**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.

**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.

**Keywords:** idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis, surfactant protein-D, usual interstitial pneumonia

**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 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]. χ² 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 (%)] | Group 1: IPF | Group 2: other IIP | Group 3: control | P value |
|---------------|-------------|-------------------|-----------------|---------|
| 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

| Groups [n (%)] | Group 1: IPF | Group 2: other IIP | P value |
|---------------|-------------|-------------------|---------|
| Smoking       |             |                   |         |
| Yes           | 12 (60.0)   | 3 (16.7)          | 0.066   |
| 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.
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 of 0.023 and 0.005, respectively. 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                 |                    |
| SO2                |                      |                    |                    |
| 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; SO2, 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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