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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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