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Clinical severity of COVID-19 and general characteristics of Koreans

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Research Article

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Abstract

This study aimed to investigate the associations between clinical severity of COVID-19 and general characteristics of the subjects using epidemiological data of 5,601 patients with confirmed COVID-19 in Korea. The subjects of this study were diagnosed with COVID-19 from January 20 to April 30, 2020. The subjects of this study acquired information on patients with confirmed COVID-19 from the Korea Disease Control & Prevention Agency, National Medical Center and the Health Information Manager in hospitals. We found that severity of COVID-19 was greater among patients aged > 60 years, with obesity, clinical symptoms, respiratory diseases, kidney disease, and other diseases (chronic liver disease, rheumatism/autoimmune disease, and dementia). Among the variables, women had reduced clinical severity of COVID-19. Therefore, people with these factors are more susceptible to COVID-19, and they require special attention.

Introduction

The total number of patients with confirmed COVID-19 has been reported to be 43,315,450 (death 1,157,049) worldwide (October 28, 2020) [1]. In Korea, there have been 26,146 (death 461) confirmed cases since the first case on January 20, 2020.

As the spread of COVID-19 continues, it is necessary to identify which characteristics of the subjects increase the clinical severity of COVID-19. People with these factors need more attention regarding COVID-19 exposure. Previous studies have reported that that elderly, men, and those with obesity and underlying diseases have increased clinical severity to COVID-19 [2-5]. However, few studies have investigated these factors in large populations. Yan et al. reported that among 193 subjects confirmed with COVID-19, those with diabetes (as an underlying disease) had 1.53 times higher mortality rate than those without diabetes [4]. Li et al. analyzed data of 182 patients with confirmed COVID-19 and reported a high rate of malnutrition among old patients with COVID-19 [2]. It is believed that the subject's underlying disease and clinical characteristics will directly or indirectly affect the mortality rate or clinical severity of COVID-19. Therefore, this study aimed to investigate the associations between clinical severity of COVID-19 and general characteristics of the subjects using epidemiological data of 5,601 patients with confirmed COVID-19 in Korea.

Results

General characteristics of the population as per clinical severity of COVID-19

Table 2 shows basic characteristics of the population as per clinical severity of COVID-19. The clinical severity of COVID-19 was high among men and men aged > 60 years. Normal Body mass index (BMI) was high among people with mild clinical severity, and those with clinical severity were more likely to be overweight. Clinical severity of COVID-19 was high among people with systolic blood pressure (SBP) ≥ 140, and there was no significant relation with diastolic blood pressure (DBP). Clinical severity of COVID-

19 was directly proportional to the rate of having diabetes, hypertension, heart disease, kidney disease, cancer, and other diseases as underlying diseases. Clinical severity was high among symptomatic people (with symptoms such as fever and cough). Clinical severity and blood parameters (hemoglobin, hematocrit, lymphocyte, platelet, and white blood cell counts) were inversely proportional.

Association between clinical severity of COVID-19 and general characteristics

Table 3 shows associations between clinical severity of COVID-19 and general characteristics of the subjects. According to model 1, which was adjusted for age, sex, BMI, SBP, DBP, symptoms and underlying diseases, women had significantly lower odd ratios (ORs) for moderate (vs. mild) (0.74, 95% Confidence Interval (CI) 0.59–0.93) and lower ORs for severe (vs. mild) (0.44, 95% CI 0.31–0.61) than men. As per model 2, which was adjusted model 1 plus blood parameters, women had significantly low ORs for severe (0.63, 95% CI 0.41–0.96). Considering age, in model 1, subjects aged 30–59 years had significantly higher ORs for moderate (vs. mild) (4.29, 95% CI 2.55, 7.22) and higher ORs for severe (vs. mild) (5.98, 95% CI 1.39, 25.65) than subjects aged < 30 years. Subjects aged ≥ 60 years had significantly higher ORs for moderate (vs. mild) (13.14, 95% CI 7.74, 22.32) and higher ORs for severe (vs. mild) (50.18, 95% CI 12.05, 208.88) than subjects aged < 30 years. In model 2, subjects aged 30–59 years had significantly higher ORs for moderate (vs. mild) (2.60, 95% CI 1.48, 4.59) than subjects aged < 30 years. Subjects aged ≥ 60 years had significantly higher ORs for moderate (vs. mild) (5.84, 95% CI 3.26, 14.75) and higher ORs for severe (vs. mild) (14.75, 95% CI 3.28, 66.22) than subjects aged < 30 years.

In model 1, overweight subjects had significantly lower ORs for severe (vs. mild) (0.55, 95% CI 0.35, 0.87) than subjects with normal BMIs. In model 2, overweight subjects had significantly higher ORs for moderate (vs. mild) (1.43, 95% CI 1.04, 1.97) than subjects with normal weight. Additionally, obese subjects had significantly higher ORs for moderate (vs. mild) (2.15, 95% CI 1.58, 2.92) and higher ORs for severe (vs. mild) (1.78, 95% CI 1.12, 2.83) than normal subjects.

Considering symptoms, in model 1, symptomatic subjects had significantly higher ORs for moderate (vs. mild) (2.52, 95% CI 1.82, 3.50) and higher ORs for severe (vs. mild) (4.75, 95% CI 2.72, 8.32) than asymptomatic subjects. In model 2, symptomatic subjects had significantly higher ORs for moderate (vs. mild) (2.05, 95% CI 1.44, 2.92) and higher ORs for severe (vs. mild) (3.08, 95% CI 1.63, 5.85) than asymptomatic subjects.

Regarding underlying diseases, in model 1, diabetic subjects had significantly higher ORs for moderate (vs. mild) (1.83, 95% CI 1.26, 2.66) than subjects without diabetes. Additionally, subjects with hypertension had significantly higher ORs for moderate (vs. mild) (1.37, 95% CI 1.06, 1.78) and higher ORs for severe (vs. mild) (1.84, 95% CI 1.28, 2.66) than subjects without hypertension. However, after adjusting the blood parameters (model 2), the significance disappeared. In model 1, subjects with respiratory diseases had significantly higher ORs for moderate (vs. mild) (1.76, 95% CI 1.05, 2.95) and higher ORs for severe (vs. mild) (2.20, 95% CI 1.10, 4.38) than subjects without respiratory diseases. In

model 2, subjects with respiratory diseases had significantly higher ORs for moderate (vs. mild) (1.73, 95% CI 1.99, 3.03) than subjects without respiratory diseases. In model 1, subjects with chronic kidney disease had significantly higher ORs for moderate (vs. mild) (3.36, 95% CI 1.47, 7.70) and higher ORs for severe (vs. mild) (6.61, 95% CI 2.67, 16.36) than subjects without respiratory diseases. In model 2, subjects with chronic kidney disease had significantly higher ORs for moderate (vs. mild) (1.70, 95% CI 1.65, 4.42) and higher ORs for severe (vs. mild) (2.93, 95% CI 1.08, 7.94) than subjects without respiratory diseases. In model 1, subjects with other diseases had significantly higher ORs for moderate (vs. mild) (2.13, 95% CI 1.43, 3.18) and higher ORs for severe (vs. mild) (3.68, 95% CI 2.30, 5.86) than subjects without other diseases. In model 2, subjects with other diseases had significantly higher ORs for moderate (vs. mild) (2.14, 95% CI 1.39, 3.30) and higher ORs for severe (vs. mild) (2.67, 95% CI 1.53, 4.67) than subjects without other diseases.

Discussion

In our study, the severity of COVID-19 was higher among patients aged ≥ 60 years, with obesity, any clinical symptoms, respiratory diseases, kidney disease, and other diseases (chronic liver disease, rheumatism/autoimmune disease, dementia). Among the variables, women had reduced clinical severity of COVID-19.

While COVID-19 continues to persist, it is important to understand which factors affect its clinical severity. Previous studies have reported that men have higher clinical severity of COVID-19 than women [7-10]. In this study, similar results were obtained in Koreans. The reason for higher clinical severity of COVID-19 in men than in women is due to greater angiotensin converting enzyme 2 (ACE2) concentrations in men than in women [9]. The androgen receptor genetic variant [10] in men is also a cause of this. Other studies have reported that women have more active immune responses than men [8].

Additionally, obesity [5, 11] has been suggested as a risk factor for COVID-19. This may be due to impaired immune function caused by changes in cytokine responses [12] and high expression of ACE2 receptors in obese individuals [13]. ACE2 receptors have a major role in the entry of COVID-19 virus into target cells [14]. In our study, there was increased clinical severity of COVID-19 with obesity.

In general, underlying diseases are more prevalent in the elderly [15], and chronic underlying diseases reduce immune functions and increase inflammation, making the body more vulnerable to viral infections [16]. Several researchers have studied and reported underlying diseases affecting clinical severity and mortality rate of COVID-19 [7, 17-19]. Ji et al. found that several comorbidities including diabetes, hypertension, respiratory disease, chronic kidney disease, and end-stage renal diseases, are associated with the risk of COVID-19 [17]. Kim et al. reported that hemorrhagic conditions, blood-related diseases, heart failure, kidney disease, cancer, myocardial infarction, diabetes, and ischemic heart disease increase the mortality rate of patients with COVID-19 [18]. Considering chronic diseases, many studies have reported associations between diabetes and COVID-19 [20, 21]. In Korea, Kim et al. also reported diabetes as a risk factor for mortality and severity of COVID-19 [19].

Additionally, other studies have reported that blood parameters could also affect the clinical severity of COVID-19 [22-24]. Fu et al. found lower lymphocyte counts and higher leukocyte counts among severely affected patients with COVID-19 than among mildly/moderately affected patients with COVID-19 [22]. Despite conducting a preliminary study with a small number of people, Wang et al. reported significantly lower hemoglobin, hematocrit, and lymphocyte parameters in severely affected patients with COVID-19 than in those who were moderately affected. However, white blood cell counts were significantly higher among the former than among the latter [24]. The same result was found in our study. A perspective study reported that both the low lymphocyte count and C-reactive protein (CRP), d-dimer, and Interleukin-6 (IL-6) concentrations could be used as predictors for the clinical severity of COVID-19 [23]. In our study, even after adjusting for blood parameters, variables such as female sex, age 60 ≥ years, obesity, clinical symptoms, respiratory diseases, chronic kidney disease, and other diseases remained factors that influenced the clinical severity of COVID-19.

However, this study had a few limitations. First, the concentrations of CRP, D-dimers, and IL-6 (among the blood indices), suggested to be associated with the clinical severity of COVID-19, could not be corrected because they did not correspond to the disclosure items as per the Korea Disease Control & Prevention Agency (KCDPA). Second, there were only few cases of diseases such as chronic liver disease, rheumatism, and dementia, in our study. We grouped these into other diseases and analyzed them. Stratified analysis will be needed in future to determine the effect of each disease on clinical severity of COVID-19.

This study also has its strengths. Compared with previous studies, this study comprises a large patient cohort. We used data of > 5,000 patients with confirmed COVID-19 and analyzed them by correcting blood indicators that were not corrected in other studies.

In our study, we not only considered patients with underlying diseases such as hypertension, diabetes, and heart disease (found in previous studies), but also included those with underlying diseases such as chronic liver disease, rheumatism/autoimmune disease, and dementia. This increased the ORs value of clinical severity of COVID-19. To overcome COVID-19, minimizing exposure to the COVID-19 virus and maintaining good nutrition are necessary. It has recently been reported that nutrients such as selenium [25], copper [26], natural product [27], and vitamin D [28], might help in overcoming COVID-19.

In conclusion, factors, such as male sex, age > 60 years, obesity, clinical symptoms, respiratory diseases, chronic kidney disease, and other diseases increase the susceptibility to COVID-19; therefore, special attention will be required for these factors. Maintaining good nutritional status by eating foods that help in boosting the immunity may help overcome COVID-19.

Methods

The subjects of this study were diagnosed with COVID-19 from January 20 to April 30, 2020. This study passed the Institutional Review Board deliberation at Eulji University (number: EUN20-038), and the analysis was conducted according to the clinical epidemiological information remote access manual for patients with confirmed COVID-19 presented by the KCDPA. The subjects of this study acquired information on patients with confirmed COVID-19 from the KCDPA, National Medical Center and the Health Information Manager in hospitals. The patients with confirmed COVID-19 patients were anonymous, and the disclosure items are shown in Table 1. We received information on 5,601 patients with confirmed COVID-19 whose quarantine periods ended (on April 30, 2020). Of these, data of 4,023 individuals were analyzed. Subjects with no data on BMI (n = 1,201), SBP, DBP, diabetes, hypertension (n = 33), and other disease statuses (n = 344) were excluded.

Confirmed case

These were cases confirmed with infection according to the diagnostic criteria, irrespective of clinical manifestations (diagnostic tests: COVID-19 real-time RT-PCR, virus isolation) [6].

Other variable classification

Considering age, the variables grouped in units of 10 years were reclassified into three groups: 0–29 years, 30–59 years, and > 60 years. BMI was reclassified as 22.9 kg/m^2 (normal), 23–24.9 kg/m^2 (overweight), and ≥25 kg/m^2 (obese). SBP was classified as < 120 mmHg, 120–139 mmHg, and > 140 mmHg, and DBP was classified as < 80 mmHg, 80–89 mmHg, and > 90 mmHg. The subjects were symptomatic if they had any of the following symptoms; history of fever (≥37.5°C), cough, sputum, sore throat, runny nose/rhinorrhea, myalgia, malaise, dyspnea, headache, altered consciousness/ confusion, vomiting/nausea, and diarrhea.

Classification of clinical severity

We reclassified the clinical severity into three stages. It was previously divided into eight stages (Figure 1). Patients at stages 1 and 2 who did not require oxygen therapy were reclassified as mild, those at stage 3.4 requiring oxygen therapy as moderate, and those at ≥ stage 5 requiring ventilation as severe.

Classification of underlying disease

We grouped and reclassified similar types of diseases in the disease section of the KCDPA. Asthma and chronic obstructive pulmonary disease were classified as respiratory diseases. Other diseases such as

chronic liver disease, rheumatism/autoimmune disease, and dementia, were also classified.

Statistical analyses

Differences in the clinical severity of COVID-19 were determined using ANOVA for continuous variables and chi-square test for categorical variables ($p < 0.05$). Statistical differences were tested using multiple logistic regression analysis, adjusting for variables of each model. Adjusted model 1 included variables such as age, sex, BMI, SBP, DBP, symptoms, and underlying diseases. The multivariate model included variables in model 2 plus blood parameters (hemoglobin, hematocrit, lymphocyte, platelet, and white blood cell).

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Declarations

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Author Contribution Statement

JHK designed and created the study concept; JHK acquired the data, performed the statistical analysis and wrote the paper; JKP contributed critical advice and revisions of the manuscript; JKP supervised the study; and both authors had full access to the study data and read and approved the final manuscript.

Additional Information

Competing Interests: The authors declare no competing interests.

Tables

Table 1. Information on a patient with COVID-19 provided by the KCDPA

Public item	Detailed variable
1. Basic data for confirmed cases	Age group, sex, death/release from quarantine, period of death/release from quarantine, pregnancy status
2. Body index	Body mass index
3. Initial examination	SBP, DBP, heart rate, temperature
4. Clinical symptoms at hospitalization	History of fever (≥ 37.5°C), cough, sputum production, sore throat, runny nose/rhinorrhea, muscle ache/myalgia, fatigue/malaise, shortness of breath/dyspnea, headache, altered consciousness/ confusion, vomiting/nausea, diarrhea
5. Underlying disease	Diabetes, hypertension, chronic heart diseases, asthma, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, rheumatism/autoimmune disease, dementia, etc.
6. Hospital room and clinical severity	Clinical severity (1. No trouble in daily life, 2. Interfering with daily life, but no need for oxygen therapy, 3. Oxygen therapy via nose, 4. Oxygen mask, 5. Non-invasive ventilator, 6. Invasive ventilator, 7. Multi-organ injury/ECMO, 8. Death)
7. General blood parameter	Hemoglobin, hematocrit, lymphocyte, platelets, whole blood cell.

Table 2. Basic characteristics of the population as per clinical severity of COVID-19.

Total	Clinical severity of COVID-19			
n = 4,023	Mild (n = 3,455)	Moderate (n = 388)	Severe (n = 180)	*p*
Sex %, (n)				0.0001
Men	41.33 (1428)	45.10 (175)	56.67 (102)	
Women	58.67 (2027)	54.90 (213)	43.33 (78)	
Age % (n)				< 0.0001
0–29 y	29.49 (1019)	4.38 (17)	1.11 (2)	
30–59 y	46.71 (1614)	33.76 (131)	13.33 (24)	
≥ 60 y	23.79 (822)	61.86 (240)	85.56 (154)	
BMI %, (n)				< 0.0001
Normal	48.97 (1692)	36.08 (140)	46.67 (84)	
Overweight	23.59 (815)	27.06 (105)	17.78 (32)	
Obesity	27.44 (948)	36.86 (143)	35.56 (64)	
SBP %, (n)				< 0.0001
< 120	25.33 (875)	20.88 (81)	22.22 (40)	
120–139	42.32 (1462)	42.01 (163)	29.44 (53)	
≥ 140	32.36 (1118)	37.11 (144)	48.33 (87)	
DBP %, (n)				0.2784
< 80	37.42 (1293)	41.24 (160)	43.89 (79)	
80–89	34.59 (1195)	31.70 (123)	30.00 (54)	
≥ 90	27.99 (967)	27.06 (105)	26.11 (47)	
Diabetes % (n)	9.75 (337)	21.91 (85)	38.33 (69)	< 0.0001
Hypertension % (n)	16.58 (573)	39.18 (152)	56.67 (102)	< 0.0001
Heart disease % (n)	2.95 (102)	8.51 (33)	14.44 (26)	< 0.0001
Respiratory disease % (n)	2.37 (82)	5.93 (23)	7.78 (14)	< 0.0001

Chronic kidney disease % (n)	0.58 (20)	2.84 (11)	6.67 (12)	< 0.0001
Cancer% (n)	2.23 (77)	4.38 (17)	6.67 (12)	0.0001
Others disease % (n)	3.65 (126)	10.82 (42)	21.67 (39)	< 0.0001
Symptoms % (n)	73.46 (2538)	87.37 (339)	91.11 (164)	< 0.0001
Period	25.68 ± 10.50	29.45 ± 12.27	23.95 ± 17.05	< 0.0001
Blood parameters				
Hemoglobin (g/dL)	13.52 ± 1.65	12.97 ± 1.83	12.20 ± 2.23	< 0.0001
Hematocrit (%)	39.84 ± 4.47	38.07 ± 5.17	36.08 ± 6.49	< 0.0001
Lymphocyte (%)	30.35 ± 10.33	22.62 ± 11.4	14.78 ± 9.82	< 0.0001
Platelet (uL)	240988.4 ± 76746.7	214633.1 ± 91340.1	197028.4 ± 90752.0	< 0.0001
White blood cell (uL)	6014.6 ± 2595.0	6135.5 ± 3106.2	7885.9 ± 4052.4	< 0.0001

Differences in the clinical severity of COVID-19 were determined using student ANOVA for continuous variables and chi-square test for categorical variables (*p for trend* < 0.05)

Table 3. Differences in clinical severity of COVID-19 according to subject characteristics.

	Clinical severity of COVID-19			
	Model 1		Model 2	
	Moderate	Severe	Moderate	Severe
General characteristics				
Sex				
Men	Ref	Ref	Ref	Ref
Women	**0.74 (0.59, 0.93)**	**0.44 (0.31, 0.61)**	0.82 (0.62,1.08)	**0.63 (0.41,0.96)**
Age				
0–29 y	Ref	Ref	Ref	Ref
30–59 y	**4.29 (2.55, 7.22)**	**5.98 (1.39, 25.65)**	**2.60 (1.48, 4.59)**	2.54 (0.55, 11.70)
≥60y	**13.14 (7.74, 22.32)**	**50.18 (12.05, 208.88)**	**5.84 (3.26, 10.47)**	**14.75 (3.28, 66.22)**
BMI				
Normal	Ref	Ref	Ref	Ref
Overweight	1.25 (0.94, 1.67)	**0.55 (0.35, 0.87)**	**1.43 (1.04, 1.97)**	0.71 (0.41, 1.22)
Obesity	1.72 (1.30, 2.26)	1.16 (0.78, 1.72)	**2.15 (1.58, 2.92)**	**1.78 (1.12, 2.83)**
SBP				
<120	Ref	Ref	Ref	Ref
120–139	1.02 (0.74, 1.41)	0.76 (0.45, 1.28)	1.04 (0.73, 1.49)	0.62 (0.34, 1.14)
≥140	0.80 (0.55, 1.15)	0.97 (0.57, 1.65)	0.83 (0.55, 1.24)	0.87 (0.46, 1.63)
DBP				
<80	Ref	Ref	Ref	Ref
80–89	0.80 (0.60, 1.06)	0.77 (0.50, 1.20)	0.79 (0.58, 1.09)	1.19 (0.71, 2.01)
≥90	0.74 (0.53, 1.02)	0.62 (0.38, 1.01)	0.81 (0.56, 1.17)	0.93 (0.52, 1.66)
Symptoms				
No	Ref	Ref	Ref	Ref

Yes	**2.52 (1.82, 3.50)**	**4.75 (2.72, 8.32)**	**2.05 (1.44, 2.92)**	**3.08 (1.63, 5.85)**
Underlying disease				
Diabetes				
No	Ref	Ref	Ref	Ref
Yes	1.09 (0.81. 1.47)	**1.83 (1.26, 2.66)**	1.05 (0.76, 1.44)	1.39 (0.90, 2.16)
Hypertension				
No	Ref	Ref	Ref	Ref
Yes	**1.37 (1.06, 1.78)**	**1.84 (1.28, 2.66)**	1.13 (0.85, 1.51)	1.28 (0.83, 1.96)
Heart disease				
No	Ref	Ref	Ref	Ref
Yes	1.24 (0.80, 1.93)	1.48 (0.87, 2.51)	1.26 (0.78, 2.05)	1.32 (0.70, 2.50)
Respiratory disease				
No	Ref	Ref	Ref	Ref
Yes	**1.76 (1.05, 2.95)**	**2.20 (1.10, 4.38)**	**1.73 (1.99, 3.03)**	**2.16 (0.96, 4.83)**
Chronic kidney disease				
No	Ref	Ref	Ref	Ref
Yes	**3.36 (1.47, 7.70)**	**6.61 (2.67, 16.36)**	**1.70 (1.65, 4.42)**	**2.93 (1.08, 7.94)**
Cancer				
No	Ref	Ref	Ref	Ref
Yes	1.49 (0.84, 2.64)	2.00 (0.97, 4.12)	1.27 (0.68, 2.35)	1.54 (0.64, 3.71)
Other diseases				
No	Ref	Ref	Ref	Ref
Yes	**2.13 (1.43, 3.18)**	**3.68 (2.30, 5.86)**	**2.14 (1.39, 3.30)**	**2.67 (1.53, 4.67)**

Statistical differences were tested using multiple logistic regression analysis, adjusting for variables of each model. Adjusted model 1 included variables such as age, sex, BMI, SBP, DBP, symptoms and underlying diseases. The multivariate model included the variables in model 2 plus blood parameters (hemoglobin, hematocrit, lymphocyte, platelet, and white blood cells).

Figures

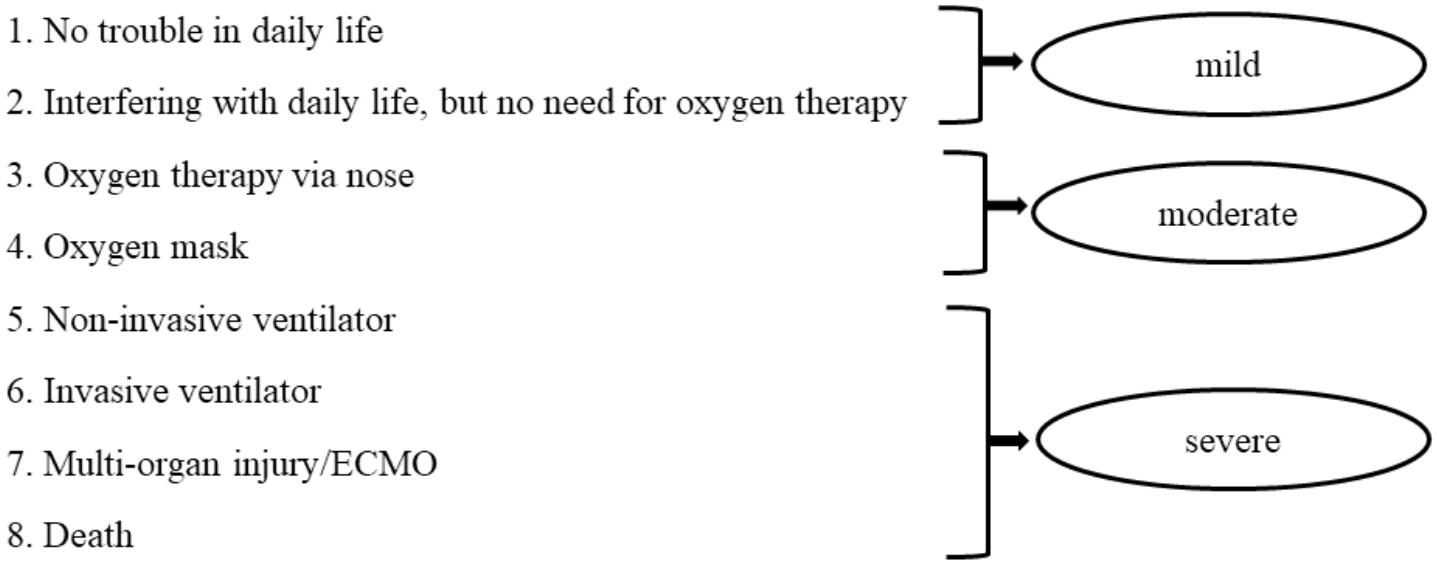
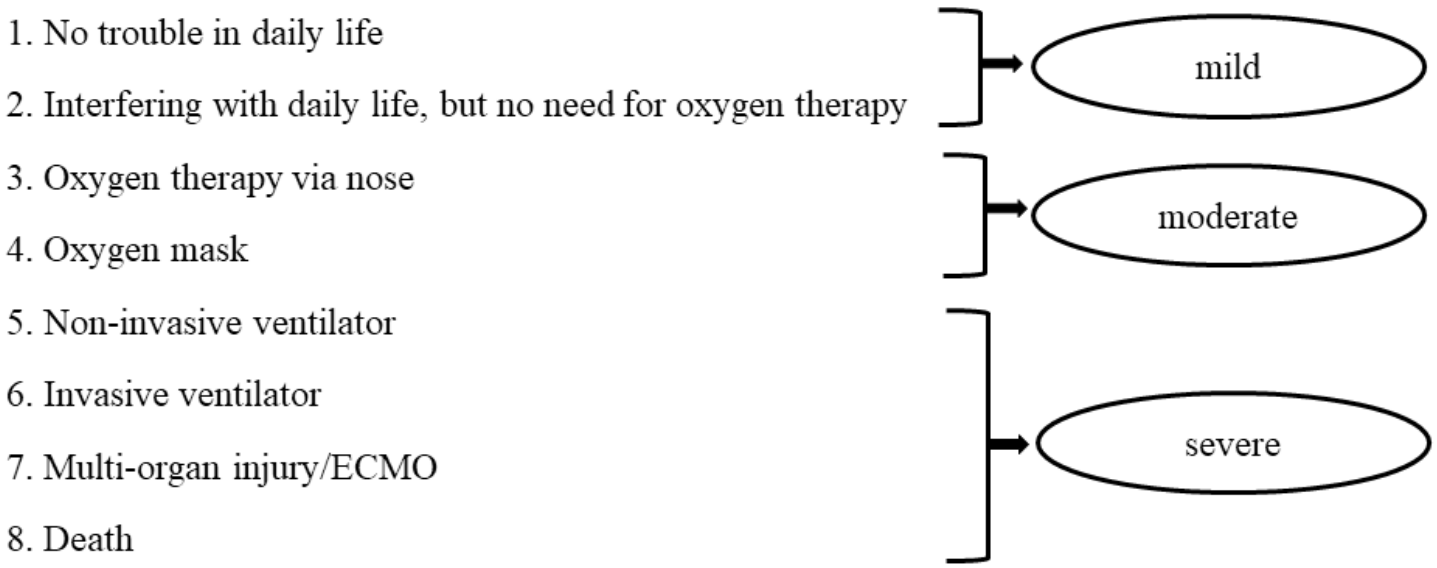


Figure 1

Classification of clinical severity of COVID-19



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