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

Shenyun Shi, Yin Liu, Xiaohua Qiu, Min Cao, Yonglong Xiao and Xin Yan

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

Date received: 10 May 2020; accepted: 10 August 2020

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. Furthermore, serum bilirubin

Corresponding authors:
Xin Yan, Yonglong Xiao and Min Cao, Department of Respiratory and Critical Care Medicine, Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing, Jiangsu 210008, China.
Emails: yanxin8612@126.com; yonglong11a@163.com; njcao min@126.com
is routinely used as a marker of hepatobiliary and hematological disorders. 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. Elevated serum bilirubin is also associated with longer survival in patients with lung cancer.

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. 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%. 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. Oxidative stress has been identified as one of the main pathogenic pathways in IPF. 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. 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 were collected and analyzed.
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 201615: (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.

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 ± 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 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

| Table 1. Comparison of the demographic, anthropometric, and biochemical parameters between 69 normal subjects and 146 patients with IPF. |
|-----------------|-----------------|-----------------|
| Variable        | Normal population | IPF patients |
| Age (years)     | 49.97 ± 9.73     | 68.05 ± 9.68*  |
| WBCC (10⁹/L)    | 5.38 ± 1.41      | 7.67 ± 2.97*  |
| Neutrophil count (10⁹/L) | 3.12 ± 1.05     | 5.13 ± 2.74a |
| Total bilirubin (umol/l) | 10.66 ± 3.70     | 9.41 ± 3.12a |
| Direct bilirubin (umol/l) | 3.91 ± 1.27      | 3.06 ± 1.34a |
| Indirect bilirubin (umol/l) | 6.76 ± 2.72     | 6.35 ± 2.24   |
| LDH (U/L)       | 154.22 ± 32.76   | 271.98 ± 101.56a |
| CEA (ng/ml)     | 1.61 ± 0.89      | 3.93 ± 4.18a  |
| CYFRA21-1 (ng/ml) | 1.90 ± 2.19     | 5.78 ± 6.73a  |
| NSE (ng/ml)     | 10.61 ± 2.33     | 16.99 ± 7.10a |
| P/F (mmHg)      | —                | 353.98 ± 108.93 |
| FVC%            | —                | 67.02 ± 17.27 |
| FEV1%           | —                | 75.08 ± 18.27 |
| DLCO-SB%        | —                | 47.18 ± 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: PaO₂/FiO₂; FVC: forced vital capacity; FEV1: forced expiratory volume; DLCO: diffusing capacity for carbon monoxide.

\(^*\)P < 0.05 compared with normal population.
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.](image)
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 \((n = 55, \text{TBIL} > 8.8 \text{ μmol/l})\) and a lower TBIL group \((n = 43, \text{TBIL} \leq 8.8 \text{ μmol/l})\) 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 \((n = 23, \text{TBIL} > 8.8 \text{ μmol/l})\) and lower TBIL \((n = 17, \text{TBIL} \leq 8.8 \text{ μmol/l})\) groups showed a significant difference between the two groups \((P = 0.024)\) (Figure 6).

**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...
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 ≥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. 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. 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. 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. 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. Accumulating evidence suggests that oxidative stress and fibrogenesis play significant roles in pathophysiology of IPF. 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. 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. Pulmonary function progression according to serum bilirubin levels in the healthy general population and patients with COPD 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 as well as several serum proteins such as surfactant protein-A 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, pirfenidone 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**

SS, YX, and XY were involved in conception and design. SS, YL, XQ, and XY were involved in analysis and interpretation. SS, YL, XQ and MC were involved in acquisition of data. SS, YX, XY were involved in writing and revisions. SS, YL, and XQ contributed equally to this work.

**Availability of data and material**

The data are available upon request.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethics approval**

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.
**Funding**
The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**
Shenyun Shi https://orcid.org/0000-0002-2022-121X
Xin Yan https://orcid.org/0000-0002-2829-3277

**References**

1. Ishibashi F, Kawasaki A, Kojima R, et al. Association between serum total bilirubin levels and the morphology of corneal nerve fibers in Japanese patients with uncontrolled type 2 diabetes. *Diabetes Care* 2014; 37(6): e131–e132.

2. Kunutsor SK, Bakker SJ, Gansevoort RT, et al. Circulating total bilirubin and risk of incident cardiovascular disease in the general population. *Arterioscler Thromb Vasc Biol* 2015; 35(3): 716–724.

3. Yu QQ, Qiu H, Zhang MS, et al. Predictive effects of bilirubin on response of colorectal cancer to irinotecan-based chemotherapy. *World J Gastroenterol* 2016; 22(16): 4250–4258.

4. Kronenberg F. Association of bilirubin with cardiovascular outcomes: more hype than substance? *Circ Cardiovasc Genet* 2010; 3(4): 308–310.

5. Horsfall LJ, Rait G, Walters K, et al. Serum bilirubin and risk of respiratory disease and death. *JAMA* 2011; 305(7): 691–697.

6. Apperley S, Park HY, Holmes DT, et al. Serum bilirubin and disease progression in mild COPD. *Chest* 2015; 148(1): 169–175.

7. Jiang D, Shi J, Yuan M, et al. Levels of serum bilirubin in small cell lung cancer and non-small cell lung cancer patients. *Cell Mol Biol (Noisy-le-grand)* 2018; 64(6): 71–76.

8. Richeldi L, Collard HR, Jones MG, et al. Idiopathic pulmonary fibrosis. *Lancet* 2017; 389(10082): 1941–1952.

9. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 176: 636–643.

10. Song JW, Hong SB, Lim CM, et al. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011; 37: 356–363.

11. Selman M, King TE, and Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 2001; 134(2): 136–151.

12. Martinez FJ, Collard HR, Pardo A, et al. Idiopathic pulmonary fibrosis. *Nat Rev Dis Primers* 2017; 3: 17074.

13. Leem AY, Kim HY, Kim YS, et al. Association of serum bilirubin level with lung function decline: a Korean community-based cohort study. *Respir Res* 2018; 19(1): 99.

14. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198(5): e44–e68.

15. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194(3): 265–275.

16. Ley B, Collard HR, and King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183(4): 431–440.

17. Nakamura T, Matsushima M, Hayashi Y, et al. Attenuation of transforming growth factor-β-stimulated collagen production in fibroblasts by quercetin-induced heme oxygenase-1. *Am J Respir Cell Mol Biol* 2011; 44(5): 614–620.

18. Brown KE, Sin DD, Voelker H, et al. Serum bilirubin and the risk of chronic obstructive pulmonary disease exacerbations. *Respir Res* 2017; 18(1): 179.

19. Li N, Xu M, Cai MY, et al. Elevated serum bilirubin levels are associated with improved survival in patients with curatively resected non-small-cell lung cancer. *Cancer Epidemiol* 2015; 39(5): 763–768.

20. Park S, Kim DH, Hwang JH, et al. Elevated bilirubin levels are associated with a better renal prognosis and ameliorate kidney fibrosis. *PLoS One* 2017; 12(2): e0172434.

21. Nishikawa H, Enomoto H, Yoh K, et al. Combined albumin-bilirubin grade and skeletal muscle mass as a predictor in liver cirrhosis. *J Clin Med* 2019; 8(6): E782.

22. Ohru T, Higuchi M, Kanda A, et al. A patient with exacerbation of idiopathic pulmonary fibrosis which was resolved probably due to the coexisting hyperbilirubinemia? *Tohoku J Exp Med* 2001; 193(3): 245–249.

23. Nathan SD, Shlobin OA, Weir N, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. *Chest* 2011; 140(1): 221–229.

24. Alqalyoobi S, Adegunsoye A, and Linderholm A. Circulating plasma biomarkers of progressive interstitial lung disease. *Am J Respir Crit Care Med* 2019; 201: 250–253.

25. Kinder BW, Brown KK, McCormack FX, et al. Serum surfactant protein-A is a strong predictor of early mortality in idiopathic pulmonary fibrosis. *Chest* 2009; 135(6): 1557–1563.