Characterization of asthma and risk factors for delayed SARS-CoV-2 clearance in adult COVID-19 inpatients in Daegu

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Abstract

BACKGROUND: The coronavirus disease-2019 (COVID-19) is still rapidly spreading worldwide, and remains a global health crisis. We investigated the impact of asthma on the prevalence and outcomes of COVID-19 and identify the risk factors for delayed viral clearance. METHODS: Adult patients with COVID-19 admitted to 10 hospitals in Daegu were retrospectively registered, and their clinical information was collected. Delayed viral clearance was divided into two groups based on 30 days. RESULTS: A total of 2,200 patents were evaluated, and the prevalence of asthma in COVID-19 was 3.2%. Compared with Korea nationwide survey data, there were no differences in asthma prevalence. In the univariate analysis, the risk of death (13.6% vs 6.4%, P = 0.021) and high flow oxygen therapy (18.2% vs 10.5%, P = 0,048) was increased in asthma patients, with a stronger tendency among elderly, women, and overweight patients. However, in a multivariate analysis using the logistic regression model, any clinical outcomes according to asthma was not significant. The risk factors for delayed viral clearance were older age >65 years (Odds ratio [95% confidence interval] 2.002 [1.292–3101]), dementia (3.123 [1.833–5.321]), skin rash (15.943 [1.613–157.535]), and anemia (2.156 [1.061–2.377]), whereas headache (0.673 [0.485–0.932]) lowered the risk. CONCLUSIONS: There may be a difference depending on phenotypes, but asthma prevalence was not significantly different in patients with COVID-19, and asthma did not affect outcomes of COVID-19. Older age, dementia, headache, skin rash, and anemia were independently associated with delayed viral clearance.

Abbreviations

COVID-19: Coronavirus disease-2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

RT-PCR: reverse transcriptase-polymerase chain reaction

ACE2: angiotensin-converting enzyme 2

TMPRSS2: transmembrane protease, serine 2

KCDC: Korea Centers for Disease Control & Prevention

BMI: body mass index

COPD: chronic obstructive pulmonary disease

ICU: intensive care unit

ECMO: extracorporeal membrane oxygenation

KNHANES: the Korea National Health and Nutrition Examination Survey

ACE2: angiotensin-converting enzyme 2

Introduction

Since December 2019, the spread of coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still rapidly spreading worldwide and worsening of the global health crisis. Older age, male sex and comorbidities such as cardiovascular disease, diabetes, obesity, chronic kidney disease, cancer, non-asthmatic chronic pulmonary disease, and dementia have been identified as risk factors for death and invasive treatment such as ventilator.[1, 2, 3, 4, 5] Laboratory findings such as white blood cell count, lymphocyte count, D-dimer, lactate dehydrogenase, C-reactive protein, interleukin-6, and infiltration of chest PA and chest CT are also presented as markers for distinguishing severe infections.[2, 6, 7, 8] Prolonged viral shedding is also related to the final prognosis.[9] And even among patients with relatively mild symptoms, there are patients in whom the virus is continuously detected in reverse transcriptase-polymerase chain reaction (RT-PCR) for a long time, which leads to an extended quarantine period. In addition, clues of the host immunological response for SARS-CoV-2 can be inferred through the risk factors that delays virus clearance. Therefore, research on risk factors for delayed viral clearance is needed. However, there is limited data except for results from relative small group studies.[10, 11]

Early data from China showed very low prevalence of asthma among COVID-19 patients.[2, 12] It has been suggested that the mechanism for this phenomenon is that type-2 inflammation suppresses the expression of the COVID-19 receptors, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2).[13] In contrast, more recently reported data from the Europe and U.S. showed that patients with COVID-19 had similar or higher asthma prevalence rates compared with the general population.[14, 15] In addition, recent studies have reported that the expression of ACE2 and TMPRSS2 in asthma patients is no different from that in the general population, and rather high expression in some asthma endotypes with high Th17 inflammation.[16] Therefore, whether asthma is a risk factor for COVID-19 prevalence and outcome is still controversial.

Daegu city collected and organized information on patients who were hospitalized in 10 large general hospitals in a shared database. In this study, 2,200 adult patients hospitalized with COVID-19 in Daegu were investigated for prevalence of asthma and clinical outcomes with COVID-19 according to asthma. In addition, the risk factors for delayed viral clearance of SARS-CoV-2 were evaluated.

Methods

Data source and participants

This retrospective cohort study used the Daegu COVID-19 database, which was established by the Korea Centers for Disease Control & Prevention (KCDC) and the Medicity Daegu Council. From February 17 (the date of the first patient with COVID-19 in Daegu) to May 9, 2020, this database registered patients with a diagnosis of COVID-19 who were hospitalized in 10 large general hospitals in Daegu. The last information registration date was May 19, 2020. The COVID-19 diagnostic criteria were limited to patients in whom SARS-CoV-2 was detected through real-time RT-PCR of pharyngeal swab or sputum samples. Patients under 18 years of age were excluded so that only adult patients with COVID-19 were included.

Data collection and definitions

Demographic, clinical, laboratory, treatment, and outcome data were retrospectively extracted from electronic medical records. Age, gender, smoking history and body mass index (BMI) were collected, and a BMI <18.5 was defined as underweight and [?]25 as overweight. Underlying comorbidity was based on physician diagnosis, and included asthma, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, heart failure, other chronic cardiac disease (chronic cardiac disease excluding hypertension and

heart failure), cancer (within 5 years after diagnosis), chronic kidney disease, chronic liver disease, autoimmune diseases, dementia and other psychological disorder (psychiatric disorders other than dementia) were identified. Clinical severities were divided into eight stages: death, multi-organ failure, invasive ventilator, non-invasive ventilator, high flow oxygen therapy, oxygen therapy with nasal prongs, activity limitations, and no activity limitations. The risk was then assessed by dividing each criterion into two groups based on death, any ventilator, high flow oxygen therapy, and oxygen therapy. The highest clinical severity during hospitalization was defined as the clinical severity of the patient. The initial symptoms were investigated within 24 hours of the patient's hospitalization. Fever was defined as temperature [?]37.5 as of the first day of hospitalization. Medications were classified into use groups if they were administered for more than two consecutive days during hospitalization. When available, laboratory tests were investigated within 24 hours of hospitalization. Chest radiographs within 24 hours of hospitalization were also investigated when available.

Prevalence of asthma

The asthma prevalence rate in patients with COVID-19 was compared with the asthma prevalence rate in the Korea National Health and Nutrition Examination Survey (KNHANES). KNHANES reports the results every year as a nationwide cross-sectional survey, which has been maintained by the KCDC since 1998.[17, 18] In this study, KNHANES data according to the total population, age, and gender, which were corrected according to the demographic structure from 2015 to 2018, was used.

Delayed viral clearance

KCDC testing guidelines for sampling and real-time RT-PCR testing of inpatients were followed.[19] The KCDC's COVID-19 quarantine termination criteria are 7 days after onset of disease, and there is no fever and the clinical symptoms are improved without taking antipyretic drugs, and real-time RT-PCR test results are negative twice consecutively at intervals of 24 hours or more. Generally, real-time RT-PCR tests were performed more than once a week, and when negative, real-time RT-PCR was performed repeatedly over 24 hours, but there were differences among hospitals. So, on the basis of 30 days from the date of diagnosis, patients were divided into two groups: the non-delayed viral clearance group and the delayed viral clearance group. The non-delayed viral clearance group was defined as patients with negative real-time RT-PCR results more than twice at intervals of [?]24 hours prior to 30 days. The delayed viral clearance group was defined as patients with SARS-CoV-2 detection in real-time RT-PCR after 30 days without two consecutive negative PCR results. Patients who did not meet the criteria were classified as unknown and were excluded from the risk factor analysis.

Statistical analysis

Categorical variables are presented as number and percentages, and they were analyzed using Pearson's chi-squared test and Fisher's exact test. Continuous variables are presented as mean ± standard deviation ranges and were analyzed using the Student's t test or the Mann–Whitney U test with a 95% confidence interval (CI). The risk of asthma on death, delayed viral negative conversion, and other prognostic factors in COVID-19 patients was confirmed through univariate analysis. Multivariate analysis was performed to control covariates for death, delayed viral negative conversion, and other prognostic factors in all COVID-19 patients. All results with P value of <0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics (Version 24.0; SPSS Inc., Chicago, IL).

Results

Prevalence of asthma in COVID-19 patients

A total of 2,311 patients were registered in the database, but 46 patients who were duplicated owing to readmission, and 65 pediatric patients were excluded. Finally, a total of 2200 adult hospitalized patients with COVID-19 confirmed by real-time RT-PCR were enrolled. Asthma had been diagnosed in 66 patients and had never been diagnosed in 1977 patients; 157 patients had no information about asthma diagnosis. As a result, the prevalence of asthma in the COVID-19 patients was 3.2%, which did not differ from the prevalence

in KNHANES 2015 - 2018 (Figure 1A and Table E1). The asthma prevalence was 3.5% (25/715) in male and 3.1% (41/1328) in female patients. An analysis by age revealed that the prevalence rate was highest in the elderly group ([?]70 years old) at 4.9% and the lowest in patients in their 40s at 1.6%. The asthma prevalence in COVID-19 patients showed a similar U-shaped pattern as the general prevalence pattern according to age in Korea. However, compared with the KNHANES data, the prevalence of asthma in the 19–29 year age group (2.1%) was lower (KNHANES 2018: 5.3%, 2017: 4.9%, 2016: 3.1 %, and 2015: 4.9%); this tendency was particularly pronounced in female patients (Figure 1B-D).

Baseline characteristics according to asthma

Table 1 compares the characteristics between the asthma group and the non-asthma group. Compared with the non-asthma group, the asthma group had a higher mean age (62.62 +- 19.63 *vs.* 55.88 +- 18.93, P= 0.008) and BMI (24.83 +- 3.50 *vs.* 23.47 +- 3.46, $P = 0.013$). Gender, smoking history, and physical activity before COVID-19 did not show any significant differences between groups. In the asthma group, the time from symptom onset to hospitalization was 9.32 +- 9.51 days, the time from diagnosis to hospitalization was 5.02 +- 5.10 days, and the average hospital stay was 23.46 +- 12.32 days; there was no statistically significant difference from the results in the non-asthma group. The incidence of COPD was significantly higher in the asthma group compared with the non-asthma group (8.2% *vs.* 1.1%, respectively, $P < 0.001$). Fever, myalgia, headache, sore throat, cough, sputum, and chest discomfort/chest pain were not more frequent in the asthma group, but dyspnea (35.5% *vs.*19.9%, $P = 0.003$) and nausea/vomiting (16.7% *vs.* 6.2%,$P = 0.001$) were more common in the asthma group. Initial laboratory parameters showed white blood cell count was higher in the asthma group (7.14 +- 3.42 *vs.* 5.93 +- 2.60, $P = 0.008$, table E2), so leukocytosis was more frequent in the asthma group (13.1%*vs.* 6.6%, $P = 0.050$). The presence of infiltration in the initial chest X-ray was not significantly different between the two groups.

Clinical outcomes of COVID-19 according to asthma

We investigated the association of asthma and the clinical outcome of COVID-19. Compared with those without asthma, COVID-19 patients with asthma had a greater risk of death (13.6% with asthma *vs.* 6.4% without asthma, $P = 0.02$) and high-flow oxygen therapy (18.2% with asthma *vs* . 10.5% without asthma, $P = 0.048$) (Figure 2A and Table E3). The higher mortality rate in asthma patients compared with non-asthmatic patients was particularly noticeable in female (14.6% with asthma *vs.* 4.6% without asthma, $P = 0.003$) and overweight patients (25.0% with asthma *vs.* 6.8% without asthma, $P = 0.007$). Older patients ($>$ 65 years) with asthma tended to have a higher mortality rate than those without asthma, but this did not meet statistical significance (28.1% with asthma*vs.* 16.6% without asthma, $P = 0.098$) (Figure 2B). After adjusting for potential confounders including age and sex (model 1), or age, sex, BMI, smoking status, underlying comorbidity, and medication for COVID-19 (model 2), asthma had no significant association with severe clinical outcomes of COVID-19 (Figure 3 and Table 2). Meanwhile, older age >65 years, male gender, BMI [?] 25 kg/m^2, and comorbid diseases including diabetes, chronic kidney disease, cancer, autoimmune disease, dementia, and other psychological disorder were significant risk factors for mortality, even after adjusting for various possible confounding factors (model 2) (Tables E4 and E5). Most of the initial laboratory abnormalities, except for alanine aminotransferase, were an indicator of death from COVID-19. Treatment with hydroxychloroquine and systemic steroids were risk factors for mortality, but this would have been reflected in the greater use of these drugs in patients with more severe disease.

Factors associated with delayed viral clearance of SARS-CoV-2

When divided according to the real-time RT-PCR criteria, 906 patients were included in the non-delayed viral clearance group and 415 patients in the delayed viral clearance group; 879 patients who could not be divided by that criterion were excluded from the analysis. In multivariate regression analyses adjusted for various possible confounders, delayed viral clearance was not significantly associated with asthma (OR 0.972, 95% CI 0.482–1.962; $P = 0.937$; Figure 3 and Table 2). However, older age >65 years (OR 2.002, 95% CI 1.292–3.101; $P = 0.002$), comorbid diseases including dementia (OR 3.123, 95% CI 1.833–5.321; P <0.001), other psychological disorder (OR 2.084, 95% CI 1.178–3.687; $P = 0.012$), and skin rash (OR 15.943, 95% CI

1.613–157.535; $P = 0.018$), and initial laboratory abnormalities including hemoglobin <10 g/dL (OR 2.156, 95% CI 1.161–4.003; $P = 0.015$) and C-reactive protein [?]1.0 mg/dL (OR 1.588, 95% CI 1.061–2.377; $P = 0.025$) were significant risk factors for delayed viral clearance. On the other hand, male sex (OR 0.752, 95% CI 0.567–0.997; $P = 0.047$), hypertension (OR 0.704, 95% CI 0.519–0.953; $P = 0.023$), and headache (OR 0.673, 95% CI 0.485–0.932; $P = 0.017$) were significant protective factors for delayed viral clearance (Figure 4A and Table E6). In particular, older age, dementia, skin rash, hemoglobin <10, g/dL, and headache showed significant differences when limited to the mild COVID-19 group classified as no activity limitations in the outcome parameters (Figure 4B and Table E7). The longer the virus conversion to PCR negative was delayed, the more frequently medication for COVID-19 was used. However, even considering the above points, hydroxychloroquine, azithromycin, and systemic steroid were shown to be risk factors for delayed viral clearance (Tables E6 and E7).

Discussion

This study covered almost all hospitalized patients diagnosed with COVID-19 in Daegu from February to May.[20] The outbreaks in Daegu were characterized by more female patients and more patients with dementia and other psychological disorders than in other regions.[1, 4, 21] On May 9, 2020, there were 6,859 patients with PCR-confirmed COVID-19 in Daegu, and among these patients those patients with mild disease who did not require hospitalization were quarantined in their own house or in quarantine facilities, so data for these asymptomatic or minimal symptomatic COVID-19 patients was not included. However, 68.6% of the patients analyzed in our data were classified as having no activity limitations and were considered as having mild disease. The mortality rate of the patients included in our data was 7.45%, compared with 2.36% for all COVID-19 patients in Korea as of June 1, 2020.

The prevalence of asthma in patients admitted with COVID-19 in Daegu was 3.2%, which was almost the same as the rate in the KNHANES data used as a reference for comparison in this study. Large-scale epidemiological data that can be used to investigate the prevalence of diseases in Korea can be obtained from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) in addition to KNHANES, and the asthma prevalence in Korea, which is generally investigated by the NHIS-NSC, tends to be higher than in KNHANES.[18] However, it was determined that KNHANES was more suitable than the NHIS-NSC because the criteria for physician-diagnosed asthma were more consistent with KNHANES standards, and the unique health insurance system in Korea can affect the prevalence rates of the NHIS-NSC. In most age groups, there was no significant difference from the general population, but the prevalence of asthma in the 19–29 year age group was less than that of KNHANES. Asthma is a heterogeneous disease and is often associated with atopic and eosinophilic asthma in younger patients.[22]Previous studies have reported that atopy and Th2 inflammation reduces the expression of angiotensin-converting enzyme 2 (ACE2) in the airway epithelium.[13] The difference in the prevalence of asthma in COVID-19 patients in each study and nation may be because the response to the virus differs according to the asthma endotype as well as the human and SARS-CoV-2 genetic characteristics. Asthma is considered to have a lower risk of death than other well-known risk factors, including older age, male gender, and several comorbidities. However, as with the prevalence, the risk of death differed according to the asthma phenotype. The increase in mortality associated with asthma was greater in the elderly, women, and overweight patients. Asthma in the elderly is more often accompanied by neutrophilic inflammation, and cytokines such as interleukin (IL)-6 and IL-8 can be used as biomarkers to reflect the inflammation of the disease.[23, 24]Obesity in asthma is also an asthma phenotype, where neutrophilic inflammation has been reported as a major mechanism.[25]Considering these points, it is possible that neutrophilic asthma is a risk factor for COVID-19 development and poor prognosis rather than eosinophilic asthma. The recent results of higher expression of ACE2 and furin in the sputum samples from the U-BIOPRED Consortium patients with neutrophil molecular phenotype compared with the eosinophil type2-high phenotype support this hypothesis.[16, 26]

Asthma was not a risk factor for delayed viral clearance of SARS-CoV-2. On the other hand, several factors related to the nervous system were identified as important risk factors. Dementia, other psychological disorder, and older age were risk factors, whereas when accompanied by nervous system symptoms such

as headaches and an abnormal sense of smell acted as a preventive factor for delayed viral clearance. The similar effects of old age and headache symptoms on virus clearance in previous studies support the results of this study.[10] Previous studies have shown that the coronavirus can initially invade the peripheral nerves and enter the central nervous system through a synapse path.[27] Recent studies have reported that the blood-brain barrier transport of plasma protein decreases with age,[28] and altered neuronal immunomodulation may cause neurodegenerative disease.[29] It is hypothesized that the ability of the immune system to find and remove viruses that have penetrated the nervous system is important for virus cleaning. Another important risk factor for delayed viral clearance was anemia. Anemia often accompanies chronic diseases such as cancer, chronic kidney disease, and autoimmune diseases, which are known to be risk factors for severe COVID-19.[30] However, given that our research corrected for various risk factors, including age, sex, and comorbidity, and was limited to patients with mild disease who had no limitation of activity, and that anemia still appeared to be a significant risk factor for delayed viral clearance, we can consider the possibility of other mechanisms. The relationship between IL-6 and hepcidin is known to be related to systemic infection, and the possibility that this relationship between immune response and iron metabolism is related to virus clearance can be considered.[31] Male sex, hypertension and elevated C - reactive protein did not show a significant difference when analyzed only mild patients (no activity limitation group), and may be an indicator associated with severity rather than a direct effect on viral clearance. However, further epidemiologic and experimental studies are needed to prove the hypothesis regarding the mechanism associated with the risk factors for delayed viral clearance.

Hydroxychloroquine, azithromycin, and systemic glucocorticoid are anti-inflammatory drugs, especially hydroxychloroquine and azithromycin, which were also expected to have antiviral effects.[32, 33, 34] However, COVID-19 patients treated with these drugs showed different results depending on the study.[34, 35] In our study, hydroxychloroquine and systemic glucocorticoid significantly increased the risk of delayed viral clearance even though we limited to patients with mild COVID-19 to correct for the use of medications according to severity. There are limitations in determining the risk factors for death and delayed viral clearance associated with medications because the use of most drugs increased depending on the severity of the disease and the length of hospitalization. In spite of, our results suggest that anti-inflammatory drugs need to be used with proper consideration of appropriate indications.

This study has some limitations. First, our data did not include information about the asthma phenotype. The prevalence of asthma was investigated, but there was no additional information to divide patients according to the phenotype of asthma, such as the onset of the asthma, inflammatory patterns, and asthma medications; therefore, it was not possible to conduct an analysis according to specific asthma phenotypes. Secondly, real-time RT-PCR kits from other companies were used depending on the hospital. Therefore, there is a limitation that the sensitivity and specificity of individual real-time RT-PCR techniques have not been confirmed. However, all PCR results used PCR techniques verified by the KCDC, and the PCR results were also confirmed by the KCDC. Third, this study is a retrospective epidemiological study, and there is a risk of recall bias and missing data. Fourth, this study was an observational study, so there are limitations in terms of evaluating the efficacy of the medications for COVID-19. Finally, our study did not include patients who did not require hospitalization. About 30% of COVID-19 patients in Daegu were included in this study, and most of the patients who were not included were asymptomatic or had minimal symptoms.

Conclusion

In summary, in adult COVID-19 inpatients in Daegu, the prevalence of asthma did not differ from the general population, and the risk of clinical outcomes did not increase significantly. However, the prevalence of asthma was low in the age group of 19-29 years, and the risk of death was high with the elderly, women, and overweight among asthma patients. Older age, dementia, anemia, headache, and skin rash were independently associated with delayed viral clearance of SARS-CoV-2.

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Figure legends

Figure 1. Prevalence of asthma in patients hospitalized with COVID-19 in Daegu and in the KNHANES. (A) Prevalence in all age groups. (B) Prevalence by age group. (C) Prevalence by age group in male patients. (D) Prevalence by age group in female patients. COVID-19 = coronavirus disease-2019. KNHANES = the Korea National Health and Nutrition Examination Survey.

Figure 2. Clinical outcomes according to asthma. (A) Univariate analysis comparing asthma and non-asthma patients. (B) Death and ongoing care according to the asthma subgroups. BMI = body mass index. $^*P<$ 0.05

Figure 3. Forest plot showing odds ratios (ORs) of asthma for the clinical outcomes. ORs are adjusted for age, sex, body mass index, smoking history, underlying comorbidity, and treatment for COVID-19 by multivariate logistic regression model. COVID-19 = coronavirus disease 2019. ICU = intensive care unit. RT-PCR = reverse transcriptase-polymerase chain reaction. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure 4. Forest plot showing odds ratios (ORs) for risk factors for delayed viral clearance (>30 days). (A) Total patients (N = 1321; the delayed viral clearance group = 415). (B) Mild (no activity limitation) group (N = 938; the delayed viral clearance group = 281). ORs are adjusted for age, sex, body mass index, smoking history, underlying comorbidity, and medication for COVID-19 by multivariate logistic regression model. COVID-19 = coronavirus disease 2019. Hb = Hemoglobin. CRP = C-reactive protein.

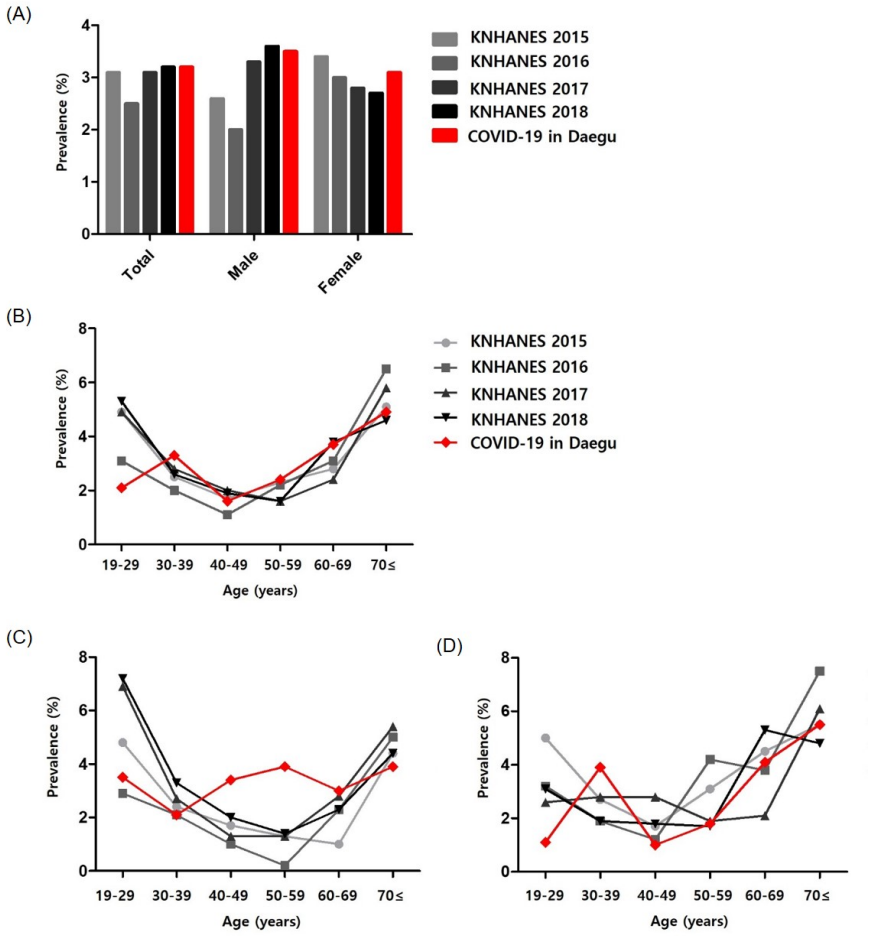

FIGURE 1

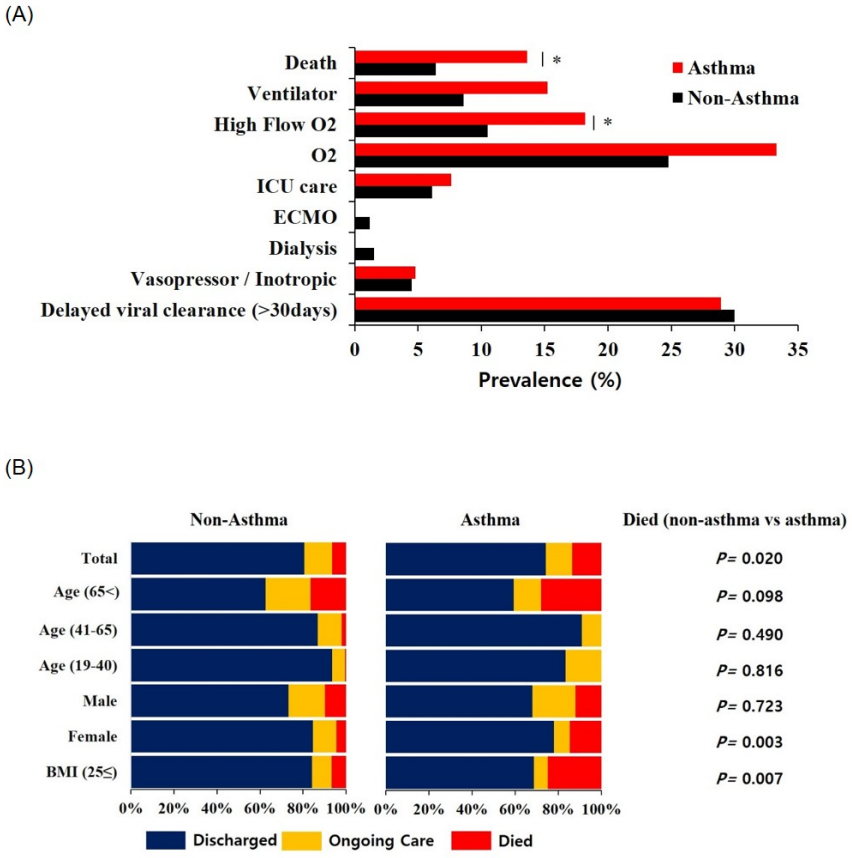

FIGURE 2

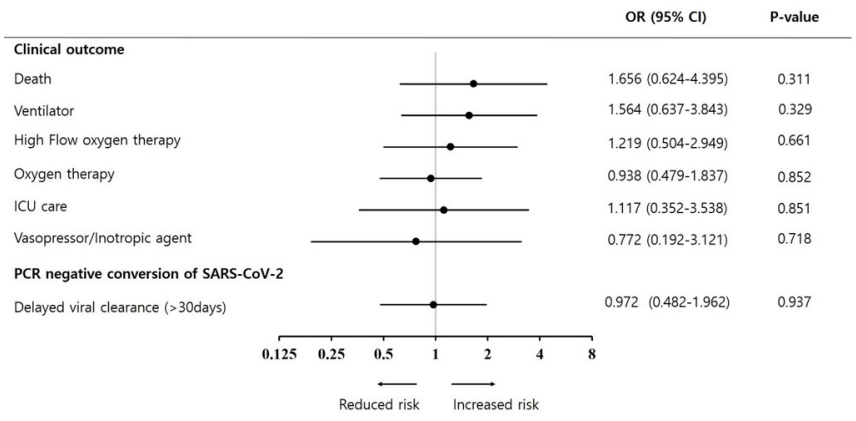

FIGURE 3

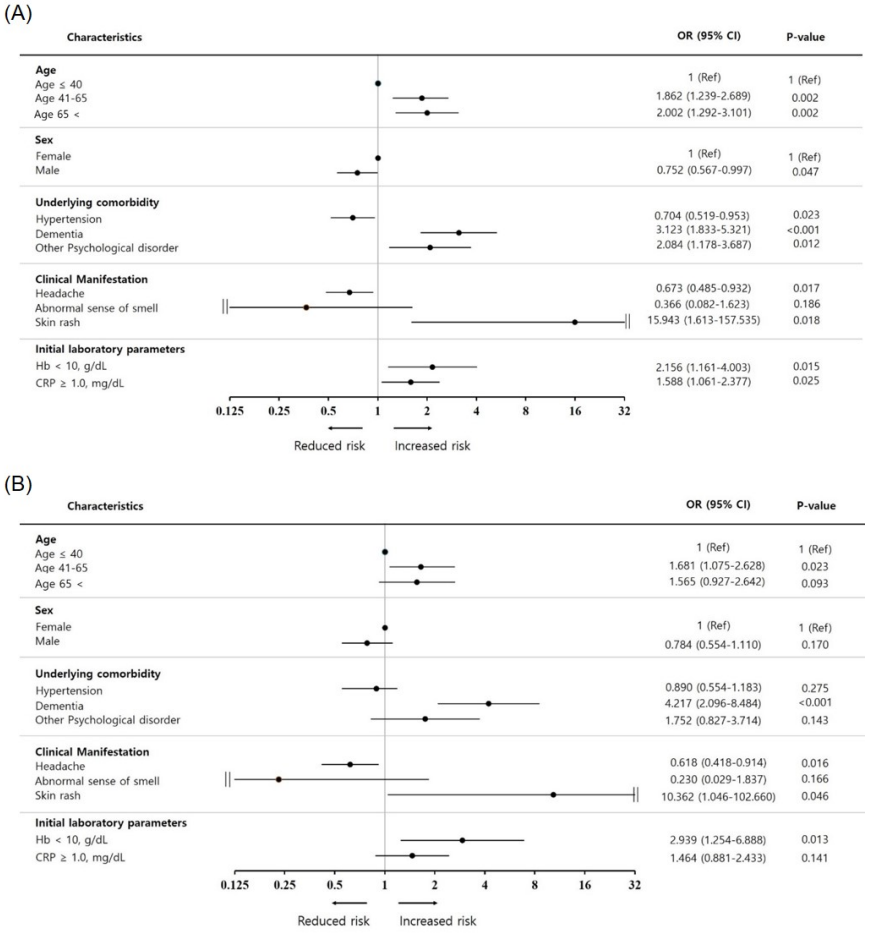

FIGURE 4

Table 1. Baseline characteristics in the study population according to asthma

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
Age (y)	56.71 ± 18.97	62.62 ± 19.63	55.88 ± 18.93	0.008
40[?]	474 of 2200 (21.5%)	12 of 66 (18.2%)	444 of 1977 (22.5%)	
41-65	967 of 2200 (44.0%)	22 of 66 (33.3%)	895 of 1977 (45.3%)	
>65	759 of 2200 (34.5%)	32 of 66 (48.5%)	638 of 1977 (32.3%)	
Sex (Male)	785 of 2200 (35.7%)	25 of 66 (37.9%)	690 of 1977 (34.9%)	0.618
Body mass index (kg/m²)	23.51 ± 3.43	24.83 ± 3.50	23.47 ± 3.46	0.013
<18.5	67 of 1442 (4.6%)	0 of 41 (0.0%)	62 of 1269 (4.9%)	
18.5˜24.9	961 of 1445 (66.6%)	25 of 41 (61.0%)	838 of 1269 (66.0%)	

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
[?]25.0	414 of 1445 (28.7%)	16 of 41 (39.0%)	369 of 1269 (29.1%)	
Smoking history	**Smoking history**	**Smoking history**	**Smoking history**	0.322
Current smoker	92 of 1787 (5.1%)	1 of 54 (1.9%)	86 of 1593 (5.4%)	
Ex-smoker	61 of 1787 (3.4%)	3 of 54 (5.6%)	49 of 1593 (3.1%)	
Non-smoker	1634 of 1787 (91.4%)	50 of 54 (92.6%)	1458 of 1593 (91.5%)	
Physical activity	**Physical activity**	**Physical activity**	**Physical activity**	0.737
Grade1	1506 of 1864 (80.8%)	52 of 65 (80.0%)	1333 of 1642 (81.2%)	
Grade2	198 of 1864 (10.6%)	6 of 65 (9.2%)	174 of 1642 (10.6%)	
Grade3	160 of 1864 (8.6%)	7 of 65 (10.8%)	135 of 1642 (8.2%)	
Underlying comorbidity	**Underlying comorbidity**	**Underlying comorbidity**	**Underlying comorbidity**	**Underlying comorbidity**
Chronic obstructive pulmonary disease	30 of 2052 (1.5%)	5 of 61 (8.2%)	21 of 1974 (1.1%)	<0.001
Diabetes	378 of 2168 (17.4%)	16 of 65 (24.6%)	320 of 1975 (16.2%)	0.072
Hypertension	645 of 2178 (29.6%)	23 of 65 (35.4%)	554 of 1976 (28.0%)	0.196
Heart Failure	44 of 2088 (2.1%)	3 of 60 (5.0%)	39 of 1950 (2.0%)	0.110
Other Chronic Heart Disease	111 of 2101 (5.3%)	4 of 62 (6.5%)	91 of 1971 (4.6%)	0.500
Chronic Kidney Disease	37 of 2030 (1.8%)	0 of 58 (0.0%)	31 of 1948 (1.6%)	0.333
Chronic Liver Disease	39 of 2050 (1.9%)	1 of 59 (1.7%)	35 of 1950 (1.8%)	0.955
Cancer	88 of 2030 (4.3%)	1 of 57 (1.8%)	74 of 1947 (3.8%)	0.422
Autoimmune Disease	15 of 1674 (0.9%)	0 of 56 (0.0%)	12 of 1613 (0.7%)	0.517
Dementia	175 of 1679 (10.4%)	7 of 56 (12.5%)	159 of 1611 (9.9%)	0.518
Other Psychological Disorder	138 of 1704 (8.1%)	2 of 54 (1.5%)	134 of 1612 (8.3%)	0.224
Hospital days	26.22 ± 16.25	23.46 ± 12.32	25.81 ± 16.34	0.251
Time From symptom onset to hospitalization (days)	8.56 ± 8.20	9.32 ± 9.51	8.76 ± 8.30	0.618

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
Time From diagnosis to hospitalization (days)	4.86 ± 5.90	5.02 ± 5.10	5.02 ± 6.07	0.992
Clinical Manifestations, (Admission date)	**Clinical Manifestations, (Admission date)**	**Clinical Manifestations, (Admission date)**	**Clinical Manifestations, (Admission date)**	**Clinical Manifestations, (Admission date)**
Fever	411 of 1849 (22.2%)	9 of 64 (14.1%)	359 of 1636 (21.9%)	0.133
Myalgia	390 of 1760 (22.2%)	10 of 59 (16.9%)	354 of 1600 (22.1%)	0.345
Headache	378 of 1802 (21.0%)	9 of 62 (14.5%)	336 of 1625 (20.7%)	0.238
Rhinorrhea/Runny Nose	179 of 1788 (10.0%)	7 of 63 (11.1%)	164 of 1618 (10.1%)	0.802
Abnormal Sense of Smell	26 of 1702 (1.5%)	1 of 58 (1.7%)	24 of 1595 (1.5%)	0.893
Sore Throat	236 of 1803 (13.1%)	6 of 62 (9.7%)	211 of 1623 (13.0%)	0.443
Cough	848 of 1837 (46.2%)	31 of 64 (48.4%)	744 of 1636 (45.5%)	0.641
Sputum	662 of 1834 (36.1%)	27 of 64 (42.2%)	579 of 1636 (35.4%)	0.265
Chest Discomfort/Chest Pain	173 of 1797 (9.6%)	4 of 61 (6.6%)	158 of 1629 (9.7%)	0.413
Dyspnea	397 of 1805 (22.0%)	22 of 62 (35.5%)	323 of 1625 (19.9%)	0.003
Blood tinged sputum/Hemoptysis	17 of 1765 (1.0%)	0 of 60 (0.0%)	14 of 1599 (0.9%)	0.467
Abdominal Pain	48 of 1772 (2.7%)	1 of 60 (1.7%)	40 of 1605 (2.5%)	0.685
Nausea/Vomiting	123 of 1786 (6.9%)	10 of 60 (16.7%)	100 of 1601 (6.2%)	0.001
Diarrhea	251 of 1794 (14.0%)	7 of 61 (11.5%)	220 of 1610 (13.7%)	0.624
Skin Rash	13 of 1735 (0.7%)	0 of 59 (0.0%)	10 of 1602 (0.6%)	0.543
Initial Chest X-ray (infiltration)	985 of 2153 (45.8%)	36 of 66 (54.5%)	847 of 1940 (43.7%)	0.080
Initial Laboratory Parameters (Admission date)	**Initial Laboratory Parameters (Admission date)**	**Initial Laboratory Parameters (Admission date)**	**Initial Laboratory Parameters (Admission date)**	**Initial Laboratory Parameters (Admission date)**
Hemoglobin < 10, g/dL	116 of 1650 (7.0%)	4 of 62 (6.5%)	95 of 1463 (6.6%)	0.967
Platelet count < 150, x10^9/L	304 of 1678 (18.1%)	8 of 61 (13.1%)	249 of 1463 (17.0%)	0.425

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
White blood cell count < 4, x10^9/L	338 of 1677 (20.2%)	7 of 61 (11.5%)	298 of 1462 (20.4%)	0.090
White blood cell count > 10, x10^9/L	117 of 1677 (7.0%)	8 of 61 (13.1%)	97 of 1462 (6.6%)	0.050
Lymphocyte count < 1.5, x10^9/L	971 of 1659 (58.5%)	33 of 60 (55.0%)	841 of 1445 (58.2%)	0.622
Lymphocyte count < 0.5, x10^9/L	82 of 1659 (4.9%)	1 of 60 (1.7%)	67 of 1445 (4.6%)	0.278
Activated partial thromboplastin time [?] 35s	128 of 1078 (11.9%)	3 of 35 (8.6%)	92 of 944 (9.7%)	0.818
Prothrombin time international normalized ratio [?] 1.5	25 of 1094 (2.3%)	0 of 36 (0.0%)	21 of 954 (2.2%)	0.368
Albumin [?] 3.0, g/dL	130 of 1827 (7.1%)	7 of 64 (10.9%)	103 of 1613 (6.4%)	0.149
Alanine aminotransferase [?] 40, U/L	289 of 1851 (15.6%)	10 of 64 (15.6%)	254 of 1634 (15.5%)	0.986
Aspartate aminotransferase [?] 40, U/L	381 of 1853 (20.6%)	13 of 64 (20.3%)	316 of 1635 (19.3%)	0.845
Total Bilirubin [?] 1.5, mg/dL	48 of 1773 (2.7%)	0 of 62 (0.0%)	37 of 1565 (2.4%)	0.221
Creatinine [?] 1.0, mg/dL	414 of 1852 (22.4%)	16 of 65 (24.6%)	357 of 1633 (21.9%)	0.599
High-sensitivity C-reactive protein [?] 1.0, mg/dL	308 of 831 (37.1%)	10 of 27 (37.0%)	275 of 760 (36.2%)	0.928
Lactate dehydrogenase [?] 445, U/L	685 of 1553 (44.1%)	25 of 52 (48.1%)	610 of 1387 (44.0%)	0.559
Procalcitonin [?] 0.5, ng/mL	49 of 759 (6.5%)	1 of 24 (4.2%)	42 of 625 (6.9%)	0.622
Medication	**Medication**	**Medication**	**Medication**	**Medication**
Antiretroviral drugs	1211 of 2200 (55.0%)	46 of 66 (69.7%)	1052 of 1977 (53.2%)	0.008
Hydroxychloroquine	1047 of 2200 (47.6%)	29 of 66 (43.9%)	902 of 1977 (45.6%)	0.787
Systemic steroid	173 of 2200 (7.9%)	6 of 66 (9.1%)	150 of 1977 (7.6%)	0.651
Azithromycin	694 of 1864 (37.2%)	22 of 65 (33.8%)	575 of 1642 (35.0%)	0.846

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
Other Antibiotics	1309 of 1864 (70.2%)	52 of 65 (80.0%)	1138 of 1642 (69.3%)	0.066

Data are expressed as mean ± standard deviation or n of N (%), where N is the total number of patients with available data.

Table 2. Multivariate analysis of outcome according to asthma

Characteristics	Model 1
	OR (95% CI)
Clinical Outcome	
Death	1.762 (0.813-3.822)
Ventilator	1.519 (0.726-3.179)
High Flow oxygen therapy	1.482 (0.740-2.968)
Oxygen therapy	1.145 (0.638-2.054)
ICU admission	1.023 (0.393-2.662)
Vasopressor or Inotropic agents	0.868 (0.260-2.896)
Real-Time RT-PCR negative conversion of SARS-CoV-2	**Real-Time RT-PCR negative conversion of SARS**
Delayed viral clearance (>30 days)	0.963 (0.495-1.876)

Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, body mass index, smoking history, underlying comorbidity (chronic obstructive pulmonary disease, diabetes, hypertension, heart failure, other heart disease, chronic kidney disease, chronic liver disease, cancer, autoimmune disease, dementia, and other psychological disorder), and medication (antiretroviral, hydroxychloroquine, systemic steroid, and azithromycin). OR = odds ratio. ICU = intensive care unit. RT-PCR = reverse transcriptase-polymerase chain reaction. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table E1. Prevalence of asthma in patients hospitalized with COVID-19 in Daegu and in KNHANES

Age Group (years)	COVID-19 in Daegu city	COVID-19 in Daegu city	COVID-19 in Daegu city	KNHANES 2018	KNHANES 2018	KNHANES 2018	KNHANES 2017	KNHANES 2017	KNHANES 2017	KNHANES 2017	KNHANES 2016	KNHANES 2016	KNHANES 2016	KNHANES 2016	KNHANES 20
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Total	Male	Female	Total	To
Total Prevalence	3.2	3.5	3.1	3.2	3.6	2.7	3.1	3.3	2.8	2.5	2.5	2.0	3.0	3.1	3.1
19-29	2.1	3.5	1.1	5.3	7.2	3.1	4.9	6.9	2.6	3.1	3.1	2.9	3.2	4.9	4.9
30-39	3.3	2.1	3.9	2.6	3.3	1.9	2.8	2.7	2.8	2.0	2.0	2.1	1.9	2.5	2.5
40-49	1.6	3.4	1.0	1.9	2.0	1.8	2.0	1.3	2.8	1.1	1.1	1.0	1.2	1.7	1.7
50-59	2.4	3.9	1.8	1.6	1.4	1.7	1.6	1.3	1.9	2.2	2.2	0.2	4.2	2.3	2.3
60-69	3.7	3.0	4.1	3.8	2.3	5.3	2.4	2.8	2.1	3.1	3.1	2.3	3.8	2.8	2.8

Age Group (years)	COVID-19 in Daegu city	COVID-19 in Daegu city	COVID-19 in Daegu city	KNHANES 2018	KNHANES 2018	KNHANES 2018	KNHANES 2017	KNHANES 2017	KNHANES 2017	KNHANES 2017	KNHANES 2016	KNHANES 2016	KNHANES 2016	KNHANES 2016	KNHANES 20
[?]70	4.9	3.9	5.5	4.6	4.4	4.8	5.8	5.4	6.1	6.5	6.5	5.0	7.5	5.1	5.1

Data are expressed as percentages. COVID-19 = coronavirus disease 2019. KNHANES = Korea National Health and Nutrition Examination Survey

Table E2. Initial laboratory parameters according to asthma

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
Laboratory Parameters				
Hemoglobin, g/dL	12.53 ± 1.72	12.73 ± 1.67	12.52 ± 1.67	0.327
Hematocrit (%)	37.53 ± 5.02	37.42 ± 5.05	37.53 ± 4.89	0.858
Platelet count, $x10^9$/L	225.72 ± 85.64	235.00 ± 79.73	226.60 ± 84.31	0.445
White blood cell count, $x10^9$/L	5.99 ± 2.73	7.14 ± 3.42	5.93 ± 2.60	0.008
Lymphocyte (%)	27.16 ± 11.88	24.61 ± 11.53	27.45 ± 11.81	0.059
Lymphocyte, $x10^9$/L	1.43 ± 0.67	1.50 ± 0.72	1.44 ± 0.67	0.499
Activated partial thromboplastin time, s	29.89 ± 6.43	29.59 ± 4.88	29.56 ± 5.85	0.976
Prothrombin time international normalized ratio	1.07 ± 0.49	1.01 ± 0.77	1.06 ± 0.50	0.510
Albumin, g/dL	3.91 ± 0.52	3.90 ± 0.53	3.93 ± 0.50	0.624
Alanine aminotransferase, U/L	31.30 ± 77.85	24.56 ± 14.79	31.17 ± 80.43	0.511
Aspartate Aminotransferase, U/L	40.31 ± 151.44	30.91 ± 19.60	39.41 ± 157.86	0.667
Total Bilirubin, mg/dL	0.58 ± 0.57	0.54 ± 0.25	0.56 ± 0.44	0.745
Creatinine, mg/dL	0.93 ± 1.06	0.88 ± 0.41	0.90 ± 0.92	0.826
High-sensitivity C-reactive protein, mg/dL	2.50 ± 5.09	1.68 ± 3.05	2.41 ± 4.97	0.447
Lactate dehydrogenase , U/L	478.34 ± 250.53	466.37 ± 178.37	475.12 ± 231.89	0.788
Procalcitonin, ng/mL	0.24 ± 1.34	0.11 ± 0.22	0.25 ± 1.46	0.621

Table E3. Univariate analysis of outcomes according to asthma

Characteristics	Total (N = 2200)	Asthma (N = 66)	Non-Asthma (N = 1977)	P-value (Asthma vs Non-Asthma)
Clinical Outcome				
Death	164 of 2200 (7.5%)	9 of 66 (13.6%)	127 of 1977 (6.4%)	0.021
Ventilator	213 of 2200 (9.7%)	10 of 66 (15.2%)	166 of 1977 (8.4%)	0.054
High Flow oxygen therapy	264 of 2200 (12.0%)	12 of 66 (18.2%)	208 of 1977 (10.5%)	0.048
Oxygen therapy	593 of 2200 (27.0%)	22 of 66 (33.3%)	491 of 1977 (24.8%)	0.117
ICU admission	158 of 2200 (7.2%)	5 of 66 (7.6%)	120 of 1977 (6.1%)	0.616
ECMO	31 of 2088 (1.5%)	0 of 62 (0.0%)	23 of 1928 (1.2%)	0.387
Renal replacement therapy	34 of 2084 (1.6%)	0 of 62 (0.0%)	29 of 1928 (1.5%)	0.331
Vasopressor or Inotropic agents	108 of 2087 (5.2%)	3 of 63 (4.8%)	86 of 1929 (4.5%)	0.909
Real-Time RT-PCR negative conversion of SARS-CoV-2	**Real-Time RT-PCR negative conversion of SARS-CoV-2**	**Real-Time RT-PCR negative conversion of SARS-CoV-2**	**Real-Time RT-PCR negative conversion of SARS-CoV-2**	**Real-Time RT-PCR negative conversion of SARS-CoV-2**
Delayed viral clearance (>30 days)	415 of 1321 (31.4%)	13 of 45 (28.9%)	350 of 1164 (30.1%)	0.865

Data are expressed as n of N (%), where N is the total number of patients with available data. ICU = intensive care unit. ECMO = extracorporeal membrane oxygenation. RT-PCR = reverse transcriptase-polymerase chain reaction. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table E4. Risk factors associated with death

Characteristics	Survive (N=2036)	Death (N=164)	
Age (y)	**Age (y)**	**Age (y)**	<0.001
40[?]	472 of 2036 (23.2%)	2 of 164 (1.2%)	
41-65	944 of 2036 (46.4%)	23 of 164 (14.0%)	
65<	620 of 2036 (30.5%)	139 of 164 (84.8%)	
Sex	**Sex**	**Sex**	**Sex**
Male	699 of 2036 (34.3%)	86 of 164 (52.4%)	<0.001
Body mass index (kg/m^2)	**Body mass index (kg/m^2)**	**Body mass index (kg/m^2)**	0.003
18.5>	61 of 1364 (4.5%)	6 of 78 (7.7%)	
18.5-24.9	923 of 1364 (67.7%)	38 of 78 (48.7%)	
25[?]	382 of 1364 (27.9%)	34 of 78 (43.6%)	
Smoking History	**Smoking History**	**Smoking History**	<0.001

Characteristics	**Survive (N=2036)**	**Death (N=164)**	
Current	90 of 1650 (5.5%)	2 of 137 (1.5%)	
Ex	49 of 1650 (3.0%)	12 of 137 (8.8%)	
None	1511 of 1650 (91.4%)	123 of 137 (89.8%)	
Physical Activity	**Physical Activity**	**Physical Activity**	<0.001
Grade 1	1464 of 1700 (86.1%)	42 of 164 (25.6%)	
Grade 2	145 of 1700 (8.5%)	53 of 164 (32.3%)	
Grade 3	91 of 1700 (5.3%)	69 of 164 (42.1%)	
Underlying comorbidity	**Underlying comorbidity**	**Underlying comorbidity**	**Underlying comorbidity**
Chronic obstructive pulmonary disease	25 of 1917 (1.3%)	5 of 135 (3.7%)	0.025
Diabetes	307 of 2013 (15.3%)	71 of 155 (45.8%)	<0.001
Hypertension	544 of 2018 (27.0%)	101 of 160 (63.1%)	<0.001
Heart Failure	30 of 1942 (1.5%)	14 of 146 (9.6%)	<0.001
Other Chronic Heart Disease	82of 1953 (4.7%)	19 of 148 (12.8%)	<0.001
Chronic Kidney Disease	25 of 1894 (1.3%)	12 of 136 (8.8%)	<0.001
Chronic Liver Disease	35 of 1910 (1.8%)	4 of 140 (2.9%)	0.392
Cancer	71 of 1892 (3.8%)	17 of 138 (12.3%)	<0.001
Autoimmune Disease	12 of 1541 (0.8%)	3 of 133 (2.3%)	0.083
Dementia	129 of 1541 (8.4%)	46 of 138 (33.3%)	<0.001
Other Psychological Disorder	121 of 1569 (7.7%)	17 of 135 (12.6%)	0.046
Clinical Manifestations, (Admission date)	**Clinical Manifestations, (Admission date)**	**Clinical Manifestations, (Admission date)**	**Clinical Manifestations, (Admission date)**
Fever	347 of 1689 (20.5%)	64 of 160 (40.0%)	<0.001
Myalgia	374 of 1615 (23.2%)	16 of 145 (11.0%)	0.001
Headache	370 of 1656 (22.3%)	8 of 146 (5.5%)	<0.001
Rhinorrhea/Runny Nose	172 of 1641 (10.5%)	7 of 147 (4.8%)	0.027
Abnormal Sense of Smell	26 of 1563 (1.7%)	0 of 139 (0.0%)	0.125
Sore Throat	228 of 1655 (13.8%)	8 of 148 (5.4%)	0.004
Cough	796 of 1685 (47.2%)	52 of 152 (34.2%)	0.002
Sputum	609 of 1682 (36.2%)	53 of 152 (34.9%)	0.742
Chest Discomfort/Chest Pain	164 of 1649 (9.9%)	9 of 148 (6.1%)	0.127
Dyspnea	322 of 1654 (19.5%)	75 of 151 (49.7%)	<0.001
Blood tinged sputum/Hemoptysis	12 of 1619 (0.7%)	5 of 146 (3.4%)	0.001
Abdominal Pain	47 of 1625 (2.9%)	1 of 147 (0.7%)	0.114
Nausea/Vomiting	111 of 1637 (6.8%)	12 of 149 (8.1%)	0.557
Diarrhea	238 of 1645 (14.5%)	13 of 149 (8.7%)	0.053
Skin Rash	11 of 1587 (0.7%)	2 of 148 (1.4%)	0.374
Initial Chest X-ray (infiltration)	858 of 1994 (43.0%)	127 of 159 (79.9%)	<0.001

Characteristics	Survive (N=2036)	Death (N=164)	
Initial Laboratory Parameters (Admission date)	**Initial Laboratory Parameters (Admission date)**	**Initial Laboratory Parameters (Admission date)**	**Initial Laboratory Parameters (Admission date)**
Hemoglobin < 10, g/dL	81 of 1499 (5.4%)	35 of 151 (23.2%)	<0.001
Platelet count < 150, x10^9/L	243 of 1521 (16.0%)	61 of 157 (38.9%)	<0.001
White blood cell count < 4, x10^9/L	322 of 1520 (21.2%)	16 of 157 (10.2%)	0.041
White blood cell count > 10, x10^9/L	74 of 1520 (4.9%)	43 of 157 (27.4%)	<0.001
Lymphocyte count < 1.5, x10^9/L	838 of 1506 (55.6%)	133 of 153 (86.9%)	<0.001
Lymphocyte count < 0.5, x10^9/L	50 of 1506 (3.3%)	32 of 153 (20.9%)	<0.001
Activated partial thromboplastin time [?] 35s	88 of 969 (9.1%)	40 of 109 (36.7%)	<0.001
Prothrombin time international normalized ratio [?] 1.5	15 of 980 (1.5%)	10 of 114 (8.8%)	<0.001
Albumin [?] 3.0, g/dL	71 of 1673 (4.2%)	59 of 154 (38.3%)	<0.001
Alanine aminotransferase [?] 40, U/L	258 of 1694 (15.2%)	31 of 157 (19.7%)	0.136
Aspartate aminotransferase [?] 40, U/L	287 of 1695 (17.0%)	94 of 158 (59.5%)	<0.001
Total Bilirubin [?] 1.5, mg/dL	37 of 1624 (2.3%)	11 of 149 (7.4%)	<0.001
Creatinine [?] 1.0, mg/dL	325 of 1692 (19.2%)	89 of 160 (55.6%)	<0.001
High-sensitivity C-reactive protein [?] 1.0, mg/dL	259 of 776 (33.4%)	49 of 55 (89.1%)	<0.001
Lactate dehydrogenase [?] 445, U/L	603 of 1435 (42.0%)	82 of 118 (69.5%)	<0.001
Procalcitonin [?] 0.5, ng/mL	25 of 680 (3.7%)	24 of 79 (30.4%)	<0.001
Medication	**Medication**	**Medication**	**Medication**
Antiretroviral drugs	1094 of 2036 (53.7%)	117 of 164 (71.3%)	<0.001
Hydroxychloroquine	930 of 2036 (45.7%)	117 of 164 (71.3%)	<0.001
Systemic steroid	121 of 2036 (5.9%)	52 of 164 (31.7%)	<0.001
Azithromycin	635 of 1700 (37.4%)	59 of 164 (36.0%)	0.728

Data are expressed as n of N (%), where N is the total number of patients with available data.

Table E5 Multivariate analysis of risk factors for death

Characteristics	Model 1	Model

Characteristics	Model 1	Model
	OR (95% CI)	P value
Age	**Age**	**Age**
40	Ref (1)	Ref (1)
41-65	5.937 (1.393-25.303)	0.016
>65	52.700 (12.976-214.038)	<0.001
Sex	**Sex**	**Sex**
Male	1.956 (1.398-2.738)	<0.001
Body mass index (kg/m^2)	**Body mass index (kg/m^2)**	**Body**
<18.5	2.857 (1.077-7.580)	0.035
18.5 - 24.9	Ref (1)	Ref (1)
25.0	2.388 (1.443-3.953)	0.001
Unknown	2.948 (1.946-4.465)	<0.001
Smoking History	**Smoking History**	**Smoki**
Current smoker	0.259 (0.061-1.106)	0.068
Ex-smoker	1.865 (0.900-3.864	0.050
None-smoker	Ref (1)	Ref (1)
Unknown	0.936 (0.593-1.478)	0.778
Underlying comorbidity	**Underlying comorbidity**	**Under**
Chronic obstructive pulmonary disease	1.747 (0.621-4.914)	0.290
Diabetes	2.477 (1.732-3.543)	<0.001
Hypertension	2.035 (1.419-2.918)	<0.001
Heart Failure	2.967 (1.495-5.890)	0.002
Other Chronic Heart Disease	1.359 (0.783-2.360)	0.276
Chronic Kidney Disease	4.748 (2.187 -10.306)	<0.001
Chronic Liver Disease	1.464 (0.480-4.467)	0.503
Cancer	2.614 (1.421-4.809)	0.002
Autoimmune Disease	4.471 (0.993-20.128)	0.051
Dementia	2.597 (1.705-3.956)	<0.001
Other Psychological Disorder	1.953 (1.090-3.500)	0.025
Clinical Manifestations, (Admission date)	**Clinical Manifestations, (Admission date)**	**Clinica**
Fever	2.596 (1.808-3.727)	<0.001
Myalgia	0.532 (0.307-0.922)	0.025
Headache	0.321 (0.153-0.672)	0.003
Rhinorrhea/Runny Nose	0.463 (0.208-1.031)	0.059
Sore Throat	0.565 (0.266-1.198)	0.137
Cough	0.678 (0.471-0.976)	0.037
Sputum	1.104 (0.765-1.594)	0.597
Chest Discomfort/Chest Pain	0.773 (0.374-1.598)	0.487
Dyspnea	3.071 (2.139-4.407)	<0.001
Blood tinged sputum/Hemoptysis	6.551 (1.875-22.882)	0.003
Abdominal Pain	0.260 (0.035-1.951)	0.190
Nausea/Vomiting	1.188 (0.618-2.284)	0.606
Diarrhea	0.782 (0.425-1.438)	0.429
Skin Rash	1.608 (0.329-7.872)	0.558
Initial Chest X-ray	**Initial Chest X-ray**	**Initial**
Infiltration	2.951 (1.949-4.468)	<0.001
Initial Laboratory Parameters (Admission date)	**Initial Laboratory Parameters (Admission date)**	**Initial**

Characteristics	Model 1	Model
Hemoglobin < 10, g/dL	3.358 (2.104-5.361)	<0.001
Platelet count < 150, x10^9/L	2.529 (1.743-3.671)	<0.001
White blood cell count < 4, x10^9/L	0.668 (0.380-1.176)	0.162
White blood cell count 4, x10^9/L [?], [?]10, x10^9/L	Ref (1)	Ref (1)
White blood cell count > 10, x10^9/L	4.677 (2.960-7.390)	<0.001
Lymphocyte count < 1.5, x10^9/L	3.511 (2.138-5.767)	<0.001
Lymphocyte count < 0.5, x10^9/L	4.713 (2.786-7.972)	<0.001
Activated partial thromboplastin time [?] 35s	4.625 (2.838-7.539)	<0.001
Prothrombin time international normalized ratio [?] 1.5	4.547 (1.838-11.246)	0.001
Albumin [?] 3.0, g/dL	7.563 (4.950-11.554)	<0.001
Alanine aminotransferase [?] 40, U/L	1.251 (0.804-1.946)	0.321
Aspartate aminotransferase [?] 40, U/L	4.840 (3.374-6.942)	<0.001
Total Bilirubin [?] 1.5, mg/dL	3.155 (1.451-6.859)	0.004
Creatinine [?] 1.0, mg/dL	3.268 (2.259-4.728)	<0.001
High-sensitivity C-reactive protein [?] 1.0, mg/dL	10620 (4.383-25.736)	<0.001
Lactate dehydrogenase [?] 445, U/L	2.483 (1.625-3.794)	<0.001
Procalcitonin [?] 0.5, ng/mL	9.593 (4.754-19.356)	<0.001
Medication	**Medication**	**Medica**
Antiretroviral drugs	1.328 (0.917-1.923)	0.133
Hydroxychloroquine	1.734 (1.199-2.507)	0.003
Systemic steroid	4.002 (2.674-5.988)	<0.001
Azithromycin	0.650 (0.458-0.924)	0.016

Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, body mass index, smoking history, underlying comorbidity (asthma, chronic obstructive pulmonary disease, diabetes, hypertension, heart failure, other heart disease, chronic kidney disease, chronic liver disease, cancer, autoimmune disease, dementia, and other psychological disorder), and medication (antiviral, hydroxychloroquine, systemic steroid, and azithromycin). OR = odds ratio. ICU = intensive care unit. RT-PCR=reverse transcriptase-polymerase chain reaction. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table E6. Adjusted ORs for delayed SARS-CoV-2 clearance (all patients)

Characteristics	Model 1	Model
	OR (95% CI)	P value
Age	**Age**	**Age**
40	Ref (1)	Ref (1)
41-65	2.060 (1.435-2.957)	<0.001
>65	2.855 (1.966-4.147)	<0.001
Sex	**Sex**	**Sex**
Male	0.836 (0.649-1.077)	0.165
Body mass index (kg/m^2)	**Body mass index (kg/m^2)**	**Body**
<18.5	1.369 (0.660-2.841)	0.399
18.5 - 24.9	Ref (1)	Ref (1)
25.0	0.847 (0.604-1.187)	0.334
Unknown	0.792 (0.608-1.032)	0.085
Smoking History	**Smoking History**	**Smoki**
Current smoker	1.086 (0.558-2.114)	0.808
Ex-smoker	1.211 (0.590-2.484)	0.602
None-smoker	Ref (1)	Ref (1)

Characteristics	**Model 1**	**Model**
Unknown	0.790 (0.592-1.055)	0.110
Underlying comorbidity	**Underlying comorbidity**	**Under**
Chronic obstructive pulmonary disease	1.865 (0.745-4.669)	0.183
Diabetes	1.246 (0.915-1.698)	0.163
Hypertension	0.803 (0.609-1.060)	0.121
Heart Failure	1.008 (0.333-3.057)	0.988
Other Chronic Heart Disease	1.053 (0.625-1.776)	0.845
Chronic Kidney Disease	0.647 (0.232-1.808)	0.407
Chronic Liver Disease	0.994 (0.399-2.481)	0.990
Cancer	1.431 (0.835-2.455)	0.193
Autoimmune Disease	1.012 (0.258-3.976)	0.986
Dementia	2.935 (1.810-4.758)	<0.001
Other Psychological Disorder	2.108 (1.240-3.584)	0.006
Clinical Manifestations, (Admission date)	**Clinical Manifestations, (Admission date)**	**Clinica**
Fever	1.097 (0.821-1.467)	0.532
Myalgia	0.950 (0.711-1.270)	0.730
Headache	0.694 (0.513-0.940)	0.018
Rhinorrhea/Runny Nose	1.065 (0.723-1.568)	0.752
Abnormal Sense of Smell	0.316 (0.720-1.383)	0.126
Sore Throat	1.066 (0.754-1.505)	0.718
Cough	1.109 (0.873-1.407)	0.397
Sputum	0.945 (0.737-1.212)	0.654
Chest Discomfort/Chest Pain	0.758 (0.504-1.140)	0.184
Dyspnea	1.194 (0.890-1.604)	0.237
Blood tinged sputum/Hemoptysis	2.220 (0.632-7.801	0.214
Abdominal Pain	0.846 (0.414-1.729)	0.646
Nausea/Vomiting	0.812 (0.504-1.308)	0.392
Diarrhea	0.879 (0.627-1.233)	0.455
Skin Rash	14.195 (1.730-116.436)	0.013
Initial Chest X-ray	**Initial Chest X-ray**	**Initial**
Infiltration	1.158 (0.906-1.480)	0.241
Initial Laboratory Parameters (Admission date)	**Initial Laboratory Parameters (Admission date)**	**Initial**
Hemoglobin < 10, g/dL	2.083 (1.199-3.619)	0.009
Platelet count < 150, x10^9/L	1.298 (0.926-1.820)	0.130
White blood cell count < 4, x10^9/L	0.781 (0.572-1.067)	0.120
White blood cell count 4, x10^9/L [?], [?]10, x10^9/L	Ref (1)	Ref (1)
White blood cell count > 10, x10^9/L	1.188 (0.646-2.187)	0.579
Lymphocyte count < 1.5, x10^9/L	1.038 (0.807-1.336)	0.771
Lymphocyte count < 0.5, x10^9/L	1.150 (0.575-2.299)	0.693
Activated partial thromboplastin time [?] 35s	1.363 (0.819-2.270)	0.233
Prothrombin time international normalized ratio [?] 1.5	1.386 (0.306-6.278)	0.672
Albumin [?] 3.0, g/dL	1.650 (0.912-2.988)	0.098
Alanine aminotransferase [?] 40, U/L	1.186 (0.858-1.639)	0.302
Aspartate aminotransferase [?] 40, U/L	0.927 (0.675-1.273)	0.639
Total Bilirubin [?] 1.5, mg/dL	0.631 (0.249-1.599)	0.332
Creatinine [?] 1.0, mg/dL	1.344 (0.968-1.867)	0.078
High-sensitivity C-reactive protein [?] 1.0, mg/dL	1.654 (1.133-2.413)	0.009
Lactate dehydrogenase [?] 445, U/L	1.211 (0.933-1.572)	0.149
Procalcitonin [?] 0.5, ng/mL	0.903 (0.350-2.330)	0.833
Medication	**Medication**	**Medica**

Characteristics	Model 1	Model
Antiretroviral drugs	1.005 (0.787-1.283)	0.968
Hydroxychloroquine	1.685 (1.321-2.149)	<0.001
Systemic steroid	1.814 (1.128-2.916)	0.014
Azithromycin	1.500 (1.175-1.915)	0.001

Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, body mass index, smoking history, underlying comorbidity (asthma, chronic obstructive pulmonary disease, diabetes, hypertension, heart failure, other heart disease, chronic kidney disease, chronic liver disease, cancer, autoimmune disease, dementia, and other psychological disorder), and medication (antiviral, hydroxychloroquine, systemic steroid, and azithromycin), OR = odds ratio. ICU = intensive care unit.

Table E7. Adjusted ORs for delayed SARS-CoV-2 clearance among patients with mild COVID-19 (no activity limitation).

Characteristics	Model 1	Model
	OR (95% CI)	P value
Age	**Age**	**Age**
40	Ref (1)	Ref (1)
41-65	1.997 (1.323-3.015)	0.001
>65	2.658 (1.719-4.112)	<0.001
Sex	**Sex**	**Sex**
Male	0.871 (0.641-1.184)	0.378
Body mass index (kg/m^2)	**Body mass index (kg/m^2)**	**Body**
<18.5	0.757 (0.287-1.996)	0.574
18.5 - 24.9	Ref (1)	Ref (1)
25.0	0.736 (0.478-1.133)	0.164
Unknown	0.726 (0.531-0.992)	0.044
Smoking History	**Smoking History**	**Smoki**
Current smoker	0.783 (0.303-2.024)	0.614
Ex-smoker	0.783 (0.303-2.024)	0.614
None-smoker	Ref (1)	Ref (1)
Unknown	0.827 (0.597-1/147)	0.256
Underlying comorbidity	**Underlying comorbidity**	**Under**
Chronic obstructive pulmonary disease	2.863 (0.972-8.431)	0.056
Diabetes	1.279 (0.864-1.891)	0.219
Hypertension	0.890 (0.636-1.247)	0.499
Heart Failure	1.021 (0.251-4.157)	0.977
Other Chronic Heart Disease	1.131 (0.608-2.103)	0.698
Chronic Kidney Disease	1.179 (0.340-4.087)	0.795
Chronic Liver Disease	1.456 (0.466-4.548)	0.518
Cancer	1.587 (0.844-2.984)	0.152
Autoimmune Disease	0.870 (0.173-4.385)	0.866
Dementia	3.956 (2.116-7.396)	<0.001
Other Psychological Disorder	1.743 (0.878-3.462)	0.112
Clinical Manifestations, (Admission date)	**Clinical Manifestations, (Admission date)**	**Clinica**
Fever	1.111 (0.785-1.571)	0.554
Myalgia	0.901 (0.640-1.268)	0.550
Headache	0.655 (0.460-0.931)	0.018
Rhinorrhea/Runny Nose	1.048 (0.662-1.657)	0.842

Characteristics	**Model 1**	**Model**
Abnormal Sense of Smell	0.209 (0.27-1.614)	0.133
Sore Throat	1.080 (0.723-1.614)	0.708
Cough	1.152 (0.865-1.533)	0.333
Sputum	0.881 (0.654-1.187)	0.406
Chest Discomfort/Chest Pain	0.642 (0.381-1.083)	0.097
Dyspnea	1.256 (0.875-1.803)	0.217
Blood tinged sputum/Hemoptysis	1.239 (0.222-6.904)	0.807
Abdominal Pain	0.806 (0.354-1.836)	0.607
Nausea/Vomiting	0.761 (0.419-1.382)	0.761
Diarrhea	0.775 (0.515-1.167)	0.222
Skin Rash	10.088 (1.165-87.359)	0.036
Initial Chest X-ray	**Initial Chest X-ray**	**Initial**
Infiltration	1.262 (0.937-1.699)	0.125
Initial Laboratory Parameters (Admission date)	**Initial Laboratory Parameters (Admission date)**	**Initial**
Hemoglobin $<$ 10, g/dL	2.877 (1.357-6.101)	0.006
Platelet count $<$ 150, x10^9/L	1.432 (0.857-2.143)	0.081
White blood cell count $<$ 4, x10^9/L	0.830 (0.574-1.199)	0.320
White blood cell count 4, x10^9/L [?], [?]10, x10^9/L	Ref (1)	Ref (1)
White blood cell count $>$ 10, x10^9/L	1.273 (0.638-2.541)	0.493
Lymphocyte count $<$ 1.5, x10^9/L	1.046 (0.772-1.419)	0.771
Lymphocyte count $<$ 0.5, x10^9/L	1.637 (0.685-3.912)	0.267
Activated partial thromboplastin time [?] 35s	1.985 (1.092-3.608)	0.024
Prothrombin time international normalized ratio [?] 1.5	1.334 (0.218-8.144)	0.755
Albumin [?] 3.0, g/dL	1.450 (0.679-3.096)	0.337
Alanine aminotransferase [?] 40, U/L	1.213 (0.823-1.788)	0.330
Aspartate aminotransferase [?] 40, U/L	0.950 (0.648-1.392)	0.792
Total Bilirubin [?] 1.5, mg/dL	0.913 (0.345-2.415)	0.913
Creatinine [?] 1.0, mg/dL	1.590 (1.065-2.373)	0.023
High-sensitivity C-reactive protein [?] 1.0, mg/dL	1.463 (0.918-2.331)	0.110
Lactate dehydrogenase [?] 445, U/L	1.191 (0.869-1.632)	0.276
Procalcitonin [?] 0.5, ng/mL	0.955 (0.309-2.955)	0.936
Medication	**Medication**	**Medica**
Antiretroviral drugs	0.934 (0.695-1.256)	0.653
Hydroxychloroquine	1.720 (1.287-2.300)	$<$0.001
Systemic steroid	3.332 (1.827-6.074)	$<$0.001
Azithromycin	1.560 (1.162-2.094)	0.003

Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, body mass index, smoking history, underlying comorbidity (asthma, chronic obstructive pulmonary disease, diabetes, hypertension, heart failure, other heart disease, chronic kidney disease, chronic liver disease, cancer, autoimmune disease, dementia, and other psychological disorder), and medication (antiviral, hydroxychloroquine, systemic steroid, and azithromycin), OR = odds ratio.