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Article type : Letter to the Editor

Title

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

To the Editor:

The spread of the coronavirus disease-2019 (COVID-19) remains a worsening global health crisis. Although many studies have reported risk factors for severe COVID-19, asthma characterization in COVID-19 is still controversial, with different early reports from China and recent reports from Europe and the United States.¹ Prolonged viral shedding is a risk factor for poor outcome of COVID-19, and may assist in inferring the immunological mechanism of virus elimination; however, no large-scale studies have explored this subject.²

Daegu Metropolitan City, the fourth largest city in the Republic of Korea with a population of 2.5million, collected and shared a database of COVID-19 patients hospitalized in 10 large general hospitals. This study used the database to evaluate the prevalence of asthma and clinical outcomes of COVID-19 according to asthma in adult patients. The risk factors for delayed viral clearance were also evaluated.

A total of 2,311 patients were registered in the database; 46 duplicated cases and 65 pediatric

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cases were excluded, leading to 2,200 patients in the final analysis. The prevalence of asthma in patients with COVID-19 was 3.2% which was similar to the prevalence of asthma in the Korea National Health and Nutrition Examination Survey (KNHANES) (Figure 1A and Table S1). The general pattern of the prevalence of asthma by age group in the KHANES was U-shaped, and the prevalence in patients with COVID-19 was similar but was lower in the 19–29-year age group (2.1%) (Figure 1B).

Table S2 compares the characteristics between the asthma group and the non-asthma group. Older age (>65 years), overweight (BMI $\geq$ 25.0), and comorbidity of chronic obstructive pulmonary disease, and initially presented with dyspnea and nausea/vomiting were more common in the asthma group. Compared with the non-asthma group, the asthma group had a higher mortality rate (13.6% vs. 6.4%, $P = 0.02$) and a greater need for high-flow oxygen therapy (18.2% vs. 10.5%, $P = 0.048$) (Figure 1C and Table S3). The higher mortality rate in asthma patients was particularly noticeable in older patients, overweight patients and females. (Figure 1D). However, after adjusting for potential confounders, asthma had no significant association with clinical outcomes of COVID-19 (Figure 2A and Table S4). Meanwhile, older age, male gender, and comorbid diseases including overweight, diabetes, chronic kidney disease, cancer, autoimmune disease, dementia, and other psychological disorder were significant risk factors for mortality (Tables S5 and S6).

In multivariate analysis, asthma was not a risk factor for death. However, asthma, a heterogeneous disease, may affect COVID-19 differently depending on asthma phenotype. Early onset allergic asthma is often accompanied by type 2 inflammation, while asthma in obesity and elderly are more frequently accompanied by non-type 2 inflammation.³ Recent studies have reported higher expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2) in respiratory samples of neutrophilic inflammation compared to eosinophilic inflammation asthma.⁴ The low prevalence of COVID-19 infection in those younger than 30 years old, and a relatively high mortality rate in patients who were female, overweight and elderly in our study suggests that neutrophilic asthma may be a risk factor for infection and poor prognosis of COVID-19.⁵

In order to analyze the risk factors of delayed viral clearance, patients were divided into two groups. The non-delayed viral clearance group was defined as patients with two consecutive

negative real-time RT-PCR results at intervals of ≥ 24 hours within 30 days since diagnosis. The delayed viral clearance group was defined as patients with a positive real-time RT-PCR test after 30 days, without two consecutive negative RT-PCR results. So, 906 patients were included in the non-delayed viral clearance group and 415 patients in the delayed viral clearance group. After adjusting for potential confounders, delayed viral clearance was not significantly associated with asthma (Figure 1E and Table S4). Older age, Underlying dementia and psychological disorders other than dementia, initial symptom of skin rash, and initial laboratory abnormalities of hemoglobin <10 g/dL and C-reactive protein (CRP) ≥ 1.0 mg/dL were significant risk factors for delayed viral clearance. On the other hand, male sex, hypertension, and initial symptom of headache reduced the risk for delayed viral clearance (Figure 2B and Table S7). When limited to patients with no activity limitation (mild COVID-19 group), older age, dementia, initial symptoms of skin rash and headache, and initial hemoglobin <10 g/dL still showed significant differences (Table S8).

Dementia and older age are identified as important risk factors for delayed viral clearance, while nervous system symptoms such as headaches and an abnormal sense of smell reduced the risk for delayed viral clearance. Previous studies have shown that the coronavirus can initially invade the peripheral nerves and enter the central nervous system.⁶ The immunological function of the brain is altered and dysregulated in neurodegenerative diseases,⁷ and it has also been reported that local neurological symptoms such as headache and olfactory symptoms may be a biomarker of the magnitude of a host's innate immune response to virus.⁸ It can be hypothesized that the immunological mechanism of detecting and removing viruses that have infiltrated the central nervous system in COVID-19 is important for virus clearance. Anemia and skin rash, which was associated with increased risk, may also be related to the mechanism of virus clearing, and further research on the mechanism is needed. Since male sex, hypertension and elevated CRP did not show a significant difference in the mild COVID-19 group, they may be more closely associated with severity of disease rather than viral clearance.

This data did not include asymptomatic or minimal symptomatic patients who did not require hospitalization. However, our study covered almost all hospitalized patients diagnosed with COVID-19 in Daegu from February 2020 to May 2020, minimizing selection bias.⁹ In addition, because most hospitals, following the guidance from the Korea Centers for Disease Control & Prevention, employed similar protocols for discharge from quarantine and RT-PCR follow-up

testing, we were able to analyze the risk factors for viral clearance in a relatively large number of patients.

In summary, despite the differences depending on phenotypes, the prevalence of asthma was not significantly different in patients with COVID-19, and asthma did not affect the outcomes of COVID-19 in multivariate analysis. Dementia, older age, and initial presentation of skin rash and anemia were independently associated with delayed viral clearance. On the other hand, in patients with headache initially, the viral clearance time was shortened.

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Conflicts of Interest

The authors declare no competing financial interest.

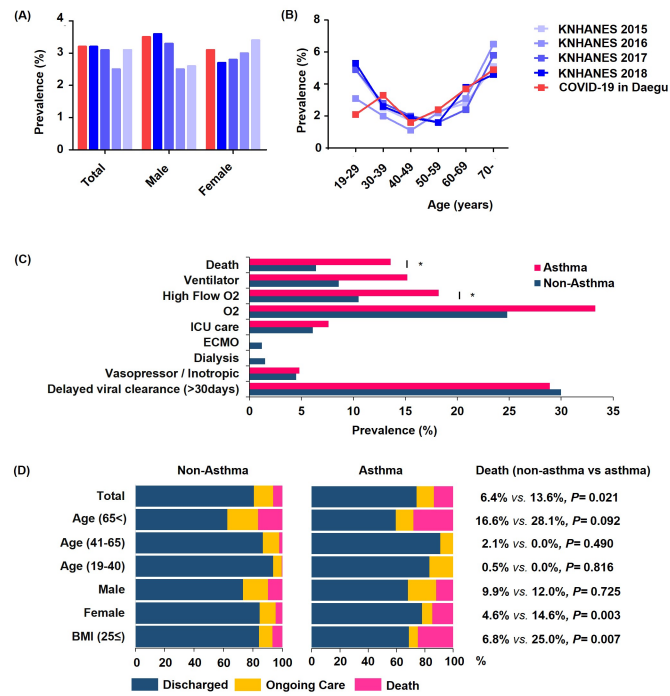
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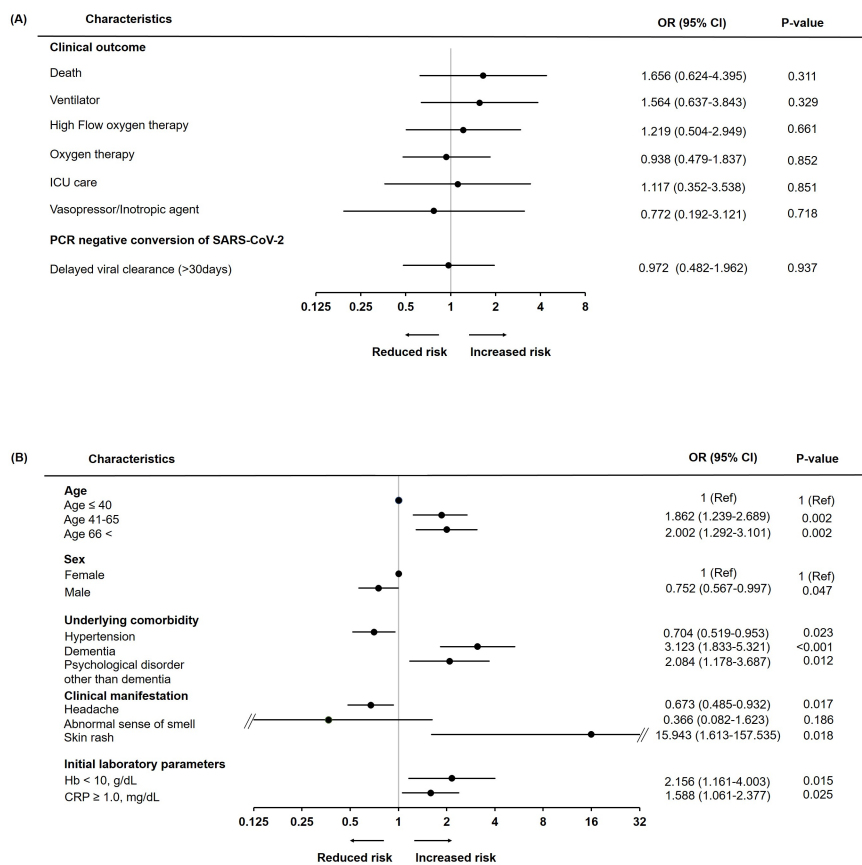
Figure legends

Figure 1. Characterization of asthma in adult COVID-19 inpatients. (A) Prevalence of asthma in COVID-19 and in the KNHANES. (B) Prevalence by age group in COVID-19 and in the KNHANES. (C) Univariate analysis of clinical outcomes according to asthma. (D) Death and ongoing care according to the asthma subgroups. Abbreviations: KNHANES = Korea National Health and Nutrition Examination Survey; COVID-19 = coronavirus disease-2019; ICU = intensive care unit; BMI = body mass index. * $P < 0.05$

Figure 2. (A) Forest plot showing odds ratios (ORs) of asthma for the clinical outcomes. (B) Forest plot showing odds ratios (ORs) for risk factors for delayed viral clearance (>30 days) of total patients (N = 1321; the non-delayed viral clearance group = 906, the delayed viral clearance group = 415). ORs are adjusted for age, sex, body mass index, smoking history, underlying comorbidity, and medication for COVID-19 by multivariate logistic regression model. Abbreviations: PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; Hb = Hemoglobin; CRP = C-reactive protein.



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Table S1. Prevalence of asthma in patients hospitalized with COVID-19 in Daegu and in KNHANES

Age Group (years)	COVID-19 in Daegu city			KNHANES 2018			KNHANES 2017			KNHANES 2016			KNHANES 2015		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total Prevalence	3.2	3.5	3.1	3.2	3.6	2.7	3.1	3.3	2.8	2.5	2.0	3.0	3.1	2.6	3.4
19-29	2.1	3.5	1.1	5.3	7.2	3.1	4.9	6.9	2.6	3.1	2.9	3.2	4.9	4.8	5.0
30-39	3.3	2.1	3.9	2.6	3.3	1.9	2.8	2.7	2.8	2.0	2.1	1.9	2.5	2.4	2.7
40-49	1.6	3.4	1.0	1.9	2.0	1.8	2.0	1.3	2.8	1.1	1.0	1.2	1.7	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	0.2	4.2	2.3	1.3	3.1
60-69	3.7	3.0	4.1	3.8	2.3	5.3	2.4	2.8	2.1	3.1	2.3	3.8	2.8	1.0	4.5
≤70	4.9	3.9	5.5	4.6	4.4	4.8	5.8	5.4	6.1	6.5	5.0	7.5	5.1	4.4	5.5

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

Table S2. 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%)	
≥ 25.0	414 of 1445 (28.7%)	16 of 41 (39.0%)	369 of 1269 (29.1%)	
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				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				

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
Psychological Disorder other than Dementia	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
Time From diagnosis to hospitalization (days)	4.86 ± 5.90	5.02 ± 5.10	5.02 ± 6.07	0.992
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)				
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
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 $\geq$ 40, U/L	381 of 1853 (20.6%)	13 of 64 (20.3%)	316 of 1635 (19.3%)	0.845
Total Bilirubin $\geq$ 1.5, mg/dL	48 of 1773 (2.7%)	0 of 62 (0.0%)	37 of 1565 (2.4%)	0.221
Creatinine $\geq$ 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 $\geq$ 1.0, mg/dL	308 of 831 (37.1%)	10 of 27 (37.0%)	275 of 760 (36.2%)	0.928
Lactate dehydrogenase $\geq$ 445, U/L	685 of 1553 (44.1%)	25 of 52 (48.1%)	610 of 1387 (44.0%)	0.559
Procalcitonin $\geq$ 0.5, ng/mL	49 of 759 (6.5%)	1 of 24 (4.2%)	42 of 625 (6.9%)	0.622
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
Other Antibiotics	1309 of 1864 (70.2%)	52 of 65 (80.0%)	1138 of 1642 (69.3%)	0.066

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

Table S3. 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				
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 S4. Multivariate analysis of outcome according to asthma

Characteristics	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Clinical Outcome				
Death	1.762 (0.813-3.822)	0.151	1.656 (0.624-4.395)	0.311
Ventilator	1.519 (0.726-3.179)	0.267	1.564 (0.637-3.843)	0.329
High Flow oxygen therapy	1.482 (0.740-2.968)	0.267	1.219 (0.504-2.949)	0.661
Oxygen therapy	1.145 (0.638-2.054)	0.650	0.938 (0.479-1.837)	0.852
ICU admission	1.023 (0.393-2.662)	0.963	1.117 (0.352-3.538)	0.851
Vasopressor or Inotropic agents	0.868 (0.260-2.896)	0.868	0.772 (0.192-3.121)	0.718
Real-Time RT-PCR negative conversion of SARS-CoV-2				
Delayed viral clearance (>30 days)	0.963 (0.495-1.876)	0.912	0.972 (0.482-1.962)	0.937

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 S5. Univariate analysis of risk factors for death

Characteristics	Survive (N=2036)	Death (N=164)	
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			
Male	699 of 2036 (34.3%)	86 of 164 (52.4%)	<0.001
Body mass index (kg/m²)			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%)	
≥ 25.0	382 of 1364 (27.9%)	34 of 78 (43.6%)	
Smoking History			<0.001
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%)	
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	82 of 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
Psychological Disorder other than Dementia	121 of 1569 (7.7%)	17 of 135 (12.6%)	0.046
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
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

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

Table S6 Multivariate analysis of risk factors for death

Characteristics	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
≤ 40	Ref (1)			
41 - 65	5.937 (1.393-25.303)	0.016	2.220 (0.498-9.886)	0.295
> 65	52.700 (12.976-214.038)	<0.001	12.448 (2.895-53.519)	0.001
Sex				
Male	1.956 (1.398-2.738)	<0.001	2.040 (1.368-3.044)	<0.001
Body mass index (kg/m²)				
18.5 - 24.9	Ref (1)			
≥ 25.0	2.388 (1.443-3.953)	0.001	2.834 (1.586-5.062)	<0.001
Smoking History				
Current smoker	0.259 (0.061-1.106)	0.068	0.159 (0.033-0.776)	0.023
Ex-smoker	1.865 (0.900-3.864)	0.050	2.184 (0.938-5.087)	0.070
None-smoker	Ref (1)			
Underlying comorbidity				
Chronic obstructive pulmonary disease	1.747 (0.621-4.914)	0.290	1.144 (0.326-4.017)	0.834
Diabetes	2.477 (1.732-3.543)	<0.001	2.484 (1.634-3.775)	<0.001
Hypertension	2.035 (1.419-2.918)	<0.001	1.346 (0.879-2.061)	0.172
Heart Failure	2.967 (1.495-5.890)	0.002	1.863 (0.820-4.229)	0.137

Other Chronic Heart Disease	1.359 (0.783-2.360)	0.276	0.864 (0.436-1.712)	0.675
Chronic Kidney Disease	4.748 (2.187 -10.306)	<0.001	4.003 (1.635-9.802)	0.002
Cancer	2.614 (1.421-4.809)	0.002	3.170 (1.504-6.681)	0.002
Dementia	2.597 (1.705-3.956)	<0.001	2.092 (1.245-3.515)	0.005
Psychological Disorder other than Dementia	1.953 (1.090-3.500)	0.025	2.392 (1.228-4.662)	0.010
Initial Chest X-ray				
Infiltration	2.951 (1.949-4.468)	<0.001	3.283 (2.038-5.288)	<0.001
Initial Laboratory Parameters (Admission date)				
Hemoglobin < 10, g/dL	3.358 (2.104-5.361)	<0.001	2.345 (1.330-4.133)	0.003
Platelet count < 150, x10 ⁹ /L	2.529 (1.743-3.671)	<0.001	2.069 (1.339-3.197)	0.001
White blood cell count 4, x10 ⁹ /L ≤, ≤10, x10 ⁹ /L	Ref (1)			
White blood cell count > 10, x10 ⁹ /L	4.677 (2.960-7.390)	<0.001	3.951 (2.301-6.782)	<0.001
Lymphocyte count < 1.5, x10 ⁹ /L	3.511 (2.138-5.767)	<0.001	3.154 (1.805-5.513)	<0.001
Lymphocyte count < 0.5, x10 ⁹ /L	4.713 (2.786-7.972)	<0.001	5.445 (2.900-10.223)	<0.001
Activated partial thromboplastin time ≥ 35s	4.625 (2.838-7.539)	<0.001	4.238 (2.400-7.484)	<0.001
Prothrombin time international normalized ratio ≤ 1.5	4.547 (1.838-11.246)	0.001	6.324 (2.152-18.582)	0.001
Albumin ≤ 3.0, g/dL	7.563 (4.950-11.554)	<0.001	5.421 (3.298-8.911)	<0.001
Aspartate aminotransferase ≥ 40, U/L	4.840 (3.374-6.942)	<0.001	3.181 (2.165-4.676)	<0.001
Total Bilirubin ≥ 1.5, mg/dL	3.155 (1.451-6.859)	0.004	4.006 (1.627-9.861)	0.003
Creatinine ≥ 1.0, mg/dL	3.268 (2.259-4.728)	<0.001	2.785 (1.813-4.277)	<0.001
High-sensitivity C-reactive protein ≥ 1.0, mg/dL	10620 (4.383-25.736)	<0.001	8.511 (3.418-21.191)	<0.001
Lactate dehydrogenase ≥ 445, U/L	2.483 (1.625-3.794)	<0.001	2.884 (1.773-4.694)	<0.001

Procalcitonin ≥ 0.5 , ng/mL	9.593 (4.754-19.356)	<0.001	10.168 (4.356-23.737)	<0.001
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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.

Table S7. Adjusted ORs for delayed SARS-CoV-2 clearance (all patients)

Delayed viral clearance group (>30 days) N=415 of 1321	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
≤ 40	Ref (1)			
41 - 65	2.060 (1.435-2.957)	<0.001	1.862 (1.239-2.689)	0.002
> 65	2.855 (1.966-4.147)	<0.001	2.002 (1.292-3.101)	0.002
Sex				
Male	0.836 (0.649-1.077)	0.165	0.752 (0.567-0.997)	0.047
Body mass index (kg/m²)				
< 18.5	1.369 (0.660-2.841)	0.399	1.244 (0.567-2.729)	0.586
18.5 - 24.9	Ref (1)			
≥ 25.0	0.847 (0.604-1.187)	0.334	0.933 (0.653-1.333)	0.704
Unknown	0.792 (0.608-1.032)	0.085	0.836 (0.586-1.192)	0.322
Smoking History				
Current smoker	1.086 (0.558-2.114)	0.808	1.162 (0.577-2.342)	0.674
Ex-smoker	1.211 (0.590-2.484)	0.602	1.038 (0.480-2.246)	0.924
None-smoker	Ref (1)			
Unknown	0.790 (0.592-1.055)	0.110	0.912 (0.604-1.377)	0.661
Underlying comorbidity				
Chronic obstructive pulmonary disease	1.865 (0.745-4.669)	0.183	1.218 (0.425-3.493)	0.714

Diabetes	1.246 (0.915-1.698)	0.163	1.319 (0.942-1.847)	0.106
Hypertension	0.803 (0.609-1.060)	0.121	0.704 (0.519-0.953)	0.023
Heart Failure	1.008 (0.333-3.057)	0.988	0.785 (0.241-2.559)	0.688
Other Chronic Heart Disease	1.053 (0.625-1.776)	0.845	1.074 (0.610-1.889)	0.805
Chronic Kidney Disease	0.647 (0.232-1.808)	0.407	0.460 (0.148-1.426)	0.179
Chronic Liver Disease	0.994 (0.399-2.481)	0.990	0.818 (0.306-2.186)	0.688
Cancer	1.431 (0.835-2.455)	0.193	1.235 (0.693-2.200)	0.474
Autoimmune Disease	1.012 (0.258-3.976)	0.986	1.329 (0.305-5.784)	0.705
Dementia	2.935 (1.810-4.758)	<0.001	3.123 (1.833-5.321)	<0.001
Psychological Disorder other than Dementia	2.108 (1.240-3.584)	0.006	2.084 (1.178-3.687)	0.012
Clinical Manifestations, (Admission date)				
Fever	1.097 (0.821-1.467)	0.532	1.015 (0.744-1.386)	0.924
Myalgia	0.950 (0.711-1.270)	0.730	1.010 (0.759-1.425)	0.808
Headache	0.694 (0.513-0.940)	0.018	0.673 (0.485-0.932)	0.017
Rhinorrhea/Runny Nose	1.065 (0.723-1.568)	0.752	1.218 (0.813-1.825)	0.338
Abnormal Sense of Smell	0.316 (0.720-1.383)	0.126	0.366 (0.082-1.623)	0.186
Sore Throat	1.066 (0.754-1.505)	0.718	1.071 (0.745-1.538)	0.712
Cough	1.109 (0.873-1.407)	0.397	1.115 (0.863-1.439)	0.405
Sputum	0.945 (0.737-1.212)	0.654	0.922 (0.707-1.201)	0.546
Chest Discomfort/Chest Pain	0.758 (0.504-1.140)	0.184	0.830 (0.543-1.268)	0.388
Dyspnea	1.194 (0.890-1.604)	0.237	1.000 (0.723-1.384)	1.000

Blood tinged sputum/Hemoptysis	2.220 (0.632-7.801)	0.214	1.595 (0.429-5.927)	0.486
Abdominal Pain	0.846 (0.414-1.729)	0.646	0.815 (0.382-1.739)	0.596
Nausea/Vomiting	0.812 (0.504-1.308)	0.392	0.872 (0.531-1.433)	0.588
Diarrhea	0.879 (0.627-1.233)	0.455	0.812 (0.566-1.164)	0.257
Skin Rash	14.195 (1.730-116.436)	0.013	15.943 (1.613-157.535)	0.018
Initial Chest X-ray				
Infiltration	1.158 (0.906-1.480)	0.241	1.018 (0.770-1.347)	0.900
Initial Laboratory Parameters (Admission date)				
Hemoglobin < 10, g/dL	2.083 (1.199-3.619)	0.009	2.156 (1.161-4.003)	0.015
Platelet count < 150, x10 ⁹ /L	1.298 (0.926-1.820)	0.130	1.094 (0.755-1.584)	0.635
White blood cell count < 4, x10 ⁹ /L	0.781 (0.572-1.067)	0.120	0.730 (0.519-1.028)	0.072
White blood cell count 4, x10 ⁹ /L ≤, ≤10, x10 ⁹ /L	Ref (1)			
White blood cell count > 10, x10 ⁹ /L	1.188 (0.646-2.187)	0.579	1.270 (0.668-2.417)	0.466
Lymphocyte count < 1.5, x10 ⁹ /L	1.038 (0.807-1.336)	0.771	0.936 (0.713-1.228)	0.633
Lymphocyte count < 0.5, x10 ⁹ /L	1.150 (0.575-2.299)	0.693	1.144 (0.535-2.447)	0.729
Activated partial thromboplastin time ≥ 35s	1.363 (0.819-2.270)	0.233	0.935 (0.524-1.669)	0.820
Prothrombin time international normalized ratio ≤ 1.5	1.386 (0.306-6.278)	0.672	1.638 (0.341-7.863)	0.538
Albumin ≤ 3.0, g/dL	1.650 (0.912-2.988)	0.098	1.203 (0.623-2.325)	0.582
Alanine aminotransferase ≥ 40, U/L	1.186 (0.858-1.639)	0.302	1.232 (0.877-1.731)	0.230
Aspartate aminotransferase ≥ 40, U/L	0.927 (0.675-1.273)	0.639	0.872 (0.619-1.228)	0.433
Total Bilirubin ≥ 1.5, mg/dL	0.631 (0.249-1.599)	0.332	0.573 (0.218-1.506)	0.259
Creatinine ≥ 1.0, mg/dL	1.344 (0.968-1.867)	0.078	1.358 (0.947-1.947)	0.096

High-sensitivity C-reactive protein ≥ 1.0 , mg/dL	1.654 (1.133-2.413)	0.009	1.588 (1.061-2.377)	0.025
Lactate dehydrogenase ≥ 445 , U/L	1.211 (0.933-1.572)	0.149	1.260 (0.951-1.669)	0.108
Procalcitonin ≥ 0.5 , ng/mL	0.903 (0.350-2.330)	0.833	0.843 (0.306-2.322)	0.741

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.

Table S8. Adjusted ORs for delayed SARS-CoV-2 clearance among patients with mild COVID-19 (no activity limitation).

Delayed viral clearance group (>30 days) N=281 of 938	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
≤ 40	Ref (1)			
41 - 65	1.997 (1.323-3.015)	0.001	1.681 (1.075-2.628)	0.023
> 65	2.658 (1.719-4.112)	<0.001	1.565 (0.927-2.642)	0.093
Sex				
Male	0.871 (0.641-1.184)	0.378	0.784 (0.554-1.110)	0.170
Underlying comorbidity				
Hypertension	0.890 (0.636-1.247)	0.499	0.890 (0.554-1.183)	0.275
Dementia	3.956 (2.116-7.396)	<0.001	4.217 (2.096-8.484)	<0.001
Psychological Disorder other than Dementia	1.743 (0.878-3.462)	0.112	1.752 (0.827-3.714)	0.143
Clinical Manifestations, (Admission date)				
Headache	0.655 (0.460-0.931)	0.018	0.618 (0.418-0.914)	0.016
Skin Rash	10.088 (1.165-87.359)	0.036	10.362 (1.046-102.660)	0.046
Initial Laboratory Parameters (Admission date)				
Hemoglobin < 10, g/dL	2.877 (1.357-6.101)	0.006	2.939 (1.254-6.888)	0.013
High-sensitivity C-reactive protein ≥ 1.0, mg/dL	1.463 (0.918-2.331)	0.110	1.464 (0.881-2.433)	0.141

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.

Supplement 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 (Kyungpook National University Hospital, Kyungpook National University Chilgok Hospital, Keimyung University Dongsan Hospital, Keimyung University Daegu Dongsan Hospital, Yeungnam University Medical Center, Daegu Catholic University Medical Center, Daegu Patima Hospital, Daegu Medical Center, Daegu Veterans Hospital, Korea Worker's Compensation & Welfare Service Daegu Hospital). 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 nasal swab, 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, psychological disorder other than dementia (schizophrenia (57cases), major

depression (39cases), bipolar disorder (4cases), alcohol abuse (11 cases), mental retardation (7cases), anxiety and panic disorder (20cases).) were identified. Initial physical activity status was classified as grade 1 if it was possible for the patient to live completely independently before the onset of the COVID-19, grade 2 if the patient needed some help in their daily life, and grade 3 if the patient needed fully help. Clinical severities were divided into eight stages: death, multi-organ failure, invasive ventilator, non-invasive ventilator, high flow oxygen therapy, oxygen therapy with nasal cannula, 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. In addition, intensive care unit (ICU) admission and use of vasopressor/inotropic agents, dialysis, and extracorporeal membrane oxygenation (ECMO) were used as additional outcome indicators. The initial symptoms were investigated within 24 hours of the patient's hospitalization. Fever was defined as temperature ≥ 37.5 °C 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, complete blood count, coagulation profile, serum biochemistry tests (including renal and liver function, creatinine, lactate dehydrogenase, high-sensitivity C-reactive protein, and pro-calcitonin) 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.^{1,2} 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.³ 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 $\pm$ 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. In

Model 1, age and gender were corrected, and in Model 2, age, gender, smoking status, BMI, underlying comorbidity (asthma, COPD, diabetes, hypertension, heart failure, chronic cardiac disease, cancer, chronic kidney disease, chronic liver disease, autoimmune disease, dementia and other psychological disorder) and medication (antiretroviral drug, hydroxychloroquine, systemic steroid and azithromycin) were corrected. 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).

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