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...
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
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/m²), 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) |
| Cough | 81 (30.1) |
| Fever or chills | 66 (24.9) |
| Sore throat | 31 (11.7) |
| Rhinorrhea | 39 (14.7) |
| 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) |

| Table 2 |
| --- |
| Laboratory results and treatment of patients with COVID-19. |
| **Variable** | **Total (n=265)** |
| **Laboratory results, median (IQR)** | |
| White blood cells (×10^9/L) | 5.1 (4.2–6.4) |
| Neutrophils (×10^9/L) | 3.2 (2.4–4.2) |
| Lymphocytes (×10^9/L) | 1.3 (1.0–1.8) |
| Hemoglobin (g/dL) | 14.1 (13.2–15.3) |
| Platelets (×10^9/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 (0.99–1.09) |
| 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) |
| Vasoressors | 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. IQR = interquartile range, MEWS = modified early warning score.

* Miscellaneous includes headache, chest pain, fatigue, shoulder pain, and diarrhea.
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] 1.010–53.0, P = .014), heart rate (OR 1.053, 95% CI 1.010–1.097, P = .020), blood urea nitrogen (mg/dL) (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).

### 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/m²), 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 (×10^3/L)                   | 5.0 (4.1–6.4)         | 5.1 (4.2–6.4)            | .530    |
| Neutrophils (×10^3/L)                         | 3.4 (2.5–4.6)         | 3.1 (2.4–4.1)            | .367    |
| Lymphocytes (×10^3/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 (×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 (3.7–4.0)         | 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.
Laboratory results

| Variable                  | Univariate analysis OR (95% CI) | P-value |
|---------------------------|---------------------------------|---------|
| White blood cells (×10^9/L) | 0.958 (0.776–1.182)             | .687    |
| Neutrophils (×10^9/L)     | 1.104 (0.896–1.360)             | .353    |
| Lymphocytes               | 0.131 (0.044–0.389)             | <.001   |
| Hemoglobin (g/dL)         | 0.804 (0.646–1.002)             | .052    |
| Platelets (×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 (2.265–5.504)            | <.001   |

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

| Variable                  | Multivariable analysis OR (95% CI) | P-value |
|---------------------------|-----------------------------------|---------|
| Current smoker            | 7.841 (1.686–34.633)              | .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. A recent meta-analysis showed that current smokers had a twofold increased risk of developing severe COVID-19,[16] 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).[15,18] 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.\cite{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.\cite{8,19} 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.\cite{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.\cite{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 1.02–1.32).\cite{23} There is also concern regarding its adverse effects and lack of proven efficacy for prophylaxis.\cite{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,\cite{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.

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