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Original article

Prognostic impact of chronic obstructive pulmonary disease on adverse prognosis in hospitalized heart failure patients with preserved ejection fraction – A report from the JASPER registry

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ABSTRACT

Background: The prognostic impact of chronic obstructive pulmonary disease (COPD) on heart failure (HF) with preserved ejection fraction (HFpEF) patients and its clinical characteristics have not yet been fully examined.
Methods: The Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry is a nationwide, observational, prospective registration of consecutive Japanese hospitalized HFpEF patients with left ventricular ejection fraction (LVEF) of ≥50%. Among 535 patients enrolled in the registry, 10 lacking COPD data, and seven who died during the first hospitalization, were excluded. Finally, 518 patients were enrolled in this analysis. We divided these patients into two groups: the COPD group (n = 40, 7.7%) and the non-COPD group (n = 478, 92.3%). This analysis had two primary endpoints: (1) all-cause death and (2) all-cause death or rehospitalization for HF.
Results: The COPD group showed a higher prevalence of male sex (70.0% vs. 48.1%, p = 0.008), history of prior hospitalization for HF (63.2% vs. 35.1%, p = 0.001), smoking history (71.8% vs. 43.3%, p = 0.001), and a higher usage of loop diuretics (70.0% vs. 50.0%, p = 0.015). In the follow-up period after discharge (median 733 days), there were 82 all-cause deaths and 127 rehospitalizations for HF. In the Kaplan–Meier analysis, the COPD group showed higher all-cause death and reached the composite endpoint more often than in the non-COPD group (all-cause death, log-rank 0.035; all-cause death or rehospitalization for HF, log-rank 0.025). In the Cox proportional hazard analysis, COPD was a predictor of all-cause death (hazard ratio 1.957, 95% confidence interval 1.037–3.694, p = 0.038) and the composite endpoint (hazard ratio 1.694, 95% confidence interval 1.064–2.697, p = 0.026).
Conclusions: COPD is associated with adverse prognosis in hospitalized patients with HFpEF.

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for approximately half of all HF prevalence, and differs from HF with reduced ejection fraction (HFrEF) in several ways [1,2]. Chronic obstructive pulmonary disease (COPD) is one of the major comorbidities that is more frequently detected in patients with HFpEF than in those with HFrEF [3]. In addition, COPD is associated with higher risk of cardiovascular (CV) events in patients with HFrEF [4]. However, there is a significant interaction between COPD and left ventricular (LV) ejection fraction (LVEF) category (preserved vs. reduced) in predicting mortality [5], and the cause of death (CV vs. non-CV) differs between patients with

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HFpEF and those with HFrEF [5,6]. Thus, we hypothesized that a comparison between HFpEF patients with and without COPD would provide a new insight.

Therefore, the aim of the present analysis was to (1) examine the associations with presence of COPD and clinical characteristics including precipitating factors for admission, clinical signs, and cardiac function, and (2) to clarify the impact of COPD on hospitalized HFpEF patients who were enrolled in the Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry.

Methods

Patient recruitment

The JASPER registry is a multicenter, observational, prospective cohort that includes consecutive patients aged ≥20 years requiring hospitalization with a diagnosis of acute HF according to the Framingham criteria [7] by at least two experienced cardiologists. Preserved LV systolic function was defined as LVEF ≥50% by the modified Simpson method or LV fractional shortening ≥25% by echocardiography. Patients with acute coronary syndrome, receiving hemodialysis or a history of heart transplantation were excluded. The patients' demographic data, including comorbid conditions, clinical signs, laboratory and echocardiographic data, and length of hospital stay, were obtained. Regarding the precipitating factors for HF admission, we used the Electronic Data Capture (EDC) system for collecting clinical data from each site. Each site could select individual precipitating factors from a dropdown list on the EDC system. Thus, expert cardiologists at each site chose the most appropriate precipitating factor from these categories based on their clinical judgment. COPD was diagnosed based on the medical record, the usage of drugs to treat COPD, or the result of spirometry at each site [8]. Current smoker was defined as a patient who currently smokes cigarettes. Smoking history was defined as current or previous smoking. Mortality was defined as death from any cause, death from CV causes including sudden cardiac death (SCD) and death from worsening HF, myocardial infarction, cerebrovascular accident or other CV disease, and death from non-CV cause. Death was considered as SCD unless a specific CV other than SCD or non-CV cause was identified by the primary physician. Follow-up was performed at discharge, as well as at 12 and 24 months after discharge by dedicated coordinators and investigators: direct contact with patients or their physicians at the hospital or outpatient clinic; telephone interview of patients or, if deceased, family members; and by mail [9].

In the current study, because patient information was anonymized and de-identified prior to analyses, written informed consent was not obtained from each patient. However, the study was publicized by posting a summary of the protocol on the National Cerebral and Cardiovascular Center website, where a notice clearly informed patients of their right to refuse enrollment. These procedures for informed consent and enrollment were in accordance with the detailed regulations regarding informed consent described in the guidelines, and this study, including the procedure for enrollment, was approved by the Institutional Review Board of each site and registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601) [9].

The patient flow chart of the present analysis is shown in Fig. 1. Of 535 patients enrolled in the JASPER registry, 10 patients were excluded because it was unknown whether they had COPD or not. Next, seven patients were excluded because they died during the first hospitalization. Finally, 518 patients were enrolled in the present analysis. We divided these patients into two groups according to the presence or absence of COPD: the CODP group ($n = 40$, 7.7%) and the non-COPD group ($n = 478$, 92.3%). We compared the patients' demographic data, laboratory and echocardiographic data, length of hospital stay, and prognosis after discharge between the two groups. This analysis had two primary endpoints: (1) all-cause death and (2) all-cause death or rehospitalization for HF.

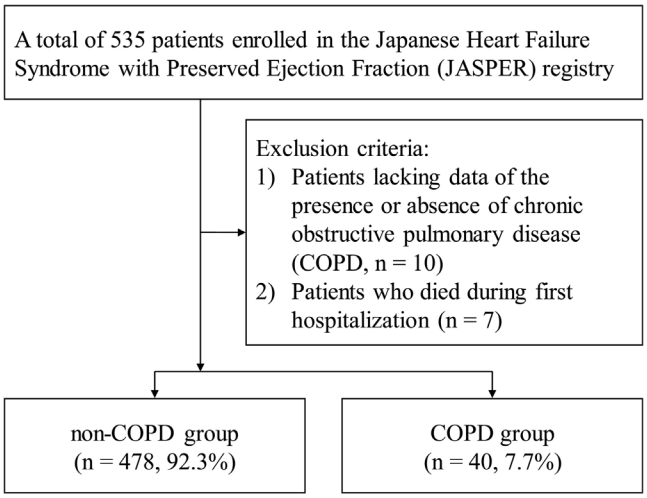


Fig. 1. Patient flow chart.

Statistical analysis

Normality was confirmed using the Shapiro–Wilk test in each group. Parametric variables were presented as mean ± standard deviation, non-parametric variables were presented as a median (interquartile range), and categorical variables were expressed as numbers and percentages. Parametric variables were compared using the Student's *t*-test, non-parametric variables were compared using the Mann–Whitney *U* test, and the chi-square test was used for comparisons of categorical variables. The Kaplan–Meier analysis was used for presenting all-cause death and the composite endpoint of all-cause death or rehospitalization for HF, and the log-rank test was used for initial comparisons. The proportional hazards assumption for the model was checked by examining log minus-log transformed data. The curves helped in identifying the non-proportionality patterns in hazard function such as convergence (the difference in risk between the two groups decreases with time), divergence, or crossing of the curves. The univariable Cox proportional hazard analysis was used to evaluate COPD as a predictor of all-cause death and the composite endpoint of all-cause death or rehospitalization for HF. To assess the potential heterogeneity of impact of COPD on these endpoints, we also conducted subgroup analyses [10]. Interactions between COPD and the clinically relevant variables, which were different between the two groups and/or generally known risk factors, were estimated by the Cox proportional hazards analysis. We chose the subgroup analysis rather than the multivariable Cox proportional hazard analysis in order to avoid over-fitting and underestimation due to multicollinearity (e.g. sex, smoking history, and hyperuricemia). Supplementarily, we performed the multivariable Cox proportional hazard analysis. The univariable factors, which were significantly different ($p < 0.05$) between the COPD and non-COPD groups, were entered into the multivariable model. A *p*-value of <0.05 was considered statistically significant for all comparisons. All analyses were performed using a statistical software package (SPSS ver. 25, IBM, Armonk, NY, USA).

Results

As shown in Fig. 1, of the 518 HFpEF patients, 40 (7.7%) had a history of COPD (the COPD group), while 478 (92.3%) did not (the

Table 1
Baseline patient characteristics on admission ($n = 518$).

	Non-COPD ($n = 478$)	COPD ($n = 40$)	p-value	Missing (%)
Age (years)	80.0 (72.0–84.0)	79.5 (74.0–83.5)	0.891	0 (0)
Male sex (%)	230 (48.1)	28 (70.0)	0.008	0 (0)
Body mass index (kg/m^2)	23.4 (21.1–26.2)	21.8 (20.7–24.6)	0.069	19 (3.7)
NYHA class III or IV (n, %)	356 (77.7)	32 (80.0)	0.740	20 (3.9)
Vital signs				
Heart rate (beats/min)	80.0 (65.0–100.0)	85.5 (68.5–104.5)	0.435	0 (0)
Systolic blood pressure (mmHg)	147.0 (125.0–171.0)	146.5 (120.0–176.5)	0.494	0 (0)
Diastolic blood pressure (mmHg)	76.0 (64.0–93.0)	76.5 (60.0–90.5)	0.885	4 (0.8)
Precipitating factors for admission				
Infection (n, %)	101 (21.1)	6 (15.0)	0.358	0 (0)
Ischemia (n, %)	12 (2.5)	2 (5.0)	0.295	0 (0)
Arrhythmia (n, %)	118 (24.7)	5 (12.5)	0.082	0 (0)
Diet non-compliance (n, %)	120 (25.1)	8 (20.0)	0.472	0 (0)
Medication non-compliance (n, %)	25 (5.2)	3 (7.5)	0.369	0 (0)
Renal failure (n, %)	18 (3.8)	2 (5.0)	0.467	0 (0)
Uncontrolled hypertension (n, %)	71 (14.9)	9 (22.5)	0.199	0 (0)
Clinical signs				
Paroxysmal nocturnal dyspnea (n, %)	192 (48.5)	21 (65.6)	0.062	90 (17.4)
Neck vein distention (n, %)	212 (50.4)	19 (52.8)	0.780	61 (11.8)
Rales (n, %)	254 (57.1)	25 (62.5)	0.506	33 (6.4)
Radiographic cardiomegaly (n, %)	358 (97.3)	33 (97.1))	0.627	116 (22.4)
Acute pulmonary edema (n, %)	219 (52.8)	23 (62.2)	0.272	66 (12.7)
S3 gallop (n, %)	139 (32.6)	11 (33.3)	0.927	58 (11.2)
Past history				
Heart failure admission (n, %)	163 (35.1)	24 (63.2)	0.001	16 (3.1)
Myocardial infarction (n, %)	56 (11.8)	7 (17.9)	0.260	4 (0.8)
Atrial fibrillation (n, %)	293 (61.8)	23 (59.0)	0.726	5 (1.0)
DM/IGT (n, %)	181 (37.9)	16 (41.0)	0.703	2 (0.4)
Hypertension (n, %)	371 (77.8)	31 (79.5)	0.805	2 (0.4)
Dyslipidemia (n, %)	200 (41.9)	19 (50.0)	0.333	3 (0.6)
Arteriosclerosis obliterans (n, %)	24 (5.1)	4 (10.3)	0.179	12 (2.3)
Cerebrovascular accident (n, %)	109 (23.1)	10 (25.6)	0.723	8 (1.5)
Chronic kidney disease (n, %)	236 (49.5)	25 (62.5)	0.114	1 (0.2)
Smoking history (n, %)	200 (43.3)	28 (71.8)	0.001	17 (3.3)
Current smoker (n, %)	42 (10.9)	5 (14.7)	0.326	97 (18.7)
Treatment on admission				
β blockers (n, %)	208 (43.5)	17 (42.5)	0.901	0 (0)
ACEIs/ARBs (n, %)	277 (57.9)	19 (47.5)	0.200	0 (0)
Loop diuretics (n, %)	239 (50.0)	28 (70.0)	0.015	0 (0)
Digitalis (n, %)	50 (10.5)	5 (12.5)	0.687	0 (0)
Home oxygen therapy (n, %)	8 (1.7)	3 (7.5)	0.014	0 (0)

COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; DM, diabetes mellitus; IGT, impaired glucose tolerance; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

non-COPD group). Comparisons of the patients' characteristics are shown in Table 1. Compared to the non-COPD group, the COPD group demonstrated higher prevalence of male sex (70.0% vs. 48.1%, $p = 0.008$), past history of smoking (71.8% vs. 43.3%, $p = 0.001$), prior HF admission (63.2% vs. 35.1%, $p = 0.001$), usage of loop diuretics (70.0% vs. 50.0%, $p = 0.015$), and home oxygen therapy (HOT, 7.5% vs. 1.7%, $p = 0.014$). The COPD group also tended to present a higher prevalence of paroxysmal nocturnal dyspnea (65.6% vs. 48.5%, $p = 0.062$). There were no statistically significant differences between the two groups regarding other clinical characteristics, such as vital signs, precipitating factors for admission (e.g. infection), or clinical signs (e.g. rales, pulmonary edema). The proportion of current smokers was comparable between the two groups. The usage of medications, including β blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) other than loop diuretics, were comparable between the groups. Laboratory data and echocardiographic parameters on admission are described in Table 2. Regarding laboratory data, the serum levels of uric acid were significantly higher in the COPD group than in the non-COPD group (7.2 mg/dL vs. 6.4 mg/dL, $p = 0.004$). There were no statistical differences in other laboratory data including plasma levels of B-type natriuretic peptide (BNP) and C-reactive protein between the two groups. In the echocardiographic parameters, LVEF and tricuspid regurgitation pressure gradient (TR-PG) did not differ between the two groups (LVEF, 60.0% vs. 60.0%, $p = 0.902$; TR-PG, 34.0 mmHg vs. 35.0 mmHg, $p = 0.517$). On the other hand, inferior vena cava diameter was smaller in the COPD group (16.8 mm vs. 19.5 mm, $p = 0.001$). Length of hospital stay did not differ between the two groups (18 vs. 15 days, $p = 0.440$). In the follow-up period after discharge (median 733 days), there were 82 all-cause deaths including 40 CV deaths and 42 non-CV deaths, and 127 rehospitalizations for HF. In the Kaplan–Meier analysis (Fig. 2), the COPD group showed higher all-cause death and reached the composite endpoint more often than the non-COPD group (all-cause death, log-rank 0.035; all-cause death or rehospitalization for HF, log-rank 0.025). In the univariable Cox proportional hazard analysis, COPD was a predictor of all-cause death (Fig. 3, hazard ratio 1.957, 95% confidence interval 1.037–3.694, $p = 0.038$) and the composite endpoint of all-cause death or rehospitalization for HF (Fig. 4, hazard ratio 1.694, 95% confidence interval 1.064–2.697, $p = 0.026$). Furthermore, to assess potential heterogeneity of impact of COPD on prognosis, we conducted subgroup analyses and examined interaction terms (Figs. 3 and 4). There were no interactions

Table 2
Laboratory data and echocardiographic parameters on admission ($n = 518$).

	Non-COPD ($n = 478$)	COPD ($n = 40$)	p-value	Missing (%)
Laboratory data				
BNP (pg/mL)	397.5 (222.6–670.3)	475.7 (282.8–702.2)	0.382	9 (1.7)
Uric acid (mg/dL)	6.4 (5.2–7.7)	7.2 (6.3–8.6)	0.004	18 (3.5)
White blood cell (/μL)	6300 (5000–8400)	6850 (5250–9400)	0.381	0 (0)
Hemoglobin (g/dL)	11.0 (9.8–12.6)	11.0 (9.8–14.1)	0.326	0 (0)
Sodium (mEq/L)	141.0 (138.0–142.0)	141.0 (137.5–142.0)	0.891	0 (0)
Potassium (mEq/L)	4.1 (3.8–4.5)	4.3 (3.8–4.7)	0.369	0 (0)
Blood urea nitrogen (mg/dL)	22.0 (16.0–31.0)	22.0 (15.0–34.2)	0.814	0 (0)
Creatinine (mg/dL)	1.03 (0.76–1.42)	1.10 (0.81–1.66)	0.354	0 (0)
C-reactive protein (mg/dL)	0.40 (0.13–1.40)	0.39 (0.20–0.83)	0.604	8 (1.5)
Albumin (g/dL)	3.7 (3.3–4.0)	3.7 (3.3–4.0)	0.678	30 (5.8)
Total cholesterol (mg/dL)	154.0 (132.0–180.0)	164.5 (133.0–190.0)	0.655	74 (14.3)
LDL cholesterol (mg/dL)	86.0 (68.0–107.0)	85.0 (62.0–104.0)	0.594	40 (7.7)
HDL cholesterol (mg/dL)	47.0 (38.0–56.0)	50.0 (43.0–54.0)	0.616	43 (8.3)
Triglyceride (mg/dL)	80.0 (57.0–108.0)	73.0 (56.0–123.0)	0.865	40 (7.7)
Total bilirubin (mg/dL)	0.7 (0.5–1.0)	0.8 (0.6–1.2)	0.960	5 (1.0)
Echocardiography				
Left atrial dimension (mm)	45.0 (39.0–50.0)	43.0 (38.5–46.9)	0.373	91 (17.6)
IVSD (mm)	11.0 (9.0–12.0)	11.0 (10.0–12.0)	0.944	73 (14.1)
LVPWD (mm)	10.2 (9.0–12.0)	10.0 (9.0–11.0)	0.261	75 (14.5)
LV diastolic diameter (mm)	46.7 ± 6.8	47.5 ± 6.1	0.457	42 (8.1)
LV systolic diameter (mm)	30.0 (26.0–34.7)	30.5 (27.0–33.9)	0.484	55 (10.6)
LV mass (g)	178.0 (145.4–214.5)	169.6 (150.7–217.7)	0.653	78 (15.1)
LV mass index (g/m^2)	114.6 (95.5–136.2)	108.3 (91.1–144.5)	0.556	97 (18.7)
LV ejection fraction (%)	60.0 (54.2–65.0)	60.0 (52.0–67.0)	0.902	37 (7.1)
IVCD (mm)	19.5 ± 6.2	16.8 ± 4.4	0.001	53 (10.2)
E wave (cm/s)	99.0 (77.4–118.0)	95.0 (75.4–106.9)	0.273	110 (21.2)
A wave (cm/s)	79.6 ± 32.1	73.5 ± 27.5	0.469	310 (59.8)
Deceleration time (ms)	178.5 (150.0–230.0)	186.5 (150.0–209.5)	0.614	122 (23.6)
TR-PG (mmHg)	35.0 (27.0–44.0)	34.0 (29.6–49.5)	0.517	65 (12.5)

COPD, chronic obstructive pulmonary disease; BNP, B-type natriuretic peptide; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IVSD, interventricular septum diameter; LVPWD, left ventricular (LV) posterior wall diameter; IVCD, inferior vena cava diameter; TR-PG, tricuspid regurgitation pressure gradient.

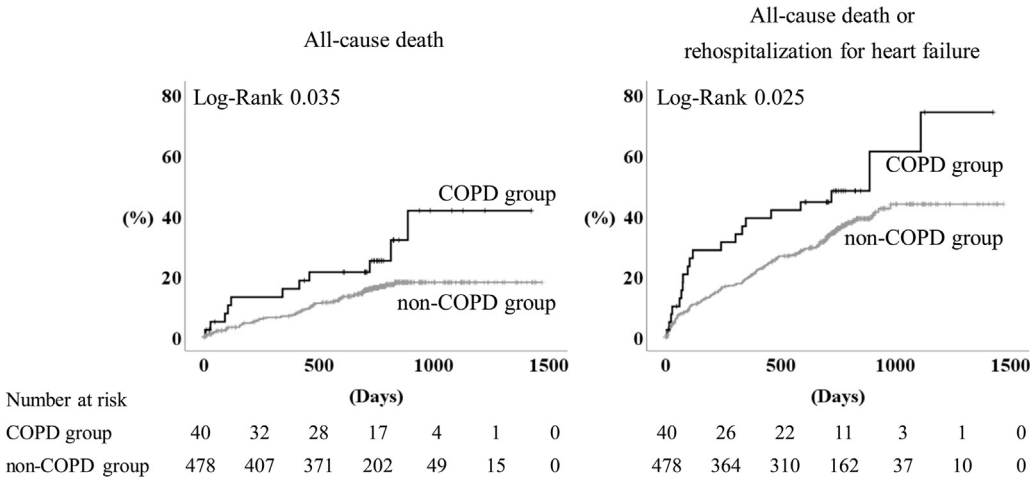


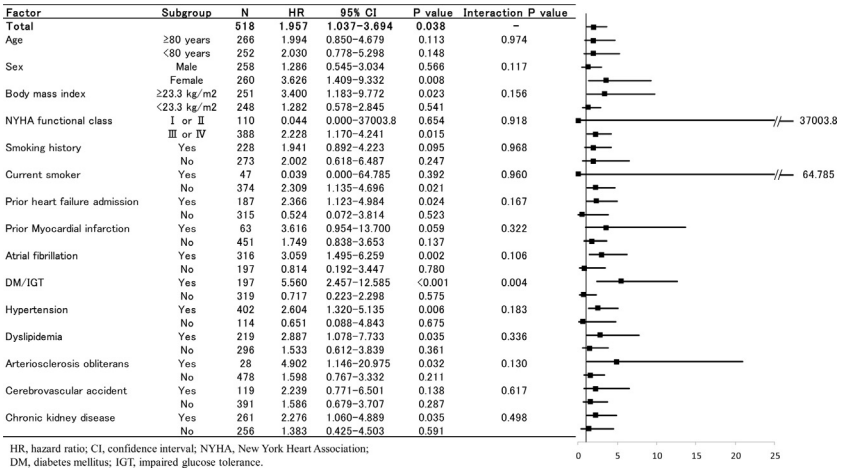
Fig. 2. The Kaplan–Meier analysis. COPD, chronic obstructive pulmonary disease.

between COPD and other clinical characteristics (e.g. age, sex, smoking, co-morbidities), except for a significant interaction with diabetes mellitus/impaired glucose tolerance for all-cause death ($p = 0.004$), and a significant interaction with atrial fibrillation for composite endpoint ($p = 0.035$). The results of the multivariable Cox proportional hazard analysis are shown in Supplemental Table 1.

Discussion

COPD was observed in 7.7% of all hospitalized HFpEF patients in this multicenter registry, and COPD was associated with (1) all-cause death and (2) all-cause death or rehospitalization for HF.

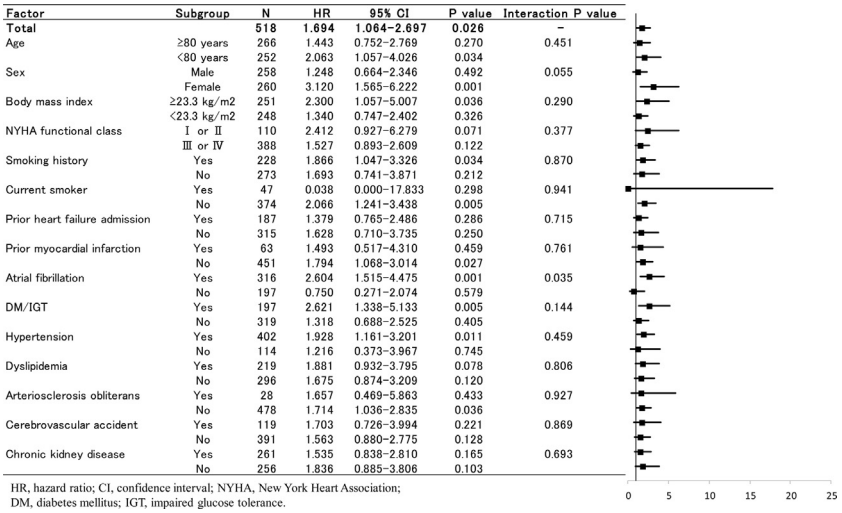
There have been several studies investigating the prognostic impact of HFpEF on COPD [11], comparing HFpEF with COPD and HFrEF with COPD [12], and searching prognostic factors of HF exploratorily [5,13]. However, except for the Acute Decompensated Heart Failure Syndromes (ATTEND) registry [13], most of them investigated chronic HF [5,12]. Moreover, considering the interaction between COPD and LVEF category [5], and the difference in the cause of death between HFpEF and HFrEF [5,6], a comparison between HFpEF patients with and without COPD is novel and necessary. This present analysis focused on acute decompensated HFpEF patients with and without COPD, and compared not only their prognosis but also clinical signs, biomarkers, and findings of echocardiography.



Factor	Subgroup	N	HR	95% CI	P value	Interaction P value
Total		**518**	**1.957**	**1.037–3.694**	**0.038**	–
Age	≥80 years	266	1.994	0.850–4.679	0.113	0.974
	<80 years	252	2.030	0.778–5.298	0.148	
Sex	Male	258	1.286	0.545–3.034	0.566	0.117
	Female	260	3.626	1.409–9.332	0.008	
Body mass index	≥23.3 kg/m2	251	3.400	1.183–9.772	0.023	0.156
	<23.3 kg/m2	248	1.282	0.578–2.845	0.541	
NYHA functional class	Ⅰ or Ⅱ	110	0.044	0.000–37003.8	0.654	0.918
	Ⅲ or Ⅳ	388	2.228	1.170–4.241	0.015	
Smoking history	Yes	228	1.941	0.892–4.223	0.095	0.968
	No	273	2.002	0.618–6.487	0.247	
Current smoker	Yes	47	0.039	0.000–64.785	0.392	0.960
	No	374	2.309	1.135–4.696	0.021	
Prior heart failure admission	Yes	187	2.366	1.123–4.984	0.024	0.167
	No	315	0.524	0.072–3.814	0.523	
Prior Myocardial infarction	Yes	63	3.616	0.954–13.700	0.059	0.322
	No	451	1.749	0.838–3.653	0.137	
Atrial fibrillation	Yes	316	3.059	1.495–6.259	0.002	0.106
	No	197	0.814	0.192–3.447	0.780	
DM/IGT	Yes	197	5.560	2.457–12.585	<0.001	0.004
	No	319	0.717	0.223–2.298	0.575	
Hypertension	Yes	402	2.604	1.320–5.135	0.006	0.183
	No	114	0.651	0.088–4.843	0.675	
Dyslipidemia	Yes	219	2.887	1.078–7.733	0.035	0.336
	No	296	1.533	0.612–3.839	0.361	
Arteriosclerosis obliterans	Yes	28	4.902	1.146–20.975	0.032	0.130
	No	478	1.598	0.767–3.332	0.211	
Cerebrovascular accident	Yes	119	2.239	0.771–6.501	0.138	0.617
	No	391	1.586	0.679–3.707	0.287	
Chronic kidney disease	Yes	261	2.276	1.060–4.889	0.035	0.498
	No	256	1.383	0.425–4.503	0.591	

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; DM, diabetes mellitus; IGT, impaired glucose tolerance.

Fig. 3. The Cox proportional hazard analysis for all-cause death: the impact of COPD. COPD, chronic obstructive pulmonary disease.



Factor	Subgroup	N	HR	95% CI	P value	Interaction P value
Total		**518**	**1.694**	**1.064–2.697**	**0.026**	–
Age	≥80 years	266	1.443	0.752–2.769	0.270	0.451
	<80 years	252	2.063	1.057–4.026	0.034	
Sex	Male	258	1.248	0.664–2.346	0.492	0.055
	Female	260	3.120	1.565–6.222	0.001	
Body mass index	≥23.3 kg/m2	251	2.300	1.057–5.007	0.036	0.290
	<23.3 kg/m2	248	1.340	0.747–2.402	0.326	
NYHA functional class	Ⅰ or Ⅱ	110	2.412	0.927–6.279	0.071	0.377
	Ⅲ or Ⅳ	388	1.527	0.893–2.609	0.122	
Smoking history	Yes	228	1.866	1.047–3.326	0.034	0.870
	No	273	1.693	0.741–3.871	0.212	
Current smoker	Yes	47	0.038	0.000–17.833	0.298	0.941
	No	374	2.066	1.241–3.438	0.005	
Prior heart failure admission	Yes	187	1.379	0.765–2.486	0.286	0.715
	No	315	1.628	0.710–3.735	0.250	
Prior myocardial infarction	Yes	63	1.493	0.517–4.310	0.459	0.761
	No	451	1.794	1.068–3.014	0.027	
Atrial fibrillation	Yes	316	2.604	1.515–4.475	0.001	0.035
	No	197	0.750	0.271–2.074	0.579	
DM/IGT	Yes	197	2.621	1.338–5.133	0.005	0.144
	No	319	1.318	0.688–2.525	0.405	
Hypertension	Yes	402	1.928	1.161–3.201	0.011	0.459
	No	114	1.216	0.373–3.967	0.745	
Dyslipidemia	Yes	219	1.881	0.932–3.795	0.078	0.806
	No	296	1.675	0.874–3.209	0.120	
Arteriosclerosis obliterans	Yes	28	1.657	0.469–5.863	0.433	0.927
	No	478	1.714	1.036–2.835	0.036	
Cerebrovascular accident	Yes	119	1.703	0.726–3.994	0.221	0.869
	No	391	1.563	0.880–2.775	0.128	
Chronic kidney disease	Yes	261	1.535	0.838–2.810	0.165	0.693
	No	256	1.836	0.885–3.806	0.103	

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; DM, diabetes mellitus; IGT, impaired glucose tolerance.

Fig. 4. The Cox proportional hazard analysis for all-cause death or rehospitalization for heart failure: the impact of chronic obstructive pulmonary disease.

COPD and HF share common risk factors and pathophysiology (e.g. age, smoking, environmental pollution, inflammation, and oxidative stress) [14–18]. Harmful particles and gas from cigarettes induce airway and/or alveolar abnormalities, resulting in airflow limitation [8]. COPD is one of the major comorbidities in HF, and the prevalence is especially high in patients with HFpEF compared to those with HFrEF [19]. COPD contributes a higher risk for all-cause mortality in HFpEF patients than in HFrEF patients [5,20]. In addition, among the patients hospitalized for HF, patients with COPD have been reported to demonstrate higher prevalence of HFpEF compared to those without COPD [21]. COPD itself can induce LV diastolic dysfunction. Tachycardia due to hypoxia and/or COPD medications (e.g. β2 agonists and theophylline) shortens diastolic filling period. Increased end-expiratory pressure due to bronchial obstruction, as well as anatomical decrease of pulmonary vein caused by emphysema, disturb venous return, leading to reduced LV preload [22]. Pericardial constraint may also reduce the LV preload. These mechanisms in turn additionally contribute to tachycardia [23,24]. Furthermore, both stiff cardiomyocyte and interstitial fibrosis caused by inflammation of COPD develop LV diastolic dysfunction [25]. Moreover, patients with COPD have higher risk of atherosclerosis causing ischemic heart disease, and this is associated with higher mortality [17,26–28]. HF patients with COPD are less likely to receive optimal medications such as β blockers and ACEIs/ARBs, since medications prescribed for HF can be affected by COPD [21]. HF also affects COPD by means of airway compression and obstruction induced by interstitial and submucosal edema. Forced expiratory volume in 1 second (% predicted) is reported to be reduced in acute decompensated HF [29]. In the present analysis, the prevalence of smoking history was significantly higher in the COPD group than in the non-COPD group. The higher male sex proportion in the COPD group may be affected by the sex difference in smoking rates. Compared to other previous registries for HFpEF performed in the USA, the proportion of COPD in the present analysis seems to be low [3,30]. However, a previous Japanese registry similarly showed a lower prevalence of COPD [31]. Similar regional variations have been reported in other large worldwide registries of HF [32] and from general populations [33,34]. The higher prevalence of prior HF admission, as well as usage of loop diuretics and HOT, in the COPD group suggest the advancement of respiratory failure and/or HF. In the present study, there were no interactions between COPD and other clinical characteristics, except for a significant interaction with diabetes mellitus/impaired glucose tolerance for all-cause death, and with atrial fibrillation for composite endpoint. Although we could not fully explain the reason for its interaction, the prognostic impact of COPD seems to be high especially in more severe complicated subjects.

In the laboratory data, BNP plasma levels were comparable between the two groups. The secretion of BNP is mainly promoted by LV stretch and diastolic wall stress [35,36]. The fact that there were no differences in LV diastolic/systolic diameter and LV wall thickness between the two groups could explain this result. In addition, HFpEF generally shows lower levels of BNP than HFrEF [37]. In the present analysis, serum levels of uric acid were significantly higher in the COPD group than in the non-COPD group. The causes of elevated serum levels of uric acid can roughly be classified as either excessive production or decreased excretion [38]. Considering the production of uric acid in the COPD group, hypoxia, systemic inflammation, and the side effect of loop diuretics could have contributed [39,40]. Previous studies have reported an increase in uric acid serum levels in patients with advanced COPD [41], as well as in those with HFpHF [42]. It has also been reported that hyperuricemia is associated with higher mortality in patients with COPD [43] and HFpEF [42,44]. In addition, hyperuricemia is associated with impaired exercise capacity, which is an independent predictor of adverse prognosis [45,46] in patients with HFpEF [44].

Regarding echocardiographic parameters in the present analysis, unexpectedly, TR-PG was similar between the two groups and inferior vena cava diameter was smaller in the COPD group. Considering that COPD can cause group three pulmonary hypertension and right ventricular dysfunction [47], these findings seem contradictory. However, from the design of observational research, it was difficult to find a reasonable explanation for these phenomena. Interestingly, concordant with the present analysis, it has been reported that there were no significant differences in echocardiographic parameters between the COPD and non-COPD groups, including patients with HFpEF and HFrEF [28]. Unlike previous reports [21], baseline medications including β blockers and ACEIs/ARBs were comparable between the groups in the present analysis.

Diagnosis and management of patients with both COPD and HFpEF is sometimes difficult [17,48,49]. In the acute phase, it is sometimes difficult to distinguish exacerbation of COPD from acute decompensated HF because the symptoms (e.g. dyspnea) are similar [11,17,48]. In the current analysis, there were no statistical differences in clinical signs on admission including paroxysmal nocturnal dyspnea between the COPD and non-COPD groups. In the chronic phase, education and self-management including smoking cessation, nutrition, and vaccination should be encouraged in patients with both COPD and HF [8,15,50]. Sometimes contradictory treatments are required (e.g. β blockers vs. β agonists), and treatments for comorbidities should be simultaneously considered [8,15,49,50]. Patients with COPD should receive long-acting β agonists, long-acting muscarinic antagonists, and/or inhaled corticosteroid on the basis of symptoms and their history of exacerbations [8,22]. In patients with HFpEF compared to those with HFrEF, hospitalizations and deaths are more likely to be due to non-CV causes [5,6]. These phenomena are consistent with previous reports that have failed to detect the effects of cardio-protective drugs, which have been reported in HFrEF [15,50], on HFpEF [51–54]. The limited prescription of β blockers is not only due to the lack of evidence in the current guidelines [50,55], but also due to the concern of bronchospasm in HFpEF patients with COPD. However, accumulating knowledge on the safety of β blockers in HF patients with COPD has led to an increase in the usage of β blockers [21]. In addition, there has been a controversial report demonstrating the prognostic efficacy of β blockers in patients with HFpEF [56]. Further studies considering the usage of cardio-protective drugs in patients with HFpEF are necessary.

Study strengths and limitations

There were several strengths to the present analysis. To the best of our knowledge, this analysis was the first to compare HFpEF patients with COPD to those without COPD, and revealed clinical differences on admission and the prognostic impact of COPD on HFpEF patients. In addition, acute HF in each patient was diagnosed according to the Framingham criteria [7] by at least two experienced cardiologists, and the participants were recruited consecutively from multiple institutions in Japan [9]. On the other hand, the current analysis had some limitations. The general limitations of the JASPER registry have been described in previous reports [9]. Focusing on COPD, since COPD was diagnosed at each site, we could not collect detailed data on the number of cigarettes used (pack-years), spirometry, exacerbation history, symptom classification such as the modified British Medical Research Council questionnaire or the COPD Assessment Test [8], or details of COPD medications. The prognostic impact of COPD medications and HOT on patients with both COPD and HFpEF remains unknown. New York Heart Association functional class could not completely exclude the symptoms caused by COPD. Because the number of participants in this analysis was relatively small, the results should be viewed as preliminary, and further studies with a larger population are needed.

Conclusion

COPD is associated with adverse prognosis in patients hospitalized for HFpEF.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.01.005.

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