Development Of A Scoring System With Multidimensional Markers For Fibrosing Interstitial Lung Disease

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Abstract

Fibrosing interstitial lung disease (ILD) can cause high mortality and sensitive evaluation of fibrosing ILD could be critical. The aim of this study is to develop a scoring system to predict prognosis of fibrosing ILD. We retrospectively reviewed 339 fibrosing ILD patients admitted to Nanjing Drum Tower Hospital from February 2017 to February 2020. All patients were followed up until September 2020. Cox multiple regression analysis indicated that smoking history (HR=3.826, P=0.001), age (HR=1.043, P=0.015), CEA (HR=1.059, P=0.049), CYFRA21-1 (HR=1.177, P=0.004) and DLCO% predicted (HR=0.979, P=0.032) were independent prognostic factors for fibrosing ILD. The clinical scoring system for fibrosing ILD was established based on the clinical variables (age [A], CEA and CYFRA21-1 [C], DLCO% predicted [D], and smoking history [S]; ACDS). The area under the receiver operating characteristic curve (AUROC) of the scoring system for predicting prognosis of fibrosing ILD was 0.91 (95%CI: 0.87-0.94, P<0.001). The cutoff value was 2.5 with their corresponding specificity (91.1%) and sensitivity (77.5%). Correlation analyses showed that the increased age, CEA and CYFRA21-1 were significantly correlated with decreased DLCO% predicted (P<0.001, P=0.028, P<0.001, respectively). The independent risk factors for mortality in patients with fibrosing ILD are higher CEA, higher CYFRA21-1, smoking history, lower DLCO% predicted at baseline and older age. ACDS is a simple and feasible clinical model for predicting survival of fibrosing ILD.

1. Background

Interstitial lung diseases (ILDs) are a group of heterogeneous lung diseases with pulmonary alveolar unit inflammation or interstitial fibrosis that are associated with substantial morbidity and mortality. The causation of ILD includes idiopathic and specific etiology including autoimmune disease, vasculitis, drugs, tumors and occupational or environmental exposure(1-2). Idiopathic pulmonary fibrosis (IPF) is one of a family of idiopathic interstitial pneumonias characterized by usual interstitial pneumonia (UIP) in high-resolution computed tomography (HRCT) and pathology(3). IPF has a poor prognosis with median survival from the time of diagnosis approximately 3 years(4). Fibrosing ILDs other than IPF, such as connective tissue disease (CTD) associated ILD, including ILD associated with rheumatoid arthritis (RA-ILD), systemic sclerosis (SSc-ILD) and polymyositis/dermatomyositis are also known to have progressive disease behaviors similar to IPF(5-7). Therefore, it is important to recognize the risk factors associated with poor prognosis in patients with fibrosing interstitial lung disease.

Several biomarkers has been reported to be as diagnostic and prognostic biomarkers of fibrosing ILD, including Krebs von den lugen-6 (KL-6), Surfactant proteins A and D (SP-A and SP-D), serum interleukin 6 (IL-6) levels and tumor markers(8-10). However, the relationship between proportion of each serum marker and fibrosing ILD is not clear. Therefore, in this study, we retrospectively studied the clinical characteristics of patients with fibrosing ILD and established a novel model to better guide personalized therapeutic choices in persons.

2. Materials And Methods

2.1 Study subjects

We retrospectively reviewed 339 patients who were newly diagnosed of fibrosing ILD (IPF and CTD-ILD) from inpatient of the department of respiration of Nanjing Drum Tower Hospital from February 2017 to February 2020(Figure 1). Patients with combined pneumonia, pulmonary tuberculosis, lung malignancy, or other pulmonary diseases were excluded. The follow-up period was from 7 months to 3 years. We analyzed demographic features, clinical characteristics, lung function parameters and therapy.

This study was consented by Ethics Committee of Nanjing Drum Tower Hospital. The Ethics Committee waived the need for informed consent as the study was retrospective and the data were analyzed anonymously.

2.2 Methods

The diagnosis for IPF was mainly based on the criteria from An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline (3). The diagnosis of CTD-ILD referred to the published guideline (11). Clinical information at admission was collected including demographics, smoking history. Pulmonary function tests including forced vital capacity (FVC), FVC% predicted, diffusion capacity for carbon monoxide (DLCO), and DLCO% predicted were extracted for analysis. All subjects had UIP pattern on chest HRCT as defined by the guidelines from the American thoracic society and the European respiratory society(3, 11).

2.3 Statistical analysis

Data were expressed as mean±standard deviation (SD). t-Test or the Mann–Whitney U test was used for continuous variables. Categorical variables were compared by Chi-square test. The independent prognostic role of variables were evaluated by Cox proportional hazard analysis. Receiver operator characteristic (ROC) analyses were performed to calculate area under the ROC curve (AUC) of markers for predicting the prognosis of fibrosing ILD. Pearson correlation analysis was used to evaluate the relationship between markers and lung function parameters. All analyses were performed with SPSS software, version 23.0 and GraphPad Prism version 7 (Graph Pad Software Inc., La Jolla, CA, USA). Statistical significance was considered at the 0.05 levels.

3. Results

3.1 Baseline clinical characteristics of fibrosing ILD patients

The baseline clinical features of subjects with IPF (n = 132) and CTD-ILD characterized by UIP on HRCT (n = 207) were summarized in Table 1. Female gender, older age were more common in the IPF group (p < 0.001 and p < 0.001, respectively). Smoking history was similar. Red blood cell distribution width(RDW) levels, serum total bilirubin (TBIL) and direct bilirubin (DBIL) also differed between the two groups (p = 0.008, p < 0.001 and p = 0.001, respectively). Patients with CTD-ILD characterized by UIP on HRCT had a higher DLCO% predicted level compared with the IPF patients.

Table 1
Baseline clinical features

Variables	UIP(n = 339)	IPF(n = 132)	CTD-UIP(n = 207)	p value
Gender (M/F)	183/156	115/17	68/139	< 0.001
Smoking history (Y/N)	60/279	31/101	29/178	0.026
Age (years old)	62.49 ± 11.24	68.27 ± 8.71	58.80 ± 11.13	< 0.001
WBC count (×10 ⁹)	7.01 ± 2.07	7.11 ± 1.91	6.94 ± 2.16	0.46
RDW(%)	13.63 ± 1.25	13.42 ± 1.03	13.76 ± 1.35	0.008
PLT(×10 ⁹)	211.68 ± 71.57	190.62 ± 73.37	225.11 ± 67.21	< 0.001
TBil(umol/l)	8.99 ± 3.28	9.81 ± 3.32	8.48 ± 3.16	< 0.001
DBil(umol/l)	2.68 ± 1.22	2.96 ± 1.23	2.50 ± 1.18	0.001
LDH (U/L)	265.18 ± 77.13	254.52 ± 63.34	271.98 ± 84.20	0.031
B cells (×10 ⁹)	0.237 ± 0.161	0.244 ± 0.148	0.233 ± 0.169	0.550
NK cells (×10 ⁹)	0.263 ± 0.197	0.329 ± 0.229	0.222 ± 0.160	< 0.001
CEA (ng/ml)	2.61 ± 2.89	3.20 ± 2.21	2.24 ± 3.17	0.003
CYFRA21-1 (ng/ml)	4.36 ± 2.14	4.58 ± 2.04	4.22 ± 2.19	0.131
NSE (ng/ml)	16.58 ± 5.56	16.69 ± 6.74	16.51 ± 4.68	0.772
PaO ₂ /FiO ₂ ratio	367.20 ± 75.55	370.36 ± 86.27	364.76 ± 66.32	0.551
FVC% predicted	67.10 ± 17.29	66.72 ± 17.17	67.35 ± 17.41	0.746
FEV1% predicted	73.50 ± 18.44	73.25 ± 17.37	73.65 ± 19.13	0.847
DLCO% predicted	52.69 ± 21.43	49.47 ± 19.02	54.74 ± 22.32	0.027

3.2 Constructing a scoring system for predicting prognosis of fibrosing ILD

According to the final follow-up data, 339 fibrosing ILD patients were divided into survivors group (n = 259) and decedents group (n = 80). Cox proportional hazards models were used to examine the influence of variables on the prognosis of patients with fibrosing ILD. The multivariate cox regression analysis showed that smoking history (HR = 3.826, P = 0.001), age (HR = 1.043, P = 0.015), carcinoem-bryonic antigen (CEA) (HR = 1.059, P = 0.049), cytokeratin 21 – 1 (CYFRA21-1) (HR = 1.177, P = 0.004) and DLCO% predicted (HR = 0.979, P = 0.032) were independent prognostic factors for fibrosing ILD (Table 2).

Table 2
Prognostic factors for survival by univariate and multivariate Cox regression models in
fibrosing ILD patients

Variables	Univariate Cox Model			Multivariate Cox Model		
	HR	95.0% CI	p value	HR	95.0% CI	p value
CTD-UIP(Y)	2.234	1.428–3.496	< 0.001	1.857	0.835–4.134	0.129
Gender	1.376	0.883–2.144	0.159	0.369	0.133–1.024	0.056
Smoking history	5.096	3.279–7.920	< 0.001	3.826	1.686–8.683	0.001
Age (years old)	1.069	1.045–1.093	< 0.001	1.043	1.008–1.079	0.015
WBC count	1.163	1.054–1.282	0.003	1.008	0.843–1.206	0.926
RDW	1.391	1.216–1.591	< 0.001	1.075	0.837–1.381	0.572
PLT	1.000	0.997–1.003	0.765	0.999	0.994–1.003	0.591
TBil	0.964	0.897–1.035	0.310	0.890	0.775–1.023	0.101
DBil	1.015	0.853–1.207	0.871	1.260	0.808–1.966	0.308
LDH	1.003	1.001–1.006	0.002	1.002	0.997–1.006	0.493
B cells	0.710	0.180–2.797	0.624	1.733	0.348–8.634	0.502
NK cells	1.652	0.572–4.772	0.354	2.173	0.417–11.324	0.357
CEA	1.084	1.046–1.123	< 0.001	1.059	1.000–1.122	0.049
CYFRA21-1	1.374	1.290–1.463	< 0.001	1.177	1.053–1.316	0.004
NSE	1.051	1.015–1.087	0.004	1.015	0.970–1.061	0.520
PaO2/FiO2 ratio	0.993	0.990–0.997	< 0.001	0.998	0.993–1.002	0.302
FVC% predicted	0.955	0.940–0.970	< 0.001	1.010	0.956–1.066	0.732
FEV1% predicted	0.970	0.957–0.983	< 0.001	0.965	0.918–1.015	0.171
DLCO% predicted	0.949	0.937–0.960	< 0.001	0.979	0.959–0.998	0.032

The accuracy of independent prognostic factors for predicting the survival of fibrosing ILD was then evaluated by Receiver Operating Characteristics (ROC) analysis. The area under the ROC curve for CYFRA21-1 in predicting the survival of fibrosing ILD was 0.85 (95% CI, 0.80–0.90; $p < 0.001$). The prediction ability for smoking history, age, CEA and DLCO%predicted were listed in Table 3. Then, we constructed a simple clinical scoring system for predicting survival of fibrosing ILD with the variables of smoking history, age, CEA, CYFRA21-1 and DLCO%predicted (Table 4). ROC curve was calculated to compare the predictive value of the scoring system. The ROC curve was shown in Fig. 2. The area under

the curve of the scoring system for predicting survival of fibrosing ILD was 0.91 (95%CI: 0.87–0.94, $P < 0.001$). The cutoff value was 2.5 with their corresponding specificity (91.1%) and sensitivity (77.5%).

Table 3
Comparisons of ROC curve analysis for predicting the survival of fibrosing ILD patients

	AUC(95%CI)	p value	Cut-off value	Sensitivity	Specificity
Smoking history	0.69(0.61, 0.76)	< 0.001	-	-	-
Age (years old)	0.69(0.63, 0.76)	< 0.001	66.5years old	64.60%	66.30%
CEA	0.62(0.55, 0.70)	< 0.001	2.29ng/ml	60.80%	61.60%
CYFRA21-1	0.85 (0.80, 0.90)	< 0.001	4.34ng/ml	88.60%	74.40%
DLCO% predicted	0.84(0.79, 0.89)	< 0.001	40.1%	72.50%	87.30%

Table 4
Development of a clinical scoring system to predict survival of interstitial pneumonia characterized by UIP in HRCT

Variables	Cut-off value	Score
A		
Age	≤ 66.5 years	0
	> 66.5 years	1
C CEA	≤ 2.29 ng/ml	0
	> 2.29 ng/ml	1
CYFRA21-1	≤ 4.34 ng/ml	0
	> 4.34 ng/ml	1
D DLCO% predicted	$> 40.1\%$	0
	$\leq 40.1\%$	1
S Smoking history	No	0
	Yes	1

3.3 Correlations between prognostic factors and lung function parameters

Correlation analyses showed that DLCO%predicted levels were negatively correlated with age ($r=-0.225$, $p < 0.001$), CEA($r=-0.119$, $p = 0.028$) and CYFRA21-1($r=-0.292$, $p < 0.001$) (Fig. 3).

4. Discussion

The present study retrospectively compared the clinical and follow-up data between 259 survivors and 80 decedents with fibrosing ILD. In this study, we demonstrated that smoking history, age, CEA, CYFRA21-1 and DLCO% predicted could predict the survival of fibrosing ILD patients independently. A new predictive scoring system namely ACDS (age [A], CEA and CYFRA21-1 [C], DLCO% predicted [D], and smoking history [S]) was proposed. Importantly, we found that scoring system level was closely associated with the prognosis of fibrosing ILD patients. Furthermore, the increased age, CEA and CYFRA21-1 were positively associated with the severity of patients with fibrosing ILD.

Fibrosing ILD had similar biological and clinical behaviours which was characterised by progressive deterioration in lung function, progressive deterioration in lung function and high mortality rate(12–13). Investigating the prognostic value of markers across fibrosing ILD was of great importance to clinical evaluation and make continues to elucidate the approach to fibrosing ILD management. In the past few years, several serum markers were identified as simple and readily accessible biomarkers to predict the survival and severity of fibrosing ILD. There were researches studying tumor markers such as CEA, carbohydrate antigen 19 – 9 (CA 19 – 9) and CYFRA21-1 that might reflect the severity and prognosis of fibrosing ILD(14–16). One retrospective study by Fahim A et al., which included 41 non-smoking patients with idiopathic pulmonary fibrosis(IPF), reported that serum CEA concentration was elevated in approximately half of patients with IPF and was correlated with disease severity(17). These results were consistent with the finding of our study of CEA as a biomarker in fibrosing ILD patients. In our study, CEA was identified as an independent prognostic factor for fibrosing ILD. CEA is a glycoprotein involved in cell adhesion and is produced by colonic epithelium. It has reported that CEA localizes in metaplastic epithelium lining honeycombed bronchioles by immunohistochemical staining. As cuboidal pneumocytes are the predominant source of epithelial renewal in severe lung damage and fibrosis, these cells are the most likely source of CEA release(18).

In this study, elevated serum levels of CYFRA21-1 were observed in decedents group with fibrosing ILD. In a study by Vercauteren et al., higher level of CYFRA 21 – 1 in BAL of IPF patients resulted in worse survival in comparison with the CYFRA 21 – 1 low counterpart (19). The expression of CYFRA21-1 in the lung has been identified in bronchiolar epithelial cells and pneumocytes. Elevation of serum CYFRA21-1 concentration might be associated with lysis or regeneration of these cells (15). Furthermore, we demonstrated that serum CEA and CYFRA21-1 were significantly correlated with decreased DLCO%predicted in this study. The severity of ILD is usually based on pulmonary function test results such as DLCO%predicted(20). Thus, serum CEA and CYFRA21-1 levels might be useful for reflecting the severity of fibrosing ILD.

A large amount of studies reported that smoking was closely associated with the onset and progress of pulmonary fibrosis(21–22). A possible explanation may be that cigarettes contain the cytotoxic, mutagenic and proinflammatory substances. According to previous reports, these substances caused cellular oxidative stress, increased epithelial cell apoptosis, and dysregulation of immune responses,

which was responsible for the progress of pulmonary fibrosis(23–24). In addition, smoking affects the function of macrophages. It induced macrophage polarization to M2 phenotype that enhance the regression of inflammation and tissue remodeling(25). Therefore, smoking cessation could be a good way to slow down the development of pulmonary fibrosis in the patients with ILD.

In the past years, few models has been proposed to predict the severity and prognosis of IPF. Glasgow prognostic score (GPS) has been reported to play an important role in predicting mortality in patients with acute exacerbation of IPF(26). In our study, smoking history, age, CEA, CYFRA21-1 and DLCO% predicted were identified as independent factors for predicting the prognosis of fibrosing ILD. Moreover, based on these variables, a new predictive scoring system namely ACDS (age [A], CEA and CYFRA21-1 [C], DLCO% predicted [D], and smoking history [S]) was proposed. The scoring system was demonstrated to be as a predictive value for the survival of fibrosing ILD. Nevertheless, serum CEA and CYFRA21-1 levels might be useful for reflecting the severity of fibrosing ILD. However, it still needs further perspective study to verify the power of this scoring system based on multicenter and large population of fibrosing ILD patients.

Some limitations of this study should be noted. First, this was a retrospective and observational study of data obtained from a single center. In addition, the mechanism underlying the association of each biomarker with fibrosing ILD remains to be clarified in further in vivo and in vitro studies.

Conclusions

In conclusion, smoking history, age, CEA, CYFRA21-1 and DLCO% predicted were independent predictors of the prognosis of fibrosing ILD patients that offers the advantages of convenience, ease of accessibility and low cost. A new predictive scoring system namely ACDS may help predict prognosis in patients with fibrosing ILD. Serum CEA and CYFRA21-1 levels might be useful for reflecting the severity of fibrosing ILD.

Declarations

Ethics approval and consent to participate

The study was conducted according to the Declaration of Helsinki. This study was approved by Ethics Committee of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. The Ethics Committee of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School waived the need for informed consent as the study was retrospective and the data were analyzed anonymously.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing Interests

All authors declare that there is no conflict of interests regarding the publication of this paper.

Conflicts of Interest

The authors declare that there is neither conflict of interest nor financial gain regarding the publication of this paper.

Funding statement

None declared.

Authors' contributions

S-Y S, L-L C, X-Q L, C W, M Y and Y-L X were involved in conception and design. S-Y S, L-L C, X-Q L and M Y were involved in analysis and interpretation. S-Y S, and L-L C were involved in acquisition of data. S-Y S, X-Q L, M Y and Y-L X were involved in writing and revisions.

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Figures

Figure 1

Flow of participants through the study

Figure 2

ROC curve of the scoring system for predicting survival of fibrosing ILD

Figure 3

Correlations between variables levels and lung function parameters in patients of fibrosing ILD at baseline