International Journal of COPD

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ORIGINAL RESEARCH

Comorbidity as a contributor to frequent severe acute exacerbation in COPD patients

This article was published in the following Dove Press journal:
International Journal of COPD
4 August 2016
Number of times this article has been viewed

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Background: Comorbidities have a serious impact on the frequent severe acute exacerbations (AEs) in patients with COPD. Previous studies have used the Charlson comorbidity index to represent a conglomerate of comorbidities; however, the respective contribution of each coexisting disease to the frequent severe AEs remains unclear.

Methods: A retrospective, observational study was performed in 77 COPD patients who experienced severe AE between January 2012 and December 2014 and had at least 1-year follow-up period from the date of admission for severe AE. We explored the incidence of frequent severe AEs (≥2 severe AEs during 1-year period) in these patients and investigated COPD-related factors and comorbidities as potential risk factors of these exacerbations.

Results: Out of 77 patients, 61 patients (79.2%) had at least one comorbidity. During a 1-year follow-up period, 29 patients (37.7%) experienced frequent severe AEs, approximately two-thirds (n=19) of which occurred within the first 90 days after admission. Compared with patients not experiencing frequent severe AEs, these patients were more likely to have poor lung function and receive home oxygen therapy and long-term oral steroids. In multiple logistic regression analysis, coexisting asthma (adjusted odds ratio [OR] =4.02, 95% confidence interval [CI] =1.30–12.46, *P*=0.016), home oxygen therapy (adjusted OR =9.39, 95% CI =1.60–55.30, *P*=0.013), and C-reactive protein (adjusted OR =1.09, 95% CI =1.01–1.19, *P*=0.036) were associated with frequent severe AEs. In addition, poor lung function, as measured by forced expiratory volume in 1 second (adjusted OR =0.16, 95% CI =0.04–0.70, *P*=0.015), was inversely associated with early (ie, within 90 days of admission) frequent severe AEs.

Conclusion: Based on our study, among COPD-related comorbidities, coexisting asthma has a significant impact on the frequent severe AEs in COPD patients.

Keywords: asthma, chronic obstructive pulmonary disease, comorbidity, exacerbation

Introduction

Acute exacerbations (AEs) of chronic obstructive pulmonary disease (COPD) are defined as an acute worsening of symptoms beyond normal day-to-day variations[1] and are a key determinant of the natural course of COPD. Frequent exacerbations are associated with more rapid decline in lung function,[2,3] poor quality of life,[4,5] considerable morbidity and mortality,[6–11] and high socioeconomic costs.[12] Moreover, it has been shown that severe exacerbation episodes, that is, those requiring an emergency department visit or hospitalization, have a deleterious effect on COPD prognosis, especially when these events occur frequently.[2,9]

COPD often coexists with other diseases that can significantly impact the prognosis of patients with COPD. Previous studies showed that severe AE is associated with a higher prevalence of comorbidities and increased hospital readmission rate,[10]

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Dovepress
http://dx.doi.org/10.2147/COPD.S103063

and demonstrated that better management of these comorbidities contributed to an improved COPD prognosis after hospital discharge.[11] However, since these studies used the Charlson comorbidity index[13] as a single compound variable for the assessment of comorbidities[10,11,14] or classified patients into two groups (with and without comorbidities) without further subdivision,[15,16] the respective contribution of each comorbid condition on the development of severe AEs remains unclear. In addition, extrapulmonary diseases such as hypertension, ischemic heart disease (IHD), depression, and diabetes mellitus were investigated, whereas coexisting pulmonary diseases, such as asthma and tuberculosis-destroyed lung (TDL), were rarely considered as comorbidities.[6–11] Therefore, we investigated factors associated with frequent severe AEs in COPD patients based on COPD-related factors and comorbidities, including coexisting pulmonary diseases.

Methods

Study population

A retrospective observational study was carried out in Samsung Medical Center, a 1,961-bed referral hospital in Seoul, South Korea. The medical records of 128 patients with COPD who visited the emergency department or were admitted to our hospital for the management of COPD AE between January 2012 and December 2014 and had at least 1-year follow-up after severe AE were reviewed. Exclusion criteria included patients who were lost to follow-up (n=33), as well as those who were transferred to other hospitals (n=5), or died either during the index admission (n=4) or of other unknown causes (n=9) during the follow-up period. A total of 77 patients were included in the present study. This study was approved by the Institutional Review Board of Samsung Medical Center, and the informed consent requirement was waived due to the retrospective nature of this study. All patient information was anonymized and de-identified before analysis.

Definitions

The severe COPD AE was defined as a COPD-associated event requiring either an emergency department visit or hospitalization and treatment with systemic steroids and/or antibiotics.[17] Frequent severe AEs were defined as two or more severe COPD AEs occurring within 1 year,[18] while early frequent severe AEs was used to describe the occurrence of two or more severe AEs within 3 months. The severity of airflow limitation was defined as follows: mild (forced expiratory volume in 1 second [FEV_1] $\geq$80% of the predicted value), moderate (50%$\leq$ FEV_1 <80% of the predicted value), severe (30%$\leq$ FEV_1 <50% of the predicted value), and very severe (FEV_1 <30% of the predicted value).

The following comorbidities were evaluated in this study: hypertension, IHD (ie, stable angina, unstable angina, and myocardial infarction), congestive heart failure, cerebrovascular disease, cor pulmonale, diabetes mellitus, malignancy, asthma, TDL, chronic liver disease, and chronic kidney disease. Patients with one or more of these comorbidities as diagnosed by a physician or on medication for these conditions were evaluated according to their respective comorbidities. Patients with congestive heart failure were defined as those with symptoms suggestive of heart failure and an ejection fraction <40% on echocardiography.[19] Patients with TDL were required to have both insufficient lung function and parenchymal lung damage, both of which had to have been caused by previous tuberculosis infection.[20] A COPD patient with prior echocardiography findings consistent with an estimate of peak systolic pulmonary pressure >30 mmHg was regarded as having cor pulmonale.[21] The COPD-related clinical factors included the following variables: body mass index (BMI), smoking history, pulmonary function, COPD-related medications, the long-term use of systemic steroids at a dose $\geq$5 mg prednisolone for >3 months, and home oxygen therapy.

Data collection

Data were retrospectively collected through a comprehensive review of each patient's medical chart, medications, and imaging studies. Clinical factors were obtained during the index admission, including age, sex, smoking history, BMI, comorbidities (hypertension, IHD, congestive heart failure, cerebrovascular disease, cor pulmonale, diabetes mellitus, malignancy, asthma, TDL, chronic liver disease, and chronic kidney disease), FEV_1, C-reactive protein (CRP), home oxygen therapy, inhaled treatments, and long-term oral steroid use. Pulmonary function test data conducted within 1 year prior to or after severe AE episode were retrieved, except one patient who performed pulmonary function test 3 years prior to severe AE. Following the index severe AE episode, the medical records were reviewed to collect data on the recurrence of severe AEs within 90 days and 1 year of the index hospitalization.

Statistical analysis

Data were presented as numbers (%) for categorical variables and as median and interquartile range values (IQR, Q1–Q3)

for continuous variables. Categorical variables were compared with either the Pearson χ^2 test or Fisher's exact test, and continuous variables were compared using Mann–Whitney *U*-test due to skewed data. To explore the clinical factors that were independently associated with frequent severe AEs within the 90-day and 1-year follow-up periods, we fitted a multiple logistic regression analysis with the stepwise selection method. We used a backward elimination with the removal criteria of $P<0.1$ to calculate the odds ratios (OR) for recurrence of severe AEs during the follow-up period. Age, sex, and factors with $P<0.20$ in univariate analyses, and clinical relevant (coexisting asthma, IHD, and congestive heart failure) were entered into the multiple stepwise logistic regression. The final model was obtained by retaining those with $P<0.05$ and some marginally significant clinical variables with $P<0.10$. All tests were two-sided, and $P<0.05$ was considered statistically significant. We used the Hosmer–Lemeshow test to verify the goodness of the model fit. All statistical analyses were evaluated using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Clinical characteristics of patients

The baseline characteristics of the 77 COPD patients are summarized in Table 1. There were 67 males (87.0%) and ten females (13.0%) with a median age of 73 years (IQR, 66–78 years). The median BMI was 22.3 kg/m^2 (IQR, 20.6–25.2 kg/m^2), and 73 patients (94.8%) were current or former smokers. Of the 77 patients, 61 (79.2%) had at least one comorbidity, the most common of which were hypertension (n=35, 45.5%), coexisting asthma (n=25, 32.5%), and malignancy (n=17, 22.1%), followed by diabetes mellitus (n=15, 19.5%), IHD (n=11, 14.3%), cor pulmonale (n=8, 10.4%), and cerebrovascular disease (n=7, 9.1%). The median arterial blood pH at the time of the index admission was 7.4 (IQR, 7.4–7.5), and the arterial partial pressure of CO_2 was 41 mmHg (IQR, 36–47 mmHg). The median FEV_1/forced vital capacity was 45% (IQR, 34%–55%) with an FEV_1 of 1.1 L (44% predicted). Regarding medical treatment, nine patients (11.7%) received home oxygen therapy, and nine patients (11.7%) were taking long-term oral corticosteroids. Fifty-three patients (68.8%) used an inhaled corticosteroid/long-acting β_2-agonist combination, 42 patients (54.5%) used a long-acting muscarinic antagonist, and 32 patients (41.6%) used triple therapy including all of the aforementioned medications. Nine patients (11.7%) did not use any inhalers, because they had mild respiratory symptoms before the index admission for severe AE. According to the Global Initiative for Chronic Obstructive Lung Disease criteria, patients were classified by the severity of airflow limitation as follows: mild (n=1, 1.3%), moderate (n=28, 36.4%), severe (n=33, 42.8%), and very severe (n=15, 19.5%).

Table 1 Baseline characteristics of 77 COPD patients with severe acute exacerbations

	Median (IQR, Q1–Q3) or number (%)
Age, years	73 (66–78)
Sex, male	67 (87.0)
Body mass index, kg/m^2	22.3 (20.6–25.2)
Smoking history	
Current or former smoker	73 (94.8)
Comorbidities	61 (79.2)
Hypertension	35 (45.5)
Asthma	25 (32.5)
Malignancy	17 (22.1)
Diabetes mellitus	15 (19.5)
Ischemic heart disease	11 (14.3)
Cor pulmonale	8 (10.4)
Cerebrovascular disease	7 (9.1)
Congestive heart failure	6 (7.8)
Tuberculosis-destroyed lung	6 (7.8)
Chronic renal disease	5 (6.5)
Chronic liver disease	1 (1.3)
Pulmonary function tests	
FEV_1/FVC, %	45 (34–55)
FEV_1, L	1.1 (0.8–1.5)
FEV_1, % predicted	44 (32–57)
Laboratory findings	
pH[a] in arterial blood	7.4 (7.4–7.5)
$PaCO_2$,[a] mmHg	41 (36–47)
ESR,[b] mm/h	34 (14–51)
CRP, mg/dL	1.7 (0.4–6.2)
Procalcitonin,[c] ng/mL	0.1 (0.1–0.2)
Medical treatments	
Home oxygen therapy	9 (11.7)
Long-term oral steroids	9 (11.7)
Inhaler[d]	
None	9 (11.7)
ICS/LABA	53 (68.8)
LAMA	42 (54.5)
LABA	4 (5.2)
Others	6 (7.8)

Notes: [a]Data for 69 patients were available. [b]Data for 56 patients were available. [c]Data for 47 patients were available. [d]Reported inhaler use prior to first admission; some patients used more than one inhaler.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β_2-agonist; LAMA, long acting muscarinic antagonist; $PaCO_2$, partial pressure of arterial CO_2.

Overall treatment outcomes in patients with severe AEs

Of the 77 patients who had severe AEs, 29 (37.7%) experienced frequent severe AEs within the 1-year follow-up

Table 2 Treatment outcomes of 77 COPD patients with severe acute exacerbations

	Total (n=77)	Patients with or without early frequent severe AEs within 90 days			Patients with or without frequent severe AEs within 1 year		
		Without severe AEs (n=58)	With severe AEs (n=19)	*P*-value	Without severe AEs (n=48)	With severe AEs (n=29)	*P*-value
Hospital stays, days	5 (2–9)	4 (2–8)	8 (3–11)	0.070	4 (2–8)	7 (3–10)	0.110
Duration of systemic steroid treatment during first severe AE event, days	7 (5–10)	7 (5–10)	6 (5–10)	0.995	6 (5–9)	7 (5–12)	0.308
Total steroid dose prescribed between the first day of AE and OPD visit, mg[a]	238 (188–376)	249 (188–360)	223 (188–400)	1.0	239 (188–338)	230 (188–429)	0.368
Deaths due to subsequent severe AEs	5 (6.5)	2 (3.4)	3 (15.8)	0.093	–	5 (17.2)	–

Notes: The data are presented as number (%) or as median and interquartile range. [a]Steroid doses were calculated as equivalent doses of prednisolone.
Abbreviations: AE, acute exacerbation; OPD, outpatient department.

periods and 19 (24.7%) had early frequent severe AEs within the 90-day follow-up periods after the index admission. As shown in Table 2, the median hospital stay was 5 days (IQR, 2–9 days). Between the day of admission and the outpatient hospital follow-up visit, systemic steroids were prescribed at a median dose of 238 mg (188–376 mg equivalent dose of prednisolone) for a median of 7 days (IQR, 5–10 days). Overall, a total of five patients (6.5%) died due to frequent severe AEs within 1 year of the index severe AE event. There was no significant difference in number of admission days or steroid usage in patients with and without frequent severe AEs, regardless of the timing of the AE recurrence (ie, within the 90-day or 1-year follow-up period).

Comparison of COPD patients with or without frequent severe AEs during 1-year of follow-up

The clinical characteristics of COPD patients with or without frequent severe AEs are summarized in Table 3. There were no significant differences in age, sex, BMI, smoking history, comorbidities, and laboratory findings in patients with or without frequent severe AEs during the 1-year follow-up period. Compared with patients without frequent severe AEs, patients who experienced frequent severe AEs were more likely to have poor lung function (median FEV_1 [L], 1.1 L vs 1.2 L, P=0.049), receive home oxygen therapy (24.1% vs 4.2%, P=0.023), and long-term oral steroids (20.7% vs 4.2%, P=0.047).

Comparison of COPD patients with and without early frequent severe AEs during a 90-day follow-up

Clinical characteristics of COPD patients with or without early frequent severe AEs (within 90 days) are summarized in Table 4. There were no significant differences in age, sex, BMI, smoking history, comorbidities, and laboratory findings between the patients with and without early frequent severe AEs. In contrast to patients without early frequent severe AEs, patients who experienced early frequent severe AEs were more likely to have poor lung function (median FEV_1 [L], 0.9 L vs 1.2 L, P=0.008), receive home oxygen therapy (26.3% vs 6.9%, P=0.036), and long-term oral steroids (26.3% vs 5.2%, P=0.019).

Clinical factors associated with frequent severe AEs within 90 days and 1 year of follow-up

As shown in Table 5, multiple logistic regression analysis revealed that patients with asthma were 4.02 times more likely to develop severe AEs (95% confidence interval [CI] =1.30–12.46, P=0.016), and those requiring home oxygen therapy were 9.39 times more likely to develop severe AEs (95% CI =1.60–55.30, P=0.013). In addition, CRP was significantly associated with development of frequent severe AEs during the 1-year follow-up period (adjusted OR =1.09, 95% CI =1.01–1.19, P=0.036). The FEV_1 (adjusted OR =0.16, 95% CI =0.04–0.70, P=0.015) was found to be inversely associated with early frequent severe AEs (Table 5).

Discussion

The most important finding of the present study was the identification of coexisting asthma as a significant factor in the development of frequent severe AEs in COPD patients within 1 year of the AE episode. Additionally, poor lung function, represented by FEV_1, was inversely associated with development of early frequent severe AEs within 90 days

Table 3 Comparison of 77 COPD patients with or without frequent severe acute exacerbations during a 1-year follow-up period

	Patients without frequent severe AEs (n=48)	Patients with frequent severe AEs (n=29)	*P*-value
Age, years	74 (66–79)	71 (64–76)	0.377
Sex, male	42 (87.5)	25 (86.2)	1.0
Body mass index, kg/m^2	22.2 (20.5–25.1)	22.4 (20.8–25.4)	0.511
Smoking history			
Current or former smoker	40 (83.3)	24 (82.8)	1.0
Comorbidities	35 (72.9)	26 (89.7)	0.079
Hypertension	20 (41.7)	15 (51.7)	0.390
Asthma	12 (25.0)	13 (44.8)	0.072
Malignancy	10 (20.8)	7 (24.1)	0.735
Diabetes mellitus	8 (16.7)	7 (24.1)	0.423
Ischemic heart disease	7 (14.6)	4 (13.8)	1.0
Cor pulmonale	4 (8.3)	4 (13.8)	0.466
Cerebrovascular disease	3 (6.2)	4 (13.8)	0.415
Congestive heart failure	3 (6.2)	3 (10.3)	0.667
Tuberculosis-destroyed lung	6 (12.5)	0 (0.0)	0.078
Chronic renal disease	2 (4.2)	3 (10.3)	0.359
Chronic liver disease	1 (2.1)	0 (0.0)	1.0
Pulmonary function tests			
FEV_1/FVC	45 (36–57)	41 (31–55)	0.254
FEV_1, L	1.2 (0.9–1.6)	1.1 (0.7–1.3)	0.049
FEV_1, % predicted	44 (33–63)	37 (27–55)	0.145
Laboratory findings			
pH in arterial blood[a]	7.4 (7.4–7.5)	7.4 (7.4–7.5)	0.651
$PaCO_2$,[a] mmHg	43 (37–47)	40 (35–50)	0.389
ESR,[b] mm/h	32 (14–51)	36 (22–55)	0.663
CRP, mg/dL	1.1 (0.3–4.9)	3.9 (0.5–10.6)	0.064
Procalcitonin,[c] ng/mL	0.1 (0.1–0.2)	0.2 (0.1–0.5)	0.083
Medical treatments			
Home oxygen therapy	2 (4.2)	7 (24.1)	0.023
Long-term oral steroids	2 (4.2)	6 (20.7)	0.047
Use of ICS after severe AE	39 (81.3)	28 (96.6)	0.080

Notes: The data are presented as number (%) or as median and interquartile range. [a]Data for 69 patients were available. [b]Data for 56 patients were available. [c]Data for 47 patients were available.

Abbreviations: AE, acute exacerbation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; $PaCO_2$, partial pressure of arterial CO_2.

of the severe AE episode. Patients requiring home oxygen therapy were also more prone to develop frequent severe AEs in the first year after severe AE.

There has been controversy surrounding the roles of comorbidities in the development of frequent severe AEs.[22] Previous studies have evaluated comorbidities using the Charlson comorbidity index, which has been widely used as a comorbidity-related predictor of AEs in COPD patients. Because this integrated index was used as a single variable,[10,11,14] the contribution of each individual comorbidity to frequent severe AEs might be underestimated. In addition, the Charlson comorbidity index does not include asthma,[13] and past studies excluded COPD patients with asthma when evaluating factors influencing AEs in COPD patients.[15,23–28] Recently, several studies have highlighted the impact of coexisting asthma in COPD patients. A cross-sectional study using previous AE history reported that a history of physician-diagnosed asthma was related to the frequency and severity of exacerbations in COPD patients.[29] In the PLATINO study using a general population, subjects with coexisting asthma and COPD had a higher risk of exacerbation and hospitalization compared to those patients with COPD alone.[30] Furthermore, an observational study in a primary care population showed that several comorbidities, including asthma, were associated with moderate-to-severe exacerbations during a 1-year follow-up period.[31] We extended these findings by demonstrating a significant association between coexisting asthma and frequent severe COPD AEs in patients cared for in a tertiary hospital setting.

Previously, it was determined that the risk of myocardial infarction increased in the postexacerbation period, and that patients who experienced frequent exacerbations had a higher incidence rate of IHD.[32,33] Furthermore, Almagro et al[10]

Table 4 Comparison of 77 COPD patients with and without early frequent severe acute exacerbations (within 90 days)

	Patients without early frequent severe AEs (n=58)	Patients with early frequent severe AEs (n=19)	*P*-value
Age, years	74 (67–79)	68 (63–75)	0.135
Sex, male	50 (86.2)	17 (89.5)	1.0
Body mass index, kg/m^2	22.3 (20.3–25.4)	22.3 (21.4–24.8)	0.855
Smoking history			
Current or former smoker	48 (82.8)	16 (84.2)	1.0
Comorbidities	43 (74.1)	18 (94.7)	0.099
Hypertension	26 (44.8)	9 (47.4)	0.847
Asthma	17 (29.3)	8 (42.1)	0.301
Malignancy	12 (20.7)	5 (26.3)	0.751
Diabetes mellitus	10 (17.2)	5 (26.3)	0.505
Ischemic heart disease	8 (13.8)	3 (15.8)	1.0
Cor pulmonale	5 (8.6)	3 (15.8)	0.400
Cerebrovascular disease	4 (6.9)	3 (15.8)	0.354
Congestive heart failure	3 (5.2)	3 (15.8)	0.156
Tuberculosis-destroyed lung	6 (10.3)	0 (0)	0.327
Chronic renal disease	4 (6.9)	1 (5.3)	1.0
Chronic liver disease	1 (1.7)	0 (0)	1.0
Pulmonary function tests			
FEV_1/FVC	45 (35–58)	41 (30–54)	0.135
FEV_1, L	1.2 (0.9–1.6)	0.9 (0.6–1.2)	0.008
FEV_1, % predicted	46 (33–62)	34 (20–48)	0.008
Laboratory findings			
pH in arterial blood[a]	7.4 (7.4–7.5)	7.4 (7.3–7.5)	0.459
$PaCO_2$,[a] mmHg	41 (36–46)	40 (35–67)	0.908
ESR,[b] mm/h	30 (15–50)	38 (20–64)	0.491
CRP, mg/dL	1.1 (0.3–5.5)	5.0 (0.4–9.5)	0.124
Procalcitonin,[c] ng/mL	0.1 (0.1–0.2)	0.2 (0.1–0.5)	0.146
Medical treatments			
Home oxygen therapy	4 (6.9)	5 (26.3)	0.036
Long-term oral steroids	3 (5.2)	5 (26.3)	0.019
Use of ICS after severe AE	49 (84.5)	18 (94.7)	0.436

Notes: The data are presented as number (%) or as median and interquartile range. [a]Data for 69 patients were available. [b]Data for 56 patients were available. [c]Data for 47 patients were available.

Abbreviations: AE, acute exacerbation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; $PaCO_2$, partial pressure of arterial CO_2.

showed that a history of IHD was associated with an increase in crude mortality in 3 months following a severe AE, and a recent study showed that COPD itself is associated with increased risk of myocardial infarction and ischemic stroke.[34] Nonetheless, the comorbidity of cardiovascular diseases as a whole (IHD, congestive heart failure, and cerebrovascular disease) was not associated with the frequency of severe AEs of COPD in the present study. There are several possible explanations for this lack of association. First, the total number of patients with cardiovascular disease, including IHD and cerebrovascular disease, was relatively small. Thus, further studies with larger study populations are needed to

Table 5 Multiple logistic regression analysis of clinical factors and comorbidities associated with frequent severe acute exacerbations during 1-year of follow-up and early frequent severe acute exacerbations during 90 days of follow-up

	Adjusted odds ratio	95% confidence interval	*P*-value
	Factors associated with frequent severe AEs during 1-year of follow-up[a]		
Asthma	4.02	1.30–12.46	0.016
Home oxygen therapy[b]	9.39	1.60–55.30	0.013
CRP	1.09	1.01–1.19	0.036
	Factors associated with early frequent severe AEs during 90 days of follow-up[a]		
FEV_1, L	0.16	0.04–0.70	0.015

Notes: [a]Adjusted for age, sex, asthma, ischemic heart disease, congestive heart failure, FEV_1 (L), CRP, home oxygen therapy, and long-term oral steroid. [b]Unstable due to the fact that only two of nine patients who used home oxygen therapy did not develop AE.

Abbreviations: AE, acute exacerbation; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second.

confirm these associations. Second, there is a possibility that the incidence rate of severe AEs following myocardial infarction might be underestimated, since AE events frequently develop during hospitalization for postmyocardial infarction management.

CRP is an inflammatory biomarker that is commonly elevated in COPD patients during exacerbations.[35–37] A large prospective cohort study with 6,574 subjects revealed that stable COPD patients with concurrent elevation in levels of CRP and other inflammatory biomarkers have an increased risk of exacerbations.[38] Despite these findings, no available data supports an association between elevated CRP level at the time of the index severe AE presentation and the occurrence of subsequent severe AEs. The present study revealed that COPD patients with elevated level of CRP upon presentation with severe exacerbations were more likely to experience subsequent severe exacerbations. However, further studies are needed to validate this correlation in more detail.

Approximately 38% of subjects in the present study experienced frequent severe AEs after the index admission during the 1-year follow-up period, and about 25% of subjects experienced frequent severe AEs within 90 days. This observation was concordant with previous studies, which reported a rate of ~35% to 46% of frequent severe AEs during 1 year[2,5,39] and 15% for frequent severe AEs within 3 months following index events.[40] Regarding the use of systemic corticosteroids, there was no significant difference in the total dose of systemic corticosteroids used in patients with or without frequent AEs. Consistent with this finding, a previous study reported that a short-term (5-day) course of systemic corticosteroid therapy was comparable to long-term use, thereby protecting COPD patients with frequent AEs from the harmful effects of excessive exposure to systemic corticosteroids.[41] Given the frequent severe AEs in a substantial proportion of COPD patients coupled with the increased risk of side effects associated with longer systemic corticosteroid courses, short-term treatment with conventional corticosteroid dosages should be considered, even in COPD patients with frequent severe AEs.

This study has several limitations. First, this retrospective study was performed at a single referral center. Second, the number of patients in this study was relatively small. Thus, the statistical power might not be sufficient to detect associations with other comorbidities. Third, a small number of female COPD patients were included, which is reflective of the low prevalence of female smokers in Korea.[42] Fourth, because the presence of mental health disorders or the use of psychotropic medications was rarely included in the medical records of our subjects, this study was not able to investigate the contributions of anxiety or depression to COPD-related comorbidity. This might reflect the higher prevalence of mental health disorders found in females than males, compounded by the small number of female COPD patients in the present study. Fifth, due to the exploratory nature of our study, some of the comorbidities are sparsely represented in our data, as reflected in the wide CIs. Sixth, in regard to the exacerbation episodes, it is possible that they were in fact asthma exacerbations in COPD patients with coexisting asthma. This challenge in discriminating between COPD and asthma exacerbations in patients with both diseases has historically led to the exclusion of patients with asthma features from COPD studies and vice versa. However, given that asthma – COPD overlap syndrome is increasingly acknowledged as a phenotype of COPD, the present study included COPD patients with coexisting asthma, despite the possibility of mixed COPD and asthma exacerbations. Finally, because adherence to inhaler therapy was not able to be examined in this study, the effect of poor adherence on frequent severe AEs in COPD patients could not be evaluated.

Nevertheless, our study found a significant and persistent association between coexisting asthma and frequent severe AEs in COPD patients. While more large-scale studies need to be conducted to confirm our conclusions, our findings suggest a need for closer attention to individual comorbidities, especially coexisting asthma, in COPD patients in order to achieve effective prevention and treatment of AEs.

Acknowledgment

This study was supported by the Samsung Medical Center Foundation for Medical Research (SMO1140211).

Disclosure

The authors report no conflicts of interest in this work.

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