosis (PTB) during coronavirus disease 2019 (COVID-19) has negatively influenced PTB management strategies.
- The long-term sequelae of PTB patients results in deteriorated functional capacity, pulmonary measures, and excessive breathlessness, ultimately affecting the overall health-related quality of life (HRQoL). This results in enhanced symptomatic burden that cannot be recovered solely by pharmacological management.
- Pulmonary rehabilitation (PR) strategies have the potential to break the vicious cycle. It has proven beneficial impact on various chronic respiratory conditions. However, the efficacy of short-term PR program on patients with PTB still remains inconclusive.
- The findings of the present study can wave paths for clinicians to optimally deliver short-term PR in post-PTB patients to maximize gains in functional capacity, HRQoL, and dyspnea. However, the efficacy of PR on pulmonary measures in these patients is still debatable.

Sample Size Calculation

Software G. Power 3.1.9.2 (Franz F, Universitat Kiel, Kiel, Germany) was used to determine the sample from a previous study conducted by Singh et al[8] using data of changes in 6-minute walk distance (6MWD). A total of 45 subjects were considered necessary in each group, and the power (1 – beta) was 0.80 with an effect size of 0.384.

The respiratory outpatient service helped in enrolling 90 stable PTB patients who had completed their pharmacological treatment. Patients who met the inclusion criteria were allocated randomly to either the rehabilitation or control group using sealed envelopes created and jumbled by an impartial individual unaffiliated with the study procedure before trial was initiated. The allocator opened the envelope sequentially, only after the participant's name was written on it. Patients who were allocated to the rehabilitation group had to complete a minimum of 16 sessions of an outpatient PR program over the course of 4 weeks (4 sessions per week). The complete exercise prescription for this PR program was carried out under the guidance of a licensed physiotherapist at the hospital while adhering to COVID-19-appropriate behavior because it was an institution-based program.

Pulmonary rehabilitation sessions were conducted in the morning hours to allow participants to travel back home in time before the evening rush hour, and the standard operating procedure for data collection was modified to ensure 2-m distancing between the study staff and study participant. Study participants underwent COVID-19 testing before starting PR and as needed during the hospital-based sessions. Before accessing the PR room, all participants and staff were required to undergo temperature measurement using a handheld non-contact thermometer and wash their hands with soap or alcohol-based hand sanitizer. The maximum number of participants participating in the PR session was reduced from 12 to 8 to ensure social distancing between participants. All study staff were required to wear N95 masks at all times and underwent COVID-19 training with an emphasis on infection prevention and control, and the study participants were screened for signs and symptoms of the disease.

Assessment

A week before baseline testing, all patients were made aware of the research procedures and potential hazards. Each patient got a primary health examination prior to initial testing. The baseline testing was conducted over 2 days. On day 1, participants were requested to complete the short form-36 questionnaire (SF-36) which is generic HRQoL questionnaire, following baseline dyspnea assessment which was conducted through modified Medical Research Council (mMRC) dyspnea scale. On day 2, the participants underwent a pulmonary function test, as recommended by the American Thoracic Society and the European Respiratory Society (ATS/ERS) guidelines. Measurements were made of the forced vital capacity (FVC), forced expiratory volume (FEV_1) in 1 second, and FEV_1/FVC ratio. According to ATS/ERS recommendations, blood pressure, heart rate, oxygen saturation (SpO_2), and dyspnea were measured before and after the 6-minute walk test (6MWT). Each patient was instructed to walk at their own pace covering the largest distance possible in 6 minutes. The

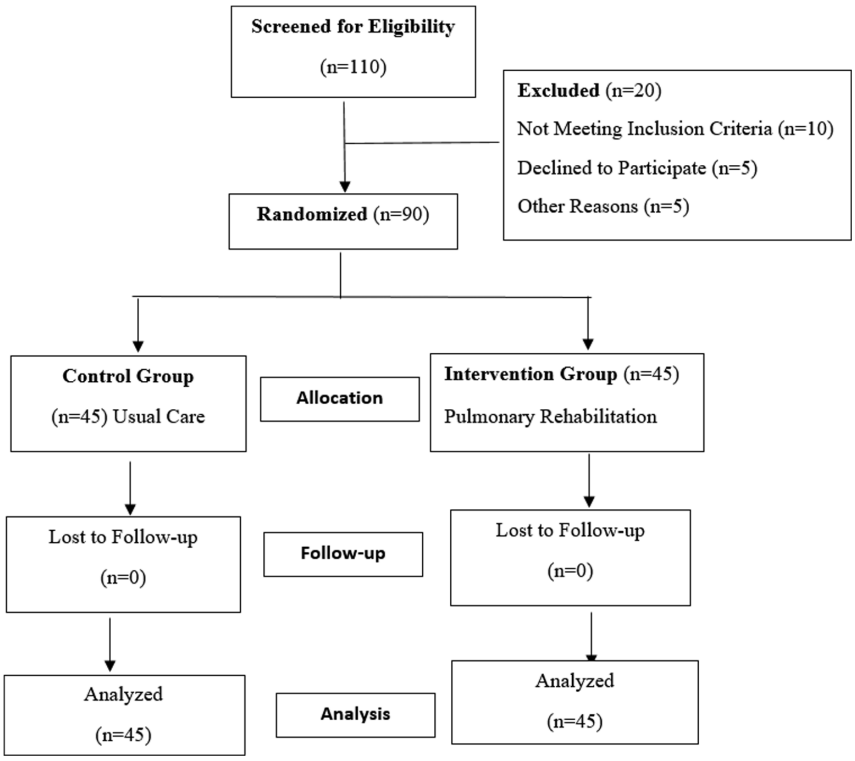


Figure 1. Study flowchart.

participant's total distance covered was calculated in meters and percentage. Enright[9] equation was used to estimate the 6MWD predicted for both males and females.

Following baseline testing, participants were randomly allocated to the PR or control group. Participant assigned to the control group were asked to continue their normal routine strategies for 4 weeks. After completion of the 4 weeks, outcome measures were reassessed for both the groups.

Pulmonary Rehabilitation Intervention

The outpatient PR sessions were individually tailored to each patient's performance during the initial assessment which comprised static circuit training to increase peripheral muscle strength and general mobility with breathing exercises, supervised endurance and resistance training, stretching of upper and lower extremity muscles, self-management, and patient education. Breathing exercises are applied in each session and last for 30 minutes.[10]

The endurance exercise program was applied in the form of ground walking. The walking prescription mostly represents the activities of daily living. It is functional, simple, inexpensive, and readily applicable. The walk speed or intensity of the training was calculated based on the distanced covered during 6MWT, as suggested by Chandrasekaran and Reddy.[11]

Maximum distance that may be walked in 20-minute walk distance (20MWD) = actual 6MWD × 3.33 m

Initial training distance to be walked in 20 minute for first 1 week = 80/100 × 20MWD m

For the second week, distance to be walked in 20 minutes = 85/100 × 20MWD m

For the third week, distance to be walked in 20 minutes = 90/100 × 20MWD m

For the fourth week, the subjects performed walking at the actual 6MWD covered in the initial testing.

This way the subjects began from 80% of their walking distance and progressively increased to 100% of the walk intensity derived from actual 6MWT conducted over a period of 4 weeks. Walking speed was gradually increased as the patients gained confidence and correlated with an intensity of 11-13 points on the Borg scale for the initial 2 weeks and progressively increased up to 15 on the Borg scale for the final 2 weeks, taking care that SpO_2 did not drop below 90%. Walking distance was 20 minutes twice a day for 4 weeks based on the above prescription. The training was done under the supervision of a physical therapist on 4 weekdays. On the weekend, the patients were instructed to perform walking as prescribed during supervised sessions.

Resistance training was performed 3 times per week at 50%-70% of 1 repetition maximum intensity (1-RM).[4] After determining the 1-RM for each exercise, the load at 50%-70% of 1-RM was approximated. Quadriceps, hamstrings, hip flexors, abductors, and extensors were all worked out. The deltoid, triceps, and biceps muscles were also exercised by the upper extremity strength training. Three sets of 8-10 repetitions of each exercise were performed with 2-3 minutes of rest interval between the sets. Resistance training intensity was progressively increased: 50% of 1-RM for the first week, 60% of 1-RM for the middle 2 weeks, and 70% of 1-RM for the fourth week.[12]

Stretching exercises targeting specific muscle groups were recommended to ensure good posture and proper body

mechanics and to minimize the incidence of joint and muscle injury resulting in improved respiratory mechanics.[13] Five minutes of flexibility training was conducted at the beginning and end of each exercise session. One set of 4-5 stretching exercises was performed for 15-30 seconds (seated single-leg hamstring stretch, standing quadriceps stretch, chest stretch, overhead reach stretch, and wall cat stretch).[14]

The researcher gave the intervention group a systematic program consisting of self-management of symptoms, involving relaxation techniques to minimize dyspnea, cessation of smoking, and nutritional suggestions based on the nutritionist's personalized recommendations.

The control group on the other hand continued with their usual activities and, if necessary, medical care as prescribed by a qualified practitioner.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp.; Armonk, NY, USA) was used for the data analysis. Results were reported in mean and SD for continuous data, whereas discrete (categorical) data were presented as number (n) and percentage (%). The normal distribution of data was tested by the Shapiro–Wilk test, skewness, and histogram. Variables that depicted non-normal distribution were log-transformed.

The outcome variables between groups were compared at baseline and 4 weeks later using an independent *t*-test. To compute the difference between PR versus control group following 4 weeks, standardized mean difference and 95% CI were estimated. Statistical significance was set at $P \leq .05$.

RESULTS

As demonstrated in Table 1, there were no appreciable variations in baseline demographic, clinical, or outcome characteristics between the PR and the control group. The 2 groups were well-matched in terms of age, weight, and height in comparison to the control group. After 4 weeks, the PR group demonstrated a significant improvement in 6MWD in meters ($P = .001$) and percentage predicted ($P = .014$). The PR group showed a significant improvement in all SF-36 domains. Modified Medical Research Council (dyspnea scale) scores in the PR group also significantly increased ($P = .001$). However, as shown in Table 2, there were no differences between the groups after 4 weeks in the pulmonary function measurements: FEV_1 (L) ($P = .142$), FVC (L) ($P = .115$), and FEV1/FVC ($P = .497$).

DISCUSSION

In the current study, the PR group had a substantial improvement in 6MWD by 198 m compared to controls; these findings are supported by previous trials conducted in PTB

Table 1. Baseline Clinical and Demographic Features of the Subject (n = 90)

Variables	PR Group (n = 45), Mean ± SD	Control Group (n = 45), Mean ± SD	*P*
Age, years	35.20 ± 11.69	35.04 ± 7.74	.95
9 × height, cm	152.25 ± 5.46	152.32 ± 5.37	.94
Weight, kg	54.93 ± 10.2	53.72 ± 11.8	.54
6MWT, m	286.85 ± 44.64	352.37 ± 36.17	.17
6MWD, %	64.2 ± 13.6	69.4 ± 12.7	.30
6MWD, RHR (bpm)	81.95 ± 9.36	76.3 ± 11.4	.48
6MWD, HRmax (bpm)	104.6 ± 16.88	105.45 ± 19.91	.38
PFT			
FEV_1, L	1.29 ± 0.44	1.25 ± 0.46	.61
FVC, L	1.64 ± 0.47	1.57 ± 0.51	.46
FEV_1/FVC	100.37 ± 16.0	101.45 ± 15.91	.71
mMRC	3.38 ± 0.49	3.60 ± 0.49	.93
SF-36			
Physical functioning	42.4 ± 7.3	47.7 ± 8.1	.42
Role physical	49.6 ± 13.6	51.2 ± 9.5	.43
Bodily pain	43.3 ± 7.3	42.7 ± 8.3	.67
General health	50.2 ± 7.1	51.2 ± 6.9	.42
Vitality	62.5 ± 8.0	61.9 ± 7.1	.70
Social functioning	56.5 ± 12.3	56.5 ± 12.3	.98
Role emotional	76.3 ± 11.4	63.3 ± 14.1	.07
Mental health	65.1 ± 8.3	62.9 ± 10.5	.20

All values expressed in mean ± SD.
6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; RHR, Resting heart rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council (dyspnea scale); PFT, pulmonary function testing; PR, pulmonary rehabilitation; SF-36, 36-item short-form survey.

Table 2. Four-Week Outcome Variable Standardized Mean Differences Between Groups

Outcome Variables	PR Group (n = 45)		Control Group (n = 45)		*t*-Value	PR Group vs. Control Group Standardized Mean Difference Random (95% CI)	*P*
	Baseline	Four weeks	Baseline	Four weeks			
6MWT, m	286.85 ± 44.64	484.15 ± 48.01	313.0 ± 48.17	321.32 ± 43.46	13.03	1.44 (0.60-2.29)	.001*
6MWD, % predicted	64.2 ± 13.6	83.2 ± 11.4	69.4 ± 12.7	71.1 ± 12.6	11.3	0.98 (0.19-1.77)	.014*
6MWD, RHR (bpm)	81.95 ± 9.36	73.60 ± 9.82	76.3 ± 11.4	88.9 ± 6.3	14.9	–9.2(69.00-78.20)	<.001
6MWD, HRmax (bpm)	104.6 ± 16.88	107.6 ± 18.50	105.45 ± 19.91	108.2 ± 19.30	18.7	–17.36 (98.94-116.3)	.381
FEV_1, L	1.29 ± 0.44	1.44 ± 0.64	1.25 ± 0.46	1.34 ± 0.58	5.59	0.51(–0.25 to 1.26)	.142
FVC, L	1.64 ± 0.47	1.64 ± 0.47	1.57 ± 0.51	1.57 ± 0.51	6.03	0.18 (–0.56 to 0.92)	.115
FEV_1/FVC	100.37 ± 16.0	100.37 ± 16.0	101.45 ± 15.91	101.45 ± 15.9	2.43	0.02 (–0.72 to 0.76)	.497
mMRC	3.38 ± 0.49	0.02 ± 0.12	3.60 ± 0.49	0.50 ± 0.65	17.96	1.49 (–2.34 to –0.64)	.005*
Physical functioning	42.4 ± 7.3	88.9 ± 6.3	47.7 ± 8.1	50.8 ± 8.3	23.8	1.22 (–2.03 to –0.40)	.003*
Role physical	49.6 ± 13.6	79.3 ± 10.0	51.2 ± 9.5	54.3 ± 9.8	13.6	1.22 (–2.03 to –0.40)	.003*
Bodily pain	43.3 ± 7.3	87.8 ± 6.9	42.7 ± 8.3	46.0 ± 9.1	26.5	1.22 (–2.03 to –0.40)	.003*
General health	50.2 ± 7.1	89.7 ± 7.2	51.2 ± 6.9	54.6 ± 7.1	18.4	1.15 (–1.96 to –0.34)	.007*
Vitality	62.5 ± 8.0	88.6 ± 6.8	61.9 ± 7.1	64.0 ± 8.0	19.8	1.06 (–1.039 to –1.082)	<.001*
Social functioning	56.5 ± 12.3	89.4 ± 5.7	56.5 ± 12.3	59.1 ± 11.9	15.77	1.019 (1.011 to –1.028)	<.001*
Role emotional	76.3 ± 11.4	88.7 ± 5.1	63.3 ± 14.1	65.8 ± 13.8	14.53	1.052 (1.016-1.091)	.005*
Mental health	65.1 ± 8.3	88.4 ± 5.1	62.9 ± 10.5	65.8 ± 10.9	17.93	1.49 (–2.34 to –0.64)	.005*

The mean and SD of the values are shown. Percent in FVC denotes a percentage change in FVC.
*Significant difference between groups after 6 weeks.
6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; RHR, Resting heart rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council (dyspnea scale); PFT, pulmonary function testing; PR, pulmonary rehabilitation.

patients.[12,15] Adults with post-PTB develop skeletal muscle dysfunction accountable to physical inactivity and systemic inflammation which is often compounded by impaired nutrition. Such patients enter a vicious cycle, which results in declining body mass index, progressive morbidity, and increased mortality.[16] Individuals affected by chronic respiratory conditions tend to avoid exercise and become increasingly deconditioned and developed exercise intolerance during exercise testing and training. Pulmonary rehabilitation results in breaking this vicious cycle and improves the exercise tolerance of the patient.[17] We may speculate that improvement in functional capacity might result from decreased ventilatory demand and switching toward aerobic metabolism as suggested by the depressed lactate levels,[13] which ultimately results in improved muscle performance and subsequent alleviation of muscle fatigue, thereby resulting in enhanced exercise tolerance.[13]

We observed significant improvements in HRQoL assessed by the SF-36, a reliable and validated generic HRQoL questionnaire appropriate for assessing patients with PTB. These improvements in HRQoL may be more significant than physiological measurements.[18] According to a study by Rossi et al[19], symptoms of mental health deterioration are present at quite high rates since the pandemic, which eventually resulted in a low quality of life. However, the current study found that by the end of the PR program, the patient's mental health improved significantly, as assessed by the SF-36 questionnaire. The findings of the current study are consistent with previous research that found that PTB patients' HRQoL significantly improved following the completion of PR sessions on both clinical and statistical level.[17] Exercise-related biological processes included improved hypothalamic–pituitary–adrenal axis modulation, higher endogenous opioid release, and lower systemic inflammation, all of which are speculated to enhance mental and emotional well-being following PR and thereby improving HRQoL among PTB patients.[20]

We found no improvement in spirometric measures in PTB post-PR. The finding of the present study is in agreement with Mbatchou Ngahane et al[21] who demonstrated a connection between pulmonary function deterioration and the interval between the onset of disease symptoms and the diagnosis of tuberculosis. Moreover, cumulative age-related FEV_1 decline predominantly in young adults will cause even more significant impairment in pulmonary function later.[22] The reason for no significant improvement in pulmonary function in the current study is a longer delay in diagnosis and treatment due to the COVID-19 pandemic, which has eventually been linked to a decline in pulmonary function outcomes.

The current study has a few limitations. First, it would be fascinating to look into the effects of a long-term PR in individuals who have been pharmacologically cured of PTB. Second, other more relevant outcome variables such as chest x-rays, sputum examination, arterial blood gas analysis, and inflammatory markers like eosinophil might provide a comprehensive picture of this population's physiological responses to PR. Despite these limitations, the study has potential strengths; the lack of dropouts from the current trial suggests that participants adhered to the treatment protocol. This suggests that short-term PR may be an effective strategy to improve outcome measures in PTB patients with an increased adherence rate. As the protocol was implemented during the time of COVID-19, COVID-19 appropriate measures have been taken for all of the patients.

CONCLUSION

The results of the study indicate that a short-term PR program enhances PTB patient's functional capacity, HRQoL, and dyspnea scores. However, short-term PR was insufficient to register changes in pulmonary function in these PTB patients.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Sharda University (Approval No: SU/SMS&R/76-A/2022/01).

Informed Consent: Patients who volunteered to participate in the trial provided written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.O.; Design – M.J.,; Supervision – A.P.; Materials - M.O., I.A.; Data Collection and/ or Processing – I.A.; Analysis and/or Interpretation – I.A.; Literature Review – A.M., M.O., M.J.; Writing – M.O., A.M.; Critical Review – M.J., A.M.

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Original Article

Breathlessness Beliefs and Related Factors in Male Patients with Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVE: Dyspnea may be a debilitating factor for people with pulmonary problems as it may cause fear of movement. The aim of the present study was to determine the related factors with breathlessness beliefs, in other words, dyspnea-related fear of movement, in patients with chronic obstructive pulmonary disease.

MATERIAL AND METHODS: Male patients with chronic obstructive pulmonary disease were included in the study. Breathlessness beliefs (Breathlessness Belief Questionnaire), perceived dyspnea severity (modified Medical Research Council Dyspnea Scale and modified Borg Scale), pulmonary function tests (forced vital capacity, forced expiration volume in 1 second, and peak expiratory flow), emotional status (Hospital Anxiety and Depression Scale), fatigue (Fatigue Impact Scale and Fatigue Severity Scale), physical activity level (International Physical Activity Questionnaire—Short Form), disease-related quality of life (St. George Respiratory Questionnaire), and generic quality of life (Short-Form 36) were evaluated.

RESULTS: A total of 70 patients were included. Significant correlations were detected between breathlessness beliefs and perceived dyspnea severity, pulmonary function tests, emotional status, fatigue, physical activity level, disease-related quality of life, and generic quality of life ($P < .001$). No correlations were detected between physical characteristics and dyspnea-related fear of movement ($P > .05$).

CONCLUSION: Dyspnea-related fear of movement was found to be strongly related to perceived dyspnea severity, pulmonary function tests, emotional status, fatigue, physical activity level, and quality of life; thus, including breathlessness beliefs assessment into clinical examination may help clinicians to understand their patients' needs comprehensively.

KEYWORDS: Dyspnea, fear of movement, pulmonary diseases
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease which not only involves the lungs and respiratory tract but also causes systematic changes in the body.[1] Chronic obstructive pulmonary disease shows characteristic symptoms such as dyspnea, cough, and increased phlegm production. Among these symptoms, dyspnea is the most reported one (71%) and was found related to decreased physical activity levels.[2] Dyspnea is defined as a multidimensional subjective experience just as pain by some authors,[3] and perceived dyspnea severity of the patient has an important role in disease management. Dyspnea may also cause decreased physical activity levels in patients with COPD. Decreased activity levels may cause muscle weakness, increased anxiety and depression, and deteriorated quality of life in patients with COPD.[4] Thus, it is important to determine the dyspnea-related fear of movement, in other words, breathlessness beliefs, and its relationships with other clinical outcomes in patients with pulmonary problems.

Previously, breathlessness beliefs were associated to perceived dyspnea level, emotional status, and disease-related quality of life.[5-7] However, there are limited data regarding the relationships among breathlessness beliefs, fatigue, and physical activity levels.[8,9] Therefore, the aim of the present study was to determine the factors related to breathlessness beliefs in male patients with COPD.

MATERIAL AND METHODS

Patients

In this cross-sectional study, patients who were diagnosed with COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[10] (forced vital capacity (FVC)/forced expiration volume in 1 second (FEV_1) <0.70) and who visited the Dokuz Eylül University Hospital, Department of Pulmonary Diseases, for their routine assessment were invited for participation. Inclusion criteria were as follows: (a) being literate in Turkish language, (b) being male, (c) being diagnosed at least 1 month prior to the study, (d) being older than 45 years old, and (e) willingness to participate in the study. Patients were excluded if they (a) had severe pain (b) had any orthopedic or musculoskeletal

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problems, (c) had trauma in the last 6 months, (d) were hospitalized in the last 6 months, (e) need non-invasive mechanical ventilation, (f) need constant/long-term oxygen therapy, (g) had ongoing pulmonary rehabilitation, or (h) had another medical condition which may cause dyspnea. An informed consent was obtained from all the participants prior to the study. The ethical approval was obtained from Dokuz Eylül University with the number of 2016/23-17.

ASSESSMENTS

Physical and Clinical Characteristics

Physical characteristics (age, height, and weight) were recorded. Body mass index (BMI) was calculated according to the formula: kg/m^2.

Breathlessness Beliefs Questionnaire

Breathlessness Beliefs Questionnaire (BBQ), which was developed from a kinesiophobia questionnaire (Tampa Scale for Kinesiophobia), was used to evaluate the breathlessness beliefs.[5] Breathlessness Beliefs Questionnaire had 11 items, and each item was scored between 1 (strongly disagree) and 5 (strongly agree). Higher scores indicated higher dyspnea-related fear of movement. Breathlessness Beliefs Questionnaire had 2 subscales such as activity avoidance (BBQ-AA, 6 items) and somatic focus (BBQ-SF, 5 items). Breathlessness Beliefs Questionnaire was validated in Turkish.[7]

Perceived Dyspnea Severity

Perceived dyspnea severity was assessed by using modified Medical Research Council (mMRC) Dyspnea Scale[11] and modified Borg Scale.[12] Modified Medical Research Council Dyspnea Scale evaluated the generic perceived dyspnea in daily activities, while the modified Borg Scale evaluated the dyspnea level during physical effort.

Pulmonary Function Tests

Pulmonary function tests were performed by using spirometry. Forced vital capacity, FEV_1, FEV_1/FVC, and peak expiratory flow (PEF) were used in the analysis. The COPD severity was determined according to GOLD criteria[10] as follows: stage 1: $FEV_1 \geq 80\%$, stage 2: $50 \leq FEV_1 < 80\%$, stage 3: $30 \leq FEV_1 < 50$, and stage 4: $FEV_1 < 30$.

Emotional Status

The Hospital Anxiety and Depression (HAD) Scale was used for assessing emotional status. Hospital Anxiety and Depression Scale consisted of 14 questions and had 2 subscales such as anxiety (HAD-A) and depression (HAD-D). Higher scores indicated poor emotional status. The Turkish version of the HAD Scale was found reliable and valid.[13]

Fatigue

Fatigue was determined by using the Fatigue Impact Scale (FIS)[14] and Fatigue Severity Scale (FSS).[15] Both scales were shown valid and reliable in Turkish language. Fatigue Impact Scale had 40 questions, and each question was scored between 0 and 4. Higher scores indicated higher negative impact of fatigue on individuals' life. Fatigue Severity Scale consisted of 9 questions, and each question was scored between 0 and 7. Higher scores indicated higher levels of fatigue.

Physical Activity Level

International Physical Activity Questionnaire—Short Form (IPAQ) was used for evaluating the physical activity level. International Physical Activity Questionnaire—Short Form evaluated the time spent during walking, moderate-level physical activities, and high-level physical activities for the last 7 days. The Turkish version of IPAQ was reported as valid and reliable.[16]

Disease-Related Quality of Life

St. George Respiratory Questionnaire (SGRQ) was used for determining the disease-related quality of life. St. George Respiratory Questionnaire was analyzed under 4 scores such as symptoms, activity, impact, and total. Higher scores indicated more limitations in daily living activities. St. George Respiratory Questionnaire was found valid and reliable in Turkish language.[17]

Generic Quality of Life

Short-Form 36 (SF-36) was used for evaluating the general quality of life. Physical composite score and mental composite score were calculated as subscores. Higher scores defined a more favorable health state. The Turkish version of SF-36 was shown valid and reliable.[18]

Procedures

After recording the physical characteristics, all patients were evaluated by using pulmonary function tests, and then they completed the BBQ, HAD, FIS, FSS, IPAQ, SGRQ, and SF-36 questionnaires.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Kolmogorov–Smirnov test and histograms were used to evaluate the distribution of the data. As the parametric conditions were not met, data were presented as median and interquartile ranges (IQR 25/75) and minimum and maximum values. Spearman's rank-order correlation coefficients (rho) were used for exploring the relationships between BBQ and other assessments. The level of correlations[19] was categorized as follows: insignificant = 0-0.29, poor = 0.30-0.49, medium = 0.50-0.69, high = 0.70-0.89, and excellent = 0.90-1.00. $P < .05$ was considered as statistically significant.

MAIN POINTS

- Patients with chronic obstructive pulmonary disease (COPD) may present dyspnea-related fear of movement.
- Dyspnea-related fear of movement is related to perceived dyspnea, pulmonary function tests, emotional status, fatigue, physical activity level, and quality of life in male patients with COPD and thus should be considered as an asset in clinical examination.
- Assessing dyspnea-related fear of movement may help health professionals to prevent secondary morbidities earlier.

RESULTS

A total of 70 males with a median (IQR 25/75) age 69 years (61/75 years) and with a median (IQR 25/75) BMI

25.6 kg/m^2 (22.3/29.6 kg/m^2) participated in the study. Thirty (43%) patients had stage GOLD 2 COPD, 28 (40%) patients had GOLD stage 3 COPD, and 12 (17%) patients had GOLD stage 4 COPD. Fifty-eight patients (83%) reported smoking history. Physical, sociodemographic, and disease-related characteristics are presented in Table 1.

Breathlessness Beliefs Questionnaire-total, BBQ-AA, and BBQ-SF scores correlated with all the assessed parameters ($P < .05$, Table 2), except FEV_1/FVC and physical characteristics ($P > .05$, Table 2). Nearly all correlations were above the predetermined significant correlation level (rho >0.30, Table 2). Breathlessness beliefs were strongly correlated to fatigue severity, disease-related quality of life, and general quality of life (rho >0.70, Table 2), while poor correlations were detected between breathlessness beliefs and FVC, FEV_1, PEF, depression, physical activity, and mental component of generic quality of life (rho <0.50, Table 2).

DISCUSSION

The aim of the present study was to investigate the related factors to breathlessness beliefs in patients with COPD. According to our results, breathlessness beliefs seem related to perceived dyspnea, pulmonary function tests, emotional status, fatigue, physical activity level, and quality of life at different levels.

Breathlessness beliefs were investigated by using BBQ in Dutch, Chinese, and Turkish patients with COPD previously.[4-7] De Peuter et al[5] determined significant correlations between BBQ and HAD anxiety (rho between 0.45 and 0.60) and depression (rho between 0.46 and 0.47) scores in a Dutch outpatient group. Gurses et al[7] reported lower correlations between BBQ scores and HAD scores (*r* between 0.309 and 0.390) for Turkish patients. Similar results to the results of De Peuter et al both for anxiety (rho between 0.443 and 0.551) and for depression (rho between 0.394 and 0.463) were obtained in the present study. Despite slight differences between studies, it seems that emotional status is poorly/moderately related to breathlessness beliefs, and patients with higher levels of dyspnea-related fear of movement may experience more depression and anxiety and vice versa.

Wu et al[6] reported a poor relationship (rho = 0.40) between mMRC scores and Chinese version of BBQ. On the other hand, moderate to strong correlations were detected between these 2 parameters (rho between 0.514 and 0.708) in the present study. Especially, BBQ-AA subscores were found to be strongly correlated to mMRC scores, indicating that higher dyspnea may more likely result in activity avoidance. These differences between studies may be related to populations investigated.

The correlation between disease-related quality of life and dyspnea-related kinesiophobia was investigated in Turkish patients with COPD by Gurses et al.[7] recently. These authors used SGRQ as in the present study and concluded that breathlessness beliefs and disease-related quality of life poorly/moderately related (*r* between 0.226 and 0.619) to each other. Slightly higher correlations (rho between 0.521 and 0.736) were detected in the present study. Highest correlations were detected between BBQ-AA and SGRQ-total in both studies. This indicates that activity avoidance may deteriorate the disease-related quality of life. Moreover, negative correlations were detected between dyspnea-related kinesiophobia and generic quality of life in the present study, and breathlessness beliefs were more correlated to physical problems than mental problems.

In addition to the available evidence, the correlations among breathlessness beliefs and other important clinical aspects such as fatigue, physical activity level, and pulmonary function tests were also investigated in the present study. Our results revealed that both impact and severity of the fatigue increase with dyspnea-related fear of movement. Moreover, the highest correlation was detected between fatigue severity and breathlessness beliefs (rho = 0.771). It seems that fatigue is strongly related to dyspnea-related kinesiophobia and vice versa. Therefore, assessing the level of dyspnea-related kinesiophobia in a patient with a high level of fatigue may help clinicians to understand the roots of the problem.

As expected, physical activity levels showed a correlation to dyspnea-related kinesiophobia. This poor but statistically significant negative correlation (rho between –0.412 and –0.485) indicated that higher levels of dyspnea-related fear of movement may limit the physical activity levels of COPD patients.

The weakest correlations were detected between pulmonary function tests and breathlessness beliefs in the present study. Our results indicate that the role of pulmonary functions in dyspnea-related fear of movement may be limited. Patients with adequate pulmonary functions may still experience breathlessness beliefs. Thus, a comprehensive assessment would provide a better understanding instead of conducting solely pulmonary functions tests.

The majority of the patients were elderly in the present study. One can argue that dyspnea-related kinesiophobia may increase due to age. On the other hand, no correlations were found between age and breathlessness beliefs in the present study. Quality of life and related factors may change by aging in patients with COPD, and younger adults with COPD presented worse correlations between quality of life and dyspnea compared to older adults in previous studies.[20-22] Therefore, we would like to exclude this effect and include older adults in their late middle ages (45-64 years) and in their late adulthood (>65 years).[23] Besides, BMI was not correlated to dyspnea-related fear of movement according to our results. It seems that physical characteristics do not have an effect on breathlessness beliefs.

As fatigue severity, disease-related quality of life, and general quality of life were strongly correlated to breathlessness beliefs in the present study, pulmonary rehabilitation programs and psychological support may improve dyspnea-related fear of movement in patients with COPD.[24-27] However, the effects of such programs on breathlessness beliefs are yet to be discovered in future studies.

We included only male patients in the present study due to 2 factors. First, the representation of female patients was

Table 1. Patient Characteristics

n = 70	Median (IQR 25/75)	Minimum/Maximum
Physical characteristics		
Age (years)	69 (61/75)	46/85
Body mass index (kg/m^2)	25.6 (22.3/29.6)	16.9/40.3
Disease-related characteristics		
Time since diagnosis (months)	54.0 (12.0/114.0)	1/360
Educational status		
Literate	12 (17%)	–
Primary education (%)	34 (49%)	–
Secondary education (%)	14 (20%)	–
Higher education (%)	10 (14%)	–
Marital status		
Married (%)	65 (93%)	–
Working status		
Working (%)	27 (39)	–
Breathlessness beliefs		
BBQ-total (score: 11-55)	35 (28/39)	13/46
BBQ-AA (score: 6-30)	18 (15/21)	6/27
BBQ-SF (score 5-25)	16 (12/20)	6/23
Perceived dyspnea severity		
mMRC (score: 0-4)	1 (1/3)	0/4
Modified Borg Scale (score: 0-10)	3 (2/5)	0/10
Pulmonary function tests		
FVC (L)	2.3 (1.7/2.9)	0.9/4.1
FVC (%)	59.0 (51.0/78.0)	24.0/99.0
FEV_1 (L)	1.4 (0.9/1.8)	0.5/2.8
FEV_1 (%)	47.5 (36.0/61.0)	19.4/79.0
FEV_1/FVC (%)	58.4 (51.8/64.0)	31.6/69.4
PEF (L/s)	3.8 (3.1/4.9)	1.5/7.6
PEF (%)	49.0 (38.0/62.0)	23.0/93.0
Emotional status		
HAD-anxiety (score: 0-21)	6 (2/9)	0/19
HAD-depression (score: 0-21)	5 (2/9)	0/16
Fatigue		
Fatigue Impact Scale (score: 0-160)	31.5 (12/59)	0/123
Fatigue Severity Scale (score: 0-63)	43 (29/54)	9/63
Physical activity level		
IPAQ (MET-min/week)	373.5 (99/1386)	0/3612
Disease-related quality of life		
SGRQ-symptom (score: 0-100)	43.7 (29.1/68.5)	0/88.8
SGRQ-activity (score: 0-100)	60.6 (41.7/92.5)	0/100
SGRQ-impact (score: 0-100)	33.8 (13.2/63.2)	0/90.1
SGRQ-total (score: 0-100)	45.3 (28.2/69.8)	0/92.9
Generic quality of life		
SF-36 PCS (score:0-100)	37.5 (25.7/47.8)	10/59.2
SF-36 MCS (score:0-100)	50.4 (38.5/57.2)	27.2/65.2

BBQ-total, Breathlessness Beliefs Questionnaire total score; BBQ-AA, Breathlessness Beliefs Questionnaire activity avoidance score; BBQ-SF, Breathlessness Beliefs Questionnaire somatic focus score; FEV_1, forced expiration volume in 1 second; FVC, forced vital capacity; HAD, Hospital Anxiety and Depression Scale; IPAQ, International Physical Activity Questionnaire—Short Form; IQR, interquartile range; MET, metabolic equivalent; mMRC, modified Medical Research Council Dyspnea Scale; PEF, peak expiratory flow; SF-36 MCS, Short-Form 36 mental composite score; SF-36 PCS, Short-Form 36 physical composite score; SGRQ, St. George Respiratory Questionnaire.

Table 2. The Correlations Between Breathlessness Beliefs and Other Parameters

	BBQ-total		BBQ-AA		BBQ-SF	
n = 70	**Rho**	***P***	**Rho**	***P***	**Rho**	***P***
Physical characteristics						
Age (years)	0.119	.329	0.179	.138	0.052	.669
Body mass index (kg/m^2)	0.134	.270	–0.006	.960	0.227	.059
Perceived dyspnea severity						
mMRC (score: 0-4)	0.665	<.001	0.708	<.001	0.514	<.001
Modified Borg Scale (score: 0-10)	0.574	<.001	0.616	<.001	0.439	<.001
Pulmonary function tests						
FVC (L)	–0.433	<.001	–.505	<.001	–0.282	.018
FEV_1 (L)	–0.383	.001	–0.515	<.001	–0.206	.087
FEV_1/FVC (%)	–0.048	.696	–0.201	.095	0.038	.757
PEF (L/s)	–0.466	<.001	–0.561	<.001	–0.299	.012
Emotional status						
HAD-anxiety (score: 0-21)	0.551	<.001	0.443	<.001	0.536	<.001
HAD-depression (score: 0-21)	0.463	<.001	0.394	.001	0.432	<.001
Fatigue						
Fatigue Impact Scale (score: 0-160)	0.655	<.001	0.588	<.001	0.609	<.001
Fatigue Severity Scale (score: 0-63)	0.771	<.001	0.765	<.001	0.631	<.001
Physical activity level						
IPAQ (MET/week)	–0.485	<.001	–0.451	<.001	–0.412	<.001
Disease-related quality of life						
SGRQ-symptom (score: 0-100)	0.589	<.001	0.584	<.001	0.521	<.001
SGRQ-activity (score: 0-100)	0.734	<.001	0.728	<.001	0.628	<.001
SGRQ-impact (score: 0-100)	0.719	<.001	0.703	<.001	0.614	<.001
SGRQ-total (score: 0-100)	0.733	<.001	0.736	<.001	0.610	<.001
Generic quality of life						
SF-36 PCS (score: 0-100)	–0.718	<.001	–0.669	<.001	–0.652	<.001
SF-36 MCS (score: 0-100)	–0.478	<.001	–0.414	<.001	–0.441	<.001

BBQ-total, Breathlessness Beliefs Questionnaire total score; BBQ-AA, Breathlessness Beliefs Questionnaire activity avoidance score; BBQ-SF, Breathlessness Beliefs Questionnaire somatic focus score; FEV_1, forced expiration volume in 1 second; FVC, forced vital capacity; HAD, Hospital Anxiety and Depression Scale; IPAQ, International Physical Activity Questionnaire—Short Form; MET, metabolic equivalent; mMRC, modified Medical Research Council Dyspnea Scale; PEF, peak expiratory flow; SF-36 MCS, Short-Form 36 mental composite score; SF-36 PCS, Short-Form 36 physical composite score; SGRQ, St. George Respiratory Questionnaire.

low in our cohort. Despite the fact that the rates of COPD are increasing among females, only 7 eligible female patients (10% of male patients) have visited our clinic during the study. Moreover, fear of movement and related factors may be affected due to sex-related differences.[28,29] Thus, we preferred to include only male patients in our study.

There were some limitations in the present study. The study was conducted in a university hospital which was preferred mostly by patients with higher socioeconomic status; therefore, the results may be different for rural areas where people have different conditions to maintain their daily living activities due to economic concerns and environmental conditions. Also, our results were obtained from patients living in the west part of Turkey, and the perceived dyspnea-related fear may differ for other patients living in other regions of Turkey, or for other countries. Including only male patients and excluding patients who need constant/long-term oxygen therapy or mechanical ventilation and patients who were recently hospitalized also limited the generalizability of our results.

In conclusion, breathlessness beliefs which is defining fear of movement due to dyspnea was found to be related to perceived dyspnea, pulmonary function tests, emotional status, fatigue, physical activity level, and quality of life. Thus, many different factors should be taken into consideration when a patient with COPD with dyspnea-related kinesiophobia seeks advice. Including breathlessness beliefs assessment into clinical examination may help clinicians to understand their patients' needs comprehensively.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Dokuz Eylül University (Approval No: 2016/23-17).

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

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Original Article

Investigation of the Prevalence of Oral Mucositis and Associated Risk Factors in Chronic Obstructive Pulmonary Disease Patients: A Prospective Cross-Sectional Study

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Abstract

OBJECTIVE: This study was conducted to determine the prevalence of oral mucositis in chronic obstructive pulmonary disease patients and the risk factors likely to be effective in the development of oral mucositis.

MATERIAL AND METHODS: This prospective cross-sectional study was carried out with 147 patients with chronic obstructive pulmonary disease who were monitored for 7 days from their admittance to the chest diseases clinic of a university hospital between January 2021 and January 2022. Patient Information Form, Oral Assessment Guide, and World Health Organization Mucositis Grading Scale were used to obtain the study data.

RESULTS: While 81% of the patients in the study were male, the mean age was 64.6 ± 10.0 years, and the duration of chronic obstructive pulmonary disease diagnosis was 8.58 ± 6.52 years. In the study, while 61.9% of the total 147 patients monitored for 7 days had findings in favor of oral mucositis, the severity of oral mucositis and the mean total oral mucosa score of the patients were found to increase significantly in these 7 days of the monitoring period (P <.001). As per the logistic regression findings, the duration of chronic obstructive pulmonary disease diagnosis (95% CI 1.05-1.49; P =.010), the presence of medication use containing corticosteroids (95% CI 6.05-72.17; P <.001), and the amount of oxygen administered to the patient (95% CI 1.07-3.44; P =.029) were found to be significant risk factors associated with the development of oral mucositis.

CONCLUSION: The results indicate that the severity of oral mucositis has a tendency to increase in chronic obstructive pulmonary disease patients from the third day of treatment, and oral care is critically important in patients, who are with a longer diagnosis of chronic obstructive pulmonary disease, who are treated with medications containing corticosteroids and who need high-intensity oxygen therapy.

KEYWORDS: COPD, corticosteroids, oral mucositis, prevalence
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important respiratory system disease that develops due to insufficient airflow together with the change in lung tissue, respiratory tract, and alveolar structure, as a result of exposure to harmful particles and gases, and it has a cough, sputum, chronic and progressive dyspnea as the prominent symptoms.[1,2]

While the prevalence of COPD, which is considered one of the most common causes of respiratory diseases characterized by chronic and irreversible airflow obstruction, varies by country, age, and gender, it is estimated to have a prevalence that corresponds to <6% of the adult population for most countries worldwide.[2] The prevalence of COPD, which is known to affect 16 million adults, ranges from 10.2% to 20.9% in the United States,[3] whereas the average global prevalence of COPD, 1 of the 5 most common health problems of the last decade in Europe, among 19 European countries has been reported as 12.38%.[4] Although the prevalence of COPD, which is considered a serious public health problem in Turkey similar to the rest of the world, has been reported to vary between 5% and 19%, a 35% increase has been noted in annual general prevalence rates of COPD patients diagnosed between 2012 and 2016.[5,6]

Chronic obstructive pulmonary disease is a disease with a complex etiology, which includes multiple genetic and environmental factors such as smoking and air pollution, among its causes. However, another point that the literature draws attention to is that there is a relationship between periodontal diseases and poor oral health and the pathogenesis and exacerbation of COPD.[7,8] Bacteria in the oral mucosa are considered a potential source of the development of lung infections due to anatomical proximity.[9] It is a known fact that about half of COPD exacerbations may be caused by bacterial infections.[10,11] It is also known that patients with COPD have insufficient awareness of oral health, and therefore they are prone to periodontal diseases and poor oral health.[12] Therefore, reducing the bacterial load in the oral mucosa and maintaining oral health in COPD patients have critical importance for the treatment and care of the disease. Besides, while the

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importance of oral health is considered an important factor in the etiology of COPD, it is another noteworthy point that various problems associated with the chronic disease process and treatment associated with COPD may also be risk factors for the deterioration of oral health.[7-13]

One of the most important problems disrupting the continuity of the integrity of the oral mucosa in patients with COPD is the development of oral mucositis.[9] Oxygen therapy, which is an important part of medical treatment in COPD, the potential effects of oral or inhalation medications on suppressing the immune system and increasing dryness of mouth, and physical weakness and inadequacies associated with the disease process that prevent patients from performing daily life activities such as oral care increase the susceptibility to deterioration of oral integrity and the development of opportunistic infections.[14,15] Therefore, identifying the conditions that contribute to the deterioration of oral health, as well as maintaining the integrity of the oral mucosa in COPD patients, have critical importance. Although there are some studies, in the literature, examining the prevalence of oral mucositis, especially among the patient groups with cancer treatment, there has been a very limited number of studies to determine the prevalence of oral mucositis and associated risk factors in COPD patients. This study, which was planned based on this need, aimed to determine the prevalence of oral mucositis in COPD patients, define the factors that are thought to be effective in the development of oral mucositis, and provide scientific data to the limited literature on this field.

MATERIAL AND METHODS

Study Design

This is a prospective cross-sectional study conducted to determine the prevalence of oral mucositis and associated risk factors in COPD patients.

Study Population and Sample Size Calculation

The study population consisted of 671 patients with a diagnosis of COPD who were admitted to the chest diseases clinic of the Health Practice and Research Center of Afyonkarahisar Health Science University between January 1, 2021, and January 1, 2022. The minimum sample size to be reached in the study was determined as 132 with a 0.05 margin of error and 80% CI, according to the formula ($n = Nt^2\ pq/d^2(N-1)+t^2pq$) which is used when the number of individuals in the study population is known.[16] A total of 147 patients, who were 18 years of age or above, admitted with the diagnosis of COPD within the date range specified in the study, did not have communication issues and could speak and understand Turkish, were fully oriented and conscious, had no infection, wound, or oral mucositis in the mouth, and whose oral mucosa could be monitored regularly for 7 days from the first day of admittance, formed the study sample. Patients who had an infection, wound, and oral mucositis in their mouth at the time of admission to the relevant clinic, wanted to leave after being included in the study, could not communicate and could not speak or understand Turkish, were disorientated and unconscious, did not want to participate, and whose oral mucosa could not be monitored continuously, were not included in the study.

MAIN POINTS

- Oral mucositis is a common, preventable health problem in patients with chronic obstructive pulmonary disease (COPD).
- Patients with COPD are a patient group with a high need for oral care aimed at protecting the integrity of the oral mucosa.
- In COPD patients, there was a trend toward an increased risk of impaired oral mucosal integrity from day 3 of medical therapy.
- The duration of COPD diagnosis, use of corticosteroid-containing drugs, and oxygen therapy were defined as risk factors associated with the development of oral mucositis in COPD patients.

Data Collection and Data Collection Tools

Patient Information Form, World Health Organization Oral Mucositis Scoring Index (WHO-OMSI), and Oral Assessment Guide (OAG) were used as data collection tools in the study.

Patient Information Form

This form, created with the literature review[1,7,14,15] and expert opinion, consists of a total of 22 questions aimed at obtaining patients' data on their demographic characteristics (3 questions) and medical histories (16 questions). The information in the Patient Information Form was obtained by the researchers during the face-to-face interview with the patients, conducted by applying infection control measures and checking the patient file.

World Health Organization Oral Mucositis Scoring Index

World Health Organization Oral Mucositis Scoring Index is one of the tools developed by the WHO and is often used for the assessment of the severity of oral mucositis, which leads to deterioration of oral health.[17] According to the assessment criteria in this tool, stage 0 means no presence of mucositis, stage 1 refers to the presence of mild mucositis, stage 2 refers to the presence of moderate mucositis, while stage 3 and stage 4 refer to the presence of severe mucositis, in which the integrity of the oral mucosa is impaired.[17,18] In this study, in order to assess the severity of oral mucositis in patients included in the study, WHO-OMSI was completed by the same researcher, scoring 0-4, during the 7-day monitoring period starting from the first day of admittance of the patient.

Oral Assessment Guide

Oral Assessment Guide, developed by Eilers et al[19] in 1988, is a tool in which the integrity of the individual's oral mucosa and changes in the oral mucosa associated with the development of mucositis are assessed in 8 categories, macroscopically and by interviewing the patient. The tool was widely used in many oral health studies in Turkey.[15,20,21] The validity and reliability of this measurement tool in Turkey were carried out by Çiftçioğlu and Efe[22] in 2017 in the population of young and pediatric patients. With OAG, changes in the individual's voice and swallowing function, saliva, tongue, lips, mucous membrane, gingiva, teeth, or oral prostheses are scored from 1 to 3 and the total oral mucosa score is obtained. The lowest score that can be obtained from OAG, a guiding tool in planning the oral care needs of the individual,

is 8 and the highest score is 24, and a high score indicates an increase in the severity of mucositis and symptoms associated with deterioration of the integrity of the oral mucosa. In this study, OAG, used in order to evaluate the changes in the oral mucosa of the patients included in the study, was completed by the same researcher with a rating from 1 to 3 by the macroscopic examination of the oral mucosa with a light source and interviewing the patient during the 7-day monitoring period from the first day of admittance of the patient, which is the monitoring days of the study.

In the clinic where the study was conducted, the standard protocol for maintaining the oral health of the patients was rinsing the mouth with water after the use of inhalers. In addition, patients with very severe findings in favor of oral mucositis were limited to the use of a pharmacological agent at the physician's order. However, patients with oral mucositis and who had to use a pharmacological agent were not included in the study, which was consistent with the exclusion criteria of this study. During the conduct of the study, in order to ensure standardization in all patients, training was provided by the researchers on the importance of oral care and the patient's routine oral care practice.

Ethical Aspect of Study

In order to be able to conduct the study, the institutional permission (15/10/2020-E.19116) from the directors of the Health Practice and Research Center of Afyonkarahisar Health Science University and the permission of the ethics (2020/470) were obtained from the non-interventional clinical research ethics committee of the relevant university. Also, the patients included in the study were informed about the purpose of the study and their verbal and written consent was obtained.

Statistical Analysis

All statistical analyses of the data obtained in the study were performed with the Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) package program. Categorical data were shown as numbers and percentages, while continuous variables data were shown as mean and standard deviation. In the study, the Friedman test was used to analyze the dependent group comparisons of categorical variables obtained during the 7-day monitoring period and more than 2 dependent group comparisons of continuous variables that did not show normal distribution. Binary logistic regression analysis was used to determine the variables that affect the oral mucositis development risk in patients included in the study. In statistical analyses, the significance level was accepted as $P < .05$.

RESULTS

Characteristics of the Patients

When the findings related to the demographic characteristics of the patients were examined, it was founded that the mean age of the patients was 64.6 ± 10.0 years, 81% were male, and 46.9% were retirees.

Medical Characteristics of the Patients

The distribution of the findings related to the medical characteristics of the patients was presented in Table 1. As per

Table 1. Medical Characteristics of the Patients (n = 147)

	Mean ± SD
Duration of COPD Diagnosis (year)	**8.58 ± 6.52 (min: 1; max: 31)**
Presence of systemic disease	**n** / **%**
Yes	97 / 66.0
Type of systemic disease* (n = 97)	
Diabetes	47 / 35.3
Hypertension	65 / 48.9
Coronary artery disease	12 / 9.0
Chronic renal failure	1 / 0.8
Asthma	8 / 6.0
Medications used in treatment*	
Antibiotic	146 / 24.1
Mucolytic	146 / 24.1
Bronchodilator	136 / 22.5
Corticosteroid	106 / 17.5
Antihypertensive	71 / 11.7
Presence of the intermittent/continuous oxygen therapy	
Yes	147 / 100.0
	Mean ± SD
The amount of oxygen in therapy (L/min)	**3.87 ± 1.71 (min: 2; max: 8)**
Smoking habits	**n** / **%**
Yes	88 / 59.9
Number of cigarettes smoked per day (n = 88)	
less than one pack	20 / 22.7
1-2 packs	29 / 33.0
more than two packs	39 / 44.3
Alcohol use	
Yes	13 / 8.8
Dietary habits	
Balanced	119 / 81.0
Irregular eating habit	28 / 19.0
The daily amount of fluid consumption	
< 1500 mL	70 / 47.6
≥ 1500 mL	77 / 52.4
Presence of prosthesis in the mouth	
Yes	51 / 34.7
Tooth brushing habits** (n = 96)	
Yes	21 / 21.8
Frequency of daily tooth brushing	
One per day	19 / 90.5
Two per day	2 / 9.5
Status of experiencing the development of oral mucositis before	
Yes	85 / 57.8
The severity of previous oral mucositis (n = 85)	
Mild	34 / 40.0
Middle	38 / 44.7
Severe	13 / 15.3

SD, standard deviation.
*Indicates more than one option. **Indicates patients who do not have a prosthesis in the mouth.

Table 2. Oral Mucositis Grades of the Patients According to the Follow-Up Days (n = 147)

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Stage 0 *(No mucositis, normal oral flora)*	147	100.0	144	98.0	109	74.1	61	41.5	48	32.7	56	38.1	56	38.1	χ^2 = 421.485 *P <.001
Stage 1 *(Pain, +/- erythema, no ulceration. Can be fed orally)*	-	-	3	2.0	34	23.1	68	46.3	55	37.4	43	29.3	38	25.9	
Stage 2 *(painful erythema, edema or ulcers, solid diet tolerated)*	-	-	-	-	4	2.7	18	12.2	43	29.3	44	29.9	46	31.3	
Stage 3 *(painful erythema, edema or ulcers, liquid diet only)*	-	-	-	-	-	-	-	-	1	0.7	4	2.7	7	4.8	
Stage 4 *(Presence of erythema, edema, ulcer, severe pain, bleeding. Requires parenteral and enteral nutritional support.)*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

*Friedman test.

the findings, the mean duration of COPD diagnosis in the patients was 8.58 ± 6.52 years and 66% of them had systemic disease, while hypertension (48.9%) and diabetes (35.3%) were the majority of these systemic diseases. During the treatment process, the patients were found to mostly use "antibiotic" (24.1%), "mucolytic" (24.1%), "bronchodilator" (22.5%) types of medication, and 17.5% of them were on medicine therapy containing corticosteroid. All of the patients were found to receive intermittent or continuous oxygen therapy, while the mean amount of oxygen administered during the therapy was 3.87 ± 1.71 L/min. The daily amount of fluid consumed was ≥1500 mL for 52.4% of the patients, whereas the majority of patients without prostheses (78.2%) did not have the habit of brushing their teeth. More than half of the patients (57.8%) reported experiencing the development of previous oral mucositis before, and 44.7% of those stated that the previous oral mucositis development was moderate (Table 1).

Characteristics of Oral Mucositis of Patients

A total of 61.9% of 147 patients monitored for 7 days were observed to have findings favoring oral mucositis, while there was no oral mucositis development in only 38.1% of the patients. The patients' findings related to the development of oral mucositis during the 7-day oral monitoring period were presented in Table 2 and Figure 1.

As per the findings, only 3 patients (2.0%) were found to have stage 1 oral mucositis on the second day of the monitoring, while 4 patients (2.7%) had stage 2 oral mucositis from the third day of the monitoring onward, in favor of disruption of the integrity of the oral mucosa. While none of the patients had stage 4 oral mucositis during the 7-day monitoring period, the rate of patients with stage 3 oral mucositis development as of the fifth day of monitoring was 0.7%, 2.7%, and 4.8%, respectively. Furthermore, the severity of oral mucositis was found to increase significantly during the 7-day monitoring period (P < .001; Table 2 and Figure 1).

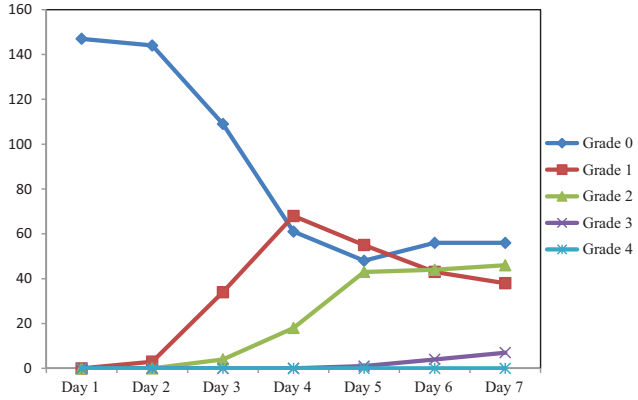


Figure 1 Observation days and the World Health Organization Oral Mucositis Scoring Index - (WHOOMSI) change curve

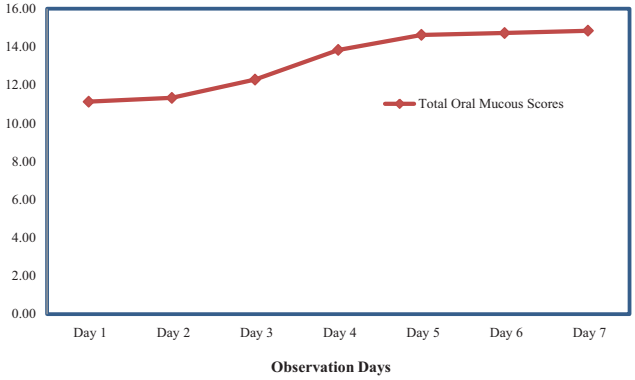


Figure 2 Total Oral Mucosa Scores change curve of the Patients According to the Follow-up Days

Table 3. Binary Logistic Regression Analysis Results Related to the Determination of Risk Factors Affecting the Oral Mucositis Development

						95% CI	
Variable	**Beta**	**SE**	**Wald**	***P***	**OR**	**Lower Bound**	**Upper Bound**
Age (year)	−0.006	0.045	0.017	.896	0.994	0.911	1.085
Duration of COPD diagnosis (year)	0.228	0.088	6.708	**.010**	1.256	1.057	1.492
Presence of systemic disease							
Reference = [No]							
Yes	−0.090	0.792	0.013	.910	0.914	0.194	4.318
Use of medication containing steroid							
Reference=[No]							
Yes	3.040	0.632	23.112	**<.001**	20.900	6.052	72.170
The amount of oxygen in therapy (lt/min)	0.653	0.299	4.781	**.029**	1.921	1.070	3.449
Smoking habits							
Reference=[No]							
Yes	−0.396	0.692	0.327	.567	0.673	0.174	2.613
Tooth brushing habits							
Reference=[No]							
Yes	−0.710	0.970	0.536	.464	0.491	0.073	3.292
The daily amount of fluid consumption (ml)							
Reference = [≥ 1500 mL]							
< 1500 mL	0.303	0.679	0.199	.656	1.354	0.357	5.127
Presence of prosthesis in the mouth							
Reference = [No]							
Yes	0.661	2.302	0.082	.774	1.936	0.021	176.404
Status of experiencing the development of oral mucositis before							
Reference = [No]							
Yes	1.205	0.780	2.385	.123	3.336	0.723	15.394
Constant	−3.401	2.673	1.619	.203	0.033		

OR, odds ratio; SE, standard error.
Cox & Snell R Square: 0.378; Nagelkerke R Square: 0.521; accuracy: 0.804.

The distribution of the total oral mucosa scores of the patients, which indicate the presence of changes in the oral mucosa associated with the development of mucositis, was presented in Figure 2. As per the findings, while the mean total oral mucosa scores of the patients were found to be similar to each other on the first (11.13 ± 1.06) and second (11.33 ± 1.11) days, it was 14.85 ± 2.78 on the seventh day. Also, the mean total oral mucosa scores of the patients were observed to increase significantly during the 7-day monitoring period ($P < .001$; Figure 2).

Risk Factors Affecting the Development of Oral Mucositis in Chronic Obstructive Pulmonary Disease Patients

In the regression model created with the independent variables included in the model, these variables were found to explain 52.1% of the model. As per the logistic regression findings, the duration of COPD diagnosis ($P = .010$), the use of medication containing corticosteroids ($P < .001$), and the amount of oxygen administered to the patient during the oxygen therapy ($P = .029$) were found to be significant risk factors contributing to the development of oral mucositis in COPD patients. Accordingly, a 1-unit increase in the duration of COPD diagnosis leads to a 1.256 (95% CI 1.05-1.49) times increase in the risk of developing oral mucositis, while the use of medication containing corticosteroids in the treatment increases the risk of developing oral mucositis 20.900 times (95% CI 6.05-72.17). Furthermore, a 1-unit increase in the amount of oxygen administered to the patient during the treatment period was found to lead to a 1.921 (95% CI 1.07-3.44) times increase in the risk of developing oral mucositis. Other independent variables in the model were observed not to be associated with the risk of oral mucositis development in this sample group ($P > .05$; Table 3).

DISCUSSION

Oral health is considered an important indicator of the systemic and mental health status of patients, including

respiratory diseases such as COPD especially.[1,7,23] Oral mucositis is one of the important health problems that patients with COPD suffer from due to various factors related to the disease itself and the treatment process.[14,15] It was aimed in this study to determine the prevalence of oral mucositis and associated risk factors from the beginning of the treatment period in 7-day monitoring of COPD patients.

Our findings revealed the presence of oral mucositis in 61.9% of the patients included in the study. It has been reported in the literature that COPD patients tend to have more oral problems that contribute to poor oral health and the development of systemic diseases.[7,15] On the other hand, some studies have also shown that poor oral health is significantly associated with an increased risk of COPD.[1,24] These findings show that oral care has critical importance for both the prognosis of the disease and the prevention and management of complications that may develop due to oral mucositis in COPD patients.

In our study, the severity of oral mucositis developed in patients with a diagnosis of COPD and total oral mucosa scores, an indication of the increase in the severity of the changes in the oral mucosa of the patients, were determined to increase significantly during the 7-day monitoring period. In their study, Korkut et al[15] reported that the severity of oral mucositis and mucositis-related symptoms were significantly higher during the 15-day monitoring period in patients with COPD in the control group compared to the group that received oral care intervention with black mulberry syrup. In another similar study, the severity of oral mucositis and complaints related to oral mucositis were found to be significantly higher in COPD patients in the control group compared to the patients in the intervention group in which oral care was carried out with aloe vera solution.[14] While these findings reveal the fact that oral mucositis is a common problem in COPD patients, they highlight the importance of oral observation assessment and the necessity of effective oral care in this patient population.

As per our findings, the increase in the duration of COPD diagnosis of the patients was determined to be associated with the risk of oral mucositis development. The literature points out that various factors associated with the disease and the treatment process contribute to the risk of deterioration of oral health in patients with COPD. This finding also suggested that the increased risk of oral mucositis development in patients with a longer duration of COPD diagnosis may be related to their increased exposure to these factors, which are associated with the risk of disruption of oral mucous membrane integrity. It is known that COPD patients are a group of patients who have to deal with more than 1 accompanying disease, and as a result of which, their ability to fulfill their self-care needs, in particular, is negatively affected.[25] Therefore, this causes COPD patients to face the risk of deterioration of the oral mucous membrane. The patients included in this study were also observed to have various systemic diseases that may negatively affect their self-care abilities. In the literature, another aspect whose importance has been emphasized in relation to the deterioration of oral health in COPD patients has been shown to be the presence of prostheses used by patients due to tooth loss in their mouth. Przybyłowska et al[26] reported a high susceptibility to oral mucosal infections in COPD patients and noted that one of the most important factors increasing this susceptibility is the effect of the prosthetic plaque biofilm layer, which has an increased risk of development due to the traumatic effect of prostheses in the mouth. This also draws attention to the importance of improving individual oral hygiene habits, especially in patients with COPD. However, studies show that the oral health status of COPD patients is generally poor and individual oral hygiene habits are insufficient.[1,7,27] Similarly, in our study findings, the fact that tooth brushing habits of the patients, which may increase the susceptibility to deterioration of the integrity of the oral mucosa, are not at the desired level and the presence of prostheses in the mouth as a result of tooth loss is noteworthy.

Oxygen therapy has an important role in the treatment of hypoxemia-related symptoms and the relief of patients with COPD.[28] However, the serious complications that may be caused by high-intensity and continuous oxygen therapy, as well as the dryness and irritation that can be caused in the oral mucosa, highlight the necessity of assessing the condition of the mucous membranes and the importance of oral care in patients under oxygen therapy.[29] Our study findings, similar to the literature, revealed that the increase in the intensity of oxygen therapy, related to the presence of mucosal dryness that it may cause, is a risk factor that increases the risk of oral mucositis development. Khijmatgar et al[13] reported that dry mouth, which can be caused by oxygen therapy, is a more common symptom in COPD patients and that dry mouth creates an opportunity for the colonization of candidal microorganisms. Ağaçdiken and Kara[14] pointed out that dry mouth, which is one of the important factors supporting the formation of oral mucositis, is among the most common symptoms experienced by COPD patients. It has been shown in another study that the frequency of prosthetic stomatitis complicated by mucosal infections is higher in COPD patients and this might be related to oxygen therapy, which increases the susceptibility to dry mouth and thinning of the oral mucosa.[26]

It is emphasized that the effect of pharmacological agents used in the treatment is another point that increases the susceptibility to deterioration of oral mucous membrane integrity in COPD patients.[14,23] During the treatment protocols of the patients, together with the presence of accompanying systemic diseases, various medications that are known to cause dryness in and around the mouth, such as inhaled β2-adrenergic receptor agonists or cholinergic receptor antagonist bronchodilators, and inhaled corticosteroids, which may jeopardize the durability of the integrity of the oral mucosa, are used. Dry mouth is reported to be one of the most important side effects of inhaled anticholinergics.[28] In studies, dry mouth was observed to be among the most commonly reported complaints by COPD patients.[1,14,15,23] Furthermore, some antibiotics used in the treatment protocol are known likely to lead to candidal infections in the oral mucosa.[13] Khijmatgar et al[13] reported that the candidal load on the oral mucosa was higher in COPD patients when compared to the

control group, and theophylline, which is often used for its bronchodilator effect, might be a risk factor for increased candidal load in COPD patients. Antibiotics and bronchodilators, known to increase the susceptibility to oral candidal infections, were observed to be among the pharmacological agents frequently used in the sample group of this study.

Our study findings showed that the most important risk factor leading to the development of oral mucositis in COPD patients in the sample group was the use of medication containing corticosteroids in the treatment protocol. Inhaled corticosteroids are often used in combination with bronchodilator medications in patients with severe complaints and accompanied by hypoxemia. Besides, oral candidiasis is known to be among the most common side effects experienced by patients due to inhaled corticosteroids.[28] Miravitlles et al[30] reported the presence of a strong relationship between the use of inhaled corticosteroids in the treatment of COPD and the development of oral candidiasis. It was pointed out in another study that the use of inhaled corticosteroids without a tool called Spacer may be an important factor in the increase of oral candidal load in COPD patients.[13] Moreover, the literature recommends teaching the correct inhalation technique to them to reduce the risk of oral candidiasis in patients treated with inhaled corticosteroids, using the inhaler with the help of a tool called Spacer, rinsing the mouth after the use of the medication and providing oral hygiene.[13,31] These results also highlight the necessity of nursing care to maintain oral health and prevent complications in patient care, while emphasizing the importance of awareness of oral health-related problems that may be caused by treatment-related factors in COPD patients.

It is known that exposure to direct and passive smoking has a significant effect on the gingival and oropharyngeal flora.[1,13] In addition, it is a well-known fact that cigarette smoke makes the oral mucosal epithelium more susceptible to the colonization of pathogens.[32] Saltnes et al[23] reported that smokers with COPD had more oral health problems and that smoking habits impaired oral health-related quality of life. In this study, according to the regression analysis findings, it was seen that having a smoking habit did not have a significant effect on the risk of developing oral mucositis. Similar to our findings, Ağaçdiken and Kara[14] reported that there was no significant effect of smoking among the factors affecting oral mucositis in the experimental and control groups. In a study conducted with a different patient population, it was reported that smoking did not significantly affect the risk of developing oral mucositis.[33] Unlike our findings, in the study conducted by Korkut et al.[15] it was reported that there was a significant relationship between the duration of smoking habit and the severity of oral mucositis in patients with COPD. Different results in the literature show that the effect of smoking on the development of oral mucositis needs further investigation.

This study has some limitations. The most important limitation is that the study was conducted in a single center and with a limited sample. Furthermore, the findings regarding the oral mucosa of the patients were obtained based on the results of a 7-day monitoring period. In addition, the findings regarding the presence of oral mucositis in patients are limited to the macroscopic evaluation. This may have led to the inability to objectively assess the prevalence and severity of oral mucositis and to overlook the changes that may develop in the oral mucosa after 7 days of the monitoring period. Therefore, these limitations restrict the generalization of the study results to all COPD patients. Therefore, future studies should focus on the design in which macroscopic changes in the oral cavity are supported by microscopic examinations in COPD patients. However, in addition to the current limitations, the findings from this study revealed some important results regarding the oral mucositis issue and its associated risk factors, which should be considered an important priority in COPD patients, and contributed to the limited literature in this field. This can be considered the strength of our study.

CONCLUSION

The results obtained from this study support that oral mucositis is a commonly experienced problem in COPD patients due to the risk factors associated with the chronic disease process and its treatment and that maintaining oral health is critical in this patient population. Furthermore, while the severity of oral mucositis and changes in favor of deterioration in the integrity of the oral mucous membrane in COPD patients tended to increase significantly from the third day onward of the treatment period, patients who were with a longer duration of COPD diagnosis, have been treated with medications containing corticosteroids and need high-intensity oxygen therapy, were determined to be at higher risk for oral mucositis development.

In line with these results, in the treatment and care process of COPD patients, it is recommended to consider the prevention and follow-up of oral health-related problems as a priority, improve the behaviors of patients to have better oral health, and maintain the integrity of the oral mucous membrane with a planned oral diagnosis and oral care in line with the evidence-based recommendations which are among preventive nursing care practices, especially for patients with reduced self-care and risk factors.

Ethics Committee Approval: This study was approved by the Ethics Committee of Afyonkarahisar Health Science University, Non-İnterventional Clinical Research Ethics Committee (Decision No: 2020-470).

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

Peer Review: Externally peer-reviewed.

Author Contributions: Conception – Ö.G.K., A.Ö., İ.G.C.; Design – Ö.G.K., A.Ö., İ.G.C.; Supervision – Ö.G.K., İ.G.C.; Materials – Ö.G.K., A.Ö.; Data Collection and/or Processing – A.Ö., İ.G.C.; Analysis and/or Interpretation – Ö.G.K., A.Ö.; Literature Review – Ö.G.K., A.Ö., Writing Manuscript – Ö.G.K., A.Ö., Critical Review – Ö.G.K., İ.G.C.

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Original Article

Factors Affecting Smoking Cessation After Acute Myocardial Infarction

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Abstract

OBJECTIVE: Persistent smoking after acute myocardial infarction is associated with an increased risk of recurrent cardiovascular events. Our aim was to determine the changes in smoking habits in patients after acute myocardial infarction and evaluate the factors affecting smoking cessation.

MATERIAL AND METHODS: A total of 322 patients who had an acute myocardial infarction while smoking were included in the study. Participants were asked to fill out a 30-question survey. According to smoking status, 2 groups were identified, those who quit smoking (n = 155) and those who continued smoking (n = 167).

RESULTS: The rate of smoking cessation among study participants was 48.2% (n = 155). Most of smoker participants had the intention to quit smoking (n = 124, 74.2%). The most common barriers for smoking cessation were nicotine withdrawal symptoms and the cessation rate was over 3 times higher in those with low nicotine dependence ($P < .01$). Weight gain was another common problem seen in 163 (50.6%) participants; among which the cessation rate was relatively low (43.6%). A total of 231 (71.7%) participants got an advice from their doctor to quit smoking and the probability of quitting was around 5 times higher in this group ($P < .01$). A total of 174 (54%) participants stated that they were considering quitting whenever they see the pictorial health warnings on cigarette packs and the probability of quitting was doubled in this group ($P < .01$).

CONCLUSION: High number of patients continue on smoking after acute myocardial infarction. The most common barriers for smoking cessation are nicotine withdrawal symptoms. Doctors should play an active role in helping the patient quit smoking. Strict regulations of tobacco control can be very helpful in this regard.

KEYWORDS: Acute myocardial infarction, nicotine dependence, smoking cessation, tobacco control
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INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide.[1] Smoking is an important risk factor for CAD.[2] Smoking causes an increase in oxidative stress, vascular inflammation, vasoconstriction, and platelet reactivity leading to vascular endothelial dysfunction.[3] A study showed that half of the nonfatal acute myocardial infarction (AMI) occurring in young and middle-aged people can be attributed to smoking.[4] In patients with CAD, persistent smoking was associated with an acceleration of an ongoing atherosclerotic process.[5] Studies have shown that smoking cessation after AMI can reduce the risk of recurrent infarctions by half.[2] This risk reduction was found to be consistent regardless of age, gender, ethnicity, or the time of diagnosis.[6] Therefore, smoking cessation after AMI can be very helpful in decreasing patients' morbidity and mortality.

Unfortunately, rates of persistent smoking following a diagnosis or hospitalization for CAD are still high.[7] Studies showed that around half of those diagnosed with CAD continue on smoking.[8,9] Similar results was observed in the EUROASPRE-V study that was conducted by the European Society of Cardiology.[10] Many patients struggle while quitting smoking after AMI and on many occasions professional help becomes a necessity. In this study, we aimed to determine the changes in smoking habits after AMI and identify the factors affecting smoking cessation.

MATERIAL AND METHODS

Setting and Participants

Between June 2021 and June 2022, patients who applied to our cardiology outpatient clinic at least 1 year after an AMI were evaluated. Patients who were smoking during the index event (n = 322) was included in this cross-sectional observational study. Nonsmokers or those who started smoking any time after AMI was not included. Any patients with psychotic illness, cognitive impairment, or inability to answer survey questions was also excluded. The sample size analysis was done with a 5% margin of error at 95% CI.

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Data Collection

Participants were asked to fill out a 30-question survey prepared specifically for this study. Patients were assigned into 2 groups according to smoking status. The first group consisted of those who continued to smoke after AMI (n = 167), while the second group consisted of those who quitted smoking (n = 155). The sociodemographic characteristics of the participants (including gender, age, body mass index, occupation, and educational level) were documented. The educational level was categorized as primary school, secondary school, high school, or university graduate. Medical records were used to document past medical history and laboratory test results.

Study Survey

The survey questions assessed the patient's desire to quit smoking as well as changes in daily lifestyles following AMI. Those who were still smoking were asked about the reasons for not being able to quit. The advice and guidance they received from their doctors in terms of quitting smoking were asked. Patients were also asked about their thoughts on tobacco control regulations imposed by the government. All the questions were closely reviewed by the authors for clarity, validity, and content after testing with 5 patients to ensure ease of use and comprehensiveness. The final part of the survey contained the Fagerström nicotine dependence test.[11] According to test results, addiction levels of the patients were classified as low (0-3 points), medium (4-6 points), and high (≥7 points) based on test results.

All procedures were conducted in accordance with the ethical standards of Helsinki Declaration and the ethical committee approval was obtained from Lokman Hekim University Faculty of Medicine (Doc. no:2021136). The patients were informed about the study and were enrolled after providing informed voluntary consent forms.

Data Management and Statistical Analysis

Descriptive statistics of the continuous variable such as mean and SD is used for summarizing. Percentages and frequencies are used for presenting categorical variables. As a preliminary analysis, the relationships between categorical variables are investigated using the chi-square test. Once relationships are found to be statistically significant with chi-square test, further analyses are conducted with logistic regression. One-way analysis of variance is used for comparing group means. *F* dependence score is taken as continuous variable of the study. This continuous variable is analyzed with ANOVA *F* test. Normality assumption of the *F* test is checked with Shapiro–Wilk test. Equality of variances of the *F* test is checked with Levene test. All assumptions are satisfied. The statistical analysis was carried out by the Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Corp.; Armonk, NY, USA).

MAIN POINTS

- High number of patients continue to smoke cigarettes after having an acute myocardial infarction.
- The most common barriers for smoking cessation were nicotine withdrawal symptoms and the cessation rate was highest among those with low nicotine dependence.
- Considering its low costs and the proven benefits, smoking cessation should be a primary goal in patients with acute myocardial infarction.
- Evidence-based programs supported by behavioral therapy in which the doctors take an active role can make smoking cessation interventions more effective.
- Strict tobacco control regulations by the government may be highly beneficial in the efforts to stop smoking.

RESULTS

Among the 322 participants of the study, 51.8% (n = 167) continued smoking after AMI and 48.2% (n = 155) have quitted smoking. There was no significant difference between the 2 groups in terms of basal sociodemographic and clinical characteristics (Table 1). A significant difference was found in the educational level of the 2 groups ($P = .04$) with smoking cessation rate being highest among university graduates (68.8%) and regression analysis showing a higher probability of quitting in this group (Table 2). On the other hand, no significant association was found between smoking cessation after AMI and other sociodemographic factors (Table 3).

Most smoker participants had the intention to quit smoking (n = 124, 74.2%) and believed that they would succeed in quitting after AMI (n = 98, 58.7%). The most common difficulty they faced was ''nervous temper'' in 197 (61.2%) participants (Table 4). Weight gain was another important problem seen in 163 (50.6%) participants among which the rate of smoking cessation was relatively low (43.6%). Physical exercise, on the other hand, was associated with a significant increase in the probability of quitting smoking ($P < .01$). Nicotine dependence level was low in 154 (47.8%), moderate in 148 (46%), and high in 20 (6.2%) participants.

Table 1. The Basal Clinical Characteristics and Sociodemographic Properties of the Study Participants

Variable	Nonsmokers, (n = 155)	Smokers, (n = 167)	*P*
Age, years	56.7 ± 5.8	57.2 ± 4.3	.38
BMI, kg/m^2	27.1 ± 3.9	26.6 ± 2.8	.18
Basal HR, b/m	88.9 ± 7.1	87.9 ± 8.8	.26
Systolic BP, mmHg	127.7 ± 11.8	129.4 ± 11.2	.19
Diastolic BP, mm Hg	86.7 ± 12.6	87.2 ± 11.3	.7
Hemoglobin, g/dL	13.8 ± 1.7	14.2 ± 2.6	.1
TC, mg/dL	196.2 ± 24.7	199.4 ± 32.2	.32
LDL, mg/dL	139.6 ± 22.7	138.7 ± 33.4	.78
Triglyceride, mg/dL	182.6 ± 32.4	185.4 ± 41.5	.5
HDL, mg/dL	32.8 ± 3.2	33.2 ± 4.5	.36
Calcium, mg/dL	9.2 ± 0.71	9.3 ± 0.82	.24
Sodium, mEq/L	140.9 ± 1.5	141.1 ± 1.3	.2
Potassium, mEq/L	4.1 ± 0.9	4.2 ± 0.2	.16
TSH, mIU/L	3.3 ± 1.4	3.5 ± 0.8	.11

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; TC, total cholesterol; TSH, thyroid-stimulating hormone.

Table 2. Logistic Regression Analysis for the Probability of Smoking Cessation in Relation to Different Variables

Variables	Standard Error	Odds Ratio	95% CI		*P*
			Lower	Upper	
Being a university graduate	0.236	2.076	1.3062	3.3013	<.01
Performing regular physical exercise	0.284	2.925	1.6742	5.1104	<.01
Having low nicotine dependence	0.264	3.143	1.8955	5.3536	<.01
Got a doctor's advice to quit smoking	0.271	5.185	3.0528	8.8069	<.01
Affected by the pictorial health warnings on cigarette packs	0.269	2.061	1.2157	3.4960	<.01

Regression analysis showed that smoking cessation rate was over 3 times higher in the group with low nicotine dependence ($P < .01$).

The number of patients who received an advice from their doctor to quit smoking was 231 (71.7%) and the probability of quitting smoking was 5 times higher in this group ($P < .01$). However, the number of those referred to a specialized smoking cessation department was small (n = 68, 21.1%). Most participants stated that they support the government's strict regulations on tobacco control, believing that it can be effective in decreasing smoking rates (Table 5). More than half of study participants (54%, n = 174) said that they were considering quitting smoking when seeing the pictorial health warnings on cigarette packs and the probability of quitting smoking was doubled in this group (Table 2).

DISCUSSION

The present study evaluated the changes in smoking habits after AMI and aimed to analyze the factors that influence smoking cessation. Study results showed that more than half of the patients continue on smoking after AMI. The most common difficulties standing against their will to quit smoking

Table 3. The Associations Between Smoking Cessation With Social and Medical Conditions

Social and Medical Conditions	Parameters	Still Smoking, n (%)		Total (%)	*P*
		Yes (167)	No (155)		
Gender	Female	79 (54.9)	65 (45.1)	144 (44.7)	.33
	Male	88 (49.4)	90 (50.6)	178 (55.3)	
Working status	Retired	81 (53.3)	71 (46.7)	152 (47.2)	.62
	Active worker	86 (50.6)	84 (49.4)	170 (52.8)	
Education level	Primary school	81 (57)	61 (43)	142 (44.1)	.04
	Secondary school	49 (55.1)	40 (44.9)	89 (27.6)	
	High school	27 (45.7)	32 (54.3)	59 (18.3)	
	University	10 (31.2)	22 (68.8)	32 (10)	
Weight gain	No	75 (47.2)	84 (52.8)	159 (49.4)	.09
	Yes	92 (56.4)	71 (43.6)	163 (50.6)	
Physical exercise	No	117 (59.7)	79 (40.3)	196 (60.9)	<.01
	Yes	50 (39.6)	76 (60.4)	126 (39.1)	
Alcohol consumption	No	119 (49.4)	122 (50.6)	241 (74.8)	.24
	Social drinker	36 (57.1)	27 (42.9)	63 (19.6)	
	Heavy drinker	12 (66.6)	6 (33.4)	18 (5.6)	
Hypertension	No	112 (51.9)	92 (48.1)	204 (63.4)	.15
	Yes	55 (43.2)	63 (56.8)	118 (36.6)	
Diabetes mellitus	No	129 (51.2)	123 (48.8)	252 (78.3)	.65
	Yes	38 (54.2)	32 (45.8)	70 (21.7)	
Dyslipidemia	No	109 (51.2)	104 (48.8)	213 (66.1)	.73
	Yes	58 (53.2)	51 (46.7)	109 (33.9)	
Cerebrovascular disease	No	162 (52.1)	149 (47.9)	311 (96.6)	.66
	Yes	5 (45.4)	6 (54.6)	11 (3.4)	
Peripheral artery disease	No	139 (53.7)	120 (46.3)	259 (80.4)	.19
	Yes	28 (44.4)	35 (55.6)	63 (19.6)	
Asthma	No	142 (52.6)	128 (47.4)	270 (83.9)	.55
	Yes	25 (48)	27 (52)	52 (16.1)	
Chronic obstructive lung disease	No	152 (52.8)	136 (47.2)	288 (89.4)	.34
	Yes	15 (44.1)	19 (55.9)	34 (10.6)	

Table 4. The Difficulties Faced the Patients While Trying to Quit Smoking

		Still Smoking n (%)			
Difficulties	**Parameters**	**Yes (167)**	**No (155)**	**Total (%)**	***P***
Nervous temper	Yes	109 (55.3)	88 (44.7)	197 (61.2)	.11
	No	58 (46.4)	67 (53.6)	125 (38.8)	
Weight gain	Yes	92 (56.4)	71 (43.6)	163 (50.6)	.09
	No	75 (47.2)	84 (52.8)	159 (49.4)	
Excessive urge to smoke	Yes	33 (47.8)	36 (52.2)	69 (21.4)	.57
	No	134 (52.9)	119 (47.1)	253 (78.6)	
Headache	Yes	27 (55.1)	22 (44.9)	49 (15.2)	.62
	No	140 (51.2)	133 (48.8)	273 (84.8)	
Sleep disturbances	Yes	12 (38.7)	19 (61.3)	31 (9.6)	.12
	No	155 (53.3)	136 (46.7)	291 (90.4)	
Concentration disturbances	Yes	7 (43.7)	9 (56.3)	16 (4.9)	.51
	No	160 (52.3)	146 (47.7)	306 (95.1)	
Numbness	Yes	7 (46.6)	8 (53.4)	15 (4.6)	.17
	No	160 (52.1)	147 (47.9)	307 (95.4)	
Oral ulcers	Yes	6 (54.5)	5 (45.5)	11 (3.4)	.03
	No	161 (51.8)	150 (48.2)	311 (96.6)	
Constipation	Yes	4 (44.6)	5 (55.6)	9 (2.7)	.65
	No	163 (52.1)	150 (47.9)	313 (97.3)	

were nicotine withdrawal symptoms. Self-motivation and desire alone were insufficient to assist the patients to quit smoking but the effects of doctors' guidance and tobacco control regulations were more effective in this regard.

Smoking is the main cause of preventable diseases and premature deaths worldwide.[12] It increases the risk of coronary heart disease and cardiovascular-related morbidity and mortality.[13] Patients who continue on smoking after the diagnosis of cardiovascular diseases constitute a high-risk group for the recurrence of major adverse cardiovascular events (MACE).[6,14] On the other hand, quitting smoking is associated with a substantial lower risk of such events.[15] Even reducing the number of cigarettes smoked per day was found to be beneficial in this regard.[16] Large-scale studies conducted in different countries showed high rates of patients who continue on smoking after AMI.[8-10] Similarly, in our study, more than half of the patients continued on smoking after AMI.

Studies have revealed that sociodemographic characteristics can affect an individual's commitment to the smoking cessation path.[17] For example, high educational level can be associated with higher confidence in the ability to quit smoking which would increase the likelihood of quitting.[18] In our study, the educational level of the participants was also found to be a significant factor as smoking cessation rates were highest among university graduates and lowest among primary school graduates (68.8% vs. 43%, respectively).

Table 5. Ratios of Patients Supporting the Government's Regulations in Controlling Tobacco Industry

		Still Smoking, n (%)			
Regulations	**Parameters**	**Yes (167)**	**No (155)**	**Total (%)**	***P***
Supporting the printing of pictorial health warnings on cigarette packs	Yes	153 (57.5)	113 (42.6)	266 (82.6)	<.01
	No	14 (25)	42 (75)	56 (17.4)	
Believing that the pictorial health warnings can help in quitting smoking	Yes	103 (59.2)	71 (40.8)	174 (54)	<.01
	No	64 (43.2)	84 (56.8)	148 (46)	
Supporting the law of banning tobacco use indoors and in public places	Yes	147 (53.1)	130 (46.9)	277 (86)	.28
	No	20 (44.4)	25 (55.6)	45 (14)	
Supporting the law of banning the advertising of tobacco products	Yes	131 (49.1)	136 (50.9)	267 (82.9)	.27
	No	36 (65.4)	19 (34.6)	55 (17.1)	
Supporting the law of "Plain design for cigarette packs" application	Yes	116 (48.9)	121 (51.1)	237 (73.6)	.08
	No	51 (60)	34 (40)	85 (26.4)	
Supporting the law of raising the tax on tobacco products	Yes	103 (54.5)	86 (45.6)	189 (58.6)	.26
	No	64 (48.1)	69 (51.9)	133 (41.4)	
Believing that these laws can help in decreasing smoking rates	Yes	83 (48.2)	89 (51.8)	172 (53.4)	.17
	No	84 (56)	66 (44)	150 (46.6)	

Additionally, regression analysis showed that the probability of smoking cessation is doubled among university graduates ($P < .01$). On the other hand, no significant association was found between smoking cessation after AMI and other sociodemographic factors like gender, working status, or alcohol consumption (Table 3).

Numerous diseases are linked to smoking; therefore, smokers may suffer from a variety of chronic illnesses. Studies evaluating the association between smoking cessation and the presence of smoking related chronic illnesses such as cardiovascular and pulmonary diseases stated that there is no direct relationship between the 2 conditions.[19] Similar results was observed in our study as no significant association was found between smoking cessation after AMI and a prior diagnosis of such comorbidities (Table 3).

Depressive symptoms are common during the hospital stay for an AMI and can reduce the effectiveness of smoking cessation interventions.[20] Patients also experience withdrawal symptoms while trying to quit smoking which makes the quitting process more challenging.[21] Among the participants of our study, nicotine withdrawal symptoms such as nervous temper, headache, and excessive urge to smoke were the main factors that stood against their will to quit smoking. The degree of nicotine dependence is very important in this regard.[21] Our study results showed that the probability of smoking cessation after AMI was over 3 times higher in the group with low nicotine dependence compared to those with high dependence ($P < .01$). Therefore, smoking cessation programs should be supported by intensive behavioral therapy and, if necessary, psychological pharmacotherapy to make such programs more effective.

Weight changes are another important factor in the smoking cessation process, as quitting increases patients' appetite and causes weight gain.[22] This was seen in 163 (50.6%) participants of our study and demotivated them while trying to quit smoking. Beside its benefits in decreasing cardiovascular morbidity and mortality, physical exercise can help patients with weight problems to quit smoking.[23,24] Our study results showed a higher probability of smoking cessation among those who perform physical exercise but the rate of patients who exercise regularly was low (39.1%). This highlights the importance of physical exercise as part of post-AMI therapy and indicates that more efforts should be implemented in this regard.

Patients with AMI can experience high levels of stress during the interventional procedures and hospitalization in intensive care units which can urge and motivate them to quit smoking. This motivation is necessary to start the quitting process but alone is insufficient to maintain smoking cessation. In our study, 74.2% of smoker participants had the intention to quit smoking and 58.7% believed that they would succeed in quitting after AMI. A professional help is needed to boost this motivation as studies showed higher smoking cessation rates among AMI patients who got advice and guidance from healthcare professionals after the index event.[25,26] Even a brief verbal physician intervention explaining the harmful effects of smoking can yield a strong influence on the patients.[27] Among the 322 patients of our study, 231 (71.7%) patients got an advice to quit smoking from their doctor and the probability of quitting was 5 times higher in this group ($P < .01$). However, not all patients follow these simple instructions and the cessation process should include a comprehensive consulting program within specialized departments.[28] Unfortunately, the number of our study participants who referred to a specialized smoking cessation department was small (n = 68, 21.1%). These results show that there is an increased need for a comprehensive smoking cessation programs to be included within the standard treatment offered to prevent the recurrence of cardiovascular events after AMI.

A public health analysis revealed that strict tobacco control regulations could avert 50 million cardiovascular deaths over the course of the next few decades.[29] In our study, patients stated that they support the government's strict regulations on tobacco control, believing that it can be effective in decreasing smoking rates (Table 5). More than half of our study participants said that they were considering quitting smoking every time they see the pictorial health warnings on cigarette packs and the probability of quitting was doubled in this group ($P < .01$).

In conclusion, our study results showed that high number of patients continue to smoke cigarettes after having an AMI. Considering its low costs and the proven benefits, smoking cessation should be one of the primary goals in these patients. Evidence-based programs supported by behavioral therapy in which the doctors take an active role can make smoking cessation treatment more effective. More strict tobacco control regulations by the government can be very beneficial in this regard. The main limitation of our study is the relatively small number of participants. Another point is that smoking status was based on patients' statements, which sometimes can be misleading.

Ethics Committee Approval: The study was approved by the ethical committee of Lokman Hekim University, Faculty of Medicine (Doc. no:2021136).

Informed Consent: Informed consents were obtained from all the participants.

Peer-review: Externally peer-reviewed.

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Original Article

Facing Pandemic: Burnout in Nurses in Turkey

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Abstract

OBJECTIVE: Burnout syndrome is a disorder that characterized by emotional exhaustion, depersonalization, and personal lack of accomplishment perception and it is common in nurses. During the coronavirus disease 2019 pandemic, nurses tried to take care of their patients and protect themselves and their families from disease and death. This study examines the factors affecting nurses' burnout in Turkey during the coronavirus disease 2019 pandemic.

MATERIAL AND METHODS: Data were collected from 3523 nurses in 69 cities across Turkey by sociodemographic questions and Maslach Burnout Scale with the electronic questionnaire created in the "SurveyMonkey" application between June 9, 2020 and June 21, 2020. To assess the impact of the pandemic on nurses' burnout, nurses were categorized as those working in pandemic units and others.

RESULTS: The response rate was 68%, and 3523 nurses from 69 cities across Turkey participated in the survey. Analyses were conducted with 2386 nurses that answered all questions. 76.45% of the nurses were from tertiary hospitals, and 54.9% (n = 1309) worked in pandemic units. Of 2386 participants, 86.13% (n = 2055) were female, the mean age was 33.9 (±8.43), and 58.76% (n = 1402) were married. Of 2386 participants, 54.9% (n = 1309) worked in pandemic units (outpatient clinics, inpatient clinics, and intensive care units). In multivariate linear regression analyses, the emotional exhaustion score was higher in nurses working in pandemic units ($P < .05$).

CONCLUSION: The factors that have been shown to cause burnout in previous studies were similar. However, in this study, it was also seen that the pandemic is a fundamental cause of burnout.

KEYWORDS: Burnout, COVID-19, nurses, pandemic
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INTRODUCTION

Healthcare professionals experience burnout due to extended working hours, excessive workload, assignments in different departments, unclear job descriptions, dangerous working environments, insufficient personal protective equipment, prolonged use of protective equipment, and risk of damage, especially in crises such as epidemics.

There have been outbreaks in different periods, mainly affecting the region where they occurred. In these outbreaks, thousands of healthcare professionals were at the forefront of attempts to diagnose the disease, treat the patient, suppress the epidemic, and provide intensive healthcare. It has been observed that healthcare professionals who struggled with significant outbreaks such as severe acute respiratory syndrome (SARS), H1N1, and Middle East respiratory syndrome (MERS) before the coronavirus disease 2019 (COVID-19) pandemic were significantly affected by these epidemics, experienced burnout, and showed post-traumatic stress disorder symptoms years later.[1-3]

SARS, which emerged in 2002, was the first example of its contagiousness and how quickly it spread to different countries, and many healthcare professionals caught it.[4,5] Symptoms of anxiety and depression have been identified in healthcare workers in areas affected by SARS.[6]

On the other hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is seen to cause significant burnout in healthcare workers due to its contagiousness, mortality, broader and faster spread that affected the whole world, and long duration than SARS in 2002. This situation affects healthcare professionals, the healthcare system, and the struggles against the pandemic.

Burnout is characterized by emotional exhaustion, depersonalization, and personal lack of accomplishment perception.[7] Burnout syndrome has been evaluated in many studies and conducted with participants from different areas of the healthcare sector, such as physicians, nurses, technicians, and administrative workers; it was observed that those who are more directly interested in patient care, especially nurses, have worse results in psychological evaluations.[8-10]

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For example, nurses have had more post-traumatic stress disorder symptoms, higher stress levels, and higher general distress levels than other healthcare professionals.[11] As a result of the studies, burnout was mainly associated with factors such as working hours, monthly income, appreciation from superiors, and support received from the family.[12,13]

Studies conducted during outbreaks show that it was essential to receive special training and be prepared for epidemics.[14] It was stated that healthcare professionals who do not have sufficient confidence in their knowledge and skills about infection control have higher stress levels, higher burnout, and post-traumatic stress disorder.[15]

In studies conducted during the SARS outbreak, nurses' greater reliance on personal protective equipment and infection control procedures has been associated with lower emotional exhaustion.[16] In many studies, working in units considered "high risk" in terms of infection was associated with poor mental health.

This study aimed to determine the burnout levels and related factors in nurses working during the COVID-19 pandemic.

MATERIAL AND METHODS

Design and Study Population

This research was designed as a cross-sectional study. The research population is nurses working in Turkey's secondary and tertiary health institutions. For the research to be conducted with broader participation, we aimed to connect with nurses working in 81 provinces. A total of 3523 nurses from 69 provinces were reached in the study, and 2386 nurses who answered the questionnaire completely were included in the study (response rate was 68%). Ministry of Health permission was obtained. Ethical approval was obtained from the institutional ethics committee of Dokuz Eylül University Faculty of Medicine (2020/12-32; June 08, 2020).

MAIN POINTS

- The coronavirus disease 2019 pandemic is not a short-distance run but a marathon, as in other outbreak cases. Healthcare professionals should be evaluated and intervene early regarding health problems that may arise later, such as psychological and physiological symptoms and post-traumatic stress disorder. It should be kept in mind that the negative consequences of burnout syndrome on healthcare workers lead to suicidal thoughts, physical injury, and death.
- Although healthcare professionals trying to meet the demands of patients in large organizations such as hospitals work under stress throughout the day, burnout is still among the unheeded issues. However, burnout syndrome is a significant indicator of mental illness that requires effective measures at the institutional and individual levels.
- Burnout syndrome adversely affects the healthcare worker and increases the risk of medical errors and patient safety. For this reason, it should be identified early, and it should be known that it is essential to create a healthy working environment by eliminating the causes of burnout.

Data Collection

The data were collected between June 9 and June 21, 2020 with the electronic survey method prepared on the "SurveyMonkey" application. The questionnaire consisted of 2 parts: the sociodemographic data form and the Maslach Burnout Inventory (MBI). The electronic questionnaire forms were delivered to nurses from the health institutions' WhatsApp communication groups. Reminders were made several times in communication groups.

The sociodemographic data form included the characteristics of the working environment and personal sociodemographic variables that may affect nurses' burnout. The researchers prepared the form, and the pre-test was applied with a small group of nurses.

The MBI-Turkish version was used to evaluate the level of burnout, which is the study's primary outcome. Maslach Burnout Inventory was developed by Maslach and Jackson and translated into Turkish by Canan Ergin.[7,17] (Maslach Burnout Inventory questions are shown in the Supplementary Table 1). Each subscale in the MBI was scored between 0 and 4 as "Never, Several times a year, Several times a month, Several times a week, Every day." The scores obtained from the subdimensions of the scale are between 0 and 36 for emotional exhaustion (EE); it varies between 0 and 20 for depersonalization (D) and 0 and 32 for lack of accomplishment (LA). Burnout was not evaluated with a single score; the scores of each participant from 3 subscales were evaluated separately.

To assess the impact of the pandemic on nurses' burnout, nurses were categorized as those working in pandemic units and others.

Statistical Analysis

Statistical analysis was performed using the IBM Statistical Package for Social Sciences software (IBM Corp.; Armonk, NY, USA) for Windows version 24.0. Its compatibility with normal distribution was checked by Kolmogorov–Smirnov and Shapiro–Wilk tests. Mann–Whitney *U* and Pearson's chi-square tests were used to compare the mean values of numerical variables of binary groups. Linear regression analysis was used to measure the effects of more than 1 independent variable on its dependent variables. Variables found to be significant in univariate analyzes were included in multivariate analyses. Assuming a 0.05 margin of error and 0.9 power, and a possible drop-out rate of 10%, a *P*-value <.05 was considered statistically significant.

RESULTS

Demographic Characteristics

In this study, which we conducted with nurses working in outpatient clinics, inpatient units, and intensive care units of hospitals where COVID-19 patients were admitted and hospitalized, a total of 2386 nurses answered all the questions. However, 67.5% of the nurses participating in the study worked in training hospitals (university hospitals or training-research hospitals). In contrast, the others worked in private or state hospitals. Of 2386 participants, 13.87% (n = 331)

Table 1. General Demographics and Working Conditions During the Pandemic

	Number (n)	Percent
Total	2386	100
Age; mean (SD) Median (minimum–maximum)	33.9 (±8.43) 33 (20-62)	
Female	2055	86.1
Married	1402	58.8
Those who have children	1227	51.4
Institution		
Public hospital	381	16
Training and research hospital	648	27.2
University	1140	47.8
Private hospital	181	7.6
Private university hospital	36	1.5
Those with chronic disease	890	37.3
Current smokers	789	34.1
Current alcohol drinkers	489	20.5
Working year (>20 years)	511	21.4
Those who think their monthly income was not enough	1630	68.3
Those who did not choose profession willingly	584	24.5
Those who will not choose the same profession again	1417	59.4
Not satisfied with business life	692	29
Working conditions during the pandemic		
Those who worked in pandemic units (outpatient clinics, inpatient clinics, and intensive care units)	1309	54.9
Shift working	1546	64.8
Those who have increased working hours	398	16.7
Weekly working hours (>45 hours)	810	33.9
Those who thinking that not appreciated by the superiors	1181	49.5
Those who thinking that the job description was unclear	1089	45.6
Those who had problems with patient relatives	1135	47.6
Those who had difficulty in attaining PPE	553	23.2
Those who had to work without PPE	706	29.6
Those who had high-risk contact (without PPE) with The COVID-19 patient	194	8.1
Those who thinking that PPE was insufficient	873	36.6
Those who had risk factors for COVID-19 in the family	1103	46.2
Those who had diagnosed with COVID-19	108	4.5
Those who did not spend enough time with the family	1884	79.0
Those who were without emotional support	1180	49.5
Those who were without childcare support	697	29.2
Those who did not feel safe	1404	58.8
Those who did not feel their families in safe	1259	52.8
Those who had to be away from their family members (>1 month)	1446	60.6
Those who had to be away from their child (>1 month)	310	13.0

COVID-19, coronavirus disease 2019; PPE, personal protective equipment.

were male, 86.13% (n = 2055) were female, and the mean age was 33.9 (±8.43). Table 1 summarizes the general demographic features of the participants and working conditions during the pandemic.

Work Environment

Of 2386 participants, 54.9% (n = 1309) worked in pandemic units (outpatient clinics, inpatient clinics, and intensive care units). Weekly working hours were <40 hours in 19.99%,

40-50 hours in 68.69%, and over 50 hours in 11.32%. During the pandemic, 16.7% (n = 398) increased weekly working hours. Most nurses working for more than 20 years have not been assigned to pandemic units (293/511, 57.3%). In the pandemic units, 48.19% (n = 493) of nurses stated that they have been in this profession for 1 to 10 years, and 26.78% (n = 274) of nurses for 11-20 years. However, 75.5% (n = 1802) of the nurses participating in the questionnaire stated that they chose their profession willingly, but the rate of those who said they would choose this profession again was 40.61% (n = 969). Those who thought their monthly income was insufficient were 68.32% (n = 1630).

Risks of Direct and Indirect Exposure to Coronavirus Disease 2019

In the whole group, 23.2% (n = 553) of nurses had difficulty attaining personal protective equipment (PPE), and 29.% (n = 706) stated that they had to work without PPE. Those who reported high-risk contact with a patient diagnosed with COVID-19 without PPE were 8.13% (n = 194) of the nurses participating in the study, and 65.50% (n = 1513) of the nurses thought that their PPE was not sufficient or partially inadequate during the pandemic. The number of nurses living in the same house with family members carrying COVID-19 risk factors was 1103 (46.23%). Almost half of the nurses (45.40%, n = 1079) themselves or at least 1 of their relatives had been diagnosed with COVID-19, and 45.27% (n = 1048) of their coworkers were diagnosed with COVID-19.

Physiological and Emotional States

Of the participants, 79% (n = 1884) did not spend enough time with their families during the pandemic, and even 68.15% (n = 1626) stated that they had to be away from their families, 29.21% (n = 697) of those stated that they had no support for childcare during the pandemic. They stated that they experienced some behavioral symptoms during the pandemic. Although they were not diagnosed with COVID-19, 50.75% (n = 1211) had symptoms, 32.94% had a sore throat, 31.97% had a headache, and 19.57% cough. We found that they frequently feel depressive emotions, get angry very quickly, experience forgetfulness and distraction, and their expressions of hating their work increased. While no physical symptoms were observed in 15.13% (n = 352) of the nurses, the most common complaints were fatigue and lack of energy in most cases.

Maslach Burnout Inventory

The mean (±SD) of EE, D, and LA subdimensions of 2386 nurses were 19.42 (±8.37), 5.80 (±4.15), and 10.03 (±5.38), and the median (min-max) was 19 (0-36), 5 (0-20), and 10 (0-32), respectively. All subdimensions scores were statistically significantly higher in nurses working in pandemic units (Table 2, Figure 1). All subdimensions scores were statistically significantly higher in those who were single and did not have children. Table 2 summarizes the factors affecting EE, depersonalization, and LA scores.

As a result of the linear regression analysis of the factors that we show to cause burnout, we have revealed that not choosing the profession willingly and not thinking again, young age, uncertain job descriptions, and problems with patient relatives are the most prominent factors that cause burnout in all subgroups of MBI. Also, monthly income insufficiency and excessive weekly working hours cause burnout. Concerning the pandemic, working without PPE, insufficiency in PPE, not feeling safe, not spending enough time with the family, and being away from family were also evaluated as important factors causing burnout, as summarized in Table 3.

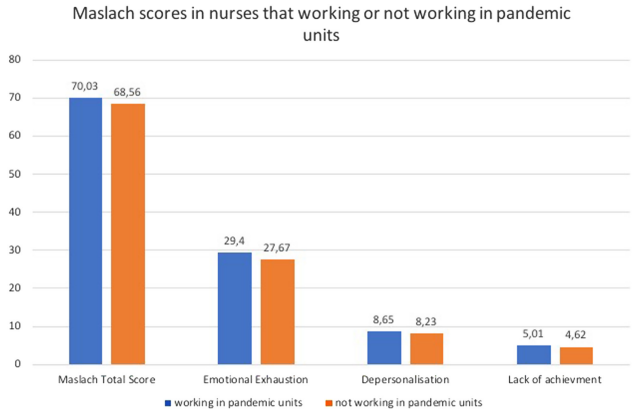


Figure 1. The subdimensions of burnout in working and non-working groups in the pandemic units.

DISCUSSION

As a result of the research, the EE score was significantly higher in those working in pandemic units than those who did not work in pandemic services. It can be said that nurses working in pandemic units experienced EE. According to the results from previous outbreaks, healthcare professionals experience high-stress levels in sudden and life-threatening outbreaks.[1-3] Many of the effects of the COVID-19 pandemic on healthcare workers' personal and mental health can have significant consequences. For instance, isolation, lack of social support, and increased workload can severely affect their physical and mental health. With the COVID-19 pandemic, images of patients connected to respiratory support and filling the hospital corridors from various countries and images of the physical fatigue and mask marks on the faces of the healthcare professionals who work tirelessly were shared. With the increasing number of patients, healthcare professionals who did not have time to rest were physically and emotionally exhausted.

Our research observed that insufficient PPE was one of the essential factors of burnout for those working in pandemic units and for all nurses participating in the survey. Nurses are the ones who provide patient care and therefore make the most and closest contact with the patient, and we know that close contact with the COVID-19 patient is the most critical risk factor identified. Therefore, PPE has become the most crucial problem for healthcare professionals.[18] The insufficiency of PPE, difficulties in procuring the equipment, and having to work without PPE have been the most tiring issues for healthcare professionals during the pandemic. The data from various countries show that the frequency of COVID-19 among healthcare workers varies between 1.9% and 12.6%.[19] With the fear of getting the disease and transmitting it to others, this situation may increase the risk of psychological consequences.

Table 2. Burnout Levels and Related Factors

		EE		D		LA	
Variables	**Categories**	**Median (Minimum–Maximum)**	***P***	**Median (Minimum–Maximum)**	***P***	**Median (Minimum–Maximum)**	***P***
Working in PU	**Who worked in PU**	**20 (0-36)**	**<.001**	**5 (0-20)**	**<.001**	**10 (0-32)‡**	**.007**
	Who non-worked in PU	**18 (0-36)**		**4 (0-20)**		**10 (0-32)**	
Age	**≤35 years**	**20 (0-36)**	**<.001**	**6 (0-20)**	**<.001**	**10 (0-32)**	**<.001**
	>35 years	**17 (0-36)**		**4 (0-20)**		**9 (0-32)**	
Gender	**Female**	**19 (0-36)‡**	**.193**	**5 (0-20)**	**.003**	**10 (0-32)**	**.017**
	Male	**19 (0-36)**		**6 (0-20)**		**11 (0-32)**	
Married	**Single**	**20 (0-36)**	**<.001**	**6 (0-20)**	**<.001**	**10 (0-26)**	**.001**
	Married	**18 (0-36)**		**4.5 (0-20)**		**9 (0-32)**	
Having children	**Those who have no children**	**20 (0-36)**	**<.001**	**6 (0-20)**	**<.001**	**10 (0-26)**	**<.001**
	Those who have children	**18 (0-36)**		**4 (0-20)**		**9 (0-32)**	
Having support for childcare	Have no support	19 (0-36)	.004	5 (0-20)	.005	10 (0-32)	.257
	Who have support	18 (0-36)		4 (0-19)		9 (0-32)	
Choosing the profession willingly or not	Not willingly	23 (0-36)	<.001	6 (0-20)	<.001	11 (0-32)	<.001
	Willingly	18 (0-36)		5 (0-20)		10 (0-32)	
Choosing the same profession again willingly or not	Not willingly	23 (0-36)	<.001	6 (0-20)	<.001	11 (0-32)	<.001
	Willingly	15 (0-36)		4 (0-20)		8 (0-24)	
Monthly income	Insufficient	21 (0-36)	<.001	6 (0-20)	<.001	10 (0-29)	.003
	Sufficient	16 (0-36)		4 (0-19)		9 (0-32)	
Weekly working hours	>45 hours per week	20 (0-36)	<.001	6 (0-20)	<.001	10 (0-32)‡	.990
	≤45 hours per week	18 (0-36)		5 (0-20)		10 (0-32)	
Shift working	Yes	20 (0-36)	<.001	6 (0-20)	<.001	10 (0-32)	<.001
	No	17 (0-36)		4 (0-20)		9 (0-28)	
Appreciating by the superiors	No	21 (0-36)	<.001	6 (0-20)	<.001	10 (0-29)	<.001
	Yes	17 (0-36)		4 (0-20)		9 (0-32)	
Job description	Unclear	22 (0-36)	<.001	7 (0-20)	<.001	11 (0-29)	<.001
	Clear	17 (0-36)		4 (0-20)		9 (0-32)	
Problems with patient relatives	Yes	22 (0-36)	<.001	7 (0-20)	<.001	10 (0-32)	<.001
	No	17 (0-36)		4 (0-20)		9 (0-32)	
Difficulty in attaining PPE	Yes	23 (0-36)	<.001	7 (0-20)	<.001	10 (0-29)‡	<.001
	No	18 (0-36)		5 (0-20)		10 (0-32)	
Working without PPE	Yes	22 (0-36)	<.001	7 (0-20)	<.001	10 (0-32)‡	.005
	No	18 (0-36)		5 (0-20)		10 (0-32)	
Having family members with risk factors for COVID-19	Yes	20 (0-36)	.002	5 (0-20)‡	.383	10 (0-32)‡	.429
	No	18 (0-36)		5 (0-20)		10 (0-32)	
Diagnosed COVID-19	Yes	20 (0-36)	.120	5 (0-20)‡	.387	10 (0-32)‡	.225
	No	18 (0-36)		5 (0-20)		10 (0-32)	
Spending enough time with the family	No	20 (0-36)	<.001	6 (0-20)	<.001	10 (0-29)	.002
	Yes	16 (0-36)		4 (0-20)		9 (0-32)	
Being without emotional support	Yes	19 (0-36)‡	.397	5 (0-20)‡	.832	10 (0-32)‡	.686
	No	19 (0-36)		5 (0-20)		10 (0-32)	

(*Continued*)

Table 2. Burnout Levels and Related Factors (*Continued*)

Variables	Categories	EE Median (Minimum–Maximum)	EE *P*	D Median (Minimum–Maximum)	D *P*	LA Median (Minimum–Maximum)	LA *P*
Not feeling safe	Yes	22 (0-36)	<.001	6 (0-20)	<.001	10 (0-32)	<.001
	No	16 (0-36)		4 (0-20)		9 (0-32)	
Not feeling families are safe	Yes	21 (0-36)	<.001	6 (0-20)	<.001	10 (0-32)	<.001
	No	17 (0-36)		4 (0-20)		9 (0-28)	
Be away from families	Yes	20 (0-36)	<.001	6 (0-20)	<.001	10 (0-32)	.060
	No	17 (0-36)		4 (0-20)		9 (0-32)	
Those who think they have difficulty in accessing information	Yes	23.5 (3-36)	<.001	7 (0-20)	<.001	11 (0-28)	.001
	No	***18 (0-36)***		***4 (0-20)***		***10 (0-32)***	

Mann–Whitney *U*-test results are shown.
‡Those with a higher mean value are shown in categories with similar median values.
COVID-19, coronavirus disease 2019; D, depersonalization; EE, emotional exhaustion; LA, lack of personal accomplishment; PPE, personal protective equipment; PU, pandemic units.

In many previous studies, excessive weekly working hours are essential for burnout. Nurses work in harsh conditions, and it was found that 1 out of every 3 nurses worked more than 45 hours a week. Although this was an essential factor that causes burnout, nurses cannot spend enough time with their families secondary to intense and long hours of work.

Table 3. Multivariate Linear Regression Analysis on EE, D, LA with Burnout-Related Factors

Variables	Emotional Exhaustion *B* (95% CI)	Depersonalization *B* (95% CI)	Lack of Personal Accomplishment *B* (95% CI)
Working in pandemic units	**0.67 (0.8, 1.25)***	0.22 (−0.10, 0.53)	0.07 (−0.37, 0.51)
Age (≤35)	**1.55 (0.90, 2.21)*****	**1.64 (1.28, 1.99)*****	**0.57 (0.08, 1.06)***
Being single	0.33 (−0.28, 0.94)	**0.36 (0.03, 0.69)** *	−0.01 (−0.46, 0.46)
Not choosing the profession willingly	**2.35 (1.68, 3.02)*****	**0.56 (0.20, 0.93)** **	**0.60 (0.09, 1.11)***
Not choosing the same profession again willingly	**4.89 (4.29, 5.50)*****	**1.29 (0.96, 1.61)*****	**1.91 (1.45, 2.36)*****
Insufficient of monthly income	**1.79 (1.20, 2.38)*****	**0.38 (0.06, 0.70)***	0.23 (−0.21, 0.68)
Weekly working hours (>45)	0.57 (−0.03, 1.18)	0.38 (0.05, 0.71)*	–
Shift working	−0.25 (−0.93, 0.42)	0.01 (−0.36, 0.37)	**0.97 (0.48, 1.47)*****
Not appreciating by the superiors	**0.66 (0.28, 1.05)****	0.19 (−0.02, 0.40)	**0.57 (0.28, 0.87)*****
Unclear job description	**1.45 (0.84, 2.06)*****	**0.78 (0.45, 1.12)*****	**1.08 (0.61, 1.54)*****
Problems with patient relatives	**2.35 (1.77, 2.92)*****	**1.45 (1.14, 1.76)*****	**0.57 (0.14, 1.00)***
Difficulty in attaining PPE	**0.91 (0.18, 1.65)***	0.10 (−0.30, 0.49)	0.15 (−0.40, 0.71)
Working without PPE	**0.64 (0.03, 1.36)***	**0.59 (0.23, 0.95)****	−0.10 (−0.61, 0.40)
Having any family member with risk factors for COVID 19	0.48 (−0.07, 1.03)	–	–
Not spending enough time with the family	**1.61 (0.89, 2.33)*****	0.26 (−0.13, 0.65)	−0.07 (−0.06, 0.46)
Not feeling safe	**2.42 (1.82, 3.03)*****	**0.58 (0.25, 0.90)****	0.30 (−0.15, 0.76)
Be away from families	0.27 (−0.36, 0.89)	−0.21 (−0.55, 0.13)	–
Those who think they have difficulty in accessing information	**0.81 (0.02, 1.60)***	0.39 (−0.04, 0.82)	−0.13 (−0.73, 0.46)

***P < .001, **P < .01, *P < .05.
Those that were significant in univariate analyses were included in the multivariate model. Some cells in the table are blank, because those variables were not included in the multivariate model of the relevant subdimension.
B, regression coefficient; COVID-19, coronavirus disease 2019; D, depersonalization; EE, emotional exhaustion; LA, lack of personal accomplishment; PPE, personal protective equipment.

Therefore not being able to allow time for a social life or even not having quality time to spend with the family is an essential factor that has been shown to cause burnout in healthcare professionals.[20] Besides, nurses who did not want to infect their families during the pandemic lived separately for months. The nurses stated they did not feel safe due to COVID-19 and agreed to this mandatory separation to protect their families.[21] It was observed that burnout scores were higher in nurses working in pandemic units separated from their families. In our research, burnout levels were significantly higher in single and childless nurses. In contrast, the rates of not being able to spend enough time with their families, not feeling safe themselves and their families, and having to leave their families were statistically significantly higher in nurses working in pandemic units compared to nurses working in non-pandemic units. Besides, there was no significant difference in EE scores compared to male nurses because the population was mainly female, but depersonalization and personal success scores were significantly higher.

It was observed that nurses working in pandemic units have statistically higher scores on having problems with their relatives. During the COVID-19 pandemic, nurses are crushed in a busy working tempo and under the emotional demands of other people.[22] Nurses experiencing EE feel powerless and inadequate in solving other people's problems. They constantly use the escape route to relieve their emotional burden and minimize their relationships with people. Also, it was thought that the problems with the relatives of the patients have increased because the facial expressions of the nurses due to the protective equipment are not being read, and the interaction and socialization have decreased.

In our research, the expressions of "lack of appreciation from their superiors" and "unclear job descriptions," known as important factors that trigger burnout, showed a statistically significant difference among nurses working in pandemic units compared to those working in non-pandemic services. The existence of role confusion in the work environment, the unclear job description, and the excessive workload cause healthcare professions to feel a loss of control of their work life.

Physical complaints such as fatigue, insomnia, and forgetfulness can be observed in burnout, and burnout syndrome has physical, emotional, and mental symptoms.[23] Fatigue, depressive feelings, irritability, forgetfulness and distraction, and lack of energy were the most common complaints stated in our research.

However, the research was limited based on a cross-sectional design. In our study, to show the effect of the pandemic on burnout, we used working status in pandemic units or not as a predictor. However, it is impossible to say that those who do not work in pandemic units are not affected by the pandemic. Therefore, studies in cohort design are needed to show the effect of the pandemic.

CONCLUSION

In this study conducted during the COVID-19 pandemic, it was seen that the most important reasons for burnout are due to administrative gaps. To protect the mental health of employees, it is critical to be aware of psychosocial risks in the workplace and to adopt organizational strategies to prevent them.

Ethics Committee Approval: This study was approved by Ethics Committee of Dokuz Eylul University Faculty of Medicine (Approval no: 2020/12-32; Date: June 08, 2020).

Informed Consent: Participants who agreed to participate in this study participated by confirming the confirmation button indicating they decided to participate.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1. Maslach Burnout Inventory

Maslach Burnout Inventory
1. I feel drained from my job.
2. I feel spiritually exhausted at the end of the workday.
3. I feel fatigued when I wake up in the morning and have to face a new workday.
4. I can immediately understand how my patients feel about many things.
5. I feel that I treat some of my patients as if they were an object devoid of personality.
6. Dealing with people all day is really a tension for me.
7. I deal with my patients' problems effectively.
8. I feel my work is consuming me.
9. I feel that my job positively affects other people's lives.
10. Ever since I started this business, I have been tough with people.
11. I'm afraid this job will harden me.
12. I feel very energetic.
13. I think my job disappointed me.
14. I feel that I am working above my strength in my job.
15. I don't care what happens to the people I meet for my job.
16. Working directly with people causes me a lot of stress.
17. I can easily provide a comfortable atmosphere for my patients.
18. After working closely with my patients, I feel joyful.
19. I have done many valuable things in this profession.
20. I feel so helpless.
21. In my job, I deal with emotional problems very calmly.
22. I feel the patients behaving as if I had created some of their problems.

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Original Article

Does Pneumococcal Vaccination Have an Effect on Hospital Costs?

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Abstract

OBJECTIVE: It is known that inpatient hospital costs are much higher than outpatient services. It was aimed to investigate the effect of pneumococcal vaccination on hospitalizations.

MATERIAL AND METHODS: The direct hospitalization costs, length of stay, and factors of the vaccinated and unvaccinated patients in the same hospital during the 12-month follow-up of the patients who received pneumococcal vaccine between November 15, 2018, and November 15, 2020, in 3 chest diseases and thoracic surgery training and research hospitals were analyzed by obtaining Hospital Information Management System records. Data were collected with Statistical Package for the Social Sciences version 23 program (IBM Corp.; Armonk, NY, USA) , and statistical evaluation was made.

RESULTS: The mean age of 800 hospitalized patients, of whom 400 were unvaccinated and 400 were vaccinated, was 68.48 ± 11.97. There was no significant difference in the mean age of vaccinated and unvaccinated patients ($P > .05$). Five hundred sixty-six patients (70.8%) were aged 65 and over. Two hundred eighty (51.2%) of men were vaccinated and 120 (47.2%) of women were vaccinated, and there was no significant difference ($P > .05$). The mean hospital stay of these patients was 11.01 days, and those in the vaccinated group had an average mean hospital stay of 9.11 days and those in the unvaccinated group had a mean hospital stay less than 12.91 days ($P < .001$). Total 1-year hospitalization costs were $501.653.53 and the cost per person was calculated as $627.07. The cost per capita for the vaccinated group was $550.52, which was lower than the average cost of the unvaccinated group ($703.62) ($P < .05$). When comparing the status of being vaccinated, comorbidity, mortality, mean length of stay, chronic obstructive pulmonary disease, and heart disease were found to be statistically significant ($P < .05$).

CONCLUSION: In our study, it was revealed that vaccination of patients hospitalized in chest disease hospitals with the pneumococcal vaccine reduced the average length of hospital stay by 41.7% and the cost of hospitalization by 27.8%.

KEYWORDS: Pneumococcal vaccination, hospital costs, vaccination and hospitalization
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INTRODUCTION

Respiratory diseases are among the leading causes of death worldwide. World Health Organization estimates that by 2030, 4 potentially fatal respiratory diseases [pneumonia, tuberculosis, lung cancer, and chronic obstructive pulmonary disease (COPD)] will be responsible for approximately 1 in 5 deaths worldwide. Asthma causes a small number of deaths but is an important cause of disability. Therefore, respiratory diseases will likely continue to be a major burden on European societies and the world for the following decades. Both the prevention and treatment of lung diseases must be improved if their impact on the longevity and quality of life of individuals worldwide and the economic burden on society is to be reduced.[1]

Pneumococcal pneumonia constitutes a significant portion (20%-50%) of community-acquired pneumonia (CAP). About 10%-30% of these are accompanied by bacteremia.[2]

Non-bacteremic pneumococcal pneumonia is responsible for approximately 30% of hospitalizations due to CAP.[3] According to the culture results obtained from studies conducted in different centers in our country, *Streptococcus pneumoniae* was the most common cause of CAP (20.9% across the country).[4]

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Morbidity and mortality due to CAP are higher in advanced age (65 years and over) compared to the young population, and it causes hospitalization more frequently (22%-42%).[5] In the elderly, the risk of pneumococcal pneumonia is high, hospitalization is higher, and the recovery period for CAP is longer.[6] Given the course and associated morbidity and mortality of pneumococcal disease in older adults and those with specific comorbidities, prevention of the disease in these individuals is important.

Chronic obstructive pulmonary disease is a severe chronic lung disease characterized by progressive airway limitation, whose importance and frequency are increasing worldwide. Chronic obstructive pulmonary disease progresses with exacerbation episodes, and it has been reported that approximately 50% of exacerbations are of bacterial origin, and the most common cause is *S. pneumoniae*.[7]

It has been reported that 6% of the general health care budget in European Union countries is related to respiratory diseases, and 56% (ğ38.6 billion) of this cost is secondary to COPD.[8]

The total annual direct and indirect cost of CAP in an adult with a risk factor in the USA is 2.7 times higher than that of a patient without a risk factor.[9] In a study conducted in our country in 2017, it was shown that the total mean cost in adults with a diagnosis of CAP over the age of 18 was 10.9 times higher in hospitalized patients (ğ556.09 ± 1004.77 vs. ğ51.16 ± 40.92).[10] The cost of those treated at the hospital was higher regarding laboratory, medication, and hospital fees.[11]

In addition to the burden that COPD, asthma, and elderly patients with these diseases bring to the health system, CAPs that may occur in these patients and therefore hospitalizations will also cause an additional cost. If the annual losses of chronic respiratory diseases due to disability are added, it is evident that there will be a significant increase in the annual costs of COPD and asthma.

Especially in risk groups, in addition to reducing the medical burden, pneumococcal vaccination may also provide economic benefits by reducing hospitalization due to its contribution to the prevention of disease and attacks. Based on this, we aimed to investigate the effect of pneumococcal vaccination on hospitalization costs in this study, which we carried out in 3 chest diseases training and research hospitals.

MATERIAL AND METHODS

This multicenter cohort study was performed after obtaining approval from the University of Health Sciences Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital scientific board and hospital ethical committee (01.11.2018/2018-32).

In a 12-month follow-up of patients who received 13-valent pneumococcal conjugate vaccine (PCV13) between November 15, 2018, and November 15, 2020, in 3 chest diseases and thoracic surgery training and research branch hospitals (İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, and İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital), those who were hospitalized and those who were not vaccinated in the same period and were hospitalized, were analyzed in terms of direct hospitalization costs, length of stay, and factors affecting them by obtaining Hospital Information Management System records. Intensive care hospitalizations were excluded from our study.

Hospitalizations due to pneumonia, COPD and Asthma attack, and malignancy and patients over the age of 18 who completed the follow-up period or died during this period were included in the study. Intensive care hospitalizations and HIMS record could not be reached, patients under the age of 18 and those with contraindications for vaccination were excluded from our study.

The total cost of hospitalization and intervention, medication, examination, and additional services were recorded by reviewing the hospital automation system, and hospitalization costs were compared according to the recorded data.

Statistical Analysis

Data were recorded and statistically evaluated with the Statistical Package for the Social Sciences version 23 program (IBM Corp.; Armonk, NY, USA). Descriptive statistics were given as numbers and percentages for categorical variables and mean and SD for numerical variables. A chi-square test was used to determine whether if there was a significant difference between vaccination status and categorical variables, and the Student's *t*-test was used for comparisons between vaccination status, cost, and length of stay. Multiple linear regression analysis was performed to determine the functional relationship between the factors affecting the cost. $P < .05$ was considered significant.

RESULTS

The mean age of 800 patients included in our study, 400 unvaccinated, 400 vaccinated, and hospitalized in 3 hospitals for 2 years, was 68.48 ± 11.97 (68.61 ± 12.95 in vaccinated and 68.34 ± 10.92 in unvaccinated patients). There was no significant difference between the mean age of the vaccinated and unvaccinated patients ($P > .05$). Five hundred sixty-six patients (70.8 %) were aged 65 and over, and there was no significant difference between the rates of vaccinated and unvaccinated patients ($P > .05$, 69.5%, 72.0%).

There were 546 (68.2%) men and 254 (31.8%) women, of which 280 (51.0%) of the men were vaccinated and 120 (47.2%) of the women were vaccinated, and there was no statistically significant difference in gender comparison (*P*

MAIN POINTS

- Patients with pneumococcal vaccine have shorter hospital stays.
- Patients with pneumococcal vaccine have lower mortality rates.
- For these reasons, hospital costs were found to be significantly less.

Table 1. Comparison of Vaccination Status and Demographic Variables

		Total (n = 800)		Unvaccinated (n = 400)		Vaccinated (n = 400)		*P*
Variables		**n**	**%**	**n**	**%**	**n**	**%**	
Gender	Male	549	68.6	269	67.3	280	70.0	.402
	Female	251	31.4	131	32.8	120	30.0	
Age group	<65	237	29.6	125	31.3	112	28.0	.314
	≥65	563	70.4	275	68.8	288	72.0	
Mortality	Live	728	91.0	341	85.3	387	96.8	<.001
	Dead	72	9.0	59	14.8	13	3.3	
Comorbidity	No	250	31.25	149	37.25	101	25.25	<.001
	Yes	550	68.75	251	62.75	299	74.75	
Asthma	No	759	94.87	382	95.5	377	94.25	.423
	Yes	41	5.125	18	4.5	23	5.75	
COPD	No	446	55.75	242	60.5	204	51.0	.007
	Yes	354	44.25	158	39.5	196	49.0	
Pneumonia	No	500	62.5	260	65.0	240	60.0	.144
	Yes	300	37.5	140	35.0	160	40.0	
Diabetes	No	788	98.5	397	99.25	391	97.75	.141
	Yes	12	1.5	3	0.75	9	2.25	
Hypertension	No	783	97.87	384	96.0	399	99.75	<.001
	Yes	17	2.125	16	4.0	1	0.25	
Heart diseases	No	738	92.25	392	98.0	346	86.5	<.001
	Yes	62	7.75	8	2.0	54	13.5	

COPD, chronic obstructive pulmonary disease.

> .05). The mortality rate of our patients was 3.3% in the vaccinated group and much less than 15.2% in the unvaccinated group, and statistical significance was found ($P < .001$). When comparing vaccination status with additional diseases, there is a statistically significant difference between the presence and absence of additional disease, COPD, and heart disease ($P < .05$). The presence of additional disease, COPD, and heart disease rates is higher in vaccinated people (Table 1), because patients in this group are vaccinated at a higher rate.

The mean hospital stay of these patients was 11.01 days and those in the vaccinated group had an average mean hospital stay of 9.11 days and those in the unvaccinated group had a mean hospital stay less than 12.91 days ($P < .001$) (Table 2).

Total 1-year hospitalization costs were $501.653.53 and the cost per person was calculated as $627.07. The cost per capita of the vaccinated group was calculated as $550.57, which was less than the average cost of the unvaccinated group, which was $703.62 ($P < .05$).

When the factors affecting the invoice amount were examined by multiple linear regression analysis, the status of being vaccinated, length of stay, mortality, and heart disease were statistically significant ($P < .05$). It was observed that the status of being vaccinated, having less length of stay, having low mortality, and not having heart disease significantly reduced the cost of hospitalization (Table 3).

DISCUSSION

The costs of diseases are evaluated in 2 groups, direct and indirect costs. Indirect costs include costs resulting from loss of workforce and productivity due to disease-related restrictions, disability, and premature death, while direct costs include medication, diagnostic methods, follow-up, outpatient, emergency room, and hospitalization. Hospitalization

Table 2. Vaccination Status vs. Length of Stay and Cost

	Total (n = 800)		Unvaccinated (n = 400)		Vaccinated (n = 400)		*P*
Variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Cost	3781.8454	5673.1697	4231.6153	6805.4092	3332.0756	4210.8405	0.025
Length of stay	10.76	12.67	12.41	15.71	9.11	8.34	<0.001

Table 3. Multiple Linear Regression Analysis of Factors Affecting the Cost

Independent variables	*B*	SE	Beta	*t*-Test Value	*P*
Vaccination	–899.540	400.140	–0.079	–2.248	.025
Gender	546.723	432.100	0.045	1.265	.206
Age	-6.582	17.212	-0.014	-0.382	.702
Length of stay	354.963	9.653	0.793	36.773	.000
Mortality	1437.879	699.462	0.073	2.056	.040
Comorbidity	–347.824	432.828	–0.028	–0.804	.422
Asthma	61.154	910.183	0.002	0.067	.946
COPD	–813.639	403.058	–0.071	–2.019	.044
Pneumonia	455.457	414.256	0.039	1.099	.272
Diabetes	876.040	1650.868	0.019	0.531	.596
Hypertension	–1980.663	1389.906	–0.050	–1.425	.155
Heart	1616.880	748.432	0.076	2.160	.031

COPD, chronic obstructive pulmonary disease.

costs constitute the most important part of the direct health costs.[12] Pneumococcal infections are a very important cause of mortality and morbidity in chronic lung diseases. The hospitalization rate in patients with CAP varies between 30% and 60%.[13,14] It has also been reported that more than 95% of the treatment costs of CAP are due to hospitalized patients.[13]

The most important factor for cost is the length of stay in the hospital. Other factors include the treatment applied and the patient's compliance with the treatment.[15,16] International studies have reported that the length of stay varies between 5 and 11 days.[17-20]

Our study found high hospitalization times of 10.76 days on average: 9.11 and 12.41 days in vaccinated and unvaccinated patients, respectively. We can attribute this situation to the fact that the centers where the study took place were branch hospitals, and most patients were patients with respiratory failure who may require oxygen or non-invasive mechanical ventilation support.

In the study of Ortaköylü et al.[21] 1-year activity-based costs related to COPD were calculated and found to be US$3 839 788.32. Annual expenditure for inpatients has been reported to be US$2 531 290.91 (630.14 USD per person = 959.70 TRY) for 4017 COPD patients with social security institute (SSI) prices.

Different studies have shown that patients with COPD and pneumonia have increased rates of intensive care unit (ICU) hospitalization, ICU length of stay, and 30- and 90-day mortality compared with those without pneumonia.[22,23] These studies reveal the significant disease burden caused by pneumonia in COPD patients.[24]

The pneumococcal vaccine is indicated for adults who are at risk for pneumonia or who may have serious adverse consequences if they contract pneumococcal pneumonia. In order to prevent pneumococcal diseases, although the recommended groups for vaccination are determined by the guidelines and the vaccines are paid for by the health authorities, the vaccination rates in chronic lung diseases in Turkey are at very low levels as in the rest of the world. At the same time, it was stated that vaccination awareness was low, and the factor most cited as the cause of not being vaccinated was not being recommended by doctors.[25]

Vaccination has significantly reduced the burden of infectious diseases worldwide. Considering that there are limited resources for health services, determining the necessary strategies and taking steps in this direction are important in terms of using health resources efficiently.[26]

Every extra day spent in the hospital will increase the total cost. Our study revealed that vaccinating patients hospitalized in chest disease hospitals with the pneumococcal vaccine reduced the average hospital stay by 41.7% and the cost of hospitalization by 27.8%. If all hospitalized patients had pneumococcal vaccination, 1518 hospitalization days would have been gained annually. Moreover, SSI would have paid less for these patients, totaling 8958.02$ per year. In order to reduce the burden on the health system, preventive medicine practices and public health planning should be done correctly and put into action. Treatment of respiratory diseases such as COPD and asthma, taking necessary measures to reduce attacks, and raising awareness of patients on this subject will reduce direct and indirect costs by preventing the progression of the disease and the loss of workforce, as well as reducing hospitalizations. Here, vaccination prevents both the exacerbation of the disease and the more severe course of the disease in patients who need hospitalization, helping them to be discharged as soon as possible. Improving home care facilities will reduce the number of emergency services applications and the total cost.

In terms of factors affecting the cost of our study, intensive care admissions were not taken into account since the results of comorbidity and bacteriological analysis were missing. The effect on mortality rates in hospitalized patients could not be found. The effect of pneumococcal vaccination on hospitalization rates could not be investigated.

Ethics Committee Approval: This study was approved by the University of Health Sciences Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Board and Hospital Ethical Committee (01.11.2018/2018-32).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Review

Home-Based Physiotherapy and Rehabilitation in Patients with Idiopathic Pulmonary Fibrosis: A Review

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Abstract

The objective of the study is to review the studies on home-based pulmonary rehabilitation practices in idiopathic pulmonary fibrosis patients in the last 5 years. Home-based randomized controlled trials in idiopathic pulmonary fibrosis patients published in the PubMed database within the previous 5 years were searched. As a result of the research, a total of 5 articles were included in the study. Five home-based rehabilitation practices used in these articles were reached. Totally, 176 patients were found to have participated in these programs. As a result, patients who have difficulty accessing hospital-based rehabilitation services due to various reasons will benefit from home-based rehabilitation services. However, the content of the home-based program and the method of follow-up and supervision affect the results.

KEYWORDS: Home-based rehabilitation, idiopathic pulmonary fibrosis, pulmonary rehabilitation
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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF), one of the forms of interstitial pneumonia, is a chronic disease. It is characterized by progressive alveolar interstitium fibrosis, causing permanent lung damage, generally seen in advanced ages, and with a poor prognosis.[1] Idiopathic pulmonary fibrosis causes severe mortality and morbidity in patients, and the life expectancy after diagnosis is approximately 3-5 years.[2] In the literature, the incidence of IPF varies between 0.22 and 16 per 100 000 individuals.[3-5] To diagnose IPF, other idiopathic interstitial pneumonia, autoimmune diseases, drugs, and occupational and environmental causes that can make the unusual interstitial pneumonia pattern should be excluded.[2] In the clinical picture of IPF patients, advanced progressive dyspnea, cough, deterioration in pulmonary function, and recurrent coughs are frequently observed. All these symptoms cause fatigue and a decrease in exercise capacity, sleep capacity, and participation in activities of daily living. As a result, depression, anxiety, dissatisfaction with life, and emotional disorders occur in IPF patients, and their quality of life deteriorates over time.[6]

Idiopathic pulmonary fibrosis treatment aims to improve the patient's symptoms and health status, protect lung function, reduce oxygen demand, reduce the frequency of acute exacerbations, and increase the patient's quality of life.[7] Treatment applications based on symptom management consist of pharmacological management, rehabilitation applications, palliative care, and transplantation.[8] Lung transplantation is preferred in patients who do not respond to medical treatment.[9] Pharmacological management consists of antifibrotic drugs used to reduce disease progression and functional losses, antacid therapy drugs, steroid-based drugs used in cough management, and bronchodilators.[10,11] In addition, rehabilitation practices, including patient education, exercise training, respiratory therapy, smoking cessation, and psychosocial support, are of great importance in symptom management.[12]

It has been shown in the literature that a decrease in respiratory rate, an increase in tidal volume and oxygen saturation, an improvement in cardiac capacity, an increase in quadriceps fatigue resistance, an increase in the efficiency of skeletal muscle function at the cellular and molecular levels, and an improvement in dyspnea, exercise capacity, and quality of life are observed with pulmonary rehabilitation applications.[13-15] Endurance exercises, resistance exercises, neuromuscular electrical stimulation (NMES) applications, respiratory muscle training, energy conservation techniques, tai chi, and whole-body vibration training methods can be used in IPF rehabilitation.[16] In the literature, it has been suggested that endurance exercises, which can be done in the form of cycling, walking, treadmill, climbing stairs, and combinations of all these, should be performed at 60%-70% of the maximum working capacity for at least 20 minutes 3-5 times a week in IPF patients. In addition, it will be safe to give oxygen support during exercise.[17,18] For strengthening exercises, high-intensity interval training is recommended for this patient group. In addition to all these, stretching and stretching exercises, and lower and upper extremity exercises can be performed.[18]

The positive effects of pulmonary rehabilitation programs on functional outcome parameters such as dyspnea, exercise capacity, and health-related quality of life have been investigated and proven mostly in patients with chronic

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obstructive pulmonary disease (COPD). However, it has been accepted that exercise programs should be adapted to the daily life of the patient in order to maintain the positive effects of the supervised pulmonary rehabilitation program.[19] Home-based programs are a viable option for pulmonary rehabilitation in daily life. In addition, these programs are effective, useful, simple, inexpensive, practical, and equivalent to inpatient/outpatient treatment programs.[20]

This study aims to review the studies on home-based pulmonary rehabilitation practices in IPF patients in the last 5 years.

MATERIAL AND METHODS

In this review, research was conducted on the studies conducted in the last 5 years in the PubMed database. While conducting the investigation, the keywords "Idiopathic Pulmonary Fibrosis and Rehabilitation," "Idiopathic Pulmonary Fibrosis and Exercise," and "Idiopathic Pulmonary Fibrosis and Home-Based Rehabilitation" were used. No limits were set in terms of age and gender in the study, but randomized controlled studies were examined.

Inclusion Criteria

It was determined that the study was published in the last 5 years and was in a randomized controlled study design, only IPF patients were included, and it was conducted only on home-based pulmonary rehabilitation practices, the study language was English, and full-text access was available.

Exclusion Criteria

As the study's exclusion criteria, non-home-based studies that evaluate the effectiveness of practices other than pulmonary rehabilitation (transplantation, pharmacological therapy, oxygen therapy, etc.), include patients with different pathologies and focus on various pathologies other than symptoms of IPF patients.

MAIN POINTS

- There is a need for home-based rehabilitation programs in patients with idiopathic pulmonary fibrosis due to some reasons, such as difficulty in accessing rehabilitation services, risk of infection, and reduced and difficult mobility.
- Some of the home-based rehabilitation practices used in idiopathic pulmonary fibrosis rehabilitation are as follows: deep breathing exercises, telerehabilitation program, including physical exercises and a patient education program, a neuromuscular electrical stimulation application, walking bike use, and Wii exercise game applications.
- Regular follow-up of patients in home-based programs directly affects patient compliance and results.
- Patient compliance problems are more common in home-based rehabilitation programs that require materials.
- The literature on the effectiveness of home-based exercise programs in idiopathic pulmonary fibrosis patients is weak, and studies with different rehabilitation methods and study protocols are needed.

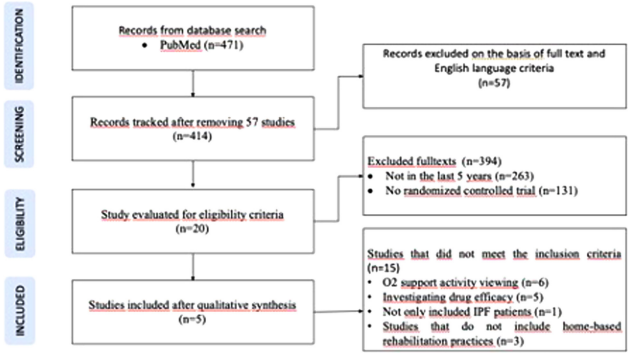


Figure 1. Flow chart showing the follow-up and inclusion process of the articles in the review.

RESULTS

As a result of this research, a total of 471 studies were reached. First, when non-full-text and non-English studies were excluded, the research continued with a total of 414 studies. Then, a total of 20 studies were selected according to the inclusion criteria of being a randomized controlled study published in the last 5 years. A total of 5 studies were included in the study by reading the full text of all these studies and considering the inclusion and exclusion criteria (Figure 1). A total of 176 patients participated in the included studies. The patient ages in the studies ranged from 65 to 77 years. A different home-based rehabilitation method was applied in all studies. These home-based rehabilitation practice studies include deep breathing exercises (n = 1), telerehabilitation programs, including physical exercises and patient education program applications (n = 1), NMES application (n = 1), walking bike using (n = 1), and Wii exergame program (n = 1). All studies were followed up with an exercise diary (n = 5).

Quality of life and functional performance were evaluated in all included studies. Exercise capacity was evaluated with the 6-minute walk test (6MWT) in 5 studies. Only 1 study evaluated the patients' 7-day pedometer data in addition to the 6MWT. St. George's Respiratory Questionnaire (SGRQ) was used for quality of life assessment in 4 studies and King's Short Interstitial Lung Disease Questionnaire (K-BILD) in 3 studies. Dyspnea was evaluated in only 1 of the studies, and the Borg scale was used in the evaluation. Only 1 study evaluated lung volume by x-ray. Respiratory function tests were performed in 3 studies. While forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO) were measured in 2 studies, forced expiratory volume in the first second (FEV1) was measured in addition to these in 1 study. The main results of the study are given in Table 1.

DISCUSSION

The effectiveness of pulmonary rehabilitation practices in symptom management in IPF patients has been demonstrated in the literature.[13] The need for home-based rehabilitation programs is increasing due to reasons, such as difficulty in accessing rehabilitation services, risk of infection, and reduced and difficult mobility.[21] Especially during the pandemic, the arrival of respiratory patients to the clinical environment increases the risk of infection.[22] For these reasons,

Table 1. Design of Included Studies, Participant Characteristics, Evaluation, Intervention, and Outcome Characteristics

Author, Year, Country, Study Design	Patient Characteristics (Group, Number, Age, Gender Ratio (Male/Female), BMI (kg/m²))	Intervention	Duration and Frequency	Supervision of the Implemented Home Program	Outcome Measurement	Evaluation and Following Times	Outcomes	Total Number of Patients Completing the Study	Key Points
Shen et al[23], China, RCT	RG (n = 39), 65 ± 6, 37/2, 24 ± 3 CG (n = 43), 65 ± 8, 40/3, 25 ± 3	RG: deep breathing exercises from a video recording + current therapy CG: current therapy	12 months/ every day/3 times/9 minutes	• Via CD	• Lung volume (x-ray) • Respiratory function (FEV1, FVC, DLCO) • Quality of life (SGRQ) • Walking distance (6MWT) • ECG	• Beginning • Month 6 • Month 12	At 6 months: • FVC, FEV1, DLCO, and SGRQ results changed significantly in the exercise group • 6MWT was improved in the exercise group, but there was no significant difference between it and the control group. • In the 12th month, respiratory functions and quality of life outcomes were better in the exercise group • The decrease in walking distance was less in the exercise group	• Sixth month 30 patients • 12th month 59 patients • 6th and 12th months 20 patients	The number of acute exacerbations and mortality rates were found to be lower in the exercise group compared to the control group.
Cerdán-de-Las-Heras et al[24], Denmark, RCT	RG (n = 15), 70 ± 9, 13/2 CG (n = 14), 72 ± 8, 8/6,	RG: telerehabilitation (e-learning packages, correspondence sessions, physical exercises via the app) + ordinary care CG: ordinary care without rehabilitation	12 weeks/3-5 times a week/10-20 minutes	• Via VAPA App (first 3 months)	• Exercise capacity [6MWT, pedometer (7 days)] • Quality of life (SGRQ, K-BILD, GAD7) • Respiratory function tests (FVC, DLCO) • Telerehabilitation satisfaction survey • Weekly working days and hours	• Beginning • Month 3 • Month 6 • Month 9	High patient compliance, exercise capacity preserved No change in quality of life, pulmonary function tests and walking distance	• Third month 22 patients • Sixth month 22 patients • Ninth month 21 patients	A useful technology for a physically active lifestyle in IPF patients

(*Continued*)

Table 1. Design of Included Studies, Participant Characteristics, Evaluation, Intervention, and Outcome Characteristics (*Continued*)

Author, Year, Country, Study Design	Patient Characteristics (Group, Number, Age, Gender Ratio (Male/Female), BMI (kg/m²))	Intervention	Duration and Frequency	Supervision of the Implemented Home Program	Outcome Measurement	Evaluation and Following Times	Outcomes	Total Number of Patients Completing the Study	Key Points
Nolan et al[25], United Kingdom, RCT	RG (n = 11), 76, 7/4, 24.2 CG (n = 11), 77, 8/3, 25.2	RG: NMES (bilateral quadriceps) + home exercises CG: placebo NMES + home exercises	6 weeks/ every day/30 minutes	• Brochure • Manual • Introductory training (40 min) • Weekly Phone Call	• Exercise capacity (6MWT) • Functional performance (short physical performance battery) • Rectus femoris length • Quality of life (K-BILD) • Physical activity parameters (step count, sedentary time, 4 m walking speed)	• Beginning • Month 6 • Month 12	Patient compliance is poor At the end of the 12th week, an increase in the rectus femoris cross-sectional area, improvement in daily living activities related to self-care, decrease in sedentary time and increase in the time allocated to physical activity in the exercise group	• Sixth week 18 patients • 12th week 19 patients	Side effects associated with the use of NMES were seen in the study group. It was concluded that the study protocol was not suitable for the evaluation of NMES activity.
Wapenaar et al[26], Denmark, RCT (crossover)	RG: (n = 12) 71, 18/5 CG: (n = 11)	RG: walking bike + standard treatment CG: standard treatment + walking bike	8 weeks/ every day/60 min	• Initial training	• Respiratory function tests (FVC, DLCO) • Exercise capacity (6MWT, O_2 saturation, number of steps per day) • Quality of life (SGRQ, K-BILD, GAD-7, perceived quality of life scale)	• Beginning • Week 9 • Week 18	Poor applicability with a large number of patients, increase in quality of life, increase in mobility, no change in functional exercise capacity	• Eighth week 16 patients • 16th week Ten patients	Although it has been shown to be effective on quality of life, problems such as the suitability of environmental conditions, comfort of use, and unwillingness to use assistive devices have been reported in patient reports.
Yuen et al[27], United Kingdom, RCT	RG: (n = 10) 67 ± 7, 5/5, 28 ± 5 CG: (n = 10) 72 ± 8, 8/2, 28 ± 4	RG: Wii Fit exergames CG: Wii video games	12 weeks/3 days a week/30 minutes	• Follow-up by phone (1 per month)	• Functional capacity (6MWT) • Dyspnea (Borg scale) • Quality of life (SGRQ)	• Beginning • Week 12	Low rate of attendance (20%), deterioration in 6DKYT and SGRQ results in both groups, improvement in dyspnea score in the exercise play group	• 12th week 20 patients	–In the case group, 3 patients never used the exercise game, 5 patients used it for 9 weeks or more.

6MWT, 6 minutes walking test; BMI, body mass index; CG, control group; DLCO, carbon monoxide diffusion capacity; ECG, electrocardiogram; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; GAD-7, Generalized Anxiety Disorder Scale; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; NMES, neuromuscular electrical stimulation; RCT, randomized controlled trial; RG, rehabilitation group; SGRQ, St. George's Respiratory Questionnaire.

it is of great importance to evaluate and prove the effectiveness of home-based pulmonary rehabilitation studies.

In 2021, Shen et al[23], in a study conducted by 82 patients for a total of 12 months, the pulmonary rehabilitation approach, including basic breathing exercises, was found to be easy and cost-effective for IPF patients, and it was shown that it could help pulmonary rehabilitation. The patients were given a home program including deep breathing exercises 3 times a day. These exercises contain deep breath of whole lung, unilateral lower lung, and upper lung movement sets. At the end of the sixth month, the patients' respiratory functions and quality of life were improved, and at the end of the twelfth month, when compared with the control group, there was an improvement in lung volume and 6-minute walking test in addition to the parameters in the sixth month.[23]

In another study conducted by Cerdán-de-Las-Heras et al[24] in 2021, the effectiveness of telerehabilitation on exercise capacity in IPF patients was evaluated. This telerehabilitation study, which used video consultation, e-learning packages, correspondence sessions, VAPA application, working hours, and questionnaires, continued for 12 weeks under the guidance of a physiotherapist. Then the patients continued to use the application alone. Within the program, the patient was given training, and in the content of the exercise program, personalized weights, step board, and exercises with elastic bands were used. Exercise intensity is 10-20 minutes, 3-5 times a week, under the therapist's guidance. As a result of this study, the telerehabilitation program with the VAPA application was found to be beneficial for IPF patients. While the exercise capacity decreased in the control group from the beginning, it was preserved in the exercise group. However, there was no change in the quality of life and 7-day pedometer measurements. Patient compliance with telerehabilitation was found to be high, and so its use in IPF patients may be beneficial.[24]

In Nolan et al[25], 22 patients were included in the study, in which the effectiveness of NMES was applied to the quadriceps muscle in IPF patients. In addition to the personalized home-based exercise program for 6 weeks, the patients were given a home-based application of bilateral quadriceps stimulation to the quadriceps muscle for 30 minutes a day for 6 weeks with the Kneehab XP device. The patients were followed up by phone. At the end of the study, it was observed that the patients' compliance with the program was not good. At the end of the 12th week, it was observed that the time spent by the exercise group on physical activity was more than the control group.[25]

In Wapenaar et al[26], a study conducted in 2020, it was reported that a home-based exercise program with a walking bike was beneficial in IPF patients. The walk bike is an ambulation aid, a form of a bicycle but without pedals. In the study, it was shown that the exercise program applied using a walking bike for 1 hour a day for 8 weeks in 2 groups of 23 people provided a significant increase in the quality of life of IPF patients and increased the mobility of the patients. However, after this application, there was no change in the patients' exercise capacity. It may be challenging to carry out the study with a large number of patients, and only 10 patients were able to apply the entire protocol.[26]

In 2019, Yuen et al[27], the study conducted by IPF to evaluate the compliance and effectiveness of a home-based exercise game program for IPF patients, the Wii Fit exergame program was applied for 12 weeks, 3 days a week for 30 minutes, and the Wii video game program was applied to the control group. The participants in the video game control group differed from those in the exergame intervention group was not having the Wii U Balance Board. The home-based exercise game intervention for patients with IPF showed no improvement in functional performance, shortness of breath, or health-related quality of life at the end of the 12-week program in either of the 2 heterogeneous groups. In addition to the following low rate, insufficient frequency and duration of exercise games were thought to contribute to the lack of improvement.[27]

Three studies included in the research examined the effect of home-based exercise programs on respiratory function parameters. In a study in which long-term follow-up was carried out that included deep breathing exercises, it was observed that the respiratory functions of the patients improved.[21] It has been shown in the literature that breathing exercises are effective on dyspnea and quality of life.[28] In a case study with long-term follow-up conducted by Naranjo-Orellana and Santalla[29] in 2020, it was reported that a supervised and systematic rehabilitation program, including inspiratory muscle training, could effectively improve functional performance and quality of life for IPF patients. In another study conducted in 2008 to evaluate the effectiveness of inspiratory muscle training in IPF patients, it was shown that adding this training to the pulmonary rehabilitation program was also effective on pulmonary function tests. However, no other study evaluating the effectiveness of deep breathing exercises in IPF patients could be found.[30] Pulmonary function test results were also evaluated in studies that included telerehabilitation and walking bicycle applications, but no change was observed.[24] The reason for this situation may be related to the compliance problem and non-use of the walking bike. In the telerehabilitation study, there was no improvement in pulmonary function parameters, but the current status of the patients was preserved.[22] Since IPF is a progressive disease, the preservation of the patient's current respiratory parameters shows the effectiveness of the therapy method.

In all of the studies included in this review, 6MWT was used to evaluate exercise capacity and walking distance. This test is simple to use in individuals with cardiopulmonary disease and provides information about the patient's exercise limitation. It is strongly correlated with the increased risk of hospitalization and mortality.[31] Previous studies in the literature have shown that 6MWT is a valid and useful tool for the management of patients with IPF.[32] In the study of Yuen et al[27], 6MWT data of the Wii exergame group deteriorated over time. However, when the investigation is examined, it is a low value that the patients' compliance with the program is 20%. Idiopathic pulmonary fibrosis is a progressive disease, and if the exercise program is not done regularly, it is possible result that its effectiveness will not be seen. In the

study of Shen et al[23], it was shown that home-based deep breathing exercises increase exercise capacity and walking distance in IPF patients. Leelarungrayub et al[33] The results of this study support Shen et al's[23] study, although it is a different group of pulmonary diseases. When we evaluated other studies included in this review, it was seen that there was no change in 6MWT results in general. This shows that a home-based exercise program is effective in a progressive disease such as IPF.

In all the studies included in the research, the quality of life assessment of the patients was assessed through questionnaires. In 3 of the 5 studies we reviewed, it was reported that there was an increase in the patients' quality of life after home-based rehabilitation practices. It has been shown in the literature that pulmonary rehabilitation practices increase the quality of life of patients, which supports the literature.[34,35] In the study that included the Wii exergame, it was observed that the patients' quality of life decreased. This situation may be associated with low compliance with the study. In the study that included telerehabilitation, there was no change in the quality of life parameters of the patients.

When the general results were examined, it was seen that the patients progressed in various areas compared to other studies in the study that included deep breathing exercises.[21] One of the reasons for this may be that the study was conducted for 12 months, longer than other studies. Another reason may be that the patient has a video recording they can use as a supervisor while exercising daily in the study of Shen et al.[23] Further studies in this area are needed to understand the cause.

When the study results were examined, it was thought that the adaptation and continuity to the home-based programs were low in general.[23-25] To increase the effectiveness of rehabilitation in home-based programs and to ensure patient compliance, follow-up programs and supervision should be well done. The reason for the low patient compliance may be inadequate follow-up programs or the supervision method. In the studies within this review, exercise diaries were given to all patients for follow-up, and the patients were supervised with different methods. In studies where follow-up was done by telephone, it was observed that compliance problems were more common.[23,25] Although compliance is high in telerehabilitation practice, there has been no improvement in outcomes in most areas. This may be due to patient differences.

In addition, when the studies were evaluated, it was thought that the results were not as expected because the patients did not comply with the study protocol in the rehabilitation programs applied at home using a material (Wii game console, NMES device, walking bike).[23-25] Device-specific reasons, such as patients not wanting to use the walking bike for social reasons or encountering the side effects of NMES application while applying it at home may cause this situation.

CONCLUSION

As a result, home-based rehabilitation approaches can be applied, especially for IPF patients who have difficulty accessing rehabilitation practices during the pandemic period, who have the risk of infection, and who do not want or cannot go to the hospital for rehabilitation services. However, continuity is essential for the benefit of patients. Appropriate supervision methods should be preferred, and patient follow-up should be done to ensure the sustainability of the program and patient continuity. In addition, the literature on the effectiveness of home-based exercise programs in IPF patients is weak and more publications are needed by practicing different rehabilitation methods and study protocols.

There are many limitations in this review. First of all, the fact that we used a single database while conducting research shows that we have done limited research in the literature. As a result of the examination, according to the inclusion and exclusion criteria in the review, a total of 5 studies were included. The small number of these is one of the limitations of the research. We believe that the inclusion of studies conducted in the last 5 years has caused this situation. First of all, the reason why we used the studies from the last 5 years in the study is that we want to present the current literature. In addition, studies with home rehabilitation in rare diseases such as IPF in the literature before the coronavirus disease-2019 pandemic are very limited. However, the use of a different home-based rehabilitation application in all the studies we included in the review was a disadvantage in terms of combining and supporting the results. Thanks to this situation, we had the opportunity to compare the effects of different home-based approaches on the same parameters. Another limitation is the heterogeneity of the patient groups in the included studies and the insufficient numbers. The lack of literature in this area and the inadequacy of studies on home-based exercises in IPF patients may be the reason for this situation. One of the limitations of the research is that one of the randomized controlled studies we included in the review was in a crossover design. Our reason for inclusion is that the study focuses on a different home-based rehabilitation approach.

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Case Report

A Postpartum Immigrant with Pulmonary, Pleural, and Intestinal Tuberculosis

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Abstract

Intestinal tuberculosis is a rare extrapulmonary condition and mainly involves the ileocecal region. Most of the patients with tuberculosis during the postpartum period present with extrapulmonary involvement. The postpartum period has a higher risk of the reactivation of tuberculosis due to changes in the immune system. We present the case of a 22-year-old postpartum immigrant patient, with pulmonary, pleural, and intestinal tuberculosis with intestinal perforation. Due to the nonspecific symptoms of intestinal tuberculosis, clinical suspicion is extremely important.

KEYWORDS: Intestinal tuberculosis, pleural tuberculosis, postpartum tuberculosis, pulmonary tuberculosis
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INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is one of the top 10 causes of death worldwide. According to the World Health Organization, in 2019, 10 million people were diagnosed with TB and 1.2 million lost their lives from this preventable and curable disease.[1] Extrapulmonary TB is diagnosed in almost 20% of all TB cases, while abdominal TB is approximately 10% of all extra-pulmonary TB.[2,3] Abdominal TB may involve the gastrointestinal tract, peritoneum, lymph nodes, and genitourinary tract.[4] The ileocecal area is the most common site of involvement in gastrointestinal TB. Severe complications such as bowel obstruction, perforation, or fistula formation can occur. Because of the nonspecific presentation, clinical suspicion is of utmost importance for the diagnosis of intestinal TB. We present the case of a 22-year-old postpartum immigrant patient, with pulmonary, pleural, and intestinal TB with intestinal perforation.

CASE REPORT

A 22-year-old immigrant female, with no significant medical history, presented to the emergency department with complaints of cough, dyspnea, loss of appetite, and fatigue. She gave birth 15 days ago. She was born and lived in a TB-endemic country. On admission, she was cachectic and in respiratory distress. Her heart rate and respiratory rate were 120 beats per minute and 25 breaths per minute, respectively. On chest auscultation, she had bilateral fine rales. Laboratory work-up showed anemia (hemoglobin 5.7 g/dL), hypoalbuminemia (19.3 g/L), mild elevation of aspartate aminotransferase (86 U/L), elevated lactate dehydrogenase (593 U/L), and elevated C-reactive protein (160 mg/L). The HIV test was negative. Her initial chest computed tomography (CT) revealed bilateral hilar and mediastinal lymphadenopathy, bilateral pleural effusions, and patchy consolidation areas (Figure 1A). Additionally, abdominal CT showed a small amount of ascites at the perihepatic and perisplenic regions.

Her sputum smear was negative for acid-fast bacilli (AFB). Thoracentesis and bronchoscopy were performed. The pleural fluid AFB smear was negative, and the adenosine deaminase level was 19.8 IU/L. While we were waiting for the other results of the thoracentesis and bronchoscopy procedure, the patient had severe abdominal pain and distension. Abdominal CT revealed multiple para-aortic and para-caval enlarged lymph nodes, air-fluid levels in the bowel at lower quadrants, and free fluid in the Douglas pouch (Figure 1B). Ileal perforation was observed in many areas in explorative laparotomy, and she underwent primary repair. In the postoperative period, pleural fluid PCR was found to be positive for *Mycobacterium tuberculosis*. Also, the bronchoalveolar lavage smear was positive for AFB.

The patient was given oral anti-tuberculosis drug therapy consisting of isoniazid 300 mg once daily, rifampicin 450 mg once daily, pyrazinamide 1000 mg once daily, and ethambutol 1000 mg once daily. After 2 weeks of antituberculous therapy, her symptoms improved. All TB drugs were stopped 19 days after it started since the aspartate aminotransferase level was 55 U/L and the alanine aminotransferase level was 108 U/L. After 8 days, liver function tests returned to normal, and the treatment was restarted. Anemia investigation demonstrated a positive fecal occult blood test. Colonoscopy and endoscopy revealed normal findings. During these procedures, no lesion, bleeding focus, or complication was recorded. Furthermore, no biopsies were performed throughout these procedures. Because of the right lower quadrant pain and tenderness, abdominal

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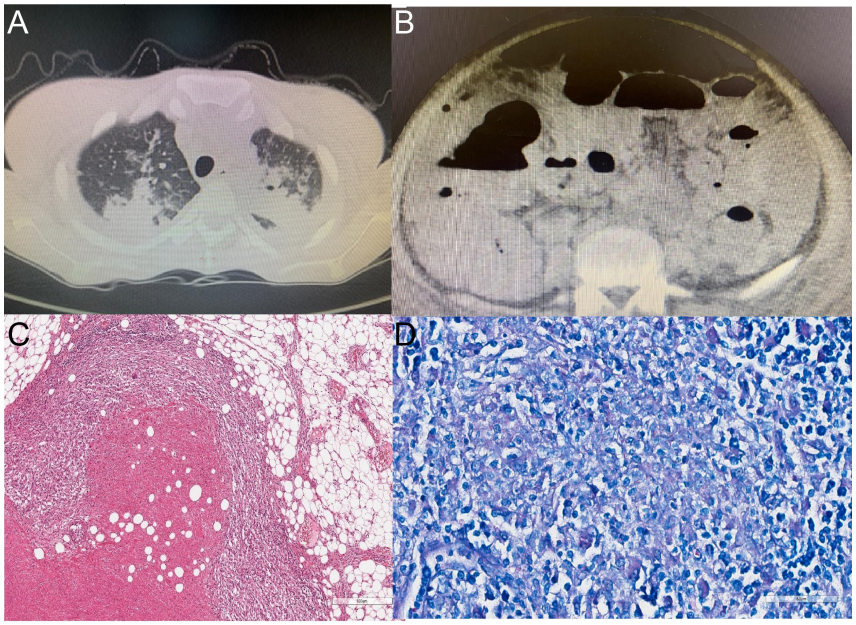


Figure 1. (A) Axial image from thorax computed tomography (CT) revealed bilateral consolidation and pleural effusion. (B) Abdominal CT revealed air-fluid levels in the bowel at lower quadrants and free fluid in the Douglas pouch. (C) Small intestinal wall with typical tuberculous granuloma consisting of well-defined cluster of epitheloid cells with central caseous necrosis and Langerhans giant cells (hematoxylin & eosin staining, ×600). (D) Ziehl–Neelsen stain reveals multiple acid-fast bacilli in the intestinal mucosa.

ultrasound was done. Abdominal ultrasound showed abscess formation in the pelvis and dilatation in bowel loops. In emergent explorative laparotomy, pelvic abscess and multiple perforations in the terminal ileum and cecum were detected. The pelvic abscess was drained, and ileal resection and right hemicolectomy were performed. Histopathological examination showed granulomatous inflammation with caseification necrosis with AFB-positive bacilli (Figure 1C and 1D). *Mycobacterium tuberculosis* culture was verified in the bronchoalveolar lavage, and no resistance was detected in the drug susceptibility test. Antituberculous treatment was reinitiated after the operation. Despite intensive surgical and medical treatment, the patient passed away.

DISCUSSION

Intestinal TB mostly affects younger adults, and living in an endemic region for TB is an important clue for the diagnosis. The diagnosis of TB requires bacteriological or histopathological confirmation. The coexistence of abdominal TB and pulmonary TB is approximately 15%-25%.[5] The bronchoalveolar lavage of our patient stain was positive for AFB, and additionally, pleural fluid PCR was found to be positive for *Mycobacterium tuberculosis* despite the AFB smear of pleural fluid being negative. This was compatible with the knowledge that the positivity of pleural fluid microscopy for TB is less than 10% and nucleic acid amplification tests on pleural fluid have a sensitivity of 62%-76.5% and specificity of 91%-98%.[6,7] Intestinal involvement in our patient was confirmed by histopathological examination.

Abdominal TB may involve any part of the gastrointestinal tract, peritoneum, genitourinary tract, and lymph nodes, but more common locations are the peritoneum, intestines, and liver.[5] In our patient, the disease involved the ileocecal area which is the most frequent site of involvement in the gastrointestinal tract.[3] According to the Turkish Ministry of Health's 2020 TB report, gastrointestinal and peritoneal involvement are approximately twice as common in women as in men. Gastrointestinal and peritoneal TB cases are 35.4% and 64.6% in men and women, respectively, according to this report.[8] Because of the vague symptoms and clinical presentations, the definitive diagnosis of intestinal TB is challenging. Clinical and radiological findings of abdominal TB are nonspecific. The symptoms are abdominal pain generally at the right lower quadrant, diarrhea, weight loss, anemia, and fever. Intestinal obstruction, perforation, bleeding, and fistula formation can be seen as complications.[4,9] Our patient underwent laparoscopy for intestinal perforation twice and also pelvic abscess formation was detected.

In most cases of intestinal TB, ulcerative lesions (53%) are detected in colonoscopy, and colonoscopy may be normal in some individuals as in our patient.[10,11] Trauma, obstruction, and tumors are the most frequent causes of intestinal perforation in developed countries; however, infections including TB are more frequently seen in developing countries. Crohn's disease, ischemia, iatrogenic causes, foreign bodies, and small bowel diverticulitis are the less common causes.[12]

Our patient became symptomatic on the 15th day after delivery with pleural and intestinal TB besides pulmonary TB and she died despite antituberculous therapy. Cheng et al[13] found that 93% of the postpartum TB cases presented with extrapulmonary involvement. They also reported 38% mortality for postpartum TB. The risk of extrapulmonary TB increases with advancing immunosuppression. Many extrapulmonary TB cases are associated with HIV infection. Our patient's HIV result is negative, but she was in postpartum period which may be a risk factor responsible for immunosuppression. It has been shown that infections and noninfectious diseases with an autoimmune basis may begin or progress during the postpartum period.[14] As a result of the immunosuppression

during pregnancy, TB is less symptomatic in pregnant women. After delivery, the lymphocytic proliferative response rapidly returns to normal. Reversal of T-helper function after pregnancy may result in the appearance of new symptoms or worsening of the former symptoms.[13]

CONCLUSION

Although nonspecific symptoms can be confusing in the diagnosis, extrapulmonary TB should be considered in every patient in the postpartum period and living in developing countries. In the suspicion of extrapulmonary TB, pulmonary TB coexistence must be researched.

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

Peer-review: Externally peer-reviewed.

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