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Risk factors associated with the need for oxygen therapy in patients with COVID-19

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Abstract

Respiratory failure is the major cause of death in patients with coronavirus disease (COVID-19). Data on factors affecting the need for oxygen therapy in early-stage COVID-19 are limited. This study aimed to evaluate the factors associated with the need for oxygen therapy in patients with COVID-19.

This is a retrospective study of consecutive COVID-19 patients who were hospitalized between February 27 and June 28, 2020, in South Korea. Logistic regression analyses were performed to identify the factors associated with the need for oxygen therapy.

Of the 265 patients included in the study, 26 (9.8%) received oxygen therapy, and 7 of these patients (29.2%) were transferred to a step-up facility, and 3 (11.5%) died. The median age of all patients was 46 years (IQR, 30–60 years), and the median modified early warning score at admission was 1 (IQR, 1–2). In a multivariate logistic regression analysis, being a current smoker (odds ratio [OR] 7.641, 95% confidence interval [CI] 1.686–34.630, $P=.008$), heart rate (OR 1.053, 95% CI 1.010–1.097, $P=.014$), aspartate aminotransferase values (OR 1.049, 95% CI 1.008–1.092, $P=.020$), blood urea nitrogen levels (OR 1.171, 95% CI 1.073–1.278, $P<.001$), and chest radiographic findings (OR 3.173, 95% CI 1.870–5.382, $P<.001$) were associated with oxygen therapy.

In patients with less severe COVID-19, the need for oxygen therapy is affected by smoking and elevated values of aspartate aminotransferase and blood urea nitrogen. Further research is warranted on the risk factors for deterioration in COVID-19 to efficiently allocate medical resources.

Abbreviations: ACE-2 = angiotensin-converting enzyme II, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CI = confidence interval, COVID-19 = coronavirus disease 2019, CT = computed tomography, MEWS = modified early warning score, OR = odds ratio, RT-PCR = reverse transcription-polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: coronavirus disease 2019, oxygen therapy, smoking

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), predominantly involves the respiratory tract. Depending on illness severity, symptoms of COVID-19 range from flu-like symptoms to acute respiratory distress syndrome (ARDS).[1] The main cause of death in patients with COVID-19 is respiratory failure,[2,3] so it is important to identify the patients likely to develop this condition. Recently, Wu et al. reported on the risk factors associated with ARDS development in patients with COVID-19 pneumonia,[4] including older age, neutrophilia, and organ and coagulation dysfunction. However, data on the need for oxygen therapy in patients in early-stage COVID-19 or with mild symptoms are limited.

Approximately 11,000 COVID-19 cases have been diagnosed in Korea since the first case was identified on January 20, 2020.[5] The majority of cases (n = 8225, 76%) occurred in the Daegu and Gyeongbuk regions. Outside of these areas, COVID-19 patients have a relatively low case fatality rate of 0.9% and are hospitalized for isolation to prevent SARS-CoV-2 transmission or treat COVID-19 pneumonia. In this clinical setting, we sought to identify the differences in clinical characteristics between COVID-19 patients requiring oxygen therapy and those who did not.

This study evaluated the factors associated with the need for oxygen therapy in patients with COVID-19.

2. Methods

2.1. Study design and patients

This is a retrospective study of consecutive COVID-19 patients who were hospitalized between February 27 and June 28, 2020, at Seongnam Citizens Medical Center in South Korea. This public

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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medical institution provides nationally designated negative-pressure isolation beds. Patients diagnosed with COVID-19 who living in the Gyeonggi Province were preferentially admitted to the hospital. COVID-19 infection was confirmed in all patients by a reverse transcription-polymerase chain reaction (RT-PCR) test per the World Health Organization interim guidelines.[6] We excluded patients younger than 18 years old and readmitted cases with positive RT-PCR results post-discharge.

The Institutional Review Board of Seongnam Citizens Medical Center approved this study and waived the need for patient consent due to the retrospective nature of the study (IRB No. 1–2020-0003-2-001).

2.2. Data collection

We retrieved data from electronic medical records on the following factors: demographic variables such as age and sex, body mass index, smoking status (current or never smoker), comorbidities, the time interval between symptom onset and hospitalization, symptoms before admission and at admission, vital signs at admission, modified early warning score (MEWS) at admission, hospital length of stay, in-hospital death, laboratory results, and chest X-ray or computed tomography findings. We investigated the medications prescribed during the hospital stay, including lopinavir/ritonavir, hydroxychloroquine, antibiotics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blocker (ARB), and vasopressors. Oxygen therapy included nasal cannula, high-flow nasal cannula, and mechanical ventilation.

Patients were discharged if they had two consecutive negative RT-PCR tests for SARS–CoV2 in nasopharyngeal swabs obtained at least 24 hours apart.[6] Community treatment centers were used to isolate patients without severe symptoms who did not require advanced medical resources.[7] Patients eligible for admission to community treatment centers were transferred within one week.

2.3. Statistical analysis

Categorical variables are presented as numbers (%) and compared using Pearson's chi-square test or Fisher exact test. Continuous variables are expressed as medians (interquartile range) and compared by Student t-test or the Mann-Whitney U test. Univariate and multivariate logistic regression analyses were performed using the forward selection method to identify the factors associated with oxygen therapy. Variables with P-values $< .1$ in univariate analyses and clinical parameters were included in the multivariate logistic regression model, and model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test. The variables entered into the model included age, current smoker, presence of a comorbidity, presence of two or more comorbidities, hypertension, diabetes mellitus, end-stage renal disease on hemodialysis, malignancy, presence of symptoms at admission, heart rate, body temperature, MEWS, hemoglobin, lymphocytes, platelets, total protein, serum albumin, aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, serum sodium, C-reactive protein, ACEi/ARB, and chest radiographic findings. The contribution of each potential risk factor was reported as an odds ratio (OR) and 95% confidence interval (CI). A P-value $< .05$ indicated statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM Corporation, Armonk, NY). We computed the sample size through the 'WebPower' package in the R program.[8] A sample size of 142 patients ensures that a two-sided test with alpha = 0.05 has 80% power when chest radiographic findings are considered as independent variables in the logistic regression model.

3. Results

During the study period, 268 patients (≥ 18 years old) with COVID-19 were admitted to the hospital. Among the 265 patients included in the analysis, 26(9.8%) received oxygen therapy (Fig. 1). Of these, seven (29.2%) were transferred to a

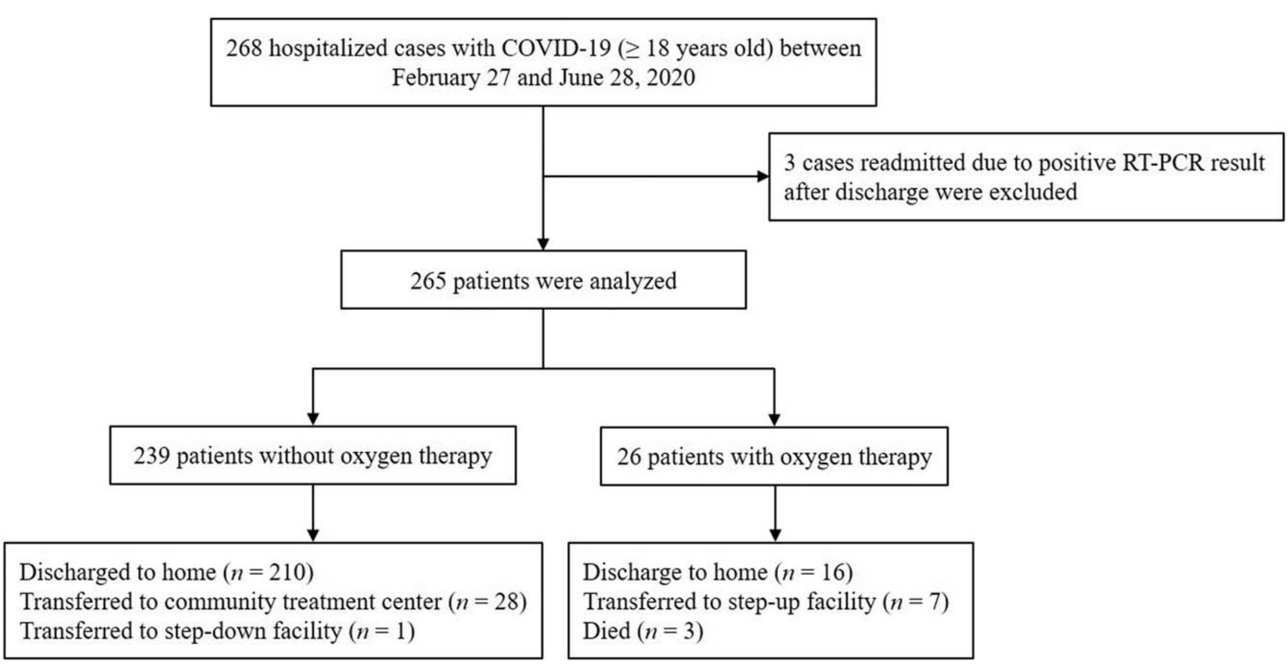

Figure 1. Flow chart of patients with COVID-19.

step-up facility and three (11.5%) died. The 239 patients who did not receive oxygen therapy were discharged home or transferred to a community treatment center.

Baseline patient characteristics are shown in Table 1. The median patient age was 46 years (IQR, 30–60 years), 70 patients (26.4%) were over the age of 60, 27 patients (10.2%) were current smokers, and 81 (30.6%) had comorbidities. At the time of admission, 203 patients (76.6%) had symptoms such as cough (24.9%) and fever (11.7%). The median MEWS at admission was 1 (IQR, 1–2), 46 patients (17.4%) had bilateral pneumonia, and 20 (7.5%) had ground-glass opacity (Table 2). Lopinavir/ritonavir was prescribed for six patients (2.3%) and hydroxychloroquine was prescribed for 79 patients (29.8%). Antibiotics were prescribed to 35 patients (13.4%) and mechanical ventilation was performed in three patients (1.1%).

These clinical variables were compared according to the need for oxygen therapy (Table 3). Patients who received oxygen therapy were older (median 65 years [IQR, 58–70] vs. 42 years [IQR, 29–57], $P<.001$), current smokers (18.5% vs 9.2%, $P=.161$), and more likely to have comorbidities (50.0% vs 28.5%, $P=.161$). There were no significant differences in symptoms or MEWS at admission between patients who received oxygen therapy and those who did not. Patients who received oxygen therapy had higher AST values (32 U/L [IQR, 23–43] vs. 22 U/L [IQR, 18–26], $P<.001$), BUN (17.8 mg/dL [IQR, 11.9–22.5] vs. 11.6 mg/dL [IQR, 9.4–14.2], $P<.001$), and C-reactive protein (2.20 mg/dL [IQR, 0.57–5.20] vs. 0.23 mg/dL [IQR, 0.07–0.59], $P<.001$) levels. They also had lower lymphocyte values (0.9×10^9/L [IQR, 0.7–1.3] vs 1.4×10^9/L [IQR, 1.0–1.8], $P<.001$). Patients who received oxygen therapy were more likely

Table 1

Baseline characteristics of patients with COVID-19.

Variable	Total ($n=265$)
Age (yr), median (IQR)	46 (30–60)
Age range (yr), *n* (%)	
≤39	117 (44.2)
40–49	31 (11.7)
50–59	47 (17.7)
60–69	49 (18.5)
70–79	16 (6.0)
≥80	5 (1.9)
Male sex, *n* (%)	127 (47.9)
Body mass index (kg/m^2), median (IQR)	24.0 (21.7–26.5)
Current smoker, *n* (%)	27 (10.2)
Comorbidities, *n* (%)	81 (30.6)
Hypertension	55 (20.8)
Diabetes mellitus	18 (6.8)
Coronary artery disease	5 (1.9)
End-stage renal disease on hemodialysis	3 (1.1)
Hepatitis B	3 (1.1)
Bronchial asthma	4 (1.5)
Hypothyroidism	4 (1.5)
Parkinson's disease	3 (1.1)
Cerebrovascular accident	4 (1.5)
Malignancy	6 (2.3)
Rheumatoid arthritis	1 (0.4)
Human immunodeficiency	2 (0.8)
Two or more comorbidities, *n* (%)	20 (7.5)
Time interval (days) between symptom onset and hospitalization, median (IQR)	2 (1–5)
Symptoms before admission, *n* (%)	203 (76.6)
Symptoms at admission, *n* (%)	81 (59.1)
Cough	66 (24.9)
Fever or chills	31 (11.7)
Sore throat	39 (14.7)
Rhinorrhea	18 (6.8)
Sputum	22 (8.3)
Ageusia or anosmia	21 (7.9)
Myalgia	32 (12.1)
Dyspnea	6 (2.3)
Miscellaneous*	11 (4.2)
Vital signs at admission, median (IQR)	
Systolic blood pressure (mmHg)	127 (116–139)
Diastolic blood pressure (mmHg)	83 (76–89)
Heart rate (beats per minute)	87 (77–96)
Body temperature (°C)	36.5 (36.1–36.9)
Respiratory rate (beats per minute)	18 (18–20)
Oxygen saturation (%)	97 (96–98)
MEWS at admission, median (IQR)	1 (1–2)
1–3, *n* (%)	254 (95.8)
4–5, *n* (%)	11 (4.2)
Length of stay (days), median (IQR)	18 (12–25)
Death, *n* (%)	3 (1.1)

Data are expressed as median (IQR) or number (%) as appropriate. IQR = interquartile range, MEWS = modified early warning score.
* Miscellaneous includes headache, chest pain, fatigue, shoulder pain, and diarrhea.

Table 2

Laboratory results and treatment of patients with COVID-19.

Variable	Total ($n=265$)
Laboratory results, median (IQR)	
White blood cells ($\times10^9$/L)	5.1 (4.2–6.4)
Neutrophils ($\times10^9$/L)	3.2 (2.4–4.2)
Lymphocytes ($\times10^9$/L)	1.3 (1.0–1.8)
Hemoglobin (g/dL)	14.1 (13.2–15.3)
Platelets ($\times10^6$/L)	218 (184–271)
Total protein (g/dL)	7.1 (6.8–7.5)
Albumin (g/dL)	4.6 (4.3–4.8)
Total bilirubin (mg/dL)	0.42 (0.30–0.61)
Aspartate aminotransferase (U/L)	22 (18–28)
Alanine aminotransferase (U/L)	19 (14–30)
Blood urea nitrogen (mg/dL)	11.8 (9.6–15.2)
Serum creatinine (mg/dL)	0.79 (0.64–0.91)
Serum sodium (mmol/L)	139 (137–140)
Serum potassium (mmol/L)	4.1 (3.9–4.3)
Serum chloride (mmol/L)	103 (100–104)
C-reactive protein (mg/dL)	0.27 (0.08–0.76)
Prothrombin time (INR)	1.04 (0.99–1.08)
Activated partial thromboplastin time (s)	28.1 (26.4–30.2)
Chest radiographic findings, *n* (%)	
Normal	151 (57.0)
Unilateral pneumonia	48 (18.1)
Bilateral pneumonia	46 (17.4)
Multiple mottling and ground-glass opacity	20 (7.5)
Treatment, *n* (%)	
Lopinavir/ritonavir	6 (2.3)
Hydroxychloroquine	79 (29.8)
Antibiotics	35 (13.4)
ACEi/ARB	45 (17.0)
Vasopressors	3 (1.1)
Oxygen therapy, *n* (%)	26 (9.8)
Nasal cannula	12 (4.5)
High-flow nasal cannula or facial mask	9 (3.4)
Mechanical ventilation	3 (1.1)

Data are expressed as median (IQR) or number (%) as appropriate. ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blocker, CT = computed tomography, INR = international normalized ratio, IQR = interquartile range.

Table 3

Comparison of patients with COVID-19 according to the need for oxygen therapy.

Variable	Oxygen therapy (n=26)	No oxygen therapy (n=239)	P-value
Age (yr), median (IQR)	65 (58–70)	42 (29–57)	<.001
Male sex, n (%)	17 (65.4)	110 (46.0)	.061
Body mass index (kg/m^2), median (IQR)	25.3 (23.7–27.2)	23.5 (21.6–26.5)	.036
Current smoker, n (%)	5 (18.5)	22 (9.2)	.161
Comorbidities, n (%)	13 (50.0)	68 (28.5)	.024
Hypertension	11 (42.3)	44 (18.4)	.004
Diabetes mellitus	5 (19.2)	13 (5.4)	.022
Coronary artery disease	0 (0.0)	5 (2.1)	1.000
End-stage renal disease on hemodialysis	2 (7.7)	1 (0.4)	.026
Malignancy	2 (7.7)	4 (1.7)	.109
Two or more comorbidities, n (%)	6 (23.1)	14 (5.9)	.007
Time interval (days) between symptom onset and hospitalization, median (IQR)	1 (0–5)	3 (1–6)	.096
Symptoms at admission, n (%)	19 (73.1)	184 (77.0)	.631
Vital signs at admission, median (IQR)			
Systolic blood pressure (mmHg)	128 (118–139)	127 (115–139)	.980
Diastolic blood pressure (mmHg)	78 (72–88)	84 (77–89)	.035
Heart rate (beats per minute)	92 (82–99)	86 (77–96)	.044
Body temperature (°C)	36.6 (36.3–37.3)	36.5 (36.1–36.9)	.019
Respiratory rate (beats per minute)	20 (18–20)	18 (18–20)	.277
Oxygen saturation (%)	96.5 (95–98)	98 (97–99)	.011
MEWS at admission, median (IQR)	1 (1–2)	1 (1–2)	.250
Length of stay (days), median (IQR)	17 (10–21)	18 (12–26)	.118
Laboratory results, median (IQR)			
White blood cells ($\times 10^9$/L)	5.0 (4.1–6.4)	5.1 (4.2–6.4)	.530
Neutrophils ($\times 10^9$/L)	3.4 (2.5–4.6)	3.1 (2.4–4.1)	.367
Lymphocytes ($\times 10^9$/L)	0.9 (0.7–1.3)	1.4 (1.0–1.8)	<.001
Hemoglobin (g/dL)	13.8 (11.9–15.1)	14.2 (13.2–15.3)	.159
Platelets ($\times 10^9$/L)	180 (134–227)	221 (189–277)	<.001
Total protein (g/dL)	7.0 (6.0–7.3)	7.1 (6.8–7.5)	.022
Albumin (g/dL)	4.4 (3.7–4.6)	4.6 (4.4–4.8)	<.001
Total bilirubin(mg/dL)	0.46 (0.33–0.54)	0.42 (0.30–0.62)	.875
Aspartate aminotransferase (U/L)	32 (23–43)	22 (18–26)	<.001
Alanine aminotransferase (U/L)	23 (16–42)	19 (14–29)	.250
Blood urea nitrogen (mg/dL)	17.8 (11.9–22.5)	11.6 (9.4–14.2)	<.001
Serum creatinine (mg/dL)	0.90 (0.77–1.26)	0.78 (0.63–0.90)	<.001
Serum sodium (mmol/L)	137 (134–138)	139 (137–141)	<.001
Serum potassium (mmol/L)	4.1 (3.8–4.4)	4.1 (3.9–4.3)	.665
Serum chloride (mmol/L)	100 (98–101)	103 (101–104)	<.001
C-reactive protein (mg/dL)	2.20 (0.57–5.20)	0.23 (0.07–0.59)	<.001
Prothrombin time (INR)	1.06 (1.01–1.11)	1.04 (0.99–1.07)	.042
Chest radiographic findings, n (%)			<.001
Normal	3 (11.5)	148 (61.9)	
Unilateral pneumonia	2 (7.7)	46 (19.2)	
Bilateral pneumonia	13 (50.0)	33 (13.8)	
Multiple mottling and ground-glass opacity	8 (30.8)	12 (5.0)	
Treatment, n (%)			
Lopinavir/ritonavir	2 (7.7)	4 (1.7)	.109
Hydroxychloroquine	12 (46.2)	67 (28.0)	.049
Antibiotics	21 (84.0)	14 (5.9)	<.001
ACEi/ARB	9 (34.6)	36 (15.1)	.023
Vasopressors	3 (12.0)	0 (0.0)	.001

Data are expressed as median (IQR) or number (%) as appropriate. ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blocker, CT = computed tomography, INR = international normalized ratio, IQR = interquartile range, MEWS = modified early warning score.

to have bilateral pneumonia or multiple ground-glass opacities on radiographs.

Tables 4 and 5 show the factors associated with oxygen therapy. Univariate logistic regression demonstrated that age, comorbidities, hypertension, diabetes mellitus, end-stage renal disease on hemodialysis, body temperature, lymphocytes, platelets, total protein, albumin, AST, BUN, serum creatinine, serum sodium, C-reactive protein, ACEi/ARB, and chest radiographic findings were significantly associated with oxygen therapy (Table 4). In the multivariate logistic regression analyses, current smoker (odds ratio [OR] 7.641, 95% confidence interval [CI] 1.686–34.630, P=.008), heart rate (OR 1.053, 95% CI 1.010–1.097, P=.014), AST (OR 1.049, 95% CI 1.008–1.092, P=.020), BUN (OR 1.171, 95% CI 1.073–1.278, P<.001), and chest radiographic findings (OR 3.173, 95% CI 1.870–5.382, P<.001) were associated with oxygen therapy (Table 5). The

Table 4

Univariate logistic regression for oxygen therapy in patients with COVID-19.

Variable	Univariate analysis OR (95% CI)	*P*-value
Age (yr)	1.078 (1.045–1.113)	<.001
Male sex, *n* (%)	2.215 (0.950–5.167)	.066
Body mass index (kg/m^2)	1.072 (0.975–1.179)	.148
Current smoker, *n* (%)	2.348 (0.806–6.842)	.118
Comorbidities, *n* (%)	2.515 (1.109–5.701)	.027
Hypertension	3.250 (1.397–7.558)	.006
Diabetes mellitus	4.139 (1.345–12.739)	.013
End-stage renal disease on hemodialysis	19.833 (1.734–226.840)	.016
Malignancy	4.896 (0.852–28.133)	.075
Two or more comorbidities, *n* (%)	4.821 (1.670–13.918)	.004
Time interval (days) between symptom onset and hospitalization	0.853 (0.704–1.033)	.104
Symptoms at admission, *n* (%)	0.811 (0.324–2.031)	.655
Systolic blood pressure (mmHg)	1.000 (0.979–1.021)	.995
Diastolic blood pressure (mmHg)	0.946 (0.907–0.987)	.011
Heart rate (beats per minute)	1.028 (0.999–1.057)	.057
Body temperature (°C)	2.715 (1.327–5.555)	.006
Respiratory rate (beats per minute)	1.209 (0.937–1.558)	.144
MEWS at admission	1.510 (1.000–2.281)	.050
Laboratory results		
White blood cells ($\times 10^9$/L)	0.958 (0.776–1.182)	.687
Neutrophils ($\times 10^9$/L)	1.104 (0.896–1.360)	.353
Lymphocytes ($\times 10^9$/L)	0.131 (0.044–0.389)	<.001
Hemoglobin (g/dL)	0.804 (0.646–1.002)	.052
Platelets ($\times 10^9$/L)	0.985 (0.977–0.993)	<.001
Total protein (g/dL)	0.232 (0.110–0.487)	<.001
Albumin (g/dL)	0.089 (0.033–0.243)	<.001
Total bilirubin (mg/dL)	0.634 (0.114–3.545)	.604
Aspartate aminotransferase (U/L)	1.051 (1.024–1.079)	<.001
Alanine aminotransferase (U/L)	1.005 (0.991–1.020)	.466
Blood urea nitrogen (mg/dL)	1.160 (1.081–1.244)	<.001
Serum creatinine (mg/dL)	2.095 (1.025–4.283)	.043
Serum sodium (mmol/L)	0.760 (0.661–0.874)	<.001
Serum potassium (mmol/L)	1.027 (0.302–3.498)	.966
Serum chloride (mmol/L)	0.979 (0.943–1.016)	.253
C-reactive protein (mg/dL)	1.420 (1.212–1.663)	<.001
Prothrombin time (INR)	3.161 (0.341–29.279)	.311
ACEi/ARB	2.985 (1.235–7.214)	.015
Chest radiographic findings	3.534 (2.269–5.504)	<.001

ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blocker, CI = confidence interval, CT = computed tomography, INR = international normalized ratio, MEWS = modified early warning score, OR = odds ratio.

equation for the regression of the need for oxygen therapy is: $Y = -13.664 + (2.0335 \times \text{smoking}) + (0.0516 \times \text{heart rate}) + (0.0478 \times \text{AST}) + (1.1547 \times \text{BUN}) + (0.1579 \times \text{chest radiographic findings})$. The model had a good fit to the data (Hosmer–Lemeshow $P = .624$). We achieved a statistical power of 97% for the study population (n = 265). The computation is based on Demidenko's formula (2007).[9]

4. Discussion

In this study, we identified the clinical characteristics and risk factors associated with oxygen therapy in patients with COVID-19. There were significant differences in age, body mass index, comorbidities, lymphocytes, total protein, albumin, AST, BUN, serum creatinine, serum sodium, C-reactive protein, antibiotics, ACEi/ARB, and chest radiographic findings between patients treated with oxygen therapy and those who were not. The risk factors for receiving oxygen therapy were current smoking status and elevated heart rate, AST and BUN, and abnormal chest radiographic findings. We suggest supplemental oxygen therapy, even if the oxygen saturation is > 90%, in patients with any of these risk factors as they will invariably require oxygen. This study, which was conducted in a region with a low case fatality rate, identified the factors associated with the need for oxygen therapy in COVID-19 patients.

Table 5

Multivariable logistic regression for oxygen therapy in patients with COVID-19.

Variable	Multivariate analysis OR (95% CI)*	*P*-value
Current smoker	7.641 (1.686–34.630)	.008
Heart rate	1.053 (1.010–1.097)	.014
Aspartate aminotransferase	1.049 (1.008–1.092)	.020
Chest radiographic findings	3.173 (1.870–5.382)	<.001
Blood urea nitrogen	1.171 (1.073–1.278)	<.001

CI = confidence interval, OR = odds ratio.

* The clinical variables entered into the model were age, current smoker, presence of one comorbidity, the presence of two or more comorbidities, hypertension, diabetes mellitus, end-stage renal disease on hemodialysis, malignancy, presence of symptoms at admission, heart rate, body temperature, modified early warning score (MEWS), hemoglobin, lymphocytes, platelets, total protein, serum albumin, aspartate aminotransferase, blood urea nitrogen, creatinine, serum sodium, C-reactive protein, angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker (ACEi/ARB), and chest radiographic findings.

In our study population, 9.7% of patients were treated with oxygen therapy, and 1.1% died. This low mortality is likely because most confirmed COVID-19 patients were hospitalized in Korea in the early stages of the pandemic. The need for oxygen therapy can be an important outcome in hospitalized patients with less severe COVID-19 that was mostly affected by smoking status and chest radiographic findings. Particularly in early disease stages, the chest radiographs of patients with COVID-19 pneumonia may be normal.[10,11] Over time, the chest radiographs of severe cases show dense consolidation or extension of the peripheral ground glass changes.[12] Therefore, the initial chest radiographic finding is a crucial indicator of disease severity and the need for oxygen therapy.

In the present study population, smoking considerably increased the risk of receiving oxygen therapy. Leung et al. reported that angiotensin-converting enzyme II (ACE-2) expression was significantly increased in the bronchial epithelial cells of smokers.[13]Current smokers had higher ACE-2 expression compared with those who have never smoked (2.77 ± 0.91 vs 1.78 ± 0.39, $P = .024$). SARS-CoV-2 uses the ACE-2 receptor for cell entry.[14] In a cross-sectional multicenter study, Yu et al reported that smoking was an independent risk factor associated with pneumonia exacerbation after treatment in patients with COVID-19.[15] According to a systematic review of the association between smoking and COVID-19 outcomes, smoking may adversely affect disease progression and outcome.[16] A recent meta-analysis showed that current smokers had a twofold increased risk of developing severe COVID-19,[17] defined as requiring intensive care or mechanical ventilation or resulting in death. However, the impact of smoking on COVID-19 progression remains inconclusive. When studies with major heterogeneity sources were excluded from a meta-analysis, the effect of smoking on the COVID-19 severity became nonsignificant (OR 1.55, 95% CI 0.83–2.87).[18] Epidemiologic data on patients with COVID-19 included a low prevalence of smokers, and there was no significant association between current smoking and severe COVID-19.[19,20] Nonetheless, our study suggests that smoking may affect the need for oxygen therapy in patients with COVID-19. Further research is warranted to elucidate this association.

Consistent with previous studies on ARDS development or disease severity, older age is a risk factor for requiring oxygen therapy in patients with COVID-19.[4,19] We also observed that several factors, including comorbidities, lymphocyte counts, and organ and coagulation dysfunction, were associated with the need for oxygen therapy. In a recent meta-analysis of the association between liver injury and COVID-19, serum levels of AST, alanine aminotransferase (ALT), and total bilirubin were significantly increased in patients with severe COVID-19.[21] This implies that liver injury could be associated with disease severity. In this study of patients with less severe COVID-19, serum levels of AST other than ALT and total bilirubin were significantly higher in patients receiving oxygen therapy. This suggests that the serum AST may be associated with early exacerbation in patients with COVID-19.

There is no evidence that any pharmacologic treatment had survival benefits. Hydroxychloroquine, which has anti-inflammatory and antiviral effects, is expected to act against SARS-CoV-2.[22] However, in a recent observational study involving a large number of patients, there was no significant association between the use of hydroxychloroquine and intubation or death (hazard ratio, 1.04; 95% CI 0.82–1.32).[23] There is also concern regarding its adverse effects and lack of proven efficacy for prophylaxis.[24] In this study hydroxychloroquine was possibly administered in more severe cases of COVID-19, but this drug was not associated with oxygen therapy in patients with COVID-19.

The present study has several limitations. It is a retrospective study with a relatively small number of subjects and we could not determine when oxygen therapy was initiated. Although the World Health Organization guidelines recommend maintaining oxygen saturation at 90% or higher,[6] the decision to initiate oxygen therapy was made by the attending physicians. Also, as smoking status was determined by self-reported smoking history, no data concerning past exposure, such as former smoking, time since quitting, or duration and cumulative dose, were available. Although the results of our study should be interpreted cautiously, we suggest that current smoking may be a risk factor for the need for oxygen therapy in COVID-19 patients.

In conclusion, the need for oxygen therapy may be affected by current smoking status, elevated AST and BUN values, and abnormal chest radiographic findings in patients with less severe COVID-19. Hydroxychloroquine was not associated with oxygen therapy. To allocate medical resources efficiently, further studies on the risk factors for deterioration in COVID-19 are required.

Author contributions

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References

[1] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[2] Vincent JL, Taccone FS. Understanding pathways to death in patients with COVID-19. Lancet Respir Med 2020;8:430–2.
[3] Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846–8.
[4] Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020;382:1787–99.
[5] Coronavirus Disease-19, Republic of Korea 2020 [cited 2020 May 8]. Available at: http://ncov.mohw.go.kr/en.
[6] Organization WH. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Published March 13, 2020. [cited 2020 May 7]. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
[7] Park PG, Kim CH, Heo Y, et al. Out-of-hospital cohort treatment of coronavirus disease 2019 patients with mild symptoms in Korea: an experience from a single community treatment center. J Korean Med Sci 2020;35.
[8] Zhang Z, Yuan K-H. Practical Statistical Power Analysis using WebPower and R. Granger, IN: ISDSA Press; 2018.
[9] Demidenko E. Sample size determination for logistic regression revisited. Stat Med 2007;26:3385–97.
[10] Yoon SH, Lee KH, Kim JY, et al. Chest radiographic and CT findings of the 2019 novel coronavirus disease (COVID-19): analysis of nine patients treated in Korea. Korean J Radiol 2020;21:494–500.
[11] Wong HYF, Lam HYS, Fong AH, et al. Frequency and distribution of chest radiographic findings in patients positive for COVID-19. Radiology 2020;296:E72–8.
[12] Cleverley J, Piper J, Jones MM. The role of chest radiography in confirming covid-19 pneumonia. BMJ 2020;370:m2426.
[13] Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 2020;55: in press.
[14] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
[15] Yu T, Cai S, Zheng Z, et al. Association between clinical manifestations and prognosis in patients with COVID-19. Clin Ther 2020;in press.
[16] Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 2020;18:20.
[17] Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of Covid-19: A systemic review and meta-analysis. J Med Virol 2020;92:1915–21. in press.
[18] Guo FR. Smoking links to the severity of Covid-19: an update of a meta-analysis. J Med Virol 2020;92:2304–5. in press.
[19] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[20] Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Intern Med 2020;75:107–8.
[21] Parohan M, Yaghoubi S, Seraj A. Liver injury is associated with severe Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies. Hepatol Res :Official J Japan Soc Hepatol 2020;50:924–35.
[22] Fantini J, Di Scala C, Chahinian H, et al. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents 2020;55:105960.
[23] Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020;382:2411–8.
[24] Khan Z, Karatas Y, Rahman H. Anti COVID-19 drugs: need for more clinical evidence and global action. Adv Ther 2020;37:2575–9.