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Factors Associated with Severe Outcomes of the Coronavirus Disease 2019 among Elderly Patients in South Korea

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Background: The coronavirus disease 2019 (COVID-19) has been rapidly spreading globally since its outbreak in December 2019 at Wuhan, Hubei Province, China. The mortality rate of the older population with COVID-19 is particularly high. Therefore, investigating risk factors related to severe outcomes in older COVID-19 patients is important for effective management of the disease. This study aimed to assess the epidemiological and medical factors in older patients to investigate the risk factors related to the severe outcomes of COVID-19.

Methods: We collected clinical and demographic data and assessed the laboratory parameters, radiologic findings, symptoms, and outcomes of older patients with COVID-19. Among the 248 older patients with COVID-19, of whom 99 had severe COVID-19.

Results: The mortality rate was 6.5%. Older and male patients have more severe COVID-19 outcomes. White blood cell counts and creatine phosphokinase, C-reactive protein, procalcitonin, aspartate transaminase, lactate dehydrogenase, and creatinine levels were higher in the severe outcome group. Age, sex, chest X-ray findings, neutrophil count, C-reactive protein level, lactate dehydrogenase level, and albumin level, total number of symptoms, within-family exposure history, and in-hospital exposure history were associated with severe outcomes in the logistic regression model.

Conclusions: Age, C-reactive protein and lactate dehydrogenase levels, and the total number of symptoms were important risk factors among older patients with COVID-19. Therefore, older patients with these factors require more careful attention and medical care.

Key Words: Coronavirus disease (COVID-19), Older patients, Risk factors, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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INTRODUCTION

The coronavirus disease (COVID-19) emerged in December 2019 at Wuhan, Hubei Province, China, and owing to the rapid increase in cases, declared a pandemic shortly afterward. By January 2021, 102 million people had been infected worldwide, and 2.2 million people had died due to the disease [1]. To date, although the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continues, effective treatment options have not yet been developed. This infectious disease is characterized by a high mortality rate among older people and patients with various comorbidities [2-4].

The spread of COVID-19 in South Korea peaked in February 2020, which is relatively early compared to most other parts of the world, and the highest number of COVID-19 patients in Korea has been recorded in Daegu [5].

To effectively manage severe COVID-19, it is crucial to identify patients with high-risk factors associated with worse outcomes. Previous reports identified some of these factors. According to previous studies, age, sex, comorbidities, symptoms, and certain laboratory findings were associated with severe outcomes [3,4,6,7]. However, in older COVID-19 patients, the factors may differ. Additionally, research conducted in the older population may provide new insights into COVID-19 pathology. Therefore, we assessed the epidemiological and medical factors in older patients to investigate risk factors related to severe outcomes of COVID-19 to further our understanding of COVID-19.

MATERIALS AND METHODS

1. Patients

This study was approved by the Institutional Ethics Board of Keimyung University Dongsan Hospital (No. 2020-03-027).

We collected the data of older hospitalized patients diagnosed with COVID-19 between February 21, 2020 and April 2, 2020 at Daegu Dongsan Hospital and monitored clinical manifestations and outcomes until April 2, 2020.

Real-time reverse transcription-polymerase chain reaction (RT-PCR) has been widely used to diagnose COVID-19. The protocols to diagnose COVID-19 vary among countries, and in Korea, the RT-PCR reactions target the RdRp, E, and N genes [8].

2. Data collection

We collected data of patients aged 65 years and older. Data on patient clinical and demographic characteristics, laboratory test results, radiological findings, and the outcome were abstracted from patient medical records. Staff members completed a structured checklist of symptoms when the patient was admitted. The reported symptoms included fever, chills, cough, sputum, rhinorrhea, sore throat, myalgia, headache, diarrhea, dyspnea, and chest pain. The symptoms were recorded daily during hospitalization, and all other data were collected retrospectively.

We assessed whether oxygen supply, mechanical ventilation support, or extracorporeal membrane oxygenation was prescribed. Additionally, we collected data on outcomes such as whether the patient died or was discharged alive based on a chart review. A severe case was defined as positive id at least one of the following symptoms were noted: (1) shortness of breath, respiratory rate ≥30 breaths/min, (2) resting oxygen saturation ≤93%, or (3) PaO_2/FiO_2 ≤300 mmHg or requirement of mechanical ventilation according to the World Health Organization (WHO) recommendation [9]. All other cases were classified as mild cases.

Data on the symptoms were collected daily, and the data obtained on the day when the patient experienced the most number of symptoms were selected for analysis.

Chest computed tomography (CT) findings were divided into positive and negative cases. Positive cases were defined as having any consolidation or ground-glass opacity (GGO) during hospitalization, and negative cases were defined as having no consolidations or GGO in the CT findings throughout their hospital stay.

3. Statistical analyses

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations. Categorical variables were analyzed

using Fisher's exact test, continuous variables using independent t-tests when the data were normally distributed, and a Mann-Whitney U test was used for non-normal data. A logistic regression model was used to investigate the factors associated with severe outcomes. A two-sided P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23.0 software (IBM Corp., Armonk, NY, USA).

Table 1. General characteristics of coronavirus disease 2019 cases

Characteristics		Mild case (n=149)	Severe case (n=99)	P value
Age, mean (standard deviation), years		72.99 (5.73)	77.77 (7.94)	0.000
Gender	Male	43 (28.9%)	44 (44.4%)	0.014
	Female	106 (71.1%)	55 (55.6%)	
Comorbidity	Hypertension	55 (49.5%)	36 (48.6%)	1.000
	Diabetes mellitus	26 (23.4%)	25 (33.8%)	0.133
	Coronary artery disease	6 (5.4%)	5 (6.8%)	0.757
	Stroke	8 (7.2%)	6 (8.1%)	1.000
	Asthma	5 (4.5%)	1 (1.4%)	0.404
	Chronic obstructive pulmonary disease	1 (0.9%)	2 (2.7%)	0.565
	Heart failure	2 (1.8%)	4 (5.4%)	0.220
	Chronic kidney disease	0 (0.0%)	4 (5.4%)	0.024
	Liver disease	1 (0.9%)	1 (1.4%)	1.000
	Thyroid disease	2 (1.8%)	2 (2.7%)	1.000
	Dementia	4 (3.6%)	5 (6.8%)	0.487
	Cancer	7 (6.3%)	4 (5.4%)	1.000
	Other diseases	8 (7.2%)	8 (10.8%)	0.431
	Total disease count	1.12 (0.99)	1.39 (1.18)	0.166
Symptoms	No symptoms	26 (19.0%)	0 (0.0%)	0.000
	Fever	15 (10.9%)	21 (38.9%)	0.000
	Chill	22 (16.1%)	19 (35.2%)	0.006
	Cough	60 (43.8%)	43 (79.65%)	0.000
	Sputum	63 (46.0%)	35 (64.8%)	0.024
	Rhinorrhea	39 (28.5%)	14 (25.9%)	0.858
	Sore throat	26 (19.0%)	20 (37.0%)	0.014
	Myalgia	24 (17.5%)	16 (29.6%)	0.076
	Headache	30 (21.9%)	16 (29.6%)	0.266
	Diarrhea	38 (27.7%)	20 (37.0%)	0.224
	Dyspnea	12 (8.8%)	24 (44.4%)	0.000
	Chest pain	22 (16.1%)	10 (18.5%)	0.672
	Symptoms count	2.56 (2.34)	4.41 (2.48)	0.000
Chest X-ray	Positive	99 (66.4%)	92 (92.9%)	0.000
	Negative	50 (33.6%)	7 (7.1%)	
CT scan	Positive	73 (74.5%)	59 (90.8%)	0.014
	Negative	25 (25.5%)	6 (9.2%)	
Exposure History	Within Family	33 (22.1%)	10 (10.1%)	0.016
	From a co-worker or friend	14 (9.4%)	3 (3.0%)	0.071
	From religious meeting	41 (27.5%)	13 (13.1%)	0.008
	In-hospital	8 (5.4%)	22 (22.2%)	0.000
	Others	2 (1.3%)	1 (1.0%)	1.000
	Unknown	51 (34.2%)	50 (50.5%)	0.012

All % present the proportions of characteristics in the mild or severe case group with the exclusion of the missing values. P values were analyzed using the t-test or Mann-Whitney test for continuous variables, and the Fisher's exact test for categorical variables.

Table 2. Laboratory findings of coronavirus disease 2019 cases

Variables	Mild case (n=149)	Severe case (n=97)	P value
White blood cell count, $\times10^3/\mu L$	5.78 (1.59)	6.55 (3.40)	0.038
Neutrophil count, $\times10^3/\mu L$	3.53 (1.39)	4.89 (3.25)	0.000
Lymphocyte count, $\times10^3/\mu L$	1.63 (0.62)	1.12 (0.54)	0.000
Monocyte count, $\times10^3/\mu L$	0.51 (0.18)	0.48 (0.25)	0.324
Hemoglobin, g/dL	12.20 (1.35)	11.94 (1.61)	0.176
Hematocrit, %	36.74 (3.93)	35.71 (4.71)	0.074
Platelet count, $\times10^3/\mu L$	245.28 (92.74)	214.34 (91.62)	0.011
Glucose, mg/dL	137.07 (61.71)	149.94 (85.82)	0.203
Creatine phosphokinase, U/L	81.55 (61.07)	119.55 (128.53)	0.008
C-reactive protein, mg/dL	1.18 (2.05)	6.59 (6.03)	0.000
Procalcitonin, ng/mL	2.16 (2.50)	3.59 (3.55)	0.005
Aspartate transaminase, U/L	23.85 (8.97)	35.55 (26.51)	0.000
Alanine transaminase, U/L	21.74 (13.78)	26.03 (19.38)	0.061
Lactate dehydrogenase, U/L	467.01 (96.83)	710.08 (510.73)	0.000
Albumin, g/dL	3.93 (0.41)	3.44 (0.51)	0.000
Blood urea nitrogen, mg/dL	15.69 (5.03)	20.91 (12.42)	0.000
Creatinine, mg/dL	0.82 (0.22)	1.02 (0.64)	0.005
Estimated glomerular filtration rate, mL/min/1.73 m^2	78.13 (14.94)	69.72 (21.94)	0.001

All data are presented as means (standard deviations). The estimated glomerular filtration rate is calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation. P values are analyzed using the t-test or Mann-Whitney test.

RESULTS

1. General characteristics

The total number of cases evaluated was 248, of which 149 were mild, and 99 were patients with severe disease. The average age was 74.9 years (range: 65-98 years). The mortality rate was 6.5% (16 cases), with older and male patients having severe outcomes more often. In addition, patients with chronic kidney disease (CKD) were more likely to have severe outcomes. Symptoms associated with severe outcomes included fever, chills, cough, sputum, sore throat, dyspnea, and the total number of symptoms. The positive group based on the chest X-ray and CT findings had more severe outcomes, along with the patients infected at the hospital (Table 1).

2. Laboratory findings

White blood cell count, neutrophil count, and creatine phosphokinase, C-reactive protein (CRP), procalcitonin, aspartate transaminase, lactate dehydrogenase (LDH), and creatinine levels were higher in the severe outcome group. Meanwhile, the lymphocyte count and platelet count were low (Table 2).

Table 3. Disease severity according to medical factors

Variables	Model 1	Model 2
Age	1.11 (1.06-1.15)	1.13 (1.01-1.27)
Sex		
Man	1	1
Woman	0.51 (0.30-0.86)	0.94 (0.27-3.34)
Chest X-ray results		
Negative	1	1
Positive	6.64 (2.87-15.38)	17.87 (0.59-537.96)
Neutrophil count	1.32 (1.15-1.52)	0.68 (0.43-1.09)
C-reactive protein	1.46 (1.30-1.63)	1.30 (1.01-1.67)
Lactate dehydrogenase	1.01 (1.01-1.01)	1.01 (1.01-1.02)
Albumin	0.10 (0.05-0.20)	1.82 (0.33-10.06)
Estimated glomerular filtration rate	0.98 (0.96-0.99)	0.97 (0.94-1.02)
Comorbid disease count	1.26 (0.96-1.66)	1.79 (0.92-3.50)
Symptoms count	1.34 (1.17-1.53)	1.66 (1.30-2.13)
Within family exposure history		
No	1	1
Yes	0.40 (0.19-0.84)	0.68 (0.10-4.46)
In-hospital exposure history		
No	1	1
Yes	5.04 (2.14-11.85)	5.57 (0.80-38.85)

Values are presented as odd ratios (95% confidence interval), 1.00: reference. Model 1: raw. Model 2: age, sex, chest X-ray results, neutrophil count, C-reactive protein, glucose, lactate dehydrogenase, albumin, estimated glomerular filtration rate, comorbid disease count, symptoms count, within family exposure history, In-hospital exposure history.

3. Logistic regression model

Age, sex, chest X-ray findings, neutrophil count, CRP level, LDH level, and albumin level, total number of symptoms, within-family exposure history, and in-hospital exposure history were associated with severe outcomes after adjusting for age and sex in the logistic regression model. Additionally, age, CRP and LDH levels, and the total number of symptoms were associated with severe outcomes after fully adjusting the logistic regression model (Table 3).

DISCUSSION

In our study, the mortality rate was 6.5% (16 cases). Previous studies have reported mortality rates between 5.6% and 19.2% in older patients with COVID-19 [3,10]. In line with the general observation that older patients have a high mortality rate, in our study, age was a significant risk factor for a severe outcome in the logistic regression model after adjusting for other variables.

Moreover, male patients were at a higher risk for severe COVID-19 outcomes, but no significant association was observed after adjusting for other risk factors. Previous reports addressing this issue have reported controversial results [4,6,7].

In our study, there was no relationship between comorbidities and severe outcomes except for CKD. However, other studies have reported a higher risk of severe outcomes in cases with pre-existing comorbidities [4,11-13]. This difference may be due to the increase in comorbidities among older individuals. Therefore, further studies are needed to confirm these findings and further describe and understand them.

In the present study, the most common symptoms were cough (53.9%) and sputum (51.3%), and the prevalence of fever was low (14.5%) compared to other studies (45.4-88.5%) [7,14,15]. This may be because, besides severe cases, asymptomatic patients were also hospitalized upon diagnosis of COVID-19 in Daegu, South Korea. We observed that illness severity and negative outcomes increased when the number of symptoms was high. This trend was conserved after adjusting for other factors in the logistic regression model. Therefore, we suggest that the total number of symptoms is a risk factor that helps predict severe COVID-19 outcomes.

Within-family infections less frequently resulted in severe outcomes than in-hospital infections. This discrepancy may be due to the fact that healthy individuals with strong immunities did not require hospitalization and were at home during illness. Furthermore, the general condition of in-hospital patients may also affect their overall health. However, there was no significant association between within-family and in-hospital infections after adjusting for other factors. Nevertheless, in-hospital infections can be fatal, and extra care should be taken to prevent in-hospital SARS-CoV-2 infections, especially among older people.

In our study, there were several laboratory findings related to severe outcomes. Among the findings, LDH and CRP levels were risk factors in the logistic regression model after adjusting for other factors. Regarding LDH, previous studies have shown a consistent association with severe COVID-19 outcomes [4,6,14,16]. Therefore, the LDH levels can be considered a strong predictive indicator of unexpectedly severe outcomes in older patients with COVID-19.

There are some limitations to our study. First, this study has a retrospective nature. Therefore, there are additional limitations in drawing conclusions. Second, in this study, we only investigated in-hospital patients which can lead to a false generalization of all COVID-19 cases. Third, data on symptoms were recorded only when the patients were conscious, so there may be missing data from the periods when the patients were drowsy or had a low level of consciousness.

In conclusion, owing to the high mortality rate in elderly patients with COVID-19, it is important to investigate the risk factors related to severe outcomes in older patients. In our study, age, CRP level, LDH level, and the total number of symptoms were important risk factors in elderly patients with COVID-19. Therefore, older patients with the afore-mentioned factors should be provided with special medical care.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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