Serum level of carbohydrate antigen 15-3 in patients with interstitial lung diseases and its correlation with pulmonary function and high-resolution computed tomography

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Background Carbohydrate antigen 15-3 (CA15-3) is a central protein core of mucin-1, a high-molecular-weight glycoprotein, found in alveolar and extrapulmonary epithelial cells that increases in interstitial lung disease. It uses antibodies against different epitopes. It is also considered a tumor marker for breast cancer.

Aim The aim was to evaluate the value of CA15-3 as a biomarker in patients with interstitial lung diseases and to evaluate the correlation between CA15-3 level and radiological findings in high-resolution computed tomography (HRCT) and pulmonary function in patients with interstitial lung diseases (ILDs).

Materials and methods The study was performed on 60 adult patients with ILD and 20 healthy controls. We classified the patients into three groups according to HRCT findings: group I ground glass (18 patients), group II reticulation (27 patients), and group III honeycombing (15 patients). All patients were subjected to HRCT, spirometry, collagen markers, and serum CA15-3 level evaluation.

Results CA15-3 level in patients with ILD was significantly higher than control ($P<0.001$). CA15-3 level in reticulation and honeycombing groups was significantly higher than ground glass group, and CA15-3 level in reticulation group was significantly higher than honeycombing group ($P=0.003$). This may be explained by that reticulation is active fibrosis, whereas honeycombing is established fibrosis. A significant negative correlation has been noticed between CA15-3 level and forced vital capacity in the three different groups ($P<0.05$, $r=-0.304$).

Conclusion The serum level of CA15-3 is strongly elevated in patients with ILD. CA15-3 is a noninvasive, nonexpensive, rapid biomarker in ILD, being proportional to the extent of lung injury.

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Keywords: carbohydrate antigen 15-3, high-resolution computed tomography, interstitial lung disease

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Introduction

Interstitial lung diseases (ILD) are respiratory conditions characterized by inflammation and fibrosis of the interstitium. Chronic hypoxia and respiratory failure might develop with progression of the disease. According to etiology, behavior of the disease and response to treatment may vary [1,2].

Causes and classification of interstitial lung diseases are as follows:

(1) Diffuse parenchymatous lung disease of known cause, for example, drugs or associated with collagen vascular disease.
(2) Idiopathic interstitial pneumonia (IIP):
  (a) Idiopathic pulmonary fibrosis (IPF).
(3) Idiopathic interstitial pneumonia (IIP) other than IPF which include:
  (a) Desquamative interstitial pneumonia.
  (b) Nonspecific interstitial pneumonia (~25% of IIPs).
  (c) Respiratory bronchiolitis ILD, occurring in smokers (~10% of IIPs).
  (d) Cryptogenic organizing pneumonia (~3% of IIPs).
  (e) Lymphoid interstitial pneumonia (~1% of IIPs).
  (f) Acute interstitial pneumonia (~1% of IIPs).
(4) Granulomatous diffuse parenchymal lung disease (DPLD), for example, sarcoidosis.
(5) Other forms, for example, lymphangioleiomyomatosis and histiocytosis x [3].

Revised ERS-ATS classification of IIP is as follows [4]:

(1) Major IIP:
  (a) IPF.
  (b) Desquamative interstitial pneumonia.
  (c) Cryptogenic organizing pneumonia.
  (d) AIP.
  (e) Nonspecific interstitial pneumonia.

(f) Respiratory bronchiolitis ILD.
(2) Rare IIP:
(a) Lymphoid interstitial pneumonia.
(b) Idiopathic pleuropulmonary fibroelastosis.
(3) Unclassifiable IIP.

Carbohydrate antigen 15-3 (CA15-3) is a central protein core of mucin-1 (MUC1), a high-molecular-weight glycoprotein, found in alveolar and extrapulmonary epithelial cells, which is increased in interstitial lung disease, and it uses antibodies against different epitopes. It is also considered a tumor marker for breast cancer [5].

It is found that MUC1 is excreted in pulmonary tissue by bronchiolar epithelial cells and bronchial serous glands [6]. Moreover, CA15-3 level increases in many pulmonary diseases. Several studies have found a strong positive correlation between increasing level of CA15-3 and severity of ILD. Moreover, it is found that the level of CA15-3 may reach up to 300 μl/ml in these patients [7].

Elevation of CA15-3 serum levels was previously detected in ILD associated with collagen diseases, like dermatomyositis (DM) and polymyositis, in absence of breast cancer [8]; therefore, serum CA15-3 levels may be considered a marker of pulmonary fibrosis and disease progression [9]. Laboratory values may vary depending on the laboratory, but the normal level of CA15-3 is usually considered 30 Ul/ml or less [6].

Patients and methods

Our study was done on 60 adult patients with interstitial lung diseases attending the chest and rheumatology outpatient clinics of Beni-Suef University hospital and from chest inpatient department. Moreover, 20 healthy volunteers were included as a control group. The FM-BSU REC has approved the protocol for the ethical point view.

According to high-resolution computed tomography (HRCT) findings, we classified the patients into three groups:

(1) Group I: ground-glass attenuation.
(2) Group II: reticular predominant.
(3) Group III: honeycombing predominant.

Inclusion criteria

Patients with diffuse interstitial lung disease were included.

Exclusion criteria

The following were the exclusion criteria:

(1) Patients with breast cancer.
(2) Patients with malignancy anywhere.
(3) Patients with other chest diseases rather than diffuse interstitial lung disease such as bronchiectasis, asthma, or chronic obstructive pulmonary disease.

Study design

Each patient was subjected to the following:

(1) Full history taking.
(2) Full clinical examination.
(3) Radiological examination.

Chest radiography

It may show reticular shadowing of the lung peripheries, which is typically more prominent in lung bases. It may cause the contour of the heart to be less distinct or shaggy. It also may show lung volume loss in pulmonary fibrosis.

High-resolution computed tomography

It is considered by radiologists and physicians to be a useful technique in the investigation of patients with suspected diffuse lung disease.

Pulmonary function tests

Resting spirometry was performed by PFT. No.781040, Master Screen (Jaeger-Hochberg, Germany).

High-resolution computed tomography technique

It is achieved by producing thin-section images (0.5–1 mm) and using special computer algorithms that increase details. Initially these high-detailed images were produced by making thin-section images every 10–20 mm, with patients holding their breath after a deep inhalation (the so-called sequential acquisition technique). This type of HRCT examination provided some 20 highly detailed images of the pulmonary parenchyma, sometimes supplemented with images obtained after exhalation or with the patient in prone position.

According to HRCT finding, we classified the patients into three groups:

(1) Group I: ground-glass attenuation.
(2) Group II: reticular predominant.
(3) Group III: honeycombing predominant.

Autoimmune profile

Serum blood samples were taken from each person, and rheumatoid factor, antinuclear antibody, and anti-cyclic citrullinated antibody were measured.

Measurement of CA15-3

A volume of 3-ml blood sample was taken from each person, poured into a clot tube, and then coagulated.

The serum sample was separated by centrifugation and stored at −20°C in 0.5-ml vials. After collecting of samples, serum CA15-3 determination using enzyme-linked immunosorbent assay kit was performed.

Statistical analysis

Data were analyzed using the software statistical package for the social sciences (released 2009, PASW Statistics for Windows, version 18.0; SPSS Inc., Chicago, Illinois, USA). Frequency distribution such as percentage and descriptive statistics in the form of mean and SD were calculated. χ^2-test, t-test, and correlations were performed whenever needed. P values of less than 0.05 were considered significant and P value greater than 0.05 was not significant.

A correlation is the direction of the relation, either negative or positive. A positive correlation coefficient means that if one variable increases, the other variable increases, and as one decreases the other decreases. A negative correlation coefficient means that if one variable increases, the other decreases, and if one decreases, the other increases.

Results

Our study was done on 60 adult patients with interstitial lung diseases attending the chest and rheumatology outpatient clinics of Beni-Suef University hospital and from the chest inpatient department in the period between November 2016 and June 2018. Moreover, 20 healthy volunteers were included as a control group.

Patients are classified into three groups:

(1) Group I: ground-glass attenuation.
(2) Group II: reticular predominant.
(3) Group III: honeycombing predominant.

Table 1 shows the demographic data, pulmonary function parameters, and CA15-3 levels in patients with interstitial lung diseases and controls. The table shows that forced vital capacity (FVC) of patients was significantly lower than controls ($P<0.05$). The table also shows that CA15-3 level of the patients was significantly higher than that of controls ($P<0.05$).

A comparison between patients and controls regarding collagen markers is presented in Table 2. The table shows that collagen markers were more prevailing in patients than controls who showed no markers at all ($P<0.05$).

An association between CT findings and FVC in the three groups is shown in Table 3. The table shows that FVC of reticulations and honeycombing groups was significantly lower than ground-glass group, and FVC of honeycombing group was significantly lower than reticulation group ($P<0.05$).

Table 1 Demographic data and pulmonary function parameters of patients with interstitial lung diseases and controls

	N	Mean	SD	Minimum	Maximum	*P* value
Age						
Cases	60	49.88	12.32	17	82	<0.001*
Controls	20	38.1	6.34	28	50	
FVC						
Cases	60	51.37	14.11	14	80	<0.001*
Controls	20	93.6	6.06	85	110	
FEV_1/FVC						
Cases	60	85.92	6.86	75	100	<0.001*
Controls	20	101.15	9.85	85	118	
CA15-3						
Cases	60	93.91	80.49	5.6	375	<0.001*
Controls	20	26.55	10.76	13	49	

CA15-3, carbohydrate antigen 15-3; FEV_1, forced expiratory volume in first second; FVC, Forced vital capacity. *P value is considered significant.

Table 2 Comparison between cases and controls regarding collagen markers

Collagen	Groups		Total	*P* value
	Cases	Controls		
Positive				
Count	18	0	18	0.003*
%	30.00	0.00	22.50	
Negative				
Count	42	20	62	
%	70.00	100.00	77.50	
Total				
Count	60	20	80	
%	100.00	100.00	100.00	

**P* value is considered significant.

Table 3 Association between computed tomography findings and forced vital capacity in the three groups

FVC	*N*	Mean	SD	Minimum	Maximum	*P* value
Ground glass	18	57.92	16.3	26.4	80	0.024*
Reticulations	27	49.7	9	36	76	
Honeycombing	15	46.36	8.99	30	62	
Total	60	51.33	12.34	26.4	80	

FVC, forced vital capacity. **P* value is considered significant.

Table 4 Association between computed tomography findings and carbohydrate antigen 15-3 in the three groups

CA15-3	*N*	Mean	SD.	Minimum	Maximum	*P* value
Ground glass	18	43.2	38.81	5.6	120	0.003*
Reticulations	27	124.6	97.86	31	375	
Honeycombing	15	99.58	50.39	35	190.7	
Total	60	93.91	80.49	5.6	375	

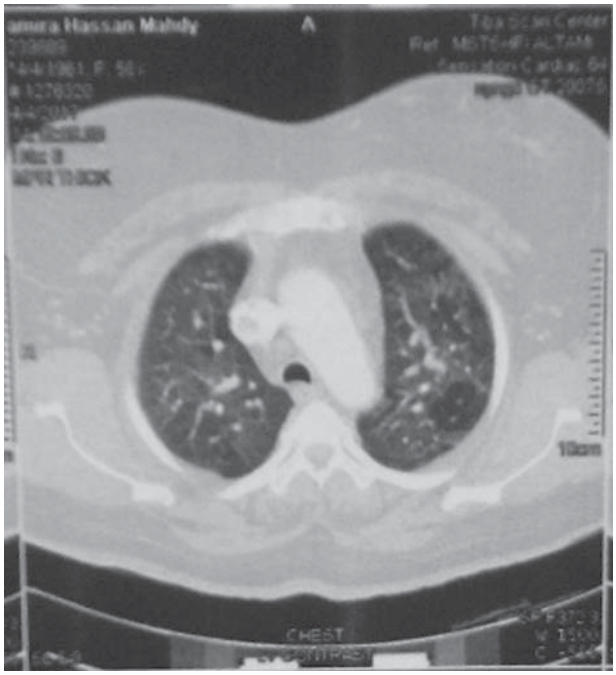
CA15-3, carbohydrate antigen 15-3. **P* value is considered significant.

Table 5 Correlations between carbohydrate antigen 15-3 and age, forced vital capacity, and forced expiratory volume in first second/forced vital capacity in the three groups

	Variables	CA15-3
Age	Correlation	–0.223
	P value	0.086
	N	60
FVC	Correlation	–0.304
	P value	0.018*
	N	60
FEV_1/FVC	Correlation	0.022
	P value	0.865
	N	60

CA15-3, carbohydrate antigen 15-3; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity. **P* value is considered significant.

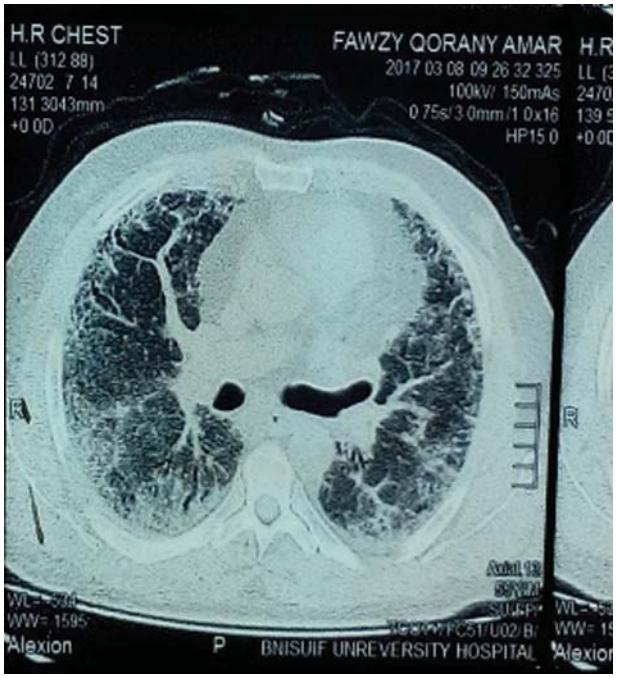
Fig. 1



Ground-glass attenuation.

The association between CT findings and CA15-3 in the three groups is shown in Table 4. The table shows that CA15-3 level in reticulation and honeycombing groups was significantly higher than ground-glass group, and CA15-3 level in reticulation group was significantly higher than honeycombing group ($P<0.05$).

Fig. 2



Reticular pattern.

Correlations between CA15-3, age, FVC, and forced expiratory volume in first second/FVC in the three groups are shown in Table 5. The table shows a statistically significant negative correlation between CA15-3 level and FVC in the three different groups ($P<0.05$, $r=-0.304$).

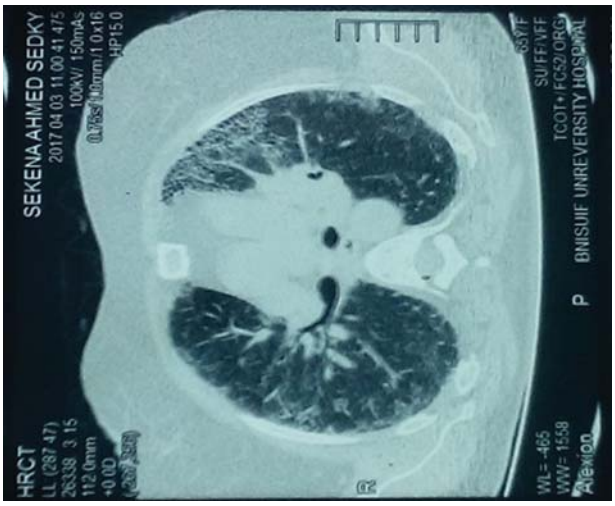
Discussion

The study shows that FVC of the patients was significantly lower than controls ($P<0.05$) (Table 1 and Figs 1–5).

This study shows that CA15-3 level of the patients was significantly higher than that of controls ($P<0.05$) (Fig. 6 and Table 1).

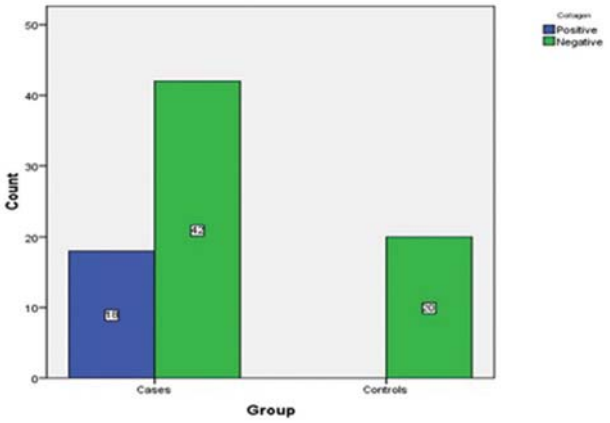
These results are in agreement with Kruit *et al.* [10] who measured serum level of CA15-3 and KI-6 in patients with ILDs and healthy controls. A total of 242 patients and 327 healthy participants were included. They found that CA15-3 and KL-6 levels were significantly higher in patients with ILD than

Fig. 3



Honeycombing.

Fig. 4



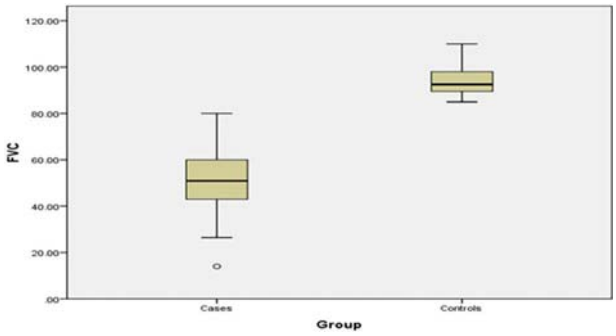
Comparison between cases and controls regarding collagen markers.

controls ($P<0.0001$). They also found a strong higher correlation between serum KL-6 and CA15-3 levels in patient groups ($r=0.85$, $P<0.0001$) and a weak correlation in the controls ($r=0.39$, $P<0.0001$). On comparison between the two markers, they found that CA15-3 is widely available, easy to use, and lower in cost.

Our study shows that collagen markers were more prevailing in patients than controls who showed no markers at all ($P<0.05$) (Fig. 4 and Table 2).

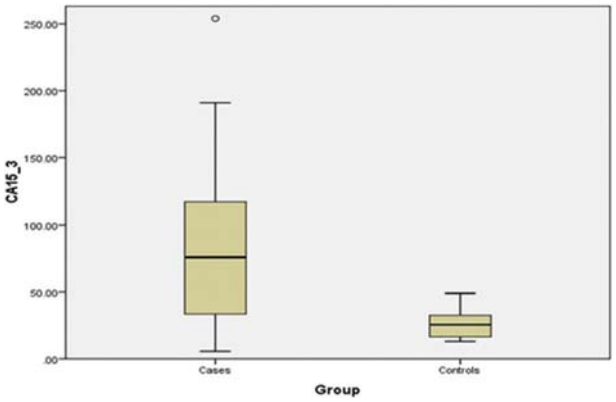
Moreover, our study agrees with Wong *et al.* [11] who proved that there is a significant elevation of serum levels of the tumor markers such as CA 15-3 and CASA (cancer-associated serum antigen) in patients with interstitial lung disease without presence of malignancy. A 37-year-old woman with severe

Fig. 5



Comparison between cases and controls regarding forced vital capacity.

Fig. 6

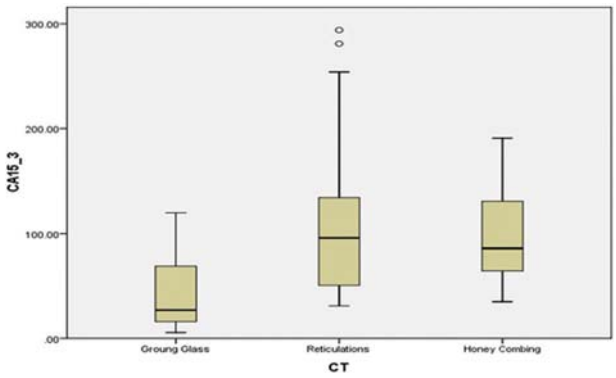


Comparison between cases and controls regarding carbohydrate antigen 15-3.

interstitial lung disease associated with DM sine myositis was reported. Serum level of CA 15-3 is significantly elevated, but no evidence of an underlying malignancy (including breast and ovarian) was found on serial clinical and radiologic examinations. The use of the CA 15-3 and CASA assays to measure serum levels of the highly glycosylated high-molecular-weight MUC1 in interstitial lung disease has not been previously described. Clinicians should therefore be aware that elevation of these tumor markers may reflect the presence of interstitial lung disease rather than an underlying malignancy in patients with DM.

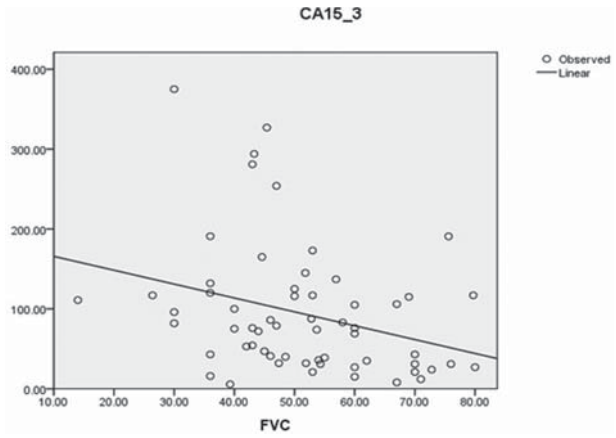
Our study agrees with Victoria *et al.* [12], who proved that CA 15-3 levels may predict disease severity in idiopathic pulmonary fibrosis. Levels decreased in patients with IPF following lung transplantation and with no malignancy. This suggests that mucin has an important role in IPF pathogenesis and can be considered as a marker of disease activity. The study was done on 61 patients with progressive idiopathic pulmonary fibrosis referred for 6-min walk test,

Fig. 7



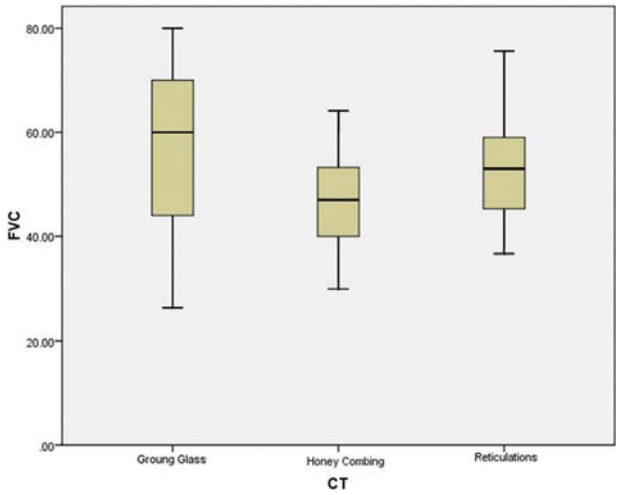
Association between computed tomography findings and carbohydrate antigen 15-3 in the three groups.

Fig. 8



Correlations between carbohydrate antigen 15-3 and age, forced vital capacity, and forced expiratory volume in first second/forced vital capacity in the three groups.

Fig. 9



Association between computed tomography findings and forced vital capacity in the three groups.

echocardiogram, cardiopulmonary exercise test, and pulmonary function tests and compared with CA15-3 level. The control group included 41 patients with chronic obstructive pulmonary disease who were lung transplantation recipients (Figs 7 and 8).

This study shows that FVC of reticulations and honeycombing groups was significantly lower than ground-glass group, and FVC of honeycombing group was significantly lower than reticulation group ($P<0.05$) (Fig. 9 and Table 3).

This study shows that CA15-3 level in reticulation and honeycombing groups was significantly higher than ground-glass group and CA15-3 level in reticulation group was significantly higher than honeycombing group ($P<0.05$) (Fig. 7 and Table 4).

This agrees with Celeste *et al.* [13] who performed a study on patients with scleroderma. The number of patients included was 221. They measured CA15-3 level, and HRCT was done for the patients. Overall, 168 patients had evidence of ILD. A correlation was done between HRCT and CA15-3 level, and they found a strong correlation between serum CA15-3 level and HRCT ($r=0.734$, $P<0.0001$). CA15-3 had an area under receiver operating characteristic curve of 0.927 to detect the meaningful 20% fibrosis extent. Abnormal CA15-3 levels can differentiate between patients at high or low risk for progression. The combination of HRCT and CA15-3 in patients with scleroderma-ILD is more useful than staging system based on HRCT scores plus FVC (heart rate=2.657, confidence interval: 95=1.703–4.147, $P<0.0001$).

This study agrees with Ricci *et al.* [14] who worked on patients with IPF ($n=20$), sarcoidosis at different stages, and systemic sclerosis and measured serum level of CA15-3 in these patients and compared with serum samples from healthy participants ($n=25$).

Levels of CA15-3 were strongly higher in patients with idiopathic pulmonary fibrosis and with clinically advanced sarcoidosis (stage 3). There is a slight increase in serum level of CA15-3 in patients with systemic sclerosis. There is no difference between serums CA15-3 levels in patients with sarcoidosis stages 1 and 2 in comparison with controls. Moreover, CA15-3 level in patients with idiopathic pulmonary fibrosis and stage 3 sarcoidosis strongly correlated with TLC, DLCO, and HRCT.

As our study reported 18 patients from total 60 as autoimmune disease (rheumatoid arthritis and systemic

lupus and scleroderma) who also shows significant increase in CA15-3 level compared with control group.

Our results agree with Wang *et al.* [15] who measured the serum levels of CA15-3, CA19-9, CA125, and CEA in 28 patients with rheumatoid arthritis with interstitial lung disease and 83 patients with rheumatoid arthritis only and found that serum level of CA15-3, CA125, and CA15-9 increase in patients with rheumatoid arthritis with interstitial lung disease in comparison with rheumatoid arthritis without interstitial lung disease.

Bergamaschi *et al.* [16] performed a study consisting of 100 patients with rheumatoid arthritis and healthy controls. Evaluation of serum levels of CA15-3, CA125, and CA19-9 was done. Patients with rheumatoid arthritis had high levels of these tumor markers than control group.

Şeber *et al.* [17] performed a study on 148 patients with rheumatoid arthritis and 36 healthy controls. They measured rheumatoid factor, anti-CCP, CA15-3, CA19.9, CA125, and CEA in patients' serum. They found that serum levels of CA15-3, CA19.9, and CA125 were strongly higher in patients with rheumatoid arthritis in comparison with the control group.

Our study is in agreement with De Luca *et al.* [18] who collected serum samples from patients with systemic sclerosis and ILD and measured tumor-associated antigens in these sera. They proved that these tumor markers can be increased in the sera of patients with systemic sclerosis and correlated with the degree of lung damage, and this suggests an important role of these biomarkers. They worked on 80 patients with systemic sclerosis with ILD and 40 SSc (systemic sclerosis) controls without ILD. An indirect correlation between CA15-3 and carcinoembryonic antigen and FVC was found and a direct correlation with interstitial scores. There was an elevation of these markers in patients with progressive lung damage.

Moreover, our results are in agreement with Szekanecz *et al.* [8] who assessed levels of tumor markers (CA15-3, CA125, and CA19.9 CEA) in the sera of patients with rheumatoid arthritis, lupus, scleroderma, and Sjögren's syndrome and healthy participants. They correlated the level of these tumor markers with disease markers such as RF and anti-CCP and found that significant high level of CA15-3, CA125, and CA19.9 in patients with RA compared with controls.

Moreover, Szekanecz *et al.* [19] measured serum levels of tumor markers CA15-3, CA125, and CA19.9 by immunoassay in 92 patients with scleroderma, 40 patients with systemic lupus, and 50 healthy controls. In patients with scleroderma, there were significant high levels of CA15-3 and CA125 compared with controls. In systemic lupus, there was elevation of CEA and CA19.9 than control.

Bevan and Richardson [20] proved that there is an elevation of serum level of tumor markers such as CA15-3 and CA125 in patients with undifferentiated connective tissue disease in absence of malignancy. Interstitial lung disease may develop later in these patients.

This study shows a statistically significant negative correlation between CA15-3 level and FVC in the three different groups ($P<0.05$, $r=-0.304$) (Table 5, Fig. 8).

This is in agreement with De Luca *et al.* [18] who worked on 80 patients with systemic sclerosis with ILD and 40 SSc controls without ILD. An indirect correlation between CA15-3 and carcinoembryonic antigen and FVC was found and a direct correlation with interstitial scores.

Conclusion

CA15-3 is a valid biomarker in patients with interstitial lung diseases.

CA15-3 was significantly higher in patients with interstitial lung disease than healthy controls.

CA15-3 level in patients with ILD with reticulation pattern and honeycombing was significantly higher than those with ground-glass attenuation.

There is a relation between CA15-3 level and degree of fibrosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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