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Poor prognosis of patients with severe COVID-19 admitted to an infectious disease intensive care unit during the pandemic caused by the Delta variant in Japan

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Abstract: During the surge of coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) delta variant, our institution operated an intensive care unit (ICU) for patients with severe COVID-19. The study aim was to determine the survival rate and treatment outcomes of patients with severe COVID-19 treated in the ICU during the surge. A total of 23 consecutive patients with severe COVID-19 were admitted to the ICU between August 5 and October 6, 2021. Patients received multidrug therapy consisting of remdesivir, tocilizumab, heparin, and methylprednisolone. The patients were divided into two groups based on the ordinal scale (OS): a non-invasive oxygen therapy (OS-6) group, and an invasive oxygen therapy (OS-7) group. There were 13 (57%) and 10 (43%) patients in the OS-7 and OS-6 groups, respectively. All patients were unvaccinated. Sixteen patients (70%) were male. The median age was 53 years; the median body mass index (BMI) was 30.3 kg/m^2; and the median P/F ratio on admission was 96. The 30-day survival rate was 69% and was significantly poorer in the OS-7 group (54%) than in the OS-6 group (89%; $p = 0.05$). The prevalence of obesity ($p = 0.05$) and the Sequential Organ Failure Assessment (SOFA) score on admission ($p < 0.01$) were significantly higher in the OS-7 group. Seven patients in the OS-7 group (54%) developed bacteremia. A low P/F ratio on admission was a significant unfavorable prognostic factor (hazard ratio: 10.9; $p = 0.03$). The survival rate was poor, especially in patients requiring invasive oxygen therapy. More measures are needed to improve the treatment outcomes of patients with severe COVID 19.

***Keywords*:** SARS-CoV-2 infection, mortality, mechanical ventilation, secondary hospital-acquired infection

Introduction

The number of cases of coronavirus disease (COVID-19) due to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection continues to increase worldwide (*1-3*). The severity of the disease varies widely, ranging from asymptomatic to fatal cases. In Japan, the overall number of patients exceeds 1,700,000, and there have been more than 18,000 COVID-19-related deaths (*4*). Coronaviruses are prone to mutation, resulting in changes in infectivity and virulence. The delta variant is extremely infectious and has spread worldwide (*5*). In Japan, the delta variant was prevalent in the summer of 2021 (*6*), and the number of newly diagnosed cases exceeded 5,000 per day (*4*).

Some patients with COVID-19 may present with respiratory failure and require intubation and mechanical ventilation. The effectiveness of extracorporeal membrane oxygenation (ECMO) for severe respiratory failure has already been demonstrated for H1N1 influenza (*7*). ECMO is also recommended for eligible patients with SARS-CoV-2 (*8,9*). The appropriate use of invasive oxygen therapy, and technology such as artificial respirators and ECMO, can be life-saving in patients with severe COVID-19.

However, due to the rapid increase in the number of infected patients, the public health center ordered individuals with mild disease to stay at home. Some patients deteriorated while staying at home, and some died without being admitted to hospital. Securing an infectious disease ward to accommodate patients with

COVID-19 was a national problem because the number of intensive care units (ICUs) with available artificial respirators and ECMO were limited. Our institution reconstructed the high care unit, which was usually used for postoperative management, and converted it into an ICU for patients with severe COVID-19.

Few studies have reported the survival rate of patients with severe COVID-19 during the surge in the COVID-19 pandemic in Japan caused by the delta variant of SARS CoV 2, and the survival rate of patients who require ICU admission is unknown. Our clinical impression of the pandemic caused by the delta variant is different from the previous pandemics. There is an increased number of patients, the age of patients is younger, the incidence of obesity is higher, and it is more difficult to save lives. In this study, we examine the survival rate of patients with severe COVID-19 treated in the infectious disease ICU at our hospital in order to improve the quality of intensive care and future treatment outcomes.

Patients and Methods

Study design and patients

Patients with severe COVID-19 who were admitted to the infectious ICU of the National Center for Global Health and Medicine in Tokyo between August 5 and October 6, 2021 were included in the analysis. The admission and discharge criteria for the ICU are described below. Patients were provided with oxygen using nasal high flow therapy (NHF; Optiflow™, Fisher and Paykel), non-invasive positive pressure ventilation (NPPV; V60 ventilator™ produced by PHILIPS), an artificial respirator (Puritan Bennett™ 840, Medtronic), or ECMO (MERA centrifugal blood pump system HCS-CFP™ produced by MERA). The severity of COVID-19 was evaluated according to the National Institute of Allergy and Infectious Disease ordinal scale (OS), depending on the method of oxygen therapy. We divided the patients into two groups based on OS. The OS-6 group received non-invasive oxygen therapy using NHF or NPPV and the OS-7 group received invasive oxygen therapy using an artificial respirator or ECMO. The diagnosis of COVID-19 was confirmed by detection of SARS-CoV-2 RNA using polymerase chain reaction tests. Samples were checked for genetic mutations of SARS-CoV-2. The P/F ratio was calculated as the ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO2). According to the Extracorporeal Life Support Organization guidelines for COVID-19 (*10*), ECMO was considered for patients with a P/F ratio < 150. The hemoglobin A1c (HbA1c) level was examined in patients with a history of diabetes mellitus (DM) and patients who were hyperglycemic at the time of ICU admission. Blood, sputum, and urine samples were cultured at least once per week. Additional cultures were performed as needed, based on clinical findings, including fever and inflammatory.

This study was approved by the National Center for Global Health and Medicine institutional review board (approval number: 004411), and the need to obtain written informed consent was waived by posting a release of information document that enabled patients to opt out of the study.

Intensive care unit admission and discharge criteria

The criteria for ICU admission were as follows: *i*) patients requiring invasive oxygen therapy (OS-7) using an artificial respirator or ECMO; *ii*) patients requiring non-invasive oxygen therapy (OS-6; NHF or NPPV) with a P/F ratio of < 200; and *iii*) patients with COVID-19 with complications such as convulsions, heart failure, or diabetic ketoacidosis. The criteria of discharge from the ICU were as follows: *i*) stable respiratory function after extubation; *ii*) improvement of the P/F ratio; or *iii*) a stable general clinical condition and a stable P/F ratio < 150, enabling the patient to be treated in the general infectious disease wards.

Treatment strategy

Patients received multidrug therapy as follows: *i*) A 5-day course of remdesivir, 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 4 days of treatment if patients had a creatinine clearance > 30 mL/min and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels less than five times the upper limit of normal (*11-13*). *ii*) Tocilizumab 8 mg/kg body weight was administered intravenously, up to a dose of 800 mg on day 1. Patients with a recent history of treatment with biologic agents or immunosuppressive therapy were excluded (*14,15*). *iii*) Heparin sodium 10,000 U/day was administered intravenously during the ICU stay (*16*) provided that the activated partial thromboplastin time was < 60 s. Heparin sodium was also administered intravenously to patients on ECMO therapy, using activated clotting time (ACT) as an index, with a target of 180-200 s. *iv*) Methylprednisolone (2 mg/kg/day) was infused intravenously over 60 min, and tapered by half dosage every 5 days. Methylprednisolone treatment was discontinued in any patient who developed severe elevations in blood pressure or blood sugar (*17*).

Statistical analyses

Differences in categorical variables were analyzed using Fisher's exact test. Univariate analysis of overall survival was performed to identify prognostic factors using Cox proportional hazards regression. Cumulative survival was estimated using the Kaplan-Meier method, and

differences between groups were evaluated using the log-rank test. The overall survival was defined as the time from the date of admission to the date of death from any cause or the date of the last follow-up. All *p*-values were two-sided, and the statistical significance level was set at $p < 0.05$. All statistical analyses were performed with R for Windows GUI front-end version 3.0.2 (R Development Core Team 2013, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria. *http://www.r-project.org*).

Results

Clinical characteristics of patients

A total of 23 patients were admitted to the ICU with severe COVID-19 between August 5 and October 6, 2021. The clinical course and terms of ICU stay of each patient are shown in Figure 1. The median length of ICU stay was 11 days. The clinical characteristics of patients with severe COVID-19 are shown in Table 1. Sixteen of the 23 patients (70%) were male and the median age was 53 years (range: 28-78 years). The median body mass index (BMI) was 30.3 kg/m^2 (range: 18.7-52.2 kg/m^2) and the prevalence of obesity (BMI ≥ 25 kg/m^2) was 70%. Seven patients (30%) had hypertension, and 14 patients (60%) had diabetes mellitus (DM). Eight patients (35%) had a smoking history. Among the patients with a smoking history, the median Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking) was 575 (range: 320-880). The median interval from onset to admission was 9 days (range: 3-43 days). One patient was transferred to our hospital from another hospital 43 days after onset. The median P/F ratios on admission and discharge were 96 (range: 62-283) and 129 (range: 36-550), respectively. The median

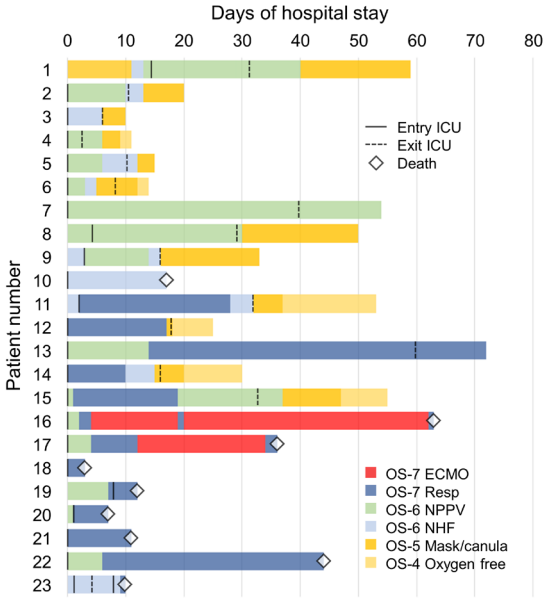

Figure 1. Clinical course of each patient. ECMO: extracorporeal membranous oxygenation; ICU: intensive care unit; Resp: artificial respirator; NHF: nasal high flow; NPPV: non-invasive positive pressure ventilation.

Table 1. Patient characteristics (*n* = 23)

Variables		All patients (*n* = 23)
Age (median, range)		53 (28-78)
Sex (*n*, %)	Male	16 (70)
BMI (median, range)		30.3 (18.7-52.2)
Obesity (*n*, %)		17 (74)
Hypertension (*n*, %)		7 (30)
Diabetes mellitus (*n*, %)		14 (60)
HbA1c (median, range)		7.7 (6.6-10.9)
Rheumatoid arthritis (*n*, %)		2 (9)
Smoking history (*n*, %)		8 (35)
Brinkman index (median, range)		575 (320-880)
Days from onset to admission		9 (3-43)
P/F ratio (median, range)	Admission	96 (62-283)
	Discharge	129 (36-550)
SOFA score (median, range)	Admission	6 (3-10)
	Discharge	4 (1-12)
SARS-CoV-2 variant (*n*, %)	L452R	18 (78)
	N501Y	2 (9)
	Unknown	3 (13)
Laboratory test results (median, range)	WBC (cells/uL)	7,290 (4,710-23,340)
	CRP (mg/dL)	11.54 (0.39-26.1)
	LDH (U/L)	654 (233-1,521)
	KL-6 (U/mL)	1,168 (295-4,396)
	D-dimer (ug/mL)	3.4 (0.5-89.5)

BMI: body mass index; CRP: C-reactive protein; FiO_2: fraction of inspired oxygen; HbA1c: hemoglobin A1c; KL-6: Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO_2: partial pressure of arterial oxygen; P/F ratio: ratio of PaO_2 to FiO_2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: Sequential Organ Failure Assessment; WBC: white blood cells.

Sequential Organ Failure Assessment (SOFA) scores on admission and discharge were 6 (range: 3-10) and 4 (range: 1-12), respectively. The L452R mutation was detected in 18 patients (78%) and the N501Y mutation was detected in 2 patients (9%). The SARS CoV 2 strain could not be determined in 2 patients because the RNA could not be amplified, and one patient who was transferred from another hospital was not tested for the SARS-CoV-2 strain. The majority of patients had elevated levels of C-reactive protein (CRP) (median: 11.54 mg/dL, upper limit of normal: 0.14 mg/dL), lactate dehydrogenase (LDH) (median: 654 U/L, upper limit of normal: 222 U/L), Krebs von den Lungen-6 (KL-6) (median: 1,168 U/L, upper limit of normal: 450 U/L), and D-dimer (median: 3.4 μg/mL, upper limit of normal 1.0 μg/mL). Two patients received immunosuppressive therapy for rheumatoid arthritis.

Invasive oxygenation was required by 13 (57%) of the 23 patients. The clinical characteristics of the OS-7 and OS-6 groups are shown in Table 2. In the OS-7 group, 8 patients (62%) were male, and the median age was 56 years (range: 28-68 years). Although there was no significant difference in BMI in the OS-7 group and OS-6 group (30.0 *vs.* 25.0; $p = 0.12$), the prevalence of obesity was significantly higher in the OS-7 group than the OS-6 group (92% *vs.* 50%; $p = 0.05$). There was no significant difference between the OS-7 and OS-6 groups in the prevalence of hypertension (38% *vs.* 20%; $p = 0.41$), DM (54% *vs.* 70%; $p = 0.67$), or smoking history (23% *vs.* 50%; $p = 0.22$). In addition, there was no significant difference in the interval from onset to admission, P/F ratio, or the laboratory test results between groups. The SOFA score on admission was significantly higher in the OS-7 group than the OS-6 group (median: 7 *vs.* 4; $p < 0.01$).

Secondary infections during the intensive care unit stay

Seven patients in the OS-7 group (54%) and no patients in the OS-6 group developed bacteremia ($p < 0.01$). The causative agents were *Klebsiella pneumoniae* in three patients, methicillin-susceptible *Staphylococcus aureus* (MSSA) in two patients, *Staphylococcus hominis* in one patient, and *Staphylococcus pneumoniae* in another patient. One patient with MSSA bacteremia developed infectious endocarditis and severe aortic regurgitation and required surgery for the aortic regurgitation. Another patient with bacteremia caused by *Klebsiella pneumoniae* died and was discovered to have had a second infection with *Pseudomonas aeruginosa* after her death. No fungal infections were detected in any patients.

Survival and prognostic factors

The median follow-up period was 33 days. Nine (39%) of the 23 patients died during the follow-up period (patient numbers #10 and #16 to #23 in Figure 1). The overall mortality rates were 10% (1/10) and 62% (8/13) in the OS-6 and OS-7 groups, respectively. The cause of death was respiratory failure due to COVID-19 in

Table 2. Patient characteristics according to disease severity

Variables		Patients with OS-7 disease ($n = 13$)	Patients with OS-6 disease ($n = 10$)	p value
Age (median, range)		56 (28-68)	52 (37-78)	0.93
Sex (n, %)	Male	8 (62)	8 (80)	0.41
BMI (median, range)		30.0 (21.2-52.2)	25.0 (18.7-40.0)	0.12
Obesity (n, %)		12 (92)	5 (50)	0.05
Hypertension (n, %)		5 (38)	2 (20)	0.41
Diabetes mellitus (n, %)		7 (54)	7 (70)	0.67
HbA1c (median, range)		8.0 (6.6-10.9)	7.4 (6.6-9.5)	-
Rheumatoid arthritis (n, %)		0 (0)	2 (20)	0.18
Smoking history (n, %)		3 (23)	5 (50)	0.22
Brinkman index (median, range)		660 (330-780)	550 (320-880)	-
Days from onset to admission (median, range)		8 (4-17)	9 (3-43)	0.27
P/F ratio (median, range)	Admission	96 (62-283)	92 (64-263)	0.94
	Discharge	86 (44-550)	138 (36-292)	0.70
SOFA score (median, range)	Admission	7 (4-10)	4 (3-7)	< 0.01
	Discharge	8 (1-12)	3 (1-7)	0.02
SARS-CoV-2 variant	L452R	10 (77)	8 (80)	> 0.99
	N501Y	1 (8)	1 (10)	-
	Unknown	2 (15)	1 (10)	-
Laboratory test results (median, range)	WBC (cells/uL)	9,210 (4,710-23,340)	6,540 (5,230-17,330)	0.29
	CRP (mg/dL)	12.0 (0.65-26.1)	9.0 (0.39-22.2)	0.76
	LDH (U/L)	781 (233-1,344)	615 (360-1,521)	0.95
	KL-6 (U/mL)	931 (295-2,617)	1,604 (697-4,396)	0.17
	D-dimer (ug/mL)	6.0 (0.5-89.5)	3.0 (1.1-23.3)	0.15

BMI: body mass index; CRP: C-reactive protein; FiO_2: fraction of inspired oxygen; HbA1c: hemoglobin A1c; KL-6: Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO_2: partial pressure of arterial oxygen; P/F ratio: ratio of PaO_2 to FiO_2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: Sequential Organ Failure Assessment; WBC: white blood cells.

all fatal cases. The 30-day survival rate of all patients was 69% (Figure 2A). The 30-day survival rate of the OS-7 group was significantly lower than that of the OS-6 group (54% *vs.* 89%, respectively; $p = 0.05$; Figure 2B). Table 3 shows the results of the univariate analyses of prognostic factors for overall survival for the study cohort. The only factor associated with a significantly worse prognosis was severe respiratory failure on admission (Hazard ratio [HR] 10.9; $p = 0.03$). Older age (HR: 1.99; $p = 0.40$), males (HR: 0.57; $p = 0.57$), hypertension (HR: 1.68; $p = 0.44$), DM (HR: 3.21; $p = 0.15$), obesity (HR: 2.75; $p = 0.35$), and invasive oxygenation (HR: 6.27; $p = 0.09$) were not significantly associated with prognosis.

Discussion

All patients included in the analysis had severe COVID-19, with a median P/F ratio of 96 on admission. Despite their relatively young age, the 30-day survival rate was poor (69%), particularly in the OS-7 group (54%).

In Japan, surges of COVID-19 infection rate occurred sixth times: from April to June in 2020 ("first wave"), from August to October in 2020 ("second wave"), from December in 2020 to March in 2021 ("third wave"), from April to July in 2021 ("fourth wave"), from August to October 2021 ("fifth wave"), and from January 2022 ("sixth wave" is still continuing presently). In our institution, the median age of patients who needed invasive oxygen therapy (the definition was the same as the OS-7 group) was 67, 74, 70, 60, for each of the first four waves respectively. The incidence of obesity was 18%, 56%, 27%, 60%, respectively. The mortality was 29%, 22%, 45%, 20% respectively (unpublished data). In the current wave in the OS-7 group, the median age was 56, the rate of obesity was 92%, and the mortality was 62%. This data supported our clinical impression described in the introduction.

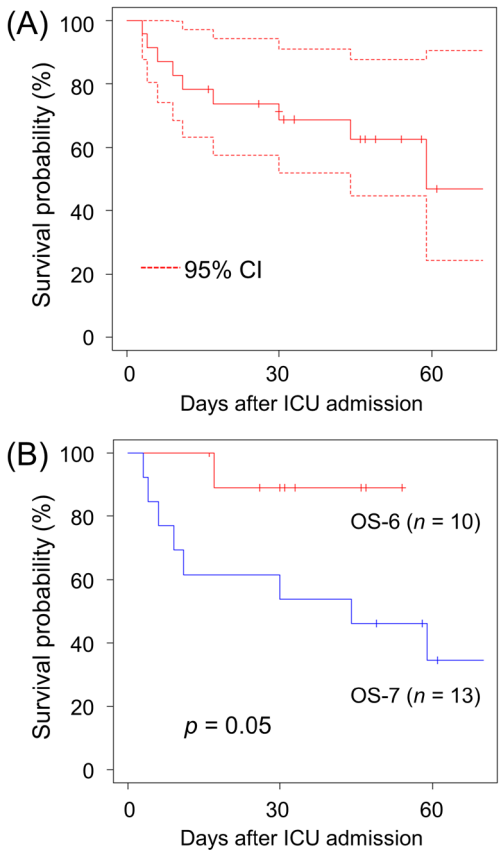

Figure 2. Patient overall survival according to time since admission to the intensive care unit. (A) Survival in all patients, **(B)** Survival according to the OS group. CI: confidence interval, OS: US National Institute of Allergy and Infectious Diseases ordinal scale of disease severity.

The delta strain is highly virulent and highly contagious and has spread worldwide (*5*). It has spread extensively in Asia (*18,19*) and caused the "fifth wave" of COVID-19 in Japan in the summer of 2021 (*4*). In this study, the L452R mutation, which is a spike protein mutation of the delta variant, was detected in approximately 80% of patients (*20*). Vaccines have been found to be highly efficacious in preventing symptomatic disease, as shown by clinical trials (*21-23*). The rapid development and deployment of vaccines has been the single greatest achievement for prevention during the COVID-19 pandemic in the United Kingdom (*24*). In Japan, COVID-19 vaccination was started in people aged 65 years or older. In our study, the patients were relatively young with a median age of 53 years and all were unvaccinated.

Treatment for COVID-19 included remdesivir, tocilizumab, heparin, and methylprednisolone, each of which has been shown to be effective in clinical trials (*11-17*). Remdesivir is less effective in severe cases, and its usefulness in patients with severe disease has not been confirmed (*13*). However, steroids and heparin

Table 3. Results of the univariate Cox proportional hazards regression analysis of risk factors for death ($n = 23$)

Variables		*n*	Hazard ratio	*p* value
Age (years)	< 50	7	*ref*	
	≥ 50	16	1.99 (0.41-9.64)	0.40
Sex	Female	7	*ref*	
	Male	16	0.68 (0.18-2.67)	0.57
Obesity	Absent	6	*ref*	
	Present	17	2.75 (0.34-22.5)	0.35
Hypertension	Absent	16	*ref*	
	Present	7	1.68 (0.45-6.32)	0.44
Diabetes mellitus	Absent	9	*ref*	
	Present	14	3.21 (0.64-16.1)	0.15
Smoking history	Absent	15	*ref*	
	Present	8	0.23 (0.03-1.81)	0.16
NIAID Ordinal Scale	OS-6	10	*ref*	
	OS-7	13	6.27 (0.77-51.2)	0.09
P/F ratio	≥ 100	11	*ref*	
	< 100	12	10.9 (0.09-13.3)	0.03

FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of arterial; NIAID: US National Institute of Allergy and Infectious Diseases; P/F ratio: ratio of PaO_2 to FiO_2; ref: reference.

have been reported to be highly effective in severe cases (*13,16*). Patients with poor response to the regimen for mild/moderate disease, worsening oxygenation, and no improvement in their condition were admitted to the infectious disease ICU. The median P/F ratio on admission was 96, indicating severe respiratory failure, which has been reported to be associated with a mortality rate of over 80% (*10*).

Despite the patients being relatively young, the 30-day survival rate was 69%, which was extremely poor even with intensive care using ECMO. The prognosis was significantly worse when the patient was intubated. Although univariate analysis did not reveal that invasive oxygenation was a prognostic factor, the P/F ratio on admission was associated with significantly poorer prognosis. A previous report has shown that the timing of invasive oxygen therapy does not affect mortality (*25*). Thus, our data demonstrated the possibility that mortality reflects respiratory function due to the progression of COVID-19. Another reason for the poor prognosis of our patients was complications. The SOFA score on admission was significantly higher in the OS-7 group than the OS-6 group due to factors such as impaired consciousness due to diabetic ketoacidosis and catecholamine activation due to low cardiac function.

In intubated patients, there is a risk of ventilator-associated pneumonia (*26,27*). In addition, the increase in the number of catheters, such as the central venous lines and ureteral catheters, and the use of immunosuppressive drugs, increases the risk of secondary healthcare-associated infections (*28*). In our study, two patients developed bacteremia that was difficult to treat. The incidence of secondary healthcare-associated infections has been reported to be approximately 10-15/1,000 days of catheter exposure (*29-31*). In our study, the OS-7 group, of whom 54% had bacteremia, had a high risk of secondary infection. The incidence of bacteremia has increased during the COVID-19 pandemic (*32*), posing an important challenge for ICU management.

Although immunosuppressive agents have been reported to be effective in suppressing cytokine storms, excessive immunosuppression increases the risk of secondary infection. There is a concern that new mutant strains may become more prevalent in the future. The increasingly large number of clinical trials and research studies with various combinations of drugs has made it difficult to establish appropriate treatment (*24*). A treatment regimen for patients with severe COVID-19 with a mechanism of action other than immunosuppression is needed.

There were some limitations to our study. First, the number of cases was small because the study was a single-center retrospective study carried out over a two-month period. However, the ICU was a temporary ICU that operated only during the fifth wave of the pandemic, and it made an important contribution to treating 23 patients with the most severe COVID-19 in just 2 months. Second, there were clear criteria for admission, but because it was an emergency situation, the criteria for discharge were unclear, and some patients who were not well enough to be discharged from the ICU under normal circumstances were discharged early. Third, although there was a clear association between a poor P/F ratio and death, we were unable to perform a multivariable analysis of the risk factors for death.

Few studies have been published on the survival rate of patients with severe COVID-19 admitted to ICUs. Many challenges were attributable to the emergency situation during the pandemic. This study provides an understanding of the current situation regarding the outcomes in patients with severe COVID-19 due to the delta variant. In conclusion, the survival rate was poor, especially in patients requiring invasive oxygen therapy. Since all patients were unvaccinated, it underlines the need for widespread vaccinations in the community. And the quality of intensive care needs to be improved in order to improve future treatment outcomes.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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