

Original Article



Clinical Characteristics and Risk Factors for Severe Disease of Coronavirus Disease 2019 in a Low Case Fatality Rate Region in Korea

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ABSTRACT



Background: Jeju island had the seventh highest incidence rate of coronavirus disease 2019 (COVID-19) but showed the lowest case fatality rate among 17 provinces of Korea, which may be associated with comorbidities and geographic differences. This study aimed to analyze the epidemiological and clinical characteristics of patients with COVID-19 and evaluate the risk factors for severe COVID-19 in Jeju island, Korea.

Materials and Methods: All patients with COVID-19 admitted between February 20, 2020, and June 19, 2021, at a single center were retrospectively enrolled in this study. The severity of illness was defined using five categories (asymptomatic, mild, moderate, severe, and critical) according to the National Institute of Health criteria. Then, patients with severe and critical illness were grouped into a severe group, whereas patients with asymptomatic, mild, and moderate illness were grouped into a non-severe group. Multivariate logistic regression analysis was performed using risk factors that were found to be significantly associated with the severe group.

Results: This study included 348 patients with a median age was 57 years, and 37.5% were aged 60 or older. Among them, 43.4% were male and 10.9% were asymptomatic, whereas 41.4%, 33.9%, 12.9%, and 1.1% had mild, moderate, severe, and critical illness. The all-cause mortality of patients with COVID-19 was 0.28% (1/348). Among confirmed patients with COVID-19, exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was mainly within Jeju island (75.9%). The mean body mass index was 24.09 ± 4.04 kg/m², the median comorbidity index score was low in each group (0 in asymptomatic; 1 in mild; 1 in moderate; 1 in severe; and 2 in critical group, $P < 0.548$). In the multivariable analysis, male sex [odds ratio (OR), 6.37; 95% confidence interval (CI), 2.69 – 15.13; $P < 0.001$], ≥ 65 years of age (OR, 2.68; 95% CI, 1.18 – 6.10; $P < 0.019$), chronic pulmonary disease (OR, 6.10; 95% CI, 1.40 – 26.61; $P = 0.016$), and length of fever duration (OR, 1.33; 95% CI, 1.19 – 1.49; $P < 0.001$) were independently associated with severe COVID-19.

Conclusion: The most relevant risk factors of COVID-19 severity were male sex, older age, underlying chronic lung diseases, and duration of fever during hospitalization. The risk factors for severe COVID-19 were not significantly different from those reported in other studies. However, a lower proportion of the older population among confirmed SARS-CoV-2 cases might contribute to the lower fatality rate than the national rate.

Keywords: COVID-19; SARS-CoV-2; Korea; Jeju; Mortality

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Conflict of Interest

No conflicts of interest.

Author Contributions

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 transmission mainly occurs through saliva droplets of an infected individual as well as through direct contact with an infected individual or contact with contaminated inanimate objects [1, 2].

Since its emergence, the disease has rapidly spread worldwide. As of September 18, 2021, 226 million confirmed cases, including 4 million deaths, have been reported worldwide, with more than 500,000 new cases diagnosed per day even after the introduction of vaccines for COVID-19 [3]. In Korea, 289,263 cases of COVID-19 were confirmed as of September 20, 2021, and four nationwide outbreaks - first outbreak (February 2020 - May 2020), second outbreak (August 2020 - November 2020), third outbreak (November 2020 - January 2021), and fourth outbreak (June 2021) - had occurred in Korea (**Supplementary Fig. 1A**) [4]. On Jeju island, the first outbreak occurred in December 2020, and the second and third outbreaks occurred in May 2021 - June 2021 and July 2021 - August 2021, respectively, which corresponds to the period when the third and fourth nationwide outbreaks occurred (**Supplementary Fig. 1B**). The trend of confirmed COVID-19 cases on Jeju Island changed as the COVID-19 epidemic continued. Jeju island had its first COVID-19 cases in the spring of 2020 which resulted in a local outbreak; they were two young foreign patients with SARS-CoV-2 (one was asymptomatic, while the other was mild) exposure either from outside Jeju island or abroad. Since November 2020, the patients diagnosed with COVID-19 were mainly inhabitants of Jeju island, and the proportion of seriously ill patients increased. Despite reduction in the sporadic cases in Jeju, the number of patients with COVID-19 in Jeju island increased rapidly in May 2021, with an increase in the number of visitors, resulting in outbreak events in the region. Although the emergence of confirmed patients on the island was initially caused by an influx of infected people from overseas, cases were detected among the inhabitants due to an influx of people from the mainland or due to unknown sources of infection in the community during the first and second outbreaks in Jeju Island [5].

Since the outbreak of COVID-19 on Jeju island, 2,782 cases have been confirmed, and the region had the seventh highest incidence rate in Korea [4]. However, this region had the lowest case fatality rate compared with that of the entire Korea on September 20, 2021 (0.2% for Jeju Island *vs.* 0.8% for Korea) (**Supplementary Fig. 2**, last updated September 20, 2021) [4]. Various factors can be considered to have contributed to the low fatality rate of COVID-19 on Jeju island. In previous studies, patients with advanced age, obesity, and comorbidities (such as hypertension, diabetes, respiratory system disease, and cardiovascular disease) were at a higher risk of developing severe COVID-19 [6, 7]. The prevalence of comorbidities and chronic diseases, such as hypertension and diabetes, was lower among the inhabitants of Jeju island than that among the general population in Korea [8]. Our hospital has been designated to treat high-risk COVID-19 patients. According to the COVID-19 triage protocols of the Jeju local government, regardless of disease severity, SARS-CoV-2-confirmed patients with underlying comorbidities, those aged ≥ 65 , or those with severe COVID-19 are classified as high-risk patients and should be admitted to our hospital.

This study aimed to analyze the epidemiological and clinical characteristics of patients with COVID-19 and evaluate factors for low case fatality rate in patients in this region.

MATERIALS AND METHODS

1. Study design

We performed a retrospective study on patients with COVID-19 at the Jeju National University Hospital in Jeju island, a nationally designated negative pressure isolation ward responsible for treating patients with high-risk COVID-19 in Jeju Province. The analysis was conducted using data from the electronic medical records of the included patients. The study was approved by the Institutional Review Board (IRB) at the Jeju National University Hospital (IRB file no. 2020-10-019).

2. Study population

Patients who were admitted for confirmed SARS-CoV-2 infection between February 20, 2020, and June 19, 2021, were eligible to participate in the study. During the study period, 1,230 cases were confirmed to be positive for SARS-CoV-2 through a reverse transcriptase polymerase chain reaction (RT-PCR) on Jeju island. Of these, 827 SARS-CoV-2-confirmed patients were admitted to other hospitals or residential treatment centers, whereas 403 SARS-CoV-2-confirmed patients were admitted to our hospital. A total of 348 patients with COVID-19 (≥ 18 years old) were analyzed in the present study. Patients aged < 18 years and those who were admitted to other clinics or residential treatment centers were excluded (Fig. 1).

Demographic and clinical characteristic data, which included the patients' demographics (age, sex, and body mass index), past medical history and comorbidity index score (CCI), source of exposure risk to SARS-CoV-2, symptom presentation, type of oxygen therapy, hospital treatment (inotropics, extracorporeal membrane oxygenation), duration of hospitalization, and mortality, were retrospectively obtained from the registry database.

3. Regional characteristics of Jeju island

Jeju island ($33^{\circ}0$ N, $126^{\circ}0$ E) is the largest island located off the coast of the Korean Peninsula. It has a humid subtropical climate and is warmer than the rest of Korea (daily mean temperature: $15.8 - 16.6^{\circ}\text{C}$). As of August 2021, the total population of Jeju was 697,108, with 675,883 Korean and 21,225 foreigner residents [8]. There is no land route that connects the Korean Peninsula and Jeju island, and it is only possible to enter and exit by air and sea.

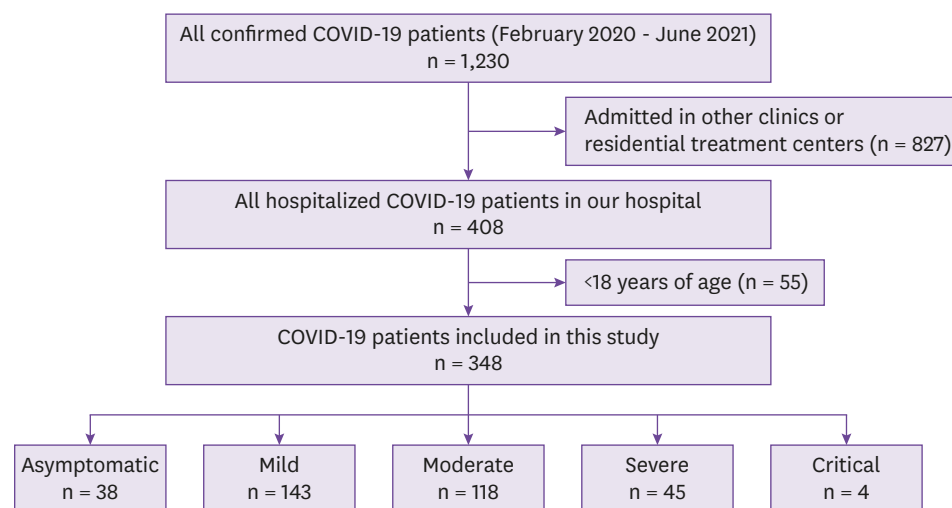


Figure 1. Flowchart of study selection. COVID-19, coronavirus disease 2019.

Tourism is an important part of the local economy. Many Koreans visit Jeju island due to the many flights and ships that connect the Korean Peninsula to Jeju island. In addition, Jeju International Airport includes many direct flights to major cities, including China, Japan, and other countries, since there are no visa requirements for visitors staying up to 90 days many foreign nationals visit Jeju annually; for instance, Chinese visitors, who account for the majority (62.5%) of the total foreign tourists as of 2019, do not require a visa to visit Jeju. Jeju Island hosts about 15,000,000 visitors per year; as of 2019, the total number of visitors were 13,560,004 Koreans and 1,726,132 foreigners. It has been noted that the numbers of both domestic and foreign tourists increase every year [9]. However, the numbers of both domestic and foreign tourists have decreased since the COVID-19 outbreak, with 10,236,445 tourists (10,023,678 Koreans and 212,767 foreigners, decreased by 26.1% and 87.7% from the previous year, respectively) visiting Jeju island in 2020. As the COVID-19 pandemic continues and overseas travel is limited, the number of Koreans visiting Jeju Island has increased compared with that in the previous year (as of July 2021, there was a 20.2% increase in cumulative visitors from January to July).

4. Definition

SARS-CoV-2 infection was confirmed using nasal and/or oropharyngeal swab RT-PCR. The severity of illness was classified into the following five groups according to the National Institute of Health criteria based on the patient's worst condition during hospitalization: asymptomatic, mild, moderate, severe, and critical [10]. The severe and critical groups were then combined as the severe group, whereas the asymptomatic, mild, and moderate groups were combined as the non-severe group, and the risk factors for the severe group were analyzed. The level of comorbidities for each patient was assessed using the CCI for each previously diagnosed disease. Influx case from outside Jeju Island (mainland) was defined as those patients who had visited other cities in Korea or had contact with confirmed cases in other cities. Patients who had unidentifiable source of infection or had contact with confirmed cases which occurred in large-scale clusters were categorized to have an unknown source of infection [4, 11].

5. Statistical analysis

Categorical variables were compared using the chi-square test, and continuous variables were compared using the two-sample *t*-test and ANOVA. Data for continuous variables are presented as means \pm standard deviations or medians and interquartile ranges. Multivariate logistic regression analysis was performed using the risk factors that were found to be significantly associated with the non-severe or severe groups in the univariate analysis. *P* < 0.05 was considered statistically significant in the multivariate analysis. Statistical analyses were performed using SPSS (version 20.0; IBM Corp., Armonk, NY, USA).

RESULTS

1. Demographic characteristics

Overall, 348 patients were included in the study. **Table 1** shows the demographic and baseline characteristics of the patients according to the severity of infection. Overall, 38 patients (10.9%) had asymptomatic, 143 (41.1%) had mild, 118 (33.9%) had moderate, 45 (12.9%) had severe, and 4 (1.1%) had critical infections. The median age of the patients was 57 years [interquartile range (IQR), 40 – 66] years, 99 (28.4%) patients were aged \geq 65 years, and 197 (56.6%) were women. The percentage of patients aged \geq 60 with confirmed COVID-19

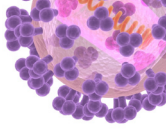
Table 1. Demographics and clinical characteristics of COVID-19 patients by severity in Jeju Island, Korea (March 2020 - June 2021)

Variable	Total no (%)	Asymptomatic no. (%)	Mild no. (%)	Moderate no. (%)	Severe no. (%)	Critical no. (%)	P-value
	n = 348	n = 38	n = 143	n = 118	n = 45	n = 4	
Male, no. (%)	151 (43.4)	17 (44.7)	52 (36.1)	47 (39.8)	32 (78.0)	3 (75)	0.004
Age, median (IQR), yr	57 (40 - 66)	46 (31 - 62)	51 (35 - 63)	60 (48 - 66)	64 (54 - 70)	73 (64 - 82)	<0.001
Age category, no. (%)							<0.001
18 - 64	249 (71.6)	32 (12.9)	111 (44.6)	82 (32.9)	23 (9.20)	1 (2.9)	
≥65	99 (28.4)	6 (6.1)	32 (32.3)	36 (36.4)	22 (22.2)	3 (3.0)	
BMI, mean ± SD, kg/m ²	24.09 ± 4.04	23.84 ± 3.70	24.10 ± 3.58	24.82 ± 3.50	26.45 ± 4.06	25.40 ± 4.60	0.013
Native Jeju residents ^a , no. (%)	249 (77.1)	22 (68.8)	100 (75.8)	86 (76.1)	37 (88.1)	4 (100)	0.238
Source of exposure risk to SARS-CoV-2, no. (%)							0.015
Within Jeju Island	264 (75.9)	264 (75.9)	27 (71.1)	109 (76.2)	89 (75.4)	35 (77.8)	4 (100)
Outside Jeju Island	64 (18.4)	64 (18.4)	2 (5.3)	25 (17.5)	27 (22.9)	10 (22.2)	0 (0.0)
Overseas	20 (5.7)	20 (5.7)	9 (23.7)	9 (6.3)	2 (1.7)	0 (0.0)	0 (0.0)
SARS-Cov-2 Vaccination status, no. (%) ^b							0.682
1st shot	9 (2.6)	2 (22.2)	1 (11.1)	3 (33.3)	3 (33.3)	0 (0.0)	
Completed vaccination	2 (0.6)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	
CCI, median (IQR)	1 (0 - 2)	0 (0 - 2)	1 (0 - 2)	1 (0 - 2.25)	1 (0 - 2.25)	2 (0.5 - 4.25)	0.548
Co-existing conditions no. (%)							
Hypertension	96 (27.6)	8 (21.1)	31 (21.7)	40 (33.9)	15 (33.3)	2 (50.0)	0.019
Dyslipidemia	53 (15.2)	3 (7.9)	21 (14.7)	22 (18.6)	5 (11.1)	2 (50.0)	0.224
Diabetes mellitus	45 (12.9)	5 (13.2)	8 (5.6)	23 (19.5)	7 (15.6)	2 (50.0)	0.012
Cardiovascular disease	25 (7.2)	5 (13.2)	9 (6.3)	6 (5.1)	3 (6.7)	2 (0.6)	1.0
Chronic lung disease	14 (4.0)	1 (2.6)	3 (2.1)	3 (2.5)	4 (8.9)	3 (75.0)	<0.001
Chronic liver disease	7 (2.0)	1 (2.6)	2 (1.4)	3 (2.5)	1 (2.2)	0 (0.0)	1.0
Dementia	5 (1.4)	1 (2.6)	1 (0.7)	3 (2.5)	0 (0.0)	0 (0.0)	0.807
Symptom to SARS-CoV-2 PCR test, median (IQR) day	1 (-1 - 3)	N/A	1 (-1 - 3)	1 (-1 - 3)	1 (-2 - 5)	0.5 (-2.5 - 0.75)	<0.001
Duration of fever, median (IQR), days	3 (0 - 18)	N/A	3 (2 - 4)	3 (2 - 5)	4 (2 - 7)	17 (17 - 17)	<0.001
Symptom presentation, no. (%) ^b							
Cough	201 (64.8)	N/A	88 (61.5)	76 (64.4)	34 (75.6)	3 (75.0)	<0.001
Fever (≥ 38.0 °C)	156 (50.3)	N/A	39 (27.3)	80 (67.8)	36 (80.0)	1 (25.0)	<0.001
Sputum	107 (34.5)	N/A	51 (35.7)	38 (32.2)	16 (35.6)	2 (50.0)	0.009
Sore throat	80 (25.8)	N/A	37 (25.9)	35 (29.7)	8 (17.8)	0 (0.0)	0.191
Rhinorrhoea	45 (14.5)	N/A	24 (16.8)	18 (15.3)	3 (6.7)	0 (0.0)	1.0
Stuffy nose	25 (8.7)	N/A	17 (11.9)	7 (7.4)	1 (2.2)	0 (0.0)	0.497
Myalgia	70 (22.6)	N/A	32 (22.4)	29 (24.6)	8 (17.8)	1 (25.0)	0.088
Headache	72 (23.2)	N/A	32 (22.4)	27 (22.9)	12 (26.7)	1 (25.0)	0.015
Dyspnea	38 (12.3)	N/A	2 (1.4)	9 (7.6)	24 (53.3)	3 (75.0)	<0.001
Diarrhea	72 (23.2)	N/A	26 (18.2)	35 (29.7)	10 (22.2)	1 (25.0)	0.003
Loss of taste or smell	55 (17.7)	N/A	33 (23.1)	18 (15.3)	4 (8.9)	0 (0.0)	0.649
Oxygen Therapy, no. (%)							<0.001
Low flow oxygen	38 (79.2)	N/A	1 (0.7)	5 (4.2)	31 (68.9)	1 (25.0)	
High flow oxygen	7 (14.6)	N/A	N/A	N/A	7 (15.6)	0 (0.0)	
Invasive mechanical ventilation	3 (6.2)	N/A	N/A	N/A	N/A	3 (75.0)	
ECMO, no. (%)	0	0	0	0	0	0	N/A
Medical treatment, no. (%)							<0.001
Hydroxychloroquine ± azithromycin	5 (1.4)	0 (0.0)	2 (1.4)	3 (2.5)	0 (0.0)	0 (0.0)	0.846
Lopinavir/ritonavir ± azithromycin	60 (17.2)	0 (0.0)	1 (0.7)	41 (34.7)	16 (35.6)	2 (50.0)	<0.001
Remdesivir	42 (12.1)	0 (0.0)	0 (0.0)	12 (10.2)	26 (57.8)	4 (100)	<0.001
Regdanvimab	70 (20.1)	4 (10.5)	21 (14.7)	38 (32.2)	7 (15.6)	0	0.002
Corticosteroid	54 (15.5)	0 (0.0)	1 (0.7)	19 (16.1)	31 (68.9)	3 (75)	<0.001
Hospitalization, days, median (IQR)	10 (10 - 14)	9 (9 - 12)	10 (9 - 12)	10 (10 - 14)	12 (10 - 16)	37 (20 - 81)	<0.001
Mortality no. (%)	1 (0.28)	0	0	0	0	1 (25)	0.009

^aNative Jeju resident is based on the electronic medical record and self-reported information.

^bN=310.

COVID-19, coronavirus disease 2019; IQR, inter quartile range; BMI, body mass index; SD, standard deviation; CCI, Charlson comorbidity index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; N/A, not applicable; ECMO, extracorporeal membrane oxygenation; PCR, polymerase chain reaction.



cases in the study was higher than that reported in the national or Jeju island. Most patients were native residents of Jeju island (77.1%) and were exposed to SARS-CoV-2 within Jeju island (75.9%). Only two patients (0.6%) were fully vaccinated, and nine (2.6%) received the first dose of SARS-CoV-2 vaccination. The mean body mass index (BMI) of the patients was 24.09 kg/m². The common comorbidities were hypertension (27.6%), hyperlipidemia (15.2%), diabetes mellitus (12.9%), cardiovascular disease (7.2%), chronic lung disease (4%), and dementia (1.4%); the median CCI was as low as 1 (IQR, 0 - 1). The most frequently observed symptoms were cough (64%), followed by fever (41.7%), sputum (30.7%), sore throat (25.8%), headache (23.2%), diarrhea (23.2%), and myalgia (22.6%). No symptoms were observed in 11.3% of the patients with COVID-19 at our hospital. The median time from symptom onset to SARS-CoV-2 RT-PCR test was 1 day. Overall, 83 (26.8%) patients were asymptomatic at the time of diagnosis and developed symptoms after admission. Furthermore, 48 (13.8%) patients received oxygen support, 38 (79.2%) received a low flow nasal cannula therapy, 7 (14.6%) received a high flow nasal cannula therapy, and 3 (6.2%) received invasive mechanical ventilation. Hydroxychloroquine was administered in 5 (1.4%), lopinavir/ritonavir in 60 (17.2%), remdesivir in 42 (12.1%), regdanvimab in 70 (20.1%), and corticosteroids in 54 (15.5%) patients. Each drug was prescribed according to the newly updated guidelines [12, 13]. The monthly percentages of medication used is shown in Fig. 2A. The median hospitalization duration was 10 days (IQR, 10 - 14). There was only one (0.28%) overall and in-hospital case fatality. The mean SARS-CoV-2 RT-PCR cycle threshold (Ct) value was 23.07 ± 6.25, and there was no significant difference between the five groups. There were differences in the mean lymphocyte counts (*P* < 0.001), platelet counts (*P* < 0.001), and levels of aspartate aminotransferase (*P* < 0.001), alanine aminotransferase (*P* = 0.016), and C-reactive protein (CRP) (*P* < 0.001) between the groups. Comparisons of laboratory findings between the groups are presented in Table 2.

2. Policy change of COVID-19 patient assignment in Jeju island

Until July 2020, our hospital accommodated all confirmed COVID-19 cases in Jeju island. However, as the number of confirmed cases gradually increased from the end of August 2020, the capacity of our hospital became insufficient, and the confirmed cases were distributed to other facilities. Our hospital was assigned to first prioritize high-risk COVID-19 patients, such as patients aged ≥65 with underlying chronic diseases and patients with more severe COVID-19 symptoms. Therefore, the proportion of patients with chronic diseases and with severe or critical COVID-19 is increasing at our hospital. During the study period, no severe or critical cases occurred until July 2020, but increased from August 2020 in Jeju island. The proportion of high-risk groups and patients with severe or critical COVID-19 has increased

Table 2. Baseline laboratory findings of patients with COVID-19 by severity

Variables	Total	Asymptomatic	Mild	Moderate	Severe	Critical	P-value
	no (%)	no (%)	no (%)	no (%)	no (%)	no (%)	
	n = 348	n = 38	n = 143	n = 118	n = 45	n = 4	
SARS-CoV-2 Ct value, mean ± SD	23.07 ± 6.25	26.20 ± 7.10	22.70 ± 5.54	22.52 ± 6.70	23.14 ± 5.60	22.18 ± 5.67	0.058
WBC count, mean ± SD (×/mm ³)	4,758 ± 1,786	5,840 ± 1,765	4,720 ± 1,513	4,507 ± 1,782	4,812 ± 2,288	4,125 ± 1,359	0.005
Lymphocyte count, mean ± SD (×/mm ³)	1426.3 ± 683.2	1882.7 ± 658.9	1558.4 ± 779.2	1252.6 ± 485.5	1231.9 ± 623.2	522.6 ± 261.3	<0.001
Platelet count, mean ± SD (×10 ³ /mm ³)	207 ± 74	252 ± 59	207 ± 62	211 ± 87	165 ± 60	157 ± 24	<0.001
AST, mean ± SD (IU/L)	35.11 ± 30.55	28.91 ± 20.71	30.64 ± 25.47	33.30 ± 23.97	57.02 ± 50.89	35.50 ± 27.15	<0.001
ALT, mean ± SD (IU/L)	31.67 ± 28.48	26.13 ± 19.23	28.64 ± 25.84	32.84 ± 32.50	41.47 ± 29.13	30.25 ± 17.17	0.016
Creatinine, mean ± SD (mg/dL)	1.05 ± 3.99	0.81 ± 0.26	0.80 ± 0.41	0.81 ± 0.23	0.80 ± 0.18	1.08 ± 0.22	0.045
CRP, mean ± SD (mg/dL)	3.48 ± 5.44	0.51 ± 0.85	1.08 ± 2.34	4.34 ± 5.35	9.20 ± 6.78	16.68 ± 10.40	<0.001

Continuous data are presented as mean and standard deviation.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ct, cycle threshold; SD, standard deviation; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

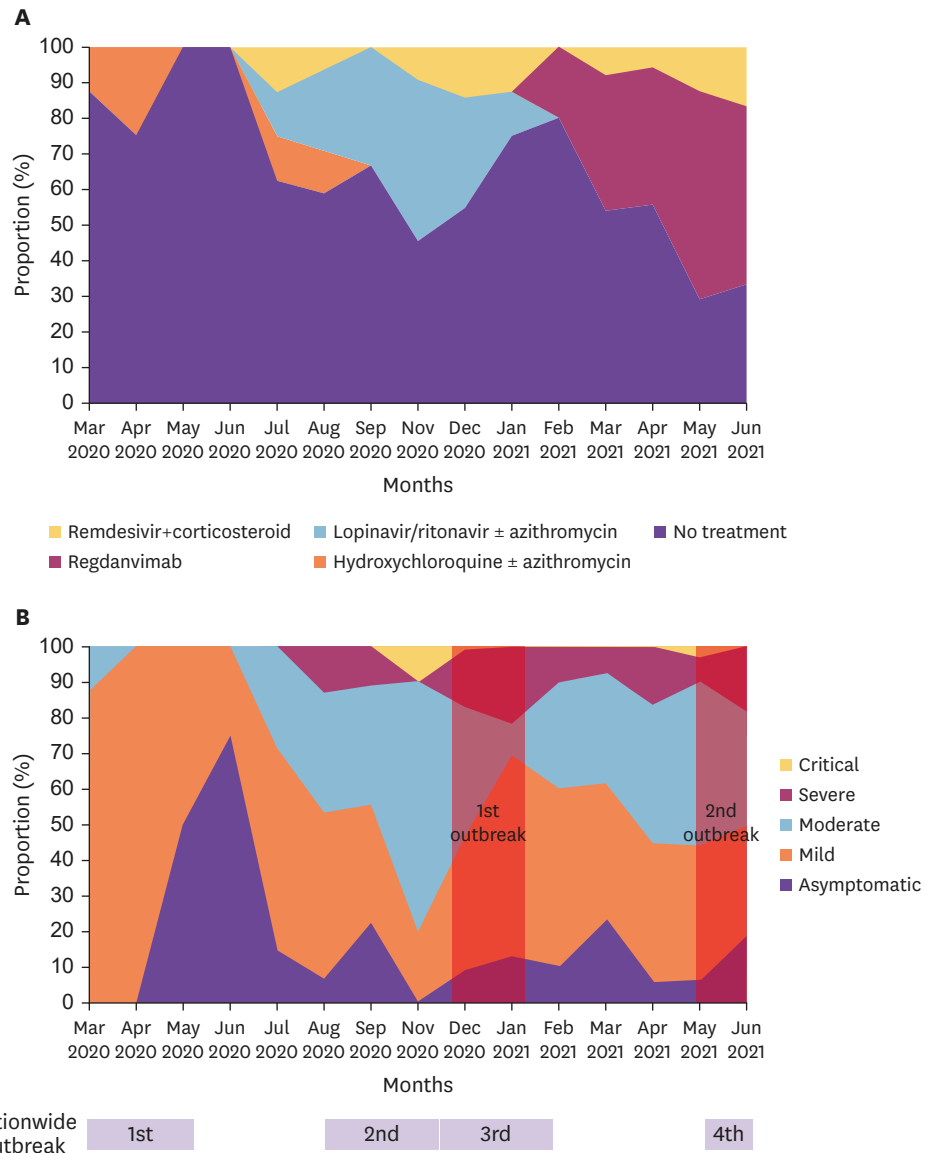
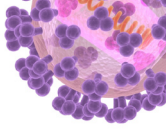


Figure 2. Monthly trends according to treatment of patients with COVID-19 (A) and severity of COVID-19 (B) in Jeju Island (March 2020 - June 2021). There was no confirmed case in our region in October 2020, and this period was excluded from the graph A and B. In Figure (B), the red box is the period of COVID-19 waves of Jeju Island outbreak, and the blue box is the period of COVID-19 waves of nationwide outbreak. COVID-19, coronavirus disease 2019.

since November 2020. The percentage of severe or critical cases among the COVID-19 confirmed cases admitted at our hospital was 13.3% in August 2020, 21.7% in January 2021, and 18.8% in June 2021. The monthly trend in the COVID-19 case severity is shown in **Fig. 2B**. In addition, the proportion of the older age group in our hospital became higher than that of the whole Jeju island among COVID-19 confirmed cases. The detailed proportion of each age group nationwide, the whole Jeju island, and our hospital is shown in **Fig. 3**.

3. Risk factors of severe COVID-19

Univariable logistic regression analysis with non-severe and severe groups is summarized in **Table 3**. Overall, 49 patients were classified into the severe group. In the univariable analysis,

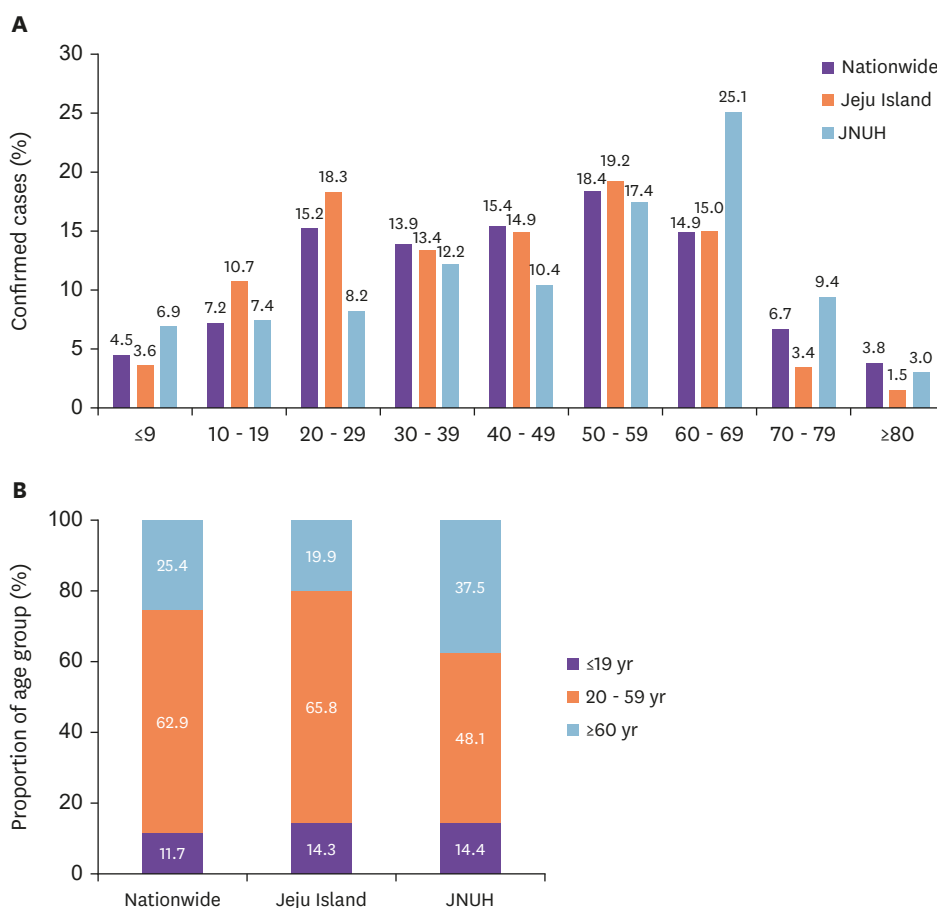
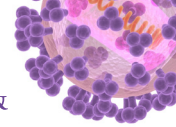


Figure 3. Age group proportion of SARS-CoV-2 PCR confirmed cases. Comparison of each age group between nationwide, Jeju Island and JNUH(A), and comparison of the cumulative proportion of younger and older age groups(B). Data is based on Korea disease Control and Prevention Agency and Jeju Center for Infection control and Prevention press release. National data is based on June 19, 2021, Jeju Island, June 23, 2021, and JNUH, June 19, 2021. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; JNUH, Jeju National University Hospital.

the proportion of males (71.4%), patients aged ≥ 65 years (51.0%), and patients with BMI ≥ 25 kg/m² (56.2%) was higher in the severe group, and the unadjusted odds ratios (OR) were 3.94 (95% CI, 2.03 – 7.64), 3.17 (95% CI, 1.70 – 5.88), and 1.92 (95% CI, 1.04 – 3.56), respectively. The mean BMI was 24.4 kg/m² in the non-severe group and 26.4 kg/m² in the severe group ($P = 0.299$). There were significant differences in the signs and symptoms associated with severity, presence of fever (39.8% in the non-severe group *vs.* 75.5% in the severe group, $P < 0.001$), dyspnea (3.7% in the non-severe group *vs.* 55.1% in the severe group, $P < 0.001$), cough or sputum (54.8% in the non-severe group *vs.* 75.5% in the severe group, $P < 0.001$), and duration of fever during hospitalization (1.60 ± 2.68 days in the non-severe group *vs.* 4.00 ± 3.76 days in the severe group, $P < 0.001$). The SARS-CoV-2 RT-PCR Ct value was not significantly different between the non-severe and severe groups (23.07 ± 6.32 in non-severe group *vs.* 23.06 ± 5.80 in severe group, $P = 0.299$). The lymphocyte counts were significantly decreased in the severe group ($P = 0.002$) compared with that in the non-severe group. The CRP levels and the proportion of patients who used antibiotics were higher in the severe group ($P < 0.001$, respectively) than in the non-severe group. In the multivariable analysis, male sex (OR, 6.37; 95% CI, 2.69 - 15.13; $P < 0.001$), age ≥ 65 years (OR, 2.68; 95% CI, 1.18 –

Table 3. Univariable comparison by non-severe and severe group with COVID 19

Variables	fatality, no. (%)		Unadjusted OR (95% CI)	P-value
	Non-severe (n=299)	severe (n=49)		
Male, no. (%)	116 (38.8)	35 (71.4)	3.94 (2.03 - 7.64)	<0.001
Age ≥65, no. (%)	74 (24.7)	25 (51.0)	3.17 (1.70 - 5.88)	<0.001
Exposure risk outside Jeju, no. (%)	74 (24.7)	10 (20.4)	0.78 (0.37 - 1.64)	0.510
Native Jeju resident, no. (%) ^a	250 (76.9)	41 (89.1)	2.46 (0.94 - 6.45)	0.060
BMI kg/m ² , mean ± SD	24.35 ± 3.57	26.35 ± 4.06	2.00 (0.89 - 3.12) ^a	<0.001
BMI ≥25 kg/m ²	119 (40.1)	27 (56.2)	1.92 (1.04 - 3.56)	0.035
CCI, mean ± SD	1.42 ± 1.74	1.51 ± 1.60	0.27 (-0.59 - 0.41) ^b	0.738
Heart disease, no. (%)	20 (6.7)	5 (10.2)	1.59 (0.57 - 4.44)	0.377
Hypertension, no. (%)	79 (26.4)	17 (34.7)	1.48 (0.78 - 2.81)	0.230
Diabetes mellitus, no. (%)	36 (12.0)	9 (18.4)	1.64 (0.74 - 3.67)	0.221
Hyperlipidemia, no. (%)	46 (15.4)	7 (14.3)	0.92 (0.39 - 2.17)	0.843
Chronic lung disease, no. (%)	7 (2.3)	7 (14.3)	6.95 (2.32 - 20.81)	<0.001
Fever (≥38.0 °C), no. (%)	119 (39.8)	37 (75.5)	4.67 (2.34 - 9.31)	<0.001
Fever duration, mean ± SD (days)	1.60 ± 2.68	4.00 ± 3.76	2.41 (1.54 - 3.27) ^b	<0.001
Cough or sputum, no. (%)	164 (54.8)	37 (75.5)	2.54 (1.27 - 5.06)	<0.001
Dyspnea, no. (%)	11 (3.7)	27 (55.1)	32.13 (14.09 - 73.27)	<0.001
SARS-CoV-2 PCR Ct value at diagnosis, mean ± SD	23.07 ± 6.32	23.06 ± 5.80	0.02 (-1.95 - 1.91) ^b	0.299
WBC, mean ± SD (/mm ³)	4,759 ± 1,703	4,756 ± 2,226	-2.9 (-548.0 - 542.2) ^b	0.992
Lymphocyte, mean ± SD (%)	1,466.6 ± 686.2	1,1195.2 ± 623.3	-271.3 (-477.7 - -65.0) ^b	0.010
CRP, mean ± SD (mg/dL)	2.37 ± 4.16	9.81 ± 7.29	7.44 (5.99 - 8.88) ^b	<0.001
Antibiotics use, no. (%)	71 (23.7)	41 (83.7)	16.46 (7.37 - 36.73) ^b	<0.001

^aNative Jeju resident is based on the electronic medical record and self-reported information.

^bContinuous variables are presented as mean difference (95% confidence interval of the difference).

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation; CCI, Charlson comorbidity index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ct, cycle threshold; PCR, polymerase chain reaction; WBC, white blood cell count; CRP, C-reactive protein.

Table 4. Multivariable logistic regression analysis of baseline characteristics with severe group

Variables	Adjusted OR (95% CI)	P-value
Male	6.37 (2.69 - 15.13)	< 0.001
Age ≥65	2.68 (1.18 - 6.10)	0.019
BMI ≥25 kg/m ²	1.26 (0.58 - 2.75)	0.557
Exposure risk outside Jeju	0.84 (2.44 - 2.85)	0.773
Native Jeju residenta	1.54 (0.37 - 2.66)	0.589
Heart disease	1.41 (0.41 - 4.85)	0.591
Hypertension	1.12 (0.46 - 2.69)	0.806
Diabetes mellitus	1.15 (0.42 - 3.14)	0.784
Chronic pulmonary disease	6.10 (1.40 - 26.61)	0.016
Length of fever, day	1.33 (1.19 - 1.49)	< 0.001

^aNative Jeju resident is based on the electronic medical record and self-reported information.

OR, odds ratio; CI, confidence interval; BMI, body mass index.

6.10; *P* < 0.019), and chronic pulmonary disease (OR, 6.10; 95% CI, 1.40 – 26.61; *P* = 0.016) were independently associated with the severe group (Table 4). However, there were no differences in other underlying comorbidities, exposure and risk of transmission, whether the patients were inhabitants of Jeju island, and BMI.

DISCUSSION

This study details the epidemiological and clinical features of patients with COVID-19 at a single teaching hospital on an isolated island in Korea with low case fatality rate. This study also identified the risk factors of severe symptoms. Of all the patients who were diagnosed with COVID-19 in Jeju island in 2020, 6.1% were from overseas and 31.7% were from areas in Korea other than the Jeju Province. In addition, there was an increase in the incidence

rate due to unknown sources from the third wave of the nationwide outbreak [11]. In this study, the proportion of native residents of Jeju island and patients exposed to SARS-CoV-2 within Jeju island was 77.1% and 75.9%, respectively. In addition, the percentage of patients aged ≥ 60 years among the COVID-19 confirmed cases was higher in our hospital than in the whole Jeju island. (37.5% and 19.9%, respectively). These results are thought to be due to the hospitalization of the high-risk COVID-19 patients at our hospital according to the patient assignment policy of Jeju Province, and the older population who were at high-risk was more likely to be Jeju island's residents. Previous studies have reported that COVID-19 is characterized by various clinical manifestations, including common symptoms such as fever, dry cough, dyspnea, muscle ache (myalgia), confusion, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea/vomiting, conjunctival congestion, nasal congestion, sputum production, fatigue (malaise), hemoptysis, and chill [14-16]. Moreover, anosmia or ageusia (loss of taste) have been reported as symptoms of COVID-19. The clinical manifestations of the patients in our study are similar to those reported in the previous studies. The risk of COVID-19 is associated with possible comorbidities such as diabetes, osteoporosis, rheumatoid arthritis, substance use, and schizophrenia in Korea [17], whereas diabetes, hypertension, chronic lower respiratory disease, and chronic kidney disease are associated with severe COVID-19 [6, 7, 18-20]. A previous large study of 7,590 patients has reported that the most common comorbidity was hypertension (19.3%), followed by chronic pulmonary disease (12.6%) and diabetes (11.9%) [18], which was also observed in our study; however, the proportion of patients with COVID-19 and comorbidities was lower in our study than that reported in other studies [14, 15, 17, 18]. In a previous study, angiotensin-converting enzyme 2 level was found to be increased in patients with hypertension, diabetes, and chronic obstructive pulmonary disease (COPD), which can increase both the risk and severity of COVID-19 [21-23]. Recent meta-analyses have identified that cardiovascular diseases and COPD can greatly affect the severity of COVID-19 [20]. In our study, hypertension and diabetes were not significantly associated with severe COVID-19, but chronic pulmonary disease showed a significant association with the severe group. Age of ≥ 65 years was also a risk factor of severe COVID-19. The proportion of patients aged ≥ 65 years was 28.4%, which is inconsistent with that reported in other studies (26.6% in Korea vs. 35.2% in Daegu–Gyeongbuk cohort) [14, 15, 19]. However, the percentage of patients aged ≥ 60 years among SARS-CoV-2 confirmed cases was 19.9% in the whole Jeju island, 25.4% nationwide, and 37.5% at our hospital during the study period (Fig. 3). The national case fatality rate of Korea during the corresponding period was 1.32%, and 95.1% of case fatalities occurred in the ≥ 60 years age group [24]. Although not analyzed using statistical methods, the lower number of confirmed cases in the older population are likely to contribute to the lower fatality rate relative to the national rate. During the study period, the only COVID-19 mortality in Jeju island occurred at our hospital, and all high-risk and severe COVID-19 confirmed cases in Jeju island were admitted to our hospital. Therefore, it might be meaningful to describe the epidemiologic and clinical characteristics and evaluate the risk factors for severe COVID-19 at our hospital. Furthermore, the results of this study might enable the estimation of risk factors for severe COVID-19 across Jeju island.

This study has some limitations. First, this was a retrospective single-center study; therefore, the generalizability of the study findings is limited. Second, the various laboratory values for the analysis of risk for mortality and SARS-CoV-2 Ct values were not serially examined. Third, data for the surge period of the delta variant of SARS-CoV-2 and the completion of full vaccination were not included. Fourth, although we additionally aimed to analyze the factors contributing to the low case fatality rate of COVID-19 in Jeju island, we could not compare the risk factors with those in other areas, except for comparison of age groups. Although this

study was conducted among patients admitted at a single hospital, the results of this study regarding the risk factors related to COVID-19 severity and case fatality could be reflective of the entire Jeju island; since all high-risk and severe COVID-19 confirmed cases are assigned to be admitted to our hospital, and the comorbidity and severity of our hospital are higher than that of all patients in Jeju island.

In conclusion, this study reports the epidemiology and characteristics of patients with COVID-19 in an isolated region in Korea. The case fatality rate was 0.2% (1/348), and the risk factors for severe and critical COVID-19 were male sex, older age, chronic pulmonary disease, and fever duration during hospitalization.

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SUPPLEMENTARY MATERIALS

Supplementary Figure 1

The outbreaks in nationwide (A) and in Jeju Island (B). The figure was produced based on the Jeju Center for Infection Control, the Jeju Provincial Office press release, and the Korea Disease Control and Prevention Agency press release.

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Supplementary Figure 2

Geographic distribution of incidence and fatality of COVID-19 in Korea (last update 20 September 2021 by Korea Disease Control and Prevention Agency).

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