Metabolic Syndrome in Early Chronic Obstructive Pulmonary Disease: Gender Differences and Impact on Exacerbation and Medical Costs

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Background: Metabolic syndrome (MetS) is a well-known comorbidity of chronic obstructive pulmonary disease (COPD). However, their interrelationship, particularly in early COPD, remains unclear. Therefore, we aimed to assess the prevalence and clinical characteristics of MetS in patients with early COPD, and to explore the impact of MetS on the frequency of COPD exacerbations and associated medical costs.

Patients and methods: We retrospectively enrolled 43,874 subjects from the KNHANES, including 2164 patients with early COPD (≥40 years old), recorded smoking history, and Global Initiative for Chronic Obstructive Lung Disease spirometric grade I or II, with data linked to the NHI database. We extracted and analyzed data regarding health-care utilization and medical costs for 5 years (2007 to 2012).

Results: Among 2164 patients with early COPD, the prevalence of MetS was 31.2%, and it was higher in women than in men (35.1% vs. 26.6%; P<0.001). Patients with MetS were older and had lower pulmonary function and greater number of comorbidities. The frequency of moderate-to-severe exacerbations for 5 years was significantly higher in women with MetS than in those without MetS (5.8/year vs. 4.9/year; P=0.02). After adjusting for confounding factors, the risk for moderate-to-severe exacerbation was significantly greater in women with MetS (IRR, 1.17; 95% CI, 1.01 to 1.36; P=0.03). COPD exacerbations leading to hospitalization and medical expenses were also higher in women with MetS than in those without MetS.

Conclusion: MetS is more prevalent in women with early COPD. MetS increased the frequency of exacerbations and the medical costs in women with early COPD.

Keywords: COPD exacerbation, metabolic syndrome

Plain Language Summary
Metabolic syndrome is a comorbidity of COPD and increases medical costs. Does metabolic syndrome increase the acute exacerbations of early COPD? Interrelationships between metabolic syndrome and early COPD remain unclear. This paper presents the first analysis that metabolic syndrome increases the acute exacerbations and medical costs in patients with early COPD, especially in women.

Introduction
Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation, alveolar destruction, and airflow limitation. Peripheral lung inflammation may cause the “spill-over” of inflammatory markers into the systemic circulation, leading to extrapulmonary comorbidities such as cardiovascular disease (CVD),
musculoskeletal wasting, osteoporosis, psychological disorders, and metabolic syndrome (MetS). Alternatively, smoking causes systemic inflammation and COPD, and genetic susceptibility or inflammatory response may have a link to triggers between systemic inflammation and COPD. Thus, COPD is considered a pulmonary component of multiple morbidities. Previous studies have shown that these comorbidities, especially CVD, diabetes, and MetS, are associated not only with a higher risk of hospitalization and mortality but also with the increased economic burden of COPD. The management of patients with COPD must include the identification and treatment of its comorbidities, as these have a significant impact on COPD prognosis.

MetS is characterized by the clustering of central obesity, hypertension, dyslipidemia, and hyperglycemia that predisposes patients to CVD. It is a representative group of conditions with systemic inflammation, which is a potential mechanism responsible for both COPD and MetS. The prevalence of MetS differs according to the sex, race, and age-group in the general population. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report of 2017 stated that the prevalence of MetS in COPD was estimated to be more than 30%, and that MetS was more frequent in patients with COPD than in controls. Moreover, a previous systematic review reported sex differences, showing that patients with COPD and MetS were more frequently women. The prevalence of MetS is also higher in early (mild-to-moderate stage) COPD and decreases with COPD progression. Most patients with COPD have early COPD, and their prognosis can be easily improved if they are provided early treatment.

Despite this crucial relationship, studies on MetS in COPD, particularly early COPD, are limited. A few studies reported that MetS increases the frequency of acute exacerbations. However, these studies either included patients with COPD admitted for exacerbations at a single center or reported preliminary results. Therefore, we aimed to investigate the prevalence of MetS in early COPD, to determine the relationship between MetS and the frequency of exacerbations in early COPD, and to assess the impact of MetS on COPD-related costs by using data from a national survey.

Materials and Methods
Study Design and Patients
This was a retrospective observational study. Data were obtained from the Korean National Health and Nutrition Examination Survey (KNHANES) (2007 to 2012) database. The KNHANES was a cross-sectional observational national study conducted by the Ministry of Health and Welfare of Korea in 2007. The KNHANES used a complex and stratified multistage cluster sampling to select a representative nationwide sample of the Korean population. Eligible patients were selected from the KNHANES database and were linked to the National Health Insurance (NHI) database. The researchers were blinded to the personal identity of all patients and they were provided only the merged data lacking any personal identification information.

The NHI database was analyzed to obtain the medical utilization and cost data of patients with early COPD selected from the KNHANES. For outpatients, the analysis was confined to visits with the International Classification of Diseases, Tenth Edition (ICD-10) codes for COPD (J42.x-J44.x, except J43.0) with a prescription of COPD-related medication. For inpatients, the analysis was confined to the ICD-10 codes for COPD (J42.x-J44.x, except J43.0) or COPD-related disease (pneumonia: J12.x-J17.x; dyspnea: R06.0; pulmonary thromboembolism: I26 or I26.0; or acute respiratory distress syndrome: J80) as from our previous studies. Moderate exacerbation of COPD was defined as medical utilization for the above ICD-10 codes and with a prescription for antibiotics or systemic corticosteroids. Severe exacerbation of COPD was defined as an emergency room visit or hospitalization for the above ICD-10 codes and with a prescription for antibiotics or systemic corticosteroids. For the patients with COPD enrolled to the KNHANES in 2007 (baseline), the outcome of exacerbation was prospectively assessed until 2012 for 5 years (follow-up), and for those enrolled to the KNHANES in 2012, the outcome of severe exacerbation was retrospectively assessed to 2007 (baseline) for 5 years (follow-up).

Patients
Patients with early COPD were selected from the KNHANES (2007 to 2012) database. All the subjects over 20 years old in KNAHNS performed spirometry. The inclusion criteria were 1) age ≥40 years; 2) forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) <0.7; 3) FEV₁ ≥ 50%; and 4) a recorded smoking history. They had no history of COPD or asthma diagnosis before study enrollment. MetS in patients with early COPD was defined on the basis of the National Cholesterol Education Program Adult Treatment Panel III, and we used ethnicity-specific values for waist circumference based on data from the Korean Society for the
Study of Obesity (KOSSO). MetS was defined on the
basis of the presence of ≥3 of the following factors:7
abdominal circumference >90 cm for men and >85 cm
for women based on the KOSSO cutoff points;14 elevated
triglyceride (TG) level (≥1.7 mmol/L, or drug treatment
for elevated TG levels); reduced high-density lipoprotein
cholesterol (HDL-C) level (<1.0 mmol/L for men or <1.3
mmol/L for women, or drug treatment for reduced HDL-
C); elevated blood pressure (≥130 mmHg systolic or ≥85
mmHg diastolic, or antihypertensive drug treatment for
patients with a history of hypertension); and an elevated
fasting plasma glucose concentration (≥5.6 mmol/L, or
drug treatment for diabetes).7

Data Collection
We obtained information such as age, sex, smoking history
(in number of pack-years), blood pressure, body mass
index (BMI), abdominal circumference, glucose level,
lung function, and laboratory data (TG and HDL-C) from
the KNHANES database. Information on comorbidities,
history of exacerbation, and COPD-related medical costs
were obtained by linking the KNHANES database to the
NHI database. Comorbidities were identified using the
ICD-10 codes. The codes for hypertension were I10–I15;
diabetes, E10–E14; ischemic heart disease (IHD), I20–I25;
congestive heart failure (CHF), I50; peripheral vascular
disease (PVD), I73; osteoporosis, M80–M81; gastroesop-
phageal reflux disease (GERD), K21; and depression,
F32–F33.

Data Analysis
Baseline characteristics were expressed as mean±standard
deviation for continuous variables and as frequencies (per-
centages) for categorical variables. Differences between
groups were analyzed using the chi-square test for catego-
rical variables and Student’s t-test for continuous vari-
able. The difference in the prevalence of MetS between
the sexes was determined using chi-square tests. The risk
of exacerbations between patients with and without MetS
was compared using negative binomial regression. The
result estimates were expressed using incidence rate ratios
(IRR) with 95% confidence intervals (CIs). The IRR of
Model 1 was adjusted for age, sex, and FEV1, and the RR
of Model 2 was adjusted for age, sex, number of pack-
years smoked, and FEV1. All tests were two-sided, and
P-values <0.05 were considered statistically significant.
All statistical analyses were performed using SAS version
9.2 software (SAS Institute Inc., Cary, NC, USA).

Results
Prevalence of MetS
The study flowchart is shown in Figure S1. In total, 2164
patients with early COPD were identified from the
KNHANES database. The overall prevalence of MetS in
early COPD was 31.2% (Table 1). The prevalence of MetS
tended to increase significantly according to the decrease
in the quartile of FVC % predicted. The quartile of FEV1 %
predicted showed no significant relationship with MetS
(Table 1). The prevalence of MetS components in early
COPD was 59.7% for hypertension, 47.3% for HDL-C
criteria, 39.8% for TG criteria, 29.8% for abdominal cir-
cumference, and 12.8% for glycemia (Figure S2).

Characteristics of Patients with Early
COPD According to MetS
The patients’ characteristics on the survey data are summa-
rized in Table 1. The patients with MetS were significantly
older and more obese than were those without MetS. Number
of pack-years smoked was smaller in patients with MetS than
in those without MetS. The number of women with COPD
and MetS was greater than that of women with COPD but
without MetS (31.1% vs. 26.1%; P=0.01). The most common
comorbidity in MetS was hypertension (78.4%), followed by
diabetes (54.5%), GERD (52.6%), PVD (32.4%), and osteo-
porosis (23.6%). The most common comorbidity in patients
without MetS was GERD (54.5%), followed by hypertension
(43.6%), diabetes (27.4%), PVD (23.9%), and osteoporosis
(20.5%). FVC liters and % predicted and FEV1 liters and %
predicted were significantly lower in patients with MetS than
in those without MetS (Table 1).

Sex Differences in the Prevalence of MetS
in Early COPD
The prevalence of MetS was 26.7% in men and 35.1% in
women (P<0.001) (Table 2). The mean age and BMI were
higher in MetS for both men and women (both P<0.001)
(Table 2). Ages and frequencies of arthritis were signifi-
cantly higher in women with MetS. Number of pack-years
smoked was smaller in women than in men (Table 2).

COPD Exacerbations and MetS
Differences in moderate-to-severe exacerbations of COPD
between patients with and without MetS are shown in
Table 3. No differences were observed in the frequencies
of moderate-to-severe exacerbations at baseline and follow-up
between patients with and without MetS. However, in
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>No MetS</th>
<th>MetS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>2164</td>
<td>1489 (68.8)</td>
<td>675 (31.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>64.6±9.9</td>
<td>63.8±10.2</td>
<td>66.2±9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td>1566 (72.4)</td>
<td>1101 (73.9)</td>
<td>465 (68.9)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>23.5±2.8</td>
<td>22.9±2.5</td>
<td>25.0±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI ≥ 25 kg/m²</strong></td>
<td>1549 (71.6)</td>
<td>283 (19.0)</td>
<td>332 (49.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Participants with a smoking history</strong></td>
<td>1504 (69.5)</td>
<td>1055 (70.9)</td>
<td>449 (66.5)</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>Smoking history, pack-years</strong></td>
<td>21.0±23.0</td>
<td>21.1±22.7</td>
<td>21.0±23.9</td>
<td>0.950</td>
</tr>
<tr>
<td><strong>SBP, mmHg</strong></td>
<td>126.8±17.5</td>
<td>124.4±17.7</td>
<td>131.5±15.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DBP, mmHg</strong></td>
<td>77.4±10.3</td>
<td>76.3±10.0</td>
<td>78.9±11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Abdominal circumference, cm</strong></td>
<td>84.9±8.1</td>
<td>82.7±7.9</td>
<td>89.0±7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TG, mg/dL</strong></td>
<td>155.5±36.2</td>
<td>124.6±36.3</td>
<td>186.5±36.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HDL-C, mg/dL</strong></td>
<td>44.5±9.95</td>
<td>48.9±11.1</td>
<td>40.2±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Glucose, mg/dL</strong></td>
<td>102.4±23.5</td>
<td>97.6±16.0</td>
<td>113.0±32.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>776 (35.9)</td>
<td>408 (27.4)</td>
<td>368 (54.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1178 (54.4)</td>
<td>649 (43.6)</td>
<td>529 (78.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IHD</strong></td>
<td>218 (10.1)</td>
<td>117 (7.9)</td>
<td>101 (15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>120 (5.6)</td>
<td>75 (5.0)</td>
<td>45 (6.7)</td>
<td>0.125</td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>575 (26.6)</td>
<td>356 (23.9)</td>
<td>219 (32.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>279 (12.9)</td>
<td>173 (11.6)</td>
<td>106 (15.7)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td>464 (21.4)</td>
<td>305 (20.5)</td>
<td>159 (23.6)</td>
<td>0.107</td>
</tr>
<tr>
<td><strong>GERD</strong></td>
<td>1167 (53.9)</td>
<td>812 (54.5)</td>
<td>355 (52.6)</td>
<td>0.401</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>339 (15.7)</td>
<td>217 (14.6)</td>
<td>122 (18.1)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>FEV₁/FVC</strong></td>
<td>0.64±0.06</td>
<td>0.64±0.06</td>
<td>0.64±0.06</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>FVC, L</strong></td>
<td>3.53±0.87</td>
<td>3.63±0.83</td>
<td>3.44±0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FVC, % predicted</strong></td>
<td>89.9±3.38</td>
<td>91.9±3.26</td>
<td>87.9±3.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PVC, % predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First quartile</td>
<td>325 (21.8)</td>
<td>216 (32.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second quartile</td>
<td>346 (23.2)</td>
<td>195 (28.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third quartile</td>
<td>404 (27.1)</td>
<td>137 (20.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>414 (27.8)</td>
<td>127 (18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FEV₁, L</strong></td>
<td>2.25±0.61</td>
<td>2.31±0.61</td>
<td>2.2±0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FEV₁, % predicted</strong></td>
<td>78.5±13.5</td>
<td>79.1±13.5</td>
<td>77.9±13.5</td>
<td>0.048</td>
</tr>
</tbody>
</table>

**Note:** Data are expressed as mean±standard deviation or number (%) as appropriate.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; CHF, congestive heart failure; PVD, peripheral vascular disease; GERD, gastroesophageal reflux disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.
women, moderate-to-severe exacerbations at baseline were higher in those with MetS than in those without MetS (4.5/year vs. 3.7/year; P=0.03) (Table 3). Moreover, during the 5-year follow-up, moderate-to-severe exacerbations were
significantly higher only in women with MetS than in those without MetS (5.8/year vs. 4.9/year; P=0.02) (Table 3).

The crude IRR of moderate-to-severe exacerbations during the 5 years in patients with MetS was significantly higher only in women with MetS than in those without MetS (IRR, 1.19; 95% CI, 1.03 to 1.37; P=0.01) (Figure 1). After adjusting for age, sex, and FEV\textsubscript{1}\% predicted (Model 1), the IRR was 1.15 (95% CI, 1.00 to 1.34; P=0.04) in women, and after adjusting for age, sex, number of pack-years smoked, and FEV\textsubscript{1}\% predicted (Model 2), the IRR was 1.17 (95% CI, 1.01 to 1.36; P=0.03) in women (Figure 1).

**COPD-Related Costs and MetS**

COPD-related hospitalization per person-year was higher in MetS (1.7 per person-year vs. 1.2 per person-year; P=0.04). Cost for pharmacy use was also higher in MetS (22.7 US dollars [USD] vs. 18.5 USD; P=0.02) (Table 4). According to sex, only women showed significantly higher COPD-related hospitalizations and costs among patients with MetS than among those without MetS (Table 5). The cumulative COPD-related medical costs per person-year were higher in MetS during the 5-year follow-up period (Figure 2). The cumulative COPD-related medical costs per person-year

<table>
<thead>
<tr>
<th>Total</th>
<th>Crude</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1.07 (0.98 to 1.16), P=.09</td>
<td>1.01 (0.93 to 1.10), P=.70</td>
<td>1.01 (0.93 to 1.10), P=.70</td>
</tr>
<tr>
<td>Men</td>
<td>1.00 (0.91 to 1.11), P=.90</td>
<td>0.98 (0.89 to 1.08), P=.77</td>
<td>0.98 (0.89 to 1.08), P=.76</td>
</tr>
<tr>
<td>Women</td>
<td>1.19 (1.03 to 1.37), P=.01</td>
<td>1.15 (1.00 to 1.34), P=.04</td>
<td>1.17 (1.01 to 1.36), P=.03</td>
</tr>
</tbody>
</table>

Figure 1. Incidence rate ratio (IRR) of exacerbations in patients with metabolic syndrome for 5 years. Model 1 was adjusted for age, sex, and FEV\textsubscript{1}\% predicted. Model 2 was adjusted for age, sex, number of pack-years smoked, and FEV\textsubscript{1}\% predicted. Data are presented as IRR (95% CI).

**Abbreviations:** CI, confidence interval; FEV\textsubscript{1}, forced expiratory volume in 1 second.
were higher in women with MetS, but not in men with MetS (Figure 2).

**Discussion**

COPD and MetS are growing causes of morbidity and mortality worldwide, with a significant impact on public health. To our knowledge, this is the first and largest study to investigate the prevalence of and sex differences in MetS among patients with early COPD, and the impact of MetS on the frequency of exacerbations and COPD-related medical costs.

In the present study, the prevalence of MetS among patients with early COPD was 31.2%, and it was significantly higher in women (35.1%) than in men (26.7%). Compared to the age-adjusted overall (27.0%) and sex-specific prevalence (27.6% in women and 25.5% in men in 2012) of MetS in the Korean adult population, the prevalence of MetS was higher in patients with early COPD and it occurred more frequently in women. These results are consistent with those of previous pooled studies, which showed that the mean overall prevalence of MetS among patients with COPD was 34%, with a wide variation according to geographical locations, ranging from 23% to 37% in Asia to 58% in North America, and it was more frequent in women than in men (35% vs. 24%). Several studies have investigated the prevalence of MetS according to the GOLD stages, and found it was more frequent in earlier spirometric stages of COPD (GOLD I-II). In a study carried out in Germany, the frequencies of MetS in GOLD stages I-IV were 50%, 53%, 37%, and 44%, respectively. Minas et al also reported it was more prevalent in GOLD II (66.7%), whereas its prevalence decreases to about 10% in GOLD stages III and IV. The reason why MetS is more prevalent in early GOLD COPD than in severe COPD is unclear, but increased weight loss frequently found in advanced stages might explain this observation. Moreover, the co-existence of COPD and MetS further increases the risk of CVD, which

<table>
<thead>
<tr>
<th>Table 4 Cumulative COPD-Related Health-Care Utilization and Medical Expenses (USD) in All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalization</strong></td>
</tr>
<tr>
<td>Number per person-year</td>
</tr>
<tr>
<td>Cost per person-year</td>
</tr>
<tr>
<td><strong>Outpatient clinic visits</strong></td>
</tr>
<tr>
<td>Number per person-year</td>
</tr>
<tr>
<td>Cost per person-year</td>
</tr>
<tr>
<td><strong>Use of pharmacy</strong></td>
</tr>
<tr>
<td>Number per person-year</td>
</tr>
<tr>
<td>Cost per person-year</td>
</tr>
</tbody>
</table>

**Notes:** Data are expressed as mean±standard deviation. **Abbreviations:** COPD, chronic obstructive pulmonary disease; USD, US dollars; MetS, metabolic syndrome.

<table>
<thead>
<tr>
<th>Table 5 COPD-Related Health-Care Utilization and Medical Expenses (USD) According to Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>Number per person-year</td>
</tr>
<tr>
<td>Cost per person-year</td>
</tr>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>Number per person-year</td>
</tr>
<tr>
<td>Cost per person-year</td>
</tr>
</tbody>
</table>

**Notes:** Data are expressed as mean±standard deviation. **Abbreviations:** COPD, chronic obstructive pulmonary disease; USD, US dollars; MetS, metabolic syndrome.
Therefore, patients with early COPD should be evaluated and treated for MetS appropriately for ensuring a better prognosis especially in women.

In our study, the three most prevalent MetS components in early COPD were hypertension, low HDL-C, and high TG. In early COPD in the Korean population, the glycemia component was the lowest contributor to MetS, whereas the pooled data showed that hypertension, glycemia, and abdominal obesity were the three most prevalent components that defined MetS in patients with COPD. Abdominal obesity is associated with MetS and restrictive lung function impairment. In our study, the patients with MetS were distributed lower trends according to the decrement of FVC % predicted, which were similar to those findings as FEV1% predicted.

Previous pooled data showed that age was not different between patients with and without MetS but another study showed that patients with MetS were younger. In contrast, this study showed that patients with MetS were older. The number of pack-years smoked was significantly smaller among our patients with MetS, similar to the findings of a previous study. The BMI was higher among patients with MetS in our study, which was similar to previous results. Comorbidities based on the ICD-10 codes extracted from the NHI database, such as hypertension, IHD, PVD, and depression, were higher in patients with MetS than in those without MetS. Comorbidities of COPD may be causally related, either as shared risk factors or when one disease increases the risk of other diseases. The most common risk factor for COPD is smoking, which is a shared risk factor for systemic inflammation with comorbidities. Smoking induces insulin resistance and can cause MetS. In this study, women with MetS and COPD were older, had smoked fewer pack-years, and had more frequent comorbidities such as osteoporosis, depression, arthritis, PVD, and arthritis than did men. Factors other than smoking might be related to the development of MetS in women. Systemic inflammation might induce MetS. We suggest that in the absence of smoking, systemic inflammation from MetS can cause COPD and could increase the risk of exacerbations. The factors inducing systemic inflammation could be air pollutants, adipose tissue, etc. The association between MetS and COPD in the absence of smoking is intriguing. Interestingly, recent data indicated elevated insulin levels may induce hypercontractility in airway smooth muscle or potentiate airway hyperresponsiveness to parasympathetic stimulation, which could reduce lung function.

In this study, MetS significantly influenced moderate-to-severe exacerbations of early COPD only in women. This trend has not been seen for severe exacerbations. The IRR for moderate-to-severe exacerbations of MetS over 5 years, evaluated using negative binomial regression, was significantly higher only in women. Similarly, previous studies have shown that MetS impacts the number of all exacerbations of COPD, but the results were obtained from hospitalized patients with COPD. Preliminary results were based on the analysis of small patient numbers. Thus, the present study is valuable because we investigated the association between MetS and COPD exacerbations by using data from a large national survey database. In the TORCH study, COPD exacerbation rate
was 25% higher in women than in men, and in Turkey, female patients with COPD might be more prone to severe exacerbations, a higher number of hospitalizations, and prolonged hospitalization. In our study, MetS was higher in women than men, and the frequency of exacerbation was higher in women with MetS than in women without MetS. Limited knowledge is available about the relationship between sex, MetS, and COPD exacerbation. Moreover, we could not ascertain whether sex difference increased exacerbation or whether MetS increased exacerbation in our study. Although this association is still poorly understood, evidence linking MetS and COPD continues to grow, and several potential mechanisms have been proposed, including the effect of adiposity, fat-induced inflammation on the lung, physical inactivity, hypogonadism, and steroid use. On the basis of our significant findings, we could suggest that MetS increased COPD exacerbation in women.

South Korea has a compulsory universal health insurance system that includes medical reimbursement records for the entire Korean population. The NHI reimbursement database provides a unique and advantageous mechanism for evaluating the nationwide magnitude of an illness and consequent health care use. Thus, we could obtain the exacerbation history and medical costs of COPD. Comorbidities increase the costs for COPD and exacerbations. Our results confirmed that COPD-related hospitalization and pharmacy use were higher in patients with MetS than in those without MetS, and were higher in women than in men. However, MetS did not affect the COPD-related medical utilization and costs in men.

This study had several limitations. First, the cutoff values used for MetS in Korea, such as a waist circumference ≥85 cm for women as defined by the KOSSO, were not based on prospective data. However, when a waist circumference ≥80 cm for women was applied to the Korean population, the prevalence of MetS in women was higher than that in men by approximately 1.5-fold, and the prevalence of abdominal obesity was higher than 50% in Korean postmenopausal women. Thus, we used KOSSO’s cutoff value of waist circumference for MetS in Koreans as ≥85 cm for women. Second, MetS was assessed only at the time of enrollment to the KNHANES. Some patients who were classified as having no MetS in the 2007 KNHANES database could develop MetS during the 5-year follow-up period. Similarly, those with moderate COPD in the 2007 KNHANES database could progress to severe COPD during the 5-year follow-up period. Nevertheless, we hypothesized and designed the study such that the pulmonary function and MetS components would remain unchanged over 6 years, and thus, the status of MetS and stages of mild-to-moderate COPD at enrollment would remain identical for 5 years. Third, exacerbations were assessed retrospectively by using the ICD-10 codes and prescription history obtained from the NHI database. Thus, we could not count the exact number of exacerbations. Fourth, we included patients with COPD who were never smokers. However, considering the risk factors for COPD other than smoking, this inclusion was justified. Fifth, we exclude asthma subjects upon the questionnaire for self-reported physician-diagnosed asthma conducted by the KNHANES. Usually, studies using national survey depend on the self-reported disease history, which could evoke the major bias.

**Conclusion**

The prevalence of MetS in early COPD was not low. Patients with COPD and MetS were older, more obese, more frequently female, and less frequent smokers, and had more comorbidities such as hypertension, PVD, IHD, and depression than did patients with COPD and no MetS. Moreover, they had more severe airflow limitation, as indicated by FEV₁ and FVC. MetS significantly impacts the moderate-to-severe exacerbations of early COPD in women. The frequency of hospitalization and pharmacy costs were higher in patients with MetS than in those without MetS, especially in women. COPD with MetS in women might be a different phenotype from smoking-induced COPD. Efforts must be made to identify MetS in patients with COPD, especially women, at the time of diagnosis, treatment, and follow-up. Individualized treatment for patients with COPD and MetS is a challenge. Therefore, further research on the role of MetS in COPD is necessary.

**Abbreviations**

BMI, body mass index; CHF, congestive heart failure; CIs, confidence intervals; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; IRRs, incidence rate ratios; KNHANES, Korean National Health and Nutrition Examination Survey; KOSSO, Korean Society for the Study of Obesity; MetS,
metabolic syndrome; NHI, National Health Insurance; PVD, peripheral vascular disease; TG, triglyceride.

**Ethics Statement**
All KNHANES participants signed an informed consent form. Thus, ethical approval was not required, because our study used data from those surveys retrospectively.

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**Disclosure**
The authors report no conflicts of interest in this work.

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