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Original Research

Prognostic value of serum oncomarkers for patients hospitalized with acute exacerbation of interstitial lung disease

Cuirong Ba, Chunguo Jiang, Huijuan Wang, Xuhua Shi, Jiawei Jin and Qiuhong Fang

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Abstract

Background: Different types of inflammatory processes and fibrosis have been implicated in the pathogenesis of interstitial lung disease (ILD), a heterogeneous, diffuse, parenchymal lung disease. Acute exacerbation (AE) of ILD is characterized by significant respiratory deterioration and is associated with high mortality rates. Several serum oncomarkers have been used to determine the prognosis of ILD; however, the prognostic value of serum oncomarker levels in patients with AE-ILD remains unclear.

Objective: To evaluate the prognostic value of serum oncomarker levels in patients with AE-ILD and its main subtypes.

Design: Retrospective study

Methods: The serum levels of 8 oncomarkers in 281 patients hospitalized with AE-ILD at our institution between 2017 and 2022 were retrospectively reviewed. The baseline characteristics and serum oncomarker levels were compared between the survival and non-survival groups of AE-ILD and its main subtypes. Multivariate logistic regression analysis was performed to identify independent prognosis-related markers, and the best prognostic predictor was analyzed using receiver operating characteristic curve (ROC) analysis.

Result: Idiopathic pulmonary fibrosis (IPF; $n = 65$), idiopathic nonspecific interstitial pneumonia (iNSIP; $n = 26$), and connective tissue disease-associated interstitial lung disease (CTD-ILD; $n = 161$) were the three main subtypes of ILD. The in-hospital mortality rate among patients with AE-ILD was 21%. The serum oncomarker levels of most patients with AE-ILD and its main subtypes in the non-survival group were higher than those in the survival group. Multivariate analysis revealed that ferritin and cytokeratin 19 fragments (CYFRA21-1) were independent prognostic risk factors for patients hospitalized with AE-ILD or AE-CTD-ILD. CYFRA21-1 was identified as an independent prognostic risk factor for patients hospitalized with AE-IPF or AE-iNSIP.

Conclusion: CYFRA21-1 may be a viable biomarker for predicting the prognosis of patients with AE-ILD, regardless of the underlying subtype of ILD. Ferritin has a prognostic value in patients with AE-ILD or AE-CTD-ILD.

Keywords: acute exacerbation, idiopathic pulmonary fibrosis; interstitial lung disease, oncomarker, tumor marker

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Correspondence to:
Qiuhong Fang
Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chaoyang Hospital, Capital Medical University, No. 8, Gongren Tiyuchang South Road, Chaoyang District, Beijing 100020, China
fangmaster123@163.com

Cuirong Ba
Department of Respiratory Medicine, Beijing Ditan Hospital, Capital Medical University, China

Chunguo Jiang
Huijuan Wang
Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Xuhua Shi
Department of Immunology and Rheumatology, Beijing Institute of Respiratory Medicine and Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Jiawei Jin
Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

The Clinical Research Center, Beijing Institute of Respiratory Medicine and Beijing Chaoyang Hospital Jingxi Branch, Capital Medical University, Beijing, China

Introduction

Interstitial lung disease (ILD), a heterogeneous, diffuse, parenchymal lung disease with different underlying inflammation and fibrotic processes, is characterized by the progressive impairment of lung function, reduced gas exchange, and

dyspnea. Idiopathic interstitial pneumonia (IIP) has been divided into the following subtypes: idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (iNSIP), and cryptogenic organizing pneumonia (COP), etc. Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a secondary form of ILD. Acute respiratory deterioration in the short term has been observed in some patients with ILD, and this phenomenon is known as acute exacerbation of ILD (AE-ILD). The incidence of AE-ILD has also been reported in patients with IPF, non-IPF IIP, and secondary ILD. AE-ILD is associated with high mortality rates, with 90-day mortality rates of 57%, 29%, and 33% in the IPF, non-IPF IIP, and secondary ILD populations, respectively, post-AE-ILD.[1] The in-hospital mortality rates of acute exacerbation of IPF (AE-IPF) and AE-ILD are high, with that of AE-IPF exceeding 50%[2,3] High-resolution computerized tomography (HRCT) and lung function play a significant role in the diagnosis and prognostication of AE-ILD; however, there is a need to identify additional practical and workable biomarkers.

Numerous studies have investigated the relationship between serum oncomarkers and the incidence of ILD[4,5] Higher levels of serum oncomarkers, which are highly linked with the severity of ILD, have been detected in patients with ILD. Consequently, they have been proposed as risk factors for ILD.[5,6] The incidence of acute exacerbation (AE) results in unfavorable effects. The prognostic significance of serum biomarkers in patients with AE-ILD remains unclear. Therefore, this study aimed to investigate the prognostic value of serum biomarkers in patients with AE-ILD and compare the serum oncomarker levels of patients with AE-ILD with those of patients with different in-hospital outcomes (survival *versus* non-survival).

Methods

Patients

The data of adult patients meeting the diagnostic criteria proposed by the American Thoracic Society consensus statement[7] for AE-ILD who were hospitalized at the Beijing Institute of Respiratory Medicine and Beijing Chaoyang Hospital between January 2017 and June 2022 with their first episode of AE-ILD were retrospectively reviewed. Patients with sarcoidosis, malignant disease, a history of cancer, other conditions that could alter the oncomarker levels, recent history of clinically significant infection (such as viral hepatitis), or severe liver and kidney failure were excluded. In total, 281 patients with AE-ILD hospitalized for the first episode of AE-ILD were included in this study. Data regarding the age, sex, body mass index (BMI), smoking index, onset, type of underlying ILD, comorbidities, oncomarkers levels, use of antifibrotic or immunosuppressive agents prior to hospitalization, and in-hospital prognosis (survival or non-survival) were collected and analyzed. Based on diagnostic criteria,[8–13] the following subtypes of ILD were observed in the study population: IPF, iNSIP, CTD-ILD, vasculitis associated with interstitial pneumonia (AAV-IP), chronic hypersensitivity pneumonia (CHP), and COP. Peripheral blood serum samples were collected on the morning of the second day of hospitalization. The oncomarker levels in these samples were assessed *via* chemiluminescence immunoassay. The oncomarker levels were as follows: squamous cell carcinoma antigen (SCC), <1.5 ng/mL; carcinoembryonic antigen (CEA) <5 ng/mL; carbohydrate antigen (CA) 199 (CA199), <37 U/mL; CA125, <30.2 U/mL; CA724, <8.2 U/mL; ferritin, 15–200 ng/mL; cytokeratin 19 fragment (CYFRA21-1), <2.08 ng/mL; and neuron-specific enolase (NSE), <16.3 ng/mL.

Diagnostic criteria

AE-ILD was diagnosed based on the criteria set forth in the International Working Group report on AE-IPF in 2016.[7] Patients who met the following criteria were diagnosed with AE-ILD: acute worsening or development of dyspnea within <1 month, new bilateral ground-glass opacity and/or consolidation superimposed on fibrosis on the HRCT images, deterioration not fully explained by fluid overload or cardiac failure, and pre-existing ILD.

The diagnosis of AE-ILD was reassessed after enrollment by two trained pulmonologists at our institution. The past and present medical records, test results, and the unique features of chest HRCT images were reviewed thoroughly. Multidisciplinary discussions were conducted to

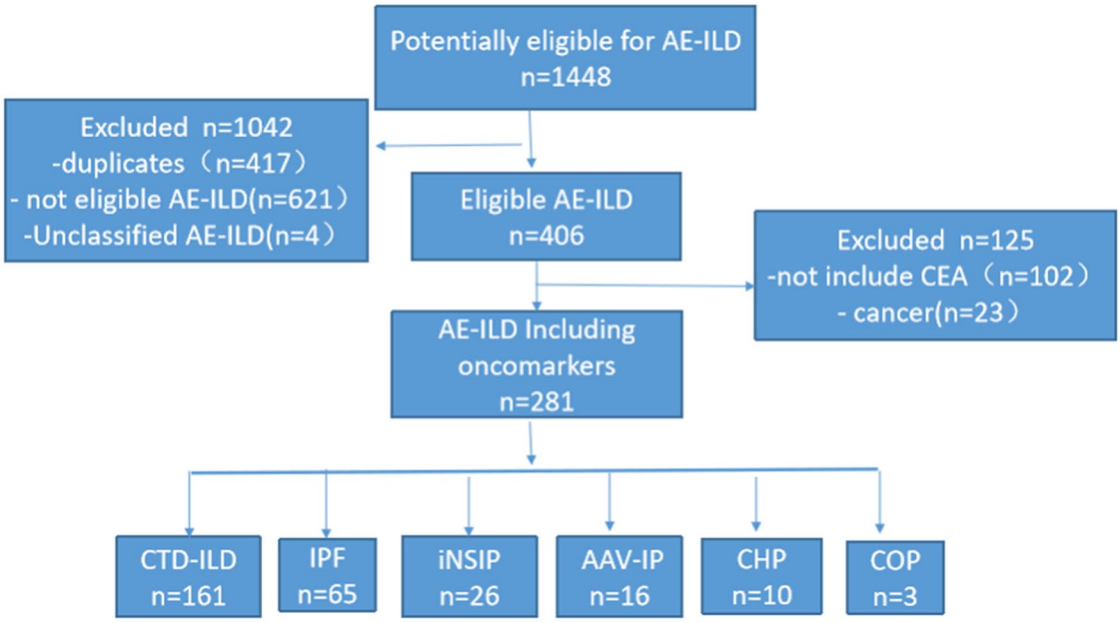

Figure 1. The study's flow diagram.
AE-ILD, acute exacerbation of interstitial lung disease; CEA, carcinoembryonic antigen; CTD-ILD, interstitial lung disease associated with connective tissue disease; iNSIP, idiopathic nonspecific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis.

confirm the diagnosis of each underlying subtype of ILD in accordance with the guidelines or ILD consensus statement.[8–13] The reporting of this study conforms to the STARD guideline.[14]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism 8.0 (San Diego, CA, USA), and MedCalc 20 (MedCalc Softward Ltd, Ostend, Belgium). Continuous variables with normal distribution are presented as mean ± standard ($X \pm S$), whereas continuous variables with non-normal distribution are presented as median [first quartile, third quartile; M(Q1, Q3)]. Categorical variables are presented as frequencies and proportions. Independent samples *T*-test or Mann–Whitney *U* test was used to analyze continuous variables. The chi-square test was used to compare the frequencies. Multiple interpolation method is used for missing values. Spearman analysis was used to analyze the correlation coefficients (range: −1 to 1) among the oncomarkers. Logistic regression analysis was performed to screen for independent prognosis-related oncomarkers in patients with AE-ILD and its major subtypes. Receiver operating characteristic curves (ROCs) were used to analyze the oncomarkers with the highest prognostic predictive value. A *p*-value of <0.05 was considered statistically significant.

Result

Patient characteristics

Figure 1 illustrates the screening flow of patients with AE-ILD and its subtypes containing oncomarkers. A total of 281 patients eligible for AE-ILD were enrolled in this study, among whom 56.94% were male. The median age and mean BMI of the participants were 65 years old and $24.32 \pm 3.93\,kg/m^2$, respectively. iNSIP, IPF, and CTD-ILD accounted for 9.25%, 23.13%, and 57.3% of all cases of AE-ILD. AAV-IP, CHP, and COP accounted for 10.32% of the total cases. The in-hospital mortality rates of the patients with IPF, iNSIP, and CTD-ILD were 27.69%, 34.62%, and 18.01%, respectively. The overall in-hospital mortality rate was 21.00%. However, no significant differences were observed among the IPF, iNSIP, and CTD-ILD subgroups (in-hospital mortality rates: 27.69%, 34.62%, and 18.01%, respectively). The AE-CTD-ILD included subclasses of rheumatoid arthritis (RA), idiopathic inflammatory

Table 1. Comparison between the baseline characteristics of the non-survival and survival groups of patients with AE-ILD.

AE-ILD	Total ($n=281$)		Survival ($n=222$)		Non-survival ($n=59$)		p
	N/X/M	%/S/(Q1,Q3)	N/X/M	%/S/(Q1,Q3)	N/X/M	%/S/(Q1,Q3)	
Gender (men)	160	56.94%	118	53.15%	42	71.19%	**0.013**
Age	65	(60,72)	65	(60,72)	67	(60,72)	0.623
BMI	24.32	3.93	24.34	4.01	24.20	3.44	0.874
Smoke (year × count)	0	(0,600)	0	(0,600)	189	(0,600)	0.378
Onset time (m)	24	(3,60)	24	(3,60)	24	(4,48)	0.869
Antifibrotic pre-hospitalization	27	9.61%	21	9.50%	6	10.20%	0.869
Immunosuppressive pre-hospitalization	56	19.93%	40	18.00%	15	25.40%	0.203
Hypertension	106	37.72%	84	37.84%	22	37.29%	0.938
Diabetes mellitus	87	30.96%	67	30.18%	20	33.90%	0.583
Coronary artery disease	96	34.16%	65	29.28%	31	52.54%	**0.001**
Cerebrovascular disease	14	4.98%	10	4.50%	4	6.78%	0.502
COPD	16	5.69%	11	4.95%	5	8.47%	0.300
Bronchial asthma	10	3.56%	9	4.05%	1	1.69%	0.694
PAH	80	28.47%	56	25.23%	24	40.68%	**0.019**

The bold values represent $p < 0.05$.
AE-ILD: acute exacerbation of interstitial lung disease; BMI: body mass index (kg/m^2); COPD, chronic obstructive pulmonary disease; PAH, pulmonary artery hypotension.

myopathy, primary Sjögren's syndrome (pSS), and systemic sclerosis (SS), et al, and there was no significant difference in in-hospital motality among these subclasses. Table 1 presents the prevalence of various comorbidities among the patients with AE-ILD.

Comparison between the baseline characteristics of the non-survival and survival groups

Table 1 and Supplemental Table 1 summarize the results of the comparison between the baseline characteristics of the non-survival and survival groups. The non-survival group comprised a higher proportion of male patients with AE-ILD, a higher proportion of patients with a history of coronary artery disease, and a higher proportion of patients with pulmonary artery hypertension (PAH) than the survival group. The proportion of patients with PAH in the IPF subgroup was higher than that in the non-survival group. No significant differences were observed between the groups in terms of the prevalence of iNSIP. The proportions of patients with a history of coronary artery disease and patients who received immunosuppressive agents pre-hospitalization in the CTD-ILD subgroup were higher than those in the non-survival group.

Comparison between the serum oncomarker levels of the non-survival and survival groups

The serum levels of the following eight oncomarkers were higher in the patients with AE-ILD: SCC (46.46%), CEA (35.23%), CA199 (51.85%), ferritin (64.65%), CYFRA21-1 (92.06%), CA125 (56.46%), NSE (61.87%), and CA72-4 (24.14%). The serum levels of all oncomarkers, except for that of CA125, were significantly higher in the non-survival group,

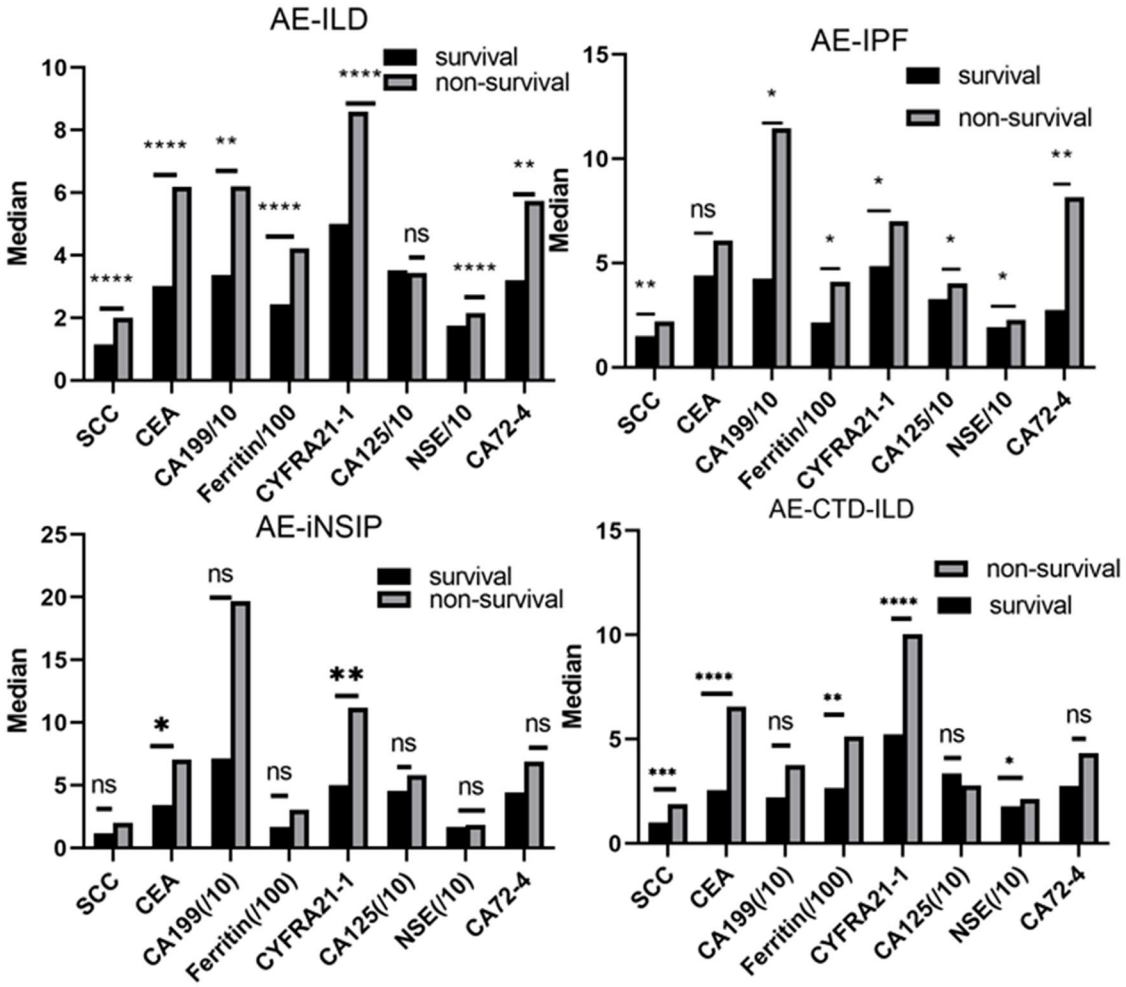

Figure 2. Comparison between the serum oncomarker levels of the non-survival and survival groups in patients with AE-ILD and its major subtypes.
The bold values represent $p < 0.05$.
AE-ILD, acute exacerbation of interstitial lung disease; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AE-iNSIP, acute exacerbation of idiopathic nonspecific interstitial pneumonia; AE-CTD-ILD, acute exacerbation of interstitial lung disease associated with connective tissue; CA724 (<8.2 U/mL), Carbohydrate antigen724; CA199 (<37 U/mL), Carbohydrate antigen199; CEA, carcinoembryonic antigen; CA125 (<30.2 U/mL), Carbohydrate antigen125; CYFRA21-1 (<2.08 ng/mL), cytokeratin 19 fragments; Ferritin (15–200 ng/mL); NSE (<16.3 ng/mL): neuron-specific enolase; SCC (<1.5 ng/mL), squamous cell carcinoma antigen.

[median levels: SCC (2.0 *versus* 1.2 ng/mL, $p < 0.001$), CEA (6.2 *versus* 3.0 ng/mL, $p < 0.001$), CA199 (65.9 *versus* 33.6 U/mL, $p = 0.003$), ferritin (−(424.3 *versus* 257.5 ng/mL, $p < 0.001$), CYFRA21-1 (8.7 *versus* 5.2 ng/mL, $p < 0.001$), NSE (23.3 *versus* 17.4 ng/mL, $p < 0.001$), and CA72-4 (7.0 *versus* 3.4 U/mL, $p = 0.004$)].

The serum levels of all eight oncomarkers, except for that of CEA, were higher in the non-survival group than those in the survival group for the IPF subtype.

Only the serum CEA and CYFRA21-1 levels were higher in the non-survival group for the iNSIP subtype.

The serum levels of all eight oncomarkers, except for those of CA199, CA125, and CA72-4, were higher in the non-survival group for the CTD-ILD subtype. Figure 2 presents the detailed serum levels. No significant differences were observed among the subclasses of patients with AE-CTD-ILD in terms of the levels of the eight serum biomarkers (Supplemental Table 3).

Table 2. Multivariate regression analysis for identifying independent risk factors of prognosis in patients with AE-ILD and its main subtypes.

Disease	Variable	OR	95% CI		*p*
AE-ILD (adjusting for age, gender, coronary artery disease, and PAH)	CYFRA21-1	1.055	1.016	1.094	**0.005**
	Ferritin	1.001	1.001	1.002	**0.000**
AE-IPF (adjusting for age and PAH)	CYFRA21-1	1.155	1.033	1.290	**0.011**
AE-iNSIP (adjusting for age)	CYFRA21-1	1.447	1.044	2.006	**0.027**
AE-CTD-ILD (adjusting for age, coronary artery disease, and immunosuppressive pre-hospitalization)	CYFRA21-1	1.036	1.003	1.070	**0.031**
	Ferritin	1.001	1.001	1.002	**0.001**

The bold values represent $p < 0.05$.
AE-CTD-ILD, Acute Exacerbation of interstitial lung disease associated with connective tissue; AE-ILD, Acute Exacerbation of Interstitial Lung Disease; AE-IPF, Acute Exacerbation of idiopathic pulmonary fibrosis; AE-iNSIP, Acute Exacerbation of idiopathic nonspecific interstitial pneumonia; 95 CI, 95% Confidence interval; CYFRA21-1(<2.08 ng/mL): cytokeratin 19 fragments; ferritin(15–200 ng/mL); OR, Odds ratio.

Multivariate regression analysis for identifying independent risk factors of prognosis in patients with AE-ILD and its main subtypes

Correlations were observed between the serum CA199 and CEA levels in patients with AE-ILD (0.937) and AE-CTD-ILD (0.967). Significant correlations were observed between the serum SCC antigen and CEA levels in patients with AE-IPF ($p = 0.996$). Supplemental Table 2 presents the correlation among the other oncomarkers. Multivariate regression analysis incorporating the two indicators with significant correlations yielded four prognostic prediction models for patients with AE-ILD and its main subtypes (Table 2).

(1) Ferritin [odds ratio (OR): 1.001, 95% CI: 1.001–1.002, $p < 0.001$] and CYFRA21-1 (OR: 1.055, 95% CI: 1.016–1.094, $p = 0.005$) were identified as independent prognostic risk variables for patients with AE-ILD after adjusting for age, sex, coronary artery disease, and PAH.
(2) CYFRA21-1 (OR: 1.155, 95% CI: 1.033–1.29, $p = 0.011$) was identified as the independent prognostic factor for patients with AE-IPF after adjusting for age and PAH.
(3) CYFRA21-1 (OR: 1.447, 95% CI: 1.044–2.006, $p = 0.027$) was identified as an independent prognostic factor for patients with AE-iNSIP after adjusting for age.
(4) Ferritin (OR: 1.001, 95% CI: 1.001–1.002, $p = 0.001$) and CYFRA21-1 (OR: 1.036, 95% CI: 1.003–1.070, $p = 0.031$) were identified as independent prognostic factors for patients with AE-CTD-ILD after adjusting for age, coronary artery disease, and the use of immunosuppressive pre-hospitalization.

The predictive values of independent prognostic risk factors based on ROC curves were as follows:

(1) The area under the ROC curve (AUC) for ferritin was 0.690 (cut-off = 343.3 ng/mL, sensitivity = 67.8%, and specificity = 63.51%), whereas the AUC for CYFRA21-1 was 0.720 (cut-off = 7.23 ng/mL, sensitivity = 64.41%, and specificity = 72.07%) for AE-ILD. No significant differences were observed between the prognostic values of ferritin and CYFRA21-1 ($p = 0.555$). The AUC of the combination of ferritin and CYFRA21-1 was superior to that of ferritin ($p = 0.006$) but not to that of CYFRA21-1 ($p = 0.288$).
(2) The AUC of CYFRA21-1 was 0.720 (cut-off = 4.03 ng/mL, sensitivity = 74.44%, and specificity = 48.94%) for AE-IPF.
(3) The AUC for CYFRA21-1 was 0.857 (cut-off = 5.49 ng/mL, sensitivity = 100%, and specificity = 63.16%) for AE-iNSIP.
(4) The AUC of ferritin was 0.698 (cut-off = 486.8 ng/mL, sensitivity = 55.17%, and specificity = 76.52%) for AE-CTD-ILD. The AUC of CYFRA21-1 was 0.710

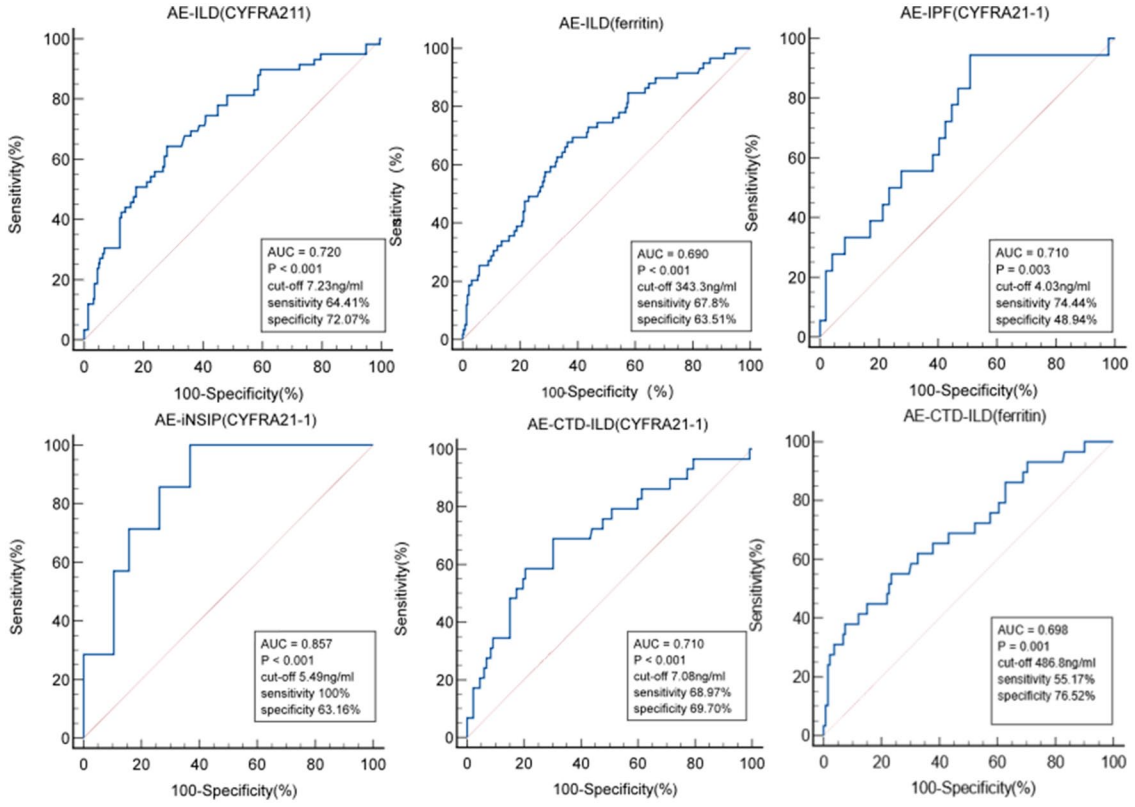

Figure 3. The ROC curves of independent prognostic risk factors in patients with AE-ILD and its major subgroups.
The bold values represent $p < 0.05$.
AE-CTD-ILD, acute exacerbation of interstitial lung disease associated with connective tissue; AE-ILD, acute exacerbation of interstitial lung disease; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AE-iNSIP, acute exacerbation of idiopathic nonspecific interstitial pneumonia; AUC, area under curve; CYFRA21-1, cytokeratin 19 fragment.

(cut-off = 7.08 ng/mL, sensitivity = 68.97%, and specificity = 69.70%). No significant differences were observed between the prognostic values of ferritin and CYFRA21-1 ($p = 0.870$). Combining ferritin with CYFRA21-1 led to the AUC increasing to 0.763 (sensitivity = 55.17% and specificity = 87.12%); however, this AUC was not superior to those of ferritin ($p = 0.072$) or CYFRA21-1 ($p = 0.391$). Figure 3 presents the detailed results.

Discussion

ILD is a diffuse parenchymal lung disease that primarily affects the alveolar units and surrounding alveolar tissues. It invades the pulmonary interstitium and eventually results in pulmonary fibrosis. AE-ILD is a serious clinical event associated with high mortality rates and morbidity that occurs during the course of the development of ILD.[15] The identification of its indicators plays a crucial role in understanding the severity and prognosis of AE-ILD. The present study examined the serum levels of oncomarkers to determine the prognosis of patients with AE-ILD.

The serum levels of eight oncomarkers, particularly those of CA199, ferritin, CYFRA21-1, CA125, and NSE (elevated in > 50% of all cases), were generally elevated in patients with AE-ILD in the present study. The serum level of CYFRA21-1 was the highest (92.06%), followed by that of ferritin (64.65%). Most oncomarkers are not tumor-specific antigens and originate from proliferating epithelial cells rather than specific organs or systems.[16,17] The serum oncomarker levels may be elevated in patients with

chronic lung disease without cancer.[18] For instance, the serum CA199[19] and CA125[6] levels are elevated in patients with pulmonary fibrosis.

CEA has been detected in the honeycomb-containing bronchiolar epithelium and lung tissues of patients with IIP. The serum CEA levels are elevated in approximately half of the patients with IPF.[20] CEA may serve as a biomarker for a subtype in patients with non-IPF-ILD.[21] Increased serum CA125 levels have been associated with a six-fold increase in the risk of developing ILD in patients with RA.[22] The serum CA125, CEA, and NSE levels of patients with pSS-ILD are significantly higher than those of patients without pSS. Similarly, the serum oncomarker levels of patients with ILD can be significantly elevated.[5] This increase may be attributed to the following mechanisms: 1. Tumor-related mechanism: patients with ILD have a higher risk of developing lung cancer and a poorer prognosis.[23–25] It may be linked to (1) common risk factors, such as smoking, infection, exposure to harmful substances, and chronic lung injury[26]; (2) a common molecular mechanism, wherein ILD and cancer are triggered by the same signaling pathway[27]; and (3) a protease that plays an important role in the development of malignant tumor is linked to the abnormal proliferation of pulmonary fibroblasts, and the process of these cells invading the extracellular matrix is similar to that occurring in metastatic tumor cells. Although cancer cells are usually detected in fibrotic areas, they have also been detected at non-fibrotic sites.[26] Certain oncomarkers, such as Ca153 (which plays an important role in the pathogenesis of IPF), are directly involved in the pathogenesis of ILD.[28] The serum CA125, CEA, and NSE levels may be directly involved in the pathogenesis of pSS-ILD.[6]

CA19-9 and CA-125 are markers of epithelial damage.[21] The elevation of serum CA19-9 levels in ILD may be caused by the regeneration of the damaged epithelial in the lung.[29] The positive correlation observed between the CA19-9 levels and disease progression may be attributed to the active phase (initiation) of the disease as well as extensive epithelial regeneration.[30] CA19-9 is also produced by the bronchial glands, and the bronchial gland cells proliferate and produce CA19-9 when chronic pulmonary fibrosis occurs.[31] Furthermore, inflammatory cells may also produce oncomarkers,[32] and the increased expression of CA19-9 may be associated with lung inflammation.[31]

The serum levels of oncomarkers, such as SCC, CYFRA21-1, CEA, CA199, CA72-4, ferritin, and NSE, in the non-survival group of patients with AE-ILD were significantly higher than those in the survival group. This finding indicates that oncomarkers may be correlated with the severity and prognosis of ILD, which is consistent with the findings of previous studies. Kodamage *et al.* reported that elevated serum CA199 levels in patients with IPF may be associated with poor prognosis. Balestro *et al.* reported that CA19-9 may be a marker of the severity of the disease, especially in patients with rapidly progressing IPF.[28] CA19-9 has been used for the diagnosis and prediction of ILD related to MPO-AAV.[33] Approximately half of the patients with IPF have elevated serum CEA levels, which correlates with the severity of the disease.[20]

The CEA levels show a significant inverse association with lung function and the severity of fibrosis.[34–36] Moreover, it has been associated with a shorter survival rate in patients with ILD. The serum CEA level is also a prognostic factor in patients with non-IPF-ILDs[5] and an indicator of poor prognosis in patients with rapid progressive (RP)-ILD.[35] CEA and CA19-9, which act as markers of disease severity in patients with CTD-ILD, are both produced by lung epithelial cells.[36] An elevated serum CA125 level at 3 months is associated with an increased risk of death in patients with IPF.[21] The serum NSE level has been used to evaluate the severity of silicosis.[37] The oncomarker levels may increase more significantly in patients with AE-ILD and are associated with poorer outcomes as infection is a common cause of AE-ILD. The serum ferritin levels are associated with the prognosis of patients with AE-IPF.[38] However, the effect of different oncomarkers on the prognosis of patients with AE-ILD is unknown.

CYFRA21-1, which was elevated in the largest proportion of patients with AE-ILD, was identified as the best prognostic marker for patients with AE-ILD or its major subgroups. Additionally, it had a lower cut-off value than that for AE-CTD-ILD and a greater prognostic correlation coefficient for AE-IPF and AE-iNSIP. This finding differs from those of previous reports. CYFRA21-1, a soluble fragment of keratin CK19, is mainly found in tissues or organs that contain epithelial cells, such as the lungs, bladder, and uterus. CYFRA21-1 is expressed only in the bronchioles

of the airways and alveolar epithelial cells of the lungs; however, its levels are elevated in benign diseases, such as acute pulmonary infection, tuberculosis, and ILD. Dobashi *et al.* reported that the serum and bronchoalveolar lavage fluid (BALF) levels of CYFRA21-1 are elevated in patients with ILD who are cancer-free.[39] CYFRA21-1 is expressed in a broader spectrum of epithelial cell types than CA125 or CA19-9 in the lungs of patients with IPF. Furthermore, CYFRA 21-1 is expressed in epithelial cells above the fibroblast foci and may serve as an indirect marker of many fibroblast foci. Thus, it has the potential to become a more informative serial biomarker in patients with IPF.

CYFRA 21-1 may play an important role in the diagnosis and treatment of patients with IPF as a biomarker for epithelial damage and turnover.[40] This may also explain the superior prognostic value of CYFRA21-1 compared with that of other oncomarkers, such as CEA and CA199, in the present study. Neutrophils and eosinophils may produce proteases and oxidants, which may lead to epithelial cell damage and the release of CYFRA21-1 in the lungs.[27] Infectious factors often induce AE-ILD *via* the elevated neutrophil levels, which damage epithelial cells in the lung. Consequently, the CYFRA21-1 levels are significantly elevated in patients with AE-ILD. The present study revealed that CYFRA21-1 is associated with the prognosis of patients with AE-ILD and that this association was stronger in patients with AE-IIP than in those with AE-CTD-ILD. This finding suggests that the degree of fibrosis may be related to the prognosis. Thus, this study is the first to report the predictive value of CYFRA21-1 for AE-ILD and its main subtypes.

The serum ferritin levels in the non-survival group of patients with AE-ILD, AE-IPF, and AE-CTD-ILD were significantly higher than those in the survival group in the present study. This finding may have contributed to the lack of statistical significance in the increase in the prevalence of AE-iNSIP. In terms of elevated serum levels, the serum ferritin levels followed those of CYFRA21-1. Moreover, iron is stored with ferritin in our bodies. In addition to infectious and inflammatory cells, certain malignant tumor cells may be able to synthesize and secrete ferritin. Ferritin is often used to determine the severity of disease and the level of infection. Furthermore, it has been used to identify patients with RP-ILD.[41] A serum ferritin level of >2200 ng/mL has been used to predict death within half a year following RP-ILD in patients with MDA5+DM.[42] These findings indicate that infections are common among patients with AE-ILD and that the severity of infection may affect the prognosis. This finding is supported by the fact that infections are typically the underlying cause of AE-ILD. Inflammation may be the cause of elevated oncomarker levels.[32] Consequently, oncomarkers derived from epithelial cells may be elevated in ILD caused by infectious agents that harm lung epithelial cells. The results of the present study indicate that ferritin has a prognostic value for patients with AE-ILD or AE-CTD-ILD but not for those with AE-IPF and AE-iNSIP. The findings of the present study indicate that patients with AE-CTD-ILD may have a greater degree of infection than those with AE-IIP. The prognostic value of ferritin combined with CYFRA21-1 was superior to that of ferritin alone but not superior to that of CYFRA21-1 alone for patients with AE-CTD-ILD. Thus, CYFRA21-1 has a higher prognostic significance for patients with AE-ILD. The present study, for the first time, reports these findings. However, it is difficult to obtain BALF from patients with AE-ILD as they cannot undergo tracheoscopy owing to their fragile condition. Moreover, it can be difficult to identify whether infection is the cause of illness in these patients. Therefore, the proportion of infections was not calculated in this study.

Limitations

This was a retrospective study with no control group. In addition, patients with stable ILD were not included in the comparison groups, and the sample size of the AE-iNSIP subtype was relatively small. Thus, the conclusions may have certain limitations. Moreover, the low specificity of CYFRA21-1 and ferritin limits their prognostic and clinical value. Furthermore, the use of certain prehospital drugs, such as immunosuppressive and antifibrotic therapies, may not have been documented adequately. Consequently, the conclusions drawn from these data have considerable limitations as the type, dosage, and duration of immunosuppressant therapy had not been documented completely. Further prospective studies and molecular experiments must be conducted in the future to validate these findings.

Conclusion

The present study revealed that CYFRA21-1 showed good prognostic value for patients with AE-ILD and its major subtypes. Ferritin also exhibited prognostic value for predicting AE-ILD and AE-CTD-ILD. Therefore, the serum CYFRA21-1 and ferritin levels should be considered when assessing the prognoses of patients with AE-ILD.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (2021-KE-295) in May 2021, and all patient information in this study was handled anonymously. As it is a retrospective study, patient consent to participate has been waived by the ethics committee.

Consent for publication

Not applicable.

Author contributions

Cuirong Ba: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review & editing.

Chunguo Jiang: Methodology; Software; Visualization; Writing – review & editing.

Huijuan Wang: Methodology; Software; Writing – review & editing.

Xuhua Shi: Formal analysis; Writing – review & editing.

Jiawei Jin: Formal analysis; Writing – review & editing.

Qiuhong Fang: Formal analysis; Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

ORCID iDs

Cuirong Ba https://orcid.org/0000-0002-8241-0841

Chunguo Jiang https://orcid.org/0000-0003-4577-7529

Qiuhong Fang https://orcid.org/0000-0003-3012-8008

Supplemental material

Supplemental material for this article is available online.

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