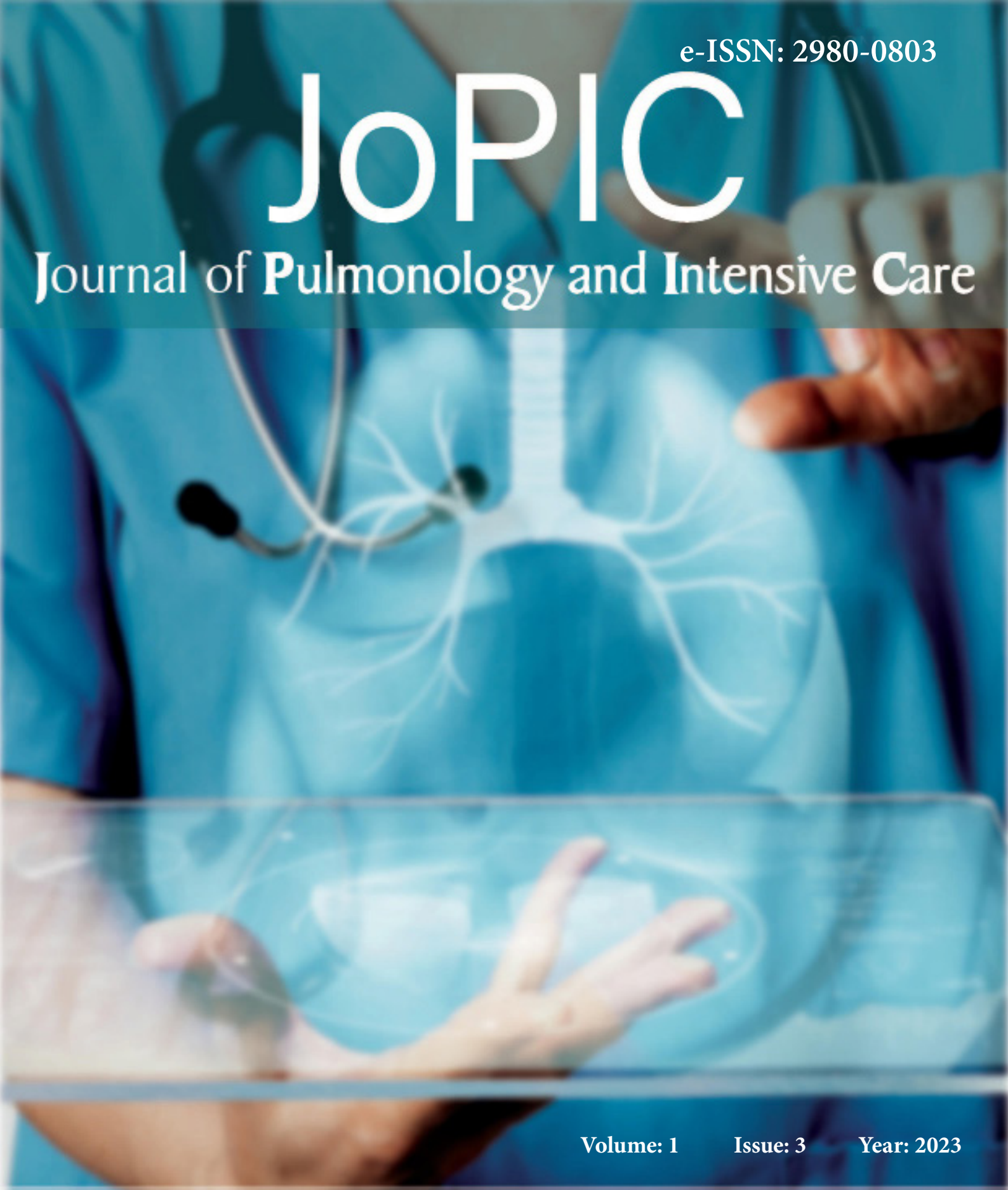
e-ISSN: 2980-0803

JoPIC

Journal of Pulmonology and Intensive Care



Volume: 1 Issue: 3 Year: 2023

MHA
MEDIHEALTH ACADEMY

Journal of
Pulmonology and
Intensive Care

EDITORIAL BOARD

EDITOR-IN-CHIEF

ASSOCIATE EDITORS-IN-CHIEF

EDITORS

EDITORIAL BOARD

Journal of
Pulmonology and
Intensive Care

EDITORIAL BOARD

EDITORIAL BOARD

Journal of
Pulmonology and
Intensive Care

EDITORIAL BOARD

Journal of
Pulmonology and
Intensive Care

EDITORIAL

Dear Colleagues,

As of August 2023, we have published the third issue of Journal of Pulmonology and Intensive Care (JoPIC) under the shield of Medihealth Academy. In addition to all researchers, referees an deditorial board who contributed to the preparation of the journal; we would like to thank the printing team for their effort in preparing it for publication. This third issue includes two original research, two review article and two case report. Periodicals are popular with their readers and researchers. In the upcoming period, with your support, our goal is for JoPICto be indexed in nationally and internationally accepted scientific indexes. I would like to thank you in advance for your contribution.

Assoc. Prof. Dr. Berna Akıncı Özyürek
Editor in Chief

Journal of
Pulmonology and
Intensive Care

CONTENTS

Volume: 1 Issue: 3 Year: 2023

ORIGINAL ARTICLE

REVIEW

CASE REPORT

Journal of
Pulmonology and
Intensive Care

Original Article

DOI: 10.51271/JOPIC-0013

The investigation of malnutrition and life quality's relation with mortality in the patients who are 65 years old and above and are hospitalized at the palliative care service

Merve Lehimcioğlu[1], Gözde Şengül Ayçiçek[2], Aydın Çifci[1]

[1] *Department of Internal Medicine, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey*
[2] *Division of Geriatrics, Department of InternalMedicine, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey*

Cite this article: Lehimcioğlu M, Ayçiçek GŞ, Çifci A. The investigation of malnutrition and life quality's relation with mortality in the patients who are 65 years old and above and are hospitilazed at the palliative care service. *J Pulmonol Intens Care.* 2023;1(3):52-59.

Corresponding Author: Merve Lehimcioğlu, m_lehimcioglu@hotmail.com

Received: 19/05/2023 ◆ **Accepted**: 27/07/2023 ◆ **Published**: 29/08/2023

ABSTRACT

Aims: Our study aims to determine the impact of malnutrition on the quality of life of elderly patients receiving palliative care and identify the factors influencing quality of life.

Methods: The study included patients aged 65 and older who were admitted to the Kırıkkale University Medical Faculty Hospital Palliative Care Service between November 2019 and February 2020. Patients with a history of active malignancy, hospitalization within the past 3 months, severe dementia precluding obtaining written consent, and patients under 65 years of age were excluded. Scores obtained from the Mini Nutritional Assessment-Short Form (MNA-SF) were recorded, with scores of 12 or higher considered as normal nutrition. Those with scores below 12 were reevaluated for malnutrition according to the Global Leadership Initiative on Malnutrition (GLIM) criteria, and those meeting any of the phenotypic and etiological criteria were considered malnourished. Malnutrition severity was reclassified according to the GLIM criteria. The 13-item OPQOL-brief questionnaire was used to evaluate their quality of life. The questionnaire was published in Turkish by Çalışkan et al. Each question was rated on a scale of 1-5, with "Strongly Disagree" scored as 1, "Disagree" as 2, "Undecided" as 3, "Agree" as 4, and "Strongly Agree" as 5.

Results: The mean total MNA score was found to be statistically lower in patients classified as mild and severe malnutrition according to the GLIM classification compared to those without malnutrition ($p<0.001$). The rate of MNA scores between 12 and 14 in patients without malnutrition was higher than that of patients with mild and severe malnutrition, while the rate of scores between 8 and 11 was higher in patients with severe malnutrition. The rate of scores between 0 and 7 was higher in patients with mild and severe malnutrition ($p<0.001$). The mean total MNA ($p<0.001$) and QOL ($p=0.021$) scores were statistically lower in patients with malnutrition compared to those without malnutrition. The rate of MNA scores between 12 and 14 and between 8 and 11 was higher in patients without malnutrition, while the percentage of MNA scores between 0 and 7 was higher in patients with malnutrition.

Conclusion: In the geriatric patient group, we believe that the GLIM criteria used in our study are more comprehensive and sensitive in detecting malnutrition in terms of phenotypic and etiological aspects through patient questioning.

Keywords: Palliative care, malnutrition, older age, life quality, mortality, GLIM criteria

INTRODUCTION

The field of geriatrics was established with the aim of preserving and treating the health of individuals aged 65 and above. It is crucial for ensuring an active and healthy lifestyle during old age. The goal in geriatrics is to improve the quality of life for elderly individuals.[1] The elderly population is steadily increasing worldwide. While there were 605 million elderly individuals in the world in 2002, it is expected to surpass 1.2 billion people by 2025.[2] A similar trend can be observed in Turkey as well. According to the Address-Based Population Registration System results by the Turkish Statistical Institute (TÜİK), in 2007, the elderly population accounted for 7.1% of the total population, which is approximately 5 million people. However, by 2020, this ratio increased to 9.5%, corresponding to around 7,954,000 individuals.[3]

As the society ages, an increased number of deaths due to chronic diseases is anticipated.[4] A significant portion of patients receiving palliative care consists of individuals hospitalized due to chronic illnesses.[5] One of the goals of palliative care is to improve the quality of life, which aligns with the objectives of geriatrics in enhancing the quality of life for the elderly.[1]

Patients receiving palliative care are hospitalized for various reasons. In palliative care, the evaluation and management of the patient's pain and other symptoms by experts in the field, as well as assessing and supporting the needs of the patient's family and caregivers, serve as the starting point. Palliative care deals with the physical, functional, psychological, practical, and spiritual aspects arising from a serious illness. It represents a patient- and family-centered approach that helps individuals with serious illnesses alleviate their symptoms and stress. Providing palliative care in severe illnesses improves the quality of life for the patient and their family through early adaptation to this type of care.6-8 Among these reasons, malnutrition holds an important place. Malnutrition has a negative impact on individuals' quality of life and mortality rates.[9-11] In the study, we aimed to reveal the relationship between malnutrition and quality of life in the elderly population, especially due to the aging population, and to draw attention to malnutrition that significantly reduces the quality of life.

METHODS

Ethics

The study was approved by the Kırıkkale University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 25.03.2021, Decision No: 2021.03.07). The participation in the study was based on voluntarism, and informed consent forms were obtained from each patient. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

This study was conducted at the Kırıkkale University Medical Faculty Hospital Palliative Care Service. Patients aged 65 years and older who were admitted to the palliative care service between November 2019 and February 2020 were included in the study.

Exclusion criteria were patients with a history of active malignancy, hospitalization within the past 3 months, severe dementia impairing the ability to provide written consent, and patients under the age of 65.

Methods

The quality of life questionnaire was completed by the patients themselves. For illiterate patients, the questionnaire was administered with the assistance of their first-degree relatives. The case report form, created by the researchers, was completed by the same individuals. The case report form included information such as gender, age, medical history, nutritional status, reason for hospitalization, presence of infectious disease, presence of oncological disease, MNA-SF score, height, weight, BMI, forearm circumference, calf circumference, weight loss, albumin, CRP, vitamin D, length of hospital stay, presence of pressure ulcers, and mortality status. Nutritional route options were recorded as normal nutrition, parenteral nutrition, oral nutritional support (ONS), nasogastric tube feeding (NG), Regime 1+2 (R1+R2), and ONS+parenteral nutrition. The form recorded the nutritional state during hospitalization. CRP, vitamin D levels, and albumin values were recorded. Blood samples were not collected from patients for the purpose of this study. Routine laboratory tests were used.

Scores obtained from the MNA-SF form were recorded: a total score of 12 or higher was considered as normal nutrition. Those with a score lower than 12 were re-evaluated for malnutrition according to GLIM criteria, and those who met any of the phenotypic and etiologic criteria were considered malnourished. Malnutrition status was reclassified according to the severity of malnutrition based on GLIM criteria.

The 13-item OPQOL-brief questionnaire was administered to assess their quality of life. The Turkish version of this questionnaire was published by Çalışkan et al.[12] Each item was evaluated on a scale of 1-5. The evaluations were made as follows: 'Strongly disagree' 1 point, 'Disagree' 2 points, 'Undecided' 3 points, 'Agree' 4 points, 'Strongly agree' 5 points.

Statistical Analysis

The analyses were performed using IBM SPSS 23.0 software package (IBM Corp., Armonk, NY). Descriptive statistics were presented as n (%) and mean±standard deviation (min-max) or median (min-max) values. The relationships between categorical variables were analyzed using the Pearson chi-square test and Fisher's exact test, and Bonferroni correction was applied for pairwise comparisons. The Shapiro-Wilk test was used to assess the normality assumption. In cases where the measurement values between two groups did not follow a normal distribution, the Mann-Whitney U test was used; in cases where it did follow a normal distribution, Student's t-test was employed. For nonparametric comparison of measurements among three or more groups, the Kruskal-Wallis test was used, and for significant results, the Bonferroni-Dunn test was employed as a post-hoc test. When the normal distribution assumption was met and variance homogeneity was ensured for comparisons among three or more groups, the ANOVA test was used, and for pairwise comparisons, the Tukey HSD test was applied if homogeneity of variances was achieved, and the Dunnett T3 test was used otherwise. In the univariate analysis, multivariate logistic regression analysis was used to independently examine the effects of statistically significant study parameters on three-month and six-month mortality. The results were presented as odds ratios (OR) with a 95% confidence interval. p-values less than 0.05 were considered statistically significant.

Table 1. Demographic and clinical charactheristics of the patients that are hospitalized in the palliative care service

	nn:68
Age (Year)	75.81±8.33 (65-97)
Gender	
Male	42 (61.8)
Female	26 (38.2)
Length (m)	1.64±0.09 (1.4-1.85)
Weight (kg)	71.3±14.81 (40-115)
BMI (kg/m²)	26.65±5.14 (17.31-0.58)
Arm circumference (cm)	26.26±4.04 (17-37)
Calf circumference (cm)	32.87±5.7 (21-53)
Phenotypic criterion	42 (61.8)
Etiological criterion	56 (82.4)
Decubitis ulcer	9 (13.2)
Infection presence	34 (50)
CRP (mg/L)	37 (0.58-337.21)
Albumin (g/dl)	3.37±0.57 (1.98-4.83)
Vitamin D (ng/ml)	10.68 (3-60.6)

Indications are shown with n (%), average±SS (min-max) or median (min-max).
Abbreviations: BMI: Body mass index, CRP: C-reactive protein

RESULTS

When the 68 patients in the study were examined, the comorbidities were as follows: coronary artery disease in 34 patients (50%), hypertension in 49 patients (72.1%), diabetes mellitus (DM) in 21 patients (30.9%), heart failure in 17 patients (25%), pulmonary thromboembolism (PTE) in 5 patients (7.4%), cerebrovascular accident (stroke) (CVA) in 8 patients (11.8%), benign prostatic hyperplasia (BPH) in 11 patients (28.9%), and chronic kidney disease (CKD) in 8 patients (11.8%). Among these 68 patients, 45.6% had oncological diseases, including lung cancer in 22.6%, rectal cancer in 3.2%, prostate cancer in 9.7%, colon cancer in 9.7%, pancreatic cancer in 3.2%, ovarian cancer in 3.2%, stomach cancer in 6.5%, hepatocellular carcinoma in 12.9%, bladder cancer in 3.2%, renal cell carcinoma in 3.2%, myelodysplastic syndrome (MDS) in 3.2%, breast cancer in 3.2%, aplastic anemia in 3.2%, and unknown primary cancer in 12.9%. Looking at the distribution of other diagnoses among the patients, 16.2% had pleural effusion, 5.4% had depression, 13.5% had hypothyroidism, 35.1% had chronic obstructive pulmonary disease (COPD), 13.5% had schizophrenia, 5.4% had cirrhosis, 8.1% had Parkinson's disease, and 2.7% had Alzheimer's disease.

The hospitalization duration, reasons for admission, nutrition methods, and mortality rates of the patients are presented in **Table 2**.

Table 2. Length of hospitalization, reasons for hospitalization, diet and mortality rates of the patients

Hospitalization time (n:68): day (min-max)	**14 (1-96)**
Hospitalization reason	**n (%)**
Pain palliation	15 (22.1)
Oral intake disorder	30 (44.1)
Hipernatremia	2 (2.9)
Hipervolemia	4 (5.9)
Respiratory failure	7 (10.3)
Pressure ulcer	1 (1.5)
Urinary tract infection	6 (8.8)
Hepatic encephalopathy	1 (1.5)
Cellulitis	1 (1.5)
Cholangitis	1 (1.5)
Feeding method	
Normal feeding	31 (45.6)
ONS	28 (41.2)
Parenteral nutrition	2 (2.9)
R1+R2	3 (4.4)
NG	1 (1.5)
ONS+parenteral	2 (2.9)
Low purine diet	1 (1.5)
Zeroth month mortality	7 (10.3)
First month mortality	11 (16.2)
Third month mortality	14 (20.6)
Sixth month mortality	17 (25)

The results are presented as n(%) or median (min-max)
Abbreviations: ONS: Oral nutrition supplement, R1: Regime 1, R2: Regime 2, NG: Nasogastric,

The general characteristics of the patients according to the malnutrition status determined by GLIM criteria are compared in **Table 3**.

Tablo 3. Comparison of general characteristics according to patients malnutrition status

	Absent (n:29)	Present (n:39)	P
Age (year)	75.55±7.32 (65-94)	76±9.1 (65-97)	0.828
Gender			**0.048**
Male	14 (48.3)	28 (71.8)	
Female	15 (51.7)	11 (28.2)	
Length (m)	1.62±0.1 (1.5-1.85)	1.65±0.09 (1.4-1.79)	0.223
Weight (kg)	76.63±14.56 (52-115)	67.33±13.89 (40-109)	**0.009**
BMI	29.11±4.24 (22.5-38.86)	24.83±5.03 (17.31-40.58)	**<0.001**
Arm circumference (cm)	27.9±4.09 (19-37)	25.04±3.58 (17-32)	**0.003**
Calf circumference (cm)	33 (27-53)	31 (21-42)	0.078
Phenotypic criterion	3 (10.3)	39 (100)	**<0.001**
Ethiological criterion	17 (58.6)	39 (100)	**<0.001**
Pressure ulcer	2 (6.9)	7 (17.9)	0.282
Infection status	15 (51.7)	19 (48.7)	0.806
CRP (mg/L)	38 (0.58-275)	36 (1-337.21)	0.472
Albumin (g/dl)	3.52±0.61 (2.25-4.83)	3.25±0.53 (1.98-4.31)	**0.049**
Vitamin D (ng/ml)	17.72 (3-60.6)	10.46 (3.39-35.27)	0.999
Coexisting diseases			
Coronery artery diseases	16 (55.2)	18 (46.2)	0.462
Hypertension	23 (79.3)	26 (66.7)	0.250
DM	11 (37.9)	10 (25.6)	0.278
Heart failure	5 (17.2)	12 (30.8)	0.203
PTE	3 (10.3)	2 (5.1)	0.644
CVA	5 (17.2)	3 (7.7)	0.272
BPH	4 (30.8)	7 (28)	0.999
Oncological disease	9 (31)	22 (56.4)	**0.038**
Chronic kidney disease	4 (13.8)	4 (10.3)	0.715
Hospitalization time (day)	14 (1-42)	14 (3-96)	0.761
Feeding method			**0.021**
Normal feeding	19 (65.5)a	12 (30.8)b	
ONS	8 (27.6)a	20 (51.3)b	
Parenteral nutrition	0 (0)a	2 (5.1)a	
R1+R2	1 (3.4)a	2 (5.1)a	
NG	0 (0)a	1 (2.6)a	
ONS+parenteral	0 (0)a	2 (5.1)a	
Low purine diet	1 (3.4)a	0 (0)a	
Zeroth month mortality	1 (3.4)	6 (15.4)	0.225
First month mortality	2 (6.9)	9 (23.1)	0.100
Third month mortality	2 (6.9)	12 (30.8)	**0.016**
Sixth month mortality	4 (13.8)	13 (33.3)	0.066

The results are presented as n (%), mean±SD (min-max), or median (min-max). Statistical analysis was performed using Student's t-test, Mann-Whitney U test, Pearson chi-square test, and Fisher's exact test. Statistically significant differences between groups were observed.
Abbreviations: DM: Diabetes mellitus, PTE: Pulmonary thromboembolism, CVA: Cerebrovascular accident (stroke), BPH: Benign prostate hypertrophy, R1: Regime 1, R2: Regime 2, NG: Nasogastric, ONS: Oral nutrition supplement

Depending on the malnutrition status, patients MNA and qualitfy of life (QOL) scores are compared in **Table 4**.

Table 4. Comparison of MNA and QOL scores of patients according to their malnutrition status

	Absent (n:29)	Present (n:39)	p
MNA total score	10.17±2.22 (6-14)	7.03±2.37 (2-11)	<0.001
MNA classification			<0.001
12-14	8 (27.6)a	0 (0)b	
8-11	19 (65.5)a	15 (38.5)b	
0-7	2 (6.9)a	24 (61.5)b	
QOL total score	52.72±7.3 (33-63)	47.77±9.41 (19-64)	0.021

The results are presented as n (%) or mean±SD (min-max). Statistical analysis was conducted using Student's t-test and Pearson chi-square test. Statistically significant differences between groups are indicated by different superscript lowercase letters.
Abbreviations: MNA: Mini nutrition assesment, QOL: Quality of life

Patients with malnutrition had statistically lower mean scores in MNA (p<0.001) and QOL (p=0.021) compared to patients without malnutrition. Among patients without malnutrition, the MNA score was found to be between 12-14 and 8-11 points, while among patients with malnutrition, the percentage of MNA scores between 0-7 points was higher.

There were no statistically significant differences in age (p=0.767), gender (p=0.134), height (p=0.367), calf circumference (p=0.184), pressure ulcer (p=0.467), infection status (p=0.713), CRP (p=0.665), albümin level (p=0.073), vitamin D levels (p=0.300), and hospital length of stay (p=0.277) according to the GLIM classification. The weight (p=0.029), BMI (p=0.001), and arm circumference (p=0.001) measurements of severely malnourished patients were lower compared to patients without malnutrition. Phenotypic and etiologic criteria were observed in all patients with mild and severe malnutrition (p<0.001). Regarding the distribution of comorbidities according to the GLIM classification, there were no statistically significant differences in coronary artery disease (p=0.229), hypertension (p=0.249), diabetes mellitus (p=0.554), pulmonary thromboembolism (p=0.842), CVD (p=0.388), and chronic kidney disease (p=0.715). The rate of heart failure was higher in patients with mild malnutrition compared to those with severe malnutrition and without malnutrition (p=0.040). BPH (benign prostatic hyperplasia) was not observed in severely malnourished patients, while it had the highest percentage in patients with mild malnutrition (p=0.019). The rate of oncological diseases was higher in severely malnourished patients compared to those without malnutrition (p=0.049). The percentage of normal nutrition was higher in patients without malnutrition compared to severely malnourished patients (p=0.039). There were no differences in terms of zero (p=0.234), one (p=0.073), and six-month mortality rates (p=0.111) according to the GLIM classification. However, the three-month mortality rate was higher in patients with mild malnutrition compared to those without malnutrition (p=0.038).

According to the GLIM classification, the mean total scores of MNA were statistically lower in patients with mild and severe malnutrition compared to those without malnutrition (p<0.001). The rate of MNA scores between 12-14 points was higher in patients without malnutrition compared to those with mild and severe malnutrition, while the rate of MNA scores between 0-7 points was higher in patients with mild and severe malnutrition (p<0.001). Although the mean total score of QOL was lower in patients with mild and severe malnutrition compared to those without malnutrition, this difference was not statistically significant (p=0.072).

According to zero and one-month mortality, there were no significant differences in MNA and QOL scores among patients. There were no statistically significant differences in age, gender, weight, BMI, arm circumference, calf circumference, phenotypic criteria, etiologic criteria, pressure ulcer, infection status, CRP, albumin, vitamin D levels, and hospital length of stay among patients with one and three-month mortality. The average height of deceased patients was higher than that of survivors (p=0.017). There were no significant differences in the distribution of comorbidities among patients based on mortality. Among patients who died within one month, the percentages of diet 1 and diet 2 were higher, while the percentage of normal nutrition was lower compared to survivors (p=0.037). In patients who died within three months, the percentage of male patients was statistically higher than in survivors (p=0.039).

According to one and three-month mortality, there were no significant differences in MNA and QOL scores among patients.

When comparing patients' characteristics based on three-month mortality, there were no statistically significant differences in age, weight, BMI, arm circumference, calf circumference, etiologic criteria, pressure ulcer, infection status, CRP, albumin, vitamin D levels, and hospital length of stay (p>0.05). The percentage of male patients was statistically higher among those who died within three months compared to survivors (p=0.039). The average height of deceased patients was higher than that of survivors (p=0.003). The percentage of phenotypic criteria was higher among deceased patients compared to survivors (p=0.039). There were no significant differences in the distribution of comorbidities among patients based on three-month mortality, except for higher percentages of PTE (p=0.044) and oncological diseases (p=0.029) among those who died within three months. The percentage of diet 1, diet 2, and ONS+parenteral nutrition was higher, while the percentage of normal nutrition was lower among patients who died within three months compared to survivors (p=0.004).

Similarly, when comparing patients' characteristics based on six-month mortality, there were no statistically significant differences in age, weight, BMI, arm circumference, calf circumference, etiologic criteria, pressure ulcer, infection status, CRP, albumin, vitamin D levels, and hospital length of stay (p>0.05). The percentage of male patients was statistically higher among those who died within six months compared to survivors (p=0.010). The average height of deceased patients was higher than that of survivors (p<0.001). The percentage of phenotypic criteria was higher among deceased patients compared to survivors (p=0.044). There were no significant differences in the distribution of comorbidities among patients based on six-month mortality, except for a higher percentage of oncological diseases (p=0.003) and a lower percentage of DM (p=0.049) among those who died within six months. The percentage of ONS+parenteral nutrition was higher, while the percentage of normal nutrition was lower among patients who died within six months compared to survivors (p=0.027)

When comparing the MNA (Mini Nutritional Assessment) total scores (p=0.304), MNA classification rates (p=0.558), and QOL (Quality of Life) total scores (p=0.286) according to six-month mortality, no statistically significant difference was observed.

Figure 1 presents the results of the correlation analysis between MNA score and QOL score. There was no statistically significant correlation observed between MNA score and QOL score (p=0.219).

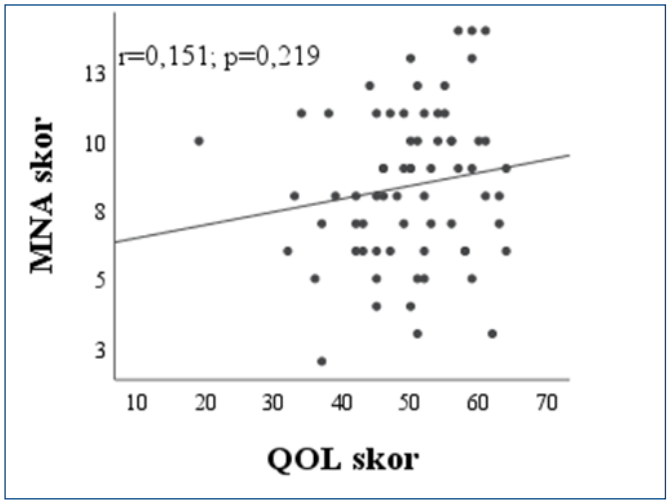


Figure 1. The correlation analysis between MNA score and QOL score

Although no statistically significant difference was found, those who died during hospitalization and in the first month had the lowest quality of life (QOL) scores, while those who died in the 3rd and 6th months had higher QOL scores. Among the survivors, the highest quality of life was observed during hospitalization, and it was found that the quality of life gradually decreased as the follow-up period progressed. According to these findings, individuals who lived longer (i.e., those who died later, in the 3rd and 6th months) had the highest quality of life.

Figure 2 presents the correlation analysis between GLIM classification and QOL score. A statistically significant weak negative correlation was found between GLIM classification and QOL score (r= -0.286; p=0.018)

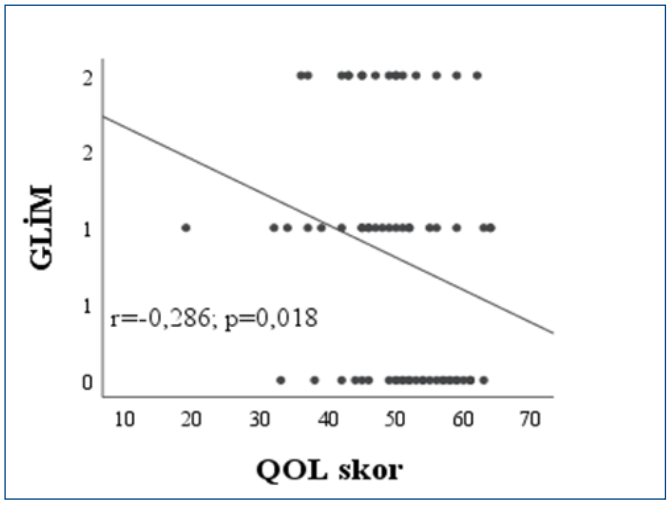


Figure 2. The correlation analysis between GLIM classification and QOL score

DISCUSSION

In the study conducted by Miniksar et al.[13] on palliative care, the reasons for hospitalization were reported as follows: inadequate oral intake 58.3%, care education 14.3%, pain palliation 12.8%, pressure ulcer care 7.5%, and other reasons 7.2%. However, Çınar et al.[14] identified the reasons as follows: 33.3% Alzheimer's disease, 16.7% CVA, 5.6% chronic kidney failure, 13% heart failure and coronary artery disease, 3.7% COPD and asthma, 1.9% cerebral palsy, 3.7% psychiatric diseases, 18.5% malignancies, and 3.7% femoral neck fracture. In our study, the top five reasons were determined as follows: 44.1% oral intake disorder, 22.1% pain palliation, 10.3% respiratory failure, 8.8% urinary tract infection, and 5.9% hypervolemia.

The study by Miniksar et al.[13] showed similar rates of oral intake disorder and pain palliation. The differences in findings between our study and the study by Turgut et al.[15] were attributed to the distinction made based on disease groups. It was also noted that the differences between our study and the study by Çınar et al.[14] might be due to the inclusion of both home and hospital palliative care patients in their study.

In the study conducted by Ülger et al.[16] on patients admitted to a geriatric clinic, they found that malnourished patients had the following rates: 27.6% diabetes mellitus (DM), 27.6% hypertension, 28.9% coronary artery disease, 32.5% CVA, 35.5% congestive heart failure, 27.2% chronic obstructive pulmonary disease (COPD), and 54.2% pressure ulcers. In the study by Döğer et al.[17] conducted at Ankara Ulus Palliative Care Hospital between January 2013 and October 2015, they found the following rates: neurological diseases 42.3%, cancer 23.4%, chronic systemic conditions (chronic lung, heart, and kidney diseases, and DM) 41.4%, infections 10.8%, and pressure ulcers 40.5%.

In our study, we identified the following rates: 50% coronary artery disease, 72.1% hypertension, 30.9% DM, 25% heart failure, 7.4% pulmonary thromboembolism (PTE), 11.8% cerebrovascular accident (stroke), 28.9% benign prostatic hyperplasia (BPH), 45.6% oncological disease, 13.5% hypothyroidism, 35.1% COPD, 13.5% schizophrenia, 8.1% Parkinson's disease, and 2.7% Alzheimer's disease. The differences in rates compared to other studies were attributed to the smaller sample size in our study.

In the study conducted by Miniksar et al.[13], malignancy was detected in 43.3% of the patients, with lung cancer accounting for 13.1%, colon cancer for 2.8%, breast cancer for 1.2%, bladder cancer for 1.2%, prostate cancer for 3.7%, stomach cancer for 5.3%, pancreatic cancer for 3.1%, and other malignancies for 12.8%. In the study by Şenel et al.[18] conducted between January and December 2014 in palliative care, the rates of malignancy were as follows: gastrointestinal system 21%, lung 19%, genitourinary system 15%, head/neck 12%, pancreas 11%, breast 10%, hepatobiliary 3%, other 5%, and unknown primary 4%. In our study, malignancy was detected in 45.6% of the patients, with the following distribution: 22.6% lung cancer, 3.2% rectal cancer, 9.7% prostate cancer, 9.7% colon cancer, 3.2% pancreatic cancer, 3.2% ovarian cancer, 6.5% stomach cancer, 12.9% hepatocellular carcinoma, 12.9% unknown primary malignancy, 3.2% bladder cancer, 3.2% renal cell carcinoma, 3.2% myelodysplastic syndrome, 3.2% breast cancer, and 3.2% aplastic anemia.

In the study by Turgut et al.[14], the distribution of nutrition was found to be 50.3% oral, 27.5% enteral, and 22.2% parenteral. In the study by Yürüyen et al.[19] conducted between August 2015 and July 2017 in palliative care, the distribution of nutrition status was found to be 72% enteral

(76% oral, 12% nasogastric tube, and 12% percutaneous endoscopic gastrostomy) and 28% parenteral. In our study, 45.6% of the patients received normal nutrition, 41.2% received oral nutritional support, 4.4% followed diet regimens 1 and 2, 2.9% received parenteral nutritional support, 2.9% received oral+parenteral nutritional support, and 1.5% received purine-restricted nutritional support. The different patterns of nutrition may be due to the patients' co-existing medical conditions, decreased oral intake, and variations in the reasons for hospitalization compared to other patients.

In the study conducted by Maier et al.[20] at a geriatric center, according to the GLIM criteria, mild malnutrition was found in 36% of the patients, while severe malnutrition was found in 16%, resulting in a prevalence of malnutrition of 52.0%. In the study by Maeda et al.[21], malnutrition according to the GLIM criteria was found to be 25.7% in patients aged 70 and above, with 13% classified as mild malnutrition and 12.6% as severe malnutrition. In our study, based on the GLIM criteria, mild malnutrition was found in 33.8% of the patients, while severe malnutrition was found in 23.5%. The variation in the prevalence of malnutrition compared to other studies may be attributed to differences in the criteria used to define study groups and variations in the number of participants.

In a study conducted by Matsumo et al.[22] on elderly patients presenting to the emergency department, the percentages of the at-risk group, malnourished group, and non-malnourished group according to the MNA short form were reported as 34%, 18%, and 48%, respectively. In a study by Abd-El-Gawad et al.[23] conducted at a geriatric center on individuals aged 60 and above using the MNA short form, they found that 46% of the individuals were at risk of malnutrition. In our study, the percentages were as follows: normal nutrition group 11.8%, at-risk group for malnutrition 50%, and malnourished group 38.2%. The differences between our study and these studies may be due to variations in the inclusion criteria and the number of participants.

Gartner et al.[24] conducted a study at a geriatric center where the average length of hospital stay was found to be 11 days, while Balcı et al.[25] reported a duration of 10.5 days in their study, which is similar to the 14-day hospital stay in our study.

In the study by Sousa-Santos26, women were found to be at higher risk in terms of malnutrition (p:0.002). In the study by Ülger et al.[16], 68% of those identified with malnutrition were women, and the risk of malnutrition was significantly higher in women (32%) compared to men (p:0.005). In our study, in contrast to these studies, the prevalence of malnutrition was found to be significantly higher in men (p:0.048). This discrepancy may be attributed to the use of the MNA short form for defining malnutrition in other studies, while our study used the GLIM criteria.

In the retrospective study conducted by Balcı et al.[25], significant differences were found in weight and BMI between patients with and without malnutrition according to the GLIM criteria (p<0.001). Similar results were found in the study by Kootaka et al.[27] based on the GLIM criteria (p<0.001). In our study, similarly, body weight and BMI were significantly lower in individuals with malnutrition. Since the same criteria were used to define malnutrition in our study, similar results were obtained as in other studies.

Shimizu et al.[28] reported the presence of phenotypic and etiological criteria in patients with malnutrition (p <0.001) in their study. Similar results were obtained in our study. In three separate studies conducted by Shimizu et al., Balcı et al.[25], and Yin et al.[29] based on the GLIM criteria, significantly lower mid-arm circumference and albumin levels were found in individuals with malnutrition (p<0.001). Similarly, in our study, mid-arm circumference (p:0.038) and albumin (p:0.0049) were significantly lower in patients with malnutrition. In Yin et al.'s study, based on the GLIM criteria, significantly lower calf circumference (p<0.001) was found in individuals with malnutrition. However, there was no statistically significant difference in calf circumference in our study. This may be due to peripheral edema secondary to low albumin levels related to underlying comorbidities in our palliative care patients, which could have affected the measurement of calf circumference.

In the study by Kootaka et al.[27], the rate of oncological diseases was found to be higher in individuals with malnutrition compared to other diseases (p<0.001). Sanchez-Rodriguez et al.[30] also reported a significantly higher prevalence of malignancies in individuals with malnutrition based on the GLIM criteria (p<0.001). Similarly, in our study, using similar criteria, a significant association was found between malnutrition and oncological diseases (p:0.038).

Yin et al.[29] reported a higher prevalence of enteral nutrition (p:0.010) and parenteral nutrition (p <0.001) in patients with malnutrition. In the study by Kootaka et al.[27] based on the GLIM criteria, a higher prevalence of comorbidities such as COPD, heart failure, and dyslipidemia was observed in individuals with malnutrition (p<0.001). In our study, the rate of normal nutrition was lower in individuals with malnutrition, while the rate of oral nutritional supplementation (ONS) was higher compared to those without malnutrition (p=0.021). This result may be attributed to the decrease in normal nutrition in patients with malnutrition and subsequent initiation of oral nutritional support therapy.

Efendioğlu et al.[31] conducted a study in a geriatric center over a one-year period and found the mean vitamin D level to be 12.64±11.12. Similarly, in our study, the vitamin D level was found to be 10.68 (3-60.6), which may be due to the selection of geriatric patients in these studies.

In the study by Abd-El-Gawad et al.[23], conducted in individuals aged 65 and above, there was no statistically significant difference in 3-month (p: 0.124) and 6-month (p: 0.330) mortality rates based on the MNA short form criteria for diagnosing malnutrition. However, in our study, individuals with malnutrition based on the GLIM criteria had a higher 3-month mortality rate (p=0.016). This difference in results could be attributed to the use of different criteria for defining malnutrition in these patients.

In the study by Sanchez-Rodriguez et al.[30], conducted in the elderly population between 2013 and 2019, individuals with malnutrition based on the GLIM criteria had significantly lower MNA scores (p<0.001). Additionally, in this study, quality of life scores were assessed using SF-36 and EUROQOL, and only SF-36 scores were significantly lower (p<0.001) in individuals with malnutrition. Rasheed et al.[32] demonstrated an association between MNA short form scores and quality of life scores (SF-36, EUROQOL) in elderly individuals. In our study, individuals with malnutrition had significantly lower MNA scores and QOL scores. The different results in terms of quality of life may be attributed to the use of different tests for assessing quality of life.

In the study by Matsumoto et al.[22], measurements of weight, BMI, and arm circumference were significantly lower ($p<0.001$) in severely malnourished patients compared to non-malnourished patients. Similarly, in our study, weight, BMI, and arm circumference measurements were lower in severely malnourished patients compared to non-malnourished patients. The similarity in results can be attributed to the use of similar patient groups and the same criteria.

Balcı et al.[25] examined the distribution of comorbidities in patients according to the GLIM classification and found no statistically significant difference in terms of coronary artery disease, hypertension, diabetes mellitus, and chronic kidney disease (CKD) rates. In our study, when patients' comorbidities were analyzed based on the GLIM criteria, there was no statistically significant difference in terms of coronary artery disease, hypertension, diabetes mellitus, and CKD rates. The similarity in results may be attributed to the use of similar patient groups and the same criteria.

In the study by Kootaka et al.[27], heart failure diagnosis was found to be significantly higher in individuals with malnutrition according to the GLIM criteria compared to those without malnutrition. In our study, the rate of heart failure was higher in individuals with mild malnutrition compared to those with severe malnutrition and those without malnutrition. This result may be due to the small sample size and the selected patient group.

In the study by Sanchez-Rodriguez et al.[30], the 5-year mortality rate in individuals with malnutrition according to the GLIM criteria was found to be 26.8%. In the study by Kootaka et al.[27], which had an average follow-up period of 2.3 years, the mortality rate in individuals with malnutrition according to the GLIM criteria was determined to be 37.9%. Both studies showed a statistically significant difference ($p<0.001$) compared to individuals without malnutrition. In the study by Yılmaz et al.[33], a 1-year follow-up study conducted on individuals with hematological diseases according to the GLIM criteria, mortality was found to be significantly different in individuals with malnutrition. In our study, according to the regression analyses conducted, malnutrition was not found to be a risk factor for mortality. This may be due to the short follow-up period and small sample size compared to other studies.

In the study by Kruger et al.[34], which primarily focused on data from individuals aged 70 and above, including the United States and five other countries, male gender was found to be associated with mortality. However, in our study, male gender was not found to be a factor influencing mortality. This could be attributed to the small number of individuals in the study

According to the study by Huang et al.[35], which involved a 10-year follow-up of older adults, diabetes mellitus (DM) and its complications were associated with mortality. However, in our study, DM was not found to be a risk factor for six-month mortality. This could be attributed to the short duration of our study.

In the study by Gentile et al.[36], which conducted a 3-month follow-up study on 924 elderly patients, the presence of malnutrition was found to be associated with increased mortality. However, in our study, this association was not found to be statistically significant. This could be due to both the smaller sample size in our study and the difference in malnutrition assessment. While other studies used the Mini Nutritional Assessment Short Form (MNA-SF) for malnutrition assessment, our study used the GLIM criteria, which might have led to different results.

Karaman et al.[37] conducted a study on elderly residents in a nursing home and found a correlation between MNA-SF scores and quality of life. However, in our study, no correlation was found. This could be attributed to the use of different questionnaires for assessing quality of life. The previous study utilized the WHOQOL questionnaire, while we used the OPQOL-bref questionnaire.

In patients with a history of hospitalization in palliative care centers, especially in the geriatric age group, it has been shown that quality of life deteriorates over time. This may be due to the lack of potential for complete recovery in palliative care patients, their continuous need for close care, and often inadequate nutritional status. Additionally, the progressive exhaustion experienced by the caregivers of these patients who have no chance of recovery and require close attention could contribute to the decrease in patients' quality of life. When comparing patients who were discharged or deceased during the hospitalization period with those who were discharged or deceased at 1, 3, and 6 months, it was observed that those with higher QOL scores had higher mortality rates, contrary to our expectations. This could be attributed to the fact that caregivers of patients with worse overall conditions and lower life expectancy tend to provide more care.

In geriatric patients requiring palliative care, quality of life decreases over time, and mortality rates increase. The fact that individuals with higher quality of life tend to die earlier suggests that the increased attention provided by caregivers to patients with poorer overall conditions may improve their quality of life. Palliative care involves a holistic approach that includes the patient, their caregivers, auxiliary healthcare personnel, and the medical team, necessitating teamwork. Improving the patient's quality of life depends not only on caring for the patient but also on enhancing the quality of life of other members of the team.

Study limitations: It is a retrospective, small number of patients and a single center.

CONCLUSION

Geriatric palliative care patients often have multiple comorbidities, which worsen their overall condition and increase the prevalence and severity of malnutrition. The addition of malnutrition in this patient group is associated with decreased quality of life and increased mortality. Palliative care management is a holistic approach that involves the patient, their caregivers, auxiliary healthcare personnel, and the medical team, requiring teamwork. Improving the patient's quality of life depends not only on caring for the patient but also on enhancing the quality of life of other members of the team. In this patient group, we believe that the GLIM criteria used in our study are more comprehensive and sensitive in assessing malnutrition in terms of both phenotypic and etiological aspects of patient evaluation. Considering the increasing number of elderly individuals and the growing demand for palliative care, we believe that more extensive studies involving a larger number of patients should be conducted in this field.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval by the Kırıkkale University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 25.03.2021, Decision No: 2021.03.07).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Şahin S. Geriatride palyatif bakım. *Türkiye Klinikleri Anesteziyoloji Reanimasyon-Özel Konular.* 2017;10(1):36-41.
2. WHO. Nutrition for older persons. Available from: https://www.who.int/nutrition/topics/ageing/en/.
3. Kurumu Tİ. Yaş grubuna göre nüfus ve toplam nüfus içindeki oranı, 2007-2020 2021 [Available from: https://data.tuik.gov.tr/Bulten/Index?p=Adrese-Dayali-Nufus-Kayit-Sistemi-Sonuclari-2020-37210.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet.* 1997;349(9064):1498-1504. doi:10.1016/S0140-6736(96)07492-2
5. Kabalak AA. Türkiye'de palyatif bakım çalışmaları. *Türkiye Klinikleri Anesteziyoloji Reanimasyon-Özel Konular.* 2017;10(1):7-12.
6. Connor SR, Bermedo MCS. World Health Organization. Global atlas of palliative care at the end of life. 2014.
7. Ferrell BR, Twaddle ML, Melnick A, Meier DE. National consensus project clinical practice guidelines for quality palliative care guidelines. *J Palliat Med.* 2018;21(12):1684-1689.
8. Öztorun HS, Aras S. Palyatif bakım nedir? *Türkiye Klinikleri Geriatri-Özel Konular.* 2018;4(1):1-6.
9. Tuncer Ö, Bayindir A. Palyatif bakım hastalarında malnütrisyon. *Klinik Tıp Aile Hekimliği.* 2017;8(3):11-14.
10. Volkert D, Beck AM, Cederholm T, et al. Management of malnutrition in older patients-current approaches, evidence and open questions. *J Clin Med.* 2019;8(7):974.
11. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nutr.* 2008;27(1):5-15.
12. Caliskan H, Aycicek GS, Ozsurekci C, et al. Turkish validation of a new scale from older people's perspectives: older people's quality of life-brief (OPQOL-brief). *Arch Gerontol Geriatr.* 2019;83:91-95.
13. Miniksar ÖH, Aydin A. Palyatif bakım ünitemizde yatan hastaların retrospektif analizi. *J Contemp Med.* 2019;10(3):429-433.
14. Çinar H, Yasemin K, Enginyurt Ö. Palyatif bakim hastalarında beslenme durumunun yaşam kalitesi üzerine etkisi / Effects of nutritional status on quality of life in palliative care patients. *Bozok Tıp Derg.* 2017;7(4):1-7.
15. Turgut Ö, Pektaş M, Aydinli B, Sagün A. Mersin Şehir Eğitim ve Araştırma Hastanesi Erişkin Palyatif Bakım Birimi'nde yatan hastaların retrospektif analizi. *Mersin Üniv Sag Bil Derg.* 2019;12(3):407-412.
16. Ülger Z, Halil M, Kalan I, et al. Comprehensive assessment of malnutrition risk and related related factors in a large group of community-dwelling older adults. *Clin Nutr.* 2010;29(4), 507-511.
17. Dincer M, Kahveci K, Döğer C, Gökçinar D, Yarici Ak, Taş H. Factors affecting the duration of admission and discharge in a palliative care center for geriatric patients. *Turk J Geriatr/Türk Geriatri Derg.* 2016;19:2.
18. Şenel G, Oğuz G, Koçak N, Karaca Ş, Kaya M, Kadıoğulları N. Opioid use and the management of cancer patient pain in palliative care clinic. *Ağrı.* 2016;28(4):171-176.
19. Uysal N, Şenel G, Karaca Ş, Kadıoğulları N, Koçak N, Oğuz G. Palyatif bakım kliniğinde yatan hastalarda görülen semptomlar ve palyatif bakımın semptom kontrolüne etkisi. *Ağrı.* 2015;27(2):104-110.
20. Clark AB, Reijnierse EM, Lim WK, Maier AB. Prevalence of malnutrition comparing the GLIM criteria, ESPEN definition and MST malnutrition risk in geriatric rehabilitation patients: *RESORT. Clin Nutr.* 2020;39(11):3504-3511.
21. Maeda K, Ishida Y, Nonogaki T, Mori N. Reference body mass index values and the prevalence of malnutrition according to the Global Leadership Initiative on Malnutrition criteria. *Clin Nutr.* 2020;39(1):180-184.
22. Matsumoto Y, Iwai K, Namikawa N, et al. The relationship between existing nutritional indicators and Global Leadership Initiative on Malnutrition (GLIM) criteria: a one-institution cross-sectional analysis. *Clin Nutr.* 2020;39(10):3099-3104.
23. Abd-El-Gawad WM, Abou-Hashem RM, El Maraghy MO, Amin GE. The validity of Geriatric Nutrition Risk Index: simple tool for prediction of nutritional-related complication of hospitalized elderly patients. Comparison with Mini Nutritional Assessment. *Clin Nutr.* 2014;33(6):1108-1116.
24. Gärtner S, Kraft M, Krüger J, et al. Geriatric nutritional risk index correlates with length of hospital stay and inflammatory markers in older inpatients. *Clin Nutr.* 2017;36(4):1048-1053.
25. Balci C, Bolayir B, Eşme M, et al. Comparison of the efficacy of the Global Leadership Initiative on Malnutrition Criteria, Subjective Global Assessment, and Nutrition Risk Screening 2002 in diagnosing malnutrition and predicting 5-year mortality in patients hospitalized for acute illnesses. *J Parenteral Enteral Nutr.* 2020;45(6):1172-1180.
26. Sousa-Santos AR, Afonso C, Borges N, et al. Factors associated with sarcopenia and undernutrition in older adults. *Nutrition Dietetics.* 2019;76(5):604-612.
27. Kootaka Y, Kamiya K, Hamazaki N, et al. The GLIM criteria for defining malnutrition can predict physical function and prognosis in patients with cardiovascular disease. *Clin Nutr.* 2021;40(1):146-152.
28. Shimizu A, Maeda K, Honda T, et al. Comparison between the global leadership initiative on malnutrition and the European Society for Clinical Nutrition and Metabolism definitions for the prevalence of malnutrition in geriatric rehabilitation care. *Geriatrics Gerontology Int.* 2020;20(12):1221-1227.
29. Yin L, Lin X, Li N, et al. Evaluation of the global leadership initiative on malnutrition criteria using different muscle mass indices for diagnosing malnutrition and predicting survival in lung cancer patients. *J Parenteral Enteral Nutr.* 2020;45(3):607-617.
30. Sanchez-Rodriguez D, Locquet M, Reginster JY, Cavalier E, Bruyère O, Beaudart C. Mortality in malnourished older adults diagnosed by ESPEN and GLIM criteria in the SarcoPhAge study. *J Cachexia Sarcopenia Muscle.* 2020;11(5):1200-1211.
31. Efendioğlu EM, Göl M, Tarakçıoğlu MS, Türkbeyler İH, Öztürk ZA. Determination of vitamin D, vitamin B12 and folic acid deficiency prevalence among geriatric palliative care patients. *Eur J Geriatr Gerontol.* 2020;2(1):9-12.
32. Rasheed S, Woods R. An investigation into the association between nutritional status and quality of life in older people admitted to hospital. *J Human Nutr Diet.* 2014;27(2):142-151.
33. Yilmaz M, Atilla FD, Sahin F, Saydam G. The effect of malnutrition on mortality in hospitalized patients with hematologic malignancy. *Supportive Care in Cancer.* 2020;28(3):1441-1448.
34. Kruger DJ, Nesse RM. Sexual selection and the male: female mortality ratio. Evolutionary Psychol. 2004;2(1):147470490400200112.
35. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Int Med.* 2014;174(2):251-258.
36. Gentile S, Lacroix O, Durand A, et al. Malnutrition: a highly predictive risk factor of short-term mortality in elderly presenting to the emergency department. *J Nutr Health Aging.* 2013;17(4):290-294.
37. Karaman D, Topal K, Aksoy H, Gereklioğlu Ç. Huzurevinde kalan yaşlılarda malnütrisyon, depresyon ve yaşam kalitesi üzerine etki eden faktörlerin belirlenmesi. *Pamukkale Tıp Derg. 2019;12(3):545-553.*

Journal of
Pulmonology and
Intensive Care

Original Article

DOI: 10.51271/JOPIC-0014

Comparison of the computed tomography COVID-19 Pneumonia Severity Scores in vaccinated and unvaccinated individuals without comorbidities

Ahmet Said Çil

[1] *Department of Radiology, Ahi Evran University Training and Research Hospital, Kırşehir, Turkey*

Cite this article: Çil AS, Comparison of the Comparison of the computed tomography COVID-19 Pneumonia Severity Scores in vaccinated and unvaccinated individuals without comorbidities. *J Pulmonol Intens Care.* 2023;1(3):60-64.

Corresponding Author: Ahmet Said Çil, asaidcil@hotmail.com

Received: 02/08/2023 ◆ **Accepted**: 12/08/2023 ◆ **Published**: 29/08/2023

ABSTRACT

Aims: The aim of this study to investigate the effect of vaccines on pneumonia severity by comparing the computed tomography pneumonia scores of vaccinated and unvaccinated individuals with COVID-19 without known comorbidities.

Methods: Between January 2021 and January 2022 a total of 270 patients, 133 vaccinated and 137 unvaccinated, with positive polymerase chain reaction tests and without any significant co-morbidity were included in the study. Computed tomography pneumonia scores, demographic characteristics, and vaccination information were evaluated through the hospital's electronic registry system.

Results: Mean pneumonia scores of individuals vaccinated for 1 dose were higher than individuals vaccinated for 2 or more doses. The shortest duration of infection after vaccination was determined in the group with 1 dose of vaccine and the longest in the group with 2 doses of vaccine. There was no significant difference between the total mean pneumonia scores of vaccinated (8.36∓3.97) and unvaccinated (7.88∓3.67) individuals (p >0.05). When the comparison was made in age groups, pneumonia scores of vaccinated individuals over 70 years of age were found to be significantly lower than unvaccinated individuals (p=0.003). A statistically significant positive correlation was found between the age of the patients and pneumonia scores in the entire study group (Rho=0.293).

Conclusion: There is no significant difference in the pneumonia scores of vaccinated and unvaccinated COVID 19 pneumonia patients without comorbidities, except for patients over 70 years of age.

Keywords: COVID-19, vaccines, multidetector computed tomography, pneumonia, comorbidity

INTRODUCTION

COVID-19, a member of the coronavirus family, spread rapidly and became a pandemic.[1] Many countries around the world began implementing vaccination programs to protect their citizens against the pandemic.[1] Breakthrough COVID-19 infections seen after vaccination have led to debate about the effectiveness of vaccines against variants.[1] Vaccines very rarely provide 100% protection. The protection of the Covid 19 vaccine has also been reported to be around 90 per cent.[1] Infections that develop as a result of inadequate immunity in vaccinated individuals are called breakthrough infections.[2] Breakthrough infections occur due to personal biological factors that affect the individual's immune system, or due to loss of vaccine efficacy as a result of mutations in viruses, as well as improper administration or storage of vaccines.[2]

COVID-19 pneumonia is more severe in patients with comorbidities that compromise the immune system.[3,4] Previous studies investigating the effects of vaccines on computed tomography (CT) pneumonia scores in vaccinated and unvaccinated individuals with comorbidities have not differentiated. In addition, the types of vaccines and vaccination procedures vary.[5-9] For these reasons, we aimed to investigate the effects of vaccines on the severity of COVID-19 pneumonia in patients without known comorbidities.

METHODS

Ethics

The study was approved by the Kırşehir Ahi Evran University Clinical Researches Ethics Committee (Date: 21.06.2022, Decision No: 2022-12/117). Because the study was designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion Criteria

Patients over 18 years of age with positive PCR tests and CT findings of viral pneumonia were included in the study. In the vaccinated group, single or more vaccinated individuals were included in the study.

Exclusion Criteria

Patients with co-morbidities (diabetes mellitus, malignancy, etc.) affecting the immune system were excluded from the study.

Vaccination Status

Vaccinated patients were categorized as having received a single dose (incomplete) or 2 or more doses (complete) of vaccine. Assuming that a single dose of vaccine did not provide sufficient immunity, the pneumonia scores of single-dose vaccinated individuals were compared with those of individuals who received 2 or more doses of vaccine, and the pneumonia scores of unvaccinated individuals were compared with those of individuals who received two or more doses of vaccine.

Image Analysis

Patients were scanned using Toshiba Alexion 16-slice and General Electric (GE) Lightspeed 128-slice CT scanners scanner using standard acquisition protocols. CT images were evaluated by using the hospital's picture archiving and communication system.

COVID-19 pneumonia can be divided into four stages based on the timeline of symptom progression: the early stage, which typically occurs within the first 0-4 days; the progressive stage, which typically occurs between days 5-8 days; the peak stage, which is typically observed between days 10-13 days ; and the resolution stage, which typically begins on 14th day or later. Although it varied according to the time of admission of each patient, a CT scan was performed at our hospital between 5-8 days. A second and, if necessary, a third CT scan can be done for patients who become clinically severe and develop respiratory distress. If a patient had multiple scans, the scan with the highest pneumonia score was used. All CT scans were interpreted by the same radiologist with more than 20 years of experience.

The CT pneumonia severity score index is a scoring system that determines the severity of pneumonia according to the lung volume affected.[10] The severity of pneumonia is determined by assigning a score between 1 and 5 according to the percentage of volume retained in each of the five lung lobes, and then summing the scores of the five lobes. A total score of less than 8 indicates mild pneumonia, 8-15 moderate pneumonia and 16-25 severe pneumonia (**Figure 1**).

Statistical Analysis

Statistical analysis of the study was performed using the Statistical Package for Social Sciences for Windows software (IBM SPSS version 28.0, Armonk, NY, USA). The normality assumption of the variables was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics of the variables are presented as mean±standard deviation, median (min-max) and frequency n (%). For univariate analysis of the variables in the study, Kruskal-Wallis and Chi-square tests were used, depending on the type of variable and the availability of assumptions.

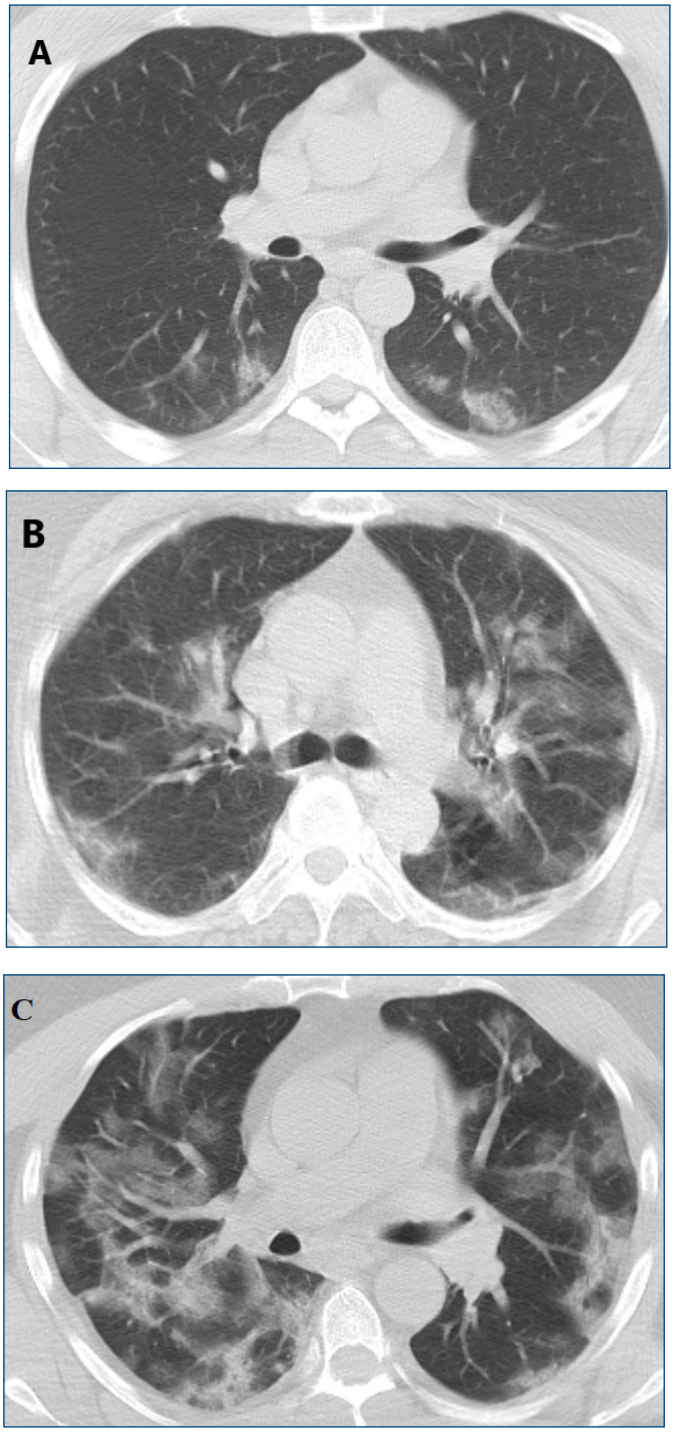


Figure 1. CT sections of different patients with mild (A), moderate (B), and severe (C) pneumonia

Pairwise comparisons of groups with significant differences between them obtained by the Kruskal-Wallis test were performed using the Mann-Whitney U test, with Bonferroni correction (0.05/number of groups). Relationships between variables were examined using Spearman's Rho correlation analysis.

RESULTS

In this study, CT images of 270 patients, 137 (50.7%) females and 133 (49.3%) males, who met fulfilling the inclusion criteria were examined. The mean age of the vaccinated group was 58.81∓14.31 years, whereas the mean age of the unvaccinated group was 56.36∓12.94 years.

The distribution of pneumonia scores and percentages of the patients in both groups is summarized in **Table 1**.

There was no significant difference in pneumonia scores between the groups in comparisons based on gender (**Table 2**).

In the vaccinated group, 43 people received 1 dose (39 Sinovac, 4 BioNTech), 66 people (60 Sinovac, 6 BioNTech) received 2 doses, 16 people (14 Sinovac, 2 BioNTech) received 3 doses and 6 people (2 Sinovac, 4 BioNTech) received 4 doses. 44 patients who received 1 dose of vaccine were considered insufficiently vaccinated. When comparing the pneumonia scores of vaccinated and unvaccinated individuals, comparisons were made with individuals who had two or more vaccinations.

When the mean pneumonia scores were compared according to the vaccine dose numbers in the vaccinated group, the difference between the pneumonia scores was not significant (p= 0.118). However, the pneumonia score of those who received 1 dose of incomplete vaccine was found to be the highest, and those who received 4 doses of vaccine had the lowest mean pneumonia scores (**Table 3**).

The difference was found to be statistically significant (p = 0.000) when the time elapsed until the infection appeared in the patients after vaccination according to the number of vaccine doses. The shortest duration of infection after vaccination was determined in the group with 1 dose of vaccine and the longest in the group with 2 doses of vaccine (**Table 3**). No significant relationship was found between the duration of disease onset and the severity of pneumonia after vaccination (Rho=-0.086, p=0.244).

When the mean pneumonia scores of vaccinated (8.36∓3.97) and unvaccinated (7.88∓3.67) individuals were compared the difference between the total mean pneumonia scores of both groups was not statistically significant (p > 0.05). When pneumonia scores were compared according to age groups, there was no significant difference between pneumonia scores in the 19–39 and 40–49 age groups. The mean pneumonia scores of the vaccinated patients were higher in the 50–59 and 60–69 age groups. Mean pneumonia scores of unvaccinated patients in the 70–80 age group were found to be higher than vaccinated patients (**Table 4**).

There was no significant difference in the frequency of CT findings such as consolidation, air bronchogram and ground-glass opacities in the comparison of all patients in the vaccinated and unvaccinated groups (p=0.569). Since the number of individuals vaccinated with BioNTech was low in the vaccinated patient group, a statistical comparison could not be made between the two vaccines. When the age of the patients and pneumonia scores were compared in all patient groups, a statistically significant positive correlation was found between age and pneumonia scores (Rho=0.293, p < 0.001). Pneumonia scores increased with age.

DISCUSSION

In this study, we aimed to evaluate the effect of the vaccine on the severity of pneumonia by comparing the CT severity scores of vaccinated and unvaccinated individuals without known comorbidity. We thought that the effect of vaccines on breakthrough pneumonia could be more objectively assessed in a study group in which comorbidities did not have a

Table 1. Pneumonia scores and percentages of vaccinated and unvaccinated patients

Severity Score		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20	23	Total	p*
G1	N	2	11	11	11	15	5	9	10	10	14	7	14	6	2	1	2	-	1	1	1	133	0.000
	%	1.5	8.3	8.3	8.3	11.3	3.8	6.8	7.5	7.5	10.5	5.3	10.5	4.5	1.5	0.8	1.5	-	0.8	0.8	0.8	100	
G2	N	4	7	4	11	13	5	9	8	21	9	8	9	8	7	2	5	3	3	1	-	137	0.000
	%	2.9	5.1	2.9	8.0	9.5	3.7	6.6	5.8	15.3	6.6	5.8	6.6	5.8	5.1	1.5	3.7	2.2	2.2	0.7	-	100	

*: Chi-Square Test. G1: vaccinated group, G2 Unvaccinated group.

Table 2. Comparison of of mean pneumonia scores groups by gender

Gender	Males	Females	p*
G1	7.90±4.41 8 (1–20)	7.85±4.40 8 (1–23)	0.796
G2	9.03±4.79 9 (1–20)	8.65±4.07 9 (1–18)	0.723
G1+G2	8.41±4.47 9 (1–20)	8.32±4.21 8,5 (1–23)	0.860

*Mann-Whitney U test. G1: vaccinated group, G2 Unvaccinated group.

Table 3. Comparisons of mean pneumonia scores according to vaccine dose and time to infection after vaccination

	1 Dose	2 Doses	3 Doses	4 Doses	p value*	Comparison Group	Post Hoc p value#
Severity Score	9.79±5.04 9 (1–20)	8.40±4.08 9 (1–17)	9.44±3.95 9 (1–18)	7.42±3.64 7 (4–14)	0.118	-	-
Time to infection after vaccination (day)	44.67±80.18 22 (3–370)	109.15±84.29 93 (2–335)	95.72±81.65 82 (7–271)	60.85±76.06 26 (5–216)	0.000	1 vs. 2 1 vs. 3 1 vs. 4 2 vs. 3 2 vs. 4 3 vs. 4	0.000 0.010 0.653 0.383 0.070 0.224

*: Kruskal–Wallis, #: Mann–Whitney U

Table 4. Comparisons of mean pneumonia scores according to age

Age	19-39	40-49	50-59	60-69	70+	Total	p#
G1	7.52±3.79 7 (3–16)	7.00±4.42 6 (2–23)	7.02±4.07 7,5 (1–18)	7.53±3.67 7 (1–13)	11.26±3.89 12 (1–16)	7.88±3.67 8 (1–23)	0.000
G2	6.75±4.53 6 (1–16)	8.02±5.22 7 (2–17)	10.38±3.38 11 (1–17)	8.51±3.87 9 (2–18)	7.62±3.28 9 (3–16)	8.36±3.97 9 (1–18)	0.000
p*	0.518	0.963	0.002	0.041	0.003	0.056	

*Mann Whitney U # Kruskal Wallis. G1: vaccinated group, G2 Unvaccinated group.

negative impact. The mean pneumonia scores of those in the study group who received one dose were higher than those who received two or more doses. The time to development of infection after one dose of vaccine is lower than that of individuals vaccinated two or more times. Studies show that serum neutralization and IgG or IgA binding levels are lower after the first dose of vaccine, especially in older individuals.[11]

Some studies have reported that pneumonia occurring less than 2 weeks after vaccination has a lower pneumonia score than pneumonia occurring more than 19 weeks after vaccination.[5] In this study, no statistically significant difference was found between the severity of pneumonia occurring shortly or long after vaccination.

Previous similar studies reported that age was an important factor influencing the pneumonia score, with patients over 50 years of age having higher pneumonia scores.[11,12] In this study, when patients in both groups were evaluated together, the pneumonia scores of patients over 50 years of age were found to be higher than the other age groups. Over the age of 70, this difference became more pronounced. Changes in the immune system with age and changes in the immune system after the age of 50 have been the subject of many studies. This situation, known as immune ageing, paves the way for many diseases .[12]

When we compared the pneumonia scores of two or more vaccinated patients in our study group with those of unvaccinated patients, we found that the pneumonia scores were close in individuals under 50 years of age. Mean pneumonia scores were found to be significantly lower in the vaccinated group (8.84±3.72) than in the unvaccinated group (11.26±3.89) in individuals older than 70 years. This finding may indicate that vaccinated individuals over 70 years of age had milder pneumonia than unvaccinated individuals. However, all these findings may only be specific to the individuals in our study group.

The pneumonia scores of vaccinated people aged 50-70 years were higher than those of unvaccinated people. This finding suggests that the vaccinated individuals in the study group did not develop an adequate protective immune response against the virus. If an effective vaccine, given under the right conditions, does not provide sufficient immunity, there may be a problem with the individual's immune system. Even if they are vaccinated, pneumonia may be more severe in people with an immune deficiency than in unvaccinated people. This finding could also be due to loss of vaccine effectiveness against the virus and new highly virulent variants. The main reason for breakthrough infections after vaccination is the emergence of different variants. These new variants cause both natural and vaccine-induced immunity to lose effectiveness.[14] As all patients in our region were not tested for variants, we could not detect variants in our study. However, this study was conducted during the period of the Delta and Omicron variants.

Most of the studies that evaluated the effectiveness of vaccines using CT pneumonia scores showed that pneumonia was milder in vaccinated individuals.[5-8] Fewer studies have reported that vaccines do not change pneumonia scores.[9] However, all these studies did not distinguish patients with comorbidities.[5-9] Differences between studies may be due to differences in the virus variants and vaccines used. The immune system is very complex and can be influenced positively or negatively by many regional and personal factors. However, it is not possible to determine a definite cause with the data from our study or similar studies. More detailed multidisciplinary studies are needed.

Limitations

There are several limitations to this study. Firstly, viral variants could not be detected. Therefore, the study results cannot be generalized to all variants and vaccines.

CONCLUSION

There is no significant difference in pneumonia scores between vaccinated and unvaccinated COVID 19 pneumonia patients without comorbidities, except for patients over 70 years of age. There is a significant correlation between pneumonia score and age.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Kırşehir Ahi Evran University Clinical Researches Ethics Committee (Date: 21.06.2022, Decision No: 2022-12/117).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Gupta RK, Topol EJ. COVID-19 vaccine breakthrough infections. *Science.* 2021;374(6575):1561-1562.
2. Maclean P, Mentzer AJ, Lambe T, Knight J. Why do breakthrough COVID-19 infections occur in the vaccinated?. *QJM.* 2022;115(2):67-68.
3. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. *SN Comprehen Clin Med* . 2020;2(8):1069-1076.

4. Guan W-j, Liang W-h, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5)2000547
5. Verma A, Kumar I, Singh PK, et al. Initial comparative analysis of pulmonary involvement on HRCT between vaccinated and non-vaccinated subjects of COVID-19. *Eur Radiol*. 2022;32(6):4275-4283.
6. Hitchings MD, Ranzani OT, Torres MSS, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. *Lancet Regional Health-Americas*. 2021; 1:100025.
7. Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. *MedRxiv*. 2021. 2021-2023
8. Naik BR, Kumar SA, Rachegowda N, Ullas LY, Revanth R, Aluru NRVS. Severity of COVID-19 infection using chest computed tomography severity score index among vaccinated and unvaccinated COVID-19-positive healthcare workers: an analytical cross-sectional study. *Cureus*. 2022;14(2):e22087.
9. Fatima S, Zafar A, Afzal H, et al. COVID-19 infection among vaccinated and unvaccinated: Does it make any difference? *PLoS One*. 2022;17(7): e0270485.
10. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology*. 2020;295(3):715-721.
11. Collier DA, Ferreira IATM, Kotagiri P, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. *Nature*. 2021;596(7872):417-422.
12. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2020;396(10267):1979-1993.
13. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol*. 2013;14(5):428-436.
14. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 variants-clinical, public health, and vaccine implications. *N Engl J Med*. 2021;384(19):1866-1868.

Journal of
Pulmonology and
Intensive Care

Review

DOI: 10.51271/JOPIC-0015

General approach to dry cough

Gülden Bilgin

Department of Chest Diseases, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article: Bilgin G. General approach to dry cough. *J Pulmonol Intens Care*. 2023;1(3):65-69.

Corresponding Author: Gülden Bilgin, fkgbilgin@gmail.com

Received: 16/07/2023 ◆ **Accepted**: 01/08/2023 ◆ **Published**: 29/08/2023

ABSTRACT

Dry cough is a common health problem and upper airway cough syndrome, asthma and gastroesophageal reflux disease are the most common causes of dry cough in adults. Diagnostic approach and algorithms are defined according to the American Academy of Chest Diseases cough guideline updated in 2006. The initial evaluation should start with history taking, physical examination, radiologic and spirometric assessment. Antihistaminic and decongestant agent combinations, inhaled corticosteroid and bronchodilator combinations, leukotriene receptor antagonists, and when necessary oral steroids are used in the treatment depending on the etiology. Treatments based on etiology and if needed evaluation with further tests are essential.

Keywords: Dry cough, etiology, diagnosis, treatment

INTRODUCTION

Although cough is a natural defense mechanism that protects the respiratory tract, it is also a symptom of all respiratory system diseases and some non-respiratory system pathologies.[1-3] Its incidence in the adult age group is between 3-12%. A simple and anatomical cough algorithm was first introduced by Richard Irwin in 1977.[4] The American College of Chest Physicians (ACCP) modified these guidelines in 2006.[1] This protocol defines the cause of cough based on the structures within the anatomical distribution of the vagal afferent nerves.[5,6] Coughing is a forced expiratory maneuver against the glottis which is closed after a deep and rapid inspiration. Meanwhile, the contraction of the expiratory muscles of the chest and abdomen generates a high intrathoracic pressure, the sudden opening of the glottis forcefully expel air from the mouth, and while passing through the vocal cords air produce coughing sound. Afferent stimuli created via receptors in the diaphragm, pleura, bronchi, trachea, larynx, pharynx, nasopharynx, nasal mucosa and external auditory canal travel through N. vagus, N. trigeminalis, N. Phrenicus, N. glossopharyngeus to the voluntary cough center in the cortex and the reflex cough center in the brain stem. Efferent stimulus formed by the N. vagus, N. phrenicus and spinal motor nerves creates cough response via contraction of the diaphragm and other respiratory muscles.[7]

A dry cough is defined as a cough that does not bring up any phlegm or mucus. Dry cough is often due to an underlying disease or a defense mechanism of the respiratory system against irritation, and it can last from a few days to a few weeks. It is classified according to the duration of the cough; acute cough <3 weeks (most common), subacute cough 3-8 weeks, chronic cough >8 weeks.[7]

Symptoms commonly associated with dry cough are tickling sensation in the airways, wheezing, dyspnea, pressure sensation in the chest, inability to sleep especially at night due to coughing, deterioration of sleep quality and a cough that sounds unproductive.[8] Other findings accompanying dry cough include flu-like symptoms (fatigue, fever, sore throat, headache, etc.), runny or stuffy nose, sore throat, vomiting, swollen neck lymph nodes, joint pain, loss of appetite, and diarrhea.[9]

Table 1 . Causes of dry cough

- Cough associated with upper respiratory tract
- Gastroesophageal reflux (GER)
- Cough variant asthma (CVA)
- Cough due to angiotensin converting enzyme inhibitors (ACEIs)
- Nonasthmatic eosinophilic bronchitis (NAEB)
- Chronic idiopathic cough (cough hypersensitivity syndrome)
- Cough due to obstructive sleep apnea syndrome (OSAS)
- Exposure to acute irritants
- Occupational asthma
- Chronic psychogenic cough
- Chronic lung diseases

COUGH ASSOCIATED WITH UPPER RESPIRATORY TRACT

Cough due to upper respiratory tract pathologies should also be considered Dry cough that develops due to upper respiratory tract related pathologies is called "upper airway cough syndrome". Upper airway cough syndrome is associated with many upper respiratory tract pathologies with allergic, infectious, vasomotor etiology and irritating particles. The most common cause of cough is respiratory tract infections caused by viruses. In recent years, the relationship between chronic

tonsillar enlargement, external auditory canal pathologies, obstructive sleep apnea syndrome (OSAS) and cough has also been described.[10,11]

in patients with normal chest X-ray, non-smoker, using agents other than angiotensin converting enzyme inhibitor (ACEI) and with symptoms such as throat clearing due to nasal discharge.[12]

However, postnasal discharge is not the only pathophysiological mechanism in dry cough seen after upper respiratory tract infection and it may not always be detected on physical examination. In their study Macedo et al.[13] reported that postnasal discharge may not be the only cause of dry cough Cough receptors located in the upper airways have been shown to be more sensitive in cough associated with the upper airways.[14] Diagnosis is made by symptoms, physical examination, radiological findings, and response to specific treatment. Empirical use of antihistamines alone or in combination with decongestants due to their anticholinergic effects is the first treatment choice.[1,2-15]

Sinus radiography should be performed in cases that do not respond to empirical treatment. Bacterial sinusitis, perennial nonallergic rhinitis and allergic rhinitis may be the underlying cause1.[12]

Cough associated with an upper airway infection usually resolves within three weeks. Although to a small extent, Bordetella pertussis might be cause persistent cough. If secretion has subsequently started in the upper airways, the diagnosis is mainly based on culture and Polymerase Chain Reaction (PCR) in the samples taken from upper ways. Azithromycin is used for treatment.[16]

GASTROESOPHAGEAL REFLUX (GER)

Normally, GER is functionally occurring 10-15 times a day during meals, after meals, and during the REM sleep phase. Microaspirations can cause coughing by producing irritation in the hypopharynx and supraglottic larynx or by stimulating the esophago-bronchial reflex at the lower esophageal level and creating chronic inflammation.[17] Three mechanisms have been identified in the onset of GER; persistent low sphincter pressure, temporary relaxation of the esophageal sphincter, and increased intra-abdominal pressure.

In addition to dry cough, if chest X-ray is normal, GER should be considered in the first-place patients with gastrointestinal system (GIS) complaints and heartburn.[17]

GERD can be diagnosed using empirical treatment without any medical examination. Antacid therapy should be applied to patients with a typical history, even if they do not describe any GI symptoms. Endoscopy, barium esophageal radiography, esophageal impedance measurement, esophageal manometry, ambulatory intraesophageal pH monitoring can be performed to confirm the diagnosis. The most sensitive and specific test for GERD diagnosis is 24-hour esophageal pH monitoring, however, usually anamnesis would be enough. For patients who do not show any improvement with treatment 24-hour esophageal pH monitoring is indicated. Treating reflux with acid-blocking drugs (proton pump inhibitors), sleeping on a high pillow, diet and lifestyle changes may help to ease the symptoms.[1,2] If the symptoms persist despite full compliance with antireflux treatment and lifestyle changes, and for those whose cough does not regress after three months of treatment, antireflux surgery can be considered. [3]

Laryngopharyngeal reflux is the retrograde flow of a small amount of gastric content into the larynx and intermittently during the day. Unlike GER, it does not cause symptoms in the esophagus, gastrointestinal and respiratory systems. Dry cough is detected in 97% of those with laryngopharyngeal reflux and the diagnosis of laryngopharyngeal reflux is performed using video-laryngoscope.[18]

COUGH VARIANT ASTHMA (CVA)

Cough may be the only symptom in 7-11% of asthma patients, and they might not have a history of wheezing, dyspnea, or asthma; this condition is called cough variant asthma. Salem and Aviado, in 1964, reported for the first time a cough due to airway obstruction and stimulated cough receptors by local bronchoconstriction.[19] Cough can occur without bronchospasm, in fact, cough can be the only symptom in 28% of asthmatic patients.[20] In patients with suspected asthma based on anamnesis, the diagnosis is confirmed by pulmonary function tests, reversibility test, daily PEF measurement, or bronchial provocation test if necessary. If bronchial provocation test cannot be performed, CVA can be diagnosed based on the response to treatment and empirical treatment should be initiated. Even if a treatment response is achieved, one should keep in mind that chronic cough causes such as nonasthmatic eosinophilic bronchitis and irritant exposure cannot be ruled out. Inhaled corticosteroids and bronchodilators are recommended for the chronic cough seen in CVA and complete recovery may require 6-8 weeks of treatment. If there is airway inflammation and increased eosinophil count, anti-inflammatory therapy can be started for the cough resistant to inhaled corticosteroids and in case of more resistant cough short-term (1-2 weeks) systemic corticosteroid can be given.

COUGH DUE TO ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIS)

Cough due to ACEIS first described in 1985, the underlaying mechanism is not fully known.[21] It has been reported that mediators such as bradykinin and substance p activate ACEIs. Treatment may be insufficient when dry cough occurs due to increased estrogen levels in pregnant women, decreased immunity and the inability to use most of the drugs. Cough emerges in 5-35% of patients treated with ACEIs.[20] This side effect is more common in non-smokers, women, black people, and Asians.[22] The best treatment option is discontinuation of the drug unless it is not contraindicated. Patients can switch to another treatment group and if the cough resolves ACEIs can be restarted.[2-23] Although, the cough disappears 1-4 weeks after the discontinuation of the drug, this process can take up to three months. Sodium cromoglycate, theophylline, indomethacin, amilodipine, nifedipine, ferrous sulfate can be used to suppress cough in patients for whom ACEIs cannot be discontinued.

Cough due to COVID-19 is like the symptoms of upper respiratory tract cough syndrome. Its treatment is the same as for upper respiratory tract cough syndrome.[24]

NONASTHMATIC EOSINOPHILIC BRONCHITIS (NAEB)

Non-asthmatic eosinophilic bronchitis (NAEB) is an important cause of chronic cough and characterized by eosinophilic infiltration of the airways.[25] Although it is known that occupational exposure and allergen exposure play a role in the etiology of the disease, it is not fully understood yet. Methacholine response and variable airway obstruction are not present in these patients.

It was first described as one of the causes of chronic cough in 1989 by Gibson et al.[7] Cough may be dry or not, the absence of bronchial obstruction should be demonstrated by pulmonary function tests, reversibility test, if necessary bronchial provocation test. Diagnosis is based on demonstration of >3% eosinophilia in sputum, induced sputum, and sometimes bronchial lavage or bronchoscopic biopsy in patients who did not smoke, has no symptoms and functional impairment due to airway obstruction and airway hypersensitivity. These tests may not be performed in cases with a dry cough. The best treatment strategy is to avoid exposure. Initial treatment is low-dose inhaled corticosteroids, in advanced cases, high-dose inhaled corticosteroids or oral corticosteroids should be considered. Cessation of smoking is important for symptom relief. However, the differential diagnosis of NAEB and cough variant asthma (CVA) may be difficult in patients who have treated response.[26]

CHRONIC IDIOPATHIC COUGH (COUGH HYPERSENSITIVITY SYNDROME)

The diagnosis of idiopathic cough is based on exclusion of others. The diagnosis of idiopathic cough should not be made before all diagnostic procedures are completed, specific and empirical treatments have been tried, and rare causes have been excluded. It is also known as sensory neuropathic cough, laryngeal sensory neuropathy, sensory hyperreactivity, and cough associated with vagal neuropathy.[6] Hyperalgesia is present in idiopathic coughs as in other neuropathic diseases. The concentration of neuropeptides is increased at the nerve endings that act as cough receptors in the airways. Magnetic resonance imaging (MRI) shows increased activation in cortical and subcortical centers associated with cough.[27] In a study in experimental animals, qualitative changes with increased expression of tachykinin in airway sensory neurons and nonnociceptive neurons were observed in animals inoculated with Sendai virus. This type of phenotype changes may cause increased cough reflex sensitivity and cough even after viral upper respiratory tract infection.[28] Another study in patients with idiopathic cough reported an increase in lymphocytes in the bronchial epithelium and bronchoalveolar lavage fluid (BAL).[1] The effect of sex hormones was emphasized as the reason why idiopathic cough is common in women. Generally, upper respiratory tract infections is common in menopausal women. Usually, there is a feeling of irritation and itching in the throat before coughing starts. Bad smells, food, talking, exercise, cold weather are the most common triggers. Non-respiratory complaints such as urinary incontinence, chest and back pain, deterioration in social relations, anxiety and depression are also prominent.[6] In a study by Ebihara et al.[29] danazol helped regression of cough in female animals with ACEI-induced cough.

COUGH DUE TO OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

OSAS should also be considered in unexplained coughs. The treatment response rate is 93% to Continuous Positive Airway Pressure (CPAP) treatment together with other treatment combinations.[11]

EXPOSURE TO ACUTE IRRITANTS

Irritants with high solubility, such as ammonia, cause mild symptoms in the upper airways, as patients will be irritated due to their foul smell. On the other hand, irritants with low solubility, such as ozone, are inhaled for a longer period of time, and they can cause serious airway damage and dry cough or irritant cough. Immunological, irritant, corrosive agents in the workplace can also cause dry cough .[7]

OCCUPATIONAL ASTHMA

Occupational asthma is a type of asthma caused by exposure to inhaled irritants in the workplace. Asthma symptoms such as dyspnea, cough, wheezing, and tickling usually regress or even improve after being away from the workplace. Usually, dry cough is the main symptom in occupational asthma patients.[30]

CHRONIC PSYCHOGENIC COUGH

It is common in childhood, and it may be habitual or part of a tic disorder. It may occur spontaneously or voluntarily. Cough usually disappears during an enjoyable activity or night and day sleep. A diagnosis of psychogenic cough should not be made without excluding all other causes.[7]

CHRONIC LUNG DISEASES

Dry cough can be seen in chronic bronchitis, tuberculosis, bronchiolitis, interstitial lung diseases, and lung cancer. Other rare causes are heart failure, external auditory canal diseases, diaphragm irritation, peritoneal dialysis, laryngeal sensory neuropathy, arteriovenous malformations, retrotracheal masses, premature ventricular beats.

STUDIES FOR INVESTIGATING THE ETIOLOGY OF DRY COUGH

Chest and sinus radiographs, pulmonary function tests (reversibility and bronchoprovocation tests with methacholine), allergy tests, tests for gastroesophageal reflux, microbiological or cytological sputum examinations.[17]

TREATMENT OF DRY COUGH

Treatment Strategies in Dry Cough

If possible, the first step is cessation of smoking.[1-3] Studies have shown that active or passive smoking increases incidence of dry cough.[31] Occupation and hobby inquiries should be made.[1,2,3] Symptoms and signs of specific diseases should be evaluated in patient history and physical examination and a Chest X-ray should be performed. In cases where treatment was started and cough persists despite this treatment, stopping the treatment and monitoring the cough response may give clues for the etiology.[2] Generally, the chance of treatment of the

cough is better when the cause of the cough is determined, and specific treatment is given. This is the basis of the cause-based treatment model.[1,2,32]

Sometimes it is an option to wait for the dry cough to resolve on its own in 1-2 days. Criteria for applying to a physician in dry cough are fever, hemoptysis, dyspnea, severe chest pain, wheezing, being in the same environment with a patient with COVID, whooping cough or tuberculosis, facial swelling or rash, confusion, sleep problems, neck lymphadenopathy.

Ambulatory treatment of dry cough may include taking plenty of fluids, honey, salt mouthwash, clearing the throat with water when the cough urges, not using the voice excessively, avoiding triggers such as extreme cold and dry air, using an air humidifier, cold steam, or an air cleaner.

Treatment of dry cough has two types: Specific and nonspecific.

Nonspecific Treatment

It is the symptom remover treatment. It is not oriented to the cause or mechanism of coughing. It is preferred for cases when cause could not be detected or specific treatment could not be conducted. Irwin is applied so as to keep couging under control and relax patient. Since it depends on no reason, success ratio of nonspecific treatment is limited. Primary medicine used in nonspesific treatment is codein, dextromethorphan, dextropheniramine and pseudoephedrine.

Specific Treatment

It is oriented to the cause coughing. Success ratio is 84-98%.

In asthma-related dry cough, a combination of inhaled corticosteroid and long-acting b2 agonist is given. The cough seen in coughing asthma and eosinophilic bronchitis also has a high response to inhaled steroids. Cough resolves within 1 week after starting inhaler therapy. The definite benefit will be in 4-8 weeks. Leukotriene receptor antagonists alone or in combination with antihistamines are another option used in asthma patients with asthma and cough.[33-34]

Intranasal corticosteroid new generation antihistamine decongestant or decongestant alone are useful in allergic rhinitis, which is one of the subgroups of postnasal drip syndrome treatment. In vasomotor rhinitis, the anticholinergic agent ipratropium bromide responds better. In sinusitis, the appropriate combination of antibiotics, antihistamines and decongestants is used.[33-35]

Treatment of GER consists of lifestyle changes, drug therapy and surgical treatment. Quitting smoking in coughs occurring in GER, keeping the head elevated while lying down, losing weight, diet rich in protein and low in fat, avoiding foods and beverages (alcohol, coffee, cola, onion, chocolate) that cause relaxation of the lower esophageal sphincter have been beneficial in most people.[34]

Proton pump inhibitors are the most effective drugs used in coughs in GER. High doses (eg lansoprazole 30-60 mg/day) are used for 3 months. Other drugs used; prokinetic agents (cisapride, metoclopramide, etc.), H2 receptor blockers (famotidine, ranitidine, etc.).[33-34]

In the treatment of ACE inhibitor-induced cough, discontinuation of the ACE inhibitor is the most successful treatment. The cough resolves approximately 3-4 weeks after the drug is discontinued.[33]

Postinfectious cough goes away on its own. In cases that do not pass, short-term oral or inhaled steroids or ipratropium bromide are used. Macrolides are effective in pertussis. The common cold responds well to first-generation antihistamine-decongestant therapy.[35]

When other causes of dry cough (eg bronchial carcinoma, bronchiectasis, sarcoidosis, etc.) are treated, the cough improves.[35]

Inhaled anesthetic agents, gabapentin and codeine administration are recommended for the symptomatic treatment of cough in end-stage patients with malignancy and in all treatment-resistant cases.[21] In general, common causes with simple treatment schemes should be given priority, etiologies requiring long term treatment should later be considered.[15]

Causes of Dry Cough Requiring Urgent Treatment

Dyspnea, saturation decrease, tachycardia, tachypnea, pain or painful cough while breathing, high fever, rib fracture, rectus abdominis rupture, pneumoperitenum, pneumomediastinum, frequent urination may require urgent treatment. Urgent treatment should be performed after the etiology has been determined.[15]

In patients whose cough cannot be controlled despite advanced treatment, such as idiopathic cough or cough hypersensitivity syndrome, chough should be treated as a disease rather than a symptom, and suppressive therapies may be considered. This kind of treatment includes peripherally acting suppressive drugs (moguistein, levodropropizin), centrally acting suppressive drugs (codeine, dextromethorphan), neuromuscular blocking drugs (succinylcholine), drugs acting on mucociliary factors (hypertonic saline, erdosteine, carbocysteine, acetylcysteine, glycerol, bromhexidine, guafenesin, ipratropium bromide) .[7]

Complications of dry cough may occur if left untreated or in persistent cases. These complications can be sorted according to the systems as follows .[7]

Table 2 . Complications of cough

Respiratory complications	Subcutaneous emphysema Asthma attack Intercostal hernia Pneumothorax Pulmonary interstitial emphysema Tracheobronchial trauma Pneumomediastinum Pneumoperiteneum Pneumoretroperitoneum *Pneumocystis intestinalis* Laryngeal trauma.
Musculoskeletal complications	Rib fracture Rupture of rectus abdominis
Cardiovascular complications	Arterial hypotension Unconsciousness Bradyarrhythmia, tachyarrhythmia Rupture of subconjunctival, nasal or anal veins Displacement of intravascular catheters
Neurological complications	Syncope Seizure Headache Cerebral air embolism Cerebrospinal fluid rhinorrhea Disruption of ventricular shunt Stroke due to vertebral artery dissection Acute cervical radiculopathy
Gastrointestinal complications	GER Inguinal hernia Spleen rupture Hydrothorax in peritoneal dialysis Gastrostomy problems
Genitourinary complications	Urinary incontinence Cystocele
Other complications	Impaired quality of life Sleep disturbance Fatigue Weakness Vomiting Voice change Petechiae and purpura

CONCLUSION

Dry cough is an important health problem, and it is essential to clarify the etiology. In cases where the cause of the cough is known exactly and specific treatment is given, the chance of controlling the cough is high. However, cough treatment is based on the cause and in the form of an empirical treatment approach in practice. In patients whose cough doesn't resolve despite empirical treatment, the causes of cough should be investigated, and the treatments should be regulated.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 Suppl):1S-23S
2. Morice AH, McGarvey L, Pavord I; British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. *Thorax*. 2006;61(Suppl 1):i1-i24. doi:10.1136/thx.2006.065144
3. Pavord ID, Chung KF. Management of chronic cough. *Lancet*. 2008;371(9621):1375-1384. doi:10.1016/S0140-6736(08)60596-6
4. Irwin RS, Rosen MJ, Braman SS. Cough. A comprehensive review. *Arch Intern Med*. 1977;137(9):1186-1191. doi:10.1001/archinte.137.9.1186
5. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis*. 1981;123(4Pt1):413-417. doi: 10.1164/arrd.1981.123.4.413
6. Birring SS. Controversies in the evaluation and management of chronic cough. *Am J Respir Crit Care Med*. 2011;183(6):708-715. doi:10.1164/rccm.201007-1017CI
7. Mülazimoğlu D, Kayacan O. Approach to chronic cough. *Tuberc Thorax J*. 2017;65(3):227-236. doi: 10.5578/tt.57253
8. Goldsobel AB, Kelkar PS. The adult with chronic cough. *J Allergy Clin Immunol*. 2012;130(3):825-6. doi: 10.1016/j.jaci.2012.05.057
9. Erkekol FÖ. Management modalities of chronic cough in adults. *Turk Thorac J*. 2013;14(3 Suppl):27-34. doi: 10.5152/ttd.2013.107
10. Birring SS, Passant C, Patel RB, et al. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. *Eur Respir J*. 2004;23(2):199-201. doi: 10.1183/09031936.03.00066403
11. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. *Cough*. 2010;6(1):2. doi: 10.1186/1745-9974-6-2
12. Irwin RS, Curley FJ, Grossman RF. Diagnosis and treatment of symptoms of the respiratory tract, Armonk, N.Y. Futura Publishing Company. 1997:1-54.
13. Macedo P, Saleh H, Torrego A, et al. Postnasal drip and chronic cough: An open interventional study. *Respir Med*. 2009;103(11):1700-1705. doi: 10.1016/j.rmed.2009.05.005
14. Tatar M, Plevkova J, Brozmanova M, Pecova R, Kollarik M. Mechanisms of the cough associated with rhinosinusitis. *Pulm Pharmacol Ther*. 2009;22(2):121-126. doi: 10.1016/j.pupt.2008.11.014
15. Chummun D, Lü H, Qiu Z. Empiric treatment of chronic cough in adults. *Allergy Asthma Proc*. 2011;32(3):193-197. doi: 10.2500/aap. 2011. 32.3432.
16. Kline LW, Smith EA, Tracy LR ,Moerschel SK. Pertussis: a remerging infection. *Am Fam Physic*. 2013;88(8):507-514.
17. Özdilekcan Ç. Chronic Cough in Adults: Etiologic, diagnostic and treatment related approaches. *Celal Bayar Univ J Sci*. 2018;5(2):47-51.
18. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA*. 2005;294(12):1534-1540. doi: 10.1001/jama.294.12.1534
19. Salem H, Aviado DM. Antitussive drugs, with special reference to a new theory for the initation of the cough reflex and the influence or bronchodilators. *Am J Med Sci*. 1964;247:585-600.
20. Dicpinigaitis PV. Chronic cough due to asthma. *Chest*. 2006;129(1 Suppl):75-79. doi: 10.1378/chest.129.1_suppl.75S
21. Kohno S, Ishida T, Uchida Y. The Japanese Respiratory Society guidelines for the management of cough. *Respirology*. 2006;11:135-186. doi: 10.1111/j.1440-1843.2006.00920_1.x
22. Irwin RS. Unexplained cough in the adult. *Otolaryngol Clin North Am*. 2010;43(1):167-180. doi: 10.1016/j.otc.2009.11.009
23. Lacourcière Y, Brunner H, Irwin R. Effects of modulators of the renin-angiotensinaldosterone system on cough. *J Hypertens*. 1994;12(12):1387-1393.
24. Karaca B. Clinical manifestations of COVID-19 in the adult age group. *J Biotechnol Strategic Health Res*. 2020;1:85-90.
25. Lai K, Chen R, Lin J, et al. A prospective multicenter survey on causes of chronic cough in China. *Chest*. 2013;143(3):613-620. doi: 10.1378/chest.12-0441
26. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough:eosinofilic bronchitis without asthma. *Lancet*. 1989;333(8651):1346-1348.
27. Birring SS. The search for the hypersensitivity in chronic cough. *Eur Respir J*. 2017;49(2):1700082. doi: 10.1183/13993003.00082-2017
28. Carr MJ, Hunter DD, Jacoby DB, Undem BJ. Expression of tachykinins in nonnociceptive vagal afferent neurons during respiratory viral infection in guinea pigs. *Am J Respir Crit Care Med*. 2002;165(8):1071-1075.
29. Ebihara T, Sekizawa K, Ohrui T, Nakazawa H, Sasaki H. Angiotensin-converting enzyme inhibitor and danazol increase sensitivity of cough reflex in female guinea pigs. *Am J Respir Crit Care Med*. 1996;153(2):812-819. doi: 10.1164/ajrccm.153.2.8564137
30. Alberts W, Brooks S. Advances in occupational asthma. *Clin Chest Med*. 1992;13(2):281-302.
31. Janson C, Chinn S, Jarvis D, Burney P. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur Respir J*. 2001;18(4):647-654. doi: 10.1183/09031936.01.00098701
32. Irwin RS, Curley FJ, French CL. Chronic cough: The spectrum and frequency of causes, key components of diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990;141(3):640-7. doi: 10.1164/ajrccm/141.3.640
33. Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defence mechanism and as a symptom. A consensus panel report of the American College of the Chest Physicians. *Chest*. 1998;114(2):133S-181S. doi: 10.1378/chest.114.2_supplement.133s
34. Morice AH, Committee Members (ERS Task Force). The diagnosis and management of chronic cough. *Eur Respir J*. 2004;24(3):481-492. doi: 10.1183/09031936.04.00027804
35. Irwin RS, Widdicome J. Cough. In: Murray JF, Nadel JA (eds); Textbook of Respiratory Medicine. WB Saunders Company, NewYork. 2000;553-566.

Journal of
Pulmonology and
Intensive Care

Review

DOI: 10.51271/JOPIC-0016

Chronic pulmonary thromboembolic disease

Nalan Ogan, Ceren İlgar

Department of Pulmonology, Ankara Etlik City Hospital, Ankara, Turkey

Cite this article: Ogan N, İlgar C. Chronic pulmonary thromboembolic disease. *J Pulmonol Intens Care.* 2023;1(3):70-72.

Corresponding Author: Nalan Ogan, nalanogan@gmail.com

Received: 24/07/2023 ◆ **Accepted**: 26/08/2023 ◆ **Published**: 29/08/2023

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH), defined as precapillary pulmonary hypertension (PH) with right heart catheterization and imaging consistent with chronic thromboembolism, is a long-term complication of pulmonary embolism (PE). CTEPH defines symptomatic patients with maladaptive perfusion disorders after at least 3 months of therapeutic anticoagulation. In this setting, pulmonary hypertension results from extensive pulmonary artery (PA) obstruction by only organized fibrotic clots and may also be present as micro vasculopathy. Echocardiographic (ECHO) examination to determine a pulmonary surgical operation if the patient complains of anticipation and/or the risk for CTEPH is widely demonstrated (prior PE episodes, existing imaging size as index event suggestive of CTEPH, key features such as hypothyroidism and cancer), It is the preferred recognition method because of its availability and the high data value and amount of data. Patients diagnosed with CTEPH or with a strong suspicion of CTEPH should be referred to a specialist pulmonary cardiovascular clinic for further multidisciplinary diagnosis and treatment, such as pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), and/or targeted pulmonary medical therapy. In recent years, significant progress has been made in evaluating patients with sequelae after a pulmonary embolism, confirming clinical, biochemical, and hemodynamic criteria. Further work is needed to elucidate and develop appropriate standing protocols to support limited purposes and ongoing archives to ensure physical care capacity and life security.

Keywords: Pulmonary embolism, chronic thromboembolism, pulmonary hypertension

INTRODUCTION

According to the International Thrombosis Society and International Hemostasis Society (ISTH) common data results, the term "post-pulmonary embolism (post-PE) syndrome" includes the presence of any of the following after 3 months of adequate therapeutic anticoagulation: 1. Post-PE functional limitation 2. Post-PE heart failure 3. Chronic without pulmonary hypertension thromboembolic lung disease and 4. Chronic thromboembolic pulmonary hypertension (CTEPH).[1,2]

Chronic thromboembolic pulmonary respiration involves patients with a progressive pulmonary vein with chronic obstruction by organized thrombi that limits the main pulmonary arteries. Furthermore, It has classified in Group 4 at the World Symposium on Pulmonary Hypertension (WSPH), and at rest, in right heart catheterization, hemodynamically mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary vascular resistance (PVR) ≥3 Wood's units (WU), and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg.[3]

EPIDEMIOLOGY

Chronic thromboembolic pulmonary hypertension is a rare disease and therefore likely to be underdiagnosed. The annual incidence rates of confirmed CTEPH have been found 0.9, 4.0, and 5 per million adults in the western world.[4] In the follow-up after acute pulmonary embolism (FOCUS) study, 16 (1.6%) patients were diagnosed with CTEPH; the estimated two-year cumulative incidence was 2.3% (1.2-4.4%).[5] Multicenter US and International CTEPH registries in Canada and Europe reported a high proportion of CTEPH patients with a prior history of acute PE (87.9% and 75%, respectively). The median age at presentation was 59-63 years, and both sexes were affected in equal numbers.[6]

PATHOPHYSIOLOGY

Chronic thromboembolic pulmonary hypertension/ Chronic thromboembolic disease (CTEH) is the hallmark of fibrotic transformation of the pulmonary artery thrombus, leading to mechanical occlusion of the pulmonary arteries. Unlike acute PE, there is no linear relationship between the degree of mechanical obstruction and hemodynamics, probably due to concomitant small vessel pulmonary arteriopathy in approximately 40% of cases. Moreover, there is no relationship between perfusion defects and oxygen consumption at peak exercise (VO2max).[7] Pulmonary arterial hypertension (PAH)-specific mutations have not been identified in CTEPH, and a relationship with ADAMTS13 has been found.[8] Lupus anticoagulant, antiphospholipid antibodies, high plasma concentrations of factor VIII,

increased von Willebrand factor, abnormal fibrinolysis and dysfibrinogenemia are associated with CTEPH. Previous splenectomy, history of infected ventriculoatrial shunts and indwelling catheters and leads to the treatment of hydrocephalus, thyroid replacement therapy, cancer and chronic inflammatory disorders such as osteomyelitis and inflammatory bowel disease have a negative impact on CTEPH and survival. Endothelial dysfunction, unbalanced fibrinolysis, dysfunctional angiogenesis, and immunological mechanisms have been associated with disease mechanisms underlying CTEPH.[9]

Organized thromboembolic occlusion in the large pulmonary arteries and secondary small vessel arteriopathy in non-occluded areas are the two main mechanisms of increased pulmonary vascular resistance (PVR) in CTEPH, progression of PH, and development of right heart failure. Distal flow obstruction from fibrotic clots increases endothelial heart stress by promoting redistribution of blood to unaffected vessels, alters vascular remodeling, and eventually causes secondary micro vasculopathy similar to pulmonary arterial hypertension (PAH). Histologically, plexiform lesions and arterial eccentric intimal fibrosis can be seen. Small vessel disease can lead to a discrepancy between PVR and the degree of mechanical occlusion on imaging. It may be responsible for residual PH following endarterectomy.[10]

In addition, microvascular remodeling and hypertrophy of the bronchial arteries are observed below the pulmonary artery occlusion.

The bronchopulmonary shunt contributes to the pathobiology by causing systemic circulation to flow into the low-pressure pulmonary system, increasing micro vasculopathy similar to hemangiomatosis-like lesions and pulmonary veno-occlusive-like lesions.[9]

CLINICAL APPROACHES

The symptoms and signs of CTEPH are non-specific and may resemble acute PE. In Europe, there is an average of 14 months between symptom onset and diagnosis in specialized pulmonary hypertension centers. Symptoms; exertional dyspnea (91%), edema (38%), chest discomfort (29%), dizziness (26%), fatigue (25.9%), cough (22.1%), shortness of breath at rest (19%).5), palpitations (14.8%), pre-syncope (10.7%), syncope (7.6%), anxiety (5.7%), and hemoptysis (4.5%) (6). Physical findings include pulmonary flow murmurs and a prominent pulmonary component of the second heart sound, tricuspid regurgitant murmur, and S4 murmur. A combination of peripheral edema, precordial right ventricular (RV) elevation, and high jugular venous pressure is suggestive of severe PH. Right ventricular S3, hepatomegaly, ascites, and cyanosis are late manifestations of advanced right heart failure.[11]

DIAGNOSIS

Patients diagnosed with chronic thromboembolic pulmonary hypertension or with a strong suspicion of CTEPH should be referred to a specialized pulmonary hypertension centers for further multidisciplinary diagnosis and treatment such as PEA, BPA, and/or targeted pulmonary hypertension medical therapy. Although CT pulmonary angiography (CTPA) is the investigation of choice for the diagnosis of acute PE, planar ventilation/perfusion (V/Q) scintigraphy is an appropriate first-line screening method for diagnosis of CTEPH, as it has a sensitivity of 96-97% and a specificity of 90-95%. In the absence of ECG findings of right ventricular hypertrophy, NT-proBNP can exclude with a sensitivity of 94% and a specificity of 65%. Both V/Q data and modern CT pulmonary angiography are used in expert hands to detect CTEPH with excellent diagnostic efficiency (100%, 93.7% and 96.5% sensitivity, accuracy and accuracy for V/Q and 96.1%).

Multi-detector (MD) CTPA has become a remote monitoring method for guiding CTEPH; However, this study alone cannot exclude the disease. CTPA helps to identify proactive behaviors such as pulmonary artery (PA) dilatation, which causes compression of the left main visual artery, and hypertrophic bronchial artery collaterals, which can lead to hemoptysis.[12]

Ultimate diagnosis and operability assessment is provided by right heart catheterization and selective pulmonary angiography in anteroposterior and lateral projections showing bronchial collaterals as well as ring-like stenosis, webs ("clefts"), sacs, wall irregularities, and complete vascular occlusions. The final diagnostic and operability assessment supports the assessment of technical operability or suitability for BPA.[13]

TREATMENT

Initial treatment includes diuretics, appropriate vaccination, pulmonary rehabilitation, and supplemental oxygen at rest, activity, or sleep as needed. Vitamin K antagonists (KVAs) targeting the International Normalized Ratio (INR) 2-3 are commonly used for lifelong anticoagulation. There is inadequate data on the efficacy and safety of direct oral anticoagulants (DOACs) for CTEPH.

Operability should be evaluated by a multidisciplinary team and should meet the criteria. An experienced PH center team should consist of a PEA surgeon, BPA intervention specialist, PH specialist, and thoracic radiologist trained in high-volume PEA and BPA centers.[2] The appropriateness of patients for PEA, BPA, medical therapy, or any combination of these therapies is determined by many factors that have not yet been standardized; these relate to patient factors, the expertise of surgical and percutaneous multidisciplinary teams, and available resources. General criteria include preoperative New York Heart Association (NYHA) functional classes and surgical accessibility of thrombi in the main, lobar, or segmental pulmonary arteries. Old age is not a contraindication for surgery. Although PEA is officially the gold standard of CTEPH treatments, available records indicate that at least 40% of patients are poor surgical candidates and do not undergo surgery. PEA is generally curative and life-saving and should be offered to all eligible patients. It alleviates PH and symptoms by up to 75% and improves survival.[14] The early death rate in experienced centers is <5%, and overall survival rates at 1, 3, 5, and 10 years are 86%, 84%, 79%, and 72%, respectively. Significant residual PH is rare and associated with in-hospital mortality. Milder residual PH is probably due to distal vasculopathy, in 50% at 3-6 months after PTE. Symptomatic patients with persistent or/recurrent post-operative PH should receive PH-targeted medical therapy and be evaluated for BPA or re-PTE if mPAP >30 mmHg.[9]

Although BPA is not widely used, it is rapidly gaining worldwide attention. One of the largest Japanese registries reported results similar to those from PEA in both short-term and long-term clinical follow-up. BPA is a proven minimally invasive procedure that safely treats inoperable CTEPH or symptomatic persistent/recurrent PH after PTE. BPA requires multiple sessions to expand occlusive fibrotic meshes/bands with an inflated balloon.[15] BPA can be combined with medical treatment in a hybrid or stepwise approach. Clinical trials comparing the efficacy and safety of BPA versus riociguat for inoperable CTEPH are currently underway in the USA (NCT02634203) and Japan. Complications of BPA include wire perforation during wire or balloon manipulation, balloon overexpansion, contrast extravasation, vascular injury such as pulmonary hemorrhage, hemoptysis or hypoxemia, and less commonly reperfusion injury. Overall complication rates are approximately 10% per procedure and are associated with severe PH during BPA.[16]

Patients with persistent or recurrent PH after PEA may be candidates for targeted medical therapy. The use of targeted therapy as a bridge to PEA in operable patients with severe hemodynamic impairment has not yet been supported by scientific evidence. Riociguat, an enteral soluble guanylate cyclase stimulant, resulted in a mean increase in 6-minute walking distance of 39 m in patients with inoperable CTEPH or persistent/recurrent PH 16 weeks after PEA, with the least squares mean difference 246 is. dyn cm·s 5 in PVR (p<.001, secondary endpoint); the time to clinical worsening did not change.[17] Recently, the dual endothelin receptor blocker macitentan has been shown to significantly improve PVR in patients with inoperable CTEPH and is well tolerated. In addition, a recent multicenter randomized controlled trial has shown that treatment with subcutaneous treprostinil is safe and improves exercise capacity in patients with severe CTEPH.[18]

CONCLUSION

Many patients are diagnosed late, and concerns remain that a large proportion of patients remain undiagnosed and/or are never referred for effective medical, interventional, and surgical treatments. A history of severe PE and acute pulmonary embolism should suggest CTEPH. ECO should be performed in symptomatic patients 3-6 months after acute PE. It should be ensured that patients have been using anticoagulation for 3 months before coming to the tests for the diagnosis of CTEPH. Careful screening and follow-up of patients after acute PE and widespread use of V/Q scans in unexplained dyspnea and all PH patients may lead to better clinical outcomes and survival. Patients should be treated in a CTEPH center. Future research is needed to identify better screening tools, explore new pathobiological pathways, and discover new treatments to reverse the disease process.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC Subcommittee on official Communication from the SSC of the ISTH. *J Thromb Haemost*. 2021;19(1):297-303.
2. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022; 43(38): 3618-3731.
3. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2021;57(6):2002828. doi:10.1183/13993003.02828-2020
4. Delcroix M, Kerr K, Fedullo P. Chronic thromboembolic pulmonary hypertension. Epidemiology and risk factors. *Ann Am Thorac Soc*. 2016; 13(Suppl 3):201-206.
5. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2):1601792.
6. Kerr KM, Elliott CG, Chin K, et al. Results from the United States chronic thromboembolic pulmonary hypertension registry: enrollment characteristics and 1-year follow-up. *Chest*. 2021;160(5):1822-1831.
7. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest*. 2017;151(5):1058–1068.
8. Newnham M, South K, Bleda M, et al. The ADAMTS13-VWF axis is dysregulated in chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(3):1801805.
9. Teerapuncharoen K, Bag R. Chronic thromboembolic pulmonary hypertension. *Lung*. 2022;200(3):283-299.
10. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019;53(1):1801887.
11. Braganza M, Shaw J, Solverson K, et al. A prospective evaluation of the diagnostic accuracy of the physical examination for pulmonary hypertension. *Chest*. 2019;155(5):982-990.
12. He J, Fang W, Lv B, et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. *Nucl Med Commun*. 2012; 33(5):459-463.
13. Lang IM, Campean IA, Sadushi-Kolici R, Badr-Eslam R, Gerges C, Skoro-Sajer N. Chronic thromboembolic disease and chronic thromboembolic pulmonary hypertension. *Clin Chest Med*. 2021;42(1): 81-90.
14. Hsieh WC, Jansa P, Huang WC, Niznansky M, Omara M, Lindner J. Residual pulmonary hypertension after pulmonary endarterectomy: a meta-analysis. *J Thorac Cardiovasc Surg*. 2018;156(3):1275-1287.
15. Zoppellaro G, Badawy MR, Squizzato A, Denas G, Tarantini G, Pengo V. Balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. *Circ J*. 2019;83(8):1660-1667.
16. Kawakami T, Matsubara H, Abe K, et al. Multicentre randomised controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: protocol for the MR BPA study. *BMJ Open*. 2020;10(2):e028831.
17. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319-329.
18. Sadushi-Kolici R, Jansa P, Kopec G, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. *Lancet Respir Med*. 2019;7(3):239-248.

Journal of
Pulmonology and
Intensive Care

Case Report

DOI: 10.51271/JOPIC-0017

Preoperative spontaneous regression of type B2 thymoma in a patient with myasthenia gravis

İsmail Tombul[1], Şevki Mustafa Demiröz[1], Berkay Şimşek[2], Irmak Akarsu[1], Elgun Valiyev[3], İsmail Cüneyt Kurul[1], Nalan Akyürek[2], Abdullah İrfan Taştepe[1],

[1]Department of Thoracic Surgery, Faculty of Medicine, Gazi University, Ankara, Turkey
[2]Department of Medical Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey
[3]Department of Thoracic Surgery, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article: Tombul İ, Demiröz ŞM, Şimşek B, et al. Preoperative spontaneous regression of type B2 thymoma in a patient with myasthenia gravis. *J Pulmonol Intens Care*. 2023;1(3):73-75.

Corresponding Author: İsmail Tombul, dr.ismailtombul@gmail.com

Received: 27/06/2023 ◆ **Accepted**: 28/07/2023 ◆ **Published**: 29/08/2023

ABSTRACT

Thymoma is the most common tumor of the anterior mediastinum. Spontaneous regression of thymoma is extremely rare. A 34-year-old female patient without any known disease, admitted by a myasthenic crisis, had a mass of 76 x 53 x 88 mm on thorax computed tomography (CT). The patient received intravenous immunoglobulin (IVIg) treatment for 5 days, pyridostigmine 60 mg/8 hours and prednisone 30 mg/day for the treatment of myasthenic crisis. Thorax CT on the 18th day showed that the mediastinal mass regressed to 63 x 30 x 63 mm. Histopathological analysis after extended thymectomy revealed the diagnosis of type B2 thymoma.

Keywords: Thymoma, neoplasm regression, spontaneous, myasthenia gravis

INTRODUCTION

Thymoma is the most common neoplasm of the anterior mediastinum originating from the thymic epithelial cell.[1] Although it is usually asymptomatic, it may present with paraneoplastic syndromes. The most common paraneoplastic syndrome is myasthenia gravis (MG) which is observed in 25-40% of patients with thymoma.[2] Although thymoma cases with spontaneous regression are very rare, cases with regression secondary to glucocorticoid therapy have been reported in the literature. In this case report, we present spontaneous regression of a type B2 thymoma during the preoperative preparation period, in a patient admitted to neurology department with myasthenic crisis without any previous diagnose of MG.

CASE

A 34-year-old female patient was admitted to the neurology department with complaints of hoarseness, numbness in the tongue, and ptosis that started a month ago. He had no known chronic diseases and had a 1-pack/year smoking history. During the diagnostic investigation, the patient developed respiratory arrest and was intubated. Upon the arrival anti-acetylcholine receptor antibody level (anti-AChR) was >15 nmol/L, a MG was diagnosed and myasthenic crisis treatment was planned. Laboratory values and tumor markers were within normal ranges (Hb 12.3 g/dl, Leukocyte 9800/uL, CRP 1.66 mg/L, LDH 260 U/L, β- HCG <5 mIU/mL). Posteroanterior chest X-ray revealed mediastinal enlargement. Thorax CT revealed a 76 x 53 x 88 mm (he mass was accepted as an ellipse in shape and the volume was calculated according to the formula $V=(4/3)\pi r^1 r^2 r^3$, total tumour volume was 182.1 cm^3) lesion in the anterior mediastinum with prevascular heterogeneity (**Figure 1A**). For the treatment of the crisis, she received pyridostigmine 60 mg/8 hours, prednisone 30 mg/day and 5 days of intravenous immunoglobulin (IVIg). On the 7th day of mechanical ventilation, symptoms have improved and the patient was extubated. Excision of the anterior mediastinal mass was planned and contrast-enhanced thorax CT taken 18 days after the first tomography revelaed that the lesion in the anterior mediastinum regressed to 63 x 30 x 63 mm (total tumour volume 60.38 cm^3, 66% reduction in diagnostic volume) (**Figure 1B**).

Extended thymectomy with left cervicotomy + partial sternotomy and right paratracheal lymph node sampling was performed on 25th day of the first admission. Histopathological examination revealed a lesion 75 x 20 x 63 mm (total tumour volume 48.05 cm^3,73% reduction in diagnostic volume) in size containing cystic components with hemorrhage, consistent with WHO type B2 thymoma invading the thymic capsule (modified masaoka classification, stage IIA) (**Figure 2**). Only reactive changes were observed in the lymph node sample. The patients' postoperative period was uneventful and she was discharged on the 7th day. She received 28 sessions of adjuvant radiotherapy. No recurrence was observed during the postoperative 18-month follow-up.

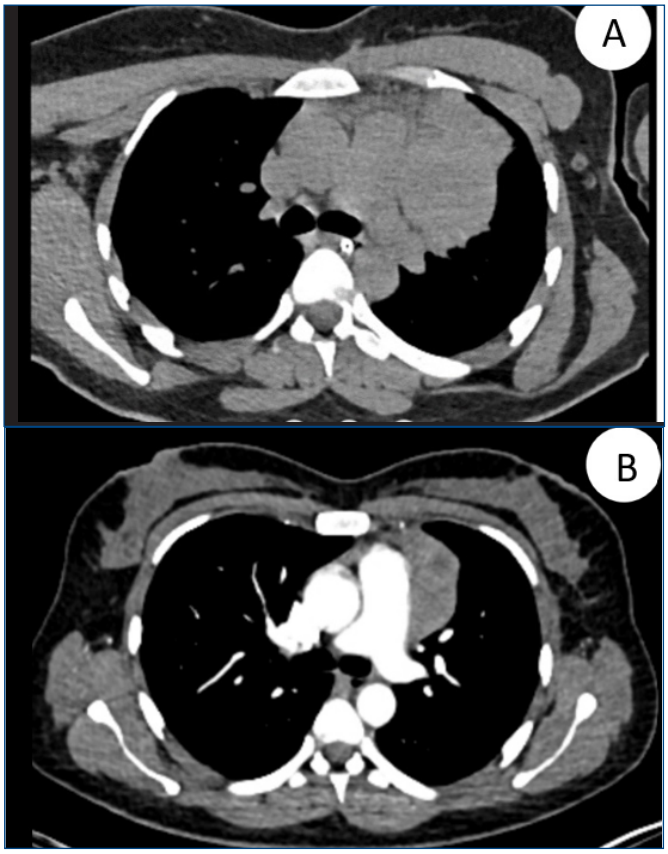


Figure 1. (A): 76 x 53 x 88 mm soft tissue lesion in the prevascular region in the anterior mediastinum on thorax CT (B): 63 x 30 x 63 mm soft tissue lesion showing regression on thorax CT taken 18 days later

DISCUSSION

While thymoma is detected in 10-15% of MG patients, MG is seen in 25-40% of cases with thymoma. In most cases, the symptoms usually worsen rapidly and respiratory distress may develop. A randomized controlled trial by Wolfe Gl et al.[3] showed that thymectomy was beneficial in anti-AChR-positive patients. In the presence of severe symptoms such as bulbar involvement; bridging therapy with IVIg or plasmapheresis is recommended to reduce the need for intensive care, artificial respiration time, and the risk of myasthenic crisis.[4] Our patient was also hospitalized in the intensive care unit due to respiratory distress, and preoperative bridging treatment was applied.

In the literature, thymoma cases with regression have been published in two main frameworks spontaneous or secondary to glucocorticoid treatment. Glucocorticoid receptors have been found in the cytosol of thymoma cells and it has been suggested that secondary regression in glucocorticoid is due to apoptosis of the lymphocytic component. Kobayashi et al.[5] evaluated 17 patients who received two preoperative cycles of glucocorticoid therapy (IV 1 g methylprednisolone for three days). They compared thorax CT before and one week after the treatment and reported that partial response (decrease in the measurable diameters of the lesion>50% reduction) was seen in 47.1% of patients, type B1 thymoma was the subtype that showed the biggest response, and that there was no difference in response rate in patients with and without a history of MG. Barrat et al.[6] reported that an incidentally detected type B1 thymoma case without MG completely regressed due to long-term dexamethasone use.[7] In our case, the patient also used 30 mg/day prednisone in the preoperative period, but two points make our case unique; i. the histopathologic type was a type B2 thymoma, ii. the steroid dose used was lower than the reported cases, and although pulsed steroids were not given, regression was seen within 18 days.

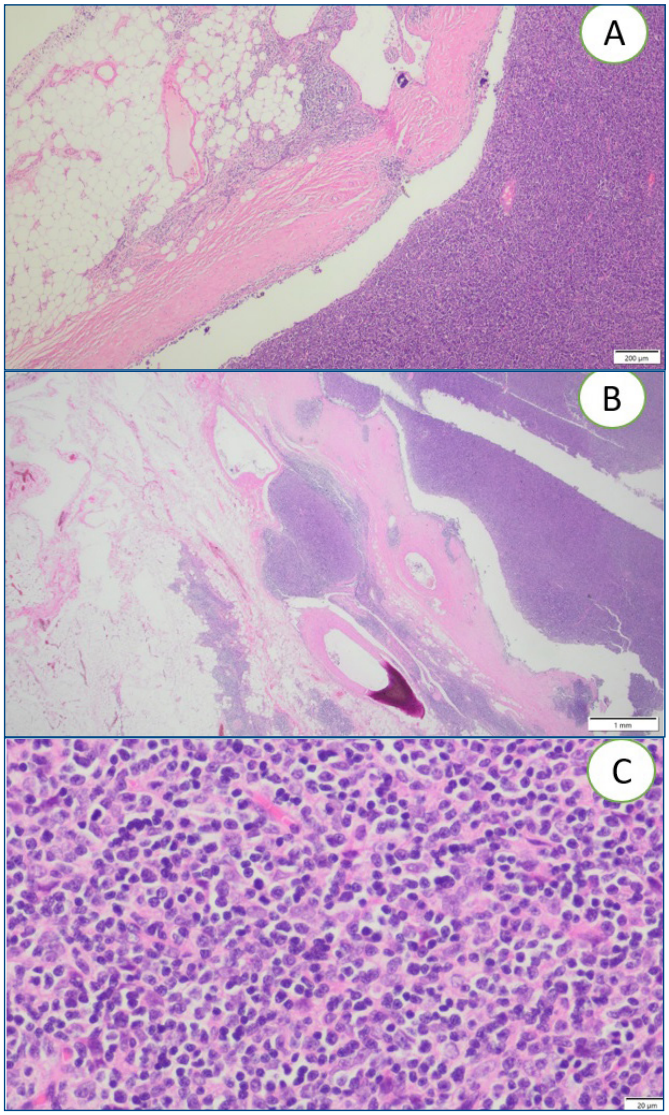


Figure 2. (A): A well-circumscribed neoplastic growth is observed, surrounded by a thick fibrous capsule (hematoxylin and eosin stain; original magnification x1.25) (B): It is observed that the tumor is mostly confined within the capsule, occasionally exceeding the thymic capsule and infiltrating the surrounding soft tissues (hematoxylin and eosin stain; original magnification x4) (C): In the cellular proliferation constituting the tumor, thymocytes with narrow cytoplasm and small hyperchromatic nuclei and epithelioid cells with large vesicular nuclei and large clear-eosinophilic cytoplasm forming groups of 2-3 scattered among them are observed. (hematoxylin and eosin stain; original magnification x40)

There are different reports on the effect of IVIg use on thymoma remission. Murie-Fernández et al.[8] reported total remission secondary to the use of IVIg in their patients with metastatic thymoma with symptoms of myasthenia gravis. In this case, the patient who underwent surgery for thymoma, received chemotherapy and radiotherapy, presented with myasthenic crisis 8 years after the diagnosis, and a pleural metastatic implant and two nodules in the lung were noticed. The patient received two cycles of IVIg (2 mg/kg) for five days, total remission of the lesions was reported one year later. Phillips et al.[9] reported the results of ketogenic diet, prednisone, IVIg, octreotide, and azathioprine treatment in a patient with WHO type AB (Masaoka stage IVA) thymoma with a diagnosis of myasthenia gravis and pleural metastases.They evaluated the effect of IVIg use on regression, but they found an increase in the size of the lesion during the IVIg treatment given every 3 weeks.

Therefore, there are reports in the literature that the use of IVIG can affect lesion size in both directions. In our case, IVIg treatment given before surgery may have contributed to the regression.

Histopathological examination of thymoma cases with spontaneous regression, showed that resected specimen includes necrotic features. In our case there was no necrosis in pathological specimen. Patients generally present with chest pain and/or low-grade fever at the time of admission.[10] Although the mechanism of spontaneous regression is not clearly explained, it is thought that an inflammatory reaction disrupts vascular nutrition and causes necrosis, and the symptoms seen in these patients are secondary to the necrosis.[11] While these symptoms were not present in our case, medical treatment given in the intensive care unit may have disguised these symptoms.

CONCLUSION

We have reported the case of invasive thymoma that spontaneously regressed in a MG patient. Regression of the lesion may occur in thymoma patients who received preoperative steroids and/or IVIG treatment. This should not be ignored when planning surgery.

ETHICAL DECLARATIONS

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Moran CA, Suster S. Thymoma with prominent cystic and hemorrhagic changes and areas of necrosis and infarction: a clinicopathologic study of 25 cases. *Am J Surg Pathol*. 2001;25(8):1086-1090. doi:10.1097/00000478-200108000-00015
2. Evoli A, Minicuci GM, Vitaliani R, et al. Paraneoplastic diseases associated with thymoma. *J Neurol*. 2007;254(6):756-762. doi:10.1007/s00415-006-0429-z
3. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*. 2016;375(6):511-522. doi:10.1056/NEJMoa 1602489
4. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and plex in patients with myasthenia gravis. *Neurology*. 2011;76(23):2017-2023. doi:10.1212/ WNL.0b013e31821e5505
5. Stewart BW. Mechanisms of apoptosis: integration of genetic, biochemical, and cellular indicators. *J Natl Cancer Inst*. 1994;86(17):1286-1296. doi:10.1093/jnci/ 86.17.1286
6. Kobayashi Y, Fujii Y, Yano M, et al. Preoperative steroid pulse therapy for invasive thymoma: clinical experience and mechanism of action. *Cancer*. 2006; 106(9):1901-1907. doi:10.1002/cncr.21875
7. Barratt S, Puthucheary ZA, Plummeridge M. Complete regression of a thymoma to glucocorticoids, commenced for palliation of symptoms. *Eur J Cardiothorac Surg*. 2007;31(6):1142-1143. doi:10.1016/j.ejcts.2007.02.032
8. Murie-Fernández M, Gurpide A, de la Cruz S, de Castro P. Total remission of thymus carcinoma after treatment with intravenous immunoglobulin. *Clin Transl Oncol*. 2006;8(9):697-699. doi:10.1007/s12094-006-0043-7
9. Phillips MCL, Murtagh DKJ, Sinha SK, Moon BG. Managing metastatic thymoma with metabolic and medical therapy: a case report. *Front Oncol*. 2020;10:578. doi:10.3389/fonc.2020.00578
10. Kikuchi N, Yanagawa M, Yoshida Y, et al. Spontaneous regression of type b3 thymoma with mesothelial cyst: a case report. *J Thorac Imaging*. 2020;35(6):W123-W126. doi:10.1097/RTI.0000000000000550
11. Moran CA, Suster S. "Ancient" (sclerosing) thymomas: a clinicopathologic study of 10 cases. *Am J Clin Pathol*. 2004;121(6):867-871. doi:10.1309/E4JB-3EBC-D3R0-8NHG

Journal of
Pulmonology and
Intensive Care

Case Report

DOI: 10.51271/JOPIC-0018

Photodermatit developed with pirfenidone treatment in patient diagnosed with IPF

Ezgi Akkuş, Deniz Çelik, Özkan Yetkin, Hüseyin Lakadamyalı

Department of Pulmonology, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Turkey

Cite this article: Akkuş E, Çelik D, Yetkin Ö, Lakadamyalı H. Photodermatit developed withpirfenidonetreatment in patient diagnosed with IPF. *J Pulmonol Intens Care.* 2023;1(3):76-78

Corresponding Author: Deniz Çelik, drdenizcelik@hotmail.com

Received: 01/08/2023 ◆ **Accepted**: 22/08/2023 ◆ **Published**: 29/08/2023

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common of the major idiopathic interstitial pneumonia (IIP) of unknown etiology, often presenting in advanced age, limited to the lungs, characterized by histopathologically and/or radiologically usual interstitial pneumonia (UIP) pattern, and progressing with chronic, progressive fibrosis. is the most common form. Since IPF is a disease with irreversible fibrosis, there is no curative treatment except lung transplantation. The aim of the treatments given is to stop the progression of the disease, to prevent exacerbations and to prolong the survival time (1). The greatest improvement in the treatment of IPF in recent years has been the use of antifibrotic drugs (Pirfenidone and nintedanib) that prevent fibrosis developing in the lung parenchyma (2). In this case, we aimed to present the side effect of photodermatitis in a patient who applied to our outpatient clinic with complaints of shortness of breath and cough for many years and was diagnosed with IPF and started on pirfenidone treatment.

Keywords: Pirfenidone, photosensitivity reaction, idiopathic pulmonary fibrosis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common of the major idiopathic interstitial pneumonia (IIP) of unknown etiology, often presenting in advanced age, limited to the lungs, characterized by histopathologically and/or radiologically usual interstitial pneumonia (UIP) pattern, and progressing with chronic, progressive fibrosis. is the most common form. Since IPF is a disease with irreversible fibrosis, there is no curative treatment except lung transplantation. The aim of the treatments given is to stop the progression of the disease, to prevent exacerbations and to prolong the survival time.[1] The greatest improvement in the treatment of IPF in recent years has been the use of antifibrotic drugs (Pirfenidone and nintedanib) that prevent fibrosis developing in the lung parenchyma.[2] In this case, we aimed to present the side effect of photodermatitis in a patient who applied to our outpatient clinic with complaints of shortness of breath and cough for many years and was diagnosed with IPF and started on pirfenidone treatment.

CASE

A 56-year-old male patient was admitted to our outpatient clinic with the complaints of cough and shortness of breath increasing with exertion for many years. There was no known history of additional disease. He had a 20 pack/year history of smoking up to 10 years ago. He had no history of alcohol use. There was no previous tuberculosis or contact history. He worked as a construction worker and was also engaged in agriculture and animal husbandry. On examination, there were bibasilar inspiratory rales. High-resolution lung tomography showed a peripheral honeycomb appearance, more prominent in the lower lobes, in both lung parenchyma, and tubular bronchiectasis and peribronchial thickness increases in these areas (**Figure 1**). Findings were consistent with interstitial lung disease. The presence of connective tissue disease was investigated in the patient. ANA profile, complements, CCP and anti DS-DNA were found to be normal. Active rheumatological disease was not considered in the rheumatology consultation. Dry eye was detected with Shirmer test and treatment was started for eye diseases. Afterwards, the patient underwent diffusion test (DLCO). DLCO/VA: 66% was measured (**Figure 2**). FVC was measured as 58.3% in pulmonary function test (PFT) (**Figure 3**). The patient was diagnosed with IPF and we started Pirfenidone treatment. During the 8-month treatment period with pirfenidone, the patient, who was followed up stably and did not develop any acute exacerbation, developed erythematous, edematous and locally dry, itchy skin lesions on his hands as a result of exposure to sunlight (**Figures 4 and 5**). We thought that a rare side effect of pirfenidone could be a photosensitivity reaction. We terminated the pirfenidone treatment and we saw a regression in the patient›s lesions in 20 days (**Figure 6 and 7**).

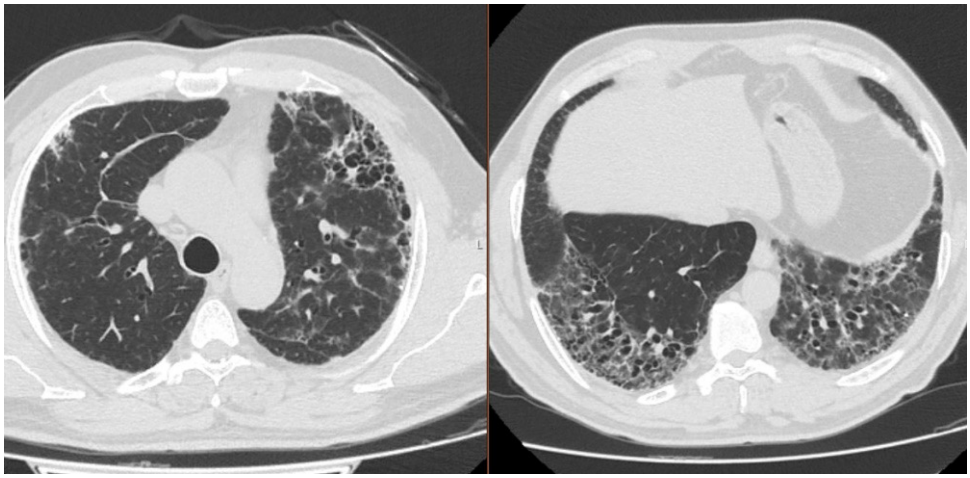


Figure 1. Patient's Chest CT at the time of diagnosis.

		Pred	Best	%(Best/Pred)
DLCO_SB	mmol/(min*kPa)	8.65	7.86	91
KCO_SB	mmol/(min*kPa*L)	1.40	1.97	141
VA_SB	L	6.03	4.00	66
Hb	g(Hb)/dL		15.00	
DLCOcSB	mmol/(min*kPa)	8.65	7.77	90
KCOc_SB	mmol/(min*kPa*L)	1.40	1.94	139
BHT	sec		11.83	
VIN_SB	L	3.88	2.35	61
TLC_SB	L	6.18	4.18	68
FRC_SB	L	3.31	3.48	105
ERV_SB	L	1.11	1.65	149
RV_SB	L	2.20	1.82	83
RV%TLC_SB	%	36	44	121
VA_SB	L	6.03	4.00	66
IC_SB	L	2.77	0.70	25
Level date			16.06.22	
Level time			09:01	

Figure 2. Patient's DLCO test result at the time of therapy beginning.

	Pred	Pre(L)	Pre(%)
VC MAX	3.91	2.20	56.2
IC	2.79		
ERV	1.12		
FVC	3.77	2.20	58.3
FEV 1	3.02	2.17	71.7
FEV1%M	77.13	98.71	128.0
PEF	7.93	7.03	88.5
FEF 25	6.97	7.03	100.8
FEF 50	4.21	6.01	142.9
FEF 75	1.54	2.90	188.7
MMEF	3.51	5.06	144.1

Figure 3. Patient's PFT results at the time of therapy beginning.

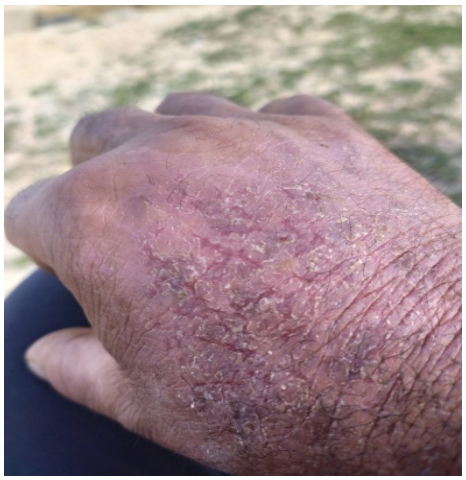


Figure 4. Skin lesions occures on the right hand with treatment of pirfenidone.

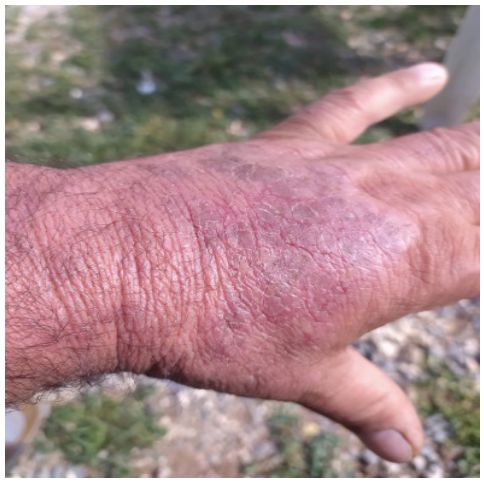


Figure 5. Skin lesions occures on the lelf hand with treatment of pirfenidone.

Figure 6. Skin lesions on the right hand regressed after withdrawal of the pirfenidone.

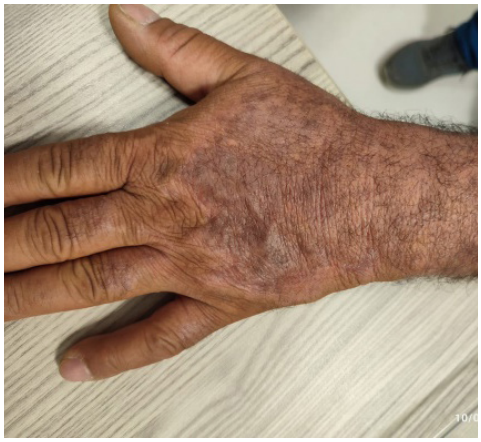


Figure 7. Skin lesions on the left hand regressed after withdrawal of the pirfenidone.

DISCUSSION

In the development of IPF, recurrent micro-damages first affect the alveolar epithelium. In the abnormal healing process after epithelial damage, myelofibroblast, fibroblast and collagen accumulation is seen as a result of the disturbed balance between fibrotic and antifibrotic mediators. Afterwards, tissue damage, fibrosis and honeycomb cysts occur (2) Antifibrotic agents are recommended as the first treatment option in treatment.

Pirfenidone is a drug with antifibrotic and anti-inflammatory effects; however, the mechanism of action is not fully known. It is thought to act by inhibiting the TGF-β pathway, preventing proliferation of fibroblasts and differentiation into myofibroblasts.[3]

Studies show that the use of pirfenidone significantly reduces IPF-related mortality. In addition, fewer acute exacerbations and a decrease in adverse events are shown in IPF patients.[4]

The first study on pirfenidone was conducted on 54 IPF patients with severe fibrosis, and it was reported that it was well tolerated and stabilized respiratory functions.[5] In the multicenter randomized double-blind placebo-controlled Phase 2 study conducted by Azuma et al.[6], a significant improvement was demonstrated in the 6-minute walking test at the end of 6 and 9 months of treatment in the subgroup that maintained SpO2 value over 80%.

Oral administration of pirfenidone has rapid absorption, high bioavailability, and wide distribution. It is slowly absorbed when taken with food and reaches its maximum plasma concentration in 2.5-4 hours. It is mainly metabolized by CYP1A2. The starting dose of pirfenidone is 800 mg/day (4x200 mg/day) and the minimum effective dose is 1200 mg/day. In weekly follow-ups, it is aimed to increase the dose to 2400 mg/day.[7] Since smoking has a CYP1A2-inducing effect, smoking should be stopped before and during the treatment.[8]

The most common side effects of pirfenidone are; skin (28-51%; rash and photosensitivity) and gastrointestinal system (5-36%; dyspepsia, anorexia, nausea, vomiting, diarrhea).[3] These side effects are mild to moderate and tolerable, and have been reported to occur early in the treatment and tend to regress over time.

Skin side effects occur on sun-exposed areas of the body as rash and photosensitivity, and this feature distinguishes it from allergic reactions. In the CAPACITY study conducted by Noble et al.[8], photosensitivity resulted in discontinuation of treatment in 3 patients and rash in 5 patients.[9] Drug-induced photosensitivity reactions depend on the drug's ability to absorb UV rays, both UVA and UVB. These side effects are proportional to UV exposure and drug dose and are temporary. Sun exposure should be avoided until 1-2 hours after taking the drug. The patient should be advised to avoid direct sunlight and fluorescent lamps, use high factor sunscreen, wear sunscreen, and stay away from photosensitizing agents.

CONCLUSION

Patient education and follow-up facilitate coping with side effects and increase the patient's treatment compliance and continuity. For this reason, the patient should be informed in detail and clearly at every stage from the diagnosis process to the treatment and follow-up of the disease.

ETHICAL DECLARATIONS

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution,

and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Kırkıl G. İdiyopatik pulmoner fibrozis. İçinde: Karadağ M, Kaya A, Özlü T. Göğüs hastalıkları tanı ve tedavi el kitabı, 1. baskı. Bilimsel Tıp; 2022:415-419.
2. Akıncı Özyürek B, Kurt HG. Bölüm 6. İdiyopatik pulmoner fibrozis. İçinde: İnterstisyel akciğer hastalıklarına güncel yaklaşım, Ed. Akıncı Özyürek B. Medihealth Academy, 1. baskı, 2022, Ankara, ISBN: 978-625-99889-3-1, s 101-188
3. Idiopathic pulmonary Fibrosis (IPF) and Progressive pulmonary Fibrosis (PPF) Diagnosis and Treatment Consensus Report, Turkish Thoracic Society, 2023. (https://toraks.org.tr/site/sf/s/2023/06/4ec31577de1525b2813c6ae02a3a901156d8b99969ad1023713180b08622bc65.pdf)
4. Wu W, Qiu L, Wu J, Liu X, Zhang G. Efficacy and safety of pirfenidone in the treatment of idiopathic pulmonary fibrosis patients: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2021;11(12):e050004. Published 2021 Dec 31. doi:10.1136/bmjopen-2021-050004
5. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. *Am J Respir Crit Care Med*. 1999;159(4 Pt 1):1061-1069. doi:10.1164/ajrccm.159.4.9805017
6. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2005;171(9):1040-1047. doi:10.1164/rccm.200404-571OC
7. Duyar SŞ. Bölüm 14. İnterstisyel akciğer hastalıklarında farmakolojik tedavi. İçinde: Akıncı Özyürek B. İnterstisyel akciğer hastalıklarına güncel yaklaşım, 1. baskı. MediHealth Academy; 2022:381-388.
8. Yaşar Z, Çetinkaya E. İdiopatik pulmoner fibroziste güncel tedavi yaklaşımı [Current management of idiopathic pulmonary fibrosis]. *Tuberk Toraks*. 2015;63(4):278-290. doi:10.5578/tt.9181
9. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760-1769. doi:10.1016/S0140-6736(11)60405-4