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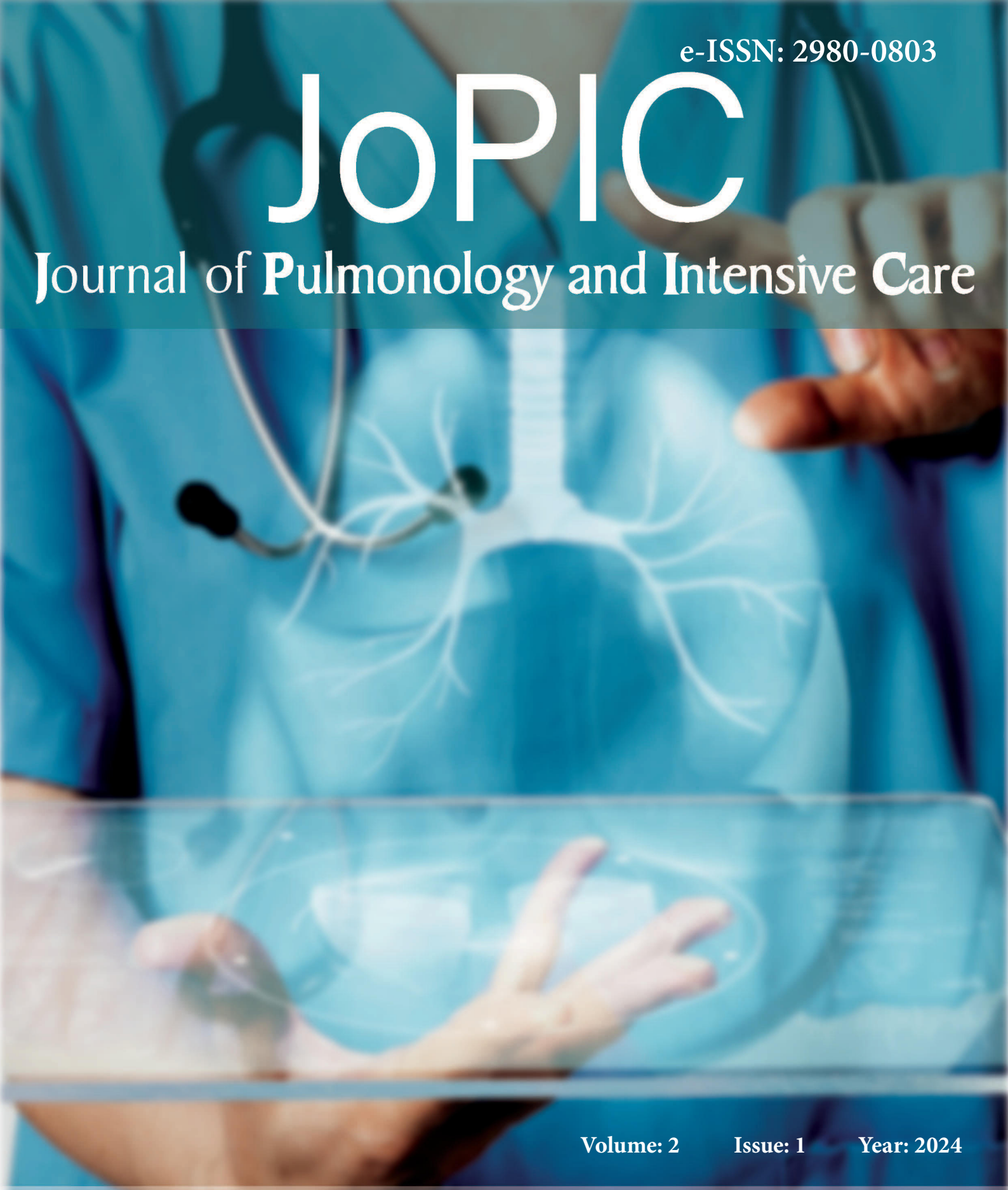

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EDITORIAL

Dear Colleagues,

As of February 2024, we have completed the first year of our journal's publication life. We have published the fifth issue of Journal of Pulmonology and Intensive Care (JoPIC) under the shield of Medihealth Academy. In addition to all researchers, referees and editorial board who contributed to the preparation of the journal; we would like to thank the printing team for their effort in preparing it for publication. This fifth issue includes two review, three original research, and a case report. Periodicals are popular with their readers and researchers. In the upcoming period, with your support, our goal is for JoPIC to be indexed in nationally and internationally accepted scientific indexes. I would like to thank you in advance for your contribution.

Assoc. Prof. Berna AKINCI ÖZYÜREK
Editor in Chief

Journal of
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Original Article

DOI: 10.51271/JOPIC-0024

Diagnostic and prognostic value of serum amiloid a in patients with idiopatic pulmonary fibrosis

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ABSTRACT

Aims: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease with a poor prognosis, characterized by the irreversible loss of pulmonary function. Despite the critical importance of early diagnosis in this disease characterized by poor prognosis, the diagnosis of IPF is usually late. Serum Amyloid A (SAA) is a member of the heterogeneous family of apo-lipoproteins. SAA is one of the most sensitive indicators of systemic inflammatory activity and is considered an acute phase protein. Therefore, a reliable biomarker to predict IPF will allow early diagnosis, warranting early treatment, which will prolong survival by halting disease progression. In our study, SAA values from IPF patients were compared with those from a control group of healthy individuals to evaluate the feasibility of SAA as a diagnostic biomarker. The aim of our study was to investigate the diagnostic and prognostic value of SAA and its usability as a biomarker in patients with IPF.

Methods: This study has been designed as a prospective, case-control study. Fifteen healthy individuals and fifteen IPF patients. The demographic data and the measures from Pulmonary Function Tests (PFT; FEV1, FVC, FEV1/FVC, DLCO, DLCO/VA), laboratory tests of the patients included in the study were retrieved from IPF follow-up files.

Results: The comparison of the IPF patient group with the group of healthy volunteers revealed significantly higher SAA values in IPF patients (p:0.005). A significant positive correlation was found between the patients' SAA and C-Reactive Protein (CRP) values. A negative significant correlation was found between the SAA values of the patients and the time to diagnosis ($p<0.05$). Despite the negative correlation between the SAA and FVC values of patients, no significant correlations were detected between these variables ($p>0.05$).This result suggests that SAA levels would be higher in newly or recently diagnosed .

Conclusion: This study shows that SAA is significantly higher in IPF patients, suggesting that it will be a reliable biomarker feasible to predict the diagnosis. Future studies with larger patient groups are needed.

Keywords: fibrosis, biomarker, prognosis

INTRODUCTION

IPF is a chronic and progressive lung disease characterized by irreversible loss of respiratory function and the typical histological and radiological pattern of interstitial pneumonia, with advanced fibrosis and a poor prognosis.[1] The survival period is usually 3-5 years after diagnosis. For a disease such as IPF, which is difficult to diagnose and when diagnosed causes irreversible functional and radiologic changes, early diagnosis is very important. Therefore, when there is a reliable biomarker that can be used to predict IPF, early diagnosis and thus early initiation of treatment will be ensured, and survival will be prolonged by preventing disease progression. In addition, the evaluation of this potential diagnostic biomarker, together with pulmonary function tests, exertional capacity and mortality risks of IPF patients, will help us determine its relationship with the course of the disease and can be used to predict prognosis.[2,14,15]

Recently, lipid metabolism has been reported to play a role in the pathogenesis of Interstitial Lung Disease (ILD) and lipid metabolites and lipoprotein imbalances have been detected in the plasma and Broncho alveolar Lavage (BAL) fluids of patients with IPF.[2,3] SAA a plasma component, is a member of the heterogeneous family of apo-lipoproteins. It is mainly secreted by activated monocytes in the liver. Its production is an acute-phase protein stimulated by proinflammatory cytokines such as IL-1, IL-6, and TNF-alpha.[4,13] In the inflammatory mechanism resulting in the basic histologic and radiologic involvement of IPF it is thought that SAA synthesis will also be stimulated in the phase when these proinflammatory mediators increase and therefore SAA levels may be high in patients diagnosed with IPF. In addition, it is thought that the stimulation caused by fibrosis and hypoxia may also stimulate SAA production. Another hypothesis is that the increase in SAA levels is a

result of advanced fibrosis in the pathogenesis of the IPF. SAA can be released not only from the liver but also from lung fibroblasts. Therefore, it is thought that SAA levels may also increase in clinical conditions such as IPF in which the activity of these fibroblasts increases.[4,7] Based on these considerations, the aim of our study was to investigate the diagnostic and prognostic value of SAA and its usability as a biomarker in patients with IPF.

METHODS

This study was designed as a prospective, case-control study. The study was conducted as a single-center study in the Chest Diseases Clinic of the Dışkapı Yıldırım Beyazıt Health Application and Research Center. The study included 15 patients with IPF (7 newly diagnosed, 8 under treatment) and 15 healthy subjects who were admitted to our clinic between 20.04.2020 and 01.01.2021. Demographic information, Pulmonary function tests, 6-min walk test (6MWT) and laboratory values of the patients included in the study were obtained from the IPF follow-up files. FEV1, FVC, FEV1/FVC predictive values, DLCO, DLCO/VA predictive values, 6MWT performances, Modified Medical Research Council dyspnea scale (mMRC) values were included in the study to evaluate the correlation of patients with IPF with SAA values. This study was carried out with the permission of University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date:20.04.2020, Decision No: 86/11). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The data obtained were analyzed using SPSS. $p<0.05$ was accepted as the significance level in all statistical analyses and the relationships were evaluated at a 95% confidence interval. The relationship between numerical dependent and independent variables was evaluated by Spearman Correlation Analysis; the relationship between numerical dependent and categorical independent variables was evaluated by the Mann-Whitney U and Kruksal-Willis tests.

RESULTS

The sociodemographic characteristics of the participants are given in **Table 1**. Categorical variables were presented as numbers and percentages; numerical values were presented as mean±standard deviation, minimum and maximum values. In the case group of our study, there were 15 patients (10 males and 5 females) with a mean age of 64.80±11.27 years. In the control group, there were 15 healthy volunteers with a mean age of 57.32±10.88 years. The mean age of IPF patients was 64.80±11.27 years; 5 of the patients had never smoked, 8 had quit smoking, and 2 were still smoking. The mean cigarette pack years of the patients were 17.20±13.45.

A control group of 15 healthy volunteers was formed to compare the SAA values of IPF patients. Mann-Whitney U test was used to checking whether there was a significant difference between the SAA values of the IPF patients and the control group.The mean SAA values of IPF patients were 14.00±34.63. The mean SAA value of the control group was 0.40±0.14. According to the Mann-Whitney U test results, there was a significant difference between the SAA values of the control group and IPF patients and the SAA values of IPF patients were much higher (p:0.005) (**Table 2**).

Table 1. General characteristics of IPF patients

Parameters	IPF Patients		
n	15		
Gender	Male (%)	Female (%)	
f (%)	10 (66.6)	5 (33.3)	
Smoking	Never	Former	Active
f (%)	5 (33.3)	8 (53.33)	2 (13.33)
Package year	17.20±13.45		
Diagnosis method	Clinic	Histopathologic	
f (%)	11 (73.33)	4 (26.66)	
	Mean (S.D.)	**Min.**	**Max.**
Age (years)	64.80±11.27	48	82
Time since diagnosis (months)	6.53±8.18	0	24
CRP (mg/l)	57.76±122.53	0.61	464
HDL (mg/dl)	42.07±12.40	21	65
LDL (mg/dl)	111.87±37.99	59	188
Total Cholesterol (mg/dl)	166.13±42.17	103	250
Triglyceride (mg/dl)	137.83±117.81	48	418
SAA (mg/dl)	14.00±34.63	0.18	135
FEV1 (%)	65.40±26.44	27	117
FVC (%)	61.87±24.89	25	116
FEV1/FVC (%)	80.47±7.48	70	93
DLCO (adj/ml)	56.50±17.80	24	94
DLCO/VA (adj/ml)	94.17±14.25	73	118
6 min distance (m)	212.67±168.04	15	480
6 min duration (min)	4.47±2.00	1	6
Desaturation after 6 min(%)	12.67±14.11	0	43
mMRC score	2.67±1.18	1	4
Medicine	None	Pirfenidone	Nintedanib
f (%)	7 (46.7)	6 (40)	2 (13.3)

Table 2. Mann-Whitney U Test results of IPF patients and control group according to SAA values.

	N	Mean (mg/dl)	S.D.	Avg. Row	Z	p
IPF Patients	15	13.999	34.633	19.97	-2.780	0.005
Control Group	15	0.401	0.138	11.03		

Mean:Mean value of SAA, S:D: Standard Deviation, Avg. Row:Average Row

Spearman correlation analysis was used to examine the relationship between SAA values and PFT, 6MWT, laboratory values and mMRC dyspnea scores . Although a negative correlation was found between SAA values and FVC values, no statistically significant correlation was found ($p>0.05$) . No significant correlation was found between SAA values and DLCO values ($p>0.05$) (**Table 3**).

Table 3. Spearman's correlation analysis results of the relationship between SAA levels and PFT values of IPF patient.

	SAA	FVC
Spearman's rho		
SAA		
Correlation coefficient	1.000	-.193
P	.	.491
N	15	15
FVC		
Correlation coefficient	-.193	1.000
p	.491	.
N	15	15
	SAA	**DLCO**
Spearman's rho		
SAA		
Correlation coefficient	1.000	.170
p	.	.597
N	15	12
DLCO		
Correlation coefficient	.170	1.000
p	.597	.
N	12	12

Spearman's rho: Spearman's rank correlation coefficient, N:The number of observations

No significant correlation was found between SAA values and 6-min distance, duration, and desaturation values (p>0.05) (**Table 4**).

Table 4. Spearman's correlation analysis results of the relationship between the SAA levels of IPF patients and 6MWT walking distances, durations, and desaturation rates.

	SAA	6 min distance	6 min duration	Desaturation
Spearman's rho				
SAA				
Correlation coefficient	1.000			
p	.			
N	15			
6 min distance				
Correlation coefficient	-.416	1.000		
p	.123	.		
N	15	15		
6 min duration				
Correlation coefficient	-.462	.859**	1.000	
p	.083	.000	.	
N	15	15	15	
Desaturation				
Correlation coefficient	.377	-.672**	-.704**	1.000
p	.165	.006	.003	.
N	15	15	15	15

**. Correlation is significant at the 0.01 level (2-tailed).
Spearman's rho:Spearman's rank correlation coefficient, N:The number of observations

No significant correlation was found between the SAA values and the mMRC score (p>0.05) .A significant negative correlation was found between the SAA values and the time since diagnosis (p<0.05). This result shows that newly diagnosed patients and/or patients in the early stages of diagnosis have higher SAA levels (**Table 5**).

Table 5. Spearman's correlation analysis results of the relationship between SAA values and the mMRC dyspnea score, duration of diagnosis in IPF patients.

	SAA	mMRC score
Spearman's rho		
SAA		
Correlation coefficient	1.000	.429
p	.	.110
N	15	15
mMRCscore		
Correlation coefficient	.429	1.000
p	.110	.
N	15	15
	SAA	**Disease month**
Spearman's rho		
SAA		
Correlation coefficient	1.000	-.670**
Sig. (2-tailed)	.	.006
N	15	15
Disease duration (Month)		
Correlation coefficient	-.670**	1.000
Sig. (2-tailed)	.006	.
N	15	15

**. Correlation is significant at the 0.01 level (2-tailed).
Spearman's rho:Spearman's rank correlation coefficient, N:The number of observations

Kruskal-Wallis analysis was used to examine the relationship between the SAA values and the initiation of drug treatment. According to the results of the analysis, there was no significant difference between the SAA values of the patients according to their drug treatments (p>0.05). However, the median SAA value of patients who did not use medication was higher than that of those who used medication (**Table 6**).

Table 6. Kruskal Wallis analysis of the relationship between SAA values of IPF patients and medication use status of the patients.

	N	Mean	S.D.	Avg. Row	Min.	Max.	Chi-square	p
None	7	10.02	11.53	10.14	0.55	30.20	3.071	0.215
Pirfenidone	6	23.10	54.83	6.33	0.18	135.00		
Nintedanib	2	0.62	0.00	5.50	0.62	0.62		
Total	15	14.00	34.63		0.18	135.00		

Mean:Mean value of SAA, S:D: Standard Deviation, Avg. Row:Average Row N:The number of observations

DISCUSSION

IPF is a chronic and progressive lung disease with a poor prognosis characterized by irreversible loss of respiratory function and advanced fibrosis. While early diagnosis is important in this poor-prognosis disease with a survival period of 3-5 years after diagnosis, IPF is usually diagnosed late.[16] In a survey study conducted by Collard et al.[8] in 2007, in which the experiences of patients diagnosed with IPF were evaluated, it was reported that most of the patients were examined by more than one doctor before the correct diagnosis was made (38% of the patients were reported to have been seen by at least three doctors before the diagnosis of IPF), were treated with different diagnoses, and waited for at least 1 year for the correct diagnosis.[8] These difficulties in making the diagnosis of IPF indicate that biomarkers are needed both for early diagnosis and early referral to the right centers and for monitoring the course of the disease. In our study, which we planned based on this idea, we investigated the diagnostic and prognostic value of SAA level, an apolipoprotein, in IPF patients, taking into account the recent studies on the role of lipid metabolism in the etiopathogenesis of respiratory diseases. In our study, as a result of the data we obtained SAA was found to be significantly higher in IPF patients. In addition, a significant positive correlation was obtained between SAA values and the CRP values of IPF patients. However, no significant correlation was found in the correlations of SAA with FVC, DLCO, and 6MWT performance, which were performed for its prognostic utility.

The primary aim of our study was to investigate the diagnostic value of SAA in IPF patients and its usability as a biomarker by comparing SAA levels in IPF patients and healthy volunteers. The secondary aim was to evaluate the utility of SAA in predicting the course of the disease, mortality risk, and thus prognosis in IPF patients.

There is only one study in the literature to evaluate the potential value of SAA as a clinical biomarker in patients with IPF. In this study, conducted by Vietri et al.[4] in Italy in 2019, SAA levels were measured in 21 patients with newly diagnosed IPF who were not receiving any treatment and 11 healthy subjects. The SAA reference value was accepted as 6067 ng/ml. The SAA levels of IPF patients were found to be significantly higher compared to healthy volunteers (p:0.0391, mean SAA value of IPF patients: 5890±1852 ng/ml, mean SAA value of healthy volunteers: 4262±2023 ng/ml).

In our study, 15 IPF patients diagnosed by multidisciplinary evaluation according to the 2018 ATS/ERS/ALAT/JRS guidelines (4 of them have a tissue diagnosis) were included in the case group, and 15 healthy volunteers were included in the control group. The SAA reference value of 0.5 mg/dl was accepted. The mean SAA values of IPF patients and the control group were 14.00±34.63 and 0.40±0.14, respectively. Consistent with the literature, the mean SAA values of IPF patients were found to be significantly higher in our study (p:0.005).

In our study, some of the IPF patients were under treatment. Therefore, unlike the study by Vietri et al., SAA levels were compared among them according to drug use. Seven patients (46.7%) were newly diagnosed and had not yet started drug treatment. Six patients (40%) were on pirfenidone, and two patients (13.3%) were on nintedanib. The minimum duration of treatment was 12 months, and the maximum duration was 24 months.

Pirfenidone is an agent that is thought to inhibit the TGF-B pathway and has been shown to have anti-inflammatory and antifibrotic effects, although its mechanism of action is not fully known.[9,10,17,18] Nintedanib is a tyrosine kinase inhibitor and an antifibrotic agent without any literature data on its anti-inflammatory activity.[11,12,19] Based on this information, in our study, it was thought that both antifibrotic agents would inhibit the activity of lung fibroblasts and thus decrease SAA production. The fact that pirfenidone is also an anti-inflammatory agent was also thought to decrease SAA levels. However, unlike our hypothesis, no significant difference was found between the SAA values of the patients according to their drug treatments (p>0.05). However, the mean SAA values of newly diagnosed IPF patients who were not yet on medication were higher than those who were on medication. These results suggest that larger cohort studies are needed to strengthen the data from our study due to the limited number of patients in our study. It is thought that studies with a larger number of patients, in which patients will be followed up throughout the treatment period and comparing SAA measurements before and after antifibrotic treatment will be more effective in investigating the use of SAA in treatment response.

In the study by Vietri et al.[4] SAA values were compared with predictive FVC values and it was observed that SAA values were significantly higher in patients with low FVC percentages (p:0.0150). Therefore, it was emphasized that a high SAA level was associated with a poor prognosis. Among the studies conducted to determine the diagnostic and prognostic value of SAA in other lung diseases, Bargagli et al.[5] found a significant negative correlation between SAA level and FEV1 (p:0.03), but no significant correlation was found with FVC (p:0.19) and DLCO (p:0.12) in the SAA analysis performed in patients with Sarcoidosis. In the study by Lakota et al.[7] SAA level was correlated with pulmonary function tests in systemic sclerosis patients with pulmonary involvement, and it was shown that SAA level was negatively correlated with FVC (p:0.01) and DLCO (p:0.022) values.

In our study, in order to determine the prognostic value of SAA, the SAA value was compared with FVC and DLCO predictive values. Although a negative correlation was found between SAA values and FVC values, there was no statistically significant relationship between them. There was also no significant correlation between DLCO values (p>0.5). Since three of the patients were non-compliant with DLCO, they could not be included in the comparison. In addition, the SFT compliance of these 3 patients was minimal, and the FEV1 and FVC values were not significant. These reasons and the small number of patients are thought to have affected the statistical results. Further studies with a larger number of patients compliant with pulmonary function tests are needed to strengthen the data.

In our study, in order to further investigate the relationship between SAA levels and pulmonary function capacity and mortality risks in patients with IPF, unlike previous studies, SAA levels were compared with 6MWT performances and the mMRC dyspnea scale. Since SAA synthesis can be stimulated by hypoxic stimulation, it was thought that SAA levels would be higher in patients with low saturation before starting 6MWT, patients with a high desaturation rate during the test, and patients with a high mMRC dyspnea score. However, no significant correlation was found between SAA level and mMRC dyspnea score, and 6MWT performances (p>0.5).

SAA and CRP are considered a class of acute-phase proteins, as they are the most sensitive plasma markers of acute inflammation.[20] Compared to CRP, SAA returns to baseline levels more slowly and remains elevated in the blood for longer.[13] Lin et al.[6] investigated whether there was a correlation between SAA and CRP levels in patients with COPD. A total of 120 patients with acute exacerbations were compared with 120 patients in the remission period, and it was shown that SAA levels were significantly higher in patients with acute exacerbations in correlation with CRP compared to patients in the remission period. In our study, SAA was compared with the CRP levels of the patients at the same time. Consistent with the study by Lin et al., a significant positive correlation was found between SAA levels and CRP levels. This strengthens the hypothesis that elevated SAA levels may be explained by the inflammatory mechanism in the pathogenesis of IPF by increasing acute phase reactant production.

Finally, in our study, we examined the relationship between SAA levels and the duration of the diagnosis. A significant negative correlation was found between the SAA values of the patients and the duration of diagnosis. (p<0.05) This result shows that SAA values were higher in the earlier period of the diagnosis, and SAA levels were lower as the time from the time of diagnosis increased. This is thought to be due to the fact that patients with a longer time since diagnosis were under antifibrotic treatment. The fact that the mean rank of SAA levels was higher in newly diagnosed patients who had not yet started antifibrotic treatment supports this idea. These data suggest that further studies with a larger number of patients are needed to evaluate the response of SAA to antifibrotic treatment.

Limitations

The main limitation of our study is the small number of patients, since IPF is a rare disease. Another limitation is that some of the patients with IPF could not be included in the study because SAA level is an acute phase reactant and can be affected by any infective condition. Therefore, patients with active infections, patients receiving anti-inflammatory therapy, and patients with any systemic disease or lung disease that may cause elevated SAA levels were not included in the study.

CONCLUSION

Our study showed that SAA was significantly higher in patients with IPF, suggesting that it may be a reliable biomarker that can be used to predict the diagnosis. In addition, the fact that the SAA level was lower in patients with a longer time since diagnosis and receiving antifibrotic treatment compared to newly diagnosed patients who had not yet started treatment suggests that treatment affects the SAA level and can also be used to monitor treatment response.

However, when compared with pulmonary function tests and other functional parameters of the patients, no statistically significant results were obtained, and therefore no statistically significant data on its prognostic utility could be obtained. Due to the small number of patients in our study, it is concluded that large cohort studies with a larger number of cases are needed in the future to confirm our data and to obtain more meaningful statistical results.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date:20.04.2020, Decision No: 86/11).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Journal of
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Original Article

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Diagnostic value of tumor M2-pyruvate kinase level in lung cancer and its relationship with tumor histological type

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ABSTRACT

Aims: To investigate the diagnostic value of pyruvate kinase isoenzyme-M2 (M2-PK) levels and their relationship with tumor histological type in patients diagnosed with lung cancer.

Methods: In this study, 98 cases diagnosed with lung cancer (Study group) and 90 cases with lung cancer excluded (control group) were included. The study group consisted of people over the age of 18 who had been diagnosed with lung cancer and had not received any treatment for the tumor. The control group consisted of 45 people who had been diagnosed with any lung disease but did not have lung cancer, and 45 of them were completely healthy people. Those with benign lung disease apart from lung cancer were named as control group-1 and healthy control group was named as control group-2.

Results: M2-PK levels were measured and compared in the lung cancer group, control group-1 with non-lung cancer lung disease and healthy control group-2. M2-PK levels were found to be significantly higher in the lung cancer group than in the control group 1 and control group 2 (respectively $p<0.0001$, $p<0.0001$). When M2-PK levels were compared in all three groups, they were statistically significant in the lung cancer group ($p<0.001$). In our study, the diagnostic cut off value was found to be 8.9 IU/ml using ROC curve. At this cut-off value, plasma m2-pk level was calculated as 100% sensitivity and 97.8% specificity in showing lung cancer. When compared, there was no statistically significant difference between histopathological diagnoses, stage of the disease and M2-PK levels in the lung cancer group.

Conclusion: As a result of this study, it was concluded that tumor M2-PK can be used to distinguish lung cancers from other benign lung lesions and as a marker in patients with suspected lung cancer.

Keywords: Lung cancer, M2 pyruvate kinase, tumor marker

INTRODUCTION

According to the 2020 world cancer statistics, lung cancer ranks 2nd among the most common cancers in the world with 2.2 million (11.4%) new cases. With 1.8 million deaths per year, lung cancer ranks first among cancer-related deaths. WHO reports that lung cancer is the most common type of cancer in men worldwide, while it ranks 3rd in women. Therefore, lung cancer remains important with its frequency and mortality rate. In our country, the number of cancer patients who receive new diagnoses annually is also increasing in parallel with the increasing population. According to the published data, in 2020, 233.34 new cancer cases and 126.335 cancer-related deaths were reported in Turkiye, where the total population was 84.339.67. Lung cancer was reported to be the leading cause of cancer-related deaths in Turkiye (18%).[1,2]

Early diagnosis of lung cancer remains important because it is the leading cause of mortality and morbidity, and new biomarkers are needed as an important part of early diagnosis and prognosis.[3] Pyruvate Kinase is located in the glycolytic pathway. It is the enzyme that controls the production of nucleotide triphosphate, which has an important role in tumor metabolism and has 4 isoenzymes: L, R, M1, M2 types. Type M2 is released mainly in the lungs, kidneys, embryos. While M2pk, which is found in blood and other body fluids, is found in tetrameric form in normal cells, it is transformed from tetramer form to dimeric form in tumor cells, and its release increases in carcinogenesis for various reasons.[4-7] Measurement of tumor M2-PK; it can be very effective for detecting possible recurrence or metastasis and for monitoring the effects of treatment, along with providing useful supporting information in the diagnosis and diagnosis of various tumors. The level of tumor M2-PK can be measured in samples of blood and other body fluids.[8]

Various isoforms of purivate kinase, a glycolytic enzyme,

are released in many tissues. This enzyme, which is usually released from tissues in tetrameric form, has been shown to be synthesized at a high level in dimeric form (M2-PK) in tumor tissues. Many studies have shown that Tu M2-PK can be used as an important marker in the differentiation of benign and malignant cancer and prognosis in different types of cancer.

In our study, we aimed to investigate the diagnostic value of M2-PK level and its relationship with tumor histological type in patients diagnosed with lung cancer at S.B Yedikule Thoracic Diseases and Thoracic Surgery Training and Research Hospital.

METHODS

Ethical Consideration

The study was carried out with the permission of Yedikule Thoracic Diseases and Thoracic Surgery Training and Research Hospital. The study protocol was approved by the Ethics Committee of Yedikule Chest Diseases and Chest Surgery Training and Research Hospital. (Date: 04.02.2012, Decision No: 0006). We obtained an informed consent form from all patients for procedure. The study was conducted between 2012- 2013 and all procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The study included 98 patients who were histopathologically diagnosed with lung cancer (study group) and control groups which 45 cases with non-malignant lung disease (control group-1) and 45 completely healthy individuals without any disease (control group-2). There were 10 Chronic obstructive lung diseases, 10 tuberculosis, 10 pneumonia, 5 idiopathic pulmonary fibrosis, 5 bronchiectasis and 5 pulmonary embolisms in the control group-1. Smoking, alcohol history, family history of lung cancer, diabetes mellitus, hypertension, and ischemic heart disease history were questioned among the variables evaluated.

Histopathological examinations were performed with surgical biopsies or bronchoscopic materials. These materials were examined in the pathology laboratory of our hospital and classified as small cell, lung cancer and non-small cell lung cancer. Patients over 18 years of age, who had been diagnosed with lung cancer histopathologically, who had not previously been diagnosed with any malignancy, and who had not received any treatment for the identified tumor were included in the study.

Determination of Plasma M2-PK Levels

After obtaining the informed consent form from the patients, a plasma sample with 5 cc of EDTA was taken and these samples were quickly frozen and stored in this way (at -80 degrees) until laboratory analysis was performed. Commercial kit based on the sandwich ELISA principle (ScheBo Biotech Ag, Tumor M2-PK ELISA kit, Germany) was used to determine plasma M2-PK levels. The intra and inter-assay variation coefficients were 5.2% (n=25) and 6.3% (n=25) respectively.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows 16 Release 16.01 package program (SPSS, Inc. Chicago, IL, USA). Only the MedCalc program was used in the ROC Analysis, which determines the cut off value and minimizes the margin of error. $p<0.05$ was considered significant.

RESULTS

The ages of the patients with lung cancer were 59.37±9.16, the ages of the control group-1 were 60.62±13.31, the ages of the control-2 were 60.22±11.04 When the correlation analysis was performed between age and M2-PK values in the study group, control group-1 and control-group-2, no significant correlation was found between age and M2-PK levels in any of the groups. (respectively, r=-0.1973, p=0.0515; r=0.0324, p=0.8323; r=- 0.0971, p=0.5306) There was a history of co-morbidity (1 coronary artery disease, 15 Hypertension, 11 Diabetes mellitus, 1 myasthenia graves, 1 chron disease) in the study group. History of co-morbidity in control group -1 (8 DM, 7 HT, 2 CHF, 1 IHD, 2 Rheumatoid Arthritis, 1 Guillain-Barre Syndrome). Mean plasma tumor M2-PK levels were 17.17± 7.75 IU/ml in the patient group with lung cancer, 4.53±2.15 IU/ml in the control group and 4.08±2.87 IU/ml in the healthy group

M2-PK levels of the groups M2-PK levels were significantly higher in the lung cancer group than in the control group-1 ($p<0.001$) and control-group-2 ($p=0.0001$). When M2-PK levels were compared in all three groups, they were statistically significant in the lung cancer group ($p<0.001$). Also student t test analyses results suggest that M2pk levels in lung cancer group were statistically significant compared with control group and healthy control group M2-PK levels (respectively, $p<0.0001$, $p<0.0001$) (**Table 1**, **Figure 1**).

Table 1. Comparison of M2pk values between 3 groups

	Patient group	Control group	Healthy control group	p
M2PK (U/ml)	17.17±7.75	4.53±2.15	4.08±2.87	<0.001
Mean±SD	9.68±45.43	0.5±10.8	0.07±17.17	<0.001

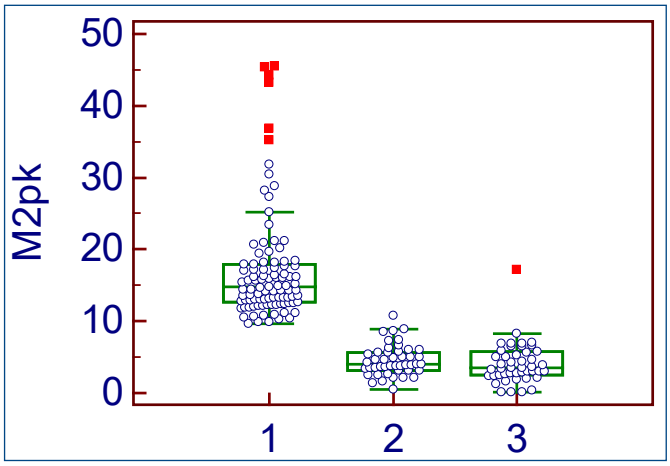

Figure 1. Comparison of M2pk values between 3 groups (1: Patient Group, 2: Control Group, 3: Healthy Control Group.)

M2-PK levels of patients in the lung cancer group were compared according to the demographic characteristics of the patients. There was no statistically significant difference between the M2-PK levels of the lung cancer group and the history of smoking, alcohol use, co-morbidities, and family history of malignancy. When compared in terms of sex, M2-PK levels were found to be statistically significantly higher in men (**Table 2**).

Table 2. Comparison of M2-PK values according to demographic characteristics in the lung cancer group

Study group		n	%	M2PK (U/ml) Mean±SD	p value
Gender	Female Male	10 88	10.20 89.79	13.56±2.03 17.58±8.06	<0.001
Cigarette	Yes None	89 9	90.81 9.18	17.38±8.04 15.01±3.4	0.111
Alcohol	Yes None	23 75	23.43 76.53	18.91±10.4 16.63±6.74	0.332
Comorbidity	Yes None	22 76	22.44 77.55	16.94±7.47 17.23±7.88	0.873
Family cancer history	Yes None	17 81	17.34 82.65	16.91±8.25 17.22±7.70	0.887

In the lung cancer group, there was no statistically significant difference between the histopathological diagnosis, stage of the disease and M2-PK levels in the lung cancer group (**Table 3**).

Table 3. Comparison of M2-PK levels according to histopathological diagnosis and cancer stages in lung cancer group

	M2PK(U/ml) Mean±SD	p
Diagnosis		0.298
Small cell ca (n=14)	19.8±10.25	
Non-small cell ca (n=84)	16.73±7.24	
Stage		
1 (n=3) 2A (n=8)	16.61±3.92 18.99±10.02	0.584
2B (n=5) 3A (n=18)	13.79±3.98 16.15±6.52	0.337
3B (n=21) 4 (n=43)	16.74±7.59 17.89±8.49	0.585

ROC analysis was performed to investigate the diagnostic value of the M2-PK marker in the diagnosis of lung cancer. The cut-off value of M2-PK level was calculated as 8.9 IU/Ml. According to these values, the sensitivity of M2-PK marker in the diagnosis of lung cancer was calculated as 100%, specificity: 97.8%, false positive value as 2.2%, false negativity value as 0%, and accuracy as 98%. Area under the ROC curve (AUC) 0,991 (**Figure 2**).

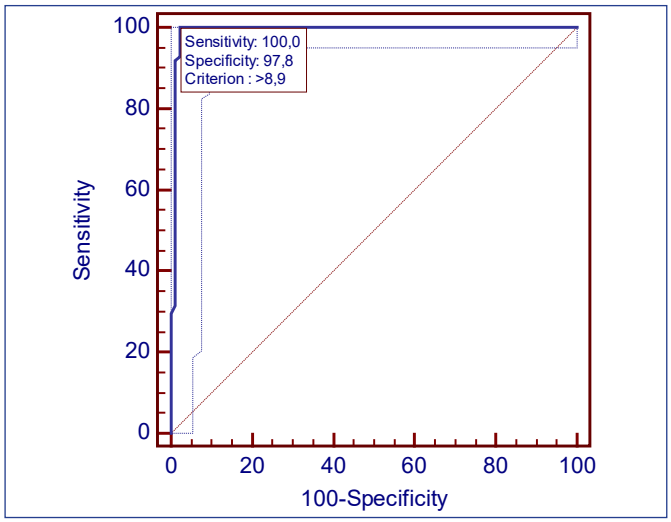

Figure 2. The value of the m2pk marker in the blood, ROC analyses

As a result of this analysis, the area under the ROC curve was calculated as 0.991 and obtained as p<0.0001. This value shows that the blood levels of the M2PK marker are 99.1% stronger in diagnosing AC cancer and can distinguish between patient with lung cancer and healthy individuals as 99.1%.

DISCUSSION

While lung cancer was a rare disease at the beginning of the 20th century, its frequency gradually increased in parallel with the increase in smoking habit and became one of the most common cancers in the world. It ranks first in cancer-related deaths all over the world.[9,10]

In our study, M2-PK levels were evaluated as tumor markers in patients with lung cancer. When the lung cancer group and the control group with non-lung cancer lung disease were compared, the tumor M2-PK level was found to be significantly higher in the lung cancer group (p<0.001). There was no significant difference between tumor M2-PK levels in terms of smoking history, alcohol use history, additional disease history, family history of malignancy.

Early diagnosis and treatment are the most effective way to prevent and reduce mortality, which numerous studies and prevention data have confirmed. Imaging and bronchoscopy have an important value in the diagnosis of lung cancer.

Numerous studies and prevention data have confirmed that early diagnosis and treatment are the most effective way to prevent and reduce mortality. Imaging and bronchoscopy have an important value in diagnosing lung cancer. In 2013, the U.S. Preventive Services Task Force (USPSTF) recommended annual lung cancer screening with low-dose computed tomography (DDCT) in adults 55 to 80 years of age who have a history of smoking 30 packs of cigarettes per year and who are currently smokers or have quit smoking in the past 15 years.[11]

On the other hand, a study was conducted in active smokers and former smokers investigating the risk of radiation-induced lung cancer associated with DDCT for annual screening and the baseline risk that the potential benefits of this screening should overcome. Given the estimated upper limit increase of 5.5% in the lung cancer risk attributable to annual CT-related radiation exposure, it was also emphasized that there would have to be a mortality benefit of more than 5% to outweigh the potential radiation risk.[12]

These are widely used clinical medical methods, but they are not easy to use in large-scale screenings. The level of tumor markers has a good correlation with the formation of tumors. Therefore, the describe of tumor markers, which is a noninvasive method that can be used for early diagnosis and prognosis, has recently become the focus of attention.

M2-PK levels were also found to be high in benign diseases. In the study conducted by Oremek et al.[13] tumor M2-PK levels were found to be high in patients with rheumatoid disease, seronegative spondylarthritis and patients with collagen tissue disorders. One study showed that a single change in the isoform of the glycolytic enzyme pyruvate kinase in tumor formation is necessary for the shift of cellular metabolism to aerobic glycolysis.[14]

It has been reported that this enzyme is high in the diagnosis and prognosis of periampullary pancreatic cancer and in the follow-up of cervical cancers and can be used as a tumor marker. A study demonstrating the role of tumor M2-PK enzyme in lung cancers has been conducted in the literature and it has been thought that this marker can be used to distinguish between benign and malignant lung lesions.[15-18] Christofk et al.[14] show that tumor M2PK is a non-invasive test to diagnose colorectal cancer and adenomatous polyps.

In a study investigating the relationship between pyruvate kinase M2 (PKM2) expression and prognosis in 86 hepatocellular cancer (HCC) patients, it was shown that M2PK expression level was significantly higher in HCC tissues than in healthy tissues. And it was concluded that M2PK expression can be used as a prognostic marker.[19]

In addition, there are studies for the sensitivity comparisons of tumor M2-PK with some markers used in tumor diagnosis and follow-up. Maurizio et al.[17] compared tumor M2-PK with CA 19-9 in a total of 265 cases with acute, chronic pancreatic cancer, benign pancreatic and control group. As a result, they reported that tumor M2-PK level could be used as a metabolic marker, but that it would be more meaningful to use it with CA 19-9 tumor marker.

In the study in which Li Li et al.[20] analyzed the diagnostic and prognostic values of serum TuM2-PK, NSE and ProGRP values in small cell lung cancer, it was shown that M2-PK, NSE and ProGRP levels were higher than the control groups with benign lung disease and healthy control groups. Tu M2 PK sensitivity was found to be 82.35% and serum Tu M2 PK level may be an effective marker of small cell lung cancer and an independent prognostic factor for shorter survival.

Chunhua et al.[21] looked at serum tu M2PK levels in patients with early-stage NSCLC and found it to be higher in patients with NSCLC than in the control group with healthy and benign lung disease (sensitivity 71.6%, specificity 98%), and high serum TUM2-PK level of early-stage NSCLC may be a potential biomarker for the diagnosis and prognosis of early-stage NSCLC patients. A Chinese meta-analysis by Juncai Liu et al.[22] concluded that serum tumor M2PK may be a potential biomarker in the diagnosis of NSCLC.

In our study, M2-PK levels were evaluated as tumor markers in patients with lung cancer. The study included 98 patients with histopathologically defined lung cancer, 45 patients with non-malignant lung disease and 45 healthy individuals. When the tumor M2-PK levels of the cases were compared, the mean value was found to be significantly higher in patients with lung than in both control groups. ($p<0.001$) When the lung cancer group and the control group with non-lung cancer lung disease were compared, the tumor M2-PK level was found to be significantly higher in the lung cancer group ($p<0.0001$). There was no significant difference between tumor M2-PK levels in terms of smoking history, alcohol use history, additional disease history, family history of malignancy.

There was no significant difference between tumor M2-PK plasma levels and histopathological types of cancer (small cell and non-small cell lung cancer) in patients with lung cancer. When patients with lung cancer were compared in terms of sex, plasma tumor M2-PK levels were significantly higher in both sexes than in control groups, but they were higher in men than in women, and the difference between them was statistically significant (male: 17.58±8.06; female: 13.56±2.037; $p=0.0005$).

In our study, the diagnostic cut-off value was found to be 8.9 IU/ml using ROC curve. At this cut-off value, the sensitivity of tumor M2-PK marker in showing lung cancer was calculated as 100% and the specificity was calculated as 97.8%.

Limitations

The limitations of the study are limited number of patients, 65% of patients have advanced-stage lung cancer, the results reflect only the population from Turkiye, the number of female patients is low, more studies are needed to reveal the role of tumor M2-PK in carcinogenesis.

CONCLUSION

As a result of this study, it was concluded that tumor M2-PK can be used as a marker in the differentiation of lung cancers from other benign pulmonary lesions as well as a screening marker in patients with suspected lung cancer Because of its low cost and high sensitivity and specificity, M2-PK can be used as a screening test for lung cancer. Comparative studies with other screening tests are needed in a larger population.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethics Committee of Yedikule Chest Diseases and Chest Surgery Training and Research Hospital. (Date: 04.02.2012, Decision No: 0006).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Effect of alpha-1 antitrypsin and alpha-1-acid glycoprotein AAT levels on prognosis in COPD exacerbation and COPD-community-acquired pneumonia patients

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is the most frequent comorbid condition that is present in patients with pneumonia. An exacerbations of chronic obstructive pulmonary disease (ECOPD) and Comminity-acquired pneumonia (CAP) are associated with high rates of hospitalizations, costs, and morbidity. Plasma levels of orosomucoid and Alpha-1 antitrypsin (AAT), also known as Alpha-1-acid glycoprotein (AGP), increase in response to inflammation and tissue necrosis. The purpose of this study is to evaluate the impact of markers in patients with ECOPD and COPD with pneumonia .

Methods: To compare the levels of AAT, and AGP, between patients diagnosed with ECOPD only and patients diagnosed with COPD and pneumonia.

Results: The study included 14 female and 22 male volunteers. The mean gender and age of groups 1 and 2 were similar. There was no statistical difference in laboratory values between the groups.

Conclusion: Alpha-1-acid glycoprotein and AAT are acute-phase proteins elevated in various inflammatory conditions such as infections, trauma, and chronic diseases such as COPD. More studies are needed on their usefulness for monitoring and/or treatment in daily practice.

Keywords: Chronic obstructive pulmonary disease, pneumonia, Alpha-1 antitripsin, Alpha-1 acid glicoprotein

INTRODUCTION

Chronic obstructive pulmonary disease is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. Chronic obstructive pulmonary disease (COPD) is a progressive but preventable disease characterized by chronic inflammation and airway restriction. It appears to be divided into two sub-phenotypes: chronic bronchitis and emphysema. Both phenotypes may be present in varying degrees in patients, increasing airflow limitation.[1]

Pneumonia is inflammation and infection of the lung parenchymal tissue and is the eighth leading cause of death and first among infectious causes of death. Inflammation is largely caused by microorganisms such as bacteria, viruses, and fungi. It can be defined as a disease that cannot be explained by other causes and is accompanied by focal lung findings on chest radiography in addition to an acutely onset cough, fever lasting more than four days, cough, sputum, chest pain, dyspnea, and/or tachypnea.[2]

Orosomucoid, also known as alpha-1-acid glycoprotein (AGP) and alpha-1 antitrypsin (AAT), are glycoproteins produced by the liver. Orosomucoid is a component of the acute phase response during systemic inflammation. Alpha-1 antitrypsin (AAT) is a highly effective protein for protecting the lungs from damage caused by enzymes released during inflammation.[3]

The aim of our study was to compare AAT and orosomucoid levels in patients with COPD-diagnosed pneumonia (Group 1) and COPD without pneumonia (Group 2), considering that they may provide information about the mechanisms underlying these conditions and potential diagnostic and prognostic markers.

METHODS

Our study included 14 female and 22 male volunteers with COPD diagnosed with pneumonia and ECOPD without pneumonia who were admitted to our center and hospitalized. This single-center, prospective, cross-sectional study was conducted at a university hospital from May to November 2018. An exacerbation of COPD have been defined using symptom-based and event-based references and a combination of the two. Symptom-based definitions rely on patient-reported worsening of respiratory symptoms. Typical symptoms include increased dyspnoea, coughing, increased sputum volume and sputum purulence. Event-based definitions capture patients whose conditions have deteriorated enough to require a change in treatment or a hospital visit or admission. Clinical diagnosis of community-acquired pneumonia based on symptoms and signs of lower respiratory tract infection in a patient and can be confirmed by a chest X-ray showing new shadowing that is not due to any other cause (such as pulmonary oedema or infarction). This might be because of the presence of focal chest signs, illness severity or other features. Patients with interstitial pneumonia, cystic fibrosis, severe neutropenia (<0.5x10^9 neutrophils-L-1) due to chemotherapy or immunosuppressive therapy, or HIV infection with a CD4 count <200 cells/mm^3, patients who did not want to participate in the study were excluded. AGP serum levels were measured in the biochemistry laboratory of our institution using a commercially available kit based on immunoturbidimetric methods according to the manufacturers' instructions. Serum and plasma samples were stored at −80°C until they were analyzed. The study was carried out with the permission of the Scientific Research Evaluation and Ethics Committee of our university hospital (Date: 28.05.2018, Decision No: 20180528/5). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

The statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Numeric values with normal distribution were expressed as means±SD, whereas variables with abnormal distribution were given as median values (min-max). Categorical variables values were given as n (percentage). Chi-square tests or Fischer exact test were used to compare two independent groups for categorical data. Student's t-test or Mann-Whitney U test were used for comparison of the two groups according to distribution pattern. All directional p values were two-tailed and significance was set to values lower than 0.05.

RESULTS

The study included 14 female and 22 male volunteers. The mean age of the patients was 76.17±10.59 in Group 1 and 75.50±9.56 in Group 2. There were 7 females and 11 males in both groups. When groups 1 and 2 were compared, the mean gender and age were similar. There was a significant difference in smoking habits, and the rates of comorbid diseases were similar (**Table 1**). When the laboratory values of group 1 patients were compared with group 2 patients, no statistical significance was found in all parameters (**Table 2**).

Table 1. Demographic characteristics

Parameters	COPD & Pneumonia		COPD Attack		p
	N	%	N	%	
Age, years, (mean ± SD)	76.17±10.59		75.50±9.56		0.844
Gender, M	11	61.1	11	61.1	0.633
Smoking status					0.002
Never used	1	5.6	11	61.1	
Quit Smoking	12	66.7	5	27.8	
Active smoker	5	27.8	2	11.1	
Comorbid Diseases					
CAD	3	16.7	4	22.2	1.000
CHF	3	16.7	5	27.8	0.691
CKD	2	11.1	1	5.6	1.000
DM	2	11.1	6	33.3	0.228
HT	9	50	14	77.8	0.083
Malignancy	1	5.6	2	11.1	1.000

Abbreviations; CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, DM: Diabetes Mellitus, HT: Hypertension

Table 2. Laboratory results

	COPD & Pneumonia (Group 1)	ECOPD (Group 2)	P
Leukocyte	14.08±6.53	14.86±16.07	0.851
Hb	13.04±1.75	12.77±2.77	0.729
Htc	38.79±4.93	38.32±8.03	0.832
Plt	243.76±64.40	240.17±87.76	0.890
Neutrophil	11.42±5.80	8.34±6.51	0.142
Lymphocyte	1.30(0.22-3.90)	1.67(0.47-59.80)	0.389
CRP	82.25(1.5-263.2)	64.30 (0.8-351.7)	0.265
BUN	21.50 (9.0-60.0)	24.50 (9.0-87.0)	0.355
Cr	1.09±0.45	1.40±0.79	0.157
Sed	35.00±19.64	47.07±25.42	0.250
AGP	182.59±70.55	179.35±60.17	0.585
AAT	2.70±0.47	2.35±0.54	0.110

Abbreviations Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelet, CRP: C- reactive protein, BUN: blood urea nitrogen, Cr: Creatinine, Sed: Sedimentation, AGP: Alpha-1-acid glycoprotein, AAT: Alpha-1 antitrypsin

DISCUSSION

According to the World Health Organization in 2014, lower respiratory tract infections and COPD represented the third and fourth leading causes of death worldwide.[3] In addition, community acquired pneumonia is cause of morbidity and mortality around the world. Therefore, it is important to understand the association between COPD and pneumonia, as well as their impact in patient's management. COPD patients may be more susceptible to develop pneumonia based on their clinical characteristics such as having chronic bronchitis with persistent mucus production, and the presence of potential pathogenic bacteria in the airways, the presence of bacteria in the airway in stable COPD patients and increased numbers during exacerbations have been associated with increased inflammation and the host immune response.[4]

An exacerbation of COPD is defined as an increase in symptoms of cough, sputum, and/or dyspnea that may be accompanied by tachypnea and/or tachycardia as a result of increased local and systemic inflammation due to air pollution, infection, or other exposure.[5] ECOPD is usually associated with increased airway inflammation, increased mucus production, and marked air trapping. These changes contribute to the increase in dyspnea, which is the main symptom of exacerbation.[6] Characteristically, inflammation is characterized by increased numbers of macrophages, activated neutrophils, and B and T lymphocytes in the

peripheral airways, lung parenchyma, and pulmonary circulation. Together with epithelial cells and other structural cells, they secrete numerous inflammatory mediators, such as tumor necrosis factor-a (TNF-a) and interleukins (IL-1b, IL-6, and IL-8).[7] The risk of developing pneumonia in COPD patients is much higher than in the healthy population. This is due to damaged airways and decreased lung function. In addition, the weakened immune system in COPD makes patients more susceptible to respiratory tract infections such as pneumonia. In addition, pneumonia can exacerbate COPD symptoms, increase the number of attacks, and worsen lung function. Molecular tests and improved imaging techniques are very helpful in classifying the disease group and identifying causative organisms. Investigations such as CRP, procalcitonin, and cytokine measurement are auxiliary laboratory tests used in the diagnosis of pneumonia in clinical practice.[8] Although there are studies showing that leukocyte and CRP values were found to be higher in COPD patients presenting with pneumonia compared to patients without pneumonia, no significant difference was found between both groups in our study.

The protein AAG (orosomucoid), which is in the α1-globulin band of serum proteins, is mostly made by parenchymal cells in the liver. Its plasma level increases in response to inflammation and tissue necrosis. CRP is the first to rise as an acute-phase reactant, and its plasma level starts to rise within the first 24 hours after α1-antichymotrypsin. Since it has a low molecular weight that can easily pass into the glomerular filtrate, its plasma half-life is 3 to 5 days. As the inflammation improves, the orosomucoid level decreases in parallel.[9] Alpha-1 antitrypsin (AAT) is produced by the liver, and one of its main functions is to inhibit an enzyme called neutrophil elastase that can break down connective tissue in the lungs. Genetic deficiency of Alpha-1 antitrypsin leads to AAT-associated emphysema. This condition causes progressive tissue damage in the lung. Individuals with COPD and alpha-1 antitrypsin deficiency have an increased risk of both pneumonia and severe lung damage. AAT deficiency impairs the ability of the lung to resist the effects of inflammation and enzyme activity, making the lungs more susceptible to infections such as pneumonia and accelerating the progression of COPD.[10] Since both AAT and AGT levels play a role in immune response and inflammatory regulation, they may vary in patients with COPD and pneumonia. Especially in pneumonia, both AAT and AGT levels are typically increased due to an acute inflammatory response. Many studies have shown an inverse correlation between elevated inflammatory biomarkers and lung function.[11] In our study related to AAT and orosomucoid levels in both groups of patients, the results were similar between the two groups. This was thought to be primarily due to the fact that the groups included a small population. Another reason was that acute-phase reactants may increase together in cases of exacerbation and pneumonia, which increase inflammation.

CONCLUSION

AAT and AGP (orosomucoid) are several acute-phase proteins that are elevated in the bloodstream in response to various inflammatory conditions such as infections, trauma, and chronic diseases such as COPD. Inflammation can cause further damage to lung tissue, exacerbating symptoms and reducing lung function. In cases of pneumonia, especially in individuals with COPD, the immune response triggers an increase in the production of acute-phase proteins, and elevated glycoprotein levels may indicate a more intense inflammatory response. Distinguishing among pneumonic and non-pneumonic exacerbations in COPD patients is still a matter of controversy. For all that reasons, further studies are needed on the potential of such markers to clarify this issue.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Ufuk University Clinical Researches (Date: 28.05.2018, Decision No: 20180528/5).

Informed Consent

All patients voluntarily signed the informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Noninvasive mechanical ventilation

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ABSTRACT

Noninvasive mechanical ventilation (NIMV) is positive pressure ventilation applied through a mask without an artificial airway and is frequently used in acute and chronic respiratory failure. It is the first choice in the weaning process for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema. The choice of device, mode, and mask is important to the application and success of NIMV. In appropriate diagnosis and indication, NIMV should be the first choice in patients who are cooperative, able to protect their airways, clinically stable, and to whom the mask can be applied. In this review the NIMV application especially in acute respiratory failure is summarized.

Keywords: Noninvasive mechanical ventilation, positive pressure ventilation, acute respiratory failure

INTRODUCTION

Noninvasive mechanical ventilation (NIMV) is a type of positive pressure ventilation applied with a mask without an artificial airway. The most important advantage is the reduction of complications such as ventilator-associated pneumonia and nasocomial infections associated with invasive mechanical ventilation. Physiologically, it prevents collapse in the airways and alveoli, reduces the afterload of the heart with increased intrathoracic pressure, workload on the diaphragm and respiratory muscles, and interstitial edema, and increases gas exchange and functional residual capacity.[1,2] Respiratory failure is defined as the inability to provide the oxygen required by tissues or to excrete carbon dioxide, which is a product of metabolism. Acute respiratory failure develops within minutes, hours, or days. A partial oxygen pressure (PaO_2) below 60 mmHg in room air in arterial blood gas is defined as type 1 respiratory failure (hypoxemic respiratory failure). Type 2 respiratory failure is defined as $PaCO_2$ (arterial partial carbon dioxide pressure) >45 mmHg in addition to hypoxemia.[1-3]

INDICATIONS, CONTRAINDICATIONS AND APPROPRIATE PATIENT SELECTION

It is frequently used in acute or chronic respiratory failure. According to the ERS/ATS guidelines, there are strong, less strong, and weak evidence-level recommendations for NIMV in acute respiratory failure. Chronic obstructive pulmonary disease (COPD) exacerbations, acute cardiogenic pulmonary edema, the weaning process in COPD and immunodeficient patients are recommended at a strong level of evidence. Asthma attacks, postoperative and acute hypoxemic respiratory failure, and extubation failure are recommended at a less strong level of evidence. Upper airway obstruction, trauma, ARDS (acute respiratory distress syndrome), OSAS (obstructive sleep apnea syndrome), and OHS (obesity hypoventilation syndrome) are recommended as indications for NIMV at a weak level of evidence.[2,4] International guidelines do not recommend the use of NIMV in COPD patients with normo- or mild hypercapnic acute respiratory failure without acidosis. In emergency departments, it is recommended for acute decompensated CAP, cardiogenic pulmonary edema, and right heart failure. Recommendations for the use of NIMV in ARDS without chronic respiratory failure and de novo acute hypoxemic respiratory failure due to pneumonia are not clear, and it is recommended not to delay invasive mechanical ventilation to reduce mortality and morbidity.[1-3,5]

Appropriate patient selection includes tachypnea (>25/min), use of auxiliary respiratory muscles, abdominal breathing, mask-face compliance, clear consciousness, adequate cough reflex, swallowing reflex, respiratory acidosis in arterial blood gas (pH<7.35-$PaCO_2$>45 mmHg), and PaO_2/FiO_2<200 mmHg (ratio of partial arterial oxygen pressure to inspired oxygen concentration). As a result, patients with appropriate diagnosis and indication, preserved airway reflexes, and communicable and hemodynamically stable patients are the most suitable candidates for NIMV.[5,6] **Table 1** presents the failure indicators of NIMV.[2,5,6]

Table 1. Failure indicators of noninvasive mechanical ventilation[2,5,6]

- Advanced age
- Multiorgan failure
- High APACHE II , SAPS and SOFA scores
- No clinical improvement in the first hour after the start of NIMV
- Arterial blood gas pH:7.25 and mean $PaCO_2$>75-90 mmHg
- PaO_2/FiO_2<150 mmHg
- High tidal volume
- ARDS and pneumonia in etiology

APACHE II: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology Score, SOFA :Sequential Organ Failure Assessment Score, PaO_2/FiO_2: Ratio of partial arterial oxygen pressure to inspired oxygen concentration, NIMV: Noninvasive mechanical ventilation, ARDS: Acute Respiratory Distress Syndrome, $PaCO_2$:Arterial partial carbon dioxide pressure

Absolute contraindications to NIMV include respiratory or cardiac arrest, complete upper airway obstruction , a high risk of aspiration due to severe vomiting, facial trauma, and burns. Shock, coma, hemodynamic instability or unstable cardiac arrhythmia, GCS (Glasgow Coma Scale) <10, upper gastrointestinal tract bleeding, multiorgan failure, dense secretions, bulbar dysfunction, upper airway, and gastrointestinal tract surgery are partial contraindications (**Table 2**).[2,5,7]

Table 2. Noninvasive mechanical ventilation contraindications[2,5,7]

- Cardiac or respiratory arrest
- Complete upper airway obstruction
- High risk of aspiration
- Severe vomiting and upper gastrointestinal tract bleeding
- Facial travma and burns
- Shock, coma , hemodynamic instability and unstable cardiac arrhythmia
- Glasgow Coma Scale <10, multiorgan failure
- Bulbar dysfunction
- Upper airway and gastrointestinal tract surgery

DEVICE-MASK SELECTION-MODES-CIRCUITS-HUMIDIFIERS

During the application, where it should be done, the appropriate interface or mask, humidifiers, ventilators, and circuit selection are the points to be considered. It can be applied in intermediate intensive care units, emergency departments, intensive care units, and during patient transfers. Patients with the possibility of endotracheal intubation, severe acute respiratory failure, and hypoventilation risk should be treated with NIMV in intensive care. Leakage compensation, rebreathing, modes, triggering, monitoring parameters, and alarms are among the criteria that should be included in device selection. Inspiratory flow rate, rise time, number of backup breaths, FiO_2, IPAP (positive airway pressure), and EPAP (expiratory positive airway pressure) levels should be technical. There are three types of ventilators: bilevel portable, transport, and intensive care. Bilevel portable ventilators are available in many different types and with different technical features. It is easy to use and inexpensive. The exhalation valve works passively. A single hose circuit is used; a leak port close to the patient or on the mask is recommended. It is recommended to be on the mask because it provides high EPAP. In the intensive care type, the exhalation valve is active, and a double circuit with inspiration and expiration valves is used. It provides high FiO_2, IPAP, and EPAP pressures and detailed monitoring.[2,4,5] There is no carbon dioxide retention associated with rebreathing compared to single-circuit systems used in bilevel ventilators.[8,9]

The interface or mask is a spacer that connects to the patient's face and allows compressed air to be delivered from the upper airways to the lungs.[10] Mouthpieces, nasal pillows, nasal, oronasal, total face, and helmet-type masks are available. The ideal mask should be robust, lightweight, leak-free, non-traumatic, non-allergenic, non-deformable, low-cost, and suitable for long-term use. It should also be of different sizes, have low dead space, and have low resistance to airflow. It is recommended that the fixation used to attach the mask to the patient's face should be easy to attach and remove, nontraumatic, soft, and of different sizes compatible with masks. The masks that are frequently used in daily practice for acute respiratory failure are oronasal, total face, and helmet types. Oronasal masks are masks that cover the mouth and nose, less air leakage and less need for cooperation are important advantages. Vomiting, claustrophobia, nasal skin ulcerations, difficulty in speaking and coughing are disadvantages. While vomiting, claustrophobia, and speech difficulty are disadvantages, minimum air leakage, less cooperation, easy wearing, and application are advantages. It is a helmet type of mask that covers the whole head and neck. Its advantage is that it can be used in cases of minimal air leakage, wounds on the face and nose root. The disadvantages are re-breathing, excessive loudness and noise, asynchronization in pressure-assisted modes, and skin lesions in the axilla due to ligaments.[5,10-12] During the application, the appropriate size mask (S, M, L, XL) should be selected for the patient. The masks used are mostly composed of two parts: the soft face-fitting part and the transparent part that forms the periphery. There are four types of cushions that protect the face: transparent, non-inflated, inflated, full hydrogel, and full foam.[5,10] The most common complication of the interface is skin complications on the nasal root, upper lip, nasal mucosa, and axilla. To minimize them, checks every four to six hours, foam pads, hydrocolloids, and transparent dressings are recommended.[5,10,13] In acute respiratory failure, oronasal and total face masks are primarily recommended.[14]

In the upper airways, air is heated to 32-35°C, humidified to 100%, and particles >2-5 mm are filtered. With NIMV and invasive mechanical ventilation, the upper airways are disabled. As a result, drying of secretions, mucus plugs, atelectasis, a decrease in ventilation perfusion ratio, damage to the tracheobronchial epithelium, and impaired mucociliary activity occur. Two types of humidifiers are used. Heat-moisture exchangers (HME) are systems in which the heat and moisture of the air supplied during expiration are condensed on the membrane in the HME and return heat and moisture on inspiration. A heated humidifier is a system in which gases are actively heated by passing over the surface of a heated water reservoir attached to the aerator.[5,15] While HME is cheaper and provides better maintenance of humidity at low ambient temperatures and high flow, the disadvantages are increased dead space, carbon dioxide retention, increased nasal airway resistance, and increased work of breathing. Heated humidifiers have the disadvantage of increased heat and electricity requirements, but the advantages of reduced dead space, carbon dioxide retention, and breathing work of breathing. There is insufficient evidence on the use of humidifiers in acute respiratory failure.[4,5,15]

In NIMV, the modes are mainly volume- or pressure-assisted. In volume-targeted ventilation, a constant volume is delivered, while the pressure varies with each breath. Airway pressure changes depending on lung compliance and airway resistance. The advantage is that it guarantees a tidal volume independent of changes in compliance and resistance. In pressure-targeted ventilation , a constant

pressure is delivered, while the volume varies with each breath. The most important advantage is the compensation for mild to moderate leaks. The most commonly used mode is PSV (Pressure Support Ventilation). This mode is a patient-triggered and flow-cycled mode. While IPAP and EPAP are adjusted in bilevel ventilators, inspiratory pressure is obtained by applying PEEP on pressure support in intensive care type ventilators. In bilevel ventilators, the difference between IPAP and EPAP is pressure support. With EPAP, collapse in the airways is prevented, and functional residual capacity is increased. IPAP increases airway pressure and tidal volume by supporting inspiration. Pressure-assisted hybrid modes are available for a constant tidal volume in clinical practice. In Average Volume Assured Pressure Support (AVAPS), minute ventilation is measured with each breath. Pressure adjustment is made in each inspiration to reach the target tidal volume. Min and max IPAP adjustments are made for pressure adjustment. It is a patient-ventilator-compatible mode. It is recommended in OHS, chest wall pathology, and neuromuscular diseases with hypoventilation risk. CPAP (Continuous Positive Airway Pressure) is not considered a clear mode because it does not support inspiration. It improves ventilation and reduces respiratory workload by increasing functional residual capacity by providing constant airway pressure.[16-18]

CONCLUSION

NIMV should be the first choice in the weaning process for patients with acute exacerbations COPD, acute cardiogenic pulmonary edema, and COPD exacerbations.. The choice of device, mode, and mask is important to the application and success of NIMV. In appropriate diagnosis and indication, NIMV should be the first choice in patients who are cooperative, able to protect their airways, clinically stable, and to whom the mask can be applied.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Sarcoidosis and skin manifestations

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ABSTRACT

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology, affecting all organs and systems. Skin involvement is seen in one-third of cases. Cutaneous findings alone do not determine the prognosis of sarcoidosis, but they are useful in early diagnosis. There are specific and nonspecific cutaneous findings. The most common cutaneous findings are papules and plaques. This review summarizes the cutaneous manifestations of sarcoidosis.

Keywords: Inflammatory disease, sarcoidosis, skin manifestations

INTRODUCTION

Sarcoidosis is a systemic disease characterized by multisystemic inflammation of unknown cause. Histopathologically, it is characterized by noncaseating granulomas consisting of epithelioid histiocytes, giant cells, and lymphocytes composed of activated macrophages.[1] It is observed more frequently between 25 and 35 years of age and in women. Lung involvement is observed in 90% of cases. Involvement of the skin, gastrointestinal tract, lymph nodes, heart, and central nervous system is also observed.[2] Clinically, it can range from asymptomatic to acute, subacute, chronic, or multiple organ failure. In the lungs, spontaneous remission may be observed in pulmonary fibrosis.[3] Symptoms, clinical findings, and organ involvement vary according to race, age, and gender. The most common symptoms are malaise, fatigue, fever, night sweats, and weight loss.[2,3] After differential diagnosis, the diagnosis is evaluated with radiologic, clinical, and histopathologic findings. The first step in treatment should be decided according to sarcoidosis-related death, organ damage, and deterioration in quality of life.[4]

DERMATOLOGICAL FINDINGS

While skin involvement in sarcoidosis is observed in one-third of cases, it may pose a diagnostic challenge due to its different morphology. According to studies in the literature, lesions can be divided into specific and nonspecific lesions. Specific lesions are associated with chronic forms, while nonspecific lesions are associated with acute forms. Nonspecific lesions have a better prognosis. Papular, maculopapular, plaque, subcutaneous nodular, and ulcerated lesions are specific lesions. The most common nonspecific lesions are erythema nodosum, calcifications, and prurigo. The most common cutaneous findings are papules and plaques. In a study evaluating patients with cutaneous sarcoidosis, cutaneous lesions were the first finding in 74% of the patients. Cutaneous findings alone do not determine the prognosis of sarcoidosis. In general, early diagnosis is also beneficial.[5-9]

Maculopapular Sarcoidosis

It is the most common form. It is frequently localized on the face, especially around the eyes and nasolabial fold, but may also involve the occipital part of the neck, trunk, extremities, and mucous membranes. On examination, it is firm and has the consistency of apple jelly under pressure. It can be one cm small, red to brown, or purplish in color. Rosacea, sebaceous hyperplasia, Xanthoma, perioral dermatitis, tinea faciei, cheilitis granulomatosa, cutaneous Crohn's disease, granuloma faciale, lymphocytoma cutis (Lyme borreliosis), lupus vulgaris, lupus miliaris disseminatus faciei, lupus erythematosus, and secondary syphilis should be considered in differential diagnosis. Lesions may regress spontaneously or coalesce into plaque or annular lesions. Clinically, it is frequently detected at the onset of sarcoidosis.[5-8] Trauma areas predispose to maculopapular areas. In the literature, it has been found that maculopapular lesions mostly heal spontaneously or with treatment in less than 2 years without scarring.[9,10]

Plaque Lesions

On examination, they are symmetrical, bilateral, oval, red, and brown lesions with the consistency of apple jelly. They are seen on the face, extremities, and trunk. They are raised lesions measuring more than 5 mm. They tend to be thick, hard, and scaly. Lesion colors can vary from red to brown and from brown

to yellow. Lichen planus, granuloma annulare, discoid eczema, syphilis, mycosis fungoides, tinea corporis, leishmaniasis, non-tuberculous mycobacteriosis, psoriasis, and cutaneous T-cell lymphoma should be considered in the differential diagnosis. Plaques tend to recur after treatment. The rate of healing with permanent scarring is higher than in papular sarcoidosis. It is associated with the chronic form of sarcoidosis.[5,6,8-10]

Scar Sarcoidosis

They are patchy, erythematous, or violet lesions that occur in areas of scar tissue due to previous trauma, surgical scars, vaccination, or herpes zoster, affecting all areas. They are often asymptomatic and associated with sarcoidosis exacerbations. Keloid or hypertrophic scars should be considered in the differential diagnosis. 29% of the studies have been found. There are cases associated with pulmonary or mediastinal involvement of sarcoidosis. Because tattoos can also cause sarcoidosis, patients should avoid getting them.[5,6,8-10]

Subcutaneous Nodular Lesions

It is also known as Darier-Roussy sarcoidosis. It is often localized in the extremities and can be seen in the eyes and face. There is no systemic involvement and it is not a sensitive lesion. They are hard, oval, multiple localized skin-colored lesions. They are 0.5-2 cm in size. They are more common in women in the fourth decade. They are mostly asymptomatic. Granuloma annulare, rheumatoid nodules, xanthomas, and lipomas should be considered in the differential diagnosis.[5,6,8-10]

Ulcerated Lesions

They are often early manifestations of systemic sarcoidosis, but they can also develop over previous sarcoidosis skin involvement. Mucous membranes and the scalp are rare sites of involvement. It is more common in women with dark skin. A differential diagnosis should be made in ulceration due to stasis dermatitis or skin involvement of tuberculosis.[5,6,8-10]

Hypopigmented Sarcoidosis

It is in the form of hypopigmented macules, papules, or nodules in patients with dark skin tones. Vitiligo, seborrheic dermatitis, leprosy, and pityriasis alba should be considered in the differential diagnosis.[5,6,8-10]

Ichthyosiform Sarcoidosis

They are sensitive and non-pruritic lesions in the form of gray, brown, scaly, and hyperpigmented plaques on the lower extremities. It should be differentiated from eczema.[5,6,8-10]

Lupus Pernio

They are hard, red-to-purple lesions consisting of papules or plaques. Lupus erythematosus, rhinophyma, lymphomas, cutaneous angiosarcoma, lupus vulgaris, and leprosy should be considered in the differential diagnosis. Lesions are seen on the nose, cheeks, lips, forehead, and ears. Bone involvement of the hands and feet is common in lupus pernio.[5,6,8,9] It is associated with sarcoidosis cases with upper respiratory tract involvement, and intrathoracic, ocular, and reticuloendothelial system involvement is more common.[10]

Erythema Nodosum

It is frequently found in patients of European origin. It is believed that ongoing inflammation is the cause. It is a nonspecific cutaneous finding frequently found in sarcoidosis patients, often on the anterior surface of the lower extremities. Tender, erythematous nodules that frequently accompany arthritis are its defining features. No granuloma is detected in biopsies. It undergoes spontaneous regression in six to eight weeks. Infection, nodular vasculitis, and thrombophlebitis should be considered in the differential diagnosis.[5-8] In studies, sarcoidosis was diagnosed in 10-22% of patients with erythema nodosum.[9,10]

Löfgren's Syndrome

It is a syndrome characterized by hilar lymphadenopathy, symmetrical polyarthralgia, anterior uveitis, and fever. It has a good prognosis and should be differentiated from infection-related conditions such as fungus or tuberculosis.[5,6,8-10]

Lichenoid Sarcoidosis

It is more common in children and accounts for 1-2% of cutaneous sarcoidosis. Multiple 1-3 mm-diameter flat or dome-shaped erythematous or skin-colored erythematous or skin-colored lesions are widely localized on the face, body, and extremities.[11]

Psoriasiform sarcoidosis

The sharply circumscribed squamous plaques seen in 0.9% of sarcoidosis patients are difficult to differentiate from psoriasis. In psoriasis, the distinction can be made by the scarless healing of the lesions.[12]

Verrucous Sarcoidosis

It is characterized by sharply circumscribed hyperkeratotic papillomatous lesions localized on the lower extremities. The warts may resemble Keratoacanthoma prurigo nodularis.[13]

Erythrodermic Sarcoidosis

It is a fusion of erythematous plaques, leaving intact areas in between. A biopsy is necessary to investigate the common causes of erythroderma.[14]

Necrobiosis-lipoidica-like Lesions

It is characterized by depressed pink-purplish plaques in the lower extremities. Sarcoidosis should be investigated in patients with necrobiosis lipoidica without diabetes.[15]

Livedo

It is a form characterized by erythematous-violaceous livedoid macules. Eye and central nervous system involvement is more common in these patients.[16]

Apart from all these cutaneous findings, there are some rare involvements. Alopecia, with or without scalp scarring, can be seen. Plaques, nodules, edema, and papules can be seen in the oral cheek mucosa, gingiva, hard palate, tongue, and posterior pharynx. Nail involvement is a rare cutaneous lesion, and genital sarcoidosis has been reported in case reports.[9-11]

TREATMENT

Topical or systemic corticosteroids, topical clobetasol and triamcinolone injections, chloroquine, and hydroxychloroquines are used in sarcoidosis. Methotrexate and cyclosporine are available for immunosuppressive treatment. In recent years, monoclonal antibodies, thalidomide, and

isotretinoin can be used as additional treatments. Drug reactions should be considered. Systemic immunosuppressives should be considered early in lupus pernio.[8-17]

CONCLUSION

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology, affecting all organs and systems. While skin involvement in sarcoidosis is observed in one-third of cases, it may pose a diagnostic challenge due to its different morphology. The most common nonspecific lesions are erythema nodosum, calcifications, and prurigo. In general, early diagnosis is also beneficial.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Asymptomatic giant thymoma

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ABSTRACT

Thymomas are tumours that originate from epithelial cells of the thymus gland. Most patients, estimated to be two thirds, remain asymptomatic and are often diagnosed following routine examinations. Symptomatic patients may present with neurological paraneoplastic syndromes as well as compression symptoms. Asymptomatic patients are usually found incidentally. In this article, we present a case of a giant thymoma that was discovered incidental/perioperatively in the light of the existing literature.

Keywords: Thymoma, paraneoplastic syndrome, incidental

The manuscript has been presented as a Poster presentation at 4-7 November Respiratory 2023 National Congress

INTRODUCTION

The thymus gland, located in the anterior mediastinum, plays an important role in the immune system. Thymic epithelial cells are involved in the development of mature T lymphocytes which play a role in cellular immunity. Thymomas are rare epithelial tumours which represent more than half of anterior mediastinal tumours.[1]

Patients with thymoma frequently do not present clinical symptoms. Approximately 30% of the patients have an asymptomatic course, while 30% develop findings related to myasthenia gravis (MG). Depending on the location of the tumour, pain may be manifested by cough, hoarseness, dyspnoea, vena cava superior syndrome and weight loss in a minority of patients. Other parathymic syndromes have been reported to a smaller percentage. Pleural and/or pericardial effusion is a serious clinical finding. In rare cases of spontaneous rupture of the tumour, severe chest pain and shortness of breath may develop due to mediastinal haemorrhage. Radiographically, CT is considered the standard method; mediastinal enlargement and haemothorax are seen; presence of irregular margins, multiple calcifications and low attenuation suggest invasion. Other malignancy rates accompanying thymomas have been reported in various series. Pan et al.[2] reported that other solid organ malignancies were significantly higher in patients with thymoma.

CASE

A 47-year-old male patient was admitted to the urology clinic because of flank pain, a 3 cm stone was detected in the left renal ureteropelvic junction and ureteroscopy was planned. He was referred to our clinic because of perioperative postero-anterior chest radiography findings. The patient had no comorbidities or medication history, and no active respiratory symptoms. Chest radiography showed homogenous opacity in the left lung adjacent to the mediastinum (**Figure 1a**). No abnormalities were found in routine laboratory investigations. Thoracic computed tomography revealed a relatively smoothly circumscribed lobulated contoured heterogeneous mass lesion with heterogeneous density, which was approximately 123×94×98 mm. It compressed the heart inferiorly at its widest point in the anterior mediastinum and had no obvious signs of invasion in the anterior wall of the chest and adjacent mediastinal structures whose borders were not clearly distinguishable from the pericardium (**Figure 1b**). A transthoracic tru-cut biopsy was performed by Interventional radiology under thoracic USG guidance. The cytology of the material obtained showed a lesion consisting of polyglonal shaped small epithelial cells mixed with thymocytes, which could not be clearly distinguished in haematoxylin-eosin sections, but immunohistochemically stained with Pan-CK and CK8/18, and immunohistochemical staining showed scattered membranous staining in thymocytes with CD45 and CD3 (**Figure 2 a, b, c**). The patient was referred to our thoracic surgery clinic to be evaluated for complete resection with the diagnosis of thymoma.

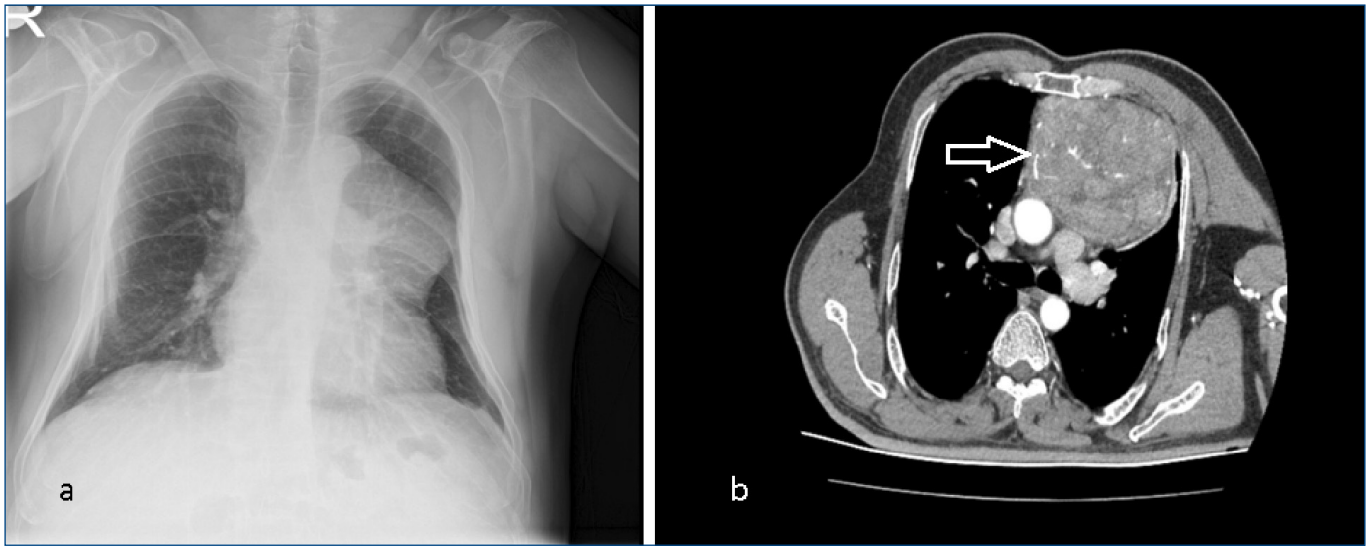

Figure 1. a. Posterio-anterior chest radiograph, **b.** Mass lesion in the anterior mediastinum on computed thoracic tomography

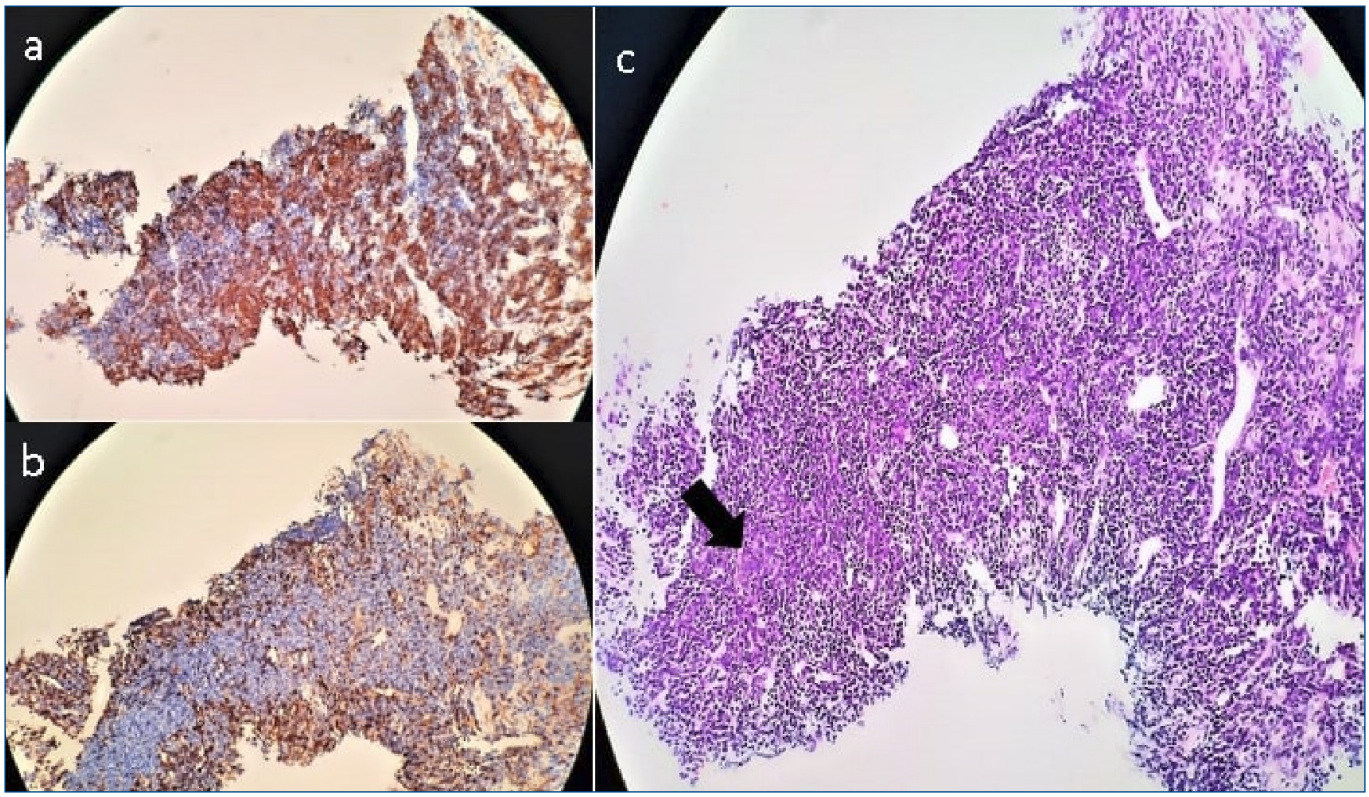

Figure 2. a. Staining in epithelial cells with CK8-18 (X200), **b.** Staining in lymphocytes with CD45 (X200), **c.** Lymphocytes (thymocytes) and scattered polygonal epithelial cells (black arrow) (HEX200)

DISCUSSION

Thymoma is a slow growing epithelial neoplasm. It represents approximately 20-30% of all mediastinal tumours. Sarcoma, solitary fibrous tumour, germ cell tumours, lymphoma, mesothelioma and metastatic tumours should be considered in the differential diagnosis of giant intrathoracic masses. Recommended investigations for the evaluation of mediastinal masses include thoracic CT with contrast and routine laboratory blood tests. Specific markers such as AFP and B-HCG may be ordered especially in young patients. Fine needle aspiration biopsy (FNAB) is a feasible and accepted diagnostic method for the diagnosis of anterior mediastinal masses and histopathological classification of thymomas. Ultrasound-guided FNA samples have been reported to be more reliable and diagnostic because they contain more cells. Annessi et al.[3] reported that the specificity and sensitivity of ultrasound-guided FNAB was 100% in anterior mediastinal masses. The most widely used and accepted staging system is the classification of Masaoka et al.[4] which includes clinical and histopathological features together with invasion and anatomical enlargement. Since complete surgical resection is the most effective method in thymic tumours, the lesions of all patients should be considered potentially resectable and should be carefully examined by an expert medical team. Complete surgical excision should be preferred in Masaoka stage I and II and selected stage III disease. However, it should be kept in mind that such an operation may carry serious, life-threatening mortal complications such as pneumonia, massive haemorrhage, pulmonary embolism and so on. The stage of the tumour is the most important prognostic factor; 5-year survival of completely resected patients is 90%, 90%, 60% and 25% for stages I, II, III and IV.[5]

CONCLUSION

Thymoma can occur at any age from 8 months to 90 years, with a mean age of 53 years. 95% of thymomas are localised in the anterior mediastinum. In this case, we present a case of thymoma which was detected during perioperative evaluation, evaluated clinically, radiologically and histopathologically and diagnosed as thymoma because it was asymptomatic despite its giant size. The accepted standards in the diagnosis of thymoma should be increased with better communication and multidisciplinary approaches.

ETHICAL DECLARATIONS

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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