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Original Article

Impact of Comorbidity of Chronic Obstructive Pulmonary Disease on Cardiovascular Events and Prognosis in Patients with Chronic Heart Failure: A Single-Center Retrospective Observational Study

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SUMMARY

Background: Although chronic obstructive pulmonary disease (COPD) is a common comorbidity of chronic heart failure (CHF), whether COPD affects either mortality or morbidity of patients with CHF remains unclear, warranting the elucidation of the impact of COPD on the cardiovascular outcome in patients with CHF.

Methods: Of 1248 patients with CHF hospitalized because of worsening of HF and discharged post-treatment between 2007 and 2009 from our institute, we enrolled 102 non-ischemic CHF patients with dilated cardiomyopathy or hypertensive heart disease.

Results: Patients with and without COPD were 25 and 77 (mean FEV1.0%, 62% ± 16% vs. 89% ± 8%; $p < 0.01$), respectively. Although the mean age in the COPD group (69 ± 13 years) was higher than the without COPD group (60 ± 16 years; $p < 0.05$), no significant differences were noted in the baseline patients' characteristics, echocardiographic parameters, such as ejection fraction (32% ± 18% vs. 27% ± 12%), and laboratory data, such as the plasma BNP levels (317 ± 272 vs. 339 ± 392 pg/dL) between the groups with and without COPD, respectively. During the median follow-up of 1239 ± 1069 days, the COPD group faced the higher risk of cardiovascular events (rehospitalization and all-cause mortality) than the without COPD group after the multivariate analyses including age, sex, echocardiographic parameters, and the use of β-blockers.

Conclusions: COPD *per se* worsens the prognosis of patients with CHF. Hence, the comorbidity of COPD merits consideration to treat patients with CHF.

1. Introduction

Cardiovascular disease (CVD) has placed a substantial burden on both individual patients and national economies worldwide.[1,2] Despite the availability of effective medical treatments, chronic heart failure (CHF) remains the main cause of increased morbidity and mortality.[3–5] Of note, hospitalization for a pathophysiological exacerbation of CHF can further augment the CHF severity, thereby activating a vicious cycle that results in cardiovascular death.[6] Thus, after the events of nonfatal hospitalization for HF, it is imperative to determine the essential comorbidity to provoke cardiovascular events, such as rehospitalization or death, because of the worsening of CHF.[6] Reportedly, comorbidities, such as hypertension or renal dysfunction, the presence of anemia or cardiomegaly, age, and sex, are significant determinants of hospitalization or cardiac death among patients with CHF.[7] Among these, chronic obstructive pulmonary disease (COPD) has recently been recognized as one of the leading causes of death in developed countries because of longevity and/or smoking.[8] Notably, hospitalization because of CVD is more often observed in patients with COPD, and CHF has represented one of the most frequent causes of the hospitalization among patients with CVD.[9] Among patients with CHF, however, the prevalence of COPD is quite high (11%–55%), suggesting the deleterious role of COPD in hospitalization because of worsening of CHF.[10] Some studies have demonstrated the role of COPD in the morbidity and mortality of patients with CHF;[11,12] however, the confounding factors of smoking, aging, and use of β-agonists/antagonists might blunt the significance of COPD in the pathophysiology of CHF.

Hence, this study aims to investigate the role of COPD in patients with CHF attributable to either dilated cardiomyopathy (DCM) or hypertension, which cannot be treated by nonpharmacological therapy, such as surgery, and is determined by comorbidities.

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2. Methods

2.1. Study design

This was a single-center, retrospective observational study. Based on the Heart Failure Registry of our institution, we examined 1248 patients with CHF who were hospitalized because of worsening of HF and discharged after appropriate treatment between 2007 and 2009. This study was approved by the National Cerebral and Cardiovascular Center Research Ethics Committee; the Committee decided that based on the Japanese Clinical Research Guidelines, it was not essential to obtain informed consent from patients selected for inclusion in this study because the study was a retrospective observational study. Instead, we made a public announcement in accordance with the Ethics Committee's request and the Japanese Clinical Research Guidelines.

2.2. Study population

Figure 1 shows the disposition of patients in the study. We excluded patients with CHF because of ischemic heart disease (IHD) because smoking is a confounding factor of both CHF because of IHD and COPD, as well as valvular diseases because these usually receive surgical therapy. Moreover, we excluded chronic myocarditis or secondary cardiomyopathy, such as cardiac sarcoidosis, because the prognosis is affected by specific treatment such as steroids. Furthermore, we excluded hypertrophic cardiomyopathy (HCM) because the prognosis of patients with HCM is affected by either genetic background or a specific treatment such as percutaneous transluminal septal myocardial ablation. After the exclusion of patients without sufficient data, we enrolled 102 non-ischemic CHF patients caused by either DCM or hypertension. All these patients received maximum tolerable doses of β-blockers and either ACE inhibitors or ARBs considering both systemic blood pressure and heart rate.

COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease[13] that defined airflow obstruction by FEV1.0/FVC < 0.70. HF was diagnosed per the criteria recommended in the Framingham Heart Study.[14] At the time of registration, both CHF and COPD were at stable phases of each disease for all patients.

2.3. Study protocol

We assessed the clinical profiles and the occurrence of cardiovascular events in enrolled CHF patients with and without COPD. All patients were followed-up in outpatient clinics along with physical examinations, blood test, and echocardiography.

2.4. Primary outcome measure

We defined the primary outcome measure as cardiovascular events of rehospitalization because of worsening of CHF and all-cause mortality. As it was difficult to separate cardiovascular and non-cardiovascular mortalities in this retrospective study, we set all-cause mortality as a part of the primary outcomes.

2.5. Secondary outcome measure

The secondary outcomes were defined as (1) each component of primary endpoints, that is, rehospitalization because of worsening of CHF and all-cause mortality, (2) echocardiogram data such as the left ventricle systolic and diastolic dimension (LVDs and LVDd), LV ejection fraction (EF), left atrium dimension (LAD), tricuspid pressure gradient (TRPG), and (3) the plasma BNP levels. We assessed secondary endpoints at the end of the follow-up in patients without the occurrence of primary outcomes or before the occurrence of primary outcomes in patients with the occurrence of primary outcomes.

2.6. Conventional echocardiography

We analyzed echocardiographic images retrospectively. A comprehensive echo-Doppler assessment was performed according to the current American Society of Echocardiography guidelines. While LVEF was obtained using the Teichholz formula, fractional shortening (FS) was evaluated using the following formula: FS = 100 × (LVEDD – LVESD)/LVEDD, where LVEDD is the LV end-diastolic dimension and LVESD is the LV end-systolic dimension. LADs were measured at the time of end-systole. In addition, the tricuspid regurgitation velocity was obtained by continuous-wave Doppler from the right ventricular inflow or the apical four-chamber view position. We evaluated TRPG as follows: TRPG = 4 × tricuspid regurgitation velocity.

2.7. Statistical analysis

The normally distributed data are presented as the median and interquartile range (IQR) or mean ± SD. For the combined endpoint analysis and the survival rate, log-rank tests and Kaplan-Meier survival analyses were performed, respectively. We estimated the relative risk of cardiovascular events using the Cox proportional hazard regression model. In this study, all tests were two-tailed; we considered $p < 0.05$ as statistically significant. These analyses were performed with the JMP software for Windows (version 8.0.2; SAS, Cary, NC).

3. Results

3.1. Comparison between the groups with and without COPD

Table 1 presents the baseline characteristics of patients at the

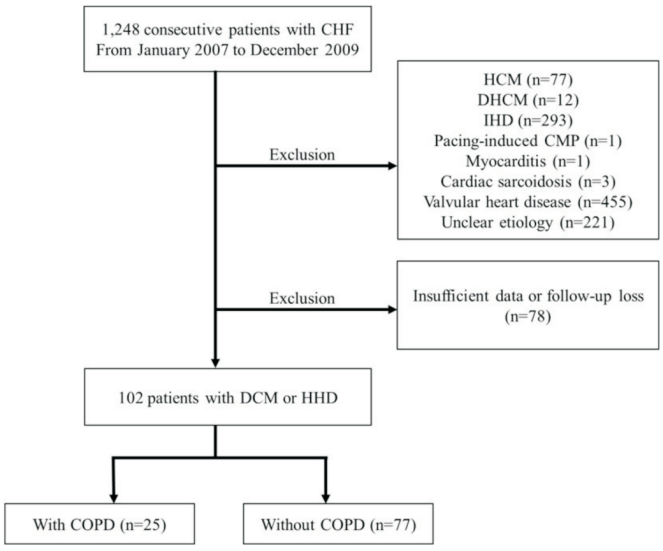

Figure 1. The schematic presentation of the study profiles. CHF, chronic heart failure; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; DHCM, dilated phase of hypertrophic cardiomyopathy; IHD, ischemic heart disease; CMP, cardiomyopathy.

time of enrollment. We observed no differences in the ratio of male and female, BMI, the prevalence of hypertension, diabetes mellitus, and atrial fibrillation or the plasma BNP levels between both groups. The age was higher, β-blockers were less frequently administered, and either ACE inhibitors or ARBs were more frequently prescribed to patients in the COPD group than patients in the without COPD group. In all patients, the incidence of either all-cause death or rehospitalization was 55.9% (57/102), with the mean follow-up period of 53.6 ± 43.6 months. The Kaplan-Meier analysis, the rate of either all-cause death or rehospitalization was higher in patients with than without COPD (Figure 2A). We observed differences in the rehospitalization rate (Figure 2B) but no differences in the rate of all-cause death between both groups (Figure 2C).

The analysis of echocardiographic parameters revealed no significant differences in LVDd, LVDs, %FS, LVEF, and LAD or the prevalence of concomitant tricuspid regurgitation between both groups (Table 2).

Table 1
The patients' characteristics of the groups with and without COPD at the baseline.

	With COPD (n = 25)	Without COPD (n = 77)	p value
Age (years)	68.8 ± 12.5	59.9 ± 16.1	< 0.01
Male gender, n (%)	22 (88)	61 (79)	0.172
Height (cm)	164.0 ± 8.1	164.4 ± 9.9	0.836
Weight (kg)	61.5 ± 9.0	58.7 ± 15.1	0.259
BMI (kg/m^2)	22.9 ± 3.6	21.6 ± 4.4	0.130
Causes of heart failure			
DCM, n (%)	12 (48)	28 (36)	0.325
HHD, n (%)	13 (52)	49 (64)	0.325
Comorbidity			
HT, n (%)	17 (68)	40 (52)	0.156
DLP, n (%)	11 (44)	25 (33)	0.321
DM, n (%)	6 (24)	19 (25)	0.947
AF, n (%)	12 (48)	24 (31)	0.152
Never smoke, n (%)	2 (8)	32 (42)	< 0.05
Respiratory Test			
FEV1.0/FVC (%)	62.4 ± 9.2	88.6 ± 8.3	< 0.01
Medication			
Diuretics, n (%)	17 (68)	67 (87)	0.073
ACEi/ARB, n (%)	23 (92)	56 (72)	< 0.05
β-blockers, n (%)	15 (60)	67 (87)	< 0.05
Aldosterone antagonist, n (%)	10 (40)	46 (60)	0.093
Laboratory data			
BNP (pg/ml)	244 (139–412)	246 (113–388)	0.754
Hemoglobin (g/dl)	13.1 ± 1.7	12.9 ± 2.1	0.603
Creatinine (mg/dl)	1.18 ± 0.36	1.17 ± 0.89	0.954
AST (IU/l)	25.6 ± 7.7	26.3 ± 10.7	0.728
ALT (IU/l)	20.1 ± 8.9	25.5 ± 18.7	0.055
CRP (mg/dl)	0.19 (0.07–0.50)	0.14 (0.05–0.39)	0.778
Transthoracic echocardiography			
LVDd (mm)	61.0 ± 10.2	63.6 ± 11.7	0.295
LVDs (mm)	49.2 ± 13.9	52.8 ± 13.6	0.269
%FS (%)	20.4 ± 12.0	17.9 ± 8.9	0.352
EF (%)	32.3 ± 18.2	26.9 ± 11.9	0.402
TRPG (mmHg)	28.6 ± 14.7	23.4 ± 14.7	0.212
LAD (mm)	48.7 ± 12.8	45.0 ± 12.7	0.077

Values expressed as the median and interquartile range (IQR), or mean ± SD. Values in parentheses are percentages.
BMI, body mass index; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; HT, hypertension; DLP, dyslipidemia; DM, diabetes mellitus; AF, atrial fibrillation; FWV1.0, forced expiratory volume in 1.0 second; FVC, forced vital capacity; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine transaminase; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; FS, fractional shortening; EF, ejection fraction; TRPG, transtricuspid pressure gradient; LAD, left atrial dimension.

3.2. Impact on prognosis

The multivariate Cox regression analysis following the univariate analysis revealed that COPD, the administration of β-blockers, LVDd, and LVDs, and the plasma BNP levels were independent predictors of the primary endpoint of all-cause death or rehospitalization after adjusting for age and sex (Table 3).

4. Discussion

The effects of the present investigation are two-fold. First, the incidence of COPD in patients with CHF because of DCM or hypertensive heart disease was 25%. Second, this study offers new

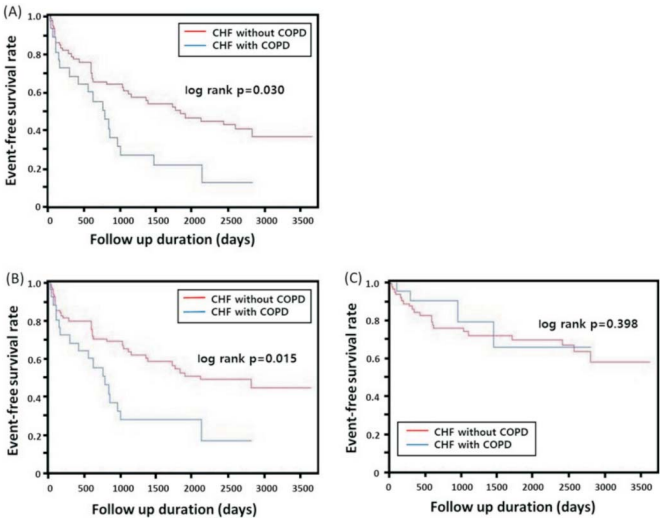

Figure 2. The Kaplan-Meier event-free survival curves in patients with COPD and without COPD groups. (A) CHF patients in the COPD group exhibited higher rehospitalization of CHF or all-cause mortality event-free rate compared with CHF patients in the without COPD group. (B) CHF patients in the COPD group exhibited higher rehospitalization of the CHF event-free rate compared with CHF patients in the without COPD group. (C) No differences of all-cause mortality between both groups.

Table 2
Comparison between the two groups with and without COPD at the endpoint.

	With COPD (n = 25)	Without COPD (n = 77)	p value
NYHA functional classification	3.20 ± 0.87	3.16 ± 0.89	0.449
Laboratory data			
BNP (pg/ml)	688 (451–1200)	793 (274–1358)	0.709
Hemoglobin (g/dl)	12.8 ± 4.4	13.1 ± 3.0	0.603
Creatinine (mg/dl)	1.40 ± 0.73	1.55 ± 1.03	0.486
AST (IU/l)	27.7 ± 13.4	31.6 ± 16.0	0.289
ALT (IU/l)	22.2 ± 15.4	25.6 ± 18.5	0.470
CRP (mg/dl)	0.50 (0.16–2.3)	0.55 (0.19–1.15)	0.734
Transthoracic echocardiography			
LVDd (mm)	62.3 ± 25.0	67.8 ± 17.8	0.152
LVDs (mm)	52.9 ± 23.5	58.3 ± 18.4	0.241
%FS (%)	16.5 ± 11.7	15.3 ± 10.3	0.692
EF (%)	29.8 ± 19.4	27.6 ± 16.7	0.698
TRPG (mmHg)	40.8 ± 23.4	35.2 ± 18.3	0.266
LAD (mm)	50.0 ± 22.6	52.2 ± 18.9	0.464

Values expressed as the median and interquartile range (IQR), or mean ± SD.
NYHA, New York Heart Association. The other abbreviations are same as in Table 1.

Table 3
Univariate and multivariate analyses for all-cause death or rehospitalization.

Variable	Hazard ratio* (95%CI)	p value
Univariate analysis		
Age (years)	1.003 (0.99–1.02)	0.69
Male gender	0.933 (0.48–1.81)	0.837
COPD	2.439 (1.38–4.31)	< 0.005
AF	1.116 (0.63–1.97)	0.705
Never smoke	0.581 (0.25–1.34)	0.202
ACEi/ARB	1.025 (0.53–1.99)	0.942
β-blockers	0.514 (0.27–0.95)	< 0.05
BNP (pg/ml)	1.0009 (1.0001–1.001)	< 0.05
Hemoglobin (g/dl)	0.946 (0.82–1.09)	0.436
Creatinine (mg/dl)	1.286 (0.76–1.75)	0.213
AST (IU/l)	1.018 (0.99–1.04)	0.166
LVDd (mm)	1.032 (1.01–1.06)	< 0.05
LVDs (mm)	1.024 (1.00–1.05)	< 0.05
%FS (%)	0.987 (0.95–1.02)	0.431
EF (%)	0.989 (0.97–1.01)	0.304
Multivariate analysis		
Age (years)	0.987 (0.97–1.01)	0.231
Male gender	0.757 (0.38–1.51)	0.43
COPD	2.902 (1.53–5.51)	< 0.01
β-blockers	0.395 (0.19–0.84)	< 0.05
Never smoke	0.821 (0.28–2.39)	0.717
BNP (pg/ml)	1.001 (1.000–1.002)	< 0.01
LVDd (mm)	1.052 (1.02–1.09)	< 0.01
%FS (%)	1.017 (0.98–1.06)	0.393

* The effect estimate represents the change in score per 1 unit change in the parameter after adjusting for all other terms in the model.
CI, confidence interval; COPD, chronic obstructive pulmonary disease. The other abbreviations are same as in Table 1.

pathophysiological evidence of COPD on cardiovascular events in CHF patients without changes in the geometry of hearts or the plasma BNP levels.

4.1. Correlation between COPD and CHF

COPD is one of the leading comorbidities of CHF, with the reported prevalence of 11%–55%,[10] which corroborates this study; the high prevalence could be attributed to the fact that both CHF and COPD share identical risk factors in each disease. Indeed, the high prevalence of smoking is observed in patients with both IHD and COPD, which could explain the high prevalence of COPD in IHD-induced CHF patients. Although smoking is a potent risk factor of IHD, such as myocardial infarction leading to CHF, we observed the high prevalence of COPD in this study in non-ischemic CHF attributable to DCM or hypertension, indicating that the reason for the high incidence of COPD in CHF patients in this study might not be attributable to shared comorbidities with IHD-induced CHF and COPD.

Another possibility to explain the close correlation between COPD and CHF is the idea that COPD worsens the CVD pathophysiology. CVD, such as DCM and hypertension, does not necessarily cause overt symptomatic CHF with NYHA II–IV. As our patients were once hospitalized because of worsening of CHF or acute-onset CHF, they belonged to the category of overt CHF. In this case, COPD might worsen the pathophysiology of CHF from latent to overt and symptomatic status. In other words, COPD might prime the onset of symptomatic CHF among latent CHF patients, which could be one of the reasons for the high incidence of COPD in patients with CHF. Indeed, COPD might cause low oxygen saturation of the blood, which might cause mild hypoxia of the myocardium.[15] Moreover, COPD might activate systemic inflammation.[16–19] Patients with COPD exhibited higher levels of CRP, serum fibrinogen, TNF-α, IL-6 in the systemic blood, suggesting that the presence of systemic inflammation in patients with COPD might further prime asymptomatic to symptomatic CHF.

4.2. The role of COPD in the cardiovascular outcomes in patients with CHF

This study demonstrated that COPD primarily worsens the cardiovascular outcomes for CHF, as well as COPD accompanies CHF, indicating that COPD not only coexists with CHF but also worsens the CHF pathophysiology to acute HF or death. Smoking is the leading cause of COPD and CVD, where COPD worsens coronary atherosclerosis and causes myocardial ischemia. However, in this study, we enrolled patients with non-ischemic CHF and determined that COPD worsens the cardiovascular outcomes in patients with CHF. In addition, the inflammation because of COPD might affect the cardiovascular outcomes in patients with CHF. Reportedly, cytokines, including TNF-α, deleteriously control the cardiovascular outcomes of CHF.[20,21] In the present study, we observed the increases in plasma CRP levels in the CHF with COPD group compared with the CHF without COPD groups, although we did not observe the plasma TNF-α levels, suggesting the involvement of inflammation in the COPD-induced worthening of the pathophysiology of CHF. Another possibility that COPD worsens the CHF pathophysiology is that COPD might limit the physical activity because of dyspnea, and less physical activity might provoke the frail or cachexia in patients with CHF. However, this may not be the case because we found no difference in either body weight or body mass index between the CHF with and without COPD groups. This may be because the pathophysiology of COPD in the patients with CHF may not so severe in the enrolled patients with CHF in the present study; this may indicate that even mild COPD may affect the severity of CHF. These vicious sequels originated from COPD might explain the correlation between COPD and CHF reported in this study.

Conversely, no differences were observed in geometric and contractile characteristics of the heart in CHF patients with and without COPD in this study because frequent occurrences of cardiovascular events might correlate with the deterioration of the cardiovascular function or high BNP levels. One possible explanation is that the existence of emphysema limits the enlargement of the heart in patients with CHF. In patients with CHF, it is normally considered that an increment in cardiac dimension or volumes is the compensatory mechanism to maintain the cardiac output; however, an increment in the ventricular size increases the ventricular wall tension and oxygen demand, which further worsens ventricular contractility, named as "cardiovascular remodeling".[22] In such a remodeling situation, emphysema attenuates ventricular enlargement in the limited space of the thorax, which also exhibits ventricular contraction.[23] However, in this condition, the intrathoracic pressure might be increased resulting in the increased LV filling pressure and, thus, LV diastolic heart failure or HF with preserved ejection fraction (HFpEF). Indeed, Barr et al. demonstrated that emphysema or COPD impairs LV filling[24] and COPD reportedly causes HFpEF.[25]

Regarding the drug interaction during treatment of COPD or CHF, patients with COPD and CHF typically receive β_2- and β_1-adrenergic antagonists such as bisoprolol/non-specific β-adrenergic antagonists such as carvedilol, respectively. Partial β_1-adrenergic agonism in the case of using β_2-adrenergic agonists might worsen the pathophysiology of CHF. However, in this study, no patient received β_2-adrenergic agonists, thereby denying this idea. Conversely, the use of β-adrenergic antagonists in CHF might worsen the COPD

pathophysiology and, thus, worsen CHF. However, this might be denied because the use of β-adrenergic antagonists is an independent predictor for the decreases in the primary cardiovascular outcomes in this study.

4.3. Study limitations

This study has several limitations. First, because this study was a single-center study, the number of patients was limited, especially those with CHF. Our hospital is a leading hospital with a high volume of patients with CHF; we have a database of > 10,000 CHF patients with precise information on the etiology and severity of CHF. Nevertheless, we cannot obtain a large number of patients who received the respiratory test in the database of patients with CHF; to resolve this, we suggest testing the present hypothesis using larger multicenter trials. Second, this is a retrospective study, and we cannot add the laboratory tests for COPD or CHF such as the presence of emphysema. Hence, a prospective study is warranted to collect all necessary data to analyze the pathophysiology of COPD and CHF.

Finally, to draw a firm conclusion of the close correlation between COPD and CHF, we need to treat COPD to test whether the severity of CHF decreases. At present, we are planning a multicenter interventional study using the drug for COPD in patients with both CHF and COPD.

4.4. Clinical perspectives

This study reveals cardiovascular outcomes in CHF patients with and without COPD and determines that COPD worsens the clinical outcomes in patients with CHF. This phenomenon indicates that the pathophysiology of COPD primed the progression of CHF. As COPD might prime the onset of COPD, we should be vigilant for COPD comorbidity in patients with CHF.

5. Conclusions

We found out the role of COPD in patients with CHF attributable to cardiomyopathy and offered new pathophysiological evidence of COPD on cardiovascular events in CHF patients without changes in the geometry of hearts or the plasma BNP levels. This study investigated that COPD primarily worsens the cardiovascular outcomes for CHF, as well as COPD accompanies CHF, indicating that COPD not only coexists with CHF but also worsens the CHF pathophysiology to acute HF or death. That is COPD *per se* worsens the prognosis of patients with CHF. Hence, the comorbidity of COPD merits consideration to treat patients with CHF.

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There is nothing to disclose of the contributions, names, degrees, affiliations, and indication (if compensation has been received for all persons who have made substantial contributions to the work but who are not authors).

Conflict of interest disclosures

All co-authors of this manuscript have read and approved the submission of the manuscript. All of the authors have made an important contribution to the study and are thoroughly familiar with the original data.

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest: Dr. Hayashi and Fukuda have nothing to disclose; Dr. Hasegawa reports other from Takeda Pharmaceutical Company Limited, other from Daiichi Sankyo Company, Limited, other from Otsuka Pharmaceutical Co., Ltd., other from Bayer Yakuhin, Ltd., other from Mitsubishi Tanabe Pharma Corporation, other from Abbott Vascular Japan Co., Ltd., other from Shionogi & Co., Ltd., during the conduct of the study; Dr. Kanzaki have nothing to disclose; Dr. Takahama reports grants from The Bayer Scholarship for Cardiovascular Research, grants from Japan ministry of education, culture, sports, science and technology, outside the submitted work; Dr. Amaki reports grants from Japan Heart Foundation/Bayer Yakuhin Research Grant Abroad, grants from Suzuken Memorial Foundation, non-financial support from Abbott Vascular Japan, non-financial support from Takeda Pharmaceutical Company, outside the submitted work; Drs Maeda, Sakamoto, Sata, Ito, Izumiya and Yoshiyama have nothing to disclose; Dr. Kitakaze reports grants and personal fees from Takeda, during the conduct of the study; grants from Japanese government, grants from Japan Heart Foundation, grants from Japan Cardiovascular Research Foundation, grants and personal fees from Asteras, grants and personal fees from Sanofi, personal fees from Daiichi-sankyo, grants and personal fees from Pfizer, grants and personal fees from Ono, personal fees from Bayer, grants and personal fees from Novartis, personal fees from Bheringer, grants and personal fees from Tanabe-mitubishi, personal fees from Kowa, grants and personal fees from Kyowa-hakko-kirin, personal fees from Dainihon-sumitomo, personal fees from Sawai, personal fees from MSD, grants and personal fees from Abott, grants and personal fees from Otsuka, grants from Calpis, grants from Nihon Kohden, personal fees from Shionogi, personal fees from Astrazeneca, personal fees from Asahikasei Med., personal fees from Novo nordisk, personal fees from Fuji-film RI, personal fees from Japan Medical Data, outside the submitted work.

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