COPD is not associated with a poor prognosis in COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a worldwide pandemic. The effect of underlying chronic obstructive pulmonary disease (COPD) on COVID-19 is controversial. We set this study to examine the clinical outcomes of COVID-19 according to the underlying COPD.

Methods: COVID-19 patients were assessed using nationwide health insurance data. COPD patients were operationally defined. Comorbidities were evaluated by using the modified Charlson Comorbidity Index (mCCI) which excluded the factors of COPD from conventional CCI scores. Baseline characteristics and clinical outcomes of COVID-19, such as mortality, hospital length of stay (LOS), and intensive care unit (ICU) admission, were assessed. Subgroup analysis about the effect of inhaled corticosteroid of COPD patients on COVID-19 was performed.

Results: COPD group were older (71.3±11.6 vs. 47.7±19.1, $p < 0.001$) and have higher CCI scores (2.6±1.9 vs. 0.8±1.3, $p < 0.001$) than non-COPD group. Mortality was higher in COPD groups than in non-COPD group (22.9% vs. 3.2%, $p < 0.001$). The ICU admission rate and hospital LOS were not significantly different between the two groups. In univariate analysis, ages, male sex, mCCI, socioeconomic status, and underlying COPD were associated with mortality. In multivariate analysis, underlying COPD was not associated with mortality after adjusted. On the other hand, other variables are still associated with mortality. Older ages (odds ratio [OR] 1.12; 95% confidence interval [CI] 1.11–1.14; $p < 0.001$), male sex (OR 2.29; 95% CI 1.67–3.12; $p < 0.001$), higher mCCI (OR 1.30; 95% CI 1.20–1.41; $p < 0.001$), and medical aid insurance (OR 1.55; 95% CI 1.03–2.32; $p = 0.035$) were associated with mortality of COVID-19. Underlying COPD was also not associated with hospital LOS and ICU admission rates in the adjusted analyses. In the subgroup analysis, there was no significant difference between the ICS user and nonuser including mortality and hospital LOS. In the adjusted analyses, the use of ICS in COPD patients was not associated with mortality and hospital LOS in COVID-19.

Conclusions: Mortality, hospital LOS, and ICU admission rate were not associated with underlying COPD in COVID-19.

Background

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly entered to the lung and targeted it (1). Therefore, the patients with chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD) have worry about COVID-19. There are several articles which reported the prevalence and the outcomes of COPD in COVID-19. However, the variability of prevalence and results were reported due to limitation of current studies (2, 3). The effects of underlying COPD in prevalence and outcomes of COVID-19 remain controversial (4). Inhaled corticosteroids (ICSs) are often used to manage COPD (5, 6). Taking ICS of COPD patients in COVID-19 have discussed until recently, but no conclusions can be reached.

A recent review found a lack of evidence for or against any benefit in COVID-19 and recommended not withdrawing them in current stable users but there are more evidence of these recommendations (1, 7). South Korea has a well-established nationwide medical claims database. Almost all medication information, including medication use, is stored in this database. We analyzed the effects of COPD on COVID-19 using this database.

Methods

Data sources

South Korea has a single mandatory government health insurance system. The Health Insurance Review and Assessment Service (HIRA) is responsible for evaluating medical claims data in South Korea and almost all South Koreans are included in this system (8). We retrospectively analyzed data from the HIRA database. To promote real-world COVID-19 research, HIRA opened the claims data for confirmed COVID-19 cases to the public; this included confirmed cases up to May 15,

2020. To analyze comorbidities and the effects of medications, we examined the data from January 20, 2019, 1 year before the first confirmed case, to May 15, 2020.

Study population

Definition of confirmed cases of COVID-19

Confirmed COVID-19 cases were defined as individuals with a confirmed infection based on diagnostic testing standards such as a COVID-19 nucleic acid testing (real-time polymerase chain reaction), which was recommended by the Korean Center for Disease Control (KCDC). Nasopharyngeal and oropharyngeal swab is required and sputum specimen is also collected if the patient has sputum.

Study population

All COVID-19 patients in South Korea are managed by the KCDC. They are all isolated at hospital after COVID-19 are confirmed. Confirmed COVID-19 patients are released from isolation after they do not exhibit any clinical symptoms for 10 days upon confirmation and test negative on PCR tests twice in a row with at least a 24-hour interval after 7 days upon confirmation. The list of these patients was de-identified and merged with the HIRA claims data. The KCDC also provides the mortality outcomes due to COVID-19 to HIRA. Patients were enrolled if they had confirmed COVID-19 or had died from COVID-19, were at least 18 years old, and had medical claims data obtained in the year before the date of COVID-19 diagnosis. Patients were excluded if they were younger than 18 years, had no linked medical claims data for confirmed or deceased cases, and had no medical claims data for the year from the date of COVID-19 diagnosis.

Operational definitions

COPD and the ICS user have clear operational definitions (6, 9-24).

Definition of COPD

The operational definition of patients with COPD was as follows: 1) age ≥ 40 years, 2) at least one International Classification of Disease–Tenth Revision (ICD-10) diagnosis code for COPD or emphysema (J43.0x–J44.x, except J43.0 as a primary or secondary [within four positions] diagnosis), and 3) the use of more than one of the following COPD medications at least twice per year: long-acting muscarinic antagonist (LAMA), LABA, ICS + LABA, LABA + LAMA, short-acting muscarinic antagonist (SAMA), short-acting β_2 agonist (SABA), SAMA + SABA, phosphodiesterase-4 (PDE-4) inhibitor, methylxanthine, or oral beta-adrenergic agonist.

Definition of inhaled corticosteroid users

The use of ICS was well estabilished in the HIRA database and it has been analyzed in many previous articles (6, 9-11, 25, 26). The use of ICS was defined as its use either alone or with a long-acting β_2 agonist (LABA). ICS users and nonuser were defined as patients who were or were not prescribed ICS±LABA within one year of being diagnosed COVID-19. The use of ICS±LABA was only approved for asthma or COPD in national health insurance system of South Korea. Details of medications which were included in our analyses were as follows:

ICS+LABA: budesonide+formoterol, beclomethasone+formoterol, fluticasone propionate+salmeterol, fluticasone propionate+formoterol, fluticasone furoate+vilanterol

Comorbidities

The modified Charlson Comorbidity Index (mCCI) is used to predict prognosis and mortality. Conventional CCI is based on ICD-10 diagnosis codes and it was calculated as in previous studies and mCCI excluded the factor of COPD diagnosis from conventional CCI. (Supplemental Method and Table S1) (27, 28).

Management of COVID-19 in this study

This study was performed with data until May 15, 2020. Until then, management of COVID-19 was mainly symptomatic treatment. Other drugs, such as Remdesivir or dexamethasone, were not used as treatment of COVID-19 to the participants of this study.

Statistical analyses

We used the Student *t*-test and chi-square test for independence to compare differences in continuous and categorical variables between groups. Simple and multiple linear regression analyses were used to find factors affecting hospital LOS. Univariable and multivariable logistic regression analyses were used to find factors affecting admission to the intensive care unit (ICU) and mortality. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics of COVID-19 patients in South Korea

There were 7,590 confirmed COVID-19 cases with medical claims data in the HIRA. After excluding young subjects (<40 years old) and those lacking medical claims data, 6,520 subjects were included (Figure 1). The mean age of COVID-19 patients was 47.9 years and 39.7% of them were male. The mean mCCI was 0.9. COPD were present in 0.5% (n=35). The total medical cost was 4,736 USD during hospitalization. The mean hospital LOS was 23.0 days. The ICU admission rate was 3.2% for confirmed COVID-19. The overall mortality was 3.3% (Table 1).

Demographics of COVID-19 patients in South Korea according to the underlying COPD

The mean age of COPD group was higher than non-COPD group (71.3±11.6 vs. 47.7±19.1, $p < 0.001$). 54.3% of COPD group were male. The mCCI was higher in COPD group than non-COPD group (2.6±1.9 vs. 0.8±1.3, $p < 0.001$). Medical aids group was 14.3% of COPD group. In COPD group, the total medical cost was 5,124 USD during hospitalization and the

mean hospital LOS was 23.5 days. The ICU admission rate was 2.9% for confirmed COVID-19. There was no significant difference between the two groups in hospital LOS and ICU admission rate. Univariable analyses indicated that mortality is higher in the COPD group versus the non-COPD group (22.9% vs. 3.2%, $p < 0.001$) (Table 2).

Underlying COPD is not associated with poor outcomes in COVID-19 patients

Univariable and multivariable logistic regression analyses were used to examine the effects of age, sex, mCCI, insurance type, and underlying COPD on the mortality and the hospital LOS of COVID-19. Multiple linear regression analyses were conducted to evaluate the contributing factors to hospital LOS in COVID-19.

In univariable analyses, all five were associated with mortality. After adjusting for confounding factors in multivariable analyses, older age (OR 1.12; 95% CI 1.11–1.14), male sex (OR 2.29; 95% CI 1.67–3.12), higher mCCI scores (OR 1.30; 95% CI 1.20–1.41), and poor socioeconomic status (OR 1.55; 95% CI 1.03–2.32) remained associated with mortality. Underlying COPD was not significantly associated with mortality in COVID-19 (OR 1.73; 95% CI 0.67–4.47; $p = 0.259$).

Underlying COPD was not contributing factor of longer hospital LOS both in univariable and multiple linear regression analyses. Ages (standardized coefficient [β] = 0.178), mCCI scores (β = 0.079), and the status of medical aids (β = -0.048) were associated with hospital LOS. No multi-collinearity between variables was observed in the analyses.

COPD group was also not associated with ICU admission rate both in univariate and multivariate analyses. Older age (OR 1.05; 95% CI 1.04–1.06), male sex (OR 1.98; 95% CI 1.48–2.63), higher mCCI scores (OR 1.21; 95% CI 1.11–1.31), and poor socioeconomic status (OR 0.59; 95% CI 0.36–0.98) were contributing factors of ICU admission rate of COPD patient in COVID-19 infection (Table 3).

ICS is not associated with clinical outcomes of COPD patients in COVID-19

In the subgroup analysis, there was no significant difference between ICS user and nonuser including demographic features and clinical outcomes such as overall medical cost, mortality, and hospital LOS (Supplement Table 2). In the multivariable analyses of mortality and hospital LOS, the use of ICS was not associated with outcomes of COVID-19 in COPD patients. Old age is only factor associated with poor mortality of COPD patients (Table 4).

Discussion

This nationwide retrospective population study examined the association between the underlying COPD and the prognosis of COVID-19. Of the 6,520 COVID-19 patients, 35 patients are diagnosed as COPD by well-defined operational definition. The COPD group was older and have more comorbidities compared to the non-COPD group. The mortality is 22.9% in COPD group which is significantly higher than that of non-COPD group (3.2%). The other clinical outcomes such as hospital LOS and ICU admission rate were not different statistically. In the univariate analyses, all five variables, such as age, male sex, mCCI, medical aids, and COPD, were associated with mortality. In the adjusted analyses, the association of COPD with COVID-19 mortality was disappeared. This means that the effect of underlying COPD in mortality of COVID-19 is not significant. In the subgroup analyses, the ICS, which is mostly used in COPD patients prior to confirmed COVID-19, is

not associated with mortality of COVID-19 also. The result from analyses of hospital LOS and ICU admission showed that there is no association of underlying COPD with outcomes of COVID-19.

Therefore, underlying COPD does not have harmful effect in the prognosis of COVID-19. And the prior use of ICS in COPD also does not have association with poor clinical outcome. These means that we should not worry about uncertain fear of COPD with COVID-19 infection. Also, we should be careful in changing medications of COPD patient with COVID-19, as ICS withdrawal can lead to the exacerbation of COPD. These are valuable results that solve the controversy surrounding the effect of underlying COPD in COVID-19 and the ICS withdrawal in COPD patients after confirmed COVID-19 infection. Another interesting finding is the low prevalence but high mortality of COPD patients who confirmed COVID-19. Although only 35 patients (0.5% of all COVID-19 patients) had COPD in this study, their mortality exceeded 20%. This result is in line with a previous meta-analysis (29). The potential reason for the low prevalence of COPD in COVID-19 patients is because patients are so afraid of infection that they may reduce social activity and wear masks. In this study, the high mortality of COPD was associated with old age, male sex, the number of underlying comorbidities, and poor socioeconomic status, rather than COPD itself.

The previous studies had several limitations that those studies were not nationwide study and did not have accurate information on pre-morbid comorbidities and medication (7). Unlike that study, ours was a nationwide population study that included detailed comorbidity and medication information, with no bias or missing data. Consequently, we were able to precisely determine the underlying COPD, the use of medications, and other confounding demographic factors. To the best of our knowledge, this was the first nationwide study to analyze the effects of COPD on COVID-19 that used a large medical claims dataset. Adjusted analyses of confounding factors clarified that COPD was not a harmful factor in COVID-19 patients. We should be careful when changing the ICS due to the fear of potentially increasing the risk for COVID-19, as ICS withdrawal is a risk factor for the exacerbation of underlying diseases. We clearly show that it is not necessary to worry about continuing ICS treatment in COPD patients, ending the controversy over this issue.

There were several limitations in this study. First, data of this study did not include lung function data and symptomatic scores of COPD because of the nature of the medical claims data. We cannot analyze the effects of the severity of COPD in COVID-19 in this study. Second, this was a retrospective study. However, a retrospective study using medical claims data was appropriate for analyses because we had all information on medical utilization before the diagnosis of COVID-19. Third, we did not have the data about mortality date of COVID-19 in the HIRA medical claim data. Therefore, the survival method which might increase the statistical power of this study could not be performed in the analysis.

Conclusions

This retrospective nationwide study is the first to report that the underlying COPD was not associated with a poor outcome in COVID-19 patients. Older age, male sex, higher mCCI scores, and poor socioeconomic status were significantly associated with mortality. We also showed that the prior ICS in COPD did not associated with clinical outcomes. Based on our results, we suggest COPD patients not to worrying about COVID-19 exaggeratedly and not changing ICSs during the COVID-19 pandemic without clear evidence of adverse effect.

List Of Abbreviations

COVID-19 - Coronavirus disease 2019

COPD – Chronic obstructive pulmonary disease

mCCI – modified Charlson Comorbidity Index

LOS – Length of stay

ICU – Intensive care unit

ICS – Inhaled corticosteroid

OR – Odds ratio

CI – Confidence Interval

HIRA – The Health Insurance Review and Assessment Service

LABA – long-acting β_2-agonist

ICD-10 – International Classification of Disease-Tenth Reivision

LAMA – long-acting muscarinic antagonist

SABA - short-acting β_2-agonist

SAMA - short-acting muscarinic antagonist

PDE-4 inhibitor – phosphodiesterase-4 inhibitor

LTRA – leukotriene antagonist

Declarations

Ethics approval: All methods of this study were carried out in accordance with relevant guidelines and regulations. Informed consent was waived due to the retrospective nature of the study and it was approved by the Institutional Review Board of The Catholic University of Korea Yeouido St. Mary's Hospital (approval no. SC20ZISE0067).

Consent for publication: Not applicable

Availability of data and materials: The datasets which was analyzed in this study are not publicly available due to characteristics of dataset. It is national health insurance data from South Korea. This data set was currently handled by the Health Insurance Review and Assessment service of South Korea. We are privileged to access and analyze this data but not it is not allowed for availability publicly due to individual privacy.

Competing interests: CK Rhee has received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer. Other authors do not have any conflict of interests.

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Tables

Table 1. Demographics of COVID-19 patients in South Korea

	Total COVID-19 (n=6520)
Age, years (mean ± SD)	47.9±19.1
Male sex, n (%)	2587 (39.7)
Comorbidities, n (%)	
Diabetes	1043 (16.0)
Myocardial infarction	85 (1.3)
Congestive heart failure	179 (2.8)
Peripheral vascular disease	448 (6.9)
Cerebrovascular disease	392 (6.0)
Dementia	96 (1.5)
Rheumatic or connective tissue	134 (2.1)
Gastric or peptic ulcer	613 (9.4)
Hemiplegia or paraplegia	98 (1.5)
Chronic kidney disease	75 (1.5)
Any malignancy	212 (3.3)
Metastatic solid tumor	26 (0.4)
Immunodeficiency	3 (0.1)
mCCI score, points (mean ± SD)	0.9±1.3
Percentage of COPD	35 (0.5)
Percentage of inhaler use, n (%)	
LAMA	11 (0.2)
LABA	-
LABA + LAMA	15 (0.2)
ICS (±LABA)	185 (2.8)
Type of insurance	
Medical aid insurance, n (%)	583 (8.9)
Clinical outcomes	
Overall medical costs/patient, USD (mean ± SD)	4,736±5,902
Mortality, n (%)	216 (3.3)
Hospital length of stay, days (mean ± SD)	23.0±14.2
ICU admission rate, n (%)	207 (3.2)

COVID-19, Coronavirus disease 2019; SD, standard deviation; mCCI, modified Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonists; LABA, long-acting β-agonists; ICS, inhaled corticosteroid; ICU, intensive care unit

Table 2. Differences of COVID-19 patients according to the underlying COPD

	Non-COPD (n=6485)	COPD (n=35)	*p*-value
Age, years (mean ± SD)	47.7±19.1	71.3±11.6	< 0.001
Male sex, n (%)	2568 (39.6)	19 (54.3)	0.077
mCCI score, points (mean ± SD)	0.8±1.3	2.6±1.9	< 0.001
Type of insurance			
Medical aid insurance, n (%)	578 (8.9)	5 (14.3)	0.264
Clinical outcomes			
Overall medical cost/patient, USD (mean ± SD)	4,726±5,898	5,124±4,802	0.691
Hospital length of stay, days (mean ± SD)	23.0±4.2	23.5±18.2	0.883
ICU admission rate, n (%)	206 (3.2)	1 (2.9)	0.914
Mortality, n (%)	208 (3.2)	8 (22.9)	< 0.001

COVID-19, Coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; SD, standard deviation; mCCI, modified Charlson Comorbidity Index; ICU, intensive care unit

Table 3. Factors associated with the clinical outcomes of COVID-19 according to the underlying COPD

	Mortality				Hospital length of stay				ICU admission			
	Univariable		Multivariable		Univariable linear regression		Multiple linear regression		Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	B	*p*-value	β	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Ages	1.13 (1.11-1.14)	< 0.001	1.12 (1.11-1.14)	< 0.001	0.207	< 0.001	0.178	< 0.001	1.06 (1.05-1.06)	< 0.001	1.05 (1.04-1.06)	< 0.001
Male sex	1.80 (1.37-2.36)	< 0.001	2.29 (1.67-3.12)	< 0.001	-0.018	0.149	-0.011	0.366	1.87 (1.41-2.46)	< 0.001	1.98 (1.48-2.63)	< 0.001
mCCI score	1.69 (1.58-1.81)	< 0.001	1.30 (1.20-1.41)	< 0.001	0.153	< 0.001	0.079	< 0.001	1.44 (1.34-1.54)	< 0.001	1.21 (1.11-1.31)	< 0.001
Medical aids	2.33 (1.63-3.34)	< 0.001	1.55 (1.03-2.32)	0.035	-0.012	0.341	-0.048	< 0.001	0.97 (0.59-1.58)	0.901	0.59 (0.36-0.98)	0.043
COPD	8.94 (4.01-19.92)	< 0.001	1.73 (0.67-4.47)	0.259	0.002	0.850	-0.021	0.091	0.90 (0.12-6.58)	0.915	0.22 (0.03-1.67)	0.142

COVID-19, Coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; mCCI, modified Charlson Comorbidity Index

Table 4. Factors associated with the clinical outcomes of COVID-19 in COPD patients

	Mortality				Hospital length of stay				ICU admission			
	Univariable		Multivariable		Univariable linear regression		Multiple linear regression		Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	B	*p*-value	β	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Ages	1.19 (1.04-1.37)	0.011	1.25 (1.01-1.55)	0.038	0.065	0.709	0.044	0.827	1.00 (0.84-1.19)	0.978	0.94 (0.75-1.16)	0.555
Male sex	1.55 (0.31-7.81)	0.597	1.46 (0.13-16.3)	0.760	-0.159	0.361	-0.199	0.295	-	-	-	-
mCCI score	1.84 (1.07-3.17)	0.027	1.65 (0.91-2.97)	0.099	-0.036	0.839	-0.027	0.890	1.60 (0.73-3.49)	0.240	1.50 (0.52-4.27)	0.452
Medical aids	-	-	-	-	-0.083	0.634	-0.230	0.271	-	-	-	-
ICS (±LABA)	0.87 (0.17-4.43)	0.870	4.93 (0.31-79.3)	0.260	0.237	0.171	0.303	0.111	-	-	-	-

COVID-19, Coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; mCCI, modified Charlson Comorbidity Index; ICS, inhaled corticosteroid; LABA, long-acting β-agonist

Figures

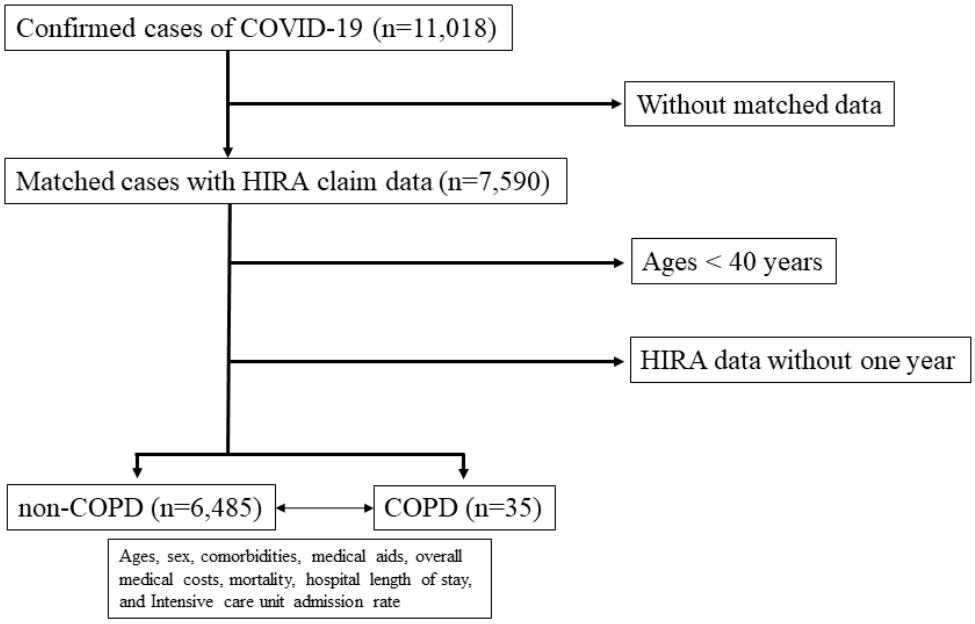
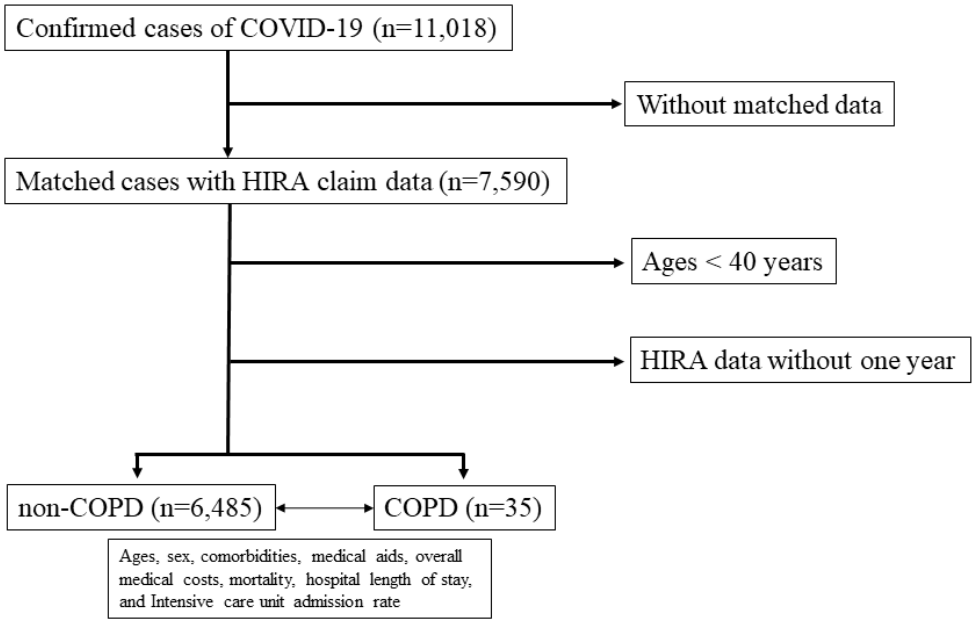


Figure 1

Confirmed cases of Coronavirus disease 2019 (COVID-19) were linked with medical claims data of the Health Insurance Review and Assessment Service (HIRA) (n=7,590). Subjects younger than 40 years and those with no HIRA database within 1 year were excluded. Ultimately, 6,520 patients with COVID-19 were included in the study. Groups were divided by the underlying COPD. 35 patients with underlying COPD were included.



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Supplementary Files

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- Supplementarymaterials.docx
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