Asia Pac Allergy. 2022 Apr;12(2):e21
https://doi.org/10.5415/apallergy.2022.12.e21
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Original Article

Impact of asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap on the prognosis of coronavirus disease 2019

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Received: Mar 6, 2022
Accepted: Apr 27, 2022
Published online: Apr 28, 2022

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ABSTRACT

Background: The effects of asthma, chronic obstructive pulmonary disease (COPD), or asthma-COPD overlap (ACO) on coronavirus disease 2019 (COVID-19) remain unclear.
Objective: We aimed to investigate the effects of chronic obstructive airway diseases such as asthma, COPD, and ACO on COVID-19.
Methods: In total, 5625 hospitalized patients with COVID-19 were divided into asthma, COPD, ACO, and control groups. A multivariate logistic regression analysis was performed to identify factors affecting the COVID-19 mortality rate. To find out whether chronic obstructive airway diseases such as asthma, COPD, and ACO affect COVID-19 mortality, 1:4 matching was performed, except for the ACO group alone due to a small number of patients.
Results: The mortality rates of asthma, COPD, and ACO groups were about 2.3, 4.8, and 5.5 times higher than that of the control group, respectively. Although not statistically significant, the survival probability tended to decrease (asthma, COPD, and combined groups of asthma and ACO, hazard ratio [HR]: 1.84, 1.31, and 1.89, respectively). The survival probability of the combined groups of COPD, ACO, and asthma and the combined groups of COPD and ACO was significantly lower than that of the matched control group (HR: 3.00 and 1.99, respectively).
Conclusion: Compared to patients with COVID-19 without chronic obstructive airway disease, patients with these comorbidities are more likely to require oxygen and mechanical ventilators and have a higher mortality rate, which can be considered when classifying and monitoring patients in the era of COVID-19. Therefore, further studies are needed to evaluate the effect of chronic obstructive airway disease, especially ACO, on COVID-19 mortality.

Keywords: COVID-19; Asthma; Pulmonary disease; Chronic obstructive; Mortality

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INTRODUCTION

We are experiencing a pandemic caused by coronavirus disease 2019 (COVID-19), and research on the clinical aspect of this new viral disease is being conducted continuously. A novel beta-coronavirus officially named “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” has rapidly spread worldwide [1, 2]. Vaccines have been produced and are being administered urgently. However, numerous problems associated with vaccines, such as speed of administration, response to mutation, delivery, differences in efficacy by platform, and the development of therapeutic medication, persist. In addition, the world is preparing for the era of COVID-19.

The clinical symptoms of COVID-19, particularly respiratory symptoms, vary widely. COVID-19 causes asymptomatic infection, mild disease, atypical pneumonia, acute respiratory distress syndrome, and death. In addition, the clinical needs of patients, such as oxygen demand, need for mechanical ventilation, and intensive care unit requirements, vary. Given the difficulty of monitoring all patients, including those who are asymptomatic, it is important to find factors that increase the mortality rate of patients with COVID-19.

Much research has been conducted on the various clinical aspects of COVID-19, although our understanding is still insufficient. Several studies have shown that age, male sex, obesity, smoking, hypertension (HTN), cardiovascular disease, diabetes mellitus (DM), and a high number of comorbidities are risk factors for COVID-19 and its clinical severity [3-8]. Infection by respiratory viruses is an important trigger factor for asthma exacerbation or chronic obstructive pulmonary disease (COPD) acute exacerbation. However, early studies showed that asthma and COPD were not risk factors [9, 10]. One study concluded that asthma was not a risk factor for clinical severity or worse prognosis [11]. Contrarily, some studies have reported that the clinical severity and mortality of COVID-19 are more severe in patients with asthma or COPD than in patients without these diseases [12-14]. Some reports have suggested that asthma is more common in children and adults with COVID-19 than what was previously reported in Asia and in the first reported data in Europe [4, 5, 15, 16]. Other studies suggest that asthma was associated with poor outcomes in COVID-19 but was not an independent factor [17]. One study evaluated the effects of ACO on COVID-19, but the effect was unclear [18]. Accordingly, questions have been raised as to whether asthma, COPD, and ACO have protective or harmful effects on COVID-19 prognosis, compared to other comorbidities [19, 20]. Therefore, based on Korean data, we aimed to investigate the effects of COPD, asthma, and ACO on the prognosis of COVID-19.

MATERIALS AND METHODS

In an effort to mitigate the COVID-19 pandemic, the Central Quarantine Countermeasure Headquarters of the Korea Disease Control and Prevention Agency (KCDC) collected the clinical and epidemiological information of 5,628 patients with COVID-19 who were hospitalized and treated in medical institutions and whose quarantine release or death during hospitalization was confirmed as of 30 April 2020 by the Central Quarantine Countermeasure Headquarters and the National Medical Center based on medical records. Based on these data, the present study was conducted. In cases of death, patients who died after diagnosis of COVID-19 and those who were diagnosed after death were included. In the available data, age, sex, death or quarantine release of the confirmed patient, the period from the date of reporting

of COVID-19 to the date of death or quarantine release, and pregnancy status were provided. There were 19 pregnant women included in the dataset, but none had any comorbidities. Of the 5,628 patients, 3 were excluded from the analysis because it was unknown whether they had asthma or COPD. The remaining 5,625 patients were classified into 4 groups. The asthma group included patients diagnosed with asthma, excluding COPD, regardless of other comorbidities. The COPD group included patients diagnosed with COPD, except for asthma, regardless of other comorbidities. The ACO group included patients diagnosed with both asthma and COPD, regardless of other comorbidities. The control group comprised patients who were not diagnosed with asthma or COPD, regardless of other comorbidities.

At the initial examination, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and body temperature were provided. At the initial examination, a history of fever ≥ 37.5°C, cough, sputum, sore throat, runny nose/rhinorrhea, muscle aches/myalgia, fatigue/malaise, shortness of breath (SOB)/dyspnea, headache, altered consciousness/confusion, vomiting/nausea, and diarrhea was recorded. The comorbidities included in the dataset were DM, HTN, heart failure (HF), chronic cardiac disease (CCD), asthma, COPD, chronic kidney disease, malignancy, chronic liver disease, rheumatic disease/autoimmune disease, and dementia. The clinical severity score (CSS) was assigned as follows: (1) no disruption to daily life; (2) disruption of daily life, but no need for oxygen therapy; (3) nasal cannula for oxygen delivery needed; (4) a mask needed for oxygen delivery; (5) noninvasive ventilator needed; (6) invasive ventilator needed; (7) multiorgan injury or extracorporeal membrane needed; (8) and death. To determine the oxygen demand, we divided the patients into 2 groups according to the CSS: those with 1–2 points were classified as the mild group, and those with 3–8 points were classified as the moderate to severe group. Additionally, 3 groups were classified to compare the patients who needed mechanical ventilation with those who needed oxygen: 1–2 points, mild group; 3–5 points, moderate group, and 6–8 points, severe group. SBP 1–2 points, mild group; 3–5 points, moderate group, and 6–8 points, severe group. SBP was expressed as follows: (1) less than 120 mmHg, (2) 120–129 mmHg, (3) 130–139 mmHg, (4) 140–159 mmHg, and (5) over 160 mmHg. DBP was expressed as follows: (1) less than 80 mmHg, (2) 80–89 mmHg, (3) 90–99 mmHg, and (4) above 100 mmHg. BMI was expressed as follows: (1) less than 18.5 kg/m^2, (2) greater than 18.5 and less than 23 kg/m^2, (3) greater than 23 and less than 25 kg/m^2, (4) greater than 25 and less than 29 kg/m^2, (5) and greater than 29 kg/m^2. Hemoglobin (Hb), hematocrit, lymphocyte, platelets, and white blood cell values were provided from blood test results.

To find out whether chronic obstructive airway diseases such as asthma, COPD, and ACO affect COVID-19 mortality, the asthma, COPD, asthma with ACO, COPD with ACO and asthma, COPD with ACO groups versus control group 1:4 matching was performed using age, sex, DM, and heart disease (**Supplementary Tables 1–5**). Owing to the small number of patients with ACO (N = 9), the ACO group was not matched alone. BMI was excluded because there were a lot of missing data, which could affect the accuracy of statistics. In addition, after 1:4 matching, conditional logistic regression was performed to check whether other variables affected mortality, but no other significant variables were found.

All information was provided and disclosed anonymously through a secure information disclosure system secured by the "no personal information leakage method" at the KCDC. This research has been approved for exemption from review by the Institutional Review Board (IRB- 2020-1073) of Asan Medical Center in accordance with the Bioethics and Safety Act of the Ministry of Health and Welfare.

Statistical analyses

To confirm a significant difference in mortality between groups, survival curves were estimated by the Kaplan-Meier method. Hazard ratios (HRs) were estimated using a Cox proportional hazard model to determine whether asthma and COPD affect the mortality of patients with COVID-19. Multivariable logistic regression analysis was performed to identify factors influencing the mortality rate and determine whether asthma or COPD influenced COVID-19 mortality even after correcting for confounding factors. All analyses were performed using R ver. 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics

Of 5,625 patients, 119 had asthma, 31 had COPD, and 9 had ACO. There were 5,466 patients without chronic obstructive airway diseases classified as asthma, COPD, or ACO. The baseline demographic and clinical characteristics for all 5,625 patients are listed in **Table 1**. CSS was categorized into 2 levels. 1. CSS with 3 levels based on oxygen demand: mild (1–2 points), moderate (3–5 points), and severe (6–8 points). 2. CSS with 2 levels based on oxygen demand: mild (1–2 points) and moderate to severe (3–8 points). All 3 disease groups had a higher proportion of patients over 60 years of age than the control group. The COPD group had the highest proportion of patients over 60 years of age. The proportion of males was highest in the COPD group. DBP showed low and high tendencies in the asthma and ACO groups, respectively. Patients in the asthma group weighed more than those in the ACO group. The duration of hospitalization was the shortest in the ACO group. The Hb, hematocrit, and lymphocyte levels were lower in the COPD group. In the asthma group, lymphopenia and leukocytosis were observed more frequently than in the other groups. The prevalence of cough and sputum was highest in the ACO group, and the rate of SOB was higher in the asthma, COPD, and ACO groups than in the control groups. Compared to other groups, the asthma group presented with rhinorrhea less frequently, but nausea and vomiting occurred more frequently (**Table 1**).

Mortality

Compared to that of the control group (4.06%), the mortality rates of the asthma, COPD, and ACO groups were approximately 2.3 (9.24%), 4.8 (19.35%), and 5.5 (22.22%) times higher, respectively (**Table 1**). A multivariate logistic regression analysis was performed to determine the factors affecting the COVID-19 mortality rate, and age, male sex, DM, and heart disease were statistically significant. For that reason, 1:4 matching is performed by age, sex, DM, and heart disease. As a variable, heart disease included HF, CCD, and HTN. Asthma had a high odds ratio of 2.256, but there was no statistical significance (**Table 2**). As mentioned above, other studies have shown that factors such as age, male sex, obesity, smoking, HTN, cardiovascular disease, and DM are associated with COVID-19 clinical severity.

Kaplan-Meier survival curves were generated by comparing each group with the matched control group. A survival analysis was performed using the Cox model. Although not statistically significant, the survival probability in the asthma group tended to decrease compared to that of the matched control group, and it tended to decrease further after the hospitalization period exceeded 40 days (HR, 1.84; 95% confidence intervals [CIs], 0.8106–4.156; $p = 0.14$). A subgroup analysis was attempted for a group with a longer hospitalization period; however, as the extraction of recognizable data were prohibited, it was not possible

https://doi.org/10.5415/apallergy.2022.12.e21

Table 1. Demographic and clinical characteristics of patients with COVID-19 classified based on chronic inflammatory airway disease

Characteristic	Control (1) (n = 5,466)	Asthma (2) (n = 119)	COPD (3) (n = 31)	ACO (4) (n = 9)	Control	Asthma	COPD	ACO
Age (<60 years)	3,764 (68.86)	66 (55.46)	7 (22.58)	3 (33.3)	5,466	119	31	9
Female sex	3,216 (58.84)	77 (64.71)	10 (32.26)	5 (55.56)	5,466	119	31	9
SBP (level)	2.76 ± 1.32	2.68 ± 1.30	2.90 ± 1.32	3.44 ± 1.13	5,330	117	30	9
DBP (level)	2.00 ± 0.98	1.76 ± 0.85	1.83 ± 0.75	2.56 ± 0.73	5,330	117	30	9
BMI (level)	2.79 ± 1.02	3.09 ± 1.03	2.48 ± 1.12	1.86 ± 0.69	4,303	93	23	7
Period (day)	25.54 ± 10.98	27.34 ± 11.94	30.32 ± 15.32	16.22 ± 5.40	5,466	119	31	9
Heart rate (bpm)	85.75 ± 15.08	88.42 ± 14.01	89.33 ± 14.81	86.11 ± 16.47	5,343	117	30	9
Temperature (°C)	36.94 ± 0.56	36.92 ± 0.50	36.99 ± 0.73	36.79 ± 0.35	5,428	119	30	9
Death	222 (4.06)	11 (9.24)	6 (19.35)	2 (22.22)	5,466	119	31	9
CSS, 3 levels					5,439	119	31	9
Mild (1–2)	4,669 (85.84)	93 (78.15)	15 (48.39)	5 (55.56)				
Moderate (3–5)	519 (9.54)	15 (12.61)	9 (29.03)	2 (22.22)				
Severe (6–8)	251 (4.61)	11 (9.24)	7 (22.58)	2 (22.22)				
CSS, 2 levels					5,439	119	31	9
Mild (1–2)	4,669 (85.84)	93 (78.15)	15 (48.39)	5 (55.56)				
Moderate to severe (3–8)	770 (14.16)	26 (21.85)	16 (51.61)	4 (44.44)				
Hb (g/dL)	13.29 ± 1.76	13.19 ± 1.65	12.49 ± 2.33	12.59 ± 1.39	3,945	99	28	9
Hematocrit (%)	39.27 ± 4.95	38.7 ± 4.95	37.18 ± 6.89**	37.23 ± 4.21	3,941	99	27	9
Lymphocyte (%)	29.26 ± 11.64	26.32 ± 11.61	24.21 ± 13.30	25.19 ± 10.56	3,923	98	27	9
Platelet (μL)	236,627.74 ± 82,683.44	244,939.39 ± 84,281.33	213,703.7 ± 99,576.73	262,111.11 ± 113,252.42	3,947	99	27	9
WBC (μL)	6,103.26 ± 2,810.63	7,022.42 ± 3,010.93**	5,986.43 ± 3,292.65	6,651.11 ± 3,984.00	3,946	99	28	9
Fever	1,266 (23.17)	25 (21.01)	11 (35.48)	3 (33.33)	5,465	119	31	9
Cough	2,265 (41.45)	54 (45.38)	15 (48.39)	7 (77.78)	5,465	119	31	9
Sputum	1,558 (28.51)	42 (35.29)	13 (41.94)	6 (66.67)	5,465	119	31	9
Sore throat	857 (15.68)	20 (16.81)	2 (6.45)	2 (22.22)	5,465	119	31	9
Rhinorrhea	613 (11.22)	6 (5.04)	1 (3.23)	1 (11.11)	5,465	119	31	9
Myalgia	901 (16.49)	20 (16.81)	3 (9.68)	2 (22.22)	5,465	119	31	9
Fatigue	227 (4.15)	4 (3.36)	3 (9.68)	0 (0)	5,465	119	31	9
Shortness of breath	619 (11.33)	33 (27.73)	11 (35.48)	3 (33.33)	5,465	119	31	9
Headache	950 (17.38)	13 (10.92)	3 (9.68)	1 (11.11)	5,465	119	31	9
Altered consciousness	33 (0.6)	2 (1.68)	0 (0)	0 (0)	5,465	119	31	9
Nausea/vomiting	228 (4.17)	14 (11.76)	1 (3.23)	1 (11.11)	5,465	119	31	9
Diarrhea	505 (9.24)	11 (9.24)	2 (6.45)	0 (0)	5,465	119	31	9

Values are presented as number (%) or mean±standard deviation.
The control group contained patients who did not have asthma or COPD. The asthma group comprised patients with asthma but not COPD. The COPD group consisted of patients who have COPD but do not have asthma. The ACO group comprised patients with both COPD and asthma. CSS was categorized into 2 levels. 1. CSS with 3 levels based on the oxygen demand: mild (1–2 points), moderate (3–5 points), and severe (6–8 points). 2. CSS with 2 levels based on the oxygen demand: mild (1–2 points) and moderate to severe (3–8 points).
COVID-19, coronavirus disease 2019; ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; period, quarantine period; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CSS, clinical severity score; Hb, hemoglobin; WBC, white blood cell.

Table 2. Multivariable logistic regression analysis of the effect factor on COVID-19 mortality

Variable	OR	95% CI for OR	Pr (>|z|)
(Intercept)	0.005	0.002–0.013	<0.001
Age > 60 yr	19.160	9.390–39.095	<0.001
Female sex	0.506	0.346–0.741	<0.001
BMI	0.830	0.679–1.014	0.068
DM	2.161	1.455–3.212	<0.001
Heart	2.517	1.652–3.837	<0.001
Asthma	2.256	0.983–5.179	0.055

Heart problems included heart failure, chronic cardiac disease, and hypertension.
COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus.

(**Fig. 1A**). The survival probability of the COPD group tended to decrease rapidly early after diagnosis compared to that of the matched control group (HR, 1.31; 95% CI, 0.4691–3.642; $p = 0.60$) (**Fig. 1B**). When the combined groups of asthma and ACO were compared with the matched control group, the difference in survival probability was also not statistically

https://doi.org/10.5415/apallergy.2022.12.e21

significant, but when considering HR, the survival probability tended to decrease more than that of the asthma group (HR, 1.89; 95% CI, 0.9093–3.937; $p = 0.088$) (**Fig. 1C**). When the COPD and ACO groups were combined and compared with the matched control group, survival probability showed statistical significance and decreased earlier after diagnosis than did the COPD group survival probability curve (HR, 3.00; 95% CI, 1.116–8.064; $p = 0.029$) (**Fig. 1D**). The survival probability of combined groups of COPD, ACO, and asthma was significantly lower

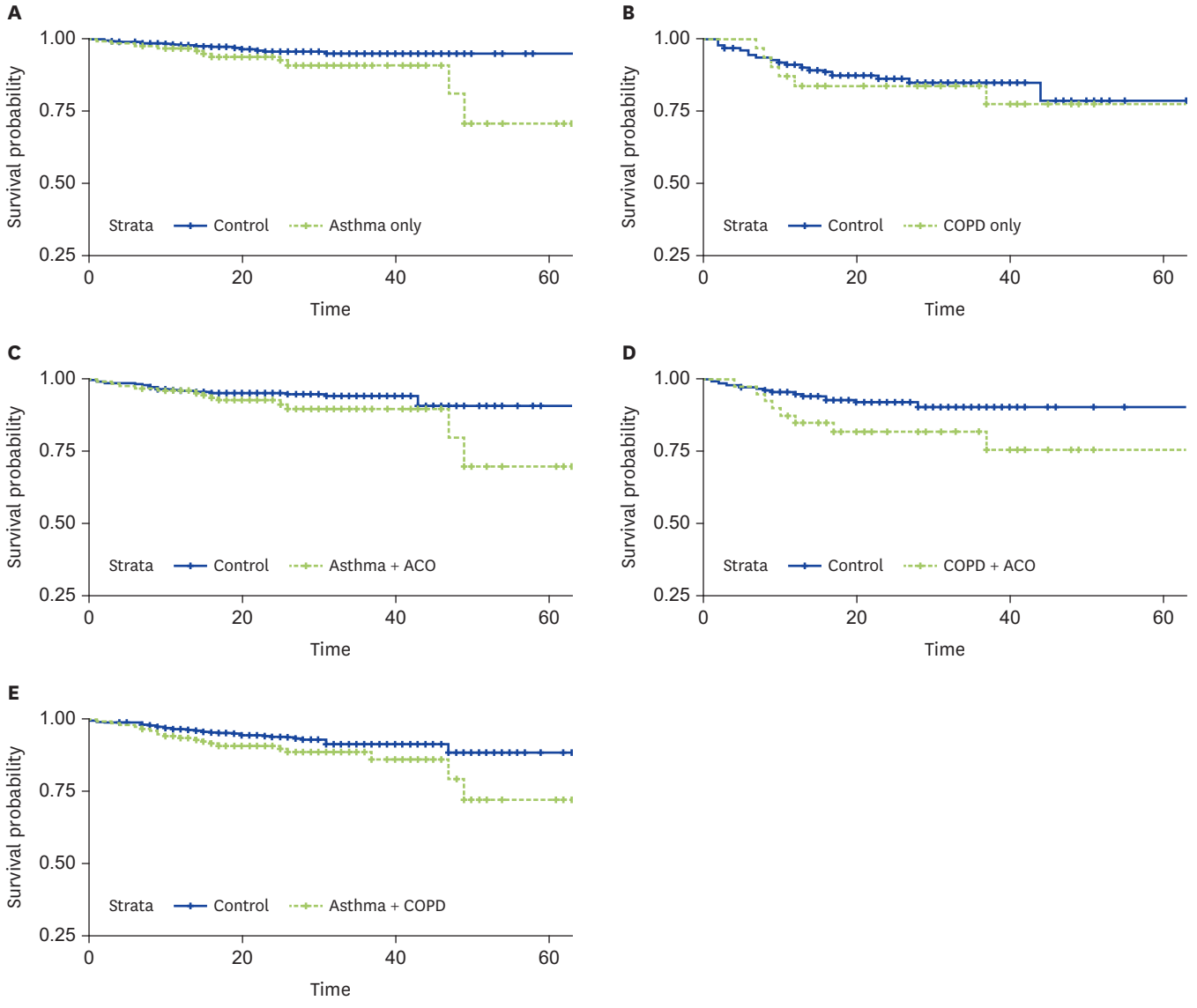

Fig. 1. Kaplan-Meier survival curves for mortality of COVID-19 with chronic inflammatory airway disease versus matched control. (A) Matched control group versus asthma group. The asthma group and control group 1:4 matching is performed by age, sex, diabetes mellitus (DM), and heart disease. Survival analysis using the Cox model showed a hazard ratio (HR) of 1.835 and a, 95% confidence interval (CI) of 0.8106–4.156 ($p = 0.14$). (B) Matched control group vs. chronic obstructive pulmonary disease (COPD) group. The COPD group and control group 1:4 matching is performed by age, sex, DM, and heart disease. Survival analysis using the Cox model showed an HR of 1.307 and a 95% CI of 0.4691–3.642 ($p = 0.60$). (C) Matched control group versus combined groups of asthma and asthma-COPD overlap (ACO). The combined groups of asthma and ACO and control group 1:4 matching is performed by age, sex, DM, and heart disease. Survival analysis using the Cox model showed HR of 1.892 and 95% CI of 0.9093–3.937 ($p = 0.088$). (D) Matched control group versus combined group of COPD and ACO. The combined groups of COPD and ACO and control group 1:4 matching is performed by age, sex, DM, and heart disease. Survival analysis using the Cox model shows an HR of 3 and a 95% CI of 1.116–8.064 ($p = 0.029$). (E) Matched control group vs. combined groups of asthma, COPD, and ACO. The combined group of asthma, COPD, and ACO and the control group 1:4 matching is performed by age, sex, DM, and heart disease. Survival analysis using the Cox model shows an HR of 1.994 and a 95% CI of 1.104–3.601 ($p = 0.022$).

https://doi.org/10.5415/apallergy.2022.12.e21

Table 3. Survival analysis with a Cox model

Case	HR	95% CI	*p* value
Asthma	1.84	0.81–4.16	0.145
COPD	1.31	0.47–3.64	0.609
Asthma + ACO	1.89	0.91–3.94	0.088
COPD + ACO	3.00	1.12–8.06	0.029
Asthma + COPD + ACO	1.99	1.10–3.60	0.022

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

than that of the matched control group (HR, 1.99; 95% CI, 1.104–3.601; $p = 0.022$) (**Fig. 1E**). When the ACO group was included in the survival analysis, there was a significant change in mortality as the HR and statistical significance gradually increased (**Table 3**).

Clinical severity

The rate of ventilator requirement was found using a 3-level CSS analysis, and the rate of oxygen needed was found using a 2-level CSS analysis. When the CSS was divided into 3 or 2 levels, the proportion of moderate to severe levels was higher than those of the control group. In patients with asthma, the rates of needing oxygen and a ventilator were approximately 1.5 (14.16% vs. 21.85%) and 2.0 times higher (4.61% vs. 9.24%) than those of the control group, respectively. The proportion of patients in the COPD group requiring oxygen and mechanical ventilators was approximately 3.6 (14.16% vs. 51.61%) and 5.0 times higher (4.61% vs. 22.85%) compared to that in the control group, respectively, and it was more than 3.1 (14.16% vs. 44.44%) and 4.8 times higher (4.61% vs. 22.22%), respectively, for the ACO group. The rates of oxygen and ventilator requirements were approximately 2.4 times higher in the COPD group than in the asthma group (oxygen demand, 21.85% vs. 51.61%; ventilator, 9.24% vs. 22.58%) (**Table 1**, **Fig. 2**).

A conditional logistic regression was performed with 2 levels of CSS as the outcome to determine whether patients with chronic obstructive airway disease continued to maintain

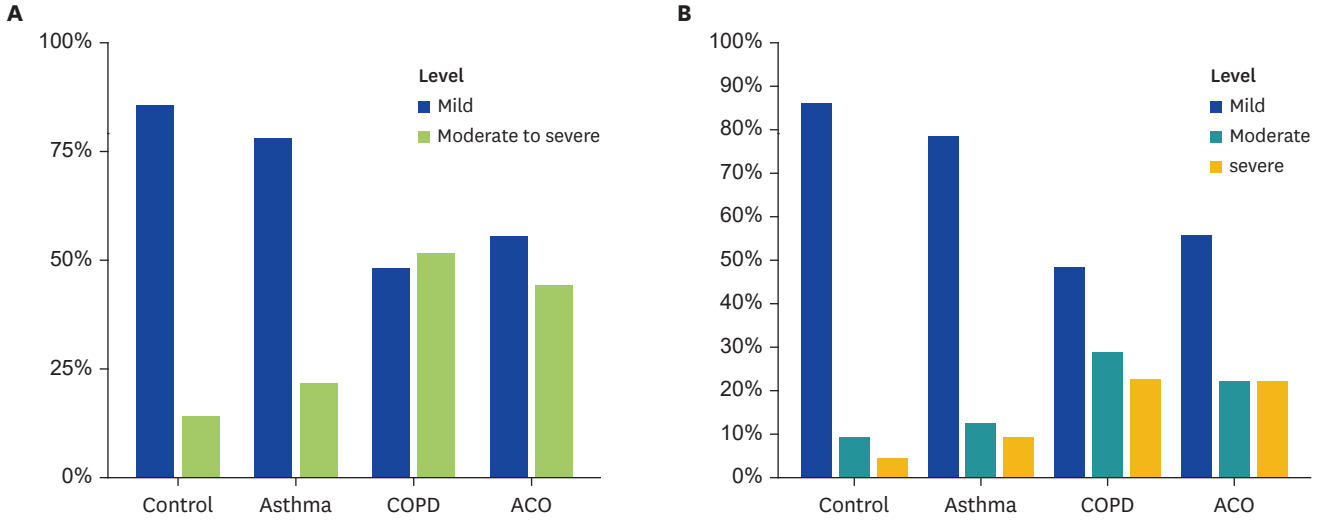

Fig. 2. Comparison of the control, asthma, COPD, and ACO groups according to CSS. (A) To assess the difference in oxygen demand, we divided the patients into 2 groups according to CSS. Based on 2 levels of CSS, which depends on oxygen demand, patients are divided into the mild group (1–2 points) and the moderate to severe group (3–8 points). (B) Three groups are classified to determine who needed mechanical ventilation among patients who needed oxygen according to CSS. Based on 3 levels of CSS, which depends on oxygen demand, patients are divided into the mild group (1–2 points), the moderate group (3–5 points), and the severe group (6–8 points). CSS, clinical severity score; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

https://doi.org/10.5415/apallergy.2022.12.e21

Table 4. Conditional logistic regression for 2 levels of CSS

Case	OR	95% CI	*p* value
Asthma	1.78	1.03–3.07	0.038
COPD	2.32	1.00–5.38	0.050
Asthma + ACO	1.52	0.91–2.53	0.112
COPD + ACO	3.52	1.61–7.69	0.002
Asthma + COPD + ACO	1.98	1.27–3.11	0.003

For CSS, 2 levels were classified as mild (1–2 points) and moderate to severe (3–8 points), depending on oxygen demand.
CSS, clinical severity score; OR, odds ratio; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

high oxygen demand even after matching. Asthma; COPD; combined groups of COPD and ACO; and combined groups of asthma, COPD, and ACO showed statistically significant results, indicating that the oxygen demand of these groups was consistently higher than that of the control group. Although it was difficult to directly compare the HR of the survival analysis with a Cox model and the odds ratio of conditional logistic regression for 2 levels of CSS, there was a tendency for positive correlation (**Tables 3**, **4**).

Comorbidities

The comorbidities of the 5,625 patients diagnosed with COVID-19 were classified. To determine the effects of asthma, COPD, and ACO on COVID-19 mortality, we divided patients into 4 groups, as mentioned in the METHODS section. The ratio of comorbidities in the asthma, COPD, ACO, and control groups was also classified. As a factor affecting the mortality rate, age had the highest effect (odds ratio = 19.160). In all patients, HTN was the most frequent comorbidity, followed by DM. Similar tendencies were observed in the asthma, COPD, and ACO groups. The ratio of comorbidities to the number of patients was approximately 47.0% (comorbidities = 2,569, n = 5,466), 157.14% (comorbidities = 187, n = 119), 219.35% (comorbidities = 68, n = 31), and 311.11% (comorbidities = 28, n = 9) in the control, asthma, COPD and ACO groups, respectively. In the cohort, HTN was the most frequent comorbidity, followed by DM. Similar patterns were observed in the ratios of comorbidities in the 4 groups. The rate of comorbidities in the asthma, COPD, and ACO groups was higher than that of the control group. In some studies, the prevalence of DM, HTN, HF, and CCD, which was considered as an independent risk factor of COVID-19 mortality, was approximately 37.34% in the control group (comorbidities = 2,041, n = 5,466), 48.74% in the asthma group (comorbidities = 58, n = 119), 74.19% in the COPD group (comorbidities = 23, n = 31), and 88.89% in the ACO group (comorbidities = 8, n = 9) (**Table 5**).

Table 5. Comorbidities of patients with COVID-19

Comorbidity	All patients (n = 5,625)	Asthma (n = 119)	COPD (n = 31)	ACO (n = 9)	Control (n = 5,466)
Diabetes	691 (12.28)	21 (17.65)	8 (25.81)	3 (33.33)	659 (12.05)
Hypertension	1,201 (21.35)	26 (21.85)	10 (32.26)	4 (44.44)	1,161 (21.24)
Heart failure	59 (1.05)	2 (1.68)	2 (6.45)	1 (11.11)	54 (0.99)
Chronic cardiac disease	179 (3.18)	9 (7.56)	3 (9.68)	0 (0)	167 (3.06)
Chronic kidney disease	55 (0.98)	0 (0)	5 (16.13)	0 (0)	50 (0.91)
Malignancy	145 (2.58)	3 (2.52)	2 (6.45)	0 (0)	140 (2.56)
Chronic liver disease	83 (1.48)	1 (0.84)	1 (3.23)	0 (0)	81 (1.48)
Rheumatic/autoimmune disease	38 (0.68)	0 (0)	0 (0)	0 (0)	38 (0.70)
Dementia	224 (3.98)	6 (5.04)	6 (19.35)	2 (22.22)	210 (3.84)

COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

https://doi.org/10.5415/apallergy.2022.12.e21

DISCUSSION

Compared to patients in the control group, patients in the asthma, COPD, and ACO groups were older, and further, the COPD group had more males than the control group. Age, male sex, obesity, smoking, HTN, cardiovascular disease, DM, and a high number of comorbidities are known risk factors for COVID-19 susceptibility and clinical severity. Information on the above risk factors, excluding smoking, which was not included in the dataset, was extracted for the control, asthma, COPD, and ACO groups. In this study, we aimed to investigate the effects of chronic obstructive airway diseases such as asthma, COPD, and ACO on COVID-19 mortality. To minimize the confounding effect, a multivariable logistic regression analysis was performed to select the effect factor, and 1:4 matching was performed. Matching was done for all patients, but the ACO group was not matched alone due to the small number of patients. A survival analysis was performed using Kaplan-Meier survival curves and a Cox model, and the survival probability was found to significantly decrease in the combined groups of asthma, COPD, and ACO compared to that of the matched control group. When survival analysis was performed for the asthma or COPD group, separately, there was a tendency for the survival probability to decrease, although it was not statistically significant. When the ACO group was included in the analysis, a significant change in mortality was observed; thus, we can assume that ACO probably affected the COVID-19 mortality rate. It can be carefully inferred that if you have chronic airway obstruction, including reversible airway obstruction, there is a high probability of transitioning to severe. It can be assumed that the prognosis can be affected depending on the severity of the disease. However, as mentioned above, the patients with ACO were few, and therefore, the interaction between variables could not be analyzed. To confirm this, analysis should be conducted using more patients with ACO.

When conditional logistic regression was performed for groups categorized according to 2 levels of CSS, a strict comparison was difficult, but they tended to be positively correlated with the HR calculated by the Cox model for mortality. This suggests that prompt diagnosis and effective preparation for oxygen demand may affect patient mortality when treating patients with COVID-19 and chronic obstructive airway diseases. Several studies have shown that asthma has no effect on the severity of COVID-19, and that ACO and COPD seem to be increased the mortality and morbidity of COVID-19 [21-23]. Nonetheless, the CDC still reports that “severe asthma” is associated with the severity of COVID-19. In this study, although the severity of asthma and how much irreversible obstruction portion included in the patient's asthma are unknown due to data limitations, asthma tends to require oxygen treatment and mechanical ventilator treatment compared to the control group. In the cases of COPD and ACO patients, medical resources were required at a higher rate. This includes reversible airway obstruction, wherein particularly, patients with chronic obstructive airway disease may require more medical resources, which can be considered when classifying and monitoring patients who may need medical resources in the era of COVID-19.

When infected with SARS-CoV-2, patients with asthma may develop digestive symptoms, such as nausea and vomiting, and dyspnea aggravation. In contrast, rhinorrhea complaints were less frequent among patients with asthma than among controls. It has been reported that patients with asthma and allergy-related factors, such as rhinitis or eczema, were less susceptible to COVID-19 infection. A link with type 2 inflammation could be thought of, but there was no data for classification; thus, the evaluation could not be performed [24]. Patients with COPD may experience dyspnea aggravation. In patients with ACO, cough

and sputum may be aggravated. As such, it may appear as an exacerbation of the existing symptoms; therefore, clinical attention is required.

In the early days of the COVID-19 outbreak, studies reported low rates of SARS-CoV-2 infection in patients with pre-respiratory diseases [6, 9, 19, 25]. It is suggested that the downregulation of the expression of angiotensin-converting enzyme 2 (ACE2, expressed in epithelial cells), a key mediator of SARS-CoV-2 infection, is regulated by interleukin-13 and that asthma with activated type 2 inflammation can protect against COVID-19. Additionally, the expression of another key factor, transmembrane protease serine 2, is upregulated. The activity of type 1 inflammation is lowered; therefore, there was a concern that the clinical severity could be high [26]. Moreover, asthma or inhaled corticosteroids (ICS), especially ciclesonide or budesonide, may be beneficial in dealing with SARS-CoV-2 infections [20, 27]. However, some studies have shown that ICS is not protective, and patients with underlying lung diseases such as asthma and COPD have poor outcomes [13, 28, 29]. One study reported an association between asthma and a prolonged duration of intubation in COVID-19 [30]. Some studies have shown that COPD increases SARS-CoV-2 infection and mortality [31-35]. ACE2 upregulation appears in COPD and may be modulated by ICS use [36]. Therefore, we may have questioned whether ACO or asthma would result in better clinical outcomes than COPD in COVID-19. Compared to patients with COPD, patients with ACO were more likely to be female and younger and had fewer ischemic heart diseases [37]. In this study, the mortality of patients with ACO was the highest among the 3 groups. There were only 9 patients with ACO who were hospitalized for COVID-19, and there were no statistical differences in age and sex compared to patients with COPD; further, the heart disease frequency was higher in the ACO group than in the COPD group.

There were some limitations to the current study. First, there was a possibility that ACO could affect mortality, although patients were too few to analyze the interaction of variables. Second, the severity of asthma and COPD disease and the drugs used were unknown, making it difficult to ascertain the effects of the drugs. Additionally, the severity of chronic obstructive airway disease was unknown. It is due to limited information from the raw data of the Korean CDC. Third, smoking status was not available due to data limitations. Finally, we could not analyze the asthma and COPD subtypes due to the absence of data on type 2 inflammation. Further research is needed on the effects of type 2 inflammation on COVID-19 [38-40].

This study analyzed a dataset of Korean patients during the early stages of COVID-19 transmission, and the situation may be different from that of other countries. Most studies that analyzed the effects of asthma, COPD, and ACO were conducted in countries where medical resources were scarce due to the pandemic, and the effects of chronic obstructive airway disease may have been diluted. Even if the number of patients is small, all patients were confirmed to be COVID-19 positive using polymerase chain reaction testing, hospitalized, and treated until the end of quarantine. Medical resources were sufficient, and the effect of chronic obstructive airway disease on COVID-19 could be observed accurately. These medical conditions could be a strength of this study. Similarly, although patients were few, we included those with ACO, which could affect the severity, and this is another strength of this study.

It is important to identify the factors such as who is likely to need a medical source and who is likely to progress to hospitalization and which factors increase the mortality of

hospitalized patients with COVID-19. Age, male sex, DM, and heart disease were found to be the factors that increased the mortality rate of COVID-19. In this study, for patients with COVID-19, with asthma, COPD, and ACO, oxygen and ventilator care are often required. COVID-19 may initially present as an exacerbation of an underlying condition, such as dyspnea aggravation. Additionally, some patients did not know if they had chronic obstructive airway disease.

In conclusion, this study supports the evidence that the mortality rate of COVID-19 may be higher in patients with asthma, COPD, and ACO than in patients without a chronic obstructive airway disease. In addition, patients with COPD or ACO are more likely to require oxygen therapy and a mechanical ventilator. Therefore, further studies are needed to evaluate the effects of chronic obstructive airway diseases, especially ACO, on COVID-19 mortality.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant numbers: HI19C0481 and HC20C0076). We acknowledge all the healthcare workers involved in the diagnosis and treatment of patients with COVID-19 in South Korea. We would like to thank the Korea Disease Control & Prevention Agency, the National Medical Center, and Health Information Managers in the various hospitals for collecting the medical records.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1-5 can be found via **10.5415/apallergy.2022.12.e21**

Supplementary Table 1

Asthma and control groups matched by age, sex, DM, and heart disease

Click here to view

Supplementary Table 2

COPD and control groups matched by age, sex, DM, and heart disease

Click here to view

Supplementary Table 3

Combined asthma and ACO and control groups matched by age, sex, DM, and heart disease

Click here to view

Supplementary Table 4

Combined COPD and ACO and control groups matched by age, sex, DM, and heart disease

Click here to view

Supplementary Table 5

Combined asthma, COPD and ACO and control groups matched by age, sex, DM, and heart disease

Click here to view

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