

## Brief Communication



# Predicting Factors of Severe COVID-19 in Patients With Asthma: A Korean National Cohort Study

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## ABSTRACT

As there are limited data on the disease course of and factors predicting severe coronavirus disease 19 (COVID-19) in patients with asthma, this study aims to perform a detailed analysis of the clinical course of asthmatic patients with COVID-19 and evaluate factors related to severe infection. Of the 5,628 patients confirmed with COVID-19, 128 (2.3%) had asthma. Among the 128 asthmatic patients, 32 (25%) had severe COVID-19 and 96 (75%) had non-severe COVID-19. Among asthmatic patients, those with severe COVID-19 were significantly older and had more dyspnea and fever, more comorbidities, and lower lymphocyte and platelet counts than those with non-severe COVID-19. In multivariable logistic regression analysis, chronic obstructive pulmonary disease (adjusted odds ratio [aOR], 6.49; 95% confidence interval [CI], 1.18–41.81), low lymphocyte proportion (aOR, 0.91; 95% CI, 0.86–0.97), and low platelet count (aOR, 0.99; 95% CI, 0.98–0.99) were independently associated with severe COVID-19.




**Keywords:** Asthma; COVID-19; chronic obstructive pulmonary disease

## INTRODUCTION

The infection caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is called coronavirus disease 2019 (COVID-19), has spread rapidly worldwide since December 2019.<sup>1</sup> The prevalence of asthma in patients with COVID-19 ranges from 0.9% to 15% in different studies,<sup>2,3</sup> which denotes the conflicting evidence regarding asthma patients' susceptibility to COVID-19. It seems that some important factors link asthma and the severe clinical course of COVID-19<sup>4</sup>; however, little information is available regarding this issue. Accordingly, we sought to perform a detailed analysis of the clinical course of asthmatic patients with COVID-19 and evaluate factors associated with severe COVID-19.

## MATERIALS AND METHODS

The Korea Disease Control and Prevention Agency (KDCA) provided researchers with an anonymized national cohort of 5,628 patients with confirmed COVID-19, who had

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completed treatment or quarantine as of April 30, 2020.<sup>5</sup> This cohort comprised information on demographics, symptoms at the time of hospitalization, vital signs, comorbidities, laboratory findings, treatment (supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation), and treatment outcomes including death. The institutional review board of our institution approved this study (application No. HYUH 2020-07-035). Since the KDCA cohort data were constructed after anonymization, the need for informed consent from the participants was waived.

Laboratory confirmation of SARS-CoV-2 infection was defined as a positive result on a real-time reverse-transcriptase polymerase chain reaction assay of nasal or pharyngeal swabs, following the Guidelines for Laboratory Diagnosis of COVID-19 in Korea.<sup>6</sup> Asthma diagnosis was based on the patient reporting physician-diagnosed asthma. Fever was defined as a body temperature of  $\geq 37.5^{\circ}\text{C}$ , and hypotension was defined as a systolic blood pressure of  $< 120$  mmHg or a diastolic pressure of  $< 80$  mmHg. Severe COVID-19 was defined based on the treatment level during hospitalization: cases requiring supplemental oxygen therapy via nasal prong or facial mask, non-invasive/invasive mechanical ventilation, or extracorporeal membrane oxygenation treatment in addition to those who died after a confirmed COVID-19 diagnosis. Accordingly, COVID-19 cases presenting dyspnea at the time of hospitalization but not requiring supplemental oxygen were classified as non-severe COVID-19. Continuous variables are presented as mean  $\pm$  standard deviation and compared using Student's *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables are presented as number (%) and compared using the chi-squared test or Fisher's exact test, as appropriate. To evaluate factors associated with severe COVID-19, we performed univariable and multivariable analyses. In multivariable analyses, age, sex, and significant factors in univariable analysis were included.

## RESULTS

During the study period, all patients who had confirmed COVID-19 were isolated in hospitals or residential treatment centers according to the policy of the KDCA. Of the 5,628 patients, 128 (2.3%) had asthma. Among the 128 asthma patients, 32 (25.0%) had severe COVID-19 and 96 (75.0%) had non-severe COVID-19. Of the 32 severe COVID-19 patients, 40.6% ( $n = 13$ ) died. Severe COVID-19 patients were significantly more likely to be aged  $\geq 60$  years (71.9% vs. 37.5%,  $P < 0.001$ ) than non-severe COVID-19 patients; however, there were no intergroup differences in sex and body mass index. Regarding symptoms at the time of hospitalization, severe COVID-19 patients had a significantly higher rate of fever (37.5% vs. 16.7%,  $P = 0.014$ ) and dyspnea (46.9% vs. 21.9%,  $P = 0.006$ ) than non-severe COVID-19. Additionally, in terms of comorbidities, severe COVID-19 patients showed a significantly higher rate of chronic obstructive pulmonary disease (COPD) (15.6% vs. 4.2%,  $P = 0.043$ ), heart failure (9.4% vs. 0%,  $P = 0.015$ ), and malignancies (9.4% vs. 0%,  $P = 0.015$ ) than non-severe COVID-19. On laboratory findings, lymphocyte proportion ( $18.3\% \pm 9.9\%$  vs.  $29.2\% \pm 10.7\%$ ,  $P < 0.001$ ) and platelet count ( $199.8 \pm 67.9$  vs.  $264.3 \pm 86.6$ ,  $P < 0.001$ ) were significantly lower in severe COVID-19 than non-severe COVID-19 (**Table 1**).

In univariable analysis, whereas age  $\geq 60$  years (odds ratio [OR], 4.26; 95% confidence interval [CI], 1.83–10.67), COPD (OR, 4.26; 95% CI, 1.06–18.28), fever (OR, 3.00; 95% CI, 1.22–7.37), and dyspnea (OR, 3.15; 95% CI, 1.35–7.41) were positively associated with severe COVID-19, lymphocyte proportion (OR, 0.90; 95% CI, 0.85–0.94) and platelet count (OR, 0.99; 95% CI, 0.98–0.99) were negatively associated with severe COVID-19. In multivariable

**Table 1.** Comparison of clinical characteristics between asthmatic patients with severe COVID-19 and those with non-severe COVID-19

| Characteristics                  | Severe COVID-19 (n = 32) | Non-severe COVID-19 (n = 96) | P value |
|----------------------------------|--------------------------|------------------------------|---------|
| Age (yr)                         |                          |                              | < 0.001 |
| < 60                             | 9 (28.1)                 | 60 (62.5)                    |         |
| ≥ 60                             | 23 (71.9)                | 36 (37.5)                    |         |
| Sex                              |                          |                              | 0.523   |
| Male                             | 13 (40.6)                | 33 (34.4)                    |         |
| Female                           | 19 (59.4)                | 63 (65.6)                    |         |
| BMI (kg/m <sup>2</sup> )         |                          |                              | 0.236   |
| < 18.5                           | 1 (4.0)                  | 4 (5.3)                      |         |
| 18.5–22.9                        | 7 (28.0)                 | 24 (32.0)                    |         |
| 23.0–24.9                        | 5 (20.0)                 | 27 (36.0)                    |         |
| ≥ 25.0                           | 12 (48.0)                | 20 (26.7)                    |         |
| Symptoms                         |                          |                              |         |
| Fever                            | 12 (37.5)                | 16 (16.7)                    | 0.014   |
| Cough                            | 15 (46.9)                | 46 (47.9)                    | 0.919   |
| Sputum                           | 13 (40.6)                | 35 (36.5)                    | 0.673   |
| Sore throat                      | 4 (12.5)                 | 18 (18.8)                    | 0.417   |
| Rhinorrhea                       | 1 (3.1)                  | 6 (6.3)                      | 0.679   |
| Fatigue or malaise               | 2 (6.3)                  | 2 (2.1)                      | 0.260   |
| Dyspnea                          | 15 (46.9)                | 21 (21.9)                    | 0.006   |
| Headache                         | 2 (6.3)                  | 12 (12.5)                    | 0.515   |
| Change of consciousness          | 1 (3.1)                  | 1 (1.0)                      | 0.439   |
| Nausea or vomiting               | 5 (15.6)                 | 10 (10.4)                    | 0.526   |
| Diarrhea                         | 1 (3.1)                  | 10 (10.4)                    | 0.289   |
| Signs                            |                          |                              |         |
| Hypotension                      | 17 (53.1)                | 50 (53.2)                    | 0.995   |
| Heart rate                       | 88.1 ± 17.2              | 88.3 ± 13.0                  | 0.939   |
| Body temperature                 | 37.2 ± 0.6               | 36.8 ± 0.4                   | 0.002   |
| Comorbidities                    |                          |                              |         |
| COPD                             | 5 (15.6)                 | 4 (4.2)                      | 0.043   |
| Diabetes mellitus                | 8 (25.0)                 | 16 (16.7)                    | 0.296   |
| Hypertension                     | 11 (34.4)                | 19 (19.8)                    | 0.092   |
| Heart failure                    | 3 (9.4)                  | 0                            | 0.015   |
| Other chronic heart disease      | 3 (9.4)                  | 6 (6.3)                      | 0.690   |
| Chronic liver disease            | 0                        | 1 (1.1)                      | > 0.999 |
| Malignancy                       | 3 (9.4)                  | 0                            | 0.015   |
| Laboratory findings              |                          |                              |         |
| WBC (/μL)                        | 7,460.7 ± 4,234.7        | 6,811.0 ± 2,515.8            | 0.435   |
| Lymphocyte (%)                   | 18.3 ± 9.9               | 29.2 ± 10.7                  | < 0.001 |
| Hemoglobin (g/dL)                | 12.9 ± 1.9               | 13.2 ± 1.5                   | 0.302   |
| Platelet (× 10 <sup>3</sup> /μL) | 199.8 ± 67.9             | 264.3 ± 86.6                 | < 0.001 |

Data are presented as frequency (%) and mean with standard deviation.

COVID-19, coronavirus disease 2019; BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cells.

analysis, whereas COPD (adjusted OR, 6.49; 95% CI, 1.18–41.81) was positively associated with severe COVID-19, lymphocyte proportion (adjusted OR, 0.91; 95% CI, 0.86–0.97) and platelet count (adjusted OR, 0.99; 95% CI, 0.98–0.99) were negatively associated with severe COVID-19 (**Table 2**).

## DISCUSSION

The presented findings showed a natural course of asthmatic patients with COVID-19 and factors associated with a severe presentation. Approximately one-fourth of asthmatic patients with COVID-19 experienced severe disease requiring at least oxygen supplementation, of

**Table 2.** Factors associated with severe COVID-19 disease in asthmatic patients

| Variables                     | Univariable       | Multivariable         |
|-------------------------------|-------------------|-----------------------|
|                               | OR (95% CI)       | Adjusted OR (95% CI)* |
| <b>Age (yr)</b>               |                   |                       |
| < 60                          | Reference         | Reference             |
| ≥ 60                          | 4.26 (1.83–10.67) | 1.72 (0.55–5.53)      |
| <b>Sex</b>                    |                   |                       |
| Male                          | Reference         | Reference             |
| Female                        | 0.77 (0.34–1.77)  | 0.87 (0.27–2.86)      |
| <b>BMI (kg/m<sup>2</sup>)</b> |                   |                       |
| < 18.5                        | 0.86 (0.04–7.09)  |                       |
| 18.5–22.9                     | Reference         |                       |
| 23.0–24.9                     | 0.64 (0.17–2.25)  |                       |
| ≥ 25                          | 2.06 (0.69–6.47)  |                       |
| <b>Comorbidities</b>          |                   |                       |
| COPD                          | 4.26 (1.06–18.28) | 6.49 (1.18–41.81)     |
| Diabetes mellitus             | 1.67 (0.61–4.29)  |                       |
| Hypertension                  | 2.12 (0.86–5.12)  |                       |
| Other chronic heart disease   | 1.55 (0.31–6.28)  |                       |
| <b>Symptoms</b>               |                   |                       |
| Fever                         | 3.00 (1.22–7.37)  | 1.59 (0.47–5.30)      |
| Cough                         | 0.96 (0.43–2.14)  |                       |
| Sputum                        | 1.19 (0.52–2.69)  |                       |
| Sore throat                   | 0.62 (0.17–1.83)  |                       |
| Rhinorrhea                    | 0.48 (0.03–2.99)  |                       |
| Fatigue or malaise            | 3.13 (0.36–27.03) |                       |
| Dyspnea                       | 3.15 (1.35–7.41)  | 2.37 (0.76–7.45)      |
| Headache                      | 0.47 (0.07–1.84)  |                       |
| Change of consciousness       | 3.07 (0.12–78.98) |                       |
| Nausea or vomiting            | 1.59 (0.46–4.91)  |                       |
| Diarrhea                      | 0.28 (0.02–1.54)  |                       |
| <b>Signs</b>                  |                   |                       |
| Hypotension                   | 1.00 (0.45–2.24)  |                       |
| Heart rate                    | 0.99 (0.97–1.03)  |                       |
| <b>Laboratory findings</b>    |                   |                       |
| WBC                           | 1.00 (0.99–1.00)  |                       |
| Lymphocyte proportion         | 0.90 (0.85–0.94)  | 0.91 (0.86–0.97)      |
| Hemoglobin                    | 0.87 (0.66–1.13)  |                       |
| Platelet count                | 0.99 (0.98–0.99)  | 0.99 (0.98–0.99)      |

Data are presented as a ratio (95% confidence interval).

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cells.

\*Age, sex, COPD, symptoms (fever and dyspnea), and laboratory findings (lymphocytes and platelets) were adjusted.

whom approximately 40% died. We further showed comorbid COPD was independently associated with a severe presentation.

As previous studies focused more on whether asthma is associated with poor outcomes in COVID-19,<sup>3,7</sup> few studies addressed factors associated with the severe presentation of COVID-19 in asthmatic patients. Although studies revealed that recent use of oral corticosteroid and non-allergic asthma are associated with severe disease course,<sup>8</sup> these studies did not provide detailed information on symptoms, comorbidities, or laboratory findings.<sup>1,4</sup> One major advantage of our study is that we used nationwide data including initial clinical characteristics of all COVID-19 patients at the time of diagnosis. Accordingly, we evaluated demographic factors, symptoms, comorbidities, and laboratory findings and showed that co-existing COPD and baseline lymphocyte proportion and platelet count are independently associated with increased risk of severe COVID-19. This is in line with previous reports showing that COPD patients are at increased risk of severe pneumonia and poor outcomes when they develop COVID-19.<sup>9</sup>

Asthmatic patients with COPD were more likely to have a history of smoking and taking more medications, including systemic corticosteroids, while they had fewer allergic symptoms,<sup>10</sup> which are associated with severe COVID-19. In addition, in agreement with a previous report,<sup>11</sup> low lymphocyte proportion and platelet count were independently associated with severe COVID-19 in asthmatic patients. The lymphopenia can be explained by detrimental effects of the inflammatory cytokine milieu plus a direct attachment of lymphocytes to the vascular wall, known as endotheliitis.<sup>11</sup> Additionally, thrombocytopenia may be indicative of coagulopathy observed in patients with severe COVID-19.<sup>11</sup>

There are limitations to this study. First, we lacked information on current asthma treatment such as inhaled corticosteroid use since the KDCA database does not provide such data. Although a recent study showed that regular inhaled corticosteroid (ICS) therapy was not associated with either increased or decreased risk of mortality,<sup>7</sup> further studies are needed to determine whether ICS use has a protective effect against the development of severe COVID-19. Second, because there is no definite consensus on the definitions of severe COVID-19, and symptoms that influence the treatment levels are thought to be clinically relevant; we determined to classify severe COVID-19 based on the treatment level. However, there might be different opinions on the classification of severe COVID-19. For example, patients with high fever or change in consciousness can be regarded as having severe COVID-19. Third, we could not decide whether dyspnea in each patient results from asthma alone or asthma plus COVID-19 as the KDCA database did not provide information about this issue. Fourth, the number of asthmatic patients was relatively small, which might explain the lack of significance in multivariable analyses (e.g., age, dyspnea, and fever). Future studies enrolling a large number of patients are needed.

In conclusion, among asthmatic patients, those with severe COVID-19 were significantly older, had more dyspnea and fever, more comorbidities including COPD, heart failure, and malignancies, and lower lymphocyte proportion and platelet count than those with non-severe COVID-19. Of these, COPD, low lymphocyte proportion, and low platelet count were independently associated with severe COVID-19.

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