Plasma surfactant protein-D as a potential biomarker in idiopathic pulmonary fibrosis

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Objectives Idiopathic pulmonary fibrosis (IPF) is a disease of an increasing burden. Its diagnosis is based on definite high-resolution computed tomography pattern and is associated with the histopathological and/or radiological pattern of usual interstitial pneumonia with exclusion of other causes of interstitial pneumonia. The surfactant protein-D (SP-D) level in the serum is measured in several lung diseases, including IPF.

Aim of study The aim of the current study is to assess the serum level of SP-D as a potential biomarker to distinguish between IPF and other idiopathic interstitial pneumonia patients.

Patients and methods This study was conducted in the Chest Department, Kasr Al Ainy Hospitals, Cairo University. The study population included 20 healthy controls, 20 IPF patients, and 18 other idiopathic interstitial pneumonia patients. All were subjected to full history taking, clinical examination, high-resolution computed tomography chest, spirometry, arterial blood gases, blood samples for measuring SP-D by enzyme-linked immunosorbent assay.

Results There was no statistical significance between the serum level of SP-D in IPF and non-IPF patients, however, there was a significant increase in the serum level of SP-D in IPF patients diagnosed at a late stage compared with those diagnosed at an early stage and those on anti-fibrotic therapy. Also, there was a statistical significance between the degree of clubbing and gastroesophageal reflux disease and the serum level of SP-D with a *P* value of 0.005 and 0.029, respectively. Serum SP-D level had a negative correlation with more severe form of the disease regarding the duration of illness, forced vital capacity percent, and it had a significant negative correlation with oxygen saturation and 6 min walk distance with a *P* value of 0.023 and 0.005, respectively.

Conclusion The level of serum SP-D level in IPF patients correlate well with the severity of the disease and could be a possible marker to use for the follow up of patients on anti-fibrotic drugs.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease of an increasing burden [1,2] and is being defined as a chronic, progressive fibrosing interstitial pneumonia of unknown cause limited to the lungs [3]. The diagnosis is based on definite high-resolution computed tomography (HRCT) pattern and is associated with the histopathological and/or radiological pattern of usual interstitial pneumonia [3]. The other causes of interstitial pneumonia should be excluded [4].

Surfactant protein-D (SP-D) is a collagenous glycoprotein [5] that is synthesized by the respiratory epithelium and secreted into the airspaces of the lung [6].

Recently, the SP-D levels in the systemic circulation have been measured in several lung diseases [7,8], including interstitial lung diseases [9,10] and it was significantly elevated [10].

The aim of the current study was to assess the serum level of SP-D as a potential biomarker to distinguish between IPF and other idiopathic interstitial pneumonia (IIP) patients.

Patients and methods

The study was conducted in the Department of Chest Diseases in collaboration with the Chemical Pathology Department at Kasr Al Ainy Hospitals, Cairo University during the period between May 2017 and March 2018. It included 58 patients who were divided into three groups. Group 1 included 20 IPF patients diagnosed according to ATS guidelines, 2011 [3]. Group 2 included 18 IIPs other than IPF patients. Group 3 had 20 healthy volunteers.

Group 1 was subdivided into three subgroups: subgroup A included eight patients who were diagnosed at early stage; subgroup B included seven

patients who were on anti-fibrotic therapy (pirfenidone for >6 months), and subgroup C included five patients who were diagnosed at a late stage.

Early and late stages were defined according to the extent of fibrosis and honeycombing on HRCT chest by the fibrosis score or interstitial score [11].

Group 2 included 10 patients with nonspecific interstitial pneumonia, four with cryptogenic organizing pneumonia, three with respiratory bronchiolitis interstitial lung disease, and one case with lymphocytic interstitial pneumonia.

All patients were subjected to thorough history taking, clinical examination, arterial blood gases, spirometry, 6-min walk test (6MWT), and HRCT chest.

Blood samples were obtained for measuring the human SP-D level using KONO Biotech Co. Ltd ELISA (KONO Biotech Co. Ltd, Zhejiang, China).

Statistical package for the social sciences, version 25 (IBM, USA) was used for data coding and entry. Data were summarized using mean, SD in quantitative data, and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the nonparametric Kruskal–Wallis and Mann–Whitney tests [12]. χ^2 test was performed for comparing categorical data. Exact test was used instead when the expected frequency is less than 5 [13]. Spearman's correlation coefficient was done for correlations between quantitative variables [14]. Statistical significance was considered when *P* values were less than 0.05.

Results

The mean age was almost matched in the three groups with mean age±SD 56.7±7.67 in group 1 and 52.06 ±10.97 in group 2, and 51.00±7.92 in group 3.

The sex distribution is shown in Table 1 presenting a statistical significance with a *P* value of 0.009.

Descriptive data for IPF and other IIP groups regarding smoking history, gastroesophageal reflux disease (GERD), and clubbing are shown in Table 2.

There was no statistical significance between IPF and other IIP groups regarding the duration of illness, spirometry, arterial blood gases, and 6MWT (Table 3).

The mean and SD of serum SP-D level in different groups of the study population are presented in Table 4 with no statistical significance with a *P* value of 0.398.

There was statistical significance between serum SP-D level and GERD history, the extent of fibrosis in the HRCT chest (Fig. 1), as well as the degree of severity of clubbing (Fig. 2) among the IPF group 1 with a *P* value

Table 1 Sex distribution among the study population

	Groups [*n* (%)]			*P* value
	Group 1: IPF	Group 2: other IIP	Group 3: control	
Sex				
Female	6 (30)	14 (77.8)	10 (50.0)	0.009
Male	14 (70.0)	4 (22.2)	10 (50.0)	

IIP, idiopathic interstitial pneumonia; IPF, interstitial pulmonary fibrosis.

Table 2 Descriptive data for smoking history, gastroesophageal reflux disease history, and clubbing among idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonia groups

	Group 1: IPF [*n* (%)]	Group 2: other IIP [*n* (%)]	*P* value
Smoking			
Yes	12 (60.0)	3 (16.7)	0.006
No	8 (40.0)	15 (83.3)	
History of GERD			
Yes	10 (50.0)	5 (27.8)	0.162
No	10 (50.0)	13 (72.2)	
Clubbing			
0	0 (0.0)	4 (22.2)	
1	4 (20.0)	5 (27.8)	0.096
2	11 (55.0)	5 (27.8)	
3	5 (25.0)	4 (22.2)	

GERD, gastroesophageal reflux disease; IIP, idiopathic interstitial pneumonia; IPF, interstitial pulmonary fibrosis.

Table 3 Comparison between idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonia groups regarding the duration of illness, spirometry, arterial blood gases, and 6 min walk test

	Group 1: IPF		Group 2: other IIP		*P* value
	Mean	SD	Mean	SD	
Duration of illness (years)	3.90	1.45	4.33	2.70	0.929
FEV1	1.36	0.38	1.27	0.29	0.308
FVC%	59.00	11.51	60.06	14.25	0.682
FEV1%	80.45	7.37	84.72	5.32	0.081
SO_2	90.90	7.06	91.94	2.60	0.837
pH	7.41	0.04	7.42	0.03	0.501
PO_2	71.95	16.54	69.42	7.71	0.815
PCO_2	42.10	5.28	43.34	6.50	0.509
HCO_3	26.32	3.63	26.08	3.37	0.826
6 min walk test	270.50	131.22	255.94	83.72	0.208

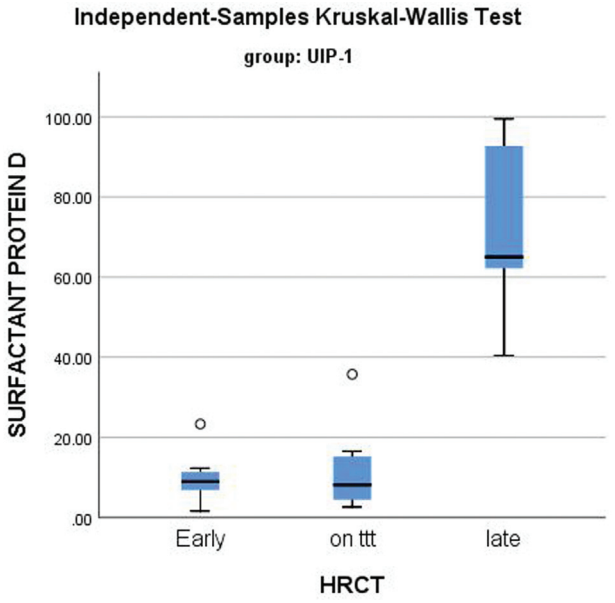
FEV1%, forced expiratory volume in the first second percent; FEV1, forced expiratory volume in first second; FVC%, forced vital capacity percent; HCO_3, bicarbonate; IIP, idiopathic interstitial pneumonia; IPF, interstitial pulmonary fibrosis; PCO_2, partial pressure of carbon dioxide; pH, potential hydrogen; PO_2, partial pressure of oxygen; SO_2, oxygen saturation.

Table 4 Serum surfactant protein-D level in different groups of the study population

	Group 1: IPF		Group 2: other IIP		Group 3: control		*P* value
	Mean	SD	Mean	SD	Mean	SD	
Surfactant protein-D level	26.22	30.25	23.86	18.46	32.92	17.10	0.398

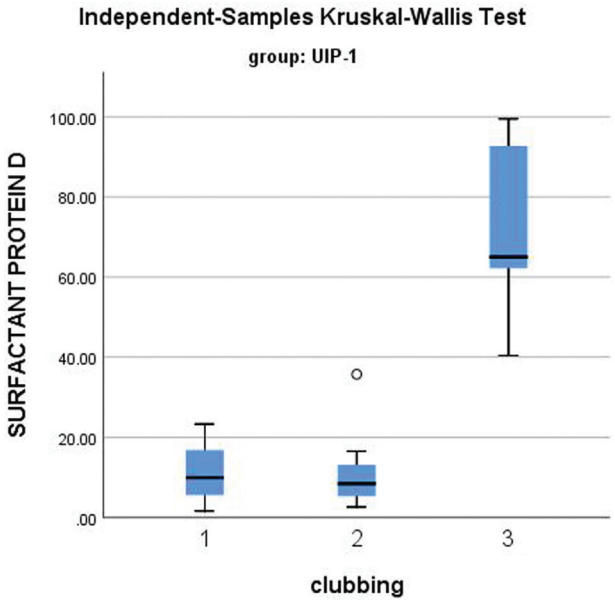
IIP, idiopathic interstitial pneumonia; IPF, interstitial pulmonary fibrosis.

Figure 1



The serum level of surfactant protein-D in the three different subgroups of UIP patients. UIP, usual interstitial pneumonia.

Figure 2



The relation between the serum level of surfactant protein-D and degree of clubbing.

of 0.029, 0.005, and 0.005, respectively (Table 5). Meanwhile it was not statistically significant among other IIP group 2 (Table 6).

Table 7 shows the correlation between the serum level of SP-D with duration of illness, forced vital capacity percent, oxygen saturation, and 6MWT was in negative direction with statistical significance regarding the oxygen saturation and 6MWT with a *P* value of 0.023 and 0.005, respectively.

Discussion

IPF is a disease of growing interest [15] and burden [1,2]. Over the last two decades many articles had been released regarding its differentiation from other forms

Table 5 The mean and SD of surfactant protein-D level in relation to sex, smoking, gastroesophageal reflux disease history, high-resolution computed tomography, and clubbing among the idiopathic pulmonary fibrosis group 1

	Surfactant protein-D		*P* value
	Mean	SD	
Sex			
Female	21.77	34.89	0.397
Male	28.13	29.26	
Smoking			
Yes	31.38	30.43	0.208
No	18.49	30.23	
History of GERD			
Yes	41.71	36.06	0.029
No	10.73	9.89	
HRCT			
Early	9.88	6.34	
On TTT	12.23	11.59	0.005
Late	71.96	24.13	
Clubbing			
1	11.18	8.99	
2	10.90	9.30	0.005
3	71.96	24.13	

GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; TTT, treatment.

Table 6 The mean and SD of surfactant protein-D level in relation to sex, smoking, gastroesophageal reflux disease history, and clubbing among other idiopathic interstitial pneumonia groups 2

	Surfactant protein-D		*P* value
	Mean	SD	
Sex			
Female	22.98	16.87	1
Male	26.94	26.09	
Smoking			
Yes	33.59	27.50	0.498
No	21.91	16.77	
History of GERD			
Yes	21.61	20.85	0.703
No	24.72	18.30	
HRCT			
NSIP	24.70	16.41	
RBILD	33.59	27.50	0.421
OP	19.08	19.44	
LIP	5.40	–	
Clubbing			
0	26.10	25.79	
1	7.74	1.97	0.052
2	36.98	14.85	
3	25.37	15.36	

GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RBILD, respiratory bronchiolitis interstitial lung disease.

Table 7 Correlation between the serum level of surfactant protein-D with duration of illness, forced vital capacity percent, oxygen saturation, and 6 min walk test

	Surfactant protein-D	
	IPF	Other IIP
Duration of illness		
R	–0.070	0.080
P	0.769	0.751
n	20	18
FVC%		
R	–0.364	–0.184
P	0.115	0.465
n	20	18
SO_2		
R	–0.504	0.104
P	**0.023**	0.683
n	20	18
6 min walk test (m)		
R	–0.605	0.337
P	**0.005**	0.172
n	20	18

FVC%, forced vital capacity percent; IIP, idiopathic interstitial pneumonia; IPF, interstitial pulmonary fibrosis; *R*, correlation coefficient; SO_2, oxygen saturation. Bold values are statistically significant p-Values.

of idiopathic interstitial lung diseases [16,17] and define the disease behavior and prognosis [15,17].

The mean age±SD 56.7±7.67 in IPF (group 1) was consistent with the fact that IPF is most common in the fifth and sixth decades [3,18,19]. The statistical significance of sex distribution with a *P* value of 0.009, where the male sex predominance in the IPF group in our study is consistent with other IPF registries [20,21]. Also, the smoking history showed statistical significance with a *P* value of 0.006 as smoking is considered one of the risk factors for IPF [3,22,23].

As the mean and SD of serum SP-D level in different groups of the study population were with no statistical significance as the *P* value is 0.398. This made its use for the diagnosis of IPF not feasible without combining it with other biomarker panels such as the three-analyte panel of SP-D, MMP-7, and osteopontin [24]. However, the SP-D level within the IPF subgroups were statistically significant with a *P* value of 0.005. A high level of SP-D in advanced cases group C without treatment and lower level in group B on treatment makes SP-D a potential biomarker for predicting the progression of the disease and effectiveness of anti-fibrotic drugs [25].

The SP-D level was statistically significant in regard of the gastroesophageal reflux disease history with a *P* value of 0.029. This draws the attention to the fact that GERD is one of the risk factors for the development of IPF [26] and an important comorbidity [27]. The results found by stating that children with GERD

had reduced level of SP-D; therefore, further studies are needed in this field [28]. Also, the degree of clubbing in relation to SP-D level showed statistical significance with a *P* value of 0.005. This may correlate to growth factor secretions and tissue proliferation [29].Our study found that there was a negative correlation between the SP-D and forced vital capacity percent, oxygen saturation, and 6MWT that was statistically significant regarding forced vital capacity percent and 6MWT making SP-D a good biomarker for assessing the severity of disease and as a potential prognostic evaluation [25,30].

Conclusion

SP-D cannot be used solely for the diagnosis of IPF; however, it could be a useful predictor for the outcome and prognosis with special concern to anti-fibrotic drugs.

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Conflicts of interest

There are no conflicts of interest.

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