EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Effect of Asthma and Asthma Medication on the Prognosis of Patients with COVID-19

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Please cite this article as: Choi YJ, Park J-Y, Lee HS, *et al*. Effect of Asthma and Asthma Medication on the Prognosis of Patients with COVID-19. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02226-2020).

Title page: Original Investigation

Effect of Asthma and Asthma Medication on the Prognosis of Patients with COVID-19

Running title: Asthma and asthma medication and COVID-19

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Word count: Text 2,970, Abstract 243

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Authors' contributions

YJC analyzed and interpreted the data, drafted and revised the article, and approved the final version of this manuscript for publication. JYP and HSL are professional biostatisticians and were responsible for the analysis and interpretation of the data. JS, JYS, MKB, JHC, HJK, JHL, and JWP collected and analyzed the data, contributed to the drafting of the manuscript, revised the article, and approved the final version of this manuscript for publication. HJP provided constructive criticism on the rationale and design of this study, interpreted the data, drafted and revised the article, and approved the final version of this manuscript for publication.

Take Home Message

Asthma increases the total medical cost burden and mortality rate associated with COVID-19. Asthma patients should not be concerned about using asthma medication during the COVID-19 pandemic, except for the use of oral short-acting β_2-agonists.

ABSTRACT

Background: Coronavirus disease (COVID-19) has rapidly spread worldwide. However, the effects of asthma, asthma medication, and asthma severity on the clinical outcomes of COVID-19 have not yet been established.

Methods: The study included 7,590 de-identified patients, who were confirmed to have COVID-19 using the severe acute respiratory syndrome-coronavirus-2 RNA–polymerase chain reaction tests conducted up to 15th May 2020; and we used the linked-medical claims data provided by the Health Insurance Review and Assessment Service. Asthma and asthma severity (step suggested by GINA) was defined using the diagnostic code and history of asthma medication usage.

Results: Among 7,590 COVID-19 patients, 218 (2.9%) had underlying asthma. The total medical cost associated with COVID-19 patients with underlying asthma was significantly higher than that of other patients. Mortality rate for COVID-19 patients with underlying asthma (7.8%) was significantly higher than that of other patients (2.8%; $P<0.001$). However, asthma was not an independent risk factor for the clinical outcomes of COVID-19 after adjustment. Asthma medication use and asthma severity also did not affect the clinical outcomes of COVID-19. However, use of oral short-acting β_2-agonists (SABA) was an independent factor to increase the total medical cost burden. Patients with step 5 asthma showed significant prolonged admission duration than those with step 1 asthma in both univariate and multivariate analysis.

Conclusions: Asthma led to poor outcomes of COVID-19; however, underlying asthma, use of asthma medication, and asthma severity were not independent factors for poor clinical outcomes of COVID-19, generally.

Keywords: Asthma, COVID-19, Mortality, Prognosis

List of abbreviations

CI, confidence interval

COVID-19, coronavirus disease 2019

GINA, Global INitiative for Asthma

HIRA, Health Insurance Review and Assessment Service

ICS, inhaled corticosteroid

LABA, long-acting β_2-agonists

LAMA, long-acting muscarine antagonists

LTRA, leukotriene receptor antagonists

OR, odds ratio

SABA, short-acting β_2-agonists

WHO, World Health Organization

INTRODUCTION

Coronavirus disease (COVID-19), named by the World Health Organization (WHO), has rapidly spread worldwide. The disease may manifest as mild upper respiratory symptoms, fever, fatigue, viral pneumonia, acute respiratory syndrome, and death [1, 2]. Coronavirus patients are usually infected through the respiratory tract, and the cause of death is mainly due to respiratory problems [3]. Asthma is a chronic airway inflammatory disease resulting in an imbalanced immunity of the airway [4]. Respiratory virus infections frequently exacerbate asthma [5, 6]. We can assume underlying asthma might affect the clinical outcomes of COVID-19 infection, since respiratory viruses broadly can increase the risk of asthma exacerbation and death. In previous studies, underlying asthma is reported to account for 0.9-17% of hospitalised patients with COVID-19 [1, 7, 8]. However, the importance of underlying asthma is still overlooked in many COVID-19 studies, and there are currently no studies determining whether asthma is a risk factor for poor prognosis of COVID-19.

Inhaled medications, especially inhaled corticosteroids (ICS), are fundamental therapeutic options for asthma patients, and ICS are administered directly through the respiratory tract. Some asthma patients were concerned about the use of inhaled medications during the COVID-19 pandemic owing to the risk of respiratory infection through their inhaler device and suppression of the airway immunity system due to the use of ICS. The worldwide asthma guideline, Global INitiative for Asthma (GINA), recommends that asthma patients should continue taking their prescribed asthma medications, particularly ICS and oral corticosteroids, even during the COVID-19 pandemic period. However, studies supporting this recommendation have not been reported to date.

Korea has a national health insurance service (NHIS) that provides universal coverage for nearly all Korean citizens. All medical cost for COVID-19 in Korea have been covered by this service. The Health Insurance Review & Assessment Service (HIRA) has extensive linked-medical claims data (including in-patient and out-patient visits) of all the COVID-19 patients in Korea. In this study, we aimed to evaluate the effects of asthma and asthma medication use on the prognosis of COVID-19 using the national medical claims data for Korean patients. To the best of our knowledge, this is the first study to report on the association between asthma and COVID-19 using national cohort data.

MATERIALS AND METHODS

COVID-19 patients and medical data

The Ministry of Health and Welfare of Korea and HIRA shared with researchers the world's first de-identified COVID-19 nationwide patient medical claims data, covering the entire Korean population, via an online portal (accessible at https://hira-covid19.net). Among 234,427 suspected COVID-19 patients, HIRA released the de-identified list of 7,590 patients, who were confirmed to have COVID-19 by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) RNA–polymerase chain reaction (RNA-PCR) tests, conducted up to 15th May 2020 (Figure 1). HIRA provided data linked to the COVID-19 patients' history of medical service use for the previous 3 years (using finalised claims data from January 2017 to May 2020).

Underlying disease and Charlson comorbidity index

We included 17 underlying diseases (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, including leukaemia and lymphoma, moderate or severe liver disease, metastatic solid tumour, and acquired immune deficiency syndrome/human immunodeficiency virus infection), which are well-known underlying conditions that affect the mortality rate and are frequently used to calculate the Charlson comorbidity index (CCI) [9]. These underlying diseases were defined when a patient's claims data included a related diagnostic code at least once from 1st January 2019 to 31st December 2019. The diagnostic code was chosen according to the suggested guideline by the HIRA (accessible at https://opendata.hira.or.kr/op/opb/selectRfrm.do?rfrmTpCd=&searchCnd=&searchWrd=&sno=11200&pageIndex=1). The CCI, which facilitates the prediction of disease prognosis and associated mortality, was calculated, as previously described and according to the HIRA guidelines [9].

Asthma, asthma medication, and asthma severity using step

An asthma diagnosis was determined when patients visited the hospital (at least once) due to asthma symptoms from January 2019 to December 2019. Furthermore, only patients who met the following criteria during the assessment period were regarded as having asthma: (1) ICD-10 codes for asthma (J45 and J46) as primary diagnosis or first sub-diagnosis; and (2) prescription of asthma medications on at least 2 occasions during outpatient visits or prescription of asthma medication following an outpatient visit and admission with treatment using systemic corticosteroids during the assessment period. This definition of asthma was established by the HIRA committee according to the authoritative opinions of respiratory and allergy experts in Korea. Since then, this definition has been commonly used by many clinical researchers, medical statisticians and the HIRA committee in Korea [10-12].

Asthma medication includes the following items: inhaled corticosteroids (ICS), inhaled long-acting β_2-agonists (LABA), oral LABA, patch LABA, systemic corticosteroids, leukotriene receptor antagonists (LTRA), xanthines, inhaled short-acting β_2-agonists (SABA), oral

SABA, and inhaled long-acting muscarine antagonists (LAMA). In addition, we defined asthma medication usage if it occurred within the last year (from March 2019 to February 2020) and in the last two months (from January 2020 to February 2020), respectively. All asthmatic patients were classified based on the asthma medications used for the last year as follows: step 1, SABA or SAMA; step 2, ICS, LTRA, or xanthine; step 3, ICS/LABA alone, ICS + LTRA, or ICS + xanthine; step 4, ICS/LABA + LAMA, ICS/LABA + LTRA, or ICS/LABA + xanthine; and step 5, oral corticosteroid with a duration over 90 days following some modifications of the Global Initiative for Asthma (GINA) treatment guidelines and a previous study [13].

Clinical outcomes

Mortality and admission to an intensive care unit (ICU), which are critical outcomes and represent severity of disease, and duration of admission and total medical costs, which represent the medical and social burden of diseases, were evaluated. Reported ICD-10 diagnostic codes B342, B972, Z208, Z290, U18, U181, Z038, Z115, U071, and U072 during the treatment period for COVID-19 were considered as clinical outcomes. Total medical cost was defined as the sum of all medical costs for all the medical claims records for COVID-19 during the assessment period. All medical institutions must charge the total medical costs incurred by COVID-19 patients to the HIRA; and all the medical costs are covered by the Korean government. Therefore, all charged costs are consistent with the total cost of care of the patient. Duration of admission was defined as the duration from the admission date to the discharge date.

Ethics

This study was approved by the Institutional Review Board of Severance Hospital (number: 3-2020-0067). The requirement of obtaining informed consent was waived due to the retrospective nature of this study.

Statistical analysis

We calculated the CCI score to evaluate comorbidities and stratified the patients according to CCI scores of 0, 1, 2, and more than 3 points. We also used logistic regression analysis to define risk factors for clinical outcomes and the results were adjusted for age, sex, underlying disease corresponding to each category in the CCI score, and/or asthma medications. The multicollinearity between variables was evaluated by the variance inflation factor (VIF). The data were analysed using SAS Enterprise version 6.1 (SAS Institute Inc., Cary, NC, USA). A $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Clinical characteristics and prognosis of COVID-19 patients

Among 7,590 COVID-19 patients, 218 patients had underlying asthma (2.9%). Age distribution was significantly different between two groups (*P*<0.001). The CCI was significantly higher in COVID-19 patients with underlying asthma compared to that in COVID-19 patients without (*P*<0.001). Total medical cost in COVID-19 patients with underlying asthma (5,388.1 USD) was higher than that in others (4,261.0 USD; *P*=0.003). Duration of admission and prevalence of admission to ICU was not significantly different between the two groups. However, mortality rate in COVID-19 patients with underlying asthma (7.8%) was significantly higher than others (2.8%; *P*<0.001).

COVID-19 patients with underlying asthma were classified according to severity of asthma. There were no significant differences in age distribution, sex, mortality, admission to ICU, and total medical cost between the steps. However, the CCI was significantly higher and duration of admission was significantly longer in patients with advanced steps (Table 1).

Usage of asthma medication in COVID-19 patients with underlying asthma

In COVID-19 patients with underlying asthma, various asthma medications were used in the last year and in the last two months, respectively, as follows. LTRA (73.4% and 66.5%) and xanthine (50.5% and 45.9%) were the most frequently used. Following them, ICS-LABA, inhaled SABA, oral LABA, and ICS alone were also frequently prescribed (Table 2).

Significant factors for mortality

Asthma was a significant factor for increased mortality rate in COVID-19 patients (OR, 2.885; 95% CI, 1.726-4.822) in univariate analysis. However, it was not a significant factor after adjustment for age, sex, and underlying conditions (OR, 1.317; 95% CI, 0.708–2.451). In the univariate analysis, only usage of inhaled SABA or inhaled LAMA were risk factors for death. However, multivariate analysis showed that no asthma medications affected the mortality rate. The severity of asthma showed no significant association with mortality in both univariate and multivariate analysis (Table 3).

Significant factors for ICU admission

Asthma was not a predictive factor for ICU admission in COVID-19 patients. Usage of oral SABA was a risk factor for ICU admission in univariate analysis; however, it was not a significant factor in multivariate analysis. In multivariate analysis, none of the asthma medications affected the risk of ICU admission. The severity of asthma was not significantly associated with ICU admission (Table 4).

Significant factors for admission durations

Among the COVID-19 patients, asthma was not a significant factor affecting the admission duration. Among the COVID-19 patients with underlying asthma, use of oral LABA in the last year and use of oral LABA in the last two months were protective factors for admission duration in the univariate analysis. However, they were not significant factors after adjustment. Patients with step 5 asthma showed significant prolonged admission duration than those with step 1 asthma in both univariate and multivariate analysis (β coefficient, 19.583; 95% CI, 6.011–33.155 and β coefficient, 18.414; 95% CI, 4.031–32.796, respectively) (Table 5).

Significant factors for total medical cost

In COVID-19 patients, asthma was a significant factor in increasing total medical cost burden (β coefficient, 1,384,449; 95% CI, 466,632–2,302,266) in univariate analysis. However, after adjustment for age, sex, and underlying conditions, it was not a significant factor (*β* coefficient, 524,590; 95% CI, -384,769-1,433,949). In the COVID-19 patients with underlying asthma, usage of asthma medications did not affect the total medical cost, except for oral SABA. Usage of oral SABA in the last year (*β* coefficient, 6,258,922; 95% CI, 1,030,068–11,487,776) and in the last two months (*β* coefficient, 5,861,499; 95% CI, 264,201–11,458,797) were significant factors to increase total medical cost burden, independently, in multivariate analysis. The severity of asthma was not significantly associated with total medical cost (Table 6).

DISCUSSION

This national study showed that COVID-19 patients with underlying asthma increase the medical cost burden and are more susceptible to mortality than COVID-19 patients without underlying asthma. However, asthma, asthma medication, and asthma severity were not independent risk factors for clinical outcomes of COVID-19, after adjustment for confounding factors. Only usage of oral SABA increased the total medical cost burden independently. Patients with step 5 asthma showed longer admission duration compared with those with step 1. This study's strength was that we included all the COVID-19 patients in Korea; however, the limitation was that we defined asthma patients based on the diagnosis code and usage of asthma medication.

The prevalence of asthma among the COVID-19 patients was 2.9% in this study, which is similar to that among the general South Korean population (1.6% to 2.2%) [13-15]. Underlying asthma is reported to account for 0.9-17% of patients hospitalised with COVID-19 in other countries [1, 7, 8]. Some studies have reported that the prevalence of asthma in the COVID-19 population is lower than that expected in the general population [16, 17], however other studies showed that asthma was reported in up to 27% cases [18]. These differences may have been caused by differences in region, race, and policies as well as criteria for hospitalization of COVID-19 patients. Additional large-scale cohort studies are required to evaluate the prevalence of asthma in patients with COVID-19 and establish whether asthma is a risk factor for COVID-19 infection.

In this study, underlying asthma was not an independent factor to predict poor clinical outcomes of COVID-19 after adjustment. Age distribution and CCI were significantly different between COVID-19 patients with and without asthma. In asthma patients, very young people (<10 years old, 9.4%) and old people (≥60 years old, 42.5%) were represented more frequently, compared to patients without asthma (0.8% and 25.3%, respectively). The negative effects of asthma on clinical outcomes in univariate analysis might be induced by these confounding effects (imbalanced distribution of age and CCI). After adjustment for basic clinical factors, the negative effects of asthma on COVID-19 disappeared. However, considering the mechanisms of asthma and COVID-19, we need further large-scale studies to confirm whether asthma is a significant factor for clinical outcomes in COVID-19.

Asthma medication did not affect the clinical outcomes in this study. The usage rate of asthma medication reported in this study is similar to that reported in general asthma patients as described in a previous study [10]. The GINA recommends that asthma patients continue taking their prescribed asthma medications during the COVID-19 pandemic period, because stopping asthma medications often leads to potentially dangerous exacerbation of asthma symptoms. Among asthma medications, steroids can have dual functions: blocking host hyperactive inflammation, including cytokine storming, and inducing the replication of coronavirus by blocking innate immunity [19, 20]. Therefore, WHO guidance proposed that systemic corticosteroids should be carefully used only in selected cases. In addition, some recent Japanese studies have reported that ciclesonide, as one type of ICS, may have positive effects in treating COVID-19 [21, 22]. However, this study concludes that recent usage of asthma medication did not affect clinical outcomes of COVID-19, independently. The result of this study also supports the GINA recommendation, indirectly. However, further research is needed.

In this study, use of oral SABA increased the total medical cost burden independently. SABA, as a bronchodilator, relieves asthma symptoms; however, it has various side effects, including tachycardia, tremors, and hypokalaemia [23, 24]. Recently, the GINA guidelines recommended that asthma patients should not receive SABA-only treatment, because SABA-only treatment increases the risk of severe exacerbation and asthma-related mortality, and addition of ICS significantly reduces the risk [25, 26]. Oral SABA has been frequently prescribed in very young or old people, as a substitutes for inhaled SABA. However, it has a slower onset of action and the associated side effects are noted more frequently compared to those for inhaled SABA. Therefore, oral SABA may lead to increased medical cost burden in COVID-19.

LAMA seems to be a significant factor for mortality in univariate analysis. This can be explained by the following reasons: 1) patients who use LAMA might have COPD features; 2) patients who use LAMA might have severe asthma because LAMA is recommended at step 4-5 based on the GINA guideline. After adjustment for other factors, LAMA was not a significant factor to predict mortality.

COVID-19 patients with underlying asthma showed a higher total medical cost and mortality rate compared to those without underlying asthma in this study. The airway epithelium is essential to control inflammatory and immune responses to allergens, viruses, and pollutants, which invade through the respiratory tract [27]. However, dysfunction of the airway epithelium in asthma patients can lead to a weakened immune defence mechanism [27, 28]. Infection from a respiratory virus frequently induces asthma exacerbation, and it can also lead to poor clinical outcomes, and even death [5]. Autopsies of COVID-19 infected patients showed airway inflammation and diffuse alveolar damage in pathologic analysis [29], indicating that COVID-19 is also an airway inflammatory disease. Therefore, asthma might negatively affect clinical outcomes in COVID-19.

The severity of asthma was not related to the mortality, ICU admission, and total medical cost in this study, but it was significantly related with the admission duration. However, because of limited evidence from previous studies and the small number of step 5 patients in this study, additional research is thought to be necessary to confirm these findings.

The strengths of this study are that we included almost all COVID-19 patients diagnosed in Korea, and we also included an adequate number of asthma patients. The Korean NHIS includes all medical utilization of almost all COVID-19 patients in Korea; and this minimises selection bias and collider bias. However, there are some limitations of this study. First, HIRA data includes only diagnostic codes and medication use, therefore the definition of asthma was based on the diagnostic code and history of use of asthma medication, while asthma was originally diagnosed based on the clinical history and objective test results. Mild asthma patients with intermittent symptoms might have been excluded in this study. However, Korea has a national health insurance service that covers almost all Korean citizens. Asthma patients in Korea can visit hospitals more freely than in other countries because of this insurance service. Hence, we considered the number of patients excluded due to mild asthma would not be large. Second, we could not obtain the date of COVID-19 confirmation; real use of asthma medications; and the type of medicinal ingredients and dose of medication. Third, we could not obtain important clinical and laboratory data, which can affect the clinical outcomes of COVID-19.

In conclusion, underlying asthma in COVID-19 patients is positively associated with medical cost burden and mortality. However, there was no evidence of an association between asthma, asthma medication, or asthma severity and the clinical outcomes of COVID-19 after adjustment for confounding factors. Reflecting these results, clinicians can recommend asthma patients to continue using their asthma medication including ICS even during the COVID-19 pandemic.

Acknowledgements

The authors appreciate healthcare professionals dedicated to treating COVID-19 patients in Korea, and the Ministry of Health and Welfare and the Health Insurance Review & Assessment Service of Korea for sharing invaluable national health insurance claims data in a prompt manner.

Conflict of interests: None

Funding: None

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Table 1. Clinical characteristics and prognosis of COVID-19 patients

Parameters	COVID-19 patients without underlying asthma	COVID-19 patients with underlying asthma	*P*-value	COVID-19 patients with underlying asthma					
				Step 1	Step 2	Step 3	Step 4	Step 5	*P*-value
Age (years); N (%)									
0–9	62 (0.8%)	20 (9.2%)	<0.001**	2 (3.9%)	0 (0.0%)	0 (0.0%)	18 (19.2%)	0 (0.0%)	0.058
10–19	343 (4.7%)	6 (2.8%)		1 (2.0%)	0 (0.0%)	1 (4.2%)	4 (4.3%)	0 (0.0%)	
20–29	1,833 (24.9%)	19 (8.7%)		8 (15.7%)	3 (6.7%)	3 (12.5%)	5 (5.3%)	0 (0.0%)	
30–39	758 (10.3%)	18 (8.2%)		4 (7.8%)	3 (6.7%)	1 (4.2%)	10 (10.6%)	0 (0.0%)	
40–49	983 (13.3%)	25 (11.5%)		7 (13.7%)	5 (11.1%)	4 (16.7%)	8 (8.5%)	1 (25.0%)	
50–59	1,468 (19.9%)	34 (15.6%)		10 (19.6%)	6 (13.3%)	5 (20.8%)	13 (13.8%)	0 (0.0%)	
60–69	1,020 (13.8%)	36 (16.5%)		7 (13.7%)	12 (26.7%)	4 (16.7%)	13 (13.8%)	0 (0.0%)	
70–	846 (11.5%)	60 (27.5%)		12 (23.5%)	16 (35.6%)	6 (25.0%)	23 (24.5%)	3 (75.0%)	
Sex; N (%)									
Male	3,000 (40.7%)	95 (43.6%)	0.393	23 (45.1%)	20 (44.4%)	12 (50.0%)	38 (40.4%)	2 (50.0%)	0.923
Female	4,372 (59.3%)	123 (56.4%)		28 (54.9%)	25 (55.6%)	12 (50.0%)	56 (59.6%)	2 (50.0%)	
Charlson comorbidity index; N (%)									
0	2,029 (27.5%)	0 (0.0%)	<0.001**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.017*
1	1,726 (23.4%)	48 (22.0%)		12 (23.5%)	3 (6.7%)	5 (20.8%)	28 (29.8%)	0 (0.0%)	
2	1,179 (16.0%)	40 (18.4%)		11 (21.6%)	5 (11.1%)	7 (29.2%)	17 (18.1%)	0 (0.0%)	
≥3	2,438 (33.1%)	130 (59.6%)		28 (54.9%)	37 (82.2%)	12 (50.0%)	49 (52.1%)	4 (100%)	
Prognosis; N (%) or mean ± standard deviation)									
Mortality	210 (2.8%)	17 (7.8%)	<0.001**	5 (9.8%)	2 (4.4%)	1 (4.2%)	9 (9.6%)	0 (0.0%)	0.703
Admission to ICU	208 (2.8%)	7 (3.2%)	0.733	3 (5.9%)	1 (2.2%)	0 (0.0%)	3 (3.2%)	0 (0.0%)	0.691
Duration of admission (days)	20.1 ± 12.2	21.0 ± 13.5	0.285	18.7 ± 12.0	23.7 ± 15.7	22.7 ± 13.0	19.9 ± 12.6	38.3 ± 16.4	0.026*
Total medical cost (USD)	4,261.0 ± 5,354.0	5,388.1 ± 10,135.3	0.003*	4403.5 ± 4992.1	6242.7 ± 9180.5	4694.6 ± 3815.9	5669.8 ± 13470.9	5868.4 ± 2789.8	0.912
Total	7,372 (97.1%)	218 (2.9%)		51 (23.4%)	45 (20.6%)	24 (11.0%)	94 (43.1%)	4 (1.8%)	

USD 1 US dollar = 1,228.40 Korean Won at 1st June 2020
** <0.001, *<0.05

Table 2. Use of asthma medication in COVID-19 patients with underlying asthma

Parameters	N (%) in the last one year	N (%) in the last two months
ICS alone	66 (30.3%)	58 (26.6%)
ICS-LABA	84 (38.5%)	78 (35.8%)
Inhaled LABA	0 (0.0%)	0 (0.0%)
Oral LABA	77 (35.3%)	70 (32.1%)
Patch LABA	41 (18.8%)	36 (16.5%)
LTRA	160 (73.4%)	145 (66.5%)
Inhaled SABA	83 (38.1%)	75 (34.4%)
Oral SABA	30 (13.8%)	8 (3.7%)
Xanthine	110 (50.5%)	100 (45.9%)
Inhaled LAMA	25 (11.5%)	25 (11.5%)

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting β_2-agonists

Table 3. Significant factors associated with mortality

		Univariate			Multivariate			VIF
		OR	95% CI	*P*-value	OR	95% CI	*P*-value	
Among all COVID-19 patients†								
Asthma		2.885	1.726–4.822	<0.001**	1.317	0.708–2.451	0.385	
Among asthma patients‡								
ICS alone	Last one year	1.685	0.612–4.637	0.313	11.741	0.765–180.151	0.077	1.630
	Last two months	2.059	0.745–5.691	0.164	17.810	0.944–336.092	0.055	1.822
ICS-LABA	Last one year	1.462	0.541–3.951	0.454	1.444	0.130–16.103	0.765	1.425
	Last two months	1.663	0.615–4.502	0.316	3.493	0.242–50.396	0.358	1.551
Oral LABA	Last one year	0.747	0.253–2.204	0.597	0.890	0.113–7.023	0.912	1.238
	Last two months	0.872	0.295–2.578	0.804	0.685	0.085–5.508	0.722	1.341
Patch LABA	Last one year	0.252	0.032–1.954	0.187	0.139	0.003–6.226	0.309	1.583
	Last two months	0.296	0.038–2.309	0.246	1.358	0.016–112.584	0.892	1.799
LTRA	Last one year	1.194	0.373–3.821	0.765	1.203	0.070–20.631	0.899	1.278
	Last two months	1.699	0.534–5.408	0.370	1.795	0.086–37.650	0.707	1.428
Inhaled SABA	Last one year	2.505	0.941–6.862	0.074	1.925	0.172–21.588	0.595	1.686
	Last two months	2.989	1.089–8.208	0.034*	1.273	0.112–14.420	0.846	1.924
Oral SABA	Last one year	1.382	0.372–5.125	0.629	1.836	0.154–21.926	0.631	1.193
	Last two months	1.509	0.405–5.621	0.540	1.626	0.113–23.347	0.721	1.284
Xanthine	Last one year	1.114	0.413–3.003	0.831	0.464	0.072–2.997	0.420	1.208
	Last two months	1.360	0.504–3.667	0.544	0.753	0.121–4.690	0.761	1.287
Inhaled LAMA	Last one year	5.225	1.737–15.716	0.003*	0.515	0.051–5.193	0.574	1.593
	Last two months	5.225	1.737–15.716	0.003*	0.371	0.038–3.643	0.395	1.617
Severity of asthma (Reference Step 1)	Step 2	0.428	0.079–2.323	0.325	0.068	0.005–1.002	0.050	1.668
	Step 3	0.400	0.044–3.627	0.415	0.055	0.001–2.059	0.117	1.397
	Step 4	0.974	0.308–3.078	0.964	0.409	0.042–3.955	0.440	1.759
	Step 5	0.000	0.000–999.999	0.987	0.000	0.000–999.999	0.978	1.171

†Adjusted for age, sex, and underlying diseases

‡Adjusted for age, sex, underlying disease, and asthma medications/severity

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting β_2-agonists; VIF, variance inflation factor

$^{**} <0.001$, $^{*}<0.05$

Table 4. Significant factors associated with ICU admission

		Univariate			Multivariate			VIF
		OR	95% CI	*P*-value	OR	95% CI	*P*-value	
Among all COVID-19 patients†								
Asthma		1.143	0.531–2.457	0.733	0.656	0.295–1.460	0.302	
Among asthma patients‡								
ICS alone	Last one year	0.919	0.174–4.861	0.921	3.802	0.137–105.589	0.431	1.630
	Last two months	1.107	0.209–5.870	0.905	2.387	0.070–81.543	0.629	1.822
ICS-LABA	Last one year	0.629	0.119–3.320	0.585	0.384	0.029–5.036	0.466	1.425
	Last two months	0.711	0.135–3.751	0.687	0.503	0.046–5.451	0.572	1.551
Oral LABA	Last one year	0.725	0.137–3.830	0.705	0.373	0.021–6.561	0.500	1.238
	Last two months	0.841	0.159–4.446	0.839	0.254	0.010–6.487	0.407	1.341
Patch LABA	Last one year	0.713	0.084–6.085	0.757	0.061	0.000–50.882	0.416	1.583
	Last two months	0.838	0.098–7.180	0.872	0.521	0.000–388.916	0.847	1.799
LTRA	Last one year	0.903	0.170–4.789	0.905	1.588	0.088–28.582	0.754	1.278
	Last two months	1.268	0.240–6.697	0.780	8.106	0.309–212.62	0.209	1.428
Inhaled SABA	Last one year	0.642	0.122–3.387	0.602	2.385	0.098–58.120	0.594	1.686
	Last two months	0.756	0.143–3.994	0.742	3.253	0.083–126.978	0.528	1.924
Oral SABA	Last one year	5.112	1.085–24.096	0.039*	4.484	0.317–63.484	0.267	1.193
	Last two months	5.581	1.180–26.402	0.030*	12.987	0.472–357.078	0.129	1.284
Xanthine	Last one year	1.321	0.289–6.045	0.720	0.319	0.019–5.444	0.430	1.208
	Last two months	1.597	0.349–7.312	0.546	0.564	0.028–11.527	0.710	1.287
Inhaled LAMA	Last one year	0.000	0.000–999.999	0.968	0.000	0.000–999.999	0.904	1.593
	Last two months	0.000	0.000–999.999	0.968	0.000	0.000–999.999	0.917	1.617
Severity of asthma (Reference Step 1)	Step 2	0.364	0.036–3.626	0.389	0.061	0.002–1.847	0.108	1.668
	Step 3	0.000	0.000–999.999	0.967	0.000	0.000–999.999	0.945	1.397
	Step 4	0.527	0.103–2.714	0.444	0.081	0.004–1.581	0.097	1.759
	Step 5	0.000	0.000–999.999	0.987	0.000	0.000–999.999	0.976	1.171

†Adjusted for age, sex, and underlying diseases

‡Adjusted for age, sex, underlying disease, and asthma medications/severity

CI, confidence interval; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β_2-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting β_2-agonists; VIF, variance inflation factor

** <0.001, *<0.05

Table 5. Significant factors affecting the admission duration (days)

		Univariate			Multivariate			VIF
		β coefficient	95% CI	*P*-value	*β* coefficient	95% CI	*P*-value	
Among all COVID-19 patients†								
Asthma		0.947	-0.693–2.587	0.258	-0.342	-1.993–1.309	0.685	
Among asthma patients‡								
ICS alone	Last one year	-1.385	-5.306–2.537	0.487	-1.083	-6.096–3.929	0.670	1.630
	Last two months	-2.805	-6.869–1.260	0.175	-3.579	-9.083–1.925	0.201	1.822
ICS-LABA	Last one year	0.611	-3.094–4.316	0.746	-0.794	-5.220–3.631	0.724	1.425
	Last two months	0.055	-3.707–3.818	0.977	-1.994	-6.675–2.688	0.402	1.551
Oral LABA	Last one year	-3.899	-7.636–-0.162	0.041*	-3.503	-7.703–0.696	0.102	1.238
	Last two months	-4.248	-8.070–-0.428	0.030*	-3.744	-8.214–0.726	0.100	1.341
Patch LABA	Last one year	0.520	-4.095–5.135	0.825	4.516	-1.292–10.324	0.127	1.583
	Last two months	-0.948	-5.804–3.908	0.701	3.302	-3.208–9.811	0.318	1.799
LTRA	Last one year	-0.273	-4.354–3.809	0.895	0.662	-3.952–5.277	0.777	1.278
	Last two months	-1.812	-5.626–2.002	0.350	-0.620	-5.184–3.944	0.789	1.428
Inhaled SABA	Last one year	-0.573	-4.286–3.141	0.762	1.076	-3.748–5.900	0.661	1.686
	Last two months	0.100	-3.697–3.896	0.959	3.915	-1.347–9.177	0.144	1.924
Oral SABA	Last one year	4.088	-1.119–9.295	0.123	5.734	0.014–11.453	0.049*	1.193
	Last two months	3.149	-2.225–8.523	0.249	4.893	-1.210–10.997	0.115	1.284
Xanthine	Last one year	1.036	-2.569–4.641	0.572	-0.129	-4.095–3.836	0.949	1.208
	Last two months	0.682	-2.937–4.300	0.711	-0.225	-4.327–3.878	0.914	1.287
Inhaled LAMA	Last one year	0.450	-5.210–6.111	0.876	-3.046	-10.192–4.099	0.402	1.593
	Last two months	0.450	-5.210–6.111	0.876	-2.431	-9.623–4.760	0.506	1.617
	Step 2	5.044	-0.301–10.390	0.064	4.565	-1.127–10.258	0.115	1.668
Severity of asthma	Step 3	4.000	-2.470–10.470	0.224	2.739	-3.998–9.475	0.424	1.397
(Reference Step 1)	Step 4	1.238	-3.308–5.783	0.592	0.976	-3.802–5.753	0.688	1.759
	Step 5	19.583	6.011–33.155	0.005*	18.414	4.031–32.796	0.012*	1.171

†Adjusted for age, sex, and underlying diseases

‡Adjusted for age, sex, underlying disease, and asthma medications/severity

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting β_2-agonists; VIF, variance inflation factor

** <0.001, *<0.05

Table 6. Significant factors affecting the total medical cost (Korean Won)

		Univariate			Multivariate			VIF
		β coefficient	95% CI	*P*-value	*β* coefficient	95% CI	*P*-value	
Among all COVID-19 patients†								
Asthma		1,384,449	466,632–2,302,266	0.003*	524,590	-384,769–1,433,949	0.258	
Among asthma patients‡								
ICS alone	Last one year	601,388	-3,023,500–4,226,276	0.744	2,018,993	-2,563,742–6,601,729	0.386	1.630
	Last two months	792,081	-2,976,253–4,560,415	0.679	1,470,824	-3,577,161–6,518,809	0.566	1.822
ICS-LABA	Last one year	2,234,375	-1,175,460–5,644,209	0.198	831,659	-3,214,054–4,877,372	0.686	1.425
	Last two months	2,179,321	-1,283,605–5,642,247	0.216	114,269	-4,179,453–4,407,991	0.958	1.551
Oral LABA	Last one year	-284,193	-3,769,291–3,200,904	0.873	-140,180	-3,979,298–3,698,937	0.943	1.238
	Last two months	-60,004	-3,627,921–3,507,914	0.974	-505,307	-4,605,237–3,594,623	0.808	1.341
Patch LABA	Last one year	-1,480,130	-5,738,525–2,778,265	0.494	-897,283	-6,207,329–4,412,762	0.739	1.583
	Last two months	-1,299,576	-5,782,702–3,183,550	0.568	-1,156,362	-7,126,157–4,813,433	0.703	1.799
LTRA	Last one year	92,820	-3,676,990–3,862,630	0.961	444,656	-3,774,074–4,663,387	0.836	1.278
	Last two months	26,391	-3,503,410–3,556,191	0.988	-47,696	-4,233,142–4,137,750	0.982	1.428
Inhaled SABA	Last one year	831,775	-2,597,167–4,260,718	0.633	2,163,713	-2,246,460–6,573,885	0.334	1.686
	Last two months	1,450,005	-2,051,288–4,951,297	0.415	2,967,195	-1,858,526–7,792,917	0.227	1.924
Oral SABA	Last one year	6,003,767	1,235,605–10,771,929	0.014*	6,258,922	1,030,068–11,487,776	0.019*	1.193
	Last two months	5,634,032	712,721–10,555,342	0.025*	5,861,499	264,201–11,458,797	0.036*	1.284
Xanthine	Last one year	2,071,992	-1,248,267–5,392,251	0.220	648,251	-2,977,102–4,273,603	0.725	1.208
	Last two months	2,312,336	-1,016,392–5,641,064	0.172	725,808	-3,036,541–4,488,158	0.704	1.287
Inhaled LAMA	Last one year	-749,120	-5,976,294–4,478,054	0.778	-5,247,311	-11,780,396–1,285,774	0.115	1.593
	Last two months	-749,120	-5,976,294–4,478,054	0.778	-5,123,303	-11,718,897–1,472,292	0.127	1.617
Severity of asthma (Reference Step 1)	Step 2	2,259,333	-2,795,248–7,313,915	0.379	487,871	-4,839,925–5,815,667	0.857	1.668
	Step 3	357,654	-5,759,943–6,475,251	0.908	-786,227	-7,091,043–5,518,589	0.806	1.397
	Step 4	1,555,508	-2,742,586–5,853,602	0.476	1,612,493	-2,858,981–6,083,966	0.478	1.759
	Step 5	1,799,480	-11,032,899–14,631,860	0.783	1,118,283	-12,342,396–14,578,962	0.870	1.171

†Adjusted for age, sex, and underlying diseases

‡Adjusted for age, sex, underlying disease, and asthma medications/severity

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting β_2-agonists; VIF, variance inflation factor

** <0.001, *<0.05

Figure legends

Figure 1. Overall study design. COVID-19, coronavirus disease-19; ICS, inhaled corticosteroid; LABA, long-acting β2-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting β2-agonists; SARS-CoV-2 RNA-PCR, severe acute respiratory syndrome-coronavirus-2 RNA–polymerase chain reaction