Heart failure as a cause of hospitalization in IPF: comparison of the HFpEF, HFrEF, and PH

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Abstract

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fibrosing lung disease. Some IPF patients require hospitalization because of heart failure (HF), including HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF), and HF due to pulmonary hypertension (HFPH). However, the association between IPF and HF has not been clarified. We retrospectively investigated the clinical features and outcomes of patients with IPF and HF.

Methods

We examined the data of patients with IPF who were admitted for HF to the Kindai University Hospital from January 2008 to December 2018.

Results

During the study period, 37 patients with IPF were hospitalized because of HF. Among the 34 patients finally included in the study, 17 (50.0%) were diagnosed with HFpEF, 6 (17.6%) with HFrEF, and 11 (32.3%) with HFPH. Patients with HFrEF had significantly higher values for B-type natriuretic peptide (BNP), and left ventricular (LV) end-systolic and end-diastolic diameters than patients with HFpEF and HFPH (BNP: $P = 0.01$ and $P = 0.0004$, LV end-systolic diameter: $P < 0.0001$ and $P < 0.0001$, and LV end-diastolic diameter: $P = 0.01$ and $P = 0.0004$, respectively). Notably, the difference between the LVEFs of the patients with HFpEF or HFPH was not significant. The patients with HFpEF had the best 30-day mortality rate (0%, $P = 0.02$).

Conclusions

In patients with IPF, HFpEF is the most common type of HF that requires nonelective hospitalization. Patients with HFpEF survived longer than patients with the 2 other types of HF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive and fibrosing lung disease of unknown etiology and poor prognosis [1]. The natural course of IPF is highly variable [2]. Many patients with IPF require hospitalization related to respiratory and/or cardiovascular disease [3, 4].

Heart failure (HF) is an important health problem worldwide. The prevalence of HF is estimated to be 1%–2% of the adult population in developed countries [5]. About 50% of patients with HF have a normal or nearly normal left ventricular ejection fraction (LVEF) [6–8]. The prevalence of this type of HF, termed HF

with preserved ejection fraction (HFpEF), is increased in older populations [9]. Because many patients with IPF are elderly, HFpEF may affect a high proportion of IPF patients with HF. Additionally, some patients with IPF have pulmonary hypertension (PH) that occasionally leads to right heart failure [10]. Hospitalization, which is sometimes required for patients with IPF, has recently been recognized as an important clinical outcome [11, 12]. HF can account for some of the hospitalizations of patients with IPF.

The clinical features and outcomes of patients with IPF and HF, including the HF subgroups HFpEF, HF with reduced ejection fraction (HFrEF), and HF due to PH (HFPH) are unknown. This study aimed to clarify the details of the clinical features and outcomes of HF in patients with IPF who needed nonelective hospitalization.

Methods

Patients

We retrospectively reviewed the clinical records of all patients with IPF who required nonelective hospitalization for HF to the Kindai University hospital from January 2008 to December 2018. The diagnosis of IPF was based on the eligibility criteria adopted in the INPULSIS trial [13]. Briefly, patients who had a histologically confirmed usual interstitial pneumonia (UIP) pattern on a surgical lung biopsy (SLB) specimen were included. In the absence of a SLB specimen used for confirmation of UIP, a high-resolution computed tomography (HRCT) scan showing honeycombing and/or a combination of reticular abnormalities and traction bronchiectasis without atypical features of UIP was required for study inclusion.

Diagnosis of HF

The diagnosis of HF at the hospitalization of the study patients was mainly based on the Framingham study, as follows: 1) clinical evidence of HF such as dyspnea on exertion, paroxysmal nocturnal dyspnea or orthopnea, or peripheral edema; 2) chest radiography or HRCT revealing pulmonary venous congestion, cardiomegaly, or pleural effusion; 3) level of B-type natriuretic peptide (BNP) ≥ 100 pg/mL recorded at admission; 4) deterioration not explained by other causes such as acute exacerbation of IPF, pulmonary infection, pulmonary embolism, mediastinal emphysema and/or pneumothorax, or anemia [14, 15]. The types of HF were as follows: HFpEF was defined as HF with LVEF $\geq 50\%$ and HFrEF as HF with LVEF $< 50\%$. Furthermore, patients with an echocardiographic right ventricular systolic pressure (RVSP) > 50 mm Hg, were classified with HF due to PH (HFPH) [16]. Finally, we divided the IPF patients with HF into 3 groups, as follows: HFpEF (LVEF $\geq 50\%$ and RVSP < 50 mm Hg), HFrEF (LVEF $< 50\%$ and RVSP < 50 mm Hg), and HFPH (RVSP ≥ 50 mm Hg).

Pulmonary function tests

The pulmonary function tests that were performed within 1 year prior to the hospitalization were used for baseline pulmonary function. Spirometry and single-breath measurements of diffusing capacity for

carbon monoxide were performed by the CHESTAC-8800 spirometer (Chest, Tokyo, Japan), according to current international best practices [17, 18]. Results were expressed as percentages of Japanese normal predicted values [19, 20].

Echocardiography

The LV end-systolic and end-diastolic diameters, and left atrial diameter were measured by M-mode echocardiography. LVEF was measured according to the modified Simpson method [21]. The RVSP was estimated based on a Doppler assessment of peak velocity of tricuspid regurgitation [22]. In our study, we used the data from the echocardiographic assessment performed at the time of admission.

Data Collection

We reviewed and recorded the clinical characteristics of all the study patients, which included the physical examination and standard laboratory tests upon admission, usage of long-term oxygen therapy as outpatient, and IPF treatment before the admission.

Survival assessments

We evaluated the hospital, 30-day, and 90-day mortality of the patients. All deaths were obtained from review of the hospital charts.

Recurrence of HF

Recurrence of HF in patients with IPF was reviewed. The time to recurrence was defined as the number of days from the date of hospitalization for the first episode of HF during the study period until the date of hospitalization for a recurrence of HF.

Statistical analysis

Continuous variables are presented as means $\pm$ standard deviation. Categorical variables are presented as frequencies. Comparisons between categorical variables were performed by the Fisher exact test. Comparisons between parameters for the types of HF (HFpEF, HFrEF, and HFPH) were performed by one-way analysis of variance, followed by the Bonferroni correction for multiple comparisons. For all tests, $P < 0.05$ was considered statistically significant. Analysis was performed by Statflex ver.6 software (Artech, CO., Ltd., Osaka, Osaka, Japan).

Results

Figure 1 shows the study inclusion flowchart. Thirty-seven patients with IPF were hospitalized because of HF from January 2008 through December 2018. Three were excluded because they did not undergo echocardiography. Eventually, a total of 34 patients were included in this study. Among the 34 patients, 17 (50.0%) were classified with HFpEF, 6 (17.6%) with HFrEF, and 11 (32.3%) with HFPH. The baseline characteristics of the patients before admission are shown in Table 1. The differences between the

parameters of the characteristics of the 3 study groups were not significant, except for the numbers of patients receiving corticosteroid therapy for IPF.

The clinical data of patients determined at admission are shown in Table 2. Significant differences were observed between the values for BNP, LV end-systolic diameter, LV end-diastolic diameter, LVEF, and RV end-systolic pressure ($P=0.01$, $P<0.0001$, $P=0.0005$, $P<0.0001$ and $P<0.0001$, respectively). Intergroup comparisons found that patients with HFpEF had significantly lower BNP levels than patients with HFrEF and HFPH ($P=0.01$ and $P=0.0004$, respectively). Patients with HFrEF had significantly higher values for LV end-systolic and end-diastolic diameters than patients with HFpEF ($P<0.0001$ and $P=0.01$, respectively) and HFPH ($P<0.0001$ and $P=0.0004$, respectively). Patients with HFpEF had a significantly higher value for LV end-diastolic diameter than patients with HFPH ($P=0.01$). Patients with HFrEF had significantly lower values for LVEF than patients with HFpEF and HFPH ($P<0.0001$ and $P<0.0001$, respectively). Patients with HFPH had significantly higher values for RV end-systolic pressure than patients with HFpEF and HFrEF ($P<0.0001$ and $P=0.0002$, respectively).

The outcomes of patients during the first hospitalization are shown in Table 3. The 30-day mortality rates of patients with HFpEF, HFrEF, and HFPH were 0%, 16.6%, and 36.3%, respectively, with a significantly better survival for the patients with HFpEF ($P=0.02$). The 90-day mortality rates were 11.7%, 16.6%, and 45.4% showing survival rates from best to worst for patients with HFpEF, HFrEF, and HFPH, respectively; although the differences were not significant. Differences between recurrence rates for the 3 patient groups were not significant. However, the recurrence rate of patients with HFpEF was approximately 2- to 3-fold higher than the recurrence rates of the 2 other patient groups.

Discussion

IPF is a progressive fibrosing interstitial pneumonia that increases in prevalence with advanced age [1]. The median age for the diagnosis of IPF is about 70 years [23, 24]. Some patients with IPF require hospitalization for HF during the clinical course of the disease [3]. We classified the patients with HF into 3 groups, those with HFpEF, HFrEF, or HFPH, and compared the groups. HFpEF was the most frequent type of HF. The patients with HFpEF showed the most favorable survival, but also recurred at the highest rate.

Approximately 50% of patients with HF have been reported to have a normal or nearly normal LVEF [6-8]. Old age, female sex, hypertension, high body mass index, smoking, and diabetes were reported to be risk factors for HFpEF [9, 25]. Patients with HFpEF also can have a respiratory comorbidity such as chronic obstructive pulmonary disease [26, 27], which leads to increased risk of mortality [27].

Although only a few studies have reported on the relationship between interstitial lung disease and left HF, it has been suggested that some patients with IPF have HFpEF, or diastolic dysfunction [28-30]. Our study focused on LV function in patients with IPF who were hospitalized because of HF. We found that some patients with IPF had HFpEF when they were hospitalized.

We defined patients with HFPH as those patients with an RVSP $\geq$ 50 mm Hg on echocardiography. The patients with HFPH showed the highest mortality rate. We could not clarify whether or not the PH we identified was a new condition that began at the time of hospitalization. Some patients with IPF and existing PH also need hospitalization. In those cases, the hospitalization may be associated with the existing PH and related right HF [10]. Patients who have IPF and chronic, stable PH have a poor prognosis [31, 32]. Although several clinical trials for patients with IPF and PH have been conducted, there is no effective treatment [33-38]. This might account for the poor survival of our hospitalized study patients with acute HF and PH coinciding with IPF.

A preventative treatment against the acute worsening of HFpEF remains unknown. Myocardial fibrosis is reported to be important in the pathophysiology of HFpEF [39]. Transforming growth factor beta (TGF- β) has a key role in both the development of myocardial fibrosis and IPF [40, 41]. Based on the hypothesis that HFpEF and IPF share common molecular pathways, antifibrotic agents are candidates for the treatment of patients with HFpEF and also for the prevention of acute worsening. Actually, pirfenidone, which was approved for patients with IPF, might be effective for patients with HFpEF, given that pirfenidone attenuates the profibrotic effects of TGF- β in human lung fibroblasts and inhibits cardiac fibrosis in animal models [42-46]. A phase II trial of pirfenidone for patients with HFpEF is now ongoing [47].

Nintedanib is a tyrosine kinase inhibitor that has also been approved for the treatment of IPF [48, 49]. Nintedanib has been shown to inhibit TGF- β -induced transformation of fibroblasts to myofibroblasts [50]. However, the effect of nintedanib on cardiac fibrosis has not been proven.

Our study has several limitations. First, the study was conducted in a retrospective fashion. Second, the study was performed at a single center with a small number of patients. Third, both the underdiagnosis and overdiagnosis of HF might have occurred, although we diagnosed HF based on the criteria proposed in the Framingham study [14]. IPF and HF share a number of common signs/symptoms such as cough, dyspnea, fatigue, and reduced exercise tolerance in patients with chronic stable disease [51-53]. In the acute setting, an accurate diagnosis is even more difficult to obtain. Fourth, PH was diagnosed by echocardiography, although right heart catheterization (RHC) is required for the definitive diagnosis of PH [22]. However, performing RHC for all patients with suspected PH who are hospitalized is impractical because it is an invasive and inconvenient procedure. Fifth, patients with HFpEF or HFrEF associated with PH were classified as a single group of patients with HF due to PH [54]. Further studies are needed that focus on hospitalized patients with IPF and PH in order to determine an accurate classification. And sixth, the LV function and RVSP of patients before hospitalization were unknown. We could not clarify if the HF and PH at hospitalization were due to the worsening of chronic HF and PH or the new onset of these conditions. A prospective study is needed to clarify the times of onset.

In conclusion, HFpEF is the most common type of HF that requires nonelective hospitalization in patients with IPF. Patients with HFpEF survived longer than patients with HFrEF and HFPH.

Abbreviations

BNP: B-type natriuretic peptide; HF: heart failure; HfpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HRCT: high-resolution computed tomography; IPF: idiopathic pulmonary fibrosis; LA: left atrium; LV: left ventricular; LVEF: left ventricular ejection fraction; HFPH: heart failure due to pulmonary hypertension; RHC: right heart catheter; RV: right ventricular; RVSP: right ventricular systolic pressure; SLB: surgical lung biopsy; UIP: usual interstitial pneumonia

Declarations

Ethics approval and consent to participate

Approval for the use of these data and the analysis was provided by the ethics committee of the Faculty of Medicine, Kindai University (No. 31-272). The need for informed consent was waived due to the retrospective nature of the study.

Availability of data and materials

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

Competing interests

There is no competing interest to declare in relation to the article.

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Authors' contributions

Manuscript conception and design: R.Y., O.N.; data collection and data analysis: R.Y., K. Y., S.S.; data interpretation: R.Y., O.N.; project administration: Y.T.; writing the draft of manuscript: R.Y.; critical revision and editing the final manuscript: O.N., H.S., T.I.

Guarantors of this manuscript; Y.T.

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Tables

Table 1 Baseline characteristics and treatments of patients with IPF

Variables	HFpEF n=17	HFrEF n=6	HFPH n=11	<i>P</i> value
Age, yr	78.7 ± 7.3	76.5 ± 6.3	75.8 ± 5.7	0.51
Sex				
Male/Female	12/5	5/1	9/2	0.71
Body mass index, kg/m ²	21.3 ± 4.6	22.1 ± 2.4 ^a	21.4 ± 4.3	0.91
Pulmonary function tests				
FVC, L	2.0 ± 0.6 ^b	2.8 ± 0.5 ^c	2.3 ± 0.9	0.23
FVC, % predicted	71.7 ± 20.3 ^b	80.6 ± 9.4 ^c	72.5 ± 23.8	0.75
FEV ₁ , L	1.6 ± 0.4 ^b	2.2 ± 0.6 ^c	1.9 ± 0.7	0.17
FEV ₁ /FVC, %	80.9 ± 10.5 ^b	77.5 ± 8.9 ^c	85.0 ± 10.0	0.41
DLco, mL/min/mmHg	7.1 ± 1.8 ^d	5.7 ± 2.0 ^e	6.2 ± 1.3	0.38
DLco, % predicted	55.6 ± 16.4 ^d	41.3 ± 21.8 ^e	45.8 ± 23.0	0.43
Smoking status				
yes/no	10/7	5/1	9/2	0.32
Long-term oxygen therapy				
yes/no	11/6	3/3	7/4	0.80
Treatment of IPF				
Antifibrotic agents	2	0	4	0.11
pirfenidone/nintedanib	1/1	—	2/2	
Corticosteroid	7	4	1*	0.04
Cyclosporine	5	1	0	0.13
None	9	2	6	0.66

a: n=52, b: n=4, c: n=40, d: n=3, e: n=29

Values are shown as actual numbers or means±standard deviation.

* *P*=0.01 and *P*=0.06 compared with HFpEF and HFrEF groups, respectively

DLco diffusing capacity for carbon monoxide; FEV₁ forced expiratory volume in 1 second; FVC forced vital capacity; HFpEF heart failure with preserved ejection fraction; HFPH heart failure due to pulmonary hypertension; HFrEF heart failure with reduced ejection fraction; IPF idiopathic pulmonary fibrosis; PH pulmonary hypertension

Table 2 Clinical data of patients with IPF at hospitalization

Variables	HFpEF n=17	HFrEF n=6	HFPH n=11	<i>P</i> value
Vital signs				
Heart rate, /min	82.7 ± 15.1	85.5 ± 6.2	81.6 ± 18.9	0.88
Systolic BP, mmHg	126.3 ± 19.0	125.8 ± 21.4	120.6 ± 18.8	0.73
Diastolic BP, mmHg	75.1 ± 18.0	68.8 ± 10.6	74.6 ± 16.3	0.71
Laboratory data				
Sodium, mEq/L	136.0 ± 8.1	141.6 ± 3.5	135.8 ± 8.7	0.28
Potassium, mEq/L	100.2 ± 8.2	106.3 ± 3.5	99.4 ± 8.8	0.20
Hemoglobin, g/dL	12.8 ± 2.2	12.6 ± 2.4	13.7 ± 2.7	0.54
BUN, mg/dL	21.7 ± 10.5	28.5 ± 9.8	17.1 ± 6.1	0.06
Creatinine, mg/dL	0.9 ± 0.5	1.2 ± 0.8	0.73 ± 0.2	0.19
BNP, pg/mL	250 ± 146*	1304 ± 1687	733 ± 437	0.01
KL-6, U/mL	1015 ± 611	968 ± 629	754 ± 599	0.53
Arterial blood gas				
pH	7.42 ± 0.02	7.44 ± 0.03	7.45 ± 0.07	0.59
PaO ₂ / FiO ₂ ratio	233 ± 73	211 ± 89	235 ± 89	0.82
PaCO ₂	39.6 ± 7.4	34.8 ± 6.4	40.8 ± 11.8	0.41
Echocardiography				
LA diameter, mm	38.0 ± 8.3	36.0 ± 10.0	35.0 ± 7.2	0.64
LV systolic diameter, mm	26.8 ± 4.2	40.6 ± 5.7†	26.0 ± 4.6	< 0.0001
LV diastolic diameter, mm	43.7 ± 5.6‡	51.1 ± 5.3§	37.8 ± 6.3	0.0005
LVEF, %	69.2 ± 4.7	38.6 ± 8.4	68.7 ± 4.9	<0.0001
RV systolic pressure, mmHg	38.6 ± 6.9	38.6 ± 10.9	67.6 ± 12.0¶	<0.0001

Values are shown as actual numbers or means±standard deviation

* $p=0.01$ and $p=0.0004$ compared with HFrEF and PH groups, respectively

† $p<0.0001$ and $p<0.0001$ compared with HFpEF and PH groups, respectively

‡ $P=0.01$ compared with both HFrEF and PH group

§ $P=0.0004$ compared with PH group

^{||} $P<0.0001$ compared with both HFpEF and PH group

¶ $P<0.0001$ and $p=0.0002$ compared with HFpEF and HFrEF groups, respectively

BNP brain natriuretic peptide; BP blood pressure; BUN blood urea nitrogen; HFpEF heart failure with preserved ejection fraction;

HFPH heart failure due to pulmonary hypertension; HFrEF heart failure with reduced ejection fraction; IPF idiopathic pulmonary

fibrosis; KL-6 Krebs von der Lungen-6; LA left atrium; LV left ventricular; LVEF left ventricular ejection fraction; PaCO₂ partial

pressure of carbon dioxide; PaO₂/FiO₂ partial pressure of oxygen/fraction of inspiratory oxygen; PH pulmonary hypertension; RV right

ventricular

Table 3 Outcomes of patients with IPF who were hospitalized for HF

Outcome measures	HFpEF n=17	HFrEF n=6	HFPH n=11	<i>P</i> value
Duration of hospitalization, days	25.0 ± 16.1	14.6 ± 10.0	21.5 ± 14.1	0.33
Hospital mortality, %	5.8	0	27.2	0.14
30-day mortality, %	0*	16.6	36.3	0.02
90-day mortality, %	11.7	16.6	45.4	0.11
Recurrence rate, %	37.5 [†]	16.6	12.5 [‡]	0.29

Values are shown as mean±standard deviation or actual number

* $P=0.007$ compared with PH group

[†] n=16 and [‡] n=8 because patients who died during the hospitalization were excluded.

HFpEF heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction; HFPH heart failure due to pulmonary hypertension

Figures

Figure 1

Flowchart of the enrollment of study patients HFpEF heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction; IPF idiopathic pulmonary fibrosis; LVEF left ventricular ejection fraction; HFPH heart failure due to pulmonary hypertension; RVSP right ventricular systolic pressure