Chronic Kidney Disease Predicts Survival in Patients with Idiopathic Pulmonary Fibrosis

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Keywords

Comorbidity · Chronic kidney disease · Glomerular filtration rate · Idiopathic pulmonary fibrosis · Prognosis

Abstract

Background: The prevalence of chronic kidney disease (CKD) increases with age as with idiopathic pulmonary fibrosis (IPF). **Objectives:** We assessed the prevalence of CKD (stages 3–5) and investigated the relationship of CKD to clinical features and outcomes in patients with IPF. **Methods:** This study comprised 123 patients with IPF; 61 subjects with chronic obstructive pulmonary disease (COPD), which was reportedly associated with CKD, were also enrolled as a disease control. CKD (stages 3–5) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². **Results:** Thirty-seven patients (30%) with IPF and 14 controls (23%) with COPD were diagnosed with CKD, and these fre-

quencies were not significantly different. The patients with IPF and CKD were older ($p < 0.01$) and had a higher frequency of hypertension ($p = 0.048$) and ischemic heart disease ($p = 0.02$) than those with IPF but without CKD. Furthermore, the diffusing capacity of the lung for carbon monoxide (DLCO) and the 6-min walking distance in the patients with CKD were significantly lower (40.0 ± 13.2 vs. $45.9 \pm 14.4\%$, $p = 0.04$, and 416 ± 129 vs. 474 ± 84 m, $p = 0.01$, respectively) than in the patients without CKD. The outcome of the patients with CKD showed significantly worse survival compared with the patients without CKD ($p = 0.04$). Moreover, eGFR remained an independent predictor of survival after adjusting for age and pulmonary function data. **Conclusion:** A substantial percentage of IPF patients have CKD. CKD with a low eGFR was associated with decreased survival in IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing, interstitial pneumonia of unknown cause with a poor prognosis (median survival of 2–5 years following diagnosis) [1, 2]. However, the natural history of IPF is highly variable and unpredictable. Therefore, it is important to identify validated predictors for its prognosis [3].

Demographic factors (age, gender, and smoking history), physiological factors (forced vital capacity [FVC] and diffusing capacity of the lung for carbon monoxide [DLCO]), radiological factors, and some serum biomarkers have been reported to predict the survival of patients with IPF [4]. Recently, the composite physiologic index (CPI), which is calculated from FVC, forced expiratory volume in 1 s (FEV₁), and DLCO, has been proposed to represent the extent of fibrosis and predict the mortality of patients with IPF [5]. In addition, the impact of comorbidities on the prognosis of IPF has been assessed [6, 7]. Lung cancer, pulmonary hypertension, gastroesophageal reflux disease, emphysema, and cardiovascular disease have been reported to be associated with increased mortality in IPF [8–14]. Against such a background, pulmonary and extrapulmonary comorbidities in IPF have recently been drawing more attention.

Chronic kidney disease (CKD) is a common disorder, and its prevalence increases with age. Age, smoking history, hypertension, diabetes mellitus, and cardiovascular disease are consistently associated with CKD [15]. Especially people with CKD stages 3–5 (with an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²) have a high risk of all-cause and cardiovascular mortality [16]. Among lung diseases, chronic obstructive pulmonary disease (COPD) was reported to have a high prevalence of CKD stages 3–5 [17]. IPF has risk factors for CKD similar to COPD, such as old age and smoking. Moreover, recent studies have reported that patients with IPF have an increased risk of hypertension, diabetes mellitus, and cardiovascular disease, and that these comorbid conditions may be associated with increased mortality [14, 18, 19].

Therefore, we hypothesized that CKD (stages 3–5) is prevalent in IPF, and that CKD is associated with disease severity and mortality in patients with IPF. To test these hypotheses, we assessed the prevalence of CKD, and investigated whether CKD and eGFR were associated with relevant clinical features and mortality in patients with IPF. Subjects with COPD were also enrolled to compare the prevalence of CKD in IPF with that of a respiratory disease which is reportedly associated with CKD.

Subjects and Methods

Study Population

This retrospective cohort study comprised 123 patients with IPF who were diagnosed at Kyoto University Hospital or Tenri Hospital between April 2006 and August 2014 (72 from Kyoto University Hospital and 51 from Tenri Hospital). IPF was diagnosed by surgical lung biopsy or high-resolution computed tomography as previously described [1, 20]. We excluded patients who had a history of malignancy within 5 years from the time of inclusion and patients who had acute deterioration (acute exacerbation, pulmonary infection, and congestive heart failure) within 4 weeks prior to inclusion. The disease control group comprised 61 subjects with COPD who had been referred to Kyoto University Hospital between 2013 and 2014. COPD was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease criteria [21]. The controls were matched by age. This study was approved by the ethics committees of Kyoto University (E2119) and Tenri Hospital (635).

Data Acquisition

A pulmonary function test was performed using the CHESTAC system (Chest M.I. Inc., Tokyo, Japan). DLCO was determined using the single-breath technique. Percent predicted values were used for the analyses. The CPI was calculated using the following formula as an index of the extent of fibrosis [22]: $91 - (0.65 \times \%DLCO) - (0.53 \times \%FVC) + (0.34 \times \%FEV_1)$. An arterial blood gas analysis was performed while the patients were breathing room air at rest in the supine position. The alveolar-arterial oxygen pressure difference was calculated according to the standard formula using a respiratory exchange ratio of 0.8. The 6-min walk test was conducted according to the American Thoracic Society guidelines [23]. We measured the 6-min walking distance (6MWD) and continuously monitored the oxygen saturation (SpO₂) levels during walking and recorded the minimum SpO₂ values. Peripheral venous blood samples were collected at the time of inclusion. The eGFR of each participant was calculated based on their serum creatinine (SCr) values and age using the Japanese equation as follows: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{SCr}^{-1.094}$ ($\times 0.739$ if female) [24]. CKD stages 3–5 was defined as two consecutive measurements of an eGFR <60 mL/min/1.73 m² [25].

The patients' comorbidities and medication histories were recorded based on the information from their medical records at the time of inclusion. Diabetes mellitus was defined as having a hemoglobin A_{1c} level of $\geq 6.5\%$ (National Glycohemoglobin Standardization Program) or taking antidiabetics. The presence of emphysema was defined based on a previous report [26]. Emphysema is a hyperlucent lung area that lacks a distinct wall on computed tomography. The emphysema score was visually determined by estimating the percentage of emphysema in the upper, middle, and lower areas of each lung and averaging them to produce a total emphysema score. In patients with IPF, we defined "the presence of emphysema" as a total emphysema score of $\geq 10\%$. Musculoskeletal diseases were defined as one or more of the following: osteoporosis, arthritis, kyphosis, scoliosis, fractures, or myasthenia. Gastrointestinal diseases were defined as one or more of the following: gastroesophageal reflux disease, peptic ulcer, liver diseases, inflammatory and/or vascular bowel diseases, or chronic pancreatitis [17]. Further, the Charlson comorbidity index was determined based on a previous study [27].

Statistical Analysis

All statistical analyses used JMP version 10 (SAS Institute, Cary, NC, USA). The results of continuous variables are presented as mean $\pm$ standard deviation (SD). A p value <0.05 was considered statistically significant. The unpaired t test was used to compare the results of continuous variables, whereas the χ^2 test was used to compare the results of categorical variables between the two groups. Survival curves were generated using the Kaplan-Meier method, and the survival rates were compared between subgroups using the log-rank test. In addition, a survival analysis was performed, using univariate and multivariate Cox proportional-hazard regression, and parameters with p values <0.05 in the univariate analysis were exclusively entered into the multivariate models.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the 123 patients with IPF and 61 age-matched disease controls with COPD. Among the patients with IPF, the mean age was 69.2 ± 7.5 years, and this group was predominated by males (80%) and ever smokers (84%). Their mean eGFR was 69.5 ± 17.9 mL/min/1.73 m², and 37 patients (30%) were diagnosed with CKD (stages 3–5). At the time of inclusion, 10 patients had previously taken medication for IPF (6 oral corticosteroids, 6 immunosuppressants [azathioprine, cyclosporine, or cyclophosphamide], and 3 pirfenidone), whereas the remaining patients had not previously taken any medication for IPF. As for other medications that may affect renal function, 2 patients (2%) used nonsteroidal anti-inflammatory drugs, 8 (6%) used sulfamethoxazole/trimethoprim, 17 (14%) used statins, 16 (13%) used histamine-2 receptor blockers, 6 (5%) used diuretics, and 17 (14%) used angiotensin II receptor blockers.

In comparison with the COPD controls, the patients with IPF included fewer males (80 vs. 98%), fewer ever smokers (84 vs. 100%), and subjects with a higher BMI (23.5 vs. 21.2). The prevalence of CKD was not significantly different between the patients with IPF and the controls with COPD (30 vs. 23%, $p = 0.31$).

Table 2 presents a comparison of the data regarding demographics, pulmonary function, and comorbidities between IPF patients with and those without CKD. The patients with CKD were older than those without CKD (72.2 ± 6.3 vs. 68.0 ± 7.6 years, $p < 0.01$). There was no significant difference in hemoglobin levels between the patients with and those without CKD. At the time of inclusion, the frequency of emphysema was not significantly different between the patients with and those without CKD. Moreover, the patients with CKD had a higher fre-

quency of hypertension (13/37, 35%, vs. 16/86, 19%, $p = 0.048$) and ischemic heart disease (IHD) (12/37, 32%, vs. 12/86, 14%, $p = 0.02$) (Table 2) than the patients without CKD. The use of diuretics was more frequent among the patients with CKD than among those without CKD (4/37, 11%, vs. 2/86, 2%, $p = 0.045$), but the frequencies with which other medications were used were not significantly different between the patients with and those without CKD.

The baseline physiological data showed significantly lower %DLCO in the patients with CKD than in the patients without CKD (40.0 ± 13.2 vs. $45.9 \pm 14.4\%$, $p = 0.04$), and the 6MWD was significantly shorter among the patients with CKD than among the patients without CKD (416 ± 129 vs. 474 ± 84 m, $p = 0.01$) (Table 3).

Outcome

During a mean follow-up period of 26.6 months (range: 0.4–94.3), 35 patients (28%) died. The main cause of death was acute exacerbation (15 patients, 43%). Other causes of death were chronic respiratory failure in 9, malignancy in 5, pulmonary infection in 2, pneumothorax in 2, and unknown causes (sudden death outside the hospital) in 2 patients. The frequencies of each cause of death were comparable between the patients with and those without CKD. During the follow-up period, 31 patients (25%) were treated with pirfenidone, 37 (30%) were treated with systemic corticosteroids, and 25 (20%) were treated with immunosuppressants, primarily for the treatment of acute exacerbation. A comparison of the survival curves using the log-rank test showed that the patients with CKD (stages 3–5) had a significantly worse survival than those without CKD ($p = 0.04$) (Fig. 1).

Next, we performed Cox proportional-hazard regression analyses to determine the effects of eGFR on mortality. The univariate analysis revealed a significant association between eGFR and mortality (hazard ratio [HR] of 0.973 for each 1 mL/min/1.73 m² increase in eGFR; 95% confidence interval (CI): 0.954–0.994; $p = 0.009$; Table 4). Age (HR: 1.092, 95% CI: 1.033–1.157, $p = 0.002$), %FVC (HR: 0.974, 95% CI: 0.956–0.991, $p = 0.003$), %DLCO (HR: 0.948, 95% CI: 0.924–0.973, $p < 0.001$), and CPI (HR: 1.065, 95% CI: 1.034–1.099, $p < 0.001$) were also significantly associated with mortality. However, male gender (HR: 1.397, 95% CI: 0.617–3.746, $p = 0.444$), BMI (HR: 0.983, 95% CI: 0.876–1.103, $p = 0.771$), and being an ever smoker (HR: 0.707, 95% CI: 0.335–1.673, $p = 0.407$) did not show any association with mortality (Table 4). Of the comorbidities at the time of inclusion, hypertension was significantly associated with mortality (HR: 3.201, 95%

Table 1. Baseline characteristics of the patients with IPF and the controls with COPD

	IPF patients (n = 123)	COPD controls (n = 61)	p value
<i>Demographics</i>			
Male	98 (80)	60 (98)	<0.01
Age, years	69.2±7.5	70.5±6.3	0.31
BMI	23.5±2.9	21.2±2.8	<0.01
Ever smokers	103 (84)	61 (100)	<0.01
Smoking, pack-years	44.0±39.0	67.4±38.7	<0.01
Hemoglobin, g/dL	13.8±1.5	14.4±1.4	<0.01
Surgical lung biopsy	28 (23)	NA	
eGFR, mL/min/1.73 m ²	69.5±17.9	68.9±14.2	0.80
CKD (stages 3–5)	37 (30)	14 (23)	0.31
<i>Physiological data</i>			
%FVC, %	87.9±20.3	93.9±21.0	0.03
FEV ₁ /FVC, %	81.2±8.4	52.1±13.4	<0.01
%FEV ₁ , %	97.8±20.5	61.4±21.8	<0.01
%DLCO, %	44.2±14.3 ^a	58.1±19.6	<0.01
PaO ₂ , mm Hg	81.5±13.0 ^b	78.8±7.9 ^c	0.16
A-aDO ₂ , mm Hg	16.6±12.5 ^b	21.9±8.3 ^c	<0.01
6MWD, m	457±102 ^d	NA	
Minimum SpO ₂ during walking, %	87.7±6.9 ^d	NA	
CPI	48.7±17.3 ^a	NA	
<i>Comorbidities at the time of inclusion</i>			
Emphysema	31 (25)	NA	
Hypertension	29 (24)	30 (49)	<0.01
Diabetes mellitus	35 (28)	8 (13)	0.15
Dyslipidemia	30 (24)	14 (23)	0.83
Ischemic heart disease	24 (20)	4 (7)	0.02
Musculoskeletal diseases	5 (4)	4 (7)	0.46
Gastrointestinal diseases	27 (22)	13 (21)	0.92
Cerebral infarction	7 (6)	1 (2)	0.20
Charlson comorbidity index 0/1/2/3/≥4	56/46/15/4/2	33/20/6/1/1	0.84
<i>Therapeutic medications at the time of inclusion</i>			
Pirfenidone	3 (2)	NA	
Corticosteroids	6 (5)	NA	
Immunosuppressants	6 (5)	NA	

Data are presented as number of cases (%) or mean ± SD. Musculoskeletal diseases: osteoporosis, arthritis, kyphosis, scoliosis, fractures, myasthenia. Gastrointestinal diseases: gastroesophageal reflux disease, peptic ulcer, liver diseases, inflammatory and/or vascular bowel diseases, chronic pancreatitis. IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; %FVC, percent predicted forced vital capacity; FEV₁, forced expiratory volume in 1 s; %DLCO, percent predicted diffusing capacity of the lung for carbon monoxide; PaO₂, arterial partial pressure of oxygen; A-aDO₂, alveolar-arterial oxygen pressure difference; 6MWD, 6-min walking distance; SpO₂, oxygen saturation; CPI, composite physiologic index. ^a n = 118. ^b n = 111. ^c n = 60. ^d n = 96.

CI: 1.493–6.613, *p* = 0.004), whereas IHD, gastrointestinal disease, and the Charlson comorbidity index were not (HR: 1.496, 95% CI: 0.547–3.503, *p* = 0.405; HR: 0.748, 95% CI: 0.299–1.634, *p* = 0.485; and HR: 1.125, 95% CI: 0.734–1.633, *p* = 0.568, respectively) (Table 4).

Based on the results of the univariate analyses, we constructed two multivariate regression models to examine the independent effect of eGFR on mortality. After adjusting for age, %FVC, %DLCO, and the presence of hypertension, eGFR remained an independent predictor of

Table 2. Demographics and comorbidities of the patients with idiopathic pulmonary fibrosis divided by renal function

	Patients without CKD (stages 3–5) (n = 86)	Patients with CKD (n = 37)	p value
<i>Demographics</i>			
Male	66 (77)	32 (86)	0.22
Age, years	68.0±7.6	72.2±6.3	<0.01
BMI	23.4±3.1	23.8±2.5	0.49
Ever smokers	70 (81)	33 (89)	0.28
Smoking, pack-years	41.1±37.2	50.8±42.9	0.22
Hemoglobin, g/dL	13.9±1.4	13.5±1.7	0.13
<i>Comorbidities</i>			
Emphysema	21 (24)	10 (27)	0.76
Hypertension	16 (19)	13 (35)	0.048
Diabetes mellitus	24 (28)	11 (30)	0.84
Dyslipidemia	21 (24)	9 (24)	0.99
Ischemic heart disease	12 (14)	12 (32)	0.02
Musculoskeletal disease	4 (5)	1 (3)	0.62
Gastrointestinal disease	18 (21)	9 (24)	0.68
Cerebral infarction	4 (5)	3 (8)	0.45
Charlson comorbidity index 0/1/2/3/≥4	45/27/11/2/1	11/19/4/2/1	0.14

Data are presented as number of cases (%) or mean ± SD. Musculoskeletal diseases: osteoporosis, arthritis, kyphosis, scoliosis, fractures, myasthenia. Gastrointestinal diseases: gastroesophageal reflux disease, peptic ulcer, liver diseases, inflammatory and/or vascular bowel diseases, chronic pancreatitis. CKD, chronic kidney disease.

Table 3. Physiological data on the patients with idiopathic pulmonary fibrosis divided by renal function

	Patients without CKD (stages 3–5)		Patients with CKD		p value
	n	value	n	value	
%FVC, %	86	86.6±20.7	37	90.8±19.0	0.29
%DLCO, %	83	45.9±14.4	35	40.0±13.2	0.04
PaO ₂ , mm Hg	77	81.4±13.3	34	81.6±12.7	0.95
A-aDO ₂ , mm Hg	77	15.5±11.9	34	19.0±13.8	0.18
6MWD, m	68	474±84	28	416±129	0.01
Minimum SpO ₂ during walking, %	68	88.3±6.4	28	86.3±7.8	0.18
CPI	83	47.9±13.3	35	50.7±13.2	0.30

Data are mean ± SD. CKD, chronic kidney disease; %FVC, percent predicted forced vital capacity; %DLCO, percent predicted diffusing capacity of the lung for carbon monoxide; PaO₂, arterial partial pressure of oxygen; A-aDO₂, alveolar-arterial oxygen pressure difference; 6MWD, 6-min walking distance; SpO₂, oxygen saturation; CPI, composite physiologic index.

mortality in the patients with IPF (HR: 0.973, 95% CI: 0.949–0.997, *p* = 0.025) (Table 4, model 1). Furthermore, after adjusting for age, CPI, and the presence of hypertension, eGFR was found to be associated with mortality (HR: 0.972, 95% CI: 0.949–0.995, *p* = 0.015) (Table 4,

model 2). In addition, eGFR remained an independent predictor of mortality in both models even when the patients already treated with medication at the time of inclusion were excluded (data not shown).

Table 4. Cox proportional-hazard model results for evaluating the risk of mortality

	HR	95% CI	p value
<i>Univariate analysis</i>			
Age (years)	1.092	1.033–1.157	0.002
Male gender	1.397	0.617–3.746	0.444
BMI	0.983	0.876–1.103	0.771
Ever smoker	0.707	0.335–1.673	0.407
%FVC (%)	0.974	0.956–0.991	0.003
%DLCO (%)	0.948	0.924–0.973	<0.001
CPI	1.065	1.034–1.099	<0.001
eGFR (mL/min/1.73 m ²)	0.973	0.954–0.994	0.009
Hypertension	3.201	1.493–6.613	0.004
Diabetes mellitus	1.011	0.375–2.313	0.980
Dyslipidemia	0.720	0.269–1.628	0.452
Ischemic heart disease	1.496	0.547–3.503	0.405
Gastrointestinal diseases	0.748	0.299–1.634	0.485
Charlson comorbidity index	1.125	0.734–1.633	0.568
Use of pirfenidone after inclusion	0.664	0.281–1.402	0.294
<i>Multivariate analyses</i>			
<i>Model 1</i>			
Age (years)	1.040	0.978–1.108	0.209
%FVC (%)	0.985	0.961–1.006	0.162
%DLCO (%)	0.963	0.931–0.995	0.026
eGFR (mL/min/1.73 m ²)	0.973	0.949–0.997	0.025
Hypertension	1.434	0.619–3.195	0.391
<i>Model 2</i>			
Age (years)	1.029	0.969–1.095	0.347
CPI	1.064	1.029–1.102	<0.001
eGFR (mL/min/1.73 m ²)	0.972	0.949–0.995	0.015
Hypertension	1.466	0.636–3.262	0.360

Gastrointestinal diseases: gastroesophageal reflux disease, peptic ulcer, liver diseases, inflammatory and/or vascular bowel diseases, chronic pancreatitis. HR, hazard ratio; CI, confidence interval; %FVC, percent predicted forced vital capacity; %DLCO, percent predicted diffusing capacity of the lung for carbon monoxide; CPI, composite physiologic index; eGFR, estimated glomerular filtration rate.

Discussion

In this study, we focused on CKD as a comorbidity in patients with IPF. We demonstrated that 30% of IPF patients had CKD (stages 3–5), and that patients with IPF and CKD had a higher frequency of hypertension and IHD and a lower lung diffusion capacity (%DLCO) and exercise capacity (6MWD) than those with IPF and without CKD. We also found that patients with CKD had a poorer prognosis than those without CKD. Moreover, eGFR was associated with survival, even when adjusted for the known prognostic factors of age, FVC, DLCO, and

Fig. 1. Kaplan-Meier survival curves for the patients with idiopathic pulmonary fibrosis grouped on the basis of the presence of CKD stages 3–5. $p = 0.04$ by the log-rank test. CKD, chronic kidney disease.

CPI. To the best of our knowledge, this is the first study to investigate the impact of renal function on the clinical features and outcome of patients with IPF.

This study showed that the prevalence of CKD (stages 3–5) was 30% among patients with IPF and 23% among disease controls with COPD. The prevalence of CKD among patients with COPD in our study was similar to the results of a previous study [28] and is likely to be higher than its prevalence in the general population [17, 29]. Our study revealed that CKD was highly prevalent among patients with IPF as well as COPD, although the patients with IPF and CKD were mostly male (80 vs. 62%), had a higher age (69.2 ± 7.5 vs. 60.8 ± 11.6 years), and suffered hypertension (24 vs. 82%) and diabetes mellitus (28 vs. 38%) less frequently than those with CKD in the Japanese general population [29, 30].

Patients with IPF with comorbid CKD had lower %DLCO and 6MWD values than those without CKD. Emphysema and pulmonary hypertension can both result in a decreased DLCO. In the present study, the frequency of emphysema was not significantly different between IPF patients with and those without CKD, although pulmonary hypertension was not evaluated for all patients. Therefore, it is suggested that a decreased DLCO in patients with IPF and CKD may reflect disease progression rather than the presence of comorbid emphysema.

There are implications regarding the reasons for the high prevalence of CKD among patients with IPF. IPF and CKD have a common clinical epidemiology. Old age and cigarette smoking are associated with both IPF and

CKD [1, 15]. CKD may also be associated with other comorbid conditions of IPF. Pulmonary hypertension and obstructive sleep apnea are frequent comorbidities of IPF, and a link between CKD and these conditions has been reported [31, 32]. Additionally, recent epidemiologic studies have revealed that patients with IPF had an increased risk of hypertension, diabetes mellitus, and cardiovascular disease [7, 14, 18, 19], all of which are closely associated with CKD. Moreover, there may be mechanistic links between CKD and IPF, such as cellular senescence and oxidative stress [33, 34]. Hence, CKD should be considered as an important comorbidity, especially in patients with severe IPF.

In this study, the patients with IPF with comorbid CKD had significantly worse survival outcomes than those without CKD, and eGFR was an independent prognostic factor when adjusted for age and physiological data (FVC and DLCO, or CPI) in patients with IPF. We found that eGFR was associated with the established prognostic factors, such as age, %DLCO, and 6MWD [3], as well as with the presence of hypertension and IHD, which may represent the risk of cardiovascular disease. Of note, eGFR predicted survival more accurately than age, 6MWD, and the presence of hypertension and IHD. These results imply that eGFR is a comprehensive index that reflects these prognostic factors, rather than just an index for renal function in IPF. eGFR may serve as a simply calculated index to estimate the prognosis for patients with IPF, although a validation study is needed.

It is known that CKD is associated with cardiovascular disease morbidity and mortality [15]. Although previous studies have shown an association of cardiovascular disease with the survival of patients with IPF, they have not specified the cause of death [14, 35]. In the present study, no patients died due to IHD, although 2 patients met a sudden death due to unknown causes. These findings suggest that CKD does not affect mortality through the direct onset of IHD. Moreover, the frequencies of each cause of death, including acute exacerbation and chronic respiratory failure, were comparable between patients with and those without CKD, suggesting that the coexistence of CKD does not influence the risk of the development and progression of a specific clinical condition leading to death. Further epidemiologic studies comprising a larger cohort are needed to determine the impact of CKD on the clinical course and outcomes of IPF.

The effect of medication on renal dysfunction is also important. In the present study, only the use of diuretics was significantly more frequent among patients with CKD, but the frequencies of other medications were not

significantly different between patients with and those without CKD. We should be careful with the use of nephrotoxic drugs. Currently, pirfenidone can be used as a therapeutic drug for IPF, but the effect of this drug on renal function remains unknown. A previous study showed that this antifibrotic drug may be effective for renal fibrosis [36]. Although the use of pirfenidone was not associated with survival in the present study, its impact on renal function and disease outcome should be elucidated in a prospective clinical trial.

The impact of CKD on patients with IPF may differ with ethnicity. In a Japanese IPF cohort, the most common cause of death was acute exacerbation and only 3% died due to cardiovascular disease [37], whereas studies from the USA and Europe reported that 16–27% of deaths among patients with IPF were caused by cardiovascular diseases [38, 39]. Considering the established link between cardiovascular disease and CKD, renal dysfunction and mortality in patients with IPF may be more closely associated in cohorts from Western countries than in those from Japan.

We further evaluated the Charlson comorbidity index, and found that this index was not associated with survival in patients with IPF. The Charlson comorbidity index does not include hypertension and mild renal disease, whereas it does include those diseases that do not affect IPF outcomes, such as peptic ulcer and liver disease [27]. We considered that eGFR or the presence of CKD stages 3–5 reflected disease progression and outcomes more favorably than the Charlson comorbidity index in patients with IPF.

In the present study, the prevalence of diabetes mellitus among patients with IPF and CKD was almost similar to that among patients with IPF but without CKD, although diabetes is an established risk factor for CKD [15]. A previous study reported that diabetes is highly prevalent, and it may be associated with survival in patients with IPF [14]. A large prospective cohort study is needed to clarify the precise relationship between IPF, diabetes, and CKD.

There are several limitations in this study. First, because of the retrospective study design, the etiology of CKD has not been identified in most cases. Second, we did not investigate the prevalence of CKD stages 1 and 2, because albuminuria was not evaluated in this study. Third, GFR-estimating equations using standardized serum cystatin C, which may predict renal function more accurately than the equations based on serum creatinine [40], were not evaluated, since standardized serum cystatin C levels were not obtained. Fourth, the presence of

pulmonary hypertension, which occurs frequently in patients with severe CKD [31], has not been evaluated in all the patients, although it has been reported as a significant predictor of mortality in IPF. Finally, the number of patients and the duration of outcome observation were limited. Despite these limitations, the results of this study warrant larger prospective studies to investigate the clinical significance of CKD in IPF.

In conclusion, we have demonstrated that CKD (stages 3–5) or a decreased eGFR is a significant risk factor for mortality in patients with IPF. In addition, eGFR may be an easily calculated and comprehensive index to estimate the prognosis for patients with IPF.

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None of the authors have any conflicts of interest.

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