Correlation between serum bilirubin levels and the severity as well as the prognosis of idiopathic pulmonary fibrosis

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Abstract

Bilirubin exerts antioxidant activity that has been associated with respiratory diseases. However, the relationship between serum bilirubin levels and idiopathic pulmonary fibrosis (IPF) is not clear. Therefore, in this study, we evaluated the relationship between serum bilirubin levels and the severity as well as the prognosis of IPF. One hundred and forty-six patients with IPF and 69 healthy individuals as the control group were enrolled as a derivation cohort. Routine blood examination and pulmonary function tests were performed and serum bilirubin levels were measured. To validate the value of serum bilirubin levels to predict the survival of patients with IPF, 40 additional IPF patients were included as a validation cohort. IPF patients were followed-up. Patients with IPF had significantly lower levels of serum total bilirubin (TBIL) and direct bilirubin (DBIL) than those in the control group ($P < 0.05$). Patients with acute exacerbation of IPF (AE-IPF) had significantly lower levels of serum TBIL and IBIL than those in patients with stable IPF ($P < 0.05$). The area under the receiver operating characteristic curve (AUROC) of serum TBIL levels for the prediction of the incidence of AE-IPF was 0.72 (95% CI: 0.56–0.87, $P = 0.0057$). The best cutoff value of serum TBIL level to predict the survival of patients with IPF was 8.8 μmol/l (AUC $= 0.75$, 95% CI: 0.64–0.87, $P = 0.022$). The log-rank test showed a significant difference in survival between the two groups (TBIL ≤ 8.8 μmol/l and TBIL >8.8 μmol/l) in derivation and validation cohort. Cox multiple regression analysis indicated that serum TBIL levels were an independent prognostic factor for IPF prognosis (HR $= 0.582$, $P = 0.026$). Serum TBIL levels might be useful for reflecting the severity and predicting the survival of patients with IPF.

Keywords

Bilirubin, idiopathic pulmonary fibrosis, acute exacerbation, prognosis

Introduction

As the main end-product of heme degradation, bilirubin is cleared from the liver and conjugated to form water-soluble direct bilirubin that is secreted into bile. Serum bilirubin exhibits anti-oxidation, anti-inflammation and anti-cancer properties and has been associated with a wide array of aging-associated pathologic conditions including diabetes, metabolic syndrome, coronary artery disease, cancer.[1–3] Furthermore, serum bilirubin

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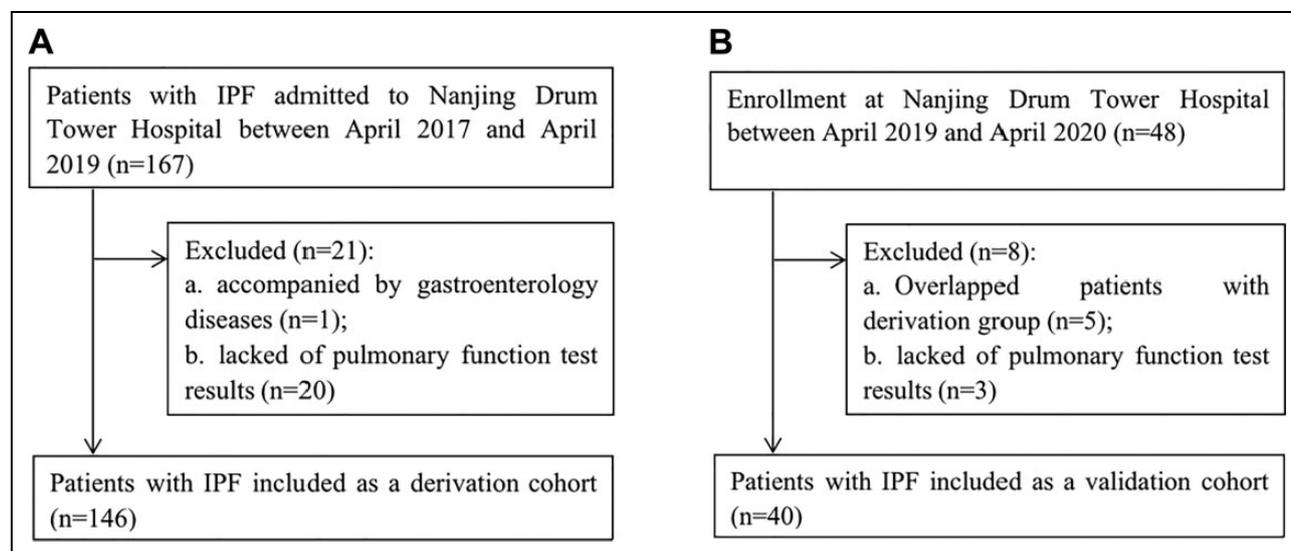**Corresponding authors:**
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Figure 1. Flow diagram describing the selection of the study population: (a) derivation cohort and (b) validation cohort.

is routinely used as a marker of hepatobiliary and hematological disorders.[4] In addition, the relationship between serum bilirubin and pulmonary disease has received increasing attention, with an inverse association between serum bilirubin and pulmonary disease reported in chronic obstructive pulmonary disease (COPD), asthma and lung cancer.[5,6] Elevated serum bilirubin is also associated with longer survival in patients with lung cancer.[7]

Idiopathic pulmonary fibrosis (IPF), which is the most common type of idiopathic interstitial pneumonia, is characterized by chronic and progressive fibrosing interstitial pneumonia leading to progressively worsening dyspnea and lung function.[8] Acute exacerbation of IPF (AE-IPF) is defined as an acute and clinically significant deterioration without an identifiable cause in patients with underlying IPF. AE-IPF can lead to a significant decline in lung function, ultimately resulting in death, with an in-hospital mortality of between 50% and 80%.[9,10] Although IPF was originally considered a chronic inflammatory disorder, this concept has been challenged following the negative results of interventional studies of anti-inflammatory therapies.[11] Oxidative stress has been identified as one of the main pathogenic pathways in IPF.[12] As a potent anti-oxidant, bilirubin is involved in the balance between anti-oxidant and pro-oxidant agents. This mechanism is implicated as an explanation for the observation that higher serum bilirubin concentrations are associated with better lung function in several large observational studies.[13] However, the possible relationship between IPF and serum bilirubin concentrations remains to be clarified. Therefore, in this study, we explored the effects of serum bilirubin levels on the progression of lung dysfunction and IPF. We also investigated the potential association of serum bilirubin levels at the time of diagnosis with the survival of patients with IPF.

Materials and methods

Study design

One hundred and sixty-seven IPF patients who were recruited from inpatient of the department of respiration of Nanjing Drum Tower Hospital between April 2017 and April 2019 were included in this retrospective study. Overall, 21 patients were excluded based on exclusion criteria. A total of 146 patients who were diagnosed with IPF were analyzed as a derivation cohort (Figure 1(a)). Sixty-nine healthy adults who had no medical histories were randomly selected in the clinic, and were classified as the control group. To validate the value of serum bilirubin levels to predict the survival of patients with IPF, a validation cohort was performed which consisted of 40 patients with IPF who were admitted to the department of respiration of Nanjing Drum Tower Hospital between April 2019 and April 2020 (Figure 1(b)). Patients with incomplete data were excluded. Exclusion criteria for all IPF subjects were: (1) subjects had gastrointestinal diseases; (2) subjects lacked of pulmonary function test results; (3) subjects of validation cohort overlapped with derivation cohort. Hospital and office records were used as data sources. The main data

collected included demographic features, clinical characteristics, lung function parameters and therapy. Survival status was determined by reviewing the medical records or telephone follow-ups until April 2020.

Methods

The diagnosis of IPF includes the exclusion of other interstitial lung diseases or overlapping conditions and depends on the identification of the usual interstitial pneumonia (UIP) pattern, usually with high-resolution computed tomography (HRCT). The specific diagnostic criteria were based on the guidelines for diagnosis of IPF published by the official American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS) and the Latin American Thoracic Society (LAT) in 2018.[14] All IPF patients included in this study fulfill the newer IPF criteria published in 2018. AE-IPF was diagnosed according to the criteria proposed in the following consensus statement published in 2016[15]: (1) a previous or concurrent diagnosis of IPF; (2) acute worsening or development of dyspnea, typically <1 month; (3) the appearance of new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP in HRCT imaging; and (4) deterioration not fully explained by cardiac failure or fluid overload. Hospital and office records of each patient were reviewed in detail and patients with AE-IPF were identified based on the criteria for diagnosis of AE-IPF.

Percent predicted forced vital capacity (FVC), percent predicted forced expiratory volume in 1 second (FEV1), percent predicted diffusion capacity for carbon monoxide (DLCO) were used in the analysis.

Thirty-four IPF patients were treated with pirfenidone. Treatment was initiated at 200 mg administered three times daily and the dose of pirfenidone increased by 100 mg per week until the target dose of 600 mg administered three times daily was reached.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation (SD). Differences between two groups were analyzed by t-test. Pearson correlation analysis was used to evaluate the relationship between serum bilirubin levels and lung function parameters. The accuracy of serum total/indirect bilirubin level in predicting the

Table 1. Comparison of the demographic, anthropometric, and biochemical parameters between 69 normal subjects and 146 patients with IPF.

Variable	Normal population ($n = 69$)	IPF patients ($n = 146$)
Age (years)	49.97 $\pm$ 9.73	68.05 $\pm$ 9.68[a]
WBCC (10^9/L)	5.38 $\pm$ 1.41	7.67 $\pm$ 2.97[a]
Neutrophil count (10^9/L)	3.12 $\pm$ 1.05	5.13 $\pm$ 2.74[a]
Total bilirubin (umol/l)	10.66 $\pm$ 3.70	9.41 $\pm$ 3.12[a]
Direct bilirubin (umol/l)	3.91 $\pm$ 1.27	3.06 $\pm$ 1.34[a]
Indirect bilirubin (umol/l)	6.76 $\pm$ 2.72	6.35 $\pm$ 2.24
LDH (U/L)	154.22 $\pm$ 32.76	271.98 $\pm$ 101.56[a]
CEA (ng/ml)	1.61 $\pm$ 0.89	3.93 $\pm$ 4.18[a]
CYFRA21-1 (ng/ml)	1.90 $\pm$ 2.19	5.78 $\pm$ 6.73[a]
NSE (ng/ml)	10.61 $\pm$ 2.33	16.99 $\pm$ 7.10[a]
P/F (mmHg)	—	353.98 $\pm$ 108.93
FVC%	—	67.02 $\pm$ 17.27
FEV1%	—	75.08 $\pm$ 18.27
DLCO-SB%	—	47.18 $\pm$ 20.28

WBC: white blood cell; TBil: total bilirubin; DBil: direct Bilirubin; IBil: indirect bilirubin; LDH: lactic dehydrogenase; NSE: neuron specific enolase; CYFRA21-1: cytokeratin 21-1; CEA: carcinoembryonic antigen; P/F: PaO_2/FiO_2; FVC: forced vital capacity; FEV1: forced expiratory volume; DLCO: diffusing capacity for carbon monoxide.

[a]$P < 0.05$ compared with normal population.

incidence of AE-IPF was then determined by Receiver Operating Characteristics (ROC) analysis. Cox proportional hazard analysis was performed on potential prognostic factors using the backward forward stepwise method for selection of covariates. The Kaplan-Meier method was used to assess survival curves with GraphPad Prism version 7 (Graph Pad Software Inc., La Jolla, CA, USA). The log-rank test was used to evaluate the statistical significance of differences between the higher TBIL and lower TBIL groups. Statistical analyses were performed using SPSS18.0 statistical software. $P < 0.05$ (two-sided) was considered to indicate statistical significance.

Results

Characteristics of study participants

In the derivation cohort, clinical characteristics and comparisons between 146 patients with IPF and 69 healthy controls are shown in Table 1. The IPF

patients were more likely to be older and had lower levels of serum total bilirubin (TBIL) and direct bilirubin (DBIL). In addition, increased WBCC and neutrophil counts, and higher levels of lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), cytokeratin 21-1 (CYFRA21-1) and neuron specific enolase (NSE) were observed in IPF patients (all $P < 0.05$).

Associations of bilirubin with lung function parameters

Table 2 showed the relationship between serum bilirubin and lung function. Serum TBIL level was positively associated with percent predicted of DLCO-SB ($P = 0.01$). However, no association was observed between TBIL and P/F, percent predicted FVC, or percent predicted FEV1 ($P = 0.642, 0.771, 0.605$, respectively). Notably, a positive relationship between indirect bilirubin (IBIL) concentration and percent predicted of DLCO-SB was observed ($P = 0.003$).

Table 2. Univariable correlations of serum bilirubin levels with lung function parameters in patients of IPF at baseline.

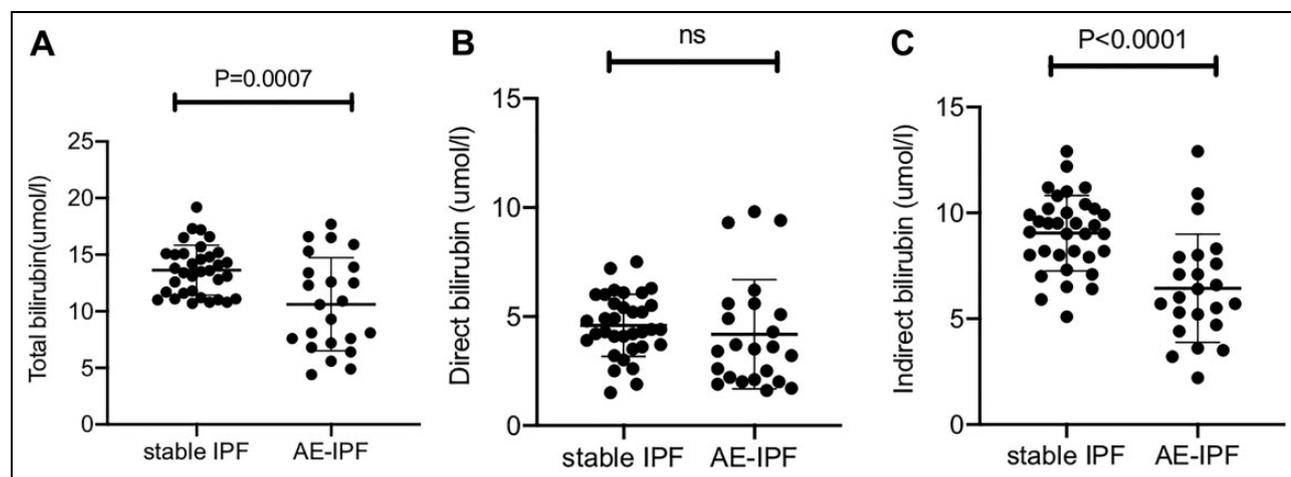|	Total bilirubin		Direct bilirubin		Indirect bilirubin	
	r	P	r	P	r	P
P/F (mmHg)	0.043	0.642	0.097	0.292	0.001	0.989
FVC%	0.026	0.771	−0.038	0.675	0.059	0.516
FEV1%	0.047	0.605	0.029	0.746	0.047	0.602
DLCO-SB%	0.238	0.010	0.104	0.264	0.268	0.003

Bilirubin and AE-IPF

Twenty-three patients with AE-IPF were identified based on the criteria for diagnosis of AE-IPF. Due to the difference in sample size between patients with stable IPF and those with AE-IPF, 34 stable IPF patients were randomly selected among 123 stable IPF patients. Patients who had lower serum TBIL or IBIL levels were more likely to have AE-IPF, while there was no difference of serum DBIL levels between patients with stable IPF and those with AE-IPF (Figure 2(a) to (c)).

The accuracy of serum TBIL levels for predicting the incidence of AE-IPF was then evaluated by Receiver Operating Characteristics (ROC) analysis. The area under the ROC curve was 0.72 (95% CI: 0.56–0.87, $P = 0.0057$) (Figure 3). The area under the ROC curve of serum IBIL level for predicting the incidence of AE-IPF was 0.81 (95% CI: 0.68–0.94, $P < 0.0001$) (Figure 4). The cutoff values for serum TBIL and serum IBIL concentrations for predicting the incidence of AEIPF were 10.65 μmol/l and 7.95 μmol/l, respectively.

Association of serum TBIL level with overall survival of patients with IPF

In the derivation cohort, complete follow-up data were available for 98 of 146 patients with IPF. Follow-up data were missing in 48 patients with IPF. The patients who didn't complete follow up were due to the following factors: (a) we could not contact patients by the phone number; (b) the patients

Figure 2. Comparison serum bilirubin levels between acute exacerbations of IPF and stable IPF. Figure 2A shows comparison serum total bilirubin levels between stable IPF and AE-IPF. Figure 2B shows comparison serum direct bilirubin levels between stable IPF and AE-IPF. Figure 2C shows comparison serum indirect bilirubin levels between stable IPF and AE-IPF.
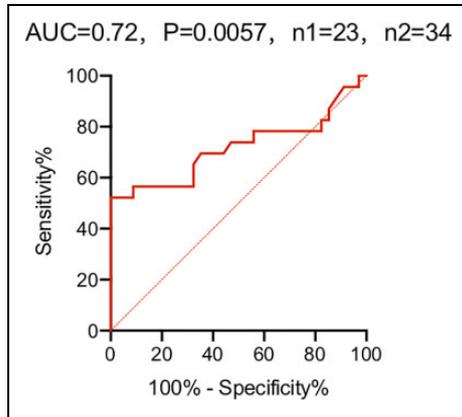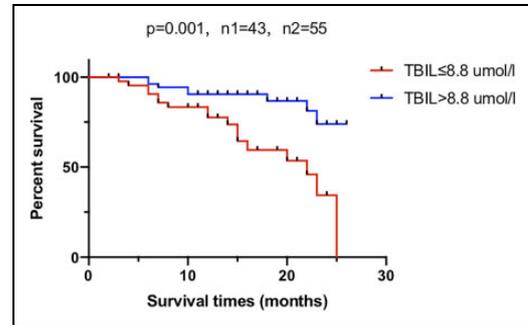
Figure 3. Receiver operating characteristic (ROC) curve of serum total bilirubin level for predicting the incidence of acute exacerbations of IPF.
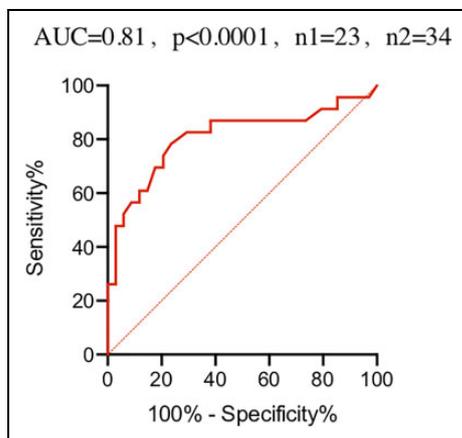
Figure 4. Receiver operating characteristic (ROC) curve of serum indirect bilirubin level for predicting the incidence of acute exacerbations of IPF.

Figure 5. The respective Kaplan-Meier curve of IPF patients with lower total bilirubin group and higher total bilirubin group in the derivation cohort.

**Table 3.** Baseline characteristics of 40 IPF patients of validation cohort.

Variable	Validation cohort (IPF patients) ($n = 40$)
Age (years)	68.25 ± 8.99
WBCC (10^9/L)	7.14 ± 1.63
Neutrophil count (10^9/L)	4.18 ± 1.42
Total bilirubin (umol/l)	9.61 ± 3.53
Direct bilirubin (umol/l)	2.43 ± 0.71
Indirect bilirubin (umol/l)	7.17 ± 3.15
LDH (U/L)	224.03 ± 57.78
CEA (ng/ml)	2.85 ± 1.47
CYFRA21-1 (ng/ml)	5.04 ± 2.70
NSE (ng/ml)	15.77 ± 4.41
P/F (mmHg)	355.63 ± 110.37
FVC%	70.32 ± 16.42
FEV1%	76.31 ± 17.23
DLCO-SB%	49.21 ± 19.76

selected Chinese traditional medicine therapy afterward. Up to April 2020, 25 patients died among 98 patients with IPF whose follow-up data were available. ROC analysis was conducted to determine the best cutoff value of serum TBIL level between the survivors and nonsurvivors (cutoff 8.8 μmol/l, AUC 0.75 (95% CI: 0.64–0.87)). The patients were divided into a higher TBIL group ($n = 55$, TBIL >8.8 μmol/l) and a lower TBIL group ($n = 43$, TBIL ≤8.8 μmol/l) to analyze the survival using the Kaplan-Meier method (Figure 5). The log-rank test showed a significant difference in survival between the two groups ($P = 0.001$). Furthermore, the cutoff value of serum TBIL was validated for the prediction of survival in the validation cohort. Table 3 showed baseline characteristics of 40 IPF patients of validation cohort. The log-rank test analyzed by the Kaplan-Meier method

for survival between the higher TBIL ($n = 23$, TBIL >8.8 μmol/l) and lower TBIL ($n = 17$, TBIL ≤8.8 μmol/l) groups showed a significant difference between the two groups ($P = 0.024$) (Figure 6).

Cox proportional hazards models were used to examine the influence of serum TBIL level on the prognosis of patients with IPF. After adjustment for age, WBCC and neutrophil counts, and levels of LDH, CEA and NSE, serum TBIL level (HR = 0.582, $P = 0.026$) was identified as an independent factor in the survival of IPF in multivariate Cox proportional regression analysis.

Bilirubin and efficacy of pirfenidone for the treatment of IPF

Pirfenidone was administered to 34 patients with IPF. Treatment was initiated at 200 mg administered three
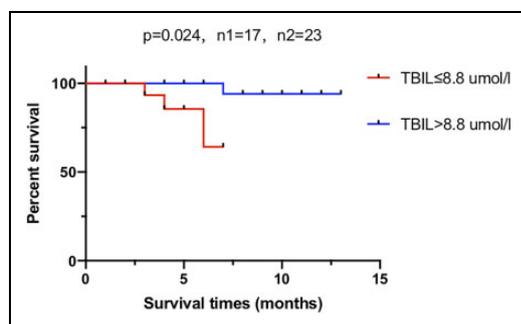
Figure 6. The respective Kaplan-Meier curve of IPF patients with lower total bilirubin group and higher total bilirubin group in the validation cohort.

Table 4. Comparison baseline bilirubin levels between effective group and ineffective group in IPF patients after pirfenidone therapy for 1 year.

	Effective group ($n = 20$)	Ineffective group ($n = 14$)
Total bilirubin (umol/l)	12.79 ± 4.81	10.88 ± 3.87
Direct bilirubin (umol/l)	4.27 ± 1.96	3.70 ± 1.47
Indirect bilirubin (umol/l)	8.52 ± 3.30	7.18 ± 2.61

times daily and the dose of pirfenidone increased by 100 mg per week until the target dose of 600 mg administered three times daily was reached. After 1 year of pirfenidone therapy, the 34 patients were classified into the ineffective group (14 patients, the change level of FVC decreased $\geq 10\%$ predicted) and the effective group (20 patients, the change level of FVC decreased $<10\%$ predicted or the level of FVC predicted increased). As shown in Table 4, no statistically significant association was identified between baseline serum bilirubin level and efficacy of pirfenidone therapy for IPF (all $P > 0.05$).

Discussion

In this study, we demonstrated for the first time that patients with IPF had lower levels of serum TBIL and DBIL than those in the healthy control group. Importantly, we also found that serum bilirubin levels were closely associated with the severity, acute exacerbations and prognosis of IPF. Significantly lower serum TBIL and IBIL levels were detected in patients with AE-IPF compared to those with stable IPF. Furthermore, patients with relatively high serum TBIL levels had significantly longer overall survival than patients with relatively low serum TBIL levels. Thus, serum

TBIL levels were identified as a significant prognostic predictor of IPF independent of any other risk factors.

IPF is a chronic, progressive lung disease characterized by progressive lung scarring and the histological features of UIP. IPF is more common in men and is rare in people younger than 50 years (median age at diagnosis is approximately 65 years). Although the disease course is variable and somewhat unpredictable, the median survival time from diagnosis is 2–4 years.[16] It is acknowledged that accurate assessment of the severity of IPF disease is central to the choice of disease management strategies. Thus, simple, inexpensive, and readily accessible biomarkers of the severity and prognosis of IPF represent an important advance for this purpose.

Bilirubin is a by-products of heme degradation to biliverdin by heme oxygenase. Heme oxygenase-1 (HO-1), which is the inducible isoform of heme oxygenase, is expressed in type 2 pneumocytes and alveolar macrophages in the lung. This enzyme has been reported to attenuate pulmonary fibrosis caused by chronic, profibrotic, inflammatory processes or apoptotic cell death.[17] In addition to its function as an oxidant scavenger, bilirubin protects lipids against oxidant stress and reduces intracellular reactive oxygen species (ROS) production by inhibiting membrane-bound nicotinamide adenine dinucleotide phosphate oxidase.[18] Numerous studies have confirmed the protective effects of bilirubin against oxidant stress-associated pulmonary diseases such as COPD. Moreover, serum bilirubin concentration has been implicated as the biomarker of severity and progression of COPD and an independent prognostic factor in non-small-cell lung cancer (NSCLC) following successful resection.[6,19] In addition to studies indicating the potential benefits of raised serum bilirubin levels against oxidant stress, the protective effects of the serum bilirubin levels on various fibrosis-related diseases have been widely reported.[20,21] Accumulating evidence suggests that oxidative stress and fibrogenesis play significant roles in pathophysiology of IPF.[8] However, few studies have focused on the association between serum bilirubin concentrations and IPF. In our study, we found that patients with IPF had lower serum TBIL and DBIL concentrations than those in healthy controls. In addition, compared with the levels detected in patients with stable IPF, we found significantly lower levels of serum TBIL and IBIL in patients with AE-IPF, an event of major clinical significance that is associated with high morbidity

and mortality. Due to the unpredictability and high fatality rate of AE-IPF, there is an urgent need for identification of novel AE-IPF-specific biomarkers. Ohrui et al. reported evidence indicating that serum bilirubin plays an important role in tissue protection against inflammatory damage in IPF and that, as an antioxidant agent, bilirubin might be effective for the treatment of AE-IPF.[22] In our study, the AUROC of serum TBIL and IBIL levels for predicting the incidence of AE-IPF were 0.72 and 0.81, respectively. The optimal cutoff points for serum TBIL and IBIL levels were 10.65 µmol/l and 7.95 µmol/l, respectively. Thus, we can predict the incidence of AE-IPF by monitoring serum TBIL and IBIL levels.

Prognostic prediction in patients with IPF is usually based on pulmonary function test results such as percent predicted FVC and percent predicted of DLCO. Based on previous studies, it has been proposed that baseline percent predicted of DLCO-SB is superior to baseline percent predicted FVC as a prognostic indicator in IPF.[23] Pulmonary function progression according to serum bilirubin levels in the healthy general population[13] and patients with COPD[18] have been investigated in human studies, but not in patients with IPF. In our study, serum TBIL and IBIL levels were found to correlate positively with percent predicted of DLCO-SB in IPF patients, while no association was observed between TBIL and pulmonary function, percent predicted of FVC, or percent predicted of FEV1. Thus, the severity of IPF can be predicted based on the level of pulmonary function impairment. The anti-oxidant and anti-inflammatory properties of bilirubin indicate its potential for treating IPF in the future.

Using multivariate analyses, we identified serum TBIL as an independent prognostic factor for IPF (HR = 0.582, P = 0.026). The best cutoff value of serum TBIL level to predict the survival of patients with IPF was 8.8 mol/l. The log-rank test showed a significant difference in survival between the two groups (TBIL ≤8.8 mol/l and TBIL >8.8 mol/l) in both derivation cohort and validation cohort. Serum tumor markers such as CY-21-1[24] as well as several serum proteins such as surfactant protein-A[25] have been recognized as prognostic factors for IPF. Compared with these prognostic indicators, serum TBIL offers a cheaper, simpler and more convenient parameter for inclusion in blood biochemistry examinations and follow-up.

As the standard first-line treatment for IPF, prifenidone slows the progress of pulmonary fibrosis. However, variety of effects for this drug in different IPF patients had been seen. In the present study, we revealed that there was no significant inverse correlation between baseline serum bilirubin level and the therapeutic efficacy of pirfenidone in IPF. However, only a small number of the IPF patients in this study were treated with pirfenidone and further studies with larger patient cohorts are required to fully elucidate the relationship between serum bilirubin levels and the mechanism underlying the effects of pirfenidone for the treatment of IPF.

Some limitations of this study should be noted. First, the cross-sectional study design limits the ability to infer causality between serum bilirubin and IPF. A prospective and comprehensive study to validate the role of serum bilirubin in IPF would be required. Second, 48 patients of 146 patients with IPF whose follow-up data were missing. The sample size was too small to infer causality between serum bilirubin and the prognosis of IPF. Finally, all patients were recruited from Nanjing, Jiangsu province, China. Therefore, it is uncertain whether these results are generalizable to other ethnic groups.

In conclusion, our study shows serum bilirubin concentration is associated with the severity and prognosis of IPF patients that offers the advantages of convenience, ease of accessibility and low cost. Further studies are required to evaluate this ratio and explore the mechanism underlying the association of bilirubin with the prognosis of IPF patients.

Author contributions

Availability of data and material

Declaration of conflicting interests

Ethics approval

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