

Serum Surfactant Protein D as a Prognostic Factor in Idiopathic Pulmonary Fibrosis Patients

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ABSTRACT

*Idiopathic pulmonary fibrosis (IPF) carries a 50% 5-years survival rate. The pathogenesis of IPF is characterized by chronic inflammation, fibroblast proliferation and extracellular matrix production with chronic scarring and honeycomb formation. This fibroproliferative response is uniformly accompanied by type II cell hyperplasia. Surfactant proteins-D (SP-D), is produced and secreted by type II cells. It can be detected in serum and is elevated in patients with certain inflammatory lung diseases. Measurement of this protein might be a useful marker for early detection of IPF and its prognosis. The present work was conducted on 30 patients, and 10 healthy volunteers obtained from chest Department, Faculty of Medicine, Cairo University, and were categorized into four groups as follows: **Group 1:** Included ten healthy volunteers as control group, **Group 2:** Consists of ten patients with idiopathic pulmonary fibrosis (IPF) received steroid therapy for one month, **Group 3:** Ten patients with idiopathic pulmonary fibrosis (IPF) not receiving steroid therapy and **Group 4:** Included ten patients with chronic chest disease without idiopathic pulmonary fibrosis. All groups were subjected to history taking, pulmonary function test and estimation of serum surfactant D (SP-D level) by ELISA. The results of the present study showed significant decrease in the pulmonary function tests represented by forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) (FEV₁/FVC%) in the three diseased groups compared to control. Mean level of SP-D in serum showed a highly significant increase in the three diseased groups compared to control. The mean level of serum SP-D is significantly higher in group 3 compared to group 2. Furthermore, significant negative correlation was found between SP-D serum level and FEV₁ and FEV₁/FVC in all IPF patients. From these results it could be concluded that the SP-D assay may be of value in estimating the rate of decline in pulmonary function in cases of IPF as well as in the follow up of disease progress. It may also assist in making clinical choices for therapeutic management of these patients.*

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening, idiopathic lung disease of unknown

etiology. The pathogenesis of IPF is characterized by fibroproliferative response uniformly accompanied by type II cell hyperplasia⁽¹⁾. For optimal

therapeutic management of IPF an accurate tool is required for discrimination between reversible and irreversible types of the disease. However, such noninvasive tools are few, and even with high-resolution computed tomography (HRCT), which is the most trusted method for doing so; the nature of the disease activity in IPF cannot always be accurately predicted. Current therapies are only marginally effective in improving pulmonary function or survival time.

The hydrophilic surfactant proteins (SP)-A and SP-D belong to the collection subgroup of the C-type lectin superfamily, along with mannose-binding glycoproteins and collectin CL43⁽²⁾. Two types of nonciliated epithelial cells, in the peripheral airways, Clara cells and alveolar type II cells produce these lung collectins⁽³⁾.

Surfactant proteins –D (SP-D), produced and secreted by type II cells, can be detected in serum and are elevated in patients with certain inflammatory lung diseases^(3,4,5). Although the exact mechanism for the increase in SP-D in the circulation is not known, it is probably a combination of loss of epithelial integrity due to injury and an increased mass of type II cells due to hyperplasia. Because the concentrations of serum SP-D probably vary with disease and lung inflammation, measurement of this protein might prove to be useful markers for detecting the pathogenesis and follow up of patients with IPF^(6,7,8).

The aim of the present study is to investigate the possible role of SP-D

in the pathogenesis and prognosis of idiopathic pulmonary fibrosis patients and its value in making clinical choices for therapeutic management of these patients.

SUBJECTS & METHODS

The present work was conducted on 30 patients, and 10 healthy volunteers obtained from chest Department, Faculty of Medicine, Cairo University, and they were categorized in four groups as follows:

- **Group 1:** Included ten healthy volunteers (Control group), six males and 4 females, nonsmokers, aged 54.7 ± 7.13 yr (mean \pm SD) (range: 45 - 65 yr).
- **Group 2:** Consists of ten patients with idiopathic pulmonary fibrosis (IPF) received steroid therapy for one month. Also, 6 were males and 4 females. Two of the patients are currently smoking, 4 ex-smokers, and 4 nonsmokers. Their mean age was 57 ± 6.63 yr (mean \pm SD) (range: 45 - 65 yr).
- **Group 3:** Ten patients with idiopathic pulmonary fibrosis (IPF) not receiving steroid therapy. Five were males and 5 females. They consist of 2 current smokers, 3 ex-smokers, and 5 nonsmokers, their mean age was 54.3 ± 5.27 yr (mean \pm SD) (range: 45 - 65 yr).
- **Group 4:** Included ten patients with chronic chest disease without idiopathic pulmonary fibrosis (5 male and 5 female). Consisting of 2 current smokers, 3 ex-smokers, and 5 nonsmokers aged 55.1 ± 8.17 yr (mean \pm SD)

(range: 45 -65 yr).

- The diagnosis of IPF was based on the accepted criteria of **Carrington, et al.**; ⁽⁹⁾ which included either evidence of varying degrees of interstitial fibrosis and alveolitis, or evidence of diffuse parenchymal infiltrates on chest radiography.

Patients were subjected to:

- Full history taking and clinical examination.
- Chest radiography. The 20 patients with IPF enrolled in the study showed the typical findings of IPF on chest radiography.
- Estimation of pulmonary function tests including forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC).
- Measurement of serum SP-D levels according to the method of Shimizu and coworkers ⁽¹⁰⁾ modified by **Honda, et al.** ⁽¹¹⁾.

Patients were selected according to the following criteria:

- Exclusion of other known causes of interstitial lung diseases (ILD), such as certain drug toxicities, environmental exposures, and connective tissue diseases.
- Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV₁/FVC ratio) and impaired gas exchange.
- Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
- Insidious onset of otherwise unexplained dyspnea on exertion.
- Bibasilar, inspiratory crackles (dry or "Velcro" type in quality).
- All patients studied were

clinically stable at the time of entry into the study.

Exclusion Criteria

Exclusion criteria consisted of a clinically relevant history of environmental or occupational exposure, hypersensitivity pneumonitis, collagen vascular disease, or other interstitial lung diseases such as acute interstitial pneumonia, diffuse alveolar damage, bronchiolitis obliterans organizing pneumonia, or lymphocytic interstitial pneumonia.

Collection and Analysis of Blood Samples

Ten ml. peripheral venous blood samples were collected from the patients at their initial visits and from healthy subjects at the time of registration for the study. The serum samples had been stored at -80°C and were analyzed in a blinded-fashion with regard to the clinical status of the patients.

Statistical Analysis

Data are expressed as mean ± SD. Differences between SP-D values on the three study groups, variables were assessed with the Mann-Whitney U test. The concentrations of SP-D were further analyzed by using student "t" test for the healthy group in order to find the cutoff levels indicating the best sensitivity and specificity of these two measures ⁽¹²⁾. Significance was defined as p < 0.05.

RESULTS

The results of the study are summarized in tables 1-4 and figures 1-4.

Table (1): Duration of smoking (months) and the number of cigarettes (per-day) in the studied groups (Means \pm SD):

	Group 1	Group 2	Group 3	Group 4
Duration of smoking (months) P ₂ P ₃		15.00 \pm 7.07	21.50 \pm 4.95 = 0.359	25.00 \pm 7.07 = 1.000 = 1.000
Number of cigarettes/day P ₂ P ₃		126.00 \pm 8.49	75.00 \pm 21.21 =1.000	120.0 \pm 33.94 = 0.655 = 1.000

- * Values are significant when P value <0.05

- o P₂ = Compared to group2.
- o P₃ = Compared to group3.

Table (1) showed no significant differences between the three groups regarding the duration and the number of cigarettes smoked per day.

Table (2): Pulmonary Function Test (PFT) in the studied groups (Mean \pm SD)

PFT	Group 1	Group 2	Group 3	Group 4
FEV1/FVC (%)	3.16 \pm 0.72	2.05 \pm 0.56	1.91 \pm 0.58	1.58 \pm 0.43
P1		0.001	0.000	0.000
P2			1.000	0.474
P3				1.000

* Values are significant when P value <0.05

- o P₁ = Compared to group1 (Controls).
- o P₂ = Compared to group2 (IPF patients receiving steroids).
- o P₃ = Compared to group3 (IPF patients not-receiving steroids).

Table (2) showed significant decrease in FEV1/FVC % in the three diseased groups compared to control. No significant difference was detected between the three diseased groups.

Table (3): Serum levels of Surfactant Protein D in the studied groups (Mean \pm SD).

	Group 1	Group 2	Group 3	Group 4
SP-D (ng/ml)	50.12 \pm 12.17	136.06 \pm 38.15	253.18 \pm 37.63	198.50 \pm 38.50
P₁		= 0.000	= 0.000	= 0.000
P₂			= 0.000	= 0.001
P₃				= 0.005

* Values are significant when P value <0.05

- o P₁ = Compared to group1 (Controls).
- o P₂ = Compared to group2 (IPF patients receiving steroids).
- o P₃ = Compared to group3 (IPF patients not-receiving steroids).

Table (3) showed a significant increase in SP-D in the three diseased groups compared to control. There is significant increase in SP-D in non-steroidal (group 3) and patients with chronic chest diseases without IPF (group 4) compared to steroid receiving patients (group 2); also there is a significant increase in non-steroidal group compared to chronic group.

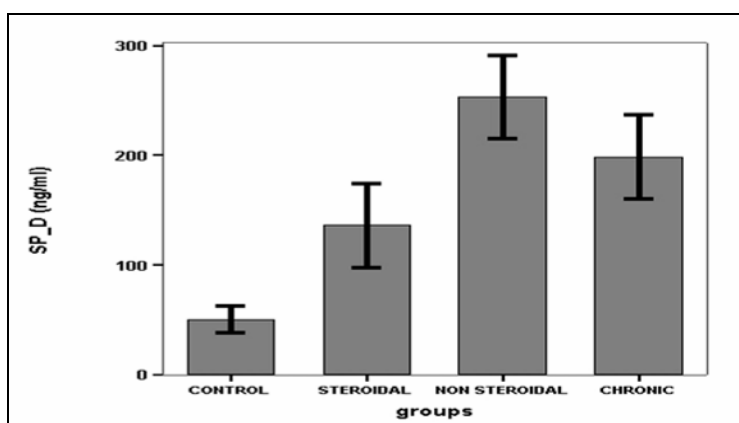


Fig (1) Serum Surfactant Protein D level (ng/ml) in the studied groups.

Figure 1 showed that non-steroidal group had the highest mean value of surfactant protein D.

Table (4): Correlation between serum surfactant protein D levels (ng/ml) and pulmonary function tests

SP D with	r	P
FEV1 (L)	-0.541	0.000
FVC (L)	-0.530	0.000
FEV1/FVC (%)	-0.530	0.000

From table (4):

A negative correlation was found between SP-D serum level and FEV1 (L) with P-value > 0.000 and r-value -0.541. In addition, a negative correlation was found between SP-D serum level and FVC (L) with P-value > 0.000 and r-value = -0.530. Also, a negative correlation was found between SP-D serum level and FEV1/FVC with P-value > 0.000 and r-value = -0.546.

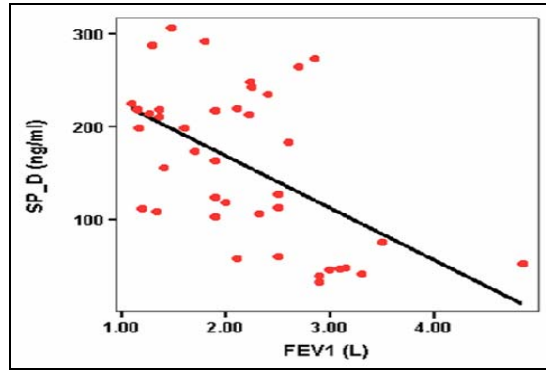


Figure (2) Serum Surfactant Protein D level (ng/ml) in relation to FEV1(L)

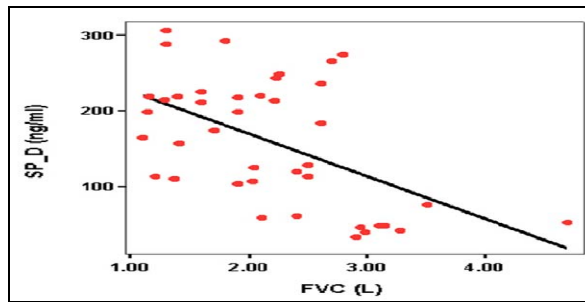


Figure (3) Serum Surfactant Protein D level (ng/ml) in relation to FVC(L)

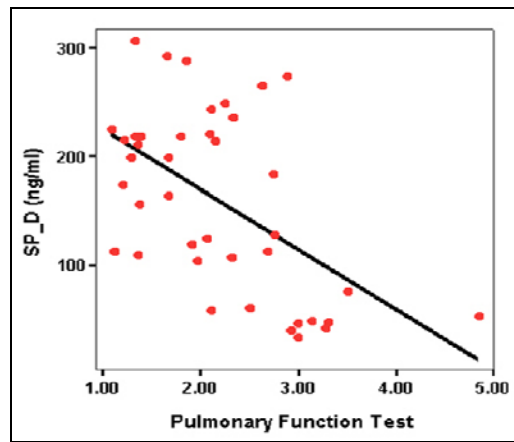


Figure (4) Serum Surfactant Protein D level (ng/ml) in relation to pulmonary function tests

DISCUSSION

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening, interstitial lung disease of unknown etiology. For optimal therapeutic management of IPF an accurate tool is required for discrimination between reversible and irreversible types of the disease. However, such noninvasive tools are few, and even with high-resolution computed tomography (HRCT), which is the most trusted method for doing so; the nature of the disease activity in IPF cannot always be accurately predicted.

Surfactant proteins (SP-A) and (SP-D) belong to the collectin subgroup of the C-type lectin superfamily, along with mannose-binding glycoproteins and collectin CL43⁽²⁾. Two types of nonciliated epithelial cells, in the peripheral airways, Clara cells and alveolar type II cells produce these lung collectins⁽³⁾.

Surfactant proteins –D (SP-D), produced and secreted by type II cells, can be detected in serum and are elevated in patients with certain inflammatory lung diseases, including IPF^(2,3,4,5).

While less than 10 to 15 percent of surfactant lipids are cleared by catabolism by alveolar macrophages, this pathway is critical in controlling steady-state surfactant concentrations in vivo.

The aims of the present study were to assess the value of surfactant protein SP-D in determining the pathogenesis of IPF disease and if it plays a role in predicting deterioration in restrictive pulmonary function.

Also, its role in determining the therapeutic response of the patients is another aim of the present study.

The present work was conducted on 30 patients, and 10 healthy volunteers obtained from Chest Department, Faculty of Medicine, Cairo University, and they were categorized into four groups. **Group 1:** Included ten healthy volunteers (Control group). **Group 2:** Consists of ten patients with idiopathic pulmonary fibrosis (IPF) received steroid therapy for one month. **Group 3 :** Ten patients with idiopathic pulmonary fibrosis (IPF) not receiving steroid therapy. **Group 4:** Included ten patients with chronic chest disease without idiopathic pulmonary fibrosis.

The diagnosis of IPF was based on the accepted criteria of **Carrington, et al.**,⁽⁹⁾ which included either evidence of varying degrees of interstitial fibrosis and alveolitis, or evidence of diffuse parenchymal infiltrates on chest radiography.

SP-D in sera was measured by enzyme-linked immunosorbent assays as previously described.

The results of the study showed that pulmonary function tests represented by forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) (FEV1/FVC%) were significantly decreased in the three diseased groups compared to control.

All the patients included in the present study gave a positive history of smoking, this finding coincide with the study of **Collard et al.**,⁽¹³⁾ who demonstrated a strong association between cigarette smoking and pulmonary fibrosis. In the present

study no significant difference was detected between the three diseased groups regarding the duration of smoking and the number of smoked cigarette/day.

The results of SP-D in the present study showed significant increase in the three diseased groups compared to control. Moreover, the mean value was significantly higher in non steroid and chronic groups compared to the steroid receiving group. Also, non steroid group was significantly higher than chronic group.

By measuring the concentrations of SP-D in sera from patients with IPF, interestingly, we found that the levels of SP-D at the initial time of study were higher in all diseased groups. Most subjects studied, even many who showed high levels of SP-D, did not have dyspnea at the initial time of study, indicating the insidious onset of the disease. Nevertheless, our results clearly indicate that high levels of SP-D are involved in the non-steroidal group. Thus, patients exhibiting higher serum levels of SP-D may have a greater chance of falling into restrictive pulmonary dysfunction, and more rapidly, than patients with low serum levels of SP-D. **Schwartz, et al.**,⁽¹⁴⁾ suggest that it may be more effective to start treatment for IPF before the manifestations of severe pulmonary fibrosis occur. Our results raise the possibility that the assay of SP-D can help to guide therapy with corticosteroids agents.

A difference between levels of SP-D was also observed in the four studied groups. The concentration of serum SP-D probably vary with disease severity and lung

inflammation^(11,15,16). The difference in the response to corticosteroid products could also affect concentrations of SP-D in serum.

Our results showed that SP-D concentration was significantly correlated with the extent of alveolitis (a reversible change), whereas they did not correlate with the progression of fibrosis (an irreversible change). The SP-D concentration was also related to the extent of parenchymal collapse and the rate of deterioration per year in pulmonary function, as proved in our study by the presence of significant negative correlation between SP-D and pulmonary function tests.

Although the exact mechanism for the increase in SP-D in the circulation is not known, it is probably a combination of a loss of epithelial integrity due to injury and an increased mass of type II cells due to hyperplasia. Because the concentrations of serum SP-D probably vary with disease and lung inflammation, measurement of this protein might prove to be useful markers for the pathogenesis and detection of IPF^(6,7,8).

Takahashi⁽¹⁷⁾ found that the concentrations of SP-A and SP-D in patients who died within 3 yr were significantly higher than in patients who were still alive after 3 yr. It has been proposed that SP-D may be a good predictive indicator of the rate of decline in pulmonary function, and that a combination of the assays for SP-A and SP-D may be helpful in predicting the outcome of patients with IPF.

Part of our results is in agreement with data from **Takahashi et al.**⁽¹⁷⁾

and Barlo et al.⁽¹⁸⁾ who demonstrated that SP-D in serum can predict worsening in IPF patients, and that the value of SP-D remains stable after adjustment for known predictors of worsening. Takahashi et al.⁽¹⁹⁾ The author mentioned that serum SP-D level higher than 460ng/ml. indicates a significantly worse prognosis compared to levels lower than 460ng/ml. This value can be useful in clinical practice. It might help in estimating survival time, which is important for optimal timing of referral for lung transplantation.

On the basis of these findings we evaluated the utility of assays of serum SP-D in establishing the prognosis of patients with IPF. None of the patients showing SP-D levels below the respective levels died throughout the period of the study (2years). Although the number of patients in our study was small, these findings suggest that a SP-D assay is useful to identify patients with the best prognosis in IPF.

According to Kinder, et al.⁽²⁰⁾, increased serum SP-D level is a strong and independent predictor of early mortality among patients with IPF. A prediction model containing SP-A and SP-D was substantially superior to a model with clinical predictors alone.

In conclusion, SP-D is a non-invasive marker that can be easily determined in serum and has been proved to be a diagnostic marker in IPF patients. This study adds clinically useful levels that could identify patients with a significantly worse prognosis by using SP-D for follow up of the patients. This prognostic value of SP-D persists after adjustment for known predictors of

mortality. Taken all previously published studies into account, we encourage the implication of routine measurement of SP-D at the time of diagnosis in IPF patients and using it as a marker for follow up of the patient to determine the degree of worsening or improvement of the case. SP-D serum levels may assist in making clinical choices for therapeutic management of patients with IPF.

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الملخص العربي

دولت المليجي^١، ليلى راشد^٢، محمد وفاني^٣ وهابدي ابوحسين^٤
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دور مصّل بروتين (د) الخافض للتوتر السطحي في متابعة التطور المرضي لمرضى التليف الرئوي مجهول السبب.
 يُعرف التليف الرئوي مجهول السبب على أنه نوع خاص من الالتهاب الرئوي المزمن ويمكن تشخيصه فقط بعد استبعاد المسببات الأخرى المعروفة لأمراض التهابات أنسجة الرئة؛ مثل سمية بعض العقاقير، التعرض للتلوث البيئي، وأمراض البروتينات للأوعية الدموية.
 والتليف الرئوي هو أحد أكثر تلك الالتهابات انتشاراً وتشخيصه يعتمد على اجراء أشعات مقطعية للمرضى او اخذ عينة من نسيج الرئة لفحصها مجهرياً. عادة ما تكون بداية ظهور الأعراض كامنه؛ حيث أنه في معظم الحالات تكون الأعراض موجودة لفترة تقرب من ستة أشهر قبل التشخيص. ومن أكثر الأعراض شيوعاً هي السعال الجاف وعدم القدرة على التنفس مع المجهود. أما عن الأعراض الجسدية فهي نادرة، ومنها: فقدان في الوزن مع الارهاق وقد يصاحبه الآم في المفاصل والعضلات.
 يُقدر العمر الافتراضي لمرضى التليف الرئوي مجهول السبب بخمس سنوات، ووسائل العلاج الحالية بالكاد تحسن فاعلية كفاءة وظائف الرئة أو العمر الافتراضي للمريض.
 معاملات انخفاض التوتر السطحي لمصّال بروتينات أ و د تنتمي إلى مجموعة اللكتين المرتبط مع مانوز البروتينات السكرية وكوليكتن سي إل ٤٣. ويوجد نوعان من الخلايا الظهارية الملساء

بالمحيط الداخلي للشعيرات الهوائية وهما خلايا كلارا والنوع الثاني من خلايا الألفيولار، مسئولان عن انتاج هذه الكوليكتينات الرئوية.

هدف هذه الدراسة هو تحرى دور مصل بروتين (د) الخافض للتوتر السطحي فى التشخيص و متابعة التطور المرضى وتحديد البرنامج العلاجى لمرضى التليف الرئوى مجهول السبب.

أجريت هذه الدراسة على ٣٠ مريضا من قسم الصدر بكلية الطب جامعة القاهرة ، و ١٠ حالات من المتطوعين، وتم تقسيمهم إلى مجموعات كالتالى:

- المجموعة الأولى: وتضم العشرة المتطوعين (المجموعة الضابطة) وتكونت من ستة من الذكور وأربعة من الإناث جميعهم من غير المدخنين بمتوسط أعمار يتراوح ما بين ٤٥ إلى ٦٥ عاما.
 - المجموعة الثانية: وقد اشتملت على عشرة مرضى يعانون من مرض التليف الرئوى مجهول السبب، وقد تناولوا عقار الكورتيكوستيرويد لمدة شهر. منهم ستة ذكور وأربعة إناث، اثنان مدخنين حاليين واربعة مدخنين سابقين وأربعة غير مدخنين. بمتوسط أعمار يتراوح ما بين ٤٥ إلى ٦٥ عاما.
 - المجموعة الثالثة: وهى عبارة عن عشرة من مرضى التليف الرئوى مجهول السبب (خمسة ذكور وخمسة إناث)، ولم يتناولوا عقار الكورتيكوستيرويد، تضمنت تلك المجموعة عدد اثنان مدخنين حاليين وثلاثة مدخنين سابقين وخمسة من غير المدخنين، تراوحت أعمارهم ما بين ٤٥ و ٦٥ عاما.
 - المجموعة الرابعة: وضمت عشرة مرضى (خمسة ذكور وخمسة إناث) يعانون من أمراض صدرية مزمنة وليسوا بمرضى تليف رئوى مجهول السبب، منهم اثنان مدخنين حاليين وثلاثة مدخنين سابقين وخمسة من غير المدخنين، تراوحت أعمارهم ما بين ٤٥ و ٦٥ عاما.
- تم تشخيص التليف الرئوى مجهول السبب بينهم على أسس المعايير المتفق عليها التى تضمنت درجات متفاوتة من الالتهابات الرئوية أو دلائل أنسجة متداخلة ظاهرة على أشعة الصدر.
- وقد خضعت كل المجموعات إلى استقصاء التاريخ المرضى، اختبارات كفاءة الرئة وقياس مستوى مصل بروتين د الخافض للتوتر السطحي بطريقة الإليزا، بالإضافة لإجراء جميع التحاليل المعملية اللازمة المتضمنة عوامل درجة تغير نشاط المرض.
- وقد اظهرت نتائج البحث انخفاض فى وظائف الرئة فى المجموعات المرضية بالمقارنة لمجموعة الاصحاء . كما لوحظ وجود ارتفاع ذو دلالة احصائية فى مصل معامل التوتر السطحي د فى جميع الحالات المرضية مقارنة بمجموعة الاصحاء . وكان الارتفاع فى المجموعة التى لم تتلقى العلاج الكورتيكوستيرويد والمجموعة المزمته اعلى من المجموعة التى تم علاجها الكورتيكوستيرويد. كما لوحظ وجود علاقة ارتباط عكسية ذو دلالة احصائية بين مصل معامل التوتر السطحي د ووظائف الرئة .
- من نتائج الدراسة يمكن استنتاج ان مصل معامل التوتر السطحي د يمكن استخدامه فى تشخيص الحالات المصابة بمرض التليف الرئوي مجهول السبب كما يمكن الاعتماد عليه فى متابعة الحالة المرضية وفعالية العلاج لدى هؤلاء المرضى.