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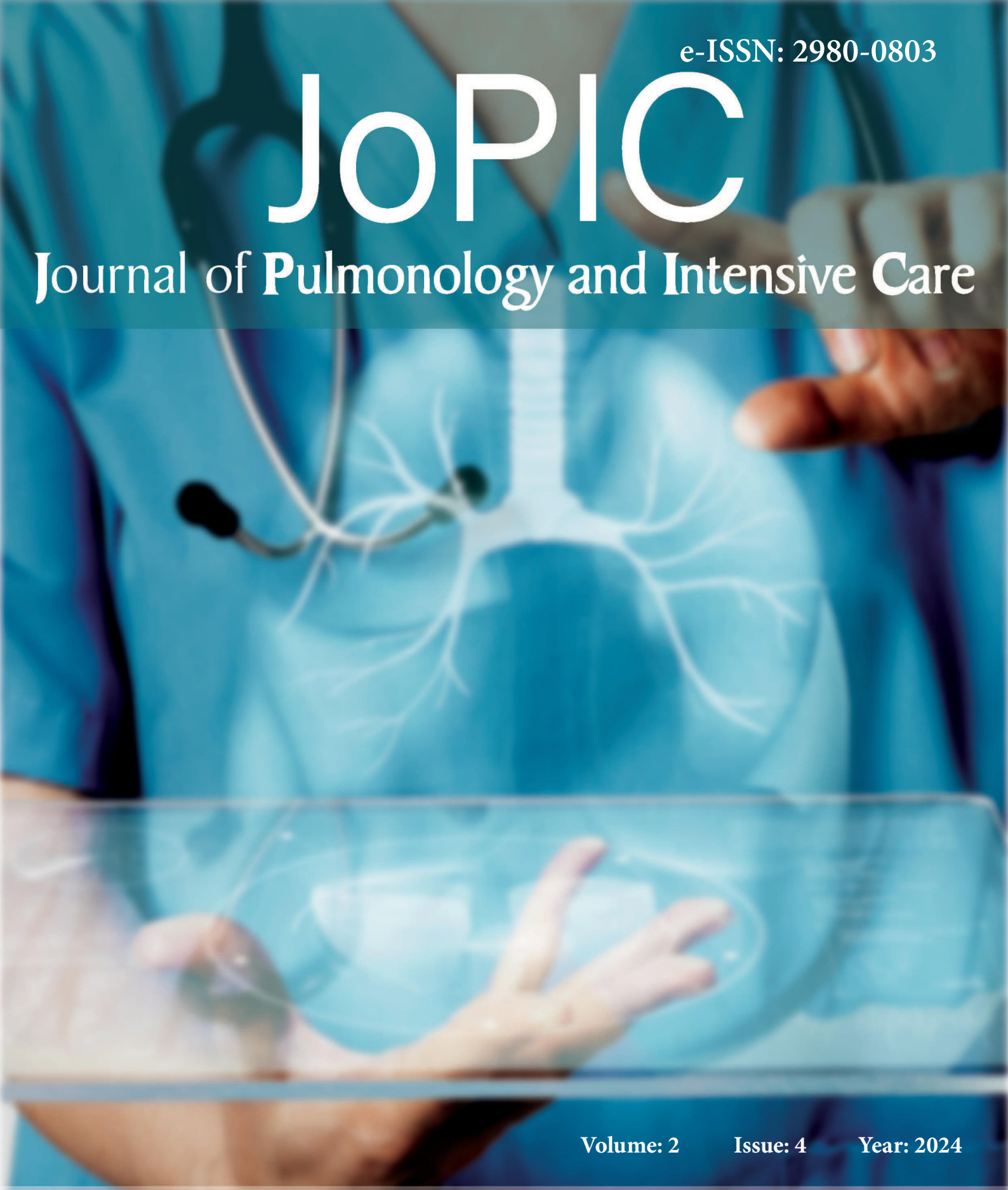

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Original Article

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Cardiovascular prognostic factors, gamma glutamil transferase levels and other biochemical parameters related to morbidity and mortality in COVID-19

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ABSTRACT

Aims: COVID-19 may exacerbate cardiovascular risk factors and pre-existing cardiovascular disease or lead to the development of new cardiovascular complications. Gama glutamil transferaz (GGT) is an enzyme found in the cell membranes of many tissues, especially the liver, bile duct and kidneys. Recent studies have shown that increased GGT levels are strongly associated with prognosis in cardiopulmonary disorders. Studies to date have reported on the increased predictive value of serum GGT level for cardiovascular disease and have shown marginal improvements in risk estimation. In the light of all this information, in this study, it was aimed to investigate the effect of serum GGT level on the clinical classification of the disease, cardiovascular risk and morbidity and mortality in COVID-19, in addition to known cardiovascular prognostic markers.

Methods: The study included 128 patients over the age of 18 who were found to have positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) in the nasopharyngeal and oropharyngeal samples taken during their admission to Kahramanmaraş Sütçü İmam University (KSU) Medical Faculty Chest Diseases Outpatient Clinic And Emergency Department. According to the most recently published 2019 novel coronavirus pneumonia diagnosis and treatment program (version 7), COVID-19 disease is divided into groups as mild, moderate, severe and critical illness. Demographic data, comorbidities, symptoms and signs, laboratory findings, and chest computed tomography (CT) scans were reviewed. The presence of heart failure, coronary artery disease or arrhythmia in the included patients was defined as cardiovascular disease. Patients were excluded if they were younger than 18 years old, pregnant, had a history of hepatobiliary disorders, alcohol abuse or other acute illnesses, died at the time of admission, had incomplete baseline data, or were transferred to other designated hospitals during hospitalization.

Results: Fifty-five (43%) of the participants were female and 73 (57%) were male, with a mean age of 55.6 years. When examined in terms of age, the difference between the groups was statistically significant. The difference between the individuals with and without hypertension and diabetes mellitus was found to be significant in terms of disease severity. When examined in terms of symptoms, 23 (71.9%) of the patients in the mild group were symptomatic, 9 (28.1%) were asymptomatic, and all of the patients in the moderate, severe and critical groups were symptomatic (100%). Cardiovascular biomarkers and GGT values were found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. However, having cardiovascular disease did not cause a significant difference in GGT levels fo the disease groups. GGT levels were found to be statistically similar in individuals with and without the disease. When blood gas parameters were analyzed in terms of disease severity, oxygen saturation (SpO_2) and PO_2 were found to be significantly lower in the severe and critical illness group than in the mild and moderate disease group. When the effect of blood parameters on mortality was analyzed by logistic regression analysis, only the effect of PO_2 parameter on mortality was found to be statistically significant. In addition, the effects of cardiovascular diseases and age variables on mortality were found to be statistically significant (p=0.031, p=0.007; respectively). The effect of cardiovascular disease on mortality was 4,325 times (ODDS ratio) higher compared to individuals without cardiovascular diseas.

Conclusion: In this study, we determined two important findings. First, the serum level of GGT was found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. Second, cardiovascular disease, advanced age, and hypoxemia were associated with mortality from COVID-19 disease. Although GGT provides no increased benefit for predicting cardiovascular disease risk, its potential causal relationship with cardiovascular disease deserves attention.

Keywords: COVID-19, gama glutamil transferaz, GGT, cardiovascular disease, mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China in late December 2019. Since then, COVID-19 has spread rapidly around the world, becoming a global pandemic affecting more than 200 countries and regions.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, non-segmented, single-stranded, positive RNA virus belonging to the coronaviridae family.[2] This novel coronavirus enters cells through binding of the viral surface spike protein to the angiotensin converting enzyme (ACE) 2 protein. ACE2 is highly expressed in lung alveolar cells and provides the virus entry route.[3] ACE2 is also commonly found in the myocardium, which raises concerns due to the possibility of direct viral infection of the cardiovascular system.[4]

Although COVID-19 patients primarily present with respiratory symptoms and therefore follow a pneumonia-like treatment plan, it is important not to ignore the cardiovascular system when following these cases and to recognize those presenting with early signs of acute myocardial injury. COVID-19 may exacerbate cardiovascular risk factors and pre-existing cardiovascular disease or increase susceptibility to the development of new cardiovascular complications.[5]

During the COVID-19 outbreak, it is necessary to evaluate patients at increased risk of adverse cardiovascular disease outcomes and/or myocardial injury with biomarkers such as serum cardiac troponin I (cTnI), brain natriuretic peptide (BNP), and creatine kinase-myocardial band (CK-MB). While these biomarkers are recognized for cardiovascular disease, they may aid the prognosis of COVID-19, particularly in those with cardiovascular comorbidities or risk factors that predispose to disease worsening.[6,7]

Identifying any new biomarkers early in the course of COVID-19 that indicate significant morbidity or mortality is also important as it can help prevent this rapid worsening later on. It is well known that GGT is increased in hepatobiliary dysfunction and alcohol abuse. Recent studies have shown that increased GGT levels are strongly associated with prognosis in cardiopulmonary disorders such as heart failure, acute myocardial infarction, and coronary artery disease.[8]

Studies to date have reported on the increased predictive value of serum GGT level for cardiovascular disease and have shown marginal improvements in risk estimation. In the light of all this information, in this study, it was aimed to investigate the effect of serum GGT level on the clinical classification of the disease, cardiovascular risk and morbidity and mortality in COVID-19, in addition to known cardiovascular prognostic markers.

METHODS

Study Population and Study Design

Our study was planned as a single-center, retrospective observational cohort study, and patients between March 2020 and December 2020 were screened from the hospital electronic data system. The study protocol was approved by the Turkish Ministry of Health General Directorate of Health Services Scientific Study Platform and Kahramanmaraş Sütçü İmam University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 14.09.2021, Decision No:07). The study was conducted in line with the ethical principles of the Declaration of Helsinki revised in 2013.

The study included 132 patients over the age of 18 who applied to the KSU Faculty of Medicine Chest Diseases outpatient clinic and emergency department and were hospitalized with positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) in their nasopharyngeal and oropharyngeal samples taken during their admission. Patients who were clinically diagnosed with COVID-19 without PCR confirmation were excluded from the study. According to the most recently published 2019 novel coronavirus pneumonia diagnosis and treatment program (version 7) COVID-19 patients are divided into mild, moderate, severe and critical classes.[17] Accordingly, the definitions of the disease are as follows:

Mild disease: Defines mild clinical symptoms and no signs of pneumonia on imaging.

Moderate disease: Defines the radiological findings of pneumonia with fever and respiratory symptoms.

Severe disease: Meeting any of the following criteria: Respiratory distress (≥30 breaths/min); Oxygen saturation at rest <93%; Partial arterial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <300 mmHg (1 mmHg=0.133 kPa). Defines the condition in which the infiltration has spread to more than 50% of the lungs on chest imaging within 24-48 hours.

Critical disease: Meeting any of the following criteria: Defines respiratory failure and requiring mechanical ventilation, septic shock and/or multiple organ failure.

Patients <18 yo, pregnant women, those with a history of hepatobiliary disorder, alcohol abuse, or other acute illness, patients who died at admission, had missing baseline data, or were transferred to other designated hospitals during hospitalization were excluded from the study. Therefore, 128 patients were included in the final analysis. Informed consent was waived since the data used in the study were anonymous. Patients' demographic data, comorbidities, symptoms and signs, laboratory findings, and chest computed tomography (CT) scans were reviewed. The presence of heart failure, coronary artery disease or arrhythmia in the included patients

was defined as cardiovascular disease. All data were obtained from the electronic hospital information system. Peripheral venous blood samples were evaluated in the central laboratory of the university hospital following standard procedures.

Routine blood tests (including leukocyte count and leukocyte subtypes, hemoglobin count and platelet count) were measured with a Sysmex XN-1000 automated hematology analyzer (Sysmex XN-1000 Corporation, Kobe, Japan). Cobas 8000 biochemistry analyzer (Cobas 8000 c702 biochemistry analyzer Roche Diagnostics Gmbh, Mannheim, Germany) was used to measure biochemical parameters. Blood coagulation tests including plasma D-dimer, prothrombin time (PT), international normalized ratio (INR), activated partial prothrombin time (APTT), and thrombin time (TT) were measured using a Sysmex CS-2500 coagulation analyzer system (Sysmex XN-1000 Corporation, Kobe, Japan). RNA isolation was performed with the Bi-Speedy viral nucleic acid isolation kit (Bioeksen, Istanbul, Turkey) according to the manufacturer's instructions. PCR was performed with the Bio-Speedy COVID-19 RT-qPCR detection kit (Bioeksen, Istanbul, Turkey) on the Rotor-Gene Q device (Qiagen, Hilden, Germany).

Statistical Analysis

In the evaluation of the data, the conformity of the variables to the normal distribution was examined with the Kolmogorov Smirnov test. Group comparisons in normally distributed variables were performed with Independent Samples T-test and one-way analysis of variance. In the variables not normally distributed, Mann Whitney U test and Kruskal Wallis H test were used. Frequency distribution between categorical variables was examined using Chi-square test and Fisher's Exact Chi-square test. The effects of independent variables on dependent variables were analyzed by logistic regression analysis. Statistical parameters were expressed as median (Quartile 25% –Quartile 75%), mean±SD, and n (%). Statistical significance was accepted as $p<0.05$. IBM SPSS version 22 software and R.3.3.2 software were used to evaluate the data.

RESULTS

A total of 128 patients who met the inclusion criteria were included in the study. Fifty-five (43%) of the participants were female and 73 (57%) were male, with a mean age of 55.6. When examined in terms of age, the difference between the groups was statistically significant. The difference between the individuals with and without hypertension and diabetes mellitus was found to be significant in terms of disease severity. The demographic data of the patients are shown in **Table 1**.

When examined in terms of symptoms, 23 (71.9%) of the patients in the mild group were symptomatic, 9 (28.1%) were asymptomatic, and all of the patients in the moderate, severe and critical groups were symptomatic (100%). In the mild group, 7 patients (21.9%) had fever, 11 patients (34.4%) had cough symptoms, and no patient had respiratory distress. In the moderate group, fever was detected in 17 patients (53.1%), cough in 26 patients (81.3%), and respiratory distress in 23 patients (71.9%). In the severe group, fever was detected in 11 patients (34.4%), cough in 29 patients (90.6%), and respiratory distress in 29 patients (90.6%). In the critical group, fever was detected in 23 patients (71.9%), cough in 31 patients (96.9%), and respiratory distress in 31 patients (96.9%). Chi-Square test; a:0.05; * The distributional difference was found to be statistically significant (**Table 1**).

When analyzed in terms of biochemical parameters, the mean value of ALT was not significantly different between each group. However, other biochemical parameters were statistically significant between the groups (**Table 2**). Cardiovascular biomarkers and GGT values were found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. However, having cardiovascular disease did not cause a significant difference in GGT levels in the disease groups. GGT levels were found to be statistically similar in individuals with and without the disease.

When the median values of blood gas parameters were examined according to disease severity, oxygen saturation (SpO_2) and PO_2 were found to be significantly lower in the severe and critical disease group than in the mild and moderate disease group.

When the effect of blood parameters on mortality was analyzed by logistic regression analysis, only the effect of PO_2 parameter on mortality was found to be statistically significant (p 0,04) (**Tablo 3**). In addition, the effects of cardiovascular diseases and age variables on mortality were found to be statistically significant (p=0.031, p=0.007; respectively). The effect of cardiovascular disease on mortality was 4,325 times (ODDS ratio) higher compared to individuals without cardiovascular disease (**Tablo 4**).

DISCUSSION

In this study, we determined two important findings. First, the serum level of GGT was found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. Second, cardiovascular disease, advanced age, and hypoxemia were associated with mortality from COVID-19 disease.

Respiratory viral infections are generally associated with cytokine production, inflammation, cell death, and other pathophysiological processes that may be associated with redox imbalance or oxidative stress (OS). It is known that overproduction of reactive oxygen species (ROS) and lack of antioxidant mechanisms are crucial for viral replication and virus-associated disease.[10] Significantly elevated blood cytokine and chemokine levels have also been observed in patients with COVID-19 infection. "Cytokine storm" triggers a proinflammatory environment that is strongly associated with severe tissue damage and contributes to the fatal outcome of COVID-19 patients.[11] Many studies have shown that overproduction of ROS and a deprived antioxidant system play an important role in the pathogenesis of SARS-CoV infection, as well as in the progression and severity of respiratory disease. Increased ROS levels and impaired antioxidant defense have been demonstrated in experimental animal models of severe acute respiratory distress syndrome.[12]

GGT hydrolyzes the gamma-glutamyl bond between glutamic acid and cysteine, which is the first step in the extracellular hydrolysis of glutathione (GSH), which acts as an important antioxidant in cells, and provides the formation of cysteine, which is necessary for the re-synthesis of GSH in the cell.[13] It has been suggested that the pathway associated with GSH catabolism of GGT may also lead to the production of

Table 1. Demographic and clinical features of the groups

		Mild (n:32)	Moderate (n:32)	Severe (n:32)	Critical (n:32)	p
Age		41.3 (±15.4[c,d])	51.1 (±20.5[c,d])	63.8 (±13.5[a,b])	66 (±16.3[a,b])	p<0.001*
Gender	Female	18 (±56.3)	14 (±43.8)	12 (±37.5)	12 (±37.5)	0.545
	Male	2 (6.3%)	18 (±56.3)	20 (±62.5)	20 (±62.5)	
Cardiovascular disease (CVD)				7 (21.9%)	10 (31.3%)	0.095
Traditional risk factors for CVD			4 (12.5%)			
Hypertension (n,%)			4 (12.5%)	17 (53.1%)	15 (46.9%)	0.004*
Diabetes mellitus (n,%)			4 (12.5%)	10 (31.3%)	12 (37.5%)	0.031*
Smoking (n,%)		5 (15.6%)	2 (6.3%)	4 (12.5%)	6 (18.8%)	0.498
Body-mass index (kg/m^2)		26.25 (±3.18)	26.44 (±2.71)	25.89 (±2.77)	27.07 (±3.26)	
Signs and symptoms						
Fever		7 (21.9%)	17 (53.1%)	11 (34.4%)	23 (71.9%)	p<0.001*
Cough		11 (34.4%)	26 (81.3%)	29 (90.6%)	31 (96.9%)	p<0.001*
Muscle pain		13 (40.6%)	20 (62.5%)	12 (37.5%)	28 (87.5%)	p<0.001*
Sputum		2 (6.3%)	20 (62.5%)	27 (84.4%)	31 (96.9%)	p<0.001*
Sore throat		7 (21.9%)	9 (28.1%)	3 (9.4%)	4 (12.5%)	0.185
Diarrhea		4 (12.5%)	2 (6.5%)	0 (0%)	0 (0%)	0.053
Nausea		2 (6.3%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	0.726
Dizziness		0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0.388
Headache		10 (31.3%)	5 (15.6%)	4 (12.5%)	3 (9.4%)	0.095
Dyspnea		0 (0%)	23 (71.9%)	29 (90.6%)	31 (96.9%)	p<0.001*
Imaging features						
Consolidation		3 (9.4%)	4 (12.5%)	4 (12.5%)	0 (0%)	p<0.001*
Ground-glass opacity		2 (6.3%)	11 (34.4%)	13 (40.6%)	4 (12.5%)	p<0.001*
Consolidation + ground-glass opacity		5 (15.6%)	11 (34.4%)	15 (46.9%)	28 (87.5%)	p<0.001*
Clinical course						
Outpatient		6 (18.8%)	0 (0%)	0 (0%)	0 (0%)	p<0.001*
Ward inpatient		31 (96.9%)	31 (96.9%)	14 (43.8%)	2 (6.3%)	p<0.001*
Admission to ICU		0 (0%)	1 (3.1%)	18 (56.3%)	30 (93.8%)	p<0.001*
The need for noninvasive mechanical ventilation		0 (0%)	0 (0%)	11 (34.4%)	25 (78.1%)	p<0.001*
Intubation		0 (0%)	0 (0%)	2 (6.3%)	15 (46.9%)	p<0.001*
Discharged		32 (100%)	32 (100%)	2 (6.3%)	17 (53.1%)	p<0.001*
Died		1 (3.1%)	0 (0%)	2 (6.3%)	15 (46.9%)	p<0.001*

One way anova: Post-hoc: Tukey HSD test; Chi-Square: a:0.05; * The difference between groups is statistically significant; a The difference is significant with the mild group; b The difference is significant with the moderate group; c The difference is significant with the Severe Group; d The difference is significant with the critical group

Table 2. Laboratory findings of the study groups

	Mild (n:32)	Moderate (n:32)	Severe (n:32)	Critical (n:32)	p
Hematologic biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
WBC count	**6230** (4940-8320)	**5420** (4425-8620)	**7765** (6040-14855)	**7765** (6040-14855)	0.021
Neutrophil count	**3660** (2675-5395)	**3600** (2665-7085)	**6390** (4630-13140)	**5980** (4155-9065)	**p<0.001**
Lymphocyte count	**1775** (1285-2120)	**1260** (785-1535)	**865** (600-1065)	**705** (525-1180)	**p<0.001**
Platelet count	**228500** (196000-280000)	**196000** (147000-232000)	**229500** (198500-291000)	**185500** (154000-229500)	
Hemoglobin	**14.4** (13.4-15.8)	**13.1** (12.0-14.3)	**13.6** (11.7-14.2)	**12.7** (11.4-13.5)	**0.001**
Biochemical biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
GGT	**22.5** (15-36.5)	**25.5** (17-60.5)	**75** (26.5-121)	**42.5** (25-65.5)	**p<0.001**
ALT	**22** (15-36)	**20.5** (11.5-41.5)	**27.5** (18-42)	**27.5** (17.5-48.5)	0.202
AST	**23.5** (18.5-29)	**25** (19.5-32.5)	**36.5** (27.5-56.5)	**45** (26.5-81)	**p<0.001**
LDH	**209.5** (186.5-265.5)	**286.5** (205.5-353.5)	**470.5** (375-803)	**495.5** (336.5-709)	**p<0.001**
CK-MB	**2** (2-2.7)	**2** (1.9-2)	**2** (2-3)	**2.15** (2-3.84)	**p<0.001**
Troponin	**0.01** (0.01-0.01)	**0.01** (0.01-0.01)	**0.01** (0.01-0.01)	**0.01** (0.01-0.05)	**0.016**
Albumin	**46** (42.2-48)	**38.9** (34.9-42.8)	**34.3** (32.2-37.5)	**33.9** (30.5-36.3)	**p<0.001**
Coagulation biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
PT	**11.5** (11-12)	**12.1** (11.5-13)	**12.8** (12.1-14.1)	**13.2** (11.9-14.1)	**p<0.001**
D-dimer	**0.32** (0.19-0.45)	**0.34** (0.23 -1.00)	**1.03** (0.61-1.63)	**1.17** (0.90-2.4)	**p<0.001**
Inflammatory biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
CRP	**3.14** (3.14-6.26)	**25.40** (12.25-78)	**97.10** (52.55-169.5)	**106** (58.5-157)	**p<0.001**
Procalcitonin	**0.04** (0.03-0.06)	**0.08** (0.06-0.25)	**0.22** (0.11-0.58)	**0.22** (0.11-1.52)	**p<0.001**
Ferritin	**96.0** (42.5-175.5)	**187** (88.5-511)	**568.5** (440.5-793.5)	**547.5** (362-1172)	**p<0.001**
Arterial blood gas biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
Ph	**7.39** (7.37-7.40)	**7.40** (7.39-7.41)	**7.44** (7.40-7.47)	**7.42** (7.40-7.47)	**p<0.001**
PO_2	**82** (78-86)	**80** (75.5-84.5)	**47.3** (33-62.5)	**50.5** (35-62)	**p<0.001**
PCO_2	**40.2** (39-42)	**40.1** (39.7-42)	**38.5** (35-42)	**35.4** (31.8-43.4)	**0.020***
SO_2	**96** (95-97)	**95** (95-96)	**86** (77.2-92.8)	**87.45** (81.2-91.35)	**p<0.001**
HCO_3	**23.7** (23.4-24.1)	**23.9** (23.6-24.5)	**25.3** (23.5-27.9)	**25.2** (22.3-27)	0.060

GGT: Gama glutamil transferaz, CK-MB: Creatine kinase-myocardial band, PT: Prothrombin time

Table 3. Laboratory findings of the study groups

Arterial blood gas biomarkers	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	
Ph	**7.39** (7.37-7.40)	**7.40** (7.39-7.41)	**7.44** (7.40-7.47)	**7.42** (7.40-7.47)	**p<0.001**
PO_2	**82** (78-86)	**80** (75.5-84.5)	**47.3** (33-62.5)	**50.5** (35-62)	**p<0.001**
PCO_2	**40.2** (39-42)	**40.1** (39.7-42)	**38.5** (35-42)	**35.4** (31.8-43.4)	**0.020***
SO_2	**96** (95-97)	**95** (95-96)	**86** (77.2-92.8)	**87.45** (81.2-91.35)	**p<0.001**
HCO_3	**23.7** (23.4-24.1)	**23.9** (23.6-24.5)	**25.3** (23.5-27.9)	**25.2** (22.3-27)	0.060

Table 4. The effects of demographic characteristics and comorbid diseases of individuals on mortality

	Wald	p	ODDS ratio	ODDS ratio 95% confidence interval	
				Lower limit	Upper limit
Smoking	.955	.328	2.467	0.403	15.080
CVD	4.649	**.031***	4.325	1.143	16.374
DM	1.629	.202	2.467	.616	9.871
HT	.670	.413	0.547	0.129	2.320
Age	7.348	**.007***	1.070	1.019	1.124
Gender	.323	.570	0.680	0.180	2.569

Dependent variable: Patient discharge/ex status, Binary logistic regression: a:0.05, *The effect is statistically significant, CVD: Cardiovascular disease

prooxidant substances. It is thought that the more reactive thiol cysteinyl glycine, which is formed as a result of the effect of GGT in GSH metabolism, can reduce ferric ions to Fe(III) and ferrous ions Fe(II), and as a result, it can initiate iron redox cycle events that result in the production of ROS.[14] Low glutathione levels increase cellular oxidative stress and are associated with various disease states and immune dysfunctions leading to higher susceptibility to viral infections, i.e. uncontrolled SARS-CoV-2 infection.[15]

Uncontrolled replication causes oxidative damage to the lungs, which increases viral load, thereby increasing the severity of viral infection. Conversely, high GSH levels can prevent the virus from replicating efficiently, resulting in lower viral loads and therefore milder symptoms. In a study investigating the impact of GSH levels on the course of COVID-19 infection, high ROS/GSH ratios were found to be strongly associated with worsening symptoms and slower healing times.[16]

Severity of SARS-CoV-2 infection or COVID-19 disease and risk of death are associated with age.[17] In many previous studies, it has been reported that the disease course is more severe and leads to mortality in older patients with COVID-19 compared to young and middle aged ones.[18] The results of our study also confirmed that the severity of the disease increases significantly with increasing age, which was an independent risk factor for mortality.

A strong association has been reported between hypoxemia occurring during the course of COVID-19 and worsening clinical outcomes of the disease. In a study of 140 patients with COVID-19-related pneumonia, it was found that oxygen saturation (SpO_2) >90.5% predicted survival with 84.6% sensitivity and 97.2% specificity. Also, in this study, SpO_2 of 90% or less provided a more robust risk factor for mortality despite supplementation with oxygen. The severity of hypoxemia in COVID-19 patients is independently associated with in-hospital mortality and may be an important indicator of the patient's risk of admission to the ICU.[19] Also in our study, decreased SpO_2 and PO_2 values as the severity of the disease increased and PO_2 being a determinant factor of mortality, is a finding of significant prognostic value of hypoxemia for hospitalized patients with pneumonia associated with COVID-19, suggesting that it provides justification for applying standard scoring strategies to predict risk and guide treatment even in this patient population.[20,21] COVID-19 appears to be associated with a wide range of cardiovascular sequelae, including acute onset heart failure, arrhythmias, acute coronary syndrome, myocarditis, and cardiac arrest. In addition, acute cardiac injury appears to be significantly associated with increased in-hospital mortality in COVID-19 patients.[22]

Serum cTnI is the worldwide gold standard necrotic biomarker for myocardial risk assessment. Other biomarkers of myocardial injury with diagnostic value include creatine CK-MB and BNP, which may provide information about the severity of symptoms in COVID-19. Although they have already been established for cardiovascular disease, the potential role of these biomarkers, particularly cTnI, as prognostic predictors in COVID-19 patients has been demonstrated in several studies. In a meta-analysis of 4 studies including 341 COVID-19 patients, a significantly higher difference in mean cTnI was reported in patients with more severe COVID-19 symptoms than those with milder symptoms.[23] Similarly, in our study, as the severity of the disease in COVID-19 cases increased, the increase in cTnI level and its effect on the severity of the disease were statistically significant, and our study confirmed the potential value of cTnI in predicting the outcome of COVID-19 patients.

Therefore, a correlation between elevated serum cTnI levels and a higher risk of mortality in COVID-19 patients can be logically predicted.[24,25]

While cTnI has shown remarkable potential in predicting COVID-19 outcomes, BNP has also shown some hope in the prognosis of COVID-19. Guo et al.[26] found that elevated cTnT levels were significantly associated with elevated serum BNP levels. The authors reported that in addition to the gradual increase in serum cTnT levels, BNP levels gradually increased in patients with deteriorating health, while patients who were successfully discharged had low and stable serum BNP levels. Similar to previous studies, we think that in our study the fact that BNP levels were found to be significantly higher in severe and critical disease groups in our study reflects the possibility of routinely measuring serum BNP levels in COVID-19 patients to reduce negative negative outcomes during the course of COVID-19.

In addition to cTnI and BNP, CK-MB may have similar prognostic value in COVID-19. In a study by Wang et al.[27] 36 (26.1%) of 138 COVID-19 patients were admitted to the ICU with severe symptoms, and in all of these patients, serum cTnI and CK-MB levels were significantly elevated compared with patients who were not admitted to the ICU.-

. Therefore, we think that further studies that clearly demonstrate a clear link between CK-MB and BNP and COVID-19 outcomes will provide a better understanding of their prognostic role.

It is known that GGT activity is closely associated with cardiometabolic risk. With several reports showing an independent association of higher GGT levels with increased risk of cardiovascular disease, there is a growing debate that adding GGT measures to existing risk estimation algorithms may be associated with improvements in the ability to predict cardiovascular disease.[28] Various mechanisms have been proposed to explain the possible link between GGT and cardiovascular disease. These mechanisms include the associations between GGT and both classic and novel cardiovascular risk factors, oxidative stress and direct involvement of GGT in atheromatous plaque formation.[29] GGT is an enzyme primarily found in the liver and is often considered a marker of hepatic oxidative stress and inflammation.[30] Its activity increases in response to cellular damage caused by ROS and other pro-oxidative agents.[31] Elevated GGT levels reflect a state of increased GSH consumption, which is a critical antioxidant defense mechanism in the body.[32] GSH is depleted as it neutralizes ROS, leading to an upregulation of GGT activity to maintain cellular redox balance. In the MeS, GGT may indicate the presence of a pro-oxidative environment that accompanies IR and its associated metabolic derangements.[33] Elevated serum GGT levels are an independent marker of activation of systemic inflammatory responses and increased oxidative stress, which are of widespread importance in the development of atherosclerosis. Serum GGT concentrations are significantly associated with ascending aortic dilatation.[34] However, it has been reported to be associated with arterial stiffness, impaired aortic elasticity, and blood pressure.[35] This environment can exacerbate endothelial dysfunction, promote atherosclerosis, and ultimately increase the risk of CVD and all-cause mortality.[36] Many studies have shown that traditional cardiovascular risk factors, systemic inflammation, metabolic syndrome, increased oxidative stress, and several comorbidities are closely associated with high serum GGT levels.[37]

Early in the pandemic, it turned out that patients with cardiovascular comorbidities were most vulnerable to severe infection. The specificity of SARS-CoV-2 for the ACE-2 protein has raised concerns about cardiovascular system damage.[38,39] Similarly, in our study the effect of cardiovascular disease on mortality was statistically significant. However, contrary to the recommendations regarding the potential benefit of GGT measurements for cardiovascular disease risk assessment, in our study, GGT level did not have a different effect on disease severity and mortality in patients with COVID-19 infection and cardiovascular disease.

In a study by Kunutsor et al.[40] it was shown that GGT measurement was not associated with any clinically significant improvement in cardiovascular disease risk assessment. The close association between GGT and cardiovascular and metabolic risk factors clustered among patients with high GGT activity at least partially explains the association between GGT and death. However, the independent association of GGT with cardiac mortality has been interpreted as the enzyme's direct role in promoting atherosclerosis and related clinical events.[41] Although Ndrepepa et al.[42] found an independent relationship between GGT and cardiac mortality, they stated that GGT did not add information beyond the information provided by cardiovascular risk factors regarding the prediction of cardiac mortality. Similarly, in our study, although the serum GGT level was high in COVID-19, patients with severe disease, no difference was found in patients with cardiovascular disease, indicating that GGT does not provide increased risk information beyond those provided by concomitant cardiovascular risk factors.

Limitations

Our study has some limitations. This is a cross-sectional study and a potential causal relationship between COVID-19 and elevated serum GGT levels cannot be concluded. However, the findings of this study have some important implications for the determination of cardiovascular outcomes during the course of COVID-19 and for the management and prognosis of these patients

CONCLUSION

In the light of all this information, we planned this study because during a crisis such as the current COVID-19 pandemic, the serum GGT level and other cardiac prognostic markers that can identify cardiovascular risk help healthcare professionals to predict prognosis, thus identifying vulnerable patients at an earlier stage and providing them with an intensive treatment plan to prevent worsening outcomes. We think that cTnI may be a preferred option over CK-MB and BNP, mainly because of the worsening prognosis in COVID-19 patients and its high sensitivity in detecting myocardial damage. Although the independent association of GGT with cardiovascular disease suggests its usefulness in estimating risk, such information is insufficient to make judgments about its potential utility in classifying or predicting cardiovascular disease risk in individuals. However, although GGT provides no increasing benefit for predicting cardiovascular disease risk, its role in cardiovascular disease etiology and its potential causal relationship with cardiovascular disease deserves attention.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the. Kahramanmaraş Sütçü İmam University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 14.09.2021, Decision No: 07).

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.

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Comparison of 18F-FDG and 68Ga-DOTATATE PET/CT in surgically treated lung carcinoid tumors

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ABSTRACT

Aims: This study aims to compare the efficacy of FDG-18 PET/CT and 68Ga-DOTATATE PET/CT imaging techniques in patients with lung carcinoid tumors, identifying the most appropriate preoperative nuclear medicine technique for diagnosis and staging.

Methods: We retrospectively analyzed data from 123 patients who underwent surgery for lung carcinoid tumors at our center between 2009 and 2021. All of the patients were scanned with FDG-18 PET/CT before surgery. In addition to FDG-18 PET/CT, 68Ga-DOTATATE PET/CT scanning was performed in 28 patients: 17 in the preoperative and 11 in the postoperative period. Demographic data, mean higher maximal standard uptake (SUVmax) values of primary mass, lymph nodes and extrathoracic foci, pathologic subtype, and type of surgery were recorded. Compliance with normal distribution for numerical data was assessed using the Shapiro-Wilk test. The Wilcoxon signed-rank test was employed for groups meeting normal distribution to compare continuous numerical variables. The Mann-Whitney U and Kruskal-Wallis tests were used when normal distribution assumptions were unsatisfied.

Results: The mean SUVmax value in 68Ga-DOTATATE PET/CT was significantly higher than FDG-18 PET/CT in patients with a lung carcinoid tumor (20 vs 4.4). For 68Ga-DOTATATE PET/CT scan, typical carcinoids had higher mean SUVmax value than atypical carcinoids (26 and 5.6 respectively), and the difference was statistically significant (p=0.002). For that FDG-18 PET/CT, on the contrary, the mean SUVmax value was higher in atypical carcinoids than typical carcinoids (5.4 and 3.8, respectively), and the difference was not significant (p=0.126)

Conclusion: The SUVmax values from 68Ga-DOTATATE PET/CT and FDG-18 PET/CT in lung carcinoid tumors vary by tumor subtype. 68Ga-DOTATATE PET/CT demonstrates higher SUVmax values in typical carcinoid tumors, indicating its superiority over FDG-18 PET/CT for this subtype. Although 68Ga-DOTATATE PET/CT also shows elevated SUVmax in atypical carcinoid tumors, the difference compared to FDG-18 PET/CT does not reach statistical significance.

Keywords: FDG-18 PET/CT, 68Ga-DOTATATE PET/CT, lung carcinoid tumor, surgery

INTRODUCTION

Positron emission tomography (PET) is a radiological imaging technique that provides tissue chemical metabolism changes as molecular radiological images. In fluorodeoxyglucose (FDG) PET/CT integrated with computed tomography (CT), an image is obtained by quantifying the increased glucose metabolism of FDG labeled with the F-18 isotope.[1,2] On the other hand, the Gallium-68 (Ga-68) PET/CT technique is a radiological method consisting of DOTATE and Ga-68 radioactive elements, a synthetic form of natural somatostatin hormone. Neuroendocrine (NET) cells have an excess of somatostatin receptors. In this way, Ga-68 adheres to the somatostatin receptors of cancerous cells, making the lesion visible on PET/CT.[3,4]

68Ga-DOTATATE PET/CT has a more specific diagnostic value in lung carcinoid tumors. Especially in typical carcinoids with pathological subtypes, higher maximal standard uptake (SUVmax) was observed in 68Ga-DOTATATE PET/CT. The success of 68Ga-DOTATATE PET CT in identifying metastatic foci also increases its usage in advanced patients.[5,6]

METHODS

Our study aimed to compare two PET/CT imaging techniques used perioperatively for diagnostic and staging purposes in patients with lung carcinoids. The study was approved by the ethics committee of Keçiören Training and Research Hospital (Date: 25.05.2021, Decision No:2012-KAEK-15/2303). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The data of 123 patients who were operated on with the diagnosis of lung carcinoid in Ankara Atatürk Sanatorium Hospital of Health Sciences University between 2009 and 2021 were retrospectively scanned. Demographic data, mean SUVmax values of primary mass, lymph nodes and extrathoracic foci, pathologic subtype, and type of surgery were recorded.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics version 25.0. Continuous numerical variables are presented as mean±standard deviation or median (minimum-maximum) values, while categorical variables are expressed as counts (percentages). The distribution of categorical variables between groups was assessed using the Pearson chi-square and Fisher's Exact tests for comparisons. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

Patients, Type of Resection, and Subtype

Patients who did not undergo PET/CT and were not diagnosed with carcinoid tumors were excluded from the study. Of 123 patients, 58 (47%) were female and 65 (53%) were male. The mean age of women was 52.4 (26-72), while the mean age of men was 50 (20-81). For surgical treatment, lobectomy was performed in 106 patients, segment resection in 9, and pneumonectomy in 8 patients. Histopathological examination revealed typical carcinoid tumors in 72 (58.5%) patients and atypical carcinoid tumors in 54 (41.5%) patients (**Table 1**).

Table 1. Age, gender, type of resection, and histopathologic subtype of the patients

	n (%)
Age (mean)	
Female	52.4 (26-72)
Male	50 (20-81)
Gender	
Female	58 (47)
Male	65 (53)
Type of resection	
Wedge/segmentectomy	9 (7.3)
Lobectomy/bilobectomy	106 (86.2)
Pneumonectomy	8 (6.5)
Histopathologic subtype	
Typical carcinoid	72 (58.5)
Atypical carcinoid	51 (41.5)

The mean ages for typical and atypical carcinoids were 53 (26-81) and 48 (20-71), respectively. Typical carcinoid tumors concluded 54% (39) of women and 46% (33) of men, while atypical carcinoid tumors concluded 37% (19) of women and 63% (32) of men. No statistically significant difference was found between the incidence of typical/atypical carcinoids within the same genus (p=0.317).

FDG-18 PET/CT and 68Ga-DOTATATE PET/CT

Primary Mass: For 123 patients evaluated with FDG-18 PET/CT preoperatively, the mean SUVmax values of the primary mass were 4.4 (0-32). The mean SUVmax value was 3.8 (0-10) in typical carcinoid tumors and 5.4 (0-32) in atypical carcinoids. There was no statistically significant difference between the SUVmax value of typical and atypical carcinoids in FDG-18 PET/CT (p=0.126).

A total of 28 patients were evaluated with a 68Ga-DOTATATE PET/CT scan. While 17 patients had a preoperative scan, 11 patients were scanned postoperatively for detection of other foci. The mean SUVmax values of the primary mass were 20 (0-120) in 17 patients who underwent preoperative 68Ga-DOTATATE PET/CT. The mean SUVmax value was 26 (0-120) in typical carcinoid tumors (n=12) and 5.6 (0-9) (n=5) in atypical carcinoids. There was a statistically significant difference between the SUVmax value of typical and atypical carcinoids in 68Ga-DOTATATE PET/CT (p=0.002).

Further analysis of 17 patients who scanned with both techniques in the perioperative period showed that the SUVmax value of the primary mass was significantly higher for 68Ga-DOTATATE PET/CT than FDG-18 PET/CT. The mean SUVmax value was 3.8 (0-11) in FDG-18 PET/CT and 20 (0-120) in 68GA-DOTATATE PET/CT, and the difference was statistically significant. On the other hand, there were false negative results for the primary mass itself in both techniques. For 68Ga-DOTATATE PET/CT, two patients (1 typical, 1 atypical) and for FDG-18 PET/CT, five patients (4 typical, 1 atypical) did not present any pathologic uptake (SUVmax=0) (**Figure, Table 2**).

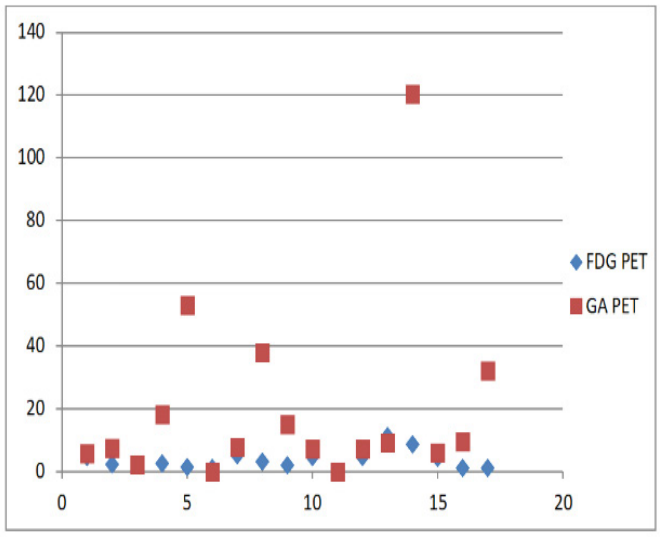

Figure. Distribution of SUVmax value of the mass in preoperative GA-68 PET and FDG-18 PET in 17 patients with two PETs

Metastatic Lymph Nodes and Other Foci: The analysis of mediastinal lymph nodes revealed that neither technique is sufficient to identify metastatic lymph nodes. Thirteen patients (10.5%) had pathologically confirmed lymph node metastasis, and four patients had multiple lymph metastatic lymph nodes. The most common metastatic lymph nodes were N1, no. 10 (hilar) and 11 (inter-lober). For patients with a metastatic no. 11 lymph node, only three of them were evaluated with both techniques, and there was no pathologic uptake on both FDG-18 PET/CT and 68Ga-DOTATATE PET/CT (SUVmax=0). For patients with metastatic no. 10 lymph nodes, none of them evaluated by preoperative 68Ga-DOTATATE PET/CT, the median SUVmax value in FDG-18 PET/CT was 3.2 (2.4-4).). In 1 patient with lymph node metastasis no. 5, SUVmax was 11 in 68Ga-DOTATATE PET/CT, while SUVmax was 4 in FDG-18 PET/CT. Number 3,4,7,8,9 nodes were metastatic for one

Table 2. The mean SUVmax values of 17 patients evaluated with both preoperative 68GA-DOTATATE PET/CT and FDG-18 PET/CT

	68GA-DOTATATE SUVmax, mean	FDG-18 SUVmax, mean	p-value
Histopathologic subtype			
All (n=17)	20	3.8	**p=0,002***
Typical carcinoid (n=12)	27	3.4	**p=0,008***
Atypical carcinoid (n=5)	5.7	4.8	p=0,5
Lymph nodes			
N1 (n=3)	0	0	p>0,05
N2 (n=1)	5	4	p>0,05
Other foci in the thoracic region (thyroid, esophagus, breast, rib, thymus) (n=9[a])	4.6	4.1	p>0,05
Other foci in the extrathoracic region (n=13[b])	7.7	5.7	p>0,05
Atelectasis/consolidated area adjacent to the primary mass (n=3[c])	4.7	5	p>0,05

*: p-value <0.05, statistically significant. [a]: 5 patients had pathologic uptake on 18-FDG and four on GA-DOTATE. [b]: 11 patients had pathologic uptake on 18-FDG and two on GA-DOTATE. [c]: 1 patient had pathologic uptake on 18-FDG and two on GA-DOTATE

patient each. No significant uptake was also present with both techniques. As a result, no statistically significant difference was found for metastatic lymph nodes in terms of SUVmax values in either technique (p>0.05) (**Table 2**).

For 17 patients who were evaluated with both techniques preoperatively, in the thoracic region, four patients had a median SUVmax of 4.5 (2.2-7.1) (thyroid, esophagus, breast, rib, thymus) on 68GA-DOTATATE PET/CT, while five patients had a median SUVmax of 3,8 (2.5-6.3) on FDG-18 PET/CT. In the extrathoracic regions (gastrointestinal, genitourinary) 2 patients had a median SUVmax of 7.7 (6.9-8.6) on 68GA-DOTATATE PET/CT, while ten patients had a median SUVmax of 5.4 (3-9.3) on FDG-18 PET/CT. No statistically significant difference was found between SUV involvement in the intrathoracic and extrathoracic regions in both PETs (p>0.05) (**Table 2**).

DISCUSSION

Because of the increased mitosis in atypical lung carcinoid tumors, the sensitivity of FDG-18 PET/CT is higher than that of typical carcinoid tumors.[7,8] Due to the somatostatin receptors of lung carcinoid tumors, 68GA-DOTATATE PET/CT shows a high affinity for these receptors.[9] On the other hand, it is known that 68GA-DOTATATE PET/CT scans show a high affinity for typical carcinoids. Typical carcinoids show higher SUVmax values on 68GA-DOTATATE PET/CT than atypical carcinoids.[10,11] Our results are also compatible with the literature.

In a study by Antunes et al., the specificity of 68GA-DOTATATE PET/CT CT in the diagnosis of the primary tumor was 91%; in comparison, its sensitivity was 93%.[10] Since the GA-68 radioisotope has a high sensitivity to somatostatin receptors, it is preferred in NETs.[11] Some researchers have argued that Ga-68 PET/CT is more sensitive than other scintigraphic methods, such as octreotide and pentetreotide.[12,13] Ga-68 PET/CT is used in preoperative staging, body scanning, metastasis, and postoperative treatment follow-up due to its high sensitivity and specificity rates in carcinoid tumors.[14-16]

In a study conducted by Lococo et al.[6] in 62 patients focusing on diagnosing carcinoid tumors, the success of 68GA-DOTATATE PET/CT in diagnosis was 88.4%, and the median SUVmax value was found to be 15.5. The success of FDG-18 PET/CT in diagnosis was 53.8%, and the median SUVmax value was 3.2 (p=0.0025). While the success of 68GA-DOTATATE PET/CT was 91.7%, especially in typical carcinoid tumors, this rate remained at 50% in FDG-18 PET/CT (p=0.076) .

In our study, 17 patients had 68GA-DOTATATE PET/CT and FDG-18 PET/CT preoperatively. In these patients, the mean SUVmax value of the tumor itself was 20 (0-120) in 68GA-DOTATATE PET/CT, while the median SUVmax value in FDG-18 PET/CT was 3.8 (0-11). 11 of these 17 patients were typical carcinoids, and the median SUVmax value on 68GA-DOTATATE PET/CT was 27 (0-120), while the median SUVmax value on FDG-18 PET/CT was 3.4 (0-11). While the median SUVmax value in 68GA-DOTATATE PET/CT was 5.7 (0-9) in 6 patients with atypical carcinoids, the median SUVmax value in FDG-18 PET/CT was 4.8 (1-11). In our study group, the difference between the success of 68GA-DOTATATE PET/CT and FDG-18 PET/CT in detecting the primary mass was statistically significant for patients with a diagnosis of typical carcinoids (p=0.008) but not for patients with a diagnosis of atypical carcinoids (p=0.5).

Our data showed that 68GA-DOTATATE PET/CT was superior to FDG-18 PET/CT in determining the primary mass, especially in typical carcinoids. However, reaching a definitive conclusion for atypical carcinoids is difficult. In our study, SUV uptake of atypical carcinoids in FDG-18 PET/CT was very close to SUV values in 68GA-DOTATATE PET/CT, and the difference was not statistically significant.

In a study by Kayani et al.[17] on 18 patients, the median SUVmax uptake value in 68GA-DOTATATE PET/CT was 15; it was 33 for typical carcinoids and 3.5 for atypical subtype (p=0.002). On the other hand, the median SUVmax value of FDG-18 PET/CT was 6; it was 4.9 for typical carcinoids and 16 for atypical subtype (p=0.005). The same study reported a 0% false positive rate for 68GA-DOTATATE PET/CT and 16.7% (3 patients) for FDG-18 PET/CT. According to the authors, one of these areas is the hilar lymph node. At the same time, the other two are parenchymal consolidated atelectasis areas adjacent to the lesion.[17] In our study, the false positivity rate of the primary mass was 0% for both techniques. However, in our study, false positive lymph nodes were observed in 4 patients (3 typical, 1 atypical) with preoperative 68GA-DOTATATE PET/CT, and the median SUVmax in the lymph nodes was 3.7 (3-5). False positivity was detected in the lymph nodes of 51 patients who underwent FDG-18 PET/CT. There was no statistically significant difference between FDG-18 PET/CT and 68GA-DOTATATE PET/CT in detecting false-positive lymph nodes (p>0.05). Our patients were evaluated based on the cut-off value of 2.5 for false lymph node positivity, and lymph nodes with an SUVmax above 2.5 were interpreted as false positive.

Jiang et al.[5] argued that 68GA-DOTATATE PET/CT is superior to FDG-18 PET/CT in detecting atelectatic areas adjacent to

the lesion in lung carcinoid tumors. While the median SUVmax values of these atelectatic tissues in 68GA-DOTATATE PET/CT were 30.5±28.1, the median SUVmax values in FDG-18 PET/CT were found to be 2.1±2.3 (p<001). In our study, uptake was observed in atelectasis and consolidated areas adjacent to the lesion in 2 patients (1 typical, 1 atypical) with a mean SUVmax value of 4.7 (2-7.2) in 68GA-DOTATATE PET/CT scan. On the other hand, FDG-18 PET/CT showed uptake in 1 (atypical) patient, and the SUVmax value was 5. There was no statistically significant difference in SUVmax values between the two PET techniques of atelectasis and consolidated areas adjacent to the lesion (p>0.05).

Limitations

The study's scope was limited by the relatively small number of patients evaluated by FDG-18 PET/CT and 68Ga-DOTATATE PET/CT. To draw definitive conclusions regarding the effectiveness of FDG-18 PET/CT, 68Ga-DOTATATE PET/CT in diagnosing carcinoid tumors, further prospective studies are needed involving larger patient cohorts, including those without a confirmed diagnosis of carcinoids.

CONCLUSION

The SUVmax levels of 68GA-DOTATATE PET/CT and FDG-18 PET/CT in lung carcinoid tumors vary by tumor subtype. Typical carcinoids exhibit slower cellular metabolism compared to atypical carcinoids. 68GA-DOTATATE PET/CT demonstrates higher SUV uptake in typical carcinoid tumors, making it superior to FDG-18 PET/CT for this subtype. Although 68GA-DOTATATE PET/CT shows increased SUV uptake in atypical carcinoid tumors, this difference does not achieve statistical significance, likely due to the limited sample size.

We recommend using 68GA-DOTATATE PET/CT for both preoperative evaluation and postoperative follow-up in patients with suspected lung carcinoid tumors scheduled for surgery. However, we do not endorse the routine use of 68GA-DOTATATE PET/CT for all patients; instead, it should be requested for lesions suggestive of carcinoid tumors.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the ethics committee of Keçiören Training and Research Hospital (Date: 25.05.2021, Decision No: 2012-KAEK-15/2303).

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.

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Evaluation of the knowledge levels of healthcare professionals about occupational diseases

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ABSTRACT

Aims: In the world and in our country, technological advancements, increased consumption, and new employment opportunities have led to an increasing number of health issues related to professionals, such as occupational diseases and workplace accidents.

Methods: This descriptive study was conducted with the participation of healthcare professionals at Erzurum City Hospital. A total of 287 healthcare professionals who agreed to participate in the study without the need for sampling were included. Descriptive statistics were presented as frequency, percentage, mean±standard deviation, and median (min:max). The chi-square test was used for the analysis of categorical data.

Results: All 91.3% of participants stated that they were aware of occupational diseases, 50.9% received education/training on occupational diseases, and 47.4% believed that occupational diseases are preventable. It was observed that women and married participants were more likely to hear occupational diseases, the difference was statistically significant ($p<0.05$).

Conclusion: Consequently, the study revealed that the knowledge of hospital employees about occupational diseases and occupational accidents was insufficient. Healthcare professionals should be informed about the risks that may cause occupational diseases in the work environment. Studies should be carried out and necessary trainings should be planned to increase the level of knowledge about the protective measures against these risks.

Keywords: Healthcare professionals, knowledge level, occupational diseases

INTRODUCTION

According to Social Insurance and General Health Insurance Law, an occupational disease is defined as a temporary or permanent illness, or a physical or mental disability, that a policyholder incurs due to repeated causes related to the nature of the work they perform or as a result of the conditions under which the work is carried out.[1] According to Occupational Health and Safety Law (OHS), a more straightforward definition is provided, describing occupational diseases as illnesses that arise as a result of exposure to occupational risks.[2] According to this law, an accident at work is an event that occurs in the workplace or in the course of work and causes death or mental or physical incapacity.[2]

A review of historical processes reveals that human beings have been compelled to engage in work since the inception of their existence in order to meet fundamental needs such as shelter and nutrition.[3] In his seminal work on occupational health and safety, Dr Bernardino Ramazzini highlighted the potential link between employees' diseases and their occupation, underscoring the significance of a comprehensive occupational history.[3]

The initial legal regulations related to occupational health and safety in our country were associated with mining activities. The Dilaver Pasha Regulation (1865) and the Maaddin Regulation (1869) represent the earliest documented instances of written legal regulations targeting occupational safety and health.[4] One of the most significant pieces of legislation to emerge during the Republican Period was Law No. 1593 on Public Hygiene, which came into force in 1930.[4] The Labour Law No. 4857, the Social Security and General Health Insurance Law No. 5510 and the OHS Law No. 6331, which entered into force in 2012, represent significant legal regulations in this field within the context of our country.[5]

In the world and in our country, the prevalence of health problems related to occupational factors is on the rise. This is due to a confluence of factors, including technological advancements, increased consumption, and the emergence of novel employment sectors. In our country, the Social Security Institution (SSI) has a very detailed list regarding the diagnosis of occupational diseases. The list includes occupational diseases related to chemical substances in group A, occupational dermatological diseases in group B, pneumoconiosis and other occupational respiratory system diseases in group C, occupational infectious diseases in group D, and finally occupational diseases due to physical factors in group E.[6]

Approximately 2 million people die every year in the world due to work-related causes.[7] According to SSI data for 2023, 945 insured persons were diagnosed with occupational diseases and 681,401 insured persons had occupational accidents.[8]

According to our legislation, hospitals are in the group of very dangerous workplaces and healthcare professionals face many risk factors during working hours. It is necessary to inform health professionals about the risks they face in working life, the prevention of occupational diseases and occupational accidents that may arise from these risks, to plan the necessary trainings and to carry out studies to raise awareness. The objective of this study was to evaluate the level of knowledge about occupational diseases among employees of a tertiary healthcare institution.

METHODS

This descriptive study was conducted with the participation of healthcare professionals from Erzurum City Hospital. A total of 287 healthcare professionals who agreed to participate in the study were interviewed, without the selection of a sample. In the study, the questionnaire form, titled "evaluation of the level of knowledge of occupational diseases of employees in a tertiary health care organisation," which was developed by the research team, was used as a data source. The questionnaire form comprises a series of questions designed to assess the socio-demographic characteristics of health professionals, their work practices, their understanding of occupational diseases, their awareness of occupational accidents and their knowledge of the OHS Law. The questionnaires were applied by face-to-face interview method and the application time of a questionnaire was approximately 5-6 minutes. The questionnaire consists of 15 multiple choice questions.

For the implementation of the study and the use of the data, the approval of the ethics committee was obtained from Erzurum Medical Faculty Ethics Committee (Date: 13.09.2023, Decision No: BAEK 2023/05-55). The research was conducted in accordance with the principles of the Declaration of Helsinki. Before the survey, the purpose and content of the study were explained to the participants and verbal consent was obtained.

Statistical Analysis

The research data were evaluated with IBM SPSS 23.0 statistical package program. Descriptive statistics were presented as frequency, percentage, mean value±standard deviation and median (min:max). Chi-square test was used to analyse categorical data. Statistical significance value was accepted as $p<0.05$. The dependent variable of the study is the status of employees' hearing about occupational diseases.

RESULTS

It was determined that 36.3% of the individuals participating in the study were between the ages of 18-29, 56.1% were female and 67.2% were married. Physicians constituted 10.8% of the participants. All 72.1% of the participants stated that their general health status was good, 22.0% stated that they had a chronic disease and 50.9% stated that they had never smoked. All 91.3% of the participants stated that they had heard occupational diseases, 50.9% stated that they had received education/training about occupational diseases and 47.4% stated that they thought that occupational diseases were preventable diseases (**Table 1**). A total of 79.4% of participants indicated that occupational diseases are mandatory notifiable diseases. The most frequently notified institution was the Provincial Health Directorate, with a notification frequency of 53%. Of the individuals who participated in the study, 60.3% stated that they did not know which occupational disease is the most frequently diagnosed/reported occupational disease in our country. All 15.3% of the participants stated that they had

Table 1. Descriptive characteristics of participants, Erzurum, 2023

	Number	(%)*
Age (n=287)		
18-29 years	104	36.3
30-39 years	87	30.3
40-49 years	65	22.6
50 years and over	31	10.8
Gender (n=287)		
Female	161	56.1
Male	126	43.9
Marrital status(n=287)		
Married	193	67.2
Single/ divorced/widowed	94	32.8
Title(n=287)		
Physician	31	10.8
Nurse/traniee nurse	126	43.9
Secretary/cleaning staff/administrative unit employees	130	45.3
General health status (n=287)		
Good	207	72.1
Middle	73	25.4
Bad	7	2.5
Chronic disease (n=287)		
Yes**	63	22.0
No	224	78.0
Smoking status (n=287)		
Never used	146	50.9
Left	35	12.2
Occasionally	41	14.3
Still using	65	22.6
Hearing about occupational diseases (n=287)		
Yes	262	91.3
No	25	8.7
Having received training/courses related to occupational diseases (n=287)		
Training/courses	146	50.9
No training/courses	141	49.1
Thinking whether occupational diseases are preventable diseases (n=287)		
Preventable	136	47.4
Unavoidable	151	52.6

*Percentage of column, **The most common chronic diseases were found to be 'thyroid diseases', 'hypertension' and 'diabetes mellitus'

Table 2. Participants' knowledge about occupational diseases, Erzurum, 2023

	Number	(%)*
Whether the notification of occupational diseases is mandatory or not (n=287)		
Notification is mandatory	228	79.4
Notification is not mandatory	59	20.6
To which organisation the notification will be made (n=258) ≠		
Provincial health directorate	135	52.3
Social security institution	113	43.7
Chief physician	112	43.4
Occupational diseases hospital	74	28.6
District health directorate	49	18.9
Other**	4	1.5
Knowledge of the most frequently diagnosed/reported occupational disease in Turkey (n=287)		
Yes***	114	39.7
No	173	60.3
Status of occupational accident (n=287)		
Yes****	44	15.3
No	243	84.7
Hearing about OHS Law No. 6331 (n=287)		
Yes	215	74.9
No	72	25.1

*Percentage of column, ≠ More than one answer was given to the related question, the percentage was calculated over the number of respondents, ** 'Occupational health and safety unit' was the most common answer among 'other', ***Those who stated that they know the most frequently diagnosed/reported occupational diseases in our country answered 'pneumoconiosis', 'respiratory system diseases' and 'lumbar/cervical hernia', **** The most common type of occupational accident was determined as 'injector injury'

an occupational accident and 74.9% stated that they had heard of the OHS Law (**Table 2**). When the participants were asked which diseases could be occupational diseases, 73.5% of them answered infectious diseases, 73.2% heavy metal poisoning, 70.4% hearing loss and 68.6% pneumoconiosis (**Table 3**). It was observed that women and married participants were more likely to hear occupational diseases, the difference was statistically significant (p<0.05) (**Table 4**).

Table 3. Participants' opinion on which diseases can be occupational diseases, Erzurum, 2023

	Number	(%)*
Which diseases can be occupational diseases (n=287) ≠		
Infectious diseases	211	73.5
Heavy metal poisoning	210	73.2
Hearing loss	202	70.4
Pneumoconiosis	197	68.6
Lumbar/cervical hernia	179	62.4
Cancers	161	56.1
Asthma	160	55.7
Carpal tunnel syndrome	159	55.4
COPD	144	50.2
Contact dermatitis	128	44.6
Lateral/medial epicondylitis	111	38.7

*Percentage of column, ≠ More than one answer was given to the relevant question, the percentage was calculated over the number of respondents

Table 4. Descriptive characteristics and having heard of occupational diseases, Erzurum, 2023

	Having heard of occupational diseases			
	Yes		No	
	Number	(%)*	Number	(%)*
Age groups (n=287)				
18-29 years	93	89.4	11	10.6
30-39 years	81	93.1	6	6.9
40-49 years	61	93.8	4	6.2
50 years and over	27	87.1	4	12.9
	p=0.565			
Gender(n=287)				
Female	152	94.4	9	5.6
Male	110	87.3	16	12.7
	p=0.035**			
Marital status(n=287)				
Married	181	93.8	12	6.2
Single/ divorced/widowed	81	86.2	13	13.8
	p=0.037**			
Title (n=287)				
Physician	30	96.8	1	3.2
Nurse/traniee nurse	117	92.9	9	7.1
Other health personnel	114	87.7	16	12.3
	p=0.173			
Status of occupational accident (n=287)				
Yes	42	95.5	2	4.5
No	220	90.5	23	9.5
	p=0.391**			
Hearing about OHS Law No. 6331 (n=287)				
Yes	197	91.6	18	8.4
No	65	90.3	7	9.7
	p=0.728**			

*Line percentage, ** Chi-Square test with yates correction was applied

DISCUSSION

It was determined that 36.3% of the individuals participating in the study were between the ages of 18-29, 56.1% were female and 67.2% were married. The mean age of the participants was 35.4±9.9 and the median age was 34 (min:18-max:61). 10.8% of the participants were physicians. Among the participants, 72.1% stated that their general health status was good, 22.0% stated that they had a chronic disease and 22.6% stated that they smoked. Among those who stated that they had a chronic disease, the most common diagnoses were thyroid diseases, hypertension and diabetes mellitus. In a similar study conducted in a training and research hospital in Ankara, 5.6% of the participants were diagnosed with hypertension.[9] In the world and in our country, the prevalence of hypertension in the general population has been increasing gradually over the years due to problems such as stress, lack of physical activity and irregular nutrition, and it has emerged as a serious public health problem.

All 91.3% of the participants stated that they had heard about occupational diseases and 50.9% stated that they had received a training or course on occupational diseases. In a study conducted with doctors and nurses at a training and research hospital, 27.3% of the participants reported that they received training on the prevention of infections, occupational accidents, and occupational diseases as part of the orientation program when starting their job.[9] In a study conducted with physicians and other healthcare professionals working in the anaesthesia department, 22.7% of the physicians and 83.3% of the other healthcare professionals reported having received training on occupational health and safety.[10] In a study conducted with employees at a university, it was found that 7.3% of the participants had no knowledge about occupational diseases.[11]

In a study conducted with physicians at a university hospital, 54.0% of the participants reported having received training on occupational diseases.[12] A review of the literature reveals that in hospitals categorized as high-risk workplaces, occupational health and safety training is not sufficiently reaching healthcare professionals and their level of knowledge on this matter is inadequate. Whereas, according to the legislation, it is obligatory for those who will work in dangerous and very dangerous workplaces to be subjected to vocational training before being employed.[13] The concept of occupational health and safety acquired a degree of significance in Turkey with the introduction of the OHS Law in 2012. Nevertheless, it is clear that the level of awareness remains insufficient.

Hospitals, according to our legislation, are categorized as high-risk workplaces, and employees are exposed to various risk factors, including infectious diseases, as well as physical (noise, temperature, lighting, radiation, etc.), chemical (formaldehyde, disinfectants, etc.), and ergonomic risks. It is very important for healthcare professionals to have information about the risks they face in the working environment and to increase their level of knowledge about the protective measures against these risks.

In our study, 47.4% of participants stated that occupational diseases are preventable diseases. In a study conducted with physicians working in a university hospital, similar to our study, 49.9% of participants stated that occupational diseases are preventable diseases.[12] Occupational diseases are preventable diseases, and the lack of knowledge of health professionals, especially physicians, on this issue is a sad fact. In the OHS Law, occupational diseases are defined as diseases that occur as a result of exposure to occupational risks.[2] Occupational diseases are preventable diseases in an environment where protective measures are taken against all risks, employees have a high level of knowledge about the risks in the working environment and the necessary personal protective equipment is used.

All 79.4% of the participants stated that occupational diseases are among the diseases that must be notified. When

asked to which institution or institutions the notification of occupational diseases should be made, 52.3% answered Provincial Health Directorate and 43.4% answered Chief Physician's Office. All 43.7% of the participants stated that the notification of occupational diseases should be made to SSI. In a study conducted with physicians working in a university hospital, 39.7% of the participants stated that the notification of occupational diseases should be made to SSI.[12] In both studies, less than half of the participants indicated that occupational disease notification should be made to SSI. In our country, occupational diseases are mandatory notifiable diseases, and the employer is obliged to notify the SSI within three working days if an occupational disease is diagnosed by an authorised health institution.

The group of participants who stated that they were most knowledgeable about the most frequently diagnosed and reported occupational diseases in our country constituted 39.7% of the total number of participants. The participants stated the most frequently diagnosed/reported occupational diseases as 'pneumoconiosis', 'respiratory system diseases' and 'lumbar/cervical hernia' respectively. In many countries, the most common occupational diseases are musculoskeletal system related diseases. In our country, the most common occupational disease reported to the SSI is pneumoconiosis, which is one of the occupational respiratory system diseases.[14] This may be related to the fact that the occupational history of the employees was not questioned in detail and the relationship between musculoskeletal diseases and work was overlooked.

In our study, 15.3% of the participants stated that they had an occupational accident and the most common occupational accident was injector injury. In a study conducted with health vocational high school students, it was stated that 31.6% of the students experienced sharps injuries and 49.5% of them were injured during the preparation of medication for the syringe.[15] In a study conducted with cleaning staff in a university hospital, 27.8% of the participants stated that they had been injured at least once with a sharp instrument.[16] In a study conducted in a hospital in Ankara with employees with a history of sharps injuries, it was found that 43.0% of the participants were injured with an injector.[17]

In institutions providing health care services, sharp piercing instruments such as syringes and lancets are frequently used during working hours. It is seen that occupational accidents are quite common due to reasons such as fatigue, stress and carelessness during the day. In occupational health and safety trainings, it is very valuable to convey information such as proper disposal of syringes in sharps boxes, not closing the cap after syringe use, not throwing syringes in household waste bins and the importance of using personal protective equipment, especially to young and inexperienced health professionals.

In a study conducted with physicians and other health professionals working in the anaesthesia department, 64% of physicians and 75.6% of other health professionals stated that they had heard of the OHS law.[10] In a study conducted with public employees of a university, 37.3% of the participants stated that they had little knowledge about the OHS law, while 20.9% stated that they had no knowledge at all.[11] It is seen that hospital employees have a higher level of knowledge about OHS Law compared to public employees.

The majority of participants (73.5%) indicated that infectious diseases could be classified as occupational diseases. Similarly, a significant proportion of participants (73.2%) identified heavy metal poisoning, (70.4%) hearing loss, (68.6%) pneumoconiosis and (62.4%) lumbar/cervical hernia as potential occupational diseases. Especially with the COVID-19 pandemic, it is seen that there is an awareness in the society that infectious diseases seen in healthcare professionals may be occupational infectious diseases.

Among the participants, the frequency of hearing about occupational diseases was higher in women and married, the difference was found to be statistically significant ($p<0.05$). Although physicians and nurses who are in one-to-one contact with patients are expected to be more knowledgeable about occupational diseases than technical or administrative staff, no significant difference was found in this study.

Limitations

One of the limitations of this study is the low participation of health professionals in the study. The study encountered significant challenges, particularly in the inclusion of physicians.

CONCLUSION

As a result, in this study, it is seen that the level of knowledge of healthcare professionals about occupational diseases, occupational accidents, what the risks are and what kind of problems they may cause, and the current legal regulations is insufficient. Due to the working conditions in the world and in our country, employees in all sectors face many problems related to occupational health and safety. For this reason, it is a fact that all employees, especially healthcare professionals, need more information about existing legal regulations, their rights, risks and ways of protection from them. Health surveillance of health professionals should be carried out within the scope of recruitment examinations, periodic examinations, return-to-work examinations after returning to work after an occupational accident or occupational disease should be carried out regularly. In addition, orientation trainings for new recruits and annual occupational health and safety trainings should be planned and regular participation of all employees to these trainings should be ensured.

ETHICAL DECLARATIONS

Ethics Committee Approval

For the implementation of the study and the use of the data, the approval of the ethics committee was obtained from Erzurum Medical Faculty Ethics Committee (Date: 13.09.2023, Decision No: BAEK 2023/05-55).

Informed Consent

Informed consent was obtained from all patients participating in the 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.

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Review

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Hypersensitivity pneumonia from the past to the future

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ABSTRACT

Hypersensitivity pneumonia (HP) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. Exploring the historical context of HP helps to understand how significant changes in risk factors over time have influenced its development. Many inciting agents have been associated with HP since its recognition in 1700. More than 300 etiologic agents have been identified as the cause of the disease. Bacteria, fungi, animal proteins, plant proteins, low molecular weight chemicals, and metals have been identified as inciting agents. New exposures continue to be suspected as causative factors in the development of HP. As occupational and unsalaried avocational practices evolve, give rise to an ever-expanding list of HP-inducing risk factors, including three-dimensional printers (thought to be due to nylon powder used in its manufacture), contaminated home continuous positive airway pressure machines and dental products (methyl acrylates affecting dental technicians).

Keywords: Hypersensitivity pneumonia, etiologic agents, new exposures

INTRODUCTION

Hypersensitivity pneumonia (HP) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. It is typically caused by an immune-mediated reaction triggered by an overt or covert inhaled antigen in susceptible individuals. HP has historically been termed extrinsic allergic alveolitis.[1] Knowing the historical development of HP not only helps to understand which antigens cause it but also helps to understand how significant changes in risk factors over time have influenced the development of HP. The history of this disease is largely uncertain. Some case reports claim that the disease can be traced back to the 18th century or earlier. Later reports and investigations suggest that the disease is a relatively modern construct, dating back only to the early 20th century.[2] Respiratory diseases in agricultural workers were described in the early 16th century. Bernardino Ramazzini (1633-1714), in his book 'De Morbis Artificium Diatriba' (Diseases of Labourers), stated that almost everyone who earned a living by sifting or measuring grain had shortness of breath, cachexia and rarely reached old age. Despite the long-standing recognition of agricultural lung diseases, the first clear clinical report of HP was in 1932, when the British physician Munro Campbell, in Westmorland during a particularly damp hay-making season, also clearly describes at least five cases in farm workers who developed dyspnea, mild fever, and dry wheezing on examination.[3] WN Pickles,[4] describing a series of several farmers who developed similar symptoms and chest radiographic appearances after working with moldy hay and whose symptoms subsided when exposure was avoided, stated that it should be called farmer's lung. Although farmers' lung remain one of the HP classes, its incidence has decreased over time. This decline is thought to be due to changes in farming practices. The first definitive report of HP in birds was described in 1965 by Reed et al.[5] reported three cases of young male pigeon breeders who developed a febrile illness and a fine diffuse interstitial pneumonia on chest radiographs, all of which cleared after avoidance of exposure and returned upon prevocational re-challenge. The evolution in manufacturing during post-World War II industrialization led to new exposures and irritants. Following the large-scale use of isocyanates in the production of polyurethane resins for flexible foam, synthetic rubber, adhesives, and paints, a series of four cases of patients with isocyanate-associated HP was described in 1976.[6] As industrialization after World War II increased the use of mechanization, the use of metalworking fluids also increased. A wide range of metalworking fluids are used for cooling and lubrication purposes in a variety of applications with varying properties and chemical compositions. Such metalworking contaminants, recirculated and aerosolized under high pressure, caused the first described outbreaks of so-called 'machine operator's lung' in the 1990s.[7]

EPIDEMIOLOGY

The prevalence and incidence of HP varies greatly depending on the intensity of exposure, geographical area, and local

climate.[8] Most of the epidemiological information on HP has been obtained from studies of farmers and bird breeders. In mild clinical or subclinical cases, the diagnosis of HP may be missed and misdiagnosed as viral disease or asthma. Both of these diseases may have non-specific clinical signs mimicking HP. In a study, the one-year prevalence rate of the disease was determined as 1.67-2.71 (11.2% over 65 years old) per hundred thousand people, half of the cases were evaluated as chronic hypersensitivity pneumonia.[9] In the United Kingdom, the incidence was found to be 0.9 per 100,000 people in the period 1991-2003.[8] Farmer's lung is one of the most common forms of HP, affecting 0.4 to 7 percent of the farming population.[10-14] The reported prevalence of HP among bird fanciers is even more variable than farmer's lung; estimates range from 20 to 20,000 affected individuals per 100,000 persons at risk.[15,16]

ETIOLOGIC AGENTS

HP is a syndrome involving the lung parenchyma and specifically the alveoli, terminal bronchioles, and alveolar interstitium due to a delayed allergic reaction. This reaction occurs secondary to repeated and prolonged inhalation of different types of organic dusts or other substances to which the patient is hypersensitive, especially organic dusts of animal or vegetable origin, less commonly chemicals.[17] More than 300 etiologic agents have been identified as the cause of the disease.[18] Many inciting agents have been associated with HP since its recognition in 1700, but antigen and exposure were not identified in up to 60% of HP patients despite an extensive history.[1] The most common forms are bird fancier's disease and farmer's lung.[19] The main source of antigens in the farmer's lung is the proliferation of thermophilic actinomycetes in straw or dust with high humidity and temperatures between 40 and 60˚C.[20] Bird or pigeon breeder's lung disease is caused by exposure to antigens in the faeces of birds. Indirect exposure from feather beds or down duvets has also been reported to cause the disease. Due to the change in working conditions in industrialized countries, the prevalence of farmer's lung decreased but HP cases due to metalworking fluids increased.[21]

NEW EXPOSURES CAUSATIVE FACTORS

New exposures continue to be suspected as causative factors in the development of HP. Central to their identification are a pattern as consistently described in the literature; symptom onset when in the presence of an exposure; improvement with avoidance; recurrence upon inhalational rechallenge; typical radiographic imaging, histopathological findings, and, in some reports, positive precipitins. As occupational and unsalaried avocational practices evolve, the application of these criteria gives rise to an ever-expanding list of HP-inducing risk factors, including three-dimensional printers (thought to be due to nylon powder used in its manufacture), contaminated home continuous positive airway pressure machines and dental products (methyl acrylates affecting dental technicians).[2]

CATEGORIZATION

For many years, the clinical forms of HP have been categorized as acute, subacute, or chronic, depending on the duration and intensity of exposure and the duration of the disease. However, this categorization has not been satisfactory due to the great variability and overlap in the clinical course of HP. Acknowledging the limitations of the previous classification system, the 2020 guidelines prepared by the American Thoracic Society, the Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/JRS/ALAT) classified HP into non-fibrotic (purely inflammatory) and fibrotic (inflammatory+fibrotic or purely fibrotic) phenotypes based on the predominant presence or absence of fibrosis on imaging or histopathological examination.[1] It is accepted that the presence of fibrosis is a critical determinant of prognosis.

CLINICAL FEATURES

Common HP symptoms include dyspnea and cough. Less frequent symptoms are chest tightness and constitutional symptoms, such as fever, chills, weight loss, and malaise. Symptom onset varies, ranging from acute (days to weeks), insidious (months to years), or recurrent episodes. Acute symptoms, potentially with systemic signs, are more typical in nonfibrotic HP, while an insidious onset is often seen in fibrotic HP.[22]

CLINICAL ASSESSMENT

Diagnosis is not easy because there is no gold standard diagnostic test in HP. The diagnosis is based on determining exposure to a causative agent and excluding other possible interstitial lung diseases. The diagnosis is based on the integration of a number of factors including exposure history, detection of precipitating antibodies, clinical features, bronchoalveolar lavage, radiology, and pathology.[23,24] The diagnosis of HP should be made with a multidisciplinary approach. Fibrotic HP should be considered in the differential diagnosis of all patients with fibrotic interstitial lung disease. It is difficult to differentiate this group of patients because exposures cannot be determined in almost half of the patients with fibrotic HP. In non-fibrotic HP, the diagnosis may be easier since the exposure can usually be easily detected. The ATS/JRS/ALAT guidelines emphasize the importance of three main points for HP diagnostic criteria. These are identification of exposure (clinical history with or without questionnaire, serum IgG test against potential antigens associated with HP), radiological pattern, and lymphocytosis/histopathological findings in bronchoalveolar lavage (BAL). Diagnostic algorithms have been developed to minimize invasive interventions.[1]

TREATMENT

Antigen avoidance is the cornerstone of treatment for symptomatic HP and usually results in regression of disease.[20] Additional treatment may be required in more severe or progressive disease. The best-studied forms of HP are farmer's lung and bird fancier's lung; treatment of other types of HP largely is extrapolated from the experiences in these populations. Corticosteroids and immunosuppressive drugs can be used in pharmacological treatment. Recently, antifibrotic treatments can be used depending on HP phenotypes. Lung transplantation may be considered in patients with severe clinical and functional loss.[25]

PROGNOSIS

The long-term outcome of HP varies and depends on factors such as the specific causal antigen, duration of antigen

exposure, and host response. Patients with acute HP who have complete avoidance of the causal antigen tend to experience near-total recovery of lung function, although full recovery may take several years after the inciting exposure ceases.[24,26] Bird fancier's HP appears to have a worse prognosis than farmer's lung. The prognoses of other varieties of HP are less well described. In general, patients with evidence of pulmonary fibrosis on surgical lung biopsy have a poorer prognosis than those without such changes.[27]

CONCLUSION

History can teach us a lot about HP, but there is still much to learn. Suffice it to say that exposures not previously known to cause HP will continue to be discovered over time. Looking back and being vigilant going forward can help us reduce the risk of HP in the years to come.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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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.

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Case Report

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Neurogenic pulmonary edema caused by epileptic attack: a case report

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ABSTRACT

Neurogenic pulmonary edema (NPE) is a life-threatening situation that progresses with acute respiratory distress caused by central neurological damage or injury. NPE may occur as aresult of different central nervous system diseases and disorders, such as brain malignancies,traumatic brain injuries, infections, and convulsions. This case report was designed to highlight thecauses, outcome, and treatment of NPE triggered by an epileptic attack.

Keywords: Neurogenic, pulmonary edema, catecholamines

INTRODUCTION

Neurogenic pulmonary edema (NPE) is a life-threatening situation that progresses with acute respiratory distress caused by central neurological damage or injury. NPE may occur as a result of different central nervous system diseases and disorders, such as brain malignancies, traumatic brain injuries, infections, and convulsions. Symptoms begin within minutes or hours and resolve after 48-72 hours. This study was designed to highlight the causes, outcome, and treatment of NPE triggered by an epileptic attack. NPE may also be keep in mind in the etiology of cases of acute respiratory failure and hypoxia.

CASE

A 43-year-old male patient with a diagnosis of epilepsy was brought to the emergency service by ambulance with a generalized tonic-clonic seizure. He was given a total of 10 mg of diazepam,with one administration in the ambulance and two in triage. He was known to have had one seizure in the last 3.5 months and he was using depakine at 2x750 mg. Almost immediately after the seizure, he became dyspneic and hypoxic; in light of these symptoms,a chest diseases consultation was requested. His temperature was 36.8°C, pulse was 134/min, blood pressure 130/65 mmHg, and saturation was 82% without oxygen. Oxygen was administered at 15 L/min with a reservoir mask. The PaO_2/FiO_2 ratio of 173 was indicative of severe hypoxia. Other physical examination findings were normal. Chest radiography and thoracic computed tomography (CT) showed bilateral diffuse bilateral infiltrates with preservation of the subpleural space, increased central opacity consistent with pulmonary edema and consolidation (**Figure 1: A-D**).

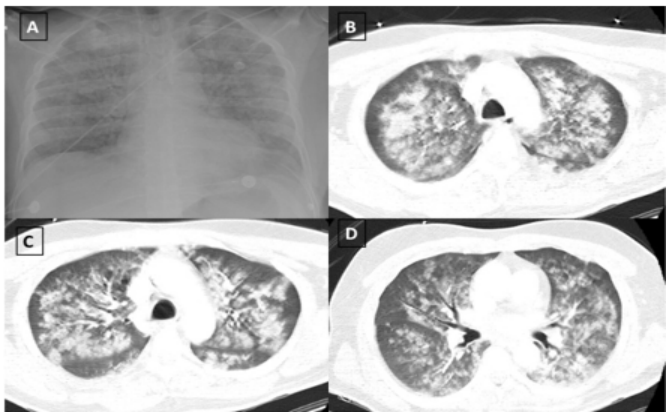

Figure 1. (**A**) Initial chest X-ray with opacity consistent with pulmonary edema, (**B-D**) bilateral alveolar filling defect and areas of consolidation consistent with pulmonary edema with preservation of the subpleural area.

Laboratory examination results were unremarkable and a polymerase chain reaction (PCR) test for COVID-19 was negative. The only abnormal electrocardiogram finding was sinus tachycardia and echocardiography was normal. No intracranial lesions were detected at cranial CT. The patient's clinical situation improved in a few hours without any further medical treatment, with saturation reaching 97% with a nasal cannula at 2 L/min. After 24 hours he no longer needed oxygen, and in an examination at 72 hours his chest radiography was completely normal (**Figure 2**). He was discharged after a consultation with neurology about his antiepileptic treatment.

DISCUSSION

NPE was first defined by Shanahan[1] in 1908 as postictal pulmonary edema in 11 epileptic patients aged between 9 and 36 years. The incidence of NPE is unknown because

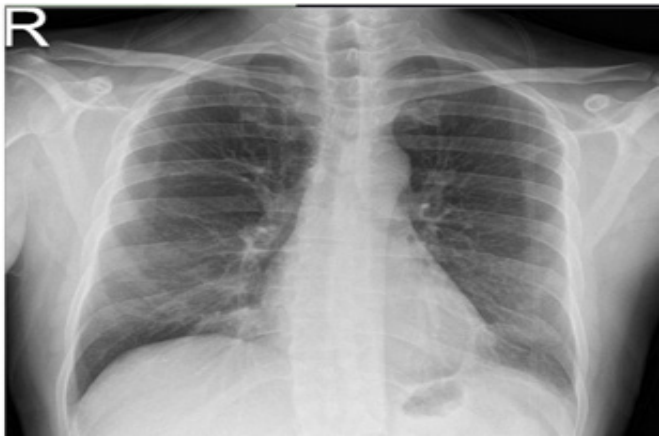

Figure 2. Control chest X-ray taken 72 hours later

it is difficult to distinguish between cardiogenic and non-cardiogenic pulmonary edema. However, it is a life-threatening situation with an unclear etiopathogenesis. The most frequent triggers are cranial trauma, subarachnoid bleeding, and epilepsy, mostly with generalized seizures. Cervical medullary trauma, electroconvulsive therapy, intoxication, postoperative complications after intracranial surgery, and meningitis are more rare triggers of NPE.[2] Due to underlying brain injury, the mortality rate is high regardless of the pulmonary effects.[3,4] Pathophysiologically, the sympathetic nervous system is the key player in the pathogenesis of NPE. Catecholamines initiate three important pathophysiological responses: systemic vasoconstriction, increased blood pressure, and increased venous return. Sympathetic activation, increased release of catecholamines and increased pulmonary capillary permeability occur.[2,5,6]

Clinical manifestations are generally nonspecific and it occurs within minutes or hours, secondary to intracranial pathologies. Dyspnea, tachycardia, hypoxemia, and hemoptysis may occur in these patients. Laboratory findings are also nonspecific and ventilation perfusion imbalance, hypoxemia, and carbon dioxide retention may be detected.[2] Acute respiratory distress syndrome (ARDS), cardiologic edema, aspiration pneumonia, and bacterial pneumonia may be involved in the differential diagnosis. NPE can be confused with many other clinical pictures from ARDS to COVID-19 pneumonia that cause similar radiological findings of diffuse infiltrations.[7,8] The radiological findings of our case were also likely with pulmonary edema. However, the COVID-19 PCR test and microbiological samples were negative. There were no remarkable laboratory results. And no pathology was detected in echocardiography.

The main principles of treatment are to prevent the increase of intracranial pressure and address the injury to the central nervous system. Providing ventilation and supportive oxygenation, as in cases of ARDS, is important along with the reduction of pulmonary vascular resistance, especially by targeting inotropic increase via β-adrenergic stimulation.[2] Experimental studies have shown that α-adrenergic blockers can be useful in the treatment of NPE by blocking the increased sympathetic response, while dobutamine increases cardiac output and reduces peripheral vasoconstriction.[9] In our case, the trigger was an epileptic seizure and antiepileptic treatment and symptomatic treatment with oxygen resolved the case. The need for oxygen supplementation was quickly reduced.

CONCLUSION

NPE is a life-threatening situation that progresses with acute respiratory distress caused by central neurological damage or injury. NPE may occur as a result of different central nervous system diseases and disorders, such as brain malignancies, traumatic brain injuries, infections, and convulsions. This case report was designed to highlight the causes, outcome, and treatment of NPE triggered by an epileptic attack.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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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.

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Letter to the Editor

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A case of byssinosis in a yarn factory foreman: an occupational lung disease forgotten over time

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Dear Editor,

I am writing this letter to discuss the diagnosis of byssinosis that occurred in a worker who was producing yarn from raw cotton. Byssinosis is a nonspecific occupational respiratory disease that occurs in textile workers exposed to cotton and cotton products.[1] It is known as "monday morning fever" and is characterized by an increase in symptoms during the first days of the work period.[2] There are non-specific findings on the chest film; air trapping is a common radiological finding on tomography. Increased bronchial wall thickness and rarely nodular opacities are also among the radiological findings.[3] The case is 38 years old and has been working in a yarn factory in Adana province for 8 years. He is a wick operator and works as a foreman in the unit where yarn is produced from cotton wool. In the work environment, he was exposed to dust from cotton raw materials and cotton varieties such as polyester, viscose, acrylic, and carded nylon. He stated in his anamnesis that he did not use personal protective equipment and that he had no pathology related to the lungs in his pre-employment examination. Although shortness of breath was constant, it has increased in the last 6 months. In addition to shortness of breath, there was a complaint of phlegm. He occasionally had a cough. He was referred to our clinic after pathology was observed in respiratory function tests during control examinations. The patient had been diagnosed with asthma at an external facility and was using inhaled medication. The inhaler medication did not alleviate her complaints. There was no history of additional disease. He quit smoking 3 months ago and had been smoking half a pack of cigarettes a day for 14 years. During the respiratory examination, both hemithoraxes participated equally in respiration, and the respiratory sounds were deep. Saturation measured from fingertip on room air was 94%. There was no reversibility in the pulmonary function test (PFT). Forced expiratory volume in 1 second (FEV1) was 55% (2.15 litres), forced vital capacity (FVC) was 57% (2.66 litres), and the rate of FEV1 to FVC was 81. In the thoracic tomography, remnant thymus tissue and less than 1 cm of lymph nodes in the mediastinum were seen. The heart dimensions were normal. The mosaic attenuation patterns were reported at the basal level of both lower lung lobes, more pronounced on the left. A ground-glass nodule with a diameter of 8 mm was observed in the posterior upper lobe of the right lung (**Figure**). Based on work history, clinical, radiological, and spirometric criteria, a diagnosis of byssinosis, an occupational lung disease, was made. Steroid treatment was not given because the ground glass areas were not visible. Legal procedures were carried out, disease notification was made, and recommendations were made to avoid exposure to cotton dust. In the control examination one month later, symptomatic improvement was observed. PFT repeated, and similar values were seen to the first PFT [FEV1: 57% (2.21 litres); FVC: 60% (2.79 litres); FEV1/FVC%: 79]. Late reversibility was accepted as a negative result. A pulmonary nodule was taken under follow-up.

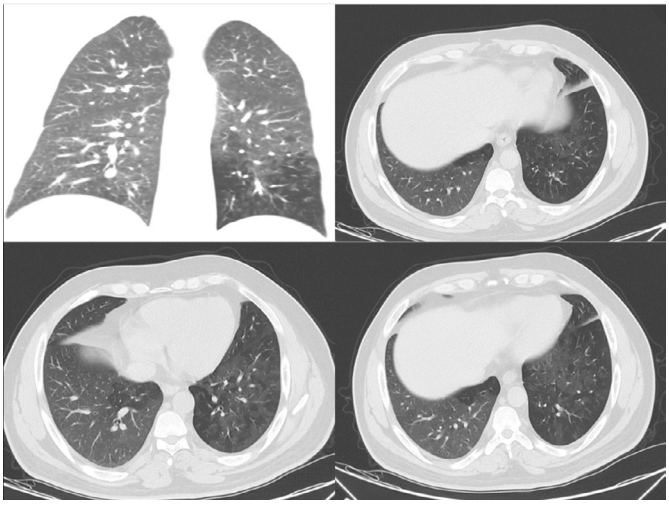

Figure. The tomography findings of the byssinosis case in four different sections

In Turkiye, occupational diseases are illnesses that are legally required to be reported. No byssinosis cases have been reported in the publicly available data of the Social Insurance Institution since 2012. It is a debatable issue whether there are really no cases of byssinosis, whether there are cases but they are not reported, or whether the reported cases are not included in the data because they do not meet the compensation criteria of the Social Insurance Institution. Tissue sampling is an important step in the diagnosis of interstitial lung diseases.[4] There are no

clear pathological features of byssinosis yet defined in biopsy materials. Some sources talk about increased size of mucous glands, mild muscle hypertrophy in the bronchi, and neutrophils gathering in groups; none of these terms are specifically used to describe byssinosis. There have not been enough studies to define bronchial biopsy or bronchoalveolar lavage (BAL) samples for the diagnosis of byssinosis.[1] For these reasons, the patient did not undergo any interventional procedures. The disease most frequently confused in differential diagnosis is occupational asthma. Mosaic perfusion areas can be seen in asthma cases. However, in our case, mosaic perfusion areas were located in a much larger area than expected in asthma. Due to the clinical presence of asthma symptoms and worsening of complaints at work, cases can often be evaluated as asthma. The most important difference with asthma is that in asthma, symptoms occur progressively on all days of the week, while in byssinosis, the most severe complaints are on the first working day, and then the complaints gradually decrease. However, in advanced cases of byssinosis, patients may experience persistent symptoms as they spread throughout the week.[3] Our case fits into the chronic, severe effect (FEV1 less than 60% of predicted value) category of byssinosis, according to the most recent classification by the World Health Organization.[5] He did not have increasing complaints in the first days of the week and was constantly describing symptoms. Severe respiratory disease, characterized by persistent airway obstruction and widespread air trapping, has caused the complaints to lose their temporal character. The absence of early and late reversibilities renders PEF monitoring meaningless. In conclusion, as with most occupational respiratory diseases, the diagnosis of byssinosis cannot be made histopathologically but is rather complex and is based on clinical and radiological findings and work history. This letter to the editor was written because byssinosis is a disease that has not been reported for the last 12 years in Turkiye.

ETHICAL DECLARATIONS

Referee Evaluation Process
Externally peer-reviewed.

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

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