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Clinical Characteristics and Risk Factors for Mortality in Critical Coronavirus Disease 2019 Patients 50 Years of Age or Younger During the Delta Wave: Comparison With Patients > 50 Years in Korea

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ABSTRACT

Background: Numerous patients around the globe are dying from coronavirus disease 2019 (COVID-19). While age is a known risk factor, risk analysis in the young generation is lacking. The present study aimed to evaluate the clinical features and mortality risk factors in younger patients (≤ 50 years) with a critical case of COVID-19 in comparison with those among older patients (> 50 years) in Korea.

Methods: We analyzed the data of adult patients only in critical condition (requiring high flow nasal cannula oxygen therapy or higher respiratory support) hospitalized with PCR-

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confirmed COVID-19 at 11 hospitals in Korea from July 1, 2021 to November 30, 2021 when the delta variant was a dominant strain. Patients' electronic medical records were reviewed to identify clinical characteristics.

Results: During the study period, 448 patients were enrolled. One hundred and forty-two were aged 50 years or younger (the younger group), while 306 were above 50 years of age (the older group). The most common pre-existing conditions in the younger group were diabetes mellitus and hypertension, and 69.7% of the patients had a body mass index (BMI) > 25 kg/m². Of 142 younger patients, 31 of 142 patients (21.8%, 19 women) did not have these pre-existing conditions. The overall case fatality rate among severity cases was 21.0%, and it differed according to age: 5.6% (n = 8/142) in the younger group, 28.1% in the older group, and 38% in the ≥ 65 years group. Age (odds ratio [OR], 7.902; 95% confidence interval [CI], 2.754–18.181), mechanical ventilation therapy (OR, 17.233; 95% CI, 8.439–35.192), highest creatinine > 1.5 mg/dL (OR, 17.631; 95% CI, 8.321–37.357), and combined blood stream infection (OR, 7.092; 95% CI, 1.061–18.181) were identified as independent predictors of mortality in total patients. Similar patterns were observed in age-specific analyses, but most results were statistically insignificant in multivariate analysis due to the low number of deaths in the younger group. The full vaccination rate was very low among study population (13.6%), and only three patients were fully vaccinated, with none of the patients who died having been fully vaccinated in the younger group. Seven of eight patients who died had a pre-existing condition or were obese (BMI > 25 kg/m²), and the one remaining patient died from a secondary infection.

Conclusion: About 22% of the patients in the young critical group did not have an underlying disease or obesity, but the rate of obesity (BMI > 25 kg/m²) was high, with a fatality rate of 5.6%. The full vaccination rate was extremely low compared to the general population of the same age group, showing that non-vaccination has a grave impact on the progression of COVID-19 to a critical condition. The findings of this study highlight the need for measures to prevent critical progression of COVID-19, such as vaccinations and targeting young adults especially having risk factors.

Keywords: COVID-19; Risk Factors; Young; Critical; Mortality; Respiratory Support

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has rapidly spread around the globe since its discovery as a case of pneumonia of unknown cause in China in December 2019.[1] Since the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020,[2] several variants of concern have emerged, leading to nearly 470 million confirmed cases and more than 6 million deaths as of March 22, 2022.[3]

While most patients suffer from a mild febrile disease, many patients progress to require hospitalization and respiratory assistance, such as high-flow nasal cannula (HFNC) oxygen therapy or mechanical ventilation (MV), and even to death.[4] Attempts to predict mortality have been made since the early days of the pandemic, and studies have shown that old age is the most evident risk factor of severe infection and mortality and that underlying diseases are also a risk factor.[4-7] While severe infections and death occur even in relatively young patients, reports on the clinical features and prognosis of COVID-19 infection in these patients are limited.[8-10] Among the younger generations, obesity (body mass index [BMI] > 30 kg/m²) as well as pre-existing conditions have been identified as key risk factors, and mechanisms such as cytokine storm have been described.[11]

Since the advent of variant viruses, such as the delta variant,[12] there has been a fourth wave of COVID-19, and the rate of severe COVID-19 cases among young patients aged 50 years or younger has increased in Korea. However, detailed data on the characteristics, clinical manifestations, and treatment outcomes of these patients and their differences with older patients are lacking in Korea. Identifying the clinical characteristics and mortality risk factors in young critical patients would help to lower the mortality rate in this patient population.

This study aims to analyze the clinical characteristics and mortality risk factors of young patients (≤ 50 years) with critical COVID-19 infection (defined as receiving respiratory support such as HFNC or greater levels of oxygen support) and evaluate their differences with older patients above age 50 years in Korea.

METHODS

Study population

Patients admitted to 11 tertiary-care hospitals located in 9 provinces in Korea between July 1, 2021 and November 30, 2021 were enrolled retrospectively. Adult patients aged 19 years and older with critically severe COVID-19 infection were included, and patients with reinfection, and patients with postmortem COVID-19 diagnosis were excluded. The patients were divided into ≤ 50 years and > 50 years age groups to compare the clinical features and prognosis.

All patients were diagnosed with COVID-19 based on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real time reverse transcription polymerase chain reaction (RT-PCR) using a nasopharyngeal swab or sputum specimen.

Electronic medical records were reviewed to identify patients' demographic characteristics, including BMI, pre-existing conditions, clinical manifestations, laboratory test results on the day of admission, clinical course, treatment, and outcomes. The Health Insurance Review Assessment (HIRA) system was used to check information about the patient's vaccination status, epidemiologic route of infection, living environment before hospitalization, and SARS-CoV-2 variant. Patients were followed-up until death or discharge, whichever came earlier.

Study outcomes and definitions

Per the definition of the Korea Disease Control and Prevention Agency (KDCA),[13] a critical case was defined as a case in which respiratory support (HFNC or greater levels of oxygen support) was given during the hospital stay. Complete vaccination included one dose of Jannsen, two doses of Moderna/Pfizer/AstraZeneca SARS-CoV-2 vaccines, and booster shots. The outcomes were all-cause mortality in hospital, MV, or extracorporeal membrane oxygenation (ECMO). The severity of the clinical course was assessed based on the highest level of respiratory support needed during the hospital stay, categorized into HFNC, MV, and ECMO. Because only critical cases were included, patients maintained on nasal prong or room air were not included. Noninvasive positive pressure ventilation was not performed on our patients. An outbreak was defined as the concurrent occurrence of numerous confirmed cases in a nursing home or hospital, workplace, religious organization, or other organizations. Hospital-acquired infection (HAI) was defined as cases confirmed while staying at an acute care hospital or long-term care facility for an irrelevant disease, excluding cases confirmed during an outbreak.

Statistical analysis

Results are expressed as mean ± standard deviation and as incidences in the study population. The all-cause mortality between the two groups was compared using a Kaplan-Meier curve. Continuous variables were analyzed using the Student's t-test or Mann-Whitney U test, while categorical variables were analyzed using the χ^2 test or Fisher's extract test. Significant variables ($P < 0.05$) were additionally analyzed using multivariate analysis (logistic regression model), and significant results are presented as the odds ratio (OR) and 95% confidence interval (CI). A logistic regression model was used to control confounding variables. Statistically significant variables in the univariate analyses were used as candidates for multivariate analysis in addition to the main variables of clinical importance. We performed a collinearity analysis on the results that were significant in the univariate analysis. A multivariate analysis was performed on the test results that emerged as independent variables in the collinearity analysis. A collinearity test was also performed to exclude the possibility of cross-influences. To evaluate the appropriate cut-off values for laboratory data, such as C-reactive protein (CRP) levels, receiver-operating characteristic analysis was performed. Risk factors are reported as ORs and 95% CIs for mortality. Continous variables are shown as the mean difference and standard deviation (SD). When the median and interquartile ranges (IQRs) were reported, the median was assumed to reflect the mean and the IQR was assumed to be 1.35 SD. All P values were reported to three decimal places, and P values of < 0.050 were considered significant. All statistical analyses were performed using IBM SPSS for Windows version 24.0 (IBM Corp., Armonk, NY, USA).

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Gil Medical Center (approval no. GCIRB2021-462). The requirement for written informed consent was waived because de-identified data were collected retrospectively. This study adhered to the principles embodied in the Declaration of Helsinki.

RESULTS

Data from 448 critical COVID-19 patients who received HFNC or greater respiratory support at 11 hospitals during the study period were collected. One hundred and forty-two patients were aged 50 years or younger (the younger group), and 306 were above 50 years of age (the older group), 191 of whom were age 65 years or older.

Clinical characteristics between age groups

Regarding baseline characteristics, the mean age of the participants was 60.18 ± 16.51 years. By group, the mean (± SD) was 40.99 ± 6.97 years in the ≤ 50 years group and 69.09 ± 11.23 years in the > 50 years group, and nearly half of both groups were female (43.7% and 44.8%, respectively). The rates of outbreak-related (6.1% vs. 18.3%. $P = 0.017$) or HAI (3.5% vs. 10.5%, $P = 0.015$) were significantly lower in the younger group compared to the older group. A total of 13.6% of the participants were fully vaccinated. Only 3 out of 142 patients in the younger group were vaccinated, and the vaccination rate was significantly lower in this group compared to that in the older group (2.1% vs. 19.2%, $P < 0.001$).

Compared to the older group, the prevalence of BMI ≥ 25 kg/m^2 was significantly higher (69.7% vs. 45.3%, $P < 0.001$), as was the number of patients without any underlying disease, in the younger group (68.3% vs. 25.5% $P < 0.001$) (**Table 1**). Of 142 patients in the younger

Table 1. Clinical characteristics of the patients by age group

Characteristics	Total (N = 448)	Age > 50 yr (n = 306)	Age ≤ 50 yr (n = 142)	P value
Female sex	100 (44.4)	137 (44.8)	62 (43.7)	0.830
Age, yr (mean ± SD)	60.18 ± 16.51	69.09 ± 11.23	40.99 ± 6.97	< 0.001
BMI ≥ 25	228 (53.4)	129 (45.3)	99 (69.7)	< 0.001
Mode of infection				
Outbreak related	47 (14.1)	40 (18.3)	7 (6.1)	0.017
Hospital acquired	37 (8.3)	32 (10.5)	5 (3.5)	0.015
No obvious exposure	152 (33.9)	94 (30.7)	58 (40.8)	0.048
Vaccination				< 0.001
Unvaccinated or 1st dose	387 (86.4)	248 (80.8)	139 (97.9)	< 0.001
2nd or 3rd dose	61 (13.6)	58 (19.2)	3 (2.1)	< 0.001
Underlying disease				
Any underlying disease	273 (60.9)	228 (74.5)	45 (31.7)	< 0.001
Diabetes mellitus	121 (27.1)	98 (32.1)	23 (16.2)	< 0.001
Hypertension	170 (37.9)	148 (48.4)	22 (15.5)	< 0.001
Chronic lung disease	39 (8.7)	37 (12.1)	2 (1.4)	< 0.001
Heart disease	53 (11.9)	52 (17.0)	1 (0.7)	< 0.001
ESRD or CKD	23 (5.1)	20 (6.5)	3 (2.1)	0.064
Chronic liver disease	10 (2.2)	7 (2.3)	3 (2.1)	1.000
Chronic neurologic disease	57 (12.7)	54 (17.6)	3 (2.1)	< 0.001
Solid tumor	29 (6.5)	25 (8.2)	4 (2.8)	0.038
Variants of concern				0.293
Unknown or no variant	355 (85)	231 (83.6)	124 (87.3)	
Alpha	1 (0.2)	0	1 (0.7)	
Delta	62 (14.8)	45 (16.3)	17 (12.0)	
Clinical manifestation on admission				
Lowest oxygen saturation (%)	89.78 ± 8.60	88.90 ± 9.05	91.68 ± 6.18	0.001
Altered mentality	37 (8.3)	33 (10.8)	4 (2.8)	0.003
Initial chest infiltration	410 (96.9)	283 (98.3)	127 (94.1)	0.030
Highest respiratory supplement				0.002
High flow nasal cannula	324 (72.3)	211 (68.9)	114 (79.6)	
MV	83 (18.5)	70 (22.9)	13 (9.9)	
ECMO	41 (9.2)	25 (8.2)	16 (11.3)	
Treatment				
Remdesivir	396 (90.6)	272 (90.7)	124 (90.5)	0.543
Steroid	437 (97.5)	300 (98)	137 (96.5)	0.336
Tocilizumab	177 (39.6)	135 (44.1)	42 (29.8)	0.450
Regdanvimab	38 (8.5)	27 (8.9)	11 (7.7)	0.318
Baricitinib	78 (17.4)	57 (18.6)	21 (14.8)	0.351
Others	102 (22.7)	71 (23.2)	31 (21.8)	0.208
MV	124 (27.7)	95 (31.0)	29 (20.4)	0.023
CRRT	40 (8.9)	35 (11.4)	5 (4.2)	0.007
ECMO	41 (9.2)	25 (8.2)	16 (11.3)	0.295
Complication				
Blood stream infection	30 (6.7)	22 (7.2)	8 (5.6)	0.685
Fungal	17 (3.8)	16 (5.2)	1 (0.7)	0.017
Bacterial pneumonia	74 (16.5)	61 (19.9)	13 (9.2)	0.004
Death	94 (21.0)	86 (28.1)	8 (5.6)	< 0.001
Mean hospital day of death	22.51 ± 17.13	22.34 ± 16.98	24.38 ± 19.89	0.750

Data are number (%), unless otherwise indicated.
SD = standard deviation, BMI= body mass index, ESRD = end-stage renal disease, CKD = chronic kidney disease, MV= mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CRRT = continuous renal replacement therapy.

group, 31 (21.8%, 19 women) did not have a risk factor such as BMI ≥ 25 or a pre-existing condition. The most common pre-existing conditions in the younger group were diabetes mellitus (DM) (n = 23) and hypertension (n = 22); chronic lung disease, heart disease, and chronic neurologic disease were rare.

Compared to the older group, the younger group had a higher mean O_2 saturation at admission (91.68 ± 6.18 vs. 88.90 ± 9.05, P = 0.001), and 6% did not show pulmonary infiltration in the early chest X-ray (CXR); hence, exacerbation of pneumonia could not be excluded solely based on the early CXR. Many patients in the younger group showed improvement with only HFNC, without requiring MV (76.9% vs. 68.9%). 90.6% and 97.5% of total patients received remdesivir and steroid therapy respectively. Tocilizumab and baricitinib were given in 39.6% and 17.4% of patients respectively. There were no significant differences between groups in terms of therapeutic agents.

Risk factors for mortality in all patients

The overall case fatality rate among severity cases (CFR-S) was 21.0%, and the rate was 5.5% in the younger group, 28.1% in the older group, and 38.2% in the ≥ 65 years group (**Fig. 1**). The mortality rate statistically significantly increased with increasing age groups, from the ≤ 50 years group to the 50–64 years group and ≥ 65 years group (P = 0.037) (**Fig. 1A**). This difference became more evident with the use of MV or ECMO, where the mortality rate of the ≤ 50 years group was 25%, while that of the ≥ 65 years group was 71.2% (**Fig. 1B**).

Table 2 shows the risk factors for mortality in the total patient population (N = 448, **Supplementary Table 1**). Multivariate analysis showed that age (OR, 7.902; 95% CI, 2.754–
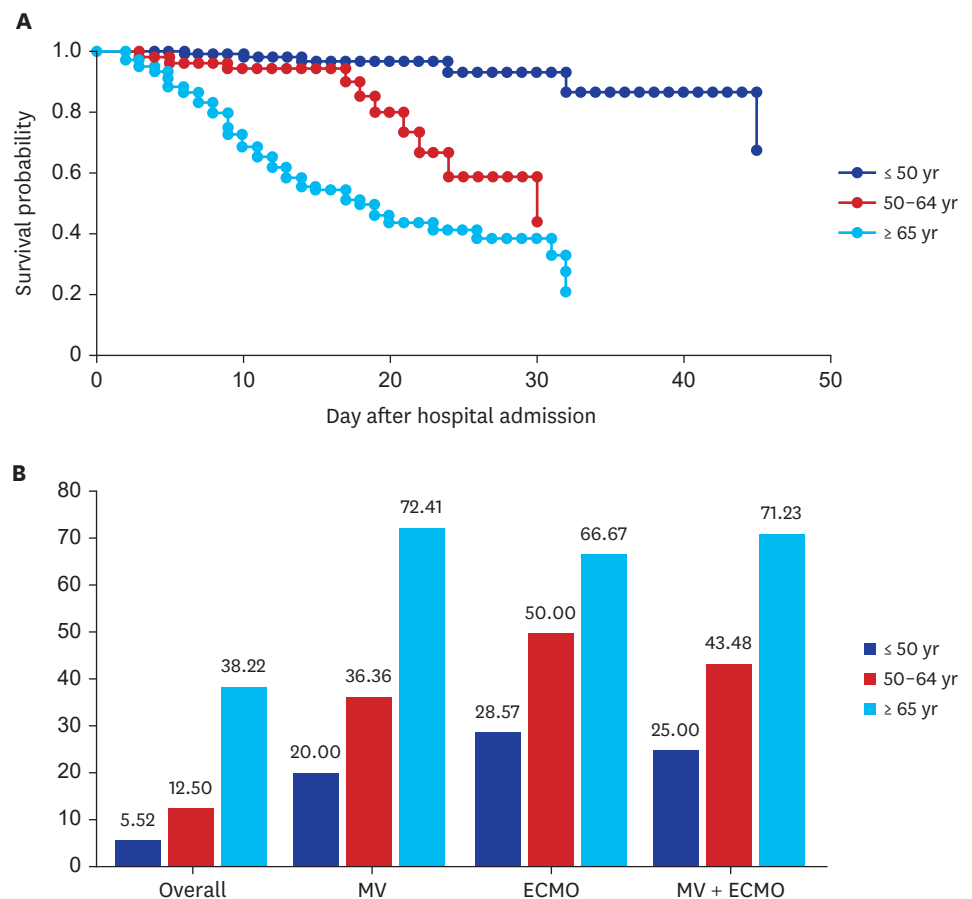

Fig. 1. Mortality and highest level of respiratory support by age group. (**A**) Survival curve of study patients by age group (P = 0.037). (**B**) Case fatality rate according to the highest level of respiratory support and age group. MV = mechanical ventilation, ECMO = extracorporeal membrane oxygenation.

Table 2. Predictors of mortality in the total patients

Risk factors	Univariate analysis			Multivariate analysis	
	Survived (n = 354)	Deceased (n = 94)	P value	Exp(B)	OR (95% CI)
Female sex	156 (44.1)	43 (45.7)	0.816		
Age ≤ 50	134 (37.9)	8 (8.5)	< 0.001	0.141	0.141 (0.055–0.363)
BMI ≥ 25	188 (55.0)	40 (47.1)	0.220		
Breakthrough infection	42 (11.9)	19 (20.2)	0.043		
Underlying					
Any underlying	197 (55.6)	76 (80.9)	< 0.001		
Diabetes mellitus	90 (25.5)	31 (33.0)	0.153		
Hypertension	114 (32.2)	56 (59.6)	< 0.001		
Chronic lung disease	25 (7.1)	14 (14.9)	0.023		
Heart disease	32 (9.1)	21 (22.3)	0.001		
ESRD or CKD	11 (3.1)	12 (12.8)	0.001		
Chronic neurologic disease	34 (9.6)	23 (24.5)	< 0.001		
Initial manifestation					
Lowest O$_2$ saturation ≤ 94	235 (66.4)	69 (73.4)	0.215		
Altered mentality	19 (5.4)	19 (19.1)	< 0.001		
Initial laboratory findings					
Platelet < 100 (10^9/L)	18 (5.1)	13 (13.8)	0.006		
Cr > 1.5, mg/dL	22 (6.3)	25 (26.6)	< 0.001		
LDH > 600, IU/L	113 (35.0)	46 (54.8)	0.001		
Laboratory finding (Hosp)					
Highest WBC > 12.000, 10^9/L	156 (44.1)	79 (84.0)	< 0.001		
Lowest lymphocyte < 900, 10^9/L	201 (58.1)	68 (72.3)	0.012		
Lowest platelet < 100, 10^9/L	54 (15.4)	65 (69.1)	< 0.001		
Highest LDH > 600, IU/L	135 (40.8)	60 (70.6)	< 0.001		
Highest Cr > 1.5, mg/dL	26 (7.4)	59 (62.8)	< 0.001	0.424	17.631 (8.321–37.357)
Highest CRP > 8, mg/dL	204 (58.0)	75 (79.8)	< 0.001		
Highest procalcitonin > 0.5, mg/dL	49 (18.4)	53 (67.1)	< 0.001		
MV	53 (15.0)	71 (75.5)	< 0.001	0.269	17.233 (8.439–35.192)
ECMO	20 (5.6)	21 (22.3)	< 0.001		
CRRT	10 (2.8)	30 (31.9)	< 0.001	0.188	
Complication					
Blood stream infection	19 (5.4)	11 (11.7)	0.037	3.921	7.092 (1.061–18.18)
Fungal infection	7 (2.0)	10 (10.6)	0.001		
Bacterial pneumonia	41 (11.6)	33 (35.1)	< 0.001		

Data are number (%), unless otherwise indicated.
OR = odds ratio, CI = confidential interval, BMI = body mass index, ESRD = end-stage renal disease, CKD = chronic kidney disease, LDH = lactate dehydrogenase, WBC = white blood cell, Cr = creatinine, CRP = C-reactive protein, MV= mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CRRT = continuous renal replacement therapy.

18.181), MV therapy (OR, 17.233; 95% CI, 8.439–35.192), highest creatinine > 1.5 mg/dL (OR, 17.631; 95% CI, 8.321–37.357), and combined blood stream infection (CLABSI) (OR, 7.092; 95% CI, 1.061–18.181) were independent predictors of mortality in critical COVID-19 patients (**Table 2**). The initial or mid-treatment RT-PCR Ct value and therapeutic agents (Steroid, baricitinib, tocilizumab, regdanvimab, remdesivir) were not significantly associated with mortality (data not shown).

Risk factors for mortality by age group

A subgroup analysis was performed for patients aged 50 years and younger and > 50 years group based on the characteristics analyzed from the entire patient population (**Table 3, Supplementary Table 2**).

Similar to previous reports, the mortality risk was high among old patients (age > 50 years) according to age, pre-existing conditions, level of alertness at admission, HR and SpO$_2$ at admission, and initial lab results for blood urea nitrogen (BUN), creatinine (Cr), lactate

Table 3. Risk factors for mortality in the young critical patients (age < 50 years; N = 142) (univariate analysis)

Risk factors	Survival (n = 134)	Death (n = 8)	OR (95% CI)	P value
Female sex	59 (44.0)	3 (37.5)	0.896 (0.513–1.564)	0.082
Age (mean ± SD)	41.14 ± 6.78	38.38 ± 9.97		0.463
BMI > 25	94 (70.1)	5 (62.5)	1.122 (0.649–1.942)	0.698
Transferred after diagnosis	100 (75.2)	6 (75.0)	0.992 (0.288–3.416)	0.084
Breakthrough infection	3 (2.2)	0		0.839
Underlying				
Any-underlying	41 (30.6)	4 (50.0)	1.388 (0.880–2.801)	0.220
Hypertension	20 (14.9)	2 (25)	1.134 (0.756–1.703)	0.359
Chronic lung disease	2 (1.5)	0		0.890
Heart disease	0	1 (12.5)		0.056
ESRD or CKD	3 (2.2)	0		0.669
Chronic neurologic disease	2 (1.5)	1 (12.5)	1.126 (0.866–1.464)	0.161
Solid tumor	2 (1.5)	2 (25.0)	1.313 (0.880–1.960)	0.016
Altered mentality	4 (3)	0		0.791
Initial laboratory results				
Platelet count < 100, 10^9/L	7 (5.3)	0		1.000
BUN ≥ 20, mg/dL	25 (18.8)	1 (12.5)	1.504 (0.220–9.729)	1.000
Cr > 1.5, U/L	9 (6.8)	1 (12.5)	1.968 (0.218–17.796)	0.454
LDH > 600, U/L	45 (37.5)	4 (50)	2.222 (0.476–10.385)	0.258
CRP > 8, mg/L	63 (47.4)	4 (50)	1.053 (0.517–2.144)	0.584
Laboratory findings (during treatment)				
Highest WBC > 12, 10^9/L	55 (41.0)	8 (100)	0.410 (0.335–0.503)	0.049
Lowest lymphocyte count < 0.9, 10^9/L	91 (68.4)	4 (50.0)	1.109 (0.545–2.257)	0.521
Lowest platelet count < 100, 10^9/L	14 (10.6)	5 (62.5)	2.384 (0.973–5.843)	0.001
Highest ALT > 200, IU/L	16 (12.0)	3 (37.5)	1.408 (0.820–2.416)	0.075
Highest AST > 200, IU/L	10 (7.5)	4 (50.0)	1.850 (0.923–3.705)	0.003
Highest TB > 1.2, IU/L	26 (19.5)	7 (87.5)	6.436 (1.027–40.335)	< 0.001
Highest LDH > 600, U/L	54 (45)	6 (75)	3.850 (0.623–23.804)	0.052
Highest Cr > 1.5, U/L	22 (16.5)	6 (75)	1.074 (0.824–1.401)	0.001
Highest procalcitonin > 0.5, mg/dL	18 (17.0)	4 (50)	2.491 (0.801–7.747)	0.013
MV	12 (16.4)	7 (87.5)	6.687 (1.067–41.889)	< 0.001
ECMO	12 (9)	4 (50)	1.821 (0.909–3.648)	0.006
CRRT	3 (2.2)	2 (25)	1.303 (0.873–1.946)	0.026
Complication				
Blood stream infection	6 (4.5)	2 (25)	1.274 (0.852–1.903)	0.066
Bacterial pneumonia	9 (7.3)	2 (28.6)	1.224 (0.818–1.832)	0.158

Data are number (%), unless otherwise indicated.
OR = odds ratio, CI = confidence interval, SD = standard deviation, BMI = body mass index, ESRD = end-stage renal disease, CKD = chronic kidney disease, BUN = blood urea nitrogen, Cr = creatinine, LDH = lactate dehydrogenase, CRP = C-reactive protein, WBC = white blood cell, ALT = alanine aminotransferase, AST = aspartate aminotransferase, TB = total bilirubin, MV= mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CRRT = continuous renal replacement therapy.

dehydrogenase (LDH), and CRP (**Supplementary Table 2**). In the older group, age (OR, 1.101; 95% CI, 1.501–1.153), MV (OR, 13.888; 95% CI, 4.950–38.461), lowest platelet count ≤ 100 (10^9/L) (OR, 3.952; 95% CI, 1.468–10.638), highest creatinine > 1.5 mg/dL (OR, 8.928; 95% CI, 3.236–24.390) were significant risk factor of mortality in multivariate analysis (data not shown). In the older group, survivors were significantly younger than those who died (66.56 ± 10.30 vs. 75.56 ± 10.96 years, *P* < 0.001), but in the younger group, there was no significant difference in the age between survivors and patients who died (38.38 ± 9.97 vs. 41.14 ± 6.78 years, *P* = 0.463) (**Table 3**). Pre-existing conditions were numerically less common, without statistical significance, in survivors than in patients who died in the younger group (30.6% vs. 50.0%, *P* = 0.220). While insignificant in the total patient population and older group, the number of patients with a solid tumor was significantly higher in patients who died in comparison to survivors in younger group (25% vs. 1.5%, *P* = 0.016).

MV, ECMO, and CRRT were performed significantly more in patients who died than who alive in both age groups. In the younger group, the mortality rate was significantly higher in patient with leukocytosis, lymphopenia, or thrombocytopenia, and with aspartate aminotransferase/alanine aminotransferase elevation over 5 upper normal range, LDH over 600, Cr over 1.5, and procalcitonin > 0.5 mg/dL in univariate analysis (**Table 3**), but it did not differ according to the CXR at admission, Ct value for RdRp gene during the hospital stay, variant infection, or treatment modality (data not shown). In multivariate analysis, there was not a single risk factors statistically significant, probable owing to relatively small number of patients were died.

The mortality rate among the unvaccinated patients in older group was 77.9%, higher than that among the vaccinated patients (22.1%) but not to a statistically significant difference (P = 0.418). All three fully vaccinated patients younger than 50 years survived.

General manifestations of deceased patients younger than 50 years

In this study, eight patients aged 50 years and younger died (5.6%). Four of them had a pre-existing condition, and three of the four remaining patients had a BMI of 25 or higher (**Table 4**). One patient who died but did not have a known pre-existing condition and a BMI of < 25 died from CLABSI. The patient had a high lactate level from the time of transfer and died on hospital day 6. At the time of admission, bilateral chest infiltration was observed in two patients, but by day 7, all patients showed bilateral chest infiltration.

All eight patients were either unvaccinated (n = 7) or did not complete the full vaccination schedule (≥ 90 days since first dose, n = 1).

DISCUSSION

The present study differs from previous studies in that the participants were limited to critical patients on respiratory support (HFNC or greater support) and it analyzed the CFR-S and risk factors for mortality in patients ≤ 50 years of age. The overall CFR-S was 21.0% in our study, markedly higher than the 1.54% reported based on the WHO data.[3] Even by age, the CFR-S was 5.6% in the ≤ 50 years group, 29.3% in the > 50 years group, and 38.22% in the ≥ 65 years group, which are also higher than the values reported (20%) in another study on patients aged 65 years and older.[14] This may be attributable to the fact that this study was only conducted on critical patients placed on HFNC or higher respiratory support, and our findings confirm that CFR-S is markedly high when COVID-19 progresses to a critical case. The CFR-S was even higher in cases that required MV or higher respiratory support, 25% for patients aged 50 years and younger and 71% for 65 years or older. A Chinese study[15] evaluated mortality among young adults showed 25% of CFR-S, which is much higher than those of our study (5.6%). This might be because they included patients younger than 60 years, while 50 years or younger in this study. The mortality would be different between patients aged 50–60 years and younger than 50 years, because age is the most important risk factor for mortality in COVID-19.[1,4,6,14] Furthermore, the Chinese study was conducted during early period of COVID-19 pandemic, when remdesivir or steroid treatment was not recommended as a standard therapy, while more than 90% of the patients were treated with remdesivir and steroid in our study. This result confirms that remdesivir and steroid treatment has contributed to reduction of case fatality. Nonetheless, CFR-S was irrelevant to age in the young population of this study, while mortality increased with advancing age in the older population.

Table 4. Clinical characteristics of the deceased patients under 50 years

Patient number	1	2	3	4	5	6	7	8
Sex (M/F)	M	F	M	F	F	M	M	M
Age, yr	50	43	47	48	35	33	25	26
BMI	20.24	24.22	31.76	27.34	18.96	29.05	37.35	27.45
Transferred after diagnosis	No	Yes	Yes	Yes	Yes	Yes	Yes	No
History of exposure	Unknown	Unknown	Unknown	Unknown	Contact	Unknown	Unknown	Family
Vaccination	1st[a]	None	None	None	None	None	None	None
Underlying diseases								
Any	Yes	Yes	No	No	No	Yes	No	Yes
Hypertension	Yes	No	No	No	No	Yes	No	No
Heart disease	No	No	No	No	No	No	No	Yes
Chronic liver disease	Yes	No	No	No	No	No	No	No
Solid tumor	Yes	Yes	No	No	No	No	No	No
Steroid or immune suppressant	No	Yes	No	No	No	No	No	No
Initial manifestation								
Body temperature	36.7	38.1	38	36.9	36.4	38.7	37.7	38.7
O_2 saturation	96	93	98	86	98	93	89	94
Lymphocyte count, 10^9/L	2.10	0.94	0.87	0.4	5.20	1.43	1.62	0.76
Lactate, mmol/L	6.2		2.3		17.23		1.5	0.7
Chest infiltration	Bilateral	None	None	None	Bilateral	None	None	None
Laboratory findings (during treatment)								
Highest WBC, 10^9/L	54.960	21.500	23.820	26.150	24.600	39.770	25.370	13.08
Lowest lymphocyte, 10^9/L	1.59	0.57	0.18	2.30	1.80	0.32	1.52	0.28
Lowest platelet, 10^9/L	8	171	53	30	78	34	140	123
Highest LDH, U/L	675	931	875	1,804	2,941		2,595	324
Highest creatinine, mg/L	4.4	0.58	2.39	1.59	2.13	5.94	3.02	0.24
Highest procalcitonin, mg/L	1	2	2			44		
Highest respiratory support	HFNC	MV	ECMO	ECMO	MV	ECMO	ECMO	MV
CRRT	No	No	Yes	Yes	No	Yes	Yes	No
Complication								
Blood stream infection	No	No	No	No	CLABSI	No	CLABSI	No
Bacterial pneumonia	No	No	Yes	Yes	No	No	No	No
Variant	Delta	None	Delta	Unknown	Unknown	Delta	Unknown	Unknown
Treatment								
Regdanvimab	Yes	No	No	No	No	No	No	No
Tocilizumab	Yes	No	Yes	Yes	No	No	No	No
Steroid treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Remdesivir	No	Yes	Yes	Yes	No	No	No	Yes
Baricitinib	No	No	No	Yes	No	No	No	No
Other	Telipressin	No	No	No	No	No	No	No
Hospital day of death	14	80	45	16	6	61	33	9

BMI = body mass index, WBC = white blood cell, LDH = lactate dehydrogenase, HFNC = high-flow nasal cannula, MV = mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CRRT = continuous renal replacement therapy, CLABSI = combined blood stream infection.
[a]1st dose (over 90 days ago).

Critical patients aged 50 years and younger included in our study had a higher BMI than their older (> 50 years) counterparts and had a lower prevalence of pre-existing conditions, and this difference seems to be attributable to the age difference. The proportion of patients having BMI higher than 25 in critical patients under 50 years old was 69.7%, which is two-fold higher than in general population, and this supports that obesity is a risk factor for severe COVID-19 in young adults.

Regarding risk factors associated with mortality, age (95% CI, 11.993–18.919), initial creatinine > 1.5 mg/dL (95% CI, 2.898–10.194), highest creatinine > 1.5 mg/dL (95% CI, 11.855–37.685), lowest platelet count < 100 (10^9/L) (95% CI, 7.268–20.770), use of MV (95% CI, 10.079–30.493), and CRRT (95% CI, 7.513–34.611) were identified as significant independent predictors of mortality in this study. This is similar to the findings of prior studies. A Korean

study on adults aged 65 years and over[14] identified HAI, DM, chronic lung disease, chronic neurologic disease, hypoxia, altered mental status, and CRP > 8.0 mg/dL as mortality risk factors, and in our study, these factors were significant mortality risk factors in the univariate analysis but not in the multivariate analysis, presumably because they are common risk factors for both severity and mortality and our study included only critical cases. Some studies reported sex-specific differences in mortality rates,[16,17] and some hypothesized this to be influenced by androgen.[16] However, sex was not a significant predictor of mortality in the entire patient population or in the ≤ 50 years and > 50 years groups.

The predictors of mortality in the ≤ 50 years group were similar to those in the total patient population, but solid tumor was another significant risk factor in this group. CFR-S is high among patients with active cancer, so prevention is important for this specific patient population. The CFR-S was high among patients with a pre-existing condition, but the result was not significant due to the small number of deaths. Regarding obesity, 5 out of 8 patients who died in the ≤ 50 years group having a BMI ≥ 25 and two having a BMI ≥ 30. A study that examined 210 patients aged 18–45 years confirmed with COVID-19 in the US[9] reported that BMI ≥ 30 (OR, 6.29; 95% CI, 1.76–22.46, P = 0.004) as well as MV (OR, 6.01; 95% CI, 2.5–14.48, P < 0.001) was a statistically significant predictor of mortality, and other studies on children[8] and adults[17] also support the hypothesis that obesity exacerbates COVID-19 infection and increases the risk for mortality. The prevalence of obesity is lower in the Korean population compared to other racial populations; thus, further studies are needed.

One notable finding is that 31 out of 142 patients aged 50 years and younger with critical COVID-19 infection (22%, 19 women) did not have a known risk factor, such as BMI > 25 or a pre-existing condition. This is more distinguishable when compares with the fact that only 14 patients who died in the > 50 years group did not have a pre-existing condition. This shows that even the young, healthy population without a pre-existing condition could—although less likely—progress to a severe case, necessitating effort to prevent the infection in advance.

In this study, patients who had been transferred into the hospital seemed to have better prognosis. This could be due to the current system in Korea, where patients without a pre-existing condition are first admitted to a residential treatment center and are transferred to a hospital only after the disease progresses, and there were no differences between the groups in the multivariate analysis. For the blood test, mid-treatment results, as opposed to early blood test results, significantly differed between survivors and patients who died in the young patient group, but this difference was also not significant in the multivariate analysis, highlighting the possibility of organ failure markers. Nosocomial infection[14] and hypertension were identified as risk factors in some studies and were insignificant in others, and these factors did not significantly predict mortality in our study. Recently, there have been doubts on the validity of various criteria for identifying predictors. This is because it is difficult to identify consistent mortality predictors, other than age, in studies that include many patients in the real world, and the actual predictability of various known criteria is not high.[18,19] Continued research is needed to determine significant risk factors.

All eight cases of death in the ≤ 50 years group were unvaccinated (n = 7) or incompletely vaccinated (≥ 90 days from first dose, n = 1). Although the results were statistically insignificant due to the small number of deaths and 0% complete vaccination rate among patients who died, only three individuals even in the entire young critical patient group (≤ 50 years) were fully vaccinated, and only 13.6% of the patients in the total patient population

were fully vaccinated. Considering that the second-dose vaccination rate among Korean adults reached 80% as of July 3,2021 and 90.54% as of November 30, 2021[20] and that the complete vaccination rate of all confirmed patients in November was more than 80%,[21] the fact that more than 95% of the critical young adult cases and none of the patients who died were not fully vaccinated is notable. A recent press release by the Korean government showing that getting a booster shot lowers the risk of progressing to a critical case[22] can also be understood in a similar context with the high rate of non-vaccination among critical patients in our study. A clinical trial and a real-world, large-scale observational study conducted in various countries around the world reported that vaccination significantly lowers the risk.[23,24] Despite the fact that usefulness and safety of vaccination have been proven in a meta-analysis[25] and systemic review,[26] there is continued controversy on the adverse events and efficacy of vaccination[27] in Korea. Our results that all cases of death in the ≤ 50 years group were non-vaccinated, and that only three out of 142 young critical patients were fully vaccinated are significant, and this data attests to the importance of vaccination to prevent critical progression and death from COVID-19.

This study has a few limitations. First, this study was a retrospective study conducted on a relatively narrow range of patients. Because we compared survivors with patients who died among those who had a critical COVID-19 infection, as opposed to the entire COVID-19 patient population, it is possible that variables that were found to be significant in other studies (vaccination, obesity) were not significant in our study. Therefore, our results cannot be generalized to the entire patient population, and follow-up studies with a broader range of patients are needed. Nevertheless, the analysis on CFR-S and risk factors for mortality in critical patients, especially in younger adults, would provide insights for management of critical patients. Furthermore, this study might represent national data because patients admitted to hospitals nationwide were included.

Second, we examined data from the fourth wave, during which the delta variant was the dominant variant. Hence, the features of the wave may differ from that involving the Omicron variant or other subsequent variants. However, the risk factors identified in our study were similar to those identified by previous studies prior to the advent of this variant, and better reflecting the delta variant surge could actually be a strength of this study. A similar type of study should be performed for the omicron surge.

Third, we defined obesity as patient with a BMI over 25, which is lower than other studies that defined obesity as a BMI over 30. This may have influenced the outcome in which BMI was not significant as a mortality risk factor. However, it should be taken into account that the BMI of Asians is generally low.[28] Also, BMI over 30 was not significant as a mortality risk factor in our study. We considered BMI over 25, considered as obesity criteria in Korea, as an analysis more suitable for the Korean situation than a BMI over 30.

Finally, there were only eight deaths in the ≤ 50 years group, which might have contributed to the lack of statistical significance for some results. Both age-related features and examination of only the Delta variant-dominant period seemed to have contributed to the results. However, we tried to complement our findings by conducting a multicenter study and by additionally analyzing the characteristics of patients who died to present information about mortality risk factors and individual patient status information. Despite these limitations, however, we believe that we have presented valuable data on the clinical outcomes and resource needs among the younger COVID-19 patient populations—a group of patients

that has been documented to be relatively safe against COVID-19 and thus has sometimes been considered an exemption to vaccination and aggressive protection policies—as well as providing evidence for further research in the future.

In conclusion, the rate of obesity was high in young (≤ 50 years) critical cases, with a CFR-S of above 5% in this patient group; more than 20% did not have an underlying disease or obesity. The vaccination rate in our total patient population was significantly lower than that in the same age group in the general population. None of the patients aged 50 years and younger who died were not fully vaccinated. It should be noted that even young, healthy adults without a pre-existing condition could progress to a critical case or even death, and more attention should be paid to preventive measures, such as vaccination, targeting this population. Additional studies are needed with larger patient population.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIALS

Definition of underlying disease
Any underlying disease: one or more underlying disease described below

Diabetes mellitus
- history of diagnosed Type 1 or Type 2 DM

Hypertension
- Systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 or taking hypertensive medication with diagnosis of hypertension

Chronic lung disease
- Chronic obstructive pulmonary disease (COPD), Asthma, asthma COPD overlap syndrome (ACOS), interstitial lung disease, bronchiectasis

Chronic heart disease (except hypertension)
- Coronary artery disease, Heart failure, pulmonary hypertension, congenital or acquired valvular heart disease

Chronic kidney disease with dialysis
- Patient with hemodialysis or peritoneal dialysis

Chronic kidney disease without dialysis
- The glomerular filtration rate (GFR) calculated by Cockcroft-Gault ≤ 60 mL/min/1.73 m2 for more than 3 months, but no dialysis.

Chronic liver disease

- Chronic HBV carrier, HCV carrier, liver cirrhosis, cholestatic liver disease, alcoholic liver disease or Non-alcoholic fatty liver disease

Chronic neurologic disease

- History of brain infarction, brain hemorrhage, or dementia with clinical dementia rating score ≥ 3

Solid tumor

- Solid organ tumor such as stomach, small bowel, large bowel, liver, pancreas, gall bladder, lung, kidney, bladder, thyroid, breast, ovary, prostate, etc.

Hematologic malignancy

- Myeloid or lymphocytic leukemia, malignant lymphoma, multiple myeloma, myelodysplastic syndrome

Definition of lowest oxygen saturation

- Lowest oxygen saturation at room air, if room air saturation is not possible, the lowest saturation with least oxygen supply status.

Definition of altered mentality

- Patient response to pain or no response

Supplementary Table 1

Predictors of mortality in study patients (univariate and multivariate analysis)

Click here to view

Supplementary Table 2

Risk factors for mortality of the patients age over 50 group (N = 306) (univariate analysis)

Click here to view

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