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ORIGINAL RESEARCH

Impacts of Comorbid Chronic Obstructive Pulmonary Disease and Congestive Heart Failure on Prognosis of Critically Ill Patients

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Background: Comorbid congestive heart failure (CHF) was associated with worse prognosis in patients with chronic obstructive pulmonary disease (COPD), while few studies specially investigated critically ill patients. This study investigated the associations between comorbid COPD with or without CHF and prognosis of patients admitted to intensive care units (ICU).

Methods: We conducted a retrospective cohort study in the Medical Information Mart for Intensive Care III database. Adult ICU patients were included and categorized as patients without COPD and CHF, patients with COPD but without CHF, patients with CHF but without COPD, and patients with both COPD and CHF. The study outcomes were 28-day mortality and 90-day mortality after ICU admission. Kaplan–Meier curves were plotted to estimate the survival distributions between groups and multivariable Cox regression analyses were employed to evaluate the associations between comorbid COPD and/or CHF and the study outcomes.

Results: A total of 29,589 patients were included with 20,507 patients without COPD and CHF, 1575 patients with COPD, 6190 patients with CHF, and 1317 patients with both COPD and CHF. The highest 28-day mortality rate and 90-day mortality rate were found in patients with both COPD and CHF (15.95% and 25.74%, respectively), while patients with COPD and patients with CHF had similar mortality rates, also observed in Kaplan–Meier curves. Compared with patients without COPD or CHF, comorbid COPD or CHF both significantly increased the risk of 28-day mortality and 90-day mortality, but comorbid COPD and CHF together was associated with the highest risk of mortality (hazard ratio 1.55 (95% confidence interval (CI) 1.33–1.80) and 1.25 (95% CI 1.16–1.35) for 28-day mortality and 90-day mortality, respectively), while no significant interaction between COPD and CHF was found.

Conclusion: ICU patients with comorbid COPD or CHF both experienced greater mortalities, while these two risk factors seemed to play an independent role.

Keywords: chronic obstructive pulmonary disease, comorbidity, heart failure, mortality, critical care

Background

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are both common in hospitalized patients, especially for elderly patients.[1,2] A population-based study from Denmark[3] found the gross cost of treating hospitalized COPD patients accounted for 10% of the total cost of treating patients aged 40 years or more. In the United States in 2004, over one million patients were discharged with a first listed diagnosis of HF.[4] These two diseases are both also associated with poor

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prognosis. An European study reported a 10.8% mortality rate of patients admitted with exacerbated COPD, of which 45.7% died in hospital and 54.3% died during the 90-day post-discharge follow-up.[5] In the REPORT-HF cohort study which included patients admitted for acute heart failure, 20% died within 1 year after discharge.[6]

Since the two diseases share similar risk factors, they frequently coexist in clinical practice.[7,8] A study including 9748 hospitalized patients with acute decompensated heart failure reported approximately 35% of patients had COPD,[9] while 20% of COPD patients were diagnosed with left heart failure after extensive cardiovascular examination, in a study that included patients aged over 65 years.[10] Moreover, the coexistence of these diseases is found to be associated with worse prognosis. A recent meta-analysis included 28 studies that compared prognosis of COPD patients with HF with those without HF, and the main finding was that comorbid HF increased risk of all-cause mortality in COPD patients with a pooled hazard ratio of 1.61.[11] Another meta-analysis that included 68 studies reported that COPD was associated with increased mortality in non-selected HF patients with a pooled hazard ratio of 1.39.[12]

However, most of the above studies mainly investigated general hospitalized patients only. Considering patients admitted to intensive care unit (ICU) usually had much more serious conditions and had high prevalence of COPD and HF,[12,13] it remains unclear whether these two comorbidities also have the same impact on prognosis of critically ill patients. Thus, to provide relevant evidence in an ICU setting, the study investigated the associations between comorbid COPD with or without congestive heart failure (CHF) and clinical outcomes of patients admitted to ICU.

Methods

Study Design and Participants

The study used a retrospective cohort study design. Data were retrieved from the Medical Information Mart for Intensive Care (MIMIC) III, which is a large, freely-available database comprising deidentified health-related data associated with patients admitted to critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012.[14] This study was exempt from institutional review board approval due to the retrospective design, lack of direct patient intervention, and the security schema for which the reidentification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA).

All adult (age ≥18 years) patients in the database were included, but for patients who had more than one ICU admission in the database, only the first ICU admission was included. We also excluded patients who stayed in ICU less than 24 hours. Detailed inclusion of the participants is showed in Figure 1.

Variables Extraction

Data on variables needed for analysis were extracted using Structured Query Language (SQL) with the help from the MIMIC Code Repository.[15] We defined the date of ICU admission as baseline and extracted baseline characteristics including age, sex, ethnicity, type of admission (elective or urgent), Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score (SAPS) II, mechanical ventilation on first day, renal replacement therapy on first day, sepsis, cardiac arrhythmias,

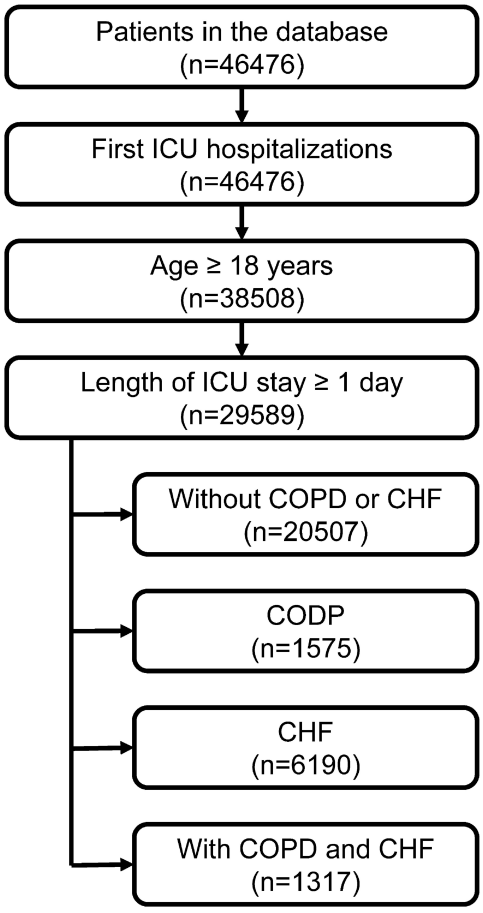

Figure 1 Inclusion of the study subjects.
Abbreviations: ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

valvular disease, pulmonary circulation disorder, hypertension, uncomplicated diabetes, complicated diabetes, renal failure, liver disease, metastatic cancer, and obesity.

COPD and CHF were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (491.20, 491.21, 491.22, and 496 for COPD; 398.91, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, and 428.9 for CHF).

Outcomes and Follow-Up

We used 28-day mortality and 90-day mortality after ICU admission as the main study outcomes. ICU mortality, hospital mortality, length of ICU stay, and length of hospital stay were also described. All included participants were categorized as patients without COPD and CHF, patients with COPD but without CHF, patients with CHF but without COPD, and patients with both COPD and CHF, and followed from the date of ICU admission for at least 90 days unless the interested outcome occurred.

Statistical Analysis

Data were presented as median (25–75% percentile) or number (percentage) based on type of variables. Comparisons between groups were examined by Kruskal–Wallis test or Chi-squared test. Kaplan–Meier curves were plotted to estimate the survival distributions of each group and multivariable Cox regression analyses were employed to evaluate the associations between comorbid COPD and/or CHF and the study outcomes. Two models were predefined for adjustment for potential confounding. Model I was adjusted for age and sex; model II was adjusted for age, sex, type of admission; ethnicity, SOFA, SAPS II, sepsis, mechanical ventilation on first day, renal replacement therapy on first day, and comorbidities including cardiac arrhythmias, valvular disease, pulmonary circulation disorder, hypertension, uncomplicated diabetes, complicated diabetes, renal failure, liver disease, metastatic cancer, and obesity. A P-value less than 0.05 is considered as statistically significant. All the analyses were performed using Empower(R) (www.empowerstats.com X&Y solutions, Inc., Boston, MA) program.

Results

Characteristics of the Participants

A total of 29,589 patients were included in the study. Among them, 20,507 patients were without COPD and CHF, 1575 patients were with COPD (without CHF), 6190 patients were with CHF (without COPD), and 1317 patients were with both COPD and CHF. The median age of all the participants was 65.75 (52.78–77.66) years, 56.90% of them were male, and 71.46% of them were white people. Compared with patients without COPD or CHF, the other groups had a greater median age, and patients with COPD and CHF had the largest median age (75.78 (67.56–82.31) years). Proportions of sex and ethnicity were similar between groups, but a higher proportion of white people could be observed in patients with COPD and patients with COPD and CHF.

Most (82.17%) patients in the study were admitted urgently, and compared with patients without COPD or CHF, the other groups had a larger SOFA and SAPS II on admission. Patients with COPD had the highest proportion (52.95%) of mechanical ventilation on first day, while patients with CHF had the highest proportion (4.30%) of renal replacement therapy on first day. Great difference could be found in some comorbidities between groups, such as a much larger prevalence of valvular disease and hypertension in patients with CHF. Detailed characteristics of the participants are shown in Table 1.

Prognosis of the Participants

The overall 28-day mortality and 90-day mortality were 8.61% and 13.73% respectively, with a length of ICU stay of 2.42 (1.58–4.46) days and a length of hospital stay 7.82 (4.98–13.00) days. The highest 28-day mortality rate and 90-day mortality rate were found in patients with both COPD and CHF (15.95% and 25.74%), while patients with COPD and patients with CHF had similar mortality rates, which were consistent with results of Kaplan–Meier curves (Figure 2). Similar results could be found for ICU mortality and hospital mortality. Detailed results are shown in Table 2.

Associations Between Comorbid COPD and/or CHF and Prognosis

Compared with patients without COPD or CHF, after multivariable adjustment, comorbid COPD or CHF both significantly increased the risk of 28-day mortality and 90-day mortality, but comorbid COPD and CHF together was associated with the highest risk of mortality (hazard ratio 1.55 (95% confidence interval (CI) 1.33–1.80) and 1.25 (95% CI 1.16–1.35) for 28-day mortality and 90-day mortality respectively). The interaction between COPD and

Table 1 Characteristics of the Study Subjects

Variables	All Subjects (n=29,589)	Without COPD or CHF (n=20,507)	COPD (n=1575)	CHF (n=6190)	With COPD and CHF (n=1317)	P value
Age (years)	65.75 (52.78–77.66)	61.29 (48.81–74.09)	70.74 (62.41–78.45)	74.66 (63.00–83.24)	75.78 (67.56–82.31)	<0.001
Male	16,835 (56.90%)	11,973 (58.38%)	873 (55.43%)	3302 (53.34%)	687 (52.16%)	<0.001
Ethnicity						<0.001
White	21,143 (71.46%)	14,429 (70.36%)	1221 (77.52%)	4492 (72.57%)	1001 (76.01%)	
Black	2278 (7.70%)	1630 (7.95%)	69 (4.38%)	511 (8.26%)	68 (5.16%)	
Asian	711 (2.40%)	561 (2.74%)	21 (1.33%)	117 (1.89%)	12 (0.91%)	
Hispanic/Latino	950 (3.21%)	763 (3.72%)	25 (1.59%)	143 (2.31%)	19 (1.44%)	
Other	4507 (15.23%)	3124 (15.23%)	239 (15.17%)	927 (14.98%)	217 (16.48%)	
Type of admission						<0.001
Elective	5276 (17.83%)	3926 (19.14%)	316 (20.06%)	886 (14.31%)	148 (11.24%)	
Urgent	24,313 (82.17%)	16,581 (80.86%)	1259 (79.94%)	5304 (85.69%)	1169 (88.76%)	
SOFA on admission	4 (2–6)	3 (2–5)	4 (2–6)	4 (3–7)	4 (2–6)	<0.001
SAPS II on admission	33 (25–42)	31 (23–40)	35 (28–44)	38 (30–46)	38 (32–46)	<0.001
Mechanical ventilation on first day	14,399 (48.66%)	10,003 (48.78%)	834 (52.95%)	2928 (47.30%)	634 (48.14%)	<0.001
Renal replacement therapy on first day	812 (2.74%)	468 (2.28%)	28 (1.78%)	266 (4.30%)	50 (3.80%)	<0.001
Sepsis	1914 (6.47%)	1152 (5.62%)	110 (6.98%)	557 (9.00%)	95 (7.21%)	<0.001
Comorbidities						
Cardiac arrhythmias	8783 (29.68%)	4451 (21.70%)	480 (30.48%)	3167 (51.16%)	685 (52.01%)	<0.001
Valvular disease	5070 (17.13%)	2423 (11.82%)	189 (12.00%)	2062 (33.31%)	396 (30.07%)	<0.001
Pulmonary circulation disorder	2038 (6.89%)	907 (4.42%)	112 (7.11%)	803 (12.97%)	216 (16.40%)	<0.001
Hypertension	16,156 (54.60%)	10,600 (51.69%)	959 (60.89%)	3803 (61.44%)	794 (60.29%)	<0.001
Uncomplicated diabetes	5960 (20.14%)	3682 (17.95%)	360 (22.86%)	1569 (25.35%)	349 (26.50%)	<0.001
Complicated diabetes	1747 (5.90%)	926 (4.52%)	56 (3.56%)	647 (10.45%)	118 (8.96%)	<0.001
Renal failure	3564 (12.05%)	1644 (8.02%)	166 (10.54%)	1432 (23.13%)	322 (24.45%)	<0.001
Liver disease	2052 (6.94%)	1607 (7.84%)	103 (6.54%)	284 (4.59%)	58 (4.40%)	<0.001
Metastatic cancer	1756 (5.93%)	1366 (6.66%)	145 (9.21%)	195 (3.15%)	50 (3.80%)	<0.001
Obesity	1602 (5.41%)	1003 (4.89%)	117 (7.43%)	370 (5.98%)	112 (8.50%)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score.

CHF was statistically significant in the crude model (P=0.0295 for 28-day mortality and P=0.0220 for 90-day mortality), but after multivariable adjustment it became non-significant either for 28-day mortality or 90-day mortality (P=0.7167 for 28-day mortality and P=0.9533 for 90-day mortality in adjusted model I; P=0.6269 for 28-day mortality and P=0.3671 for 90-day mortality in adjusted model II). Detailed results are shown in Table 3.

Discussion

This study included a large sample size of critically ill patients and investigated differences in the prognosis of

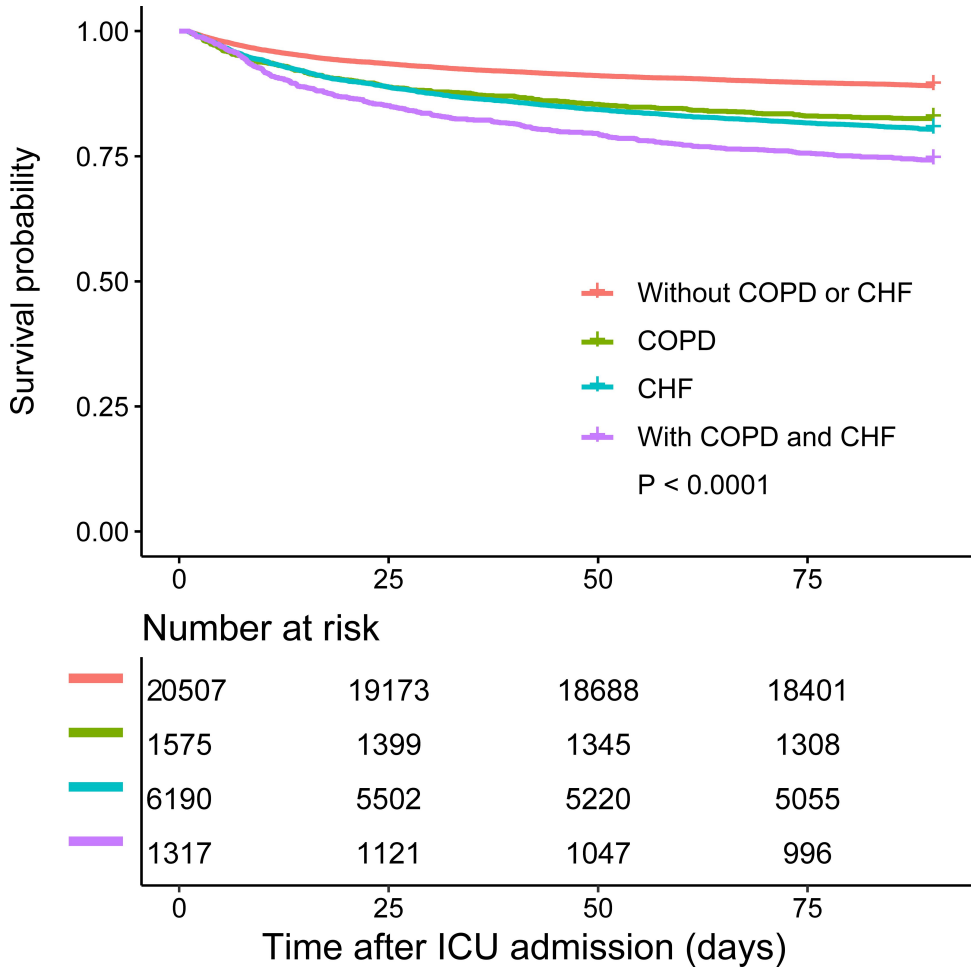

Figure 2 Kaplan–Meier curves for survival after ICU admission.
Abbreviations: ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

patients without COPD and CHF, patients with COPD, patients with CHF, and patients with both COPD and CHF. After taking various confounding factors (including disease severity scores) into account, comorbid COPD and CHF together was found to be associated with worse prognosis compared with patients with one of the comorbidities, but no interaction between COPD and CHF was observed. The results provided prevalence of COPD and

Table 2 Clinical Outcomes of the Study Subjects

Variables	All Subjects (n=29,589)	Without COPD or CHF (n=20,507)	COPD (n=1575)	CHF (n=6190)	With COPD and CHF (n=1317)	P-value
28-day mortality	2549 (8.61%)	1419 (6.92%)	185 (11.75%)	735 (11.87%)	210 (15.95%)	<0.001
90-day mortality	4063 (13.73%)	2236 (10.90%)	275 (17.46%)	1213 (19.60%)	339 (25.74%)	<0.001
ICU mortality	880 (2.97%)	490 (2.39%)	54 (3.43%)	271 (4.38%)	65 (4.94%)	<0.001
Hospital mortality	1961 (6.63%)	1092 (5.33%)	123 (7.81%)	606 (9.79%)	140 (10.63%)	<0.001
Length of ICU stay (days)	2.42 (1.58–4.46)	2.22 (1.47–4.01)	2.61 (1.59–4.85)	3.05 (1.88–5.44)	3.08 (1.88–6.01)	<0.001
Length of hospital stay (days)	7.82 (4.98–13.00)	7.20 (4.68–12.08)	8.01 (5.26–13.00)	9.24 (6.02–14.97)	9.60 (6.07–15.16)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; ICU, intensive care unit.

Table 3 Associations Between Comorbid COPD and/or CHF and Clinical Outcomes

Outcome	Crude		Adjust Model I		Adjust Model II	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
28-day mortality						
Without COPD or CHF	Reference		Reference		Reference	
COPD	1.74 (1.49–2.03)	<0.0001	1.37 (1.17–1.60)	<0.0001	1.25 (1.07–1.46)	0.0046
CHF	1.76 (1.61–1.92)	<0.0001	1.25 (1.14–1.37)	<0.0001	1.18 (1.07–1.30)	0.0012
With COPD and CHF	2.40 (2.08–2.78)	<0.0001	1.64 (1.41–1.90)	<0.0001	1.55 (1.33–1.80)	<0.0001
90-day mortality						
Without COPD or CHF	Reference		Reference		Reference	
COPD	1.67 (1.47–1.89)	<0.0001	1.30 (1.15–1.48)	<0.0001	1.21 (1.07–1.37)	0.0031
CHF	1.88 (1.75–2.01)	<0.0001	1.33 (1.23–1.43)	<0.0001	1.25 (1.16–1.35)	<0.0001
With COPD and CHF	2.55 (2.28–2.86)	<0.0001	1.73 (1.55–1.95)	<0.0001	1.64 (1.46–1.85)	<0.0001

Notes: Model I was adjusted for age and sex; model II was adjusted for age, sex, type of admission; ethnicity, SOFA, SAPS II, sepsis, mechanical ventilation on first day, renal replacement therapy on first day, and comorbidities including cardiac arrhythmias, valvular disease, pulmonary circulation disorder, hypertension, uncomplicated diabetes, complicated diabetes, renal failure, liver disease, metastatic cancer, and obesity.

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; HR, hazard ratio; CI, confidence interval.

CHF in general ICU patients, and evidence about how COPD and CHF impact prognosis of ICU patients, which might help to raise clinicians' awareness of the importance of these two common comorbidities and take appropriate measures when necessary to further improve prognosis of patients staying in ICU.

Among the 29,589 ICU patients we included, 9.77% (2892/29,589) had COPD, and 25.37% (7507/29,589) had CHF. The prevalence of these two comorbidities was similar to that reported in studies which involved critically ill patients. Funk et al reported the prevalence of COPD was 8.6% in a study that included about 200 thousand adult ICU patients in Austria between 1998 and 2008.[13] This figure is slightly lower than our results, which might be because we included a slightly older population. It was estimated that at least 20% of hospital admissions among persons older than 65 were due to HF,[16] but prevalence of CHF reported in numerous studies varied due to difference in study population and definition of CHF.[17] In our study, 45.54% (1317/2892) COPD patients suffered from CHF, and 17.54% (1317/7507) CHF patients had COPD. The prevalence was different from that reported in hospitalized patients mentioned above (20% and 35%),[9,10] which might be related to a difference in disease severity of the study population, definitions of CHF, or different awareness of CHF recognition. Nevertheless, all these results suggest that COPD and CHF are common to see in the same patient.

The associations between the two comorbidities and prognosis we observed in the study were consistent with most of other studies including those pooled estimations from meta-analyses.[11,12] Apart from the difference in study population, that our study only included patients admitted to ICU, we included patients without COPD or CHF and took this group as the reference, while most other studies only excluded these patients.[18–20] This study design increased our understanding of the impact of COPD and CHF on prognosis of ICU patients. According to our results, after adjusted for potential confounding factors, comorbid COPD or CHF only would increase the risk of 28-day mortality by 25% (95% CI 7–46%) and 18% (95% CI 7–30%) when compared to patients without COPD or CHF, while when a patient had COPD and CHF together, it would increase the risk of 28-day mortality by 55% (95% CI 33–80%), which suggested a combination of these two common diseases would further worsen the prognosis. Although these findings might not be novel to the clinicians, as far as we know it for the first time investigated critically ill patients specially on the impact of these two diseases on prognosis. In addition, we also examined whether there was an interaction effect between COPD and CHF, but the results showed non-significant interaction after multivariable adjustment. This suggested COPD and CHF might play an independent role on deteriorating prognosis of the patients, but it should be noticed that the interaction

mentioned here only referred to statistical interaction, which could not be simply equal to biological interaction.[21]

Although the main findings of our study are known on an anecdotal level, it provided information on the magnitude of the increased risk of mortality in ICU patients when they were comorbid with COPD and CHF (either alone or together). Considering ICU patients were usually with a high baseline risk of mortality, a relative increase of mortality risk by about 20–50% should not be ignored and thus in clinical practice patients comorbid with COPD and CHF should get more attention to improve prognosis. In addition, the increased risk was also observed in a relatively long-term outcome (i.e., 90-day mortality), an outcome which might be usually neglected by clinicians since most ICU patients might stay in ICU less than 90 days, our study suggested efforts should also be put to improve prognosis of discharged ICU patients who were comorbid with COPD and CHF.

Although the large sample size strengthened the power of the study, it had some limitations which should be noted. In the study all the variables were extracted retrospectively, and COPD and CHF were both identified only based on ICD-9-CM instead of using strict definitions. This could be a source of bias of our findings, but the direction of the bias was difficult to evaluate without further data. In addition, since we only included patients from a single center, and the study period was between 2001 and 2012, the generality of our findings might be limited. Similar investigations on updated data using strict definitions are needed to provide evidence on the prevalence of comorbid COPD and CHF.

Conclusion

ICU patients with comorbid COPD or CHF both experienced greater mortality, while these two risk factors seemed to play an independent role.

Abbreviations

COPD, Chronic obstructive pulmonary disease; HF, heart failure; ICU, intensive care unit; CHF, congestive heart failure; MIMIC, Medical Information Mart for Intensive Care; SQL, Structured Query Language; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; HR, hazard ratio; CI, confidence interval.

Data Sharing Statement

The data used in this study was retrieved from a restricted-access database. Steps to get access to the data was provided at https://mimic.physionet.org/gettingstarted/access/.

Ethics Approval and Consent to Participate

This study was exempt from institutional review board approval due to the retrospective design, lack of direct patient intervention, and the security schema for which the reidentification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA).

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Disclosure

The authors report no conflicts of interest for this work.

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