Clinical characteristics and outcomes of critically ill patients with COVID-19 in Kobe, Japan: a single-center, retrospective, observational study

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Abstract
Purpose  Coronavirus disease 2019 (COVID-19) has placed a great burden on critical care services worldwide. Data regarding critically ill COVID-19 patients and their demand of critical care services outside of initial COVID-19 epicenters are lacking. This study described clinical characteristics and outcomes of critically ill COVID-19 patients and the capacity of a COVID-19-dedicated intensive care unit (ICU) in Kobe, Japan.

Methods  This retrospective observational study included critically ill COVID-19 patients admitted to a 14-bed COVID-19-dedicated ICU in Kobe between March 3, 2020 and June 21, 2020. Clinical and daily ICU occupancy data were obtained from electrical medical records. The last follow-up day was June 28, 2020.

Results  Of 32 patients included, the median hospital follow-up period was 27 (interquartile range 19–50) days. The median age was 68 (57–76) years; 23 (72%) were men and 25 (78%) had at least one comorbidity. Nineteen (59%) patients received invasive mechanical ventilation for a median duration of 14 (8–27) days. Until all patients were discharged from the ICU on June 5, 2020, the median daily ICU occupancy was 50% (36–71%). As of June 28, 2020, six (19%) died during hospitalization. Of 26 (81%) survivors, 23 (72%) were discharged from the hospital and three (9%) remained in the hospital.

Conclusion  During the first months of the outbreak in Kobe, most critically ill patients were men aged ≥ 60 years with at least one comorbidity and on mechanical ventilation; the ICU capacity was not strained, and the case-fatality rate was 19%.

Keywords  Coronavirus · Severe acute respiratory syndrome coronavirus 2 · Critical care · Mortality · Respiration, artificial · Respiratory distress syndrome, adult · Bed occupancy

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally. As of June 21, 2020, there have been 17,864 confirmed cases of COVID-19 with 953 deaths in Japan [1]. In Kobe, which is located in West Japan with a population of approximately 1.5 million, there have been 285 confirmed cases and 12 deaths [2].

Previous studies from Wuhan in China, the first COVID-19 epicenter, reported significant increases in demand for critical care services, and the case-fatality rate ranged from 39 to 62% in critically ill patients [3–5]. Outside of the epicenters, however, insufficient data on the clinical course of critically ill patients with COVID-19 and their strain on the critical care capacity exist. The objective of the present study...
was to describe the clinical characteristics and outcomes of critically ill patients with COVID-19 and the capacity of a COVID-19-dedicated intensive care unit (ICU) in Kobe during the first months of the city’s outbreak.

Methods

Study design

This single-center, retrospective, observational study was conducted at the Kobe City Medical Center General Hospital (KCGH), a 760-bed tertiary referral center providing emergency medical care to approximately 35,000 patients per year in Kobe.

Since the first case of COVID-19 in Kobe on March 3, 2020, the city’s surge capacity strategies were implemented as follows. Critically ill patients with COVID-19 were preferentially admitted or transferred to KCGH, while non-critically ill patients with COVID-19 and non-COVID-19 patients were admitted to the surrounding hospitals in Kobe. Pre-existing medical and cardiac ICUs at KCGH were combined into the COVID-19-dedicated ICU with 14 beds and ventilators; 24/7 intensivists and intensive care nurses with a nurse:patient ratio of 1:1 were staffed by deploying them from medical, cardiac, and surgical ICUs. Non-COVID-19 patients who had been admitted to the ICUs before March 3, 2020, were scheduled for transfer to the surgical ICU or step-down wards in the hospital. Non-urgent elective surgeries were rescheduled to maintain ICU capacity for both COVID-19 and non-COVID-19 patients. A pre-existing 32-bed step-down ward was used for COVID-19 patients discharged from the ICU. COVID-19 protocols, which were based on the World Health Organization (WHO) interim guidance [6] and/or relevant evidence for management of critically ill patients, were prepared (Supplemental Material 1: p2).

Study population

This study included critically ill patients with laboratory-confirmed COVID-19 admitted to the COVID-19-dedicated ICU at KCGH between March 3, 2020 and June 21, 2020. Laboratory confirmation of COVID-19 was based on the detection of SARS-CoV-2 RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of a nasopharyngeal swab specimen in accordance with the Centers for Disease Control and Prevention guidelines [6]. Data on the number of COVID-19 patients in Kobe during the study period were also obtained from the Kobe city official COVID-19 control site [2]. Our local Institutional Review Board approved the study (approval number: Zn200518) and waived the need for written informed consent.

Predetermined ICU admission criteria for COVID-19 patients included (1) the need for immediate intubation, (2) mechanical ventilation, (3) deteriorating respiratory status requiring ≥ 5 L/min supplemental oxygenation to meet a peripheral capillary oxygen saturation (SpO2) of ≥ 90%, (4) shock, (5) acute organ dysfunction, or (6) need for close monitoring as judged by treating physicians. Critically ill patients were defined according to the WHO interim guidance [7], which included patients with acute respiratory distress syndrome (ARDS) [8, 9] or sepsis with acute organ dysfunction [10].

Data collection

Using electronic medical records, we reviewed data on age, sex, body-mass index (BMI), smoking history, comorbidities, onset of symptoms, do-not-intubate (DNI) orders, presenting symptoms, hospital admission route, laboratory tests, imaging tests, microbiological tests, and patient management in the ICU. Chest computed tomography (CT) images were independently reviewed by two intensivists with approximately 5 years of experience (JI and DK). Lung laterality, presence of ground glass opacity (GGO) or consolidation, distribution pattern (peripheral, multifocal, central, diffuse), and other findings were recorded. The final decisions reached by consensus are reported. We calculated the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, Sequential Organ Failure Assessment (SOFA) scores, and the partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2) ratios during ICU stay to assess disease severity [8, 11, 12]. We calculated daily ICU occupancy as the percentage of beds in use out of the total number of beds available for each day at midnight to assess ICU capacity [13, 14]. The clinical outcomes included ICU deaths, in-hospital deaths, dispositions of the survivors, length of ICU and hospital stays, duration of invasive mechanical ventilation, complications documented during ICU stay, and time from symptom onset to negative RT-PCR. The last follow-up day was June 28, 2020.

Statistical analysis

No statistical sample size calculation was performed a priori owing to the nature of the study. Continuous variables are presented as medians (interquartile range). Categorical variables are presented as n (%). All data were analyzed using JMP 11 (SAS Institute, Cary, NC, USA).

Results

Between March 3, 2020 and June 21, 2020, of 285 patients with laboratory-confirmed COVID-19 in Kobe, 189 (66%), including two with critical illness, were treated in other
hospitals. Ninety-six (34%) patients were admitted to KCGH, of whom 32 (11%) with critical illness admitted to the ICU were included (Fig. 1). The median hospital follow-up period was 27 (19–50) days. All patients were Japanese adults with a median age of 68 (57–76) years; 23 (72%) were men (Table 1). The median BMI obtained from 23 patients was 24.8 (22.9–27.2) kg/m². Twenty-five (78%) patients had at least one comorbidity; the most common comorbidities were hypertension (19 [59%]) and diabetes (8 [25%]). Four (13%) patients had DNI orders. The most common presenting symptoms were fever (29 [91%]), dyspnea (20 [63%]), cough (19 [59%]), fatigue (17 [53%]), and anorexia (9 [28%]). The median duration from onset of symptoms to hospital admission and ICU admission was 7 (4–9) days and 8 (5–10) days, respectively. Twelve (38%) patients were admitted through the emergency department at KCGH; 18 (56%) transferred from surrounding hospitals, and two (6%) were considered to be infected during the course of hospitalization at KCGH for acute illnesses other than COVID-19.

All patients were admitted to the ICU because of respiratory failure and met the criteria for both ARDS and sepsis at the time of ICU admission (Table 2). The median APACHE II and SOFA scores during the first 24 h after ICU admission were 17 (13–21) and 6 (3–7), respectively. The median PaO₂/FiO₂ ratio on ICU admission, obtained from 31 patients, was 150 (115–172). The most common laboratory abnormalities on ICU admission were lymphocytopenia and elevated concentrations of aspartate aminotransferase and C-reactive protein. Chest CT images prior to ICU admission were obtained from 29 patients, with a median duration from symptom onset to CT scan of 6 (4–8) days. Bilateral lung involvement was observed in 28 patients (97%). GGO and consolidation were observed in 29 (100%) and 20 (69%) patients, respectively. Common distribution patterns were peripheral (25 [86%]) and multifocal (19 [66%]). None of the patients with coinfection with influenza or mycoplasma were identified. Sputum samples were obtained from 18 patients, from which microorganisms including \textit{Staphylococcus aureus} \((n = 6)\), \textit{Streptococcus pneumoniae} \((n = 1)\), \textit{Klebsiella pneumoniae} \((n = 1)\), and \textit{Enterobacter cloacae} complex \((n = 1)\) were identified in nine patients. Blood samples were obtained from all patients, with \textit{Escherichia coli} identified in one patient. During the ICU stay, 13 (41%) patients received invasive mechanical ventilation, of whom 13 received neuromuscular blockade, four were placed in the prone position, and none met the predetermined criteria for the initiation of venovenous extracorporeal membrane oxygenation (Table 3). The lowest PaO₂/FiO₂ ratio during the first three days of invasive mechanical ventilation was 119 (106–142).

Fourteen (44%) patients presented with hypotension requiring vasoconstrictive agents for \(\geq 6\) h and 11 (34%) hypertensive patients were treated with antihypertensive agents. Seventeen (53%) patients were treated with diuretics and seven (22%) with renal replacement therapy. All 19 mechanically ventilated patients received enteral nutrition and one also received parenteral nutrition; the remaining 13 non-intubated patients received only oral nutrition. Prophylaxis for stress ulcers and venous thromboembolism was administered in 24 (75%) and 32 (100%) patients, respectively. Nine (28%) patients also received therapeutic anticoagulation with intravenous unfractionated heparin for at least one of the following indications: atrial fibrillation.

Fig. 1 Study flow diagram. COVID-19 coronavirus disease 2019, KCGH Kobe City Medical Center General Hospital, ICU intensive care unit. During the study period, critically ill patients with COVID-19 in Kobe were preferentially admitted or transferred to KCGH.

| 285 patients with confirmed COVID-19 in Kobe, Japan between Mar 3, 2020 and June 21, 2020 |
| --- |
| 189 excluded: 189 patients including 2 with critical illness treated in hospitals other than KCGH |
| 96 patients admitted or transferred to KCGH |
| 64 excluded: 64 patients without critical illness managed outside the ICU |
| 32 patients with critical illness admitted to the ICU at KCGH included in the study |
Table 1 Demographics and presenting symptoms of study population

| Study population (n = 32) |  |
|--------------------------|--|
| Japanese                | 32 (100) |
| Age, years              | 68 (57–76) |
| 30–39                   | 1 (3) |
| 40–49                   | 4 (13) |
| 50–59                   | 5 (16) |
| 60–69                   | 7 (22) |
| 70–79                   | 9 (28) |
| 80–89                   | 6 (19) |
| Sex                      |  |
| Female                  | 9 (28) |
| Male                    | 23 (72) |
| Body-mass index, kg/m²  | 24.8 (22.9–27.2) |
| ≤ 18.4                  | 1 (3) |
| 18.5–24.9               | 12 (38) |
| 25.0–29.9               | 8 (25) |
| 30.0–34.9               | 2 (6) |
| Unknown                 | 9 (28) |
| Current or former smoker, no./total no. (%) a | 11/31 (42) |
| Comorbidities           |  |
| None                    | 7 (22) |
| Hypertension            | 19 (59) |
| Diabetes                | 8 (25) |
| Cardiovascular disease b | 6 (19) |
| Chronic kidney disease  | 5 (16) |
| Hemodialysis            | 2 (6) |
| Chronic lung disease c  | 2 (6) |
| Malignancy              | 1 (3) |
| Immunodeficiency        | 1 (3) |
| Chronic liver disease   | 0 |
| Do-not-intubate order   | 4 (13) |
| Duration from onset of symptoms to hospital admission, days d | 7 (4–9) |
| Duration from onset of symptoms to ICU admission, days d | 8 (5–10) |
| Symptoms                |  |
| Fever e                 | 29 (91) |
| Dyspnea                 | 20 (63) |
| Cough                   | 19 (59) |
| Fatigue                 | 17 (53) |
| Anorexia                | 9 (28) |
| Diarrhea                | 5 (16) |
| Myalgias                | 2 (6) |
| Olfactory and taste disorders | 2 (6) |
| Arthralgia              | 1 (3) |
| Sore throat             | 1 (3) |
| Hospital admission route of patients |  |
| Admission through emergency department | 12 (38) |
| Transferred from other hospital | 18 (56) |
| Others f                | 2 (6) |

Data are presented as number (%) or median (interquartile range) unless otherwise noted

COVID-19 coronavirus disease 2019, ICU intensive care unit

aData available for 31 patients

bCoronary artery disease or heart failure
cAsthma or interstitial lung disease
dData available for 27 patients
eSelf-reported history of temperature ≥ 37.5 °C or feeling feverish

fTwo patients considered to be infected during hospitalization
(n = 8), renal replacement therapy (n = 6), or venous thromboembolism (n = 1). Regarding pharmacotherapies, 30 (94%) patients received empiric antibiotics; 27 (84%), compassionate-use favipiravir; six (19%), ciclesonide, and six (19%), systemic glucocorticoids. Other antiviral agents or immunosuppressive agents were not used.

Until all patients included in the study were discharged from the ICU on June 5, 2020, the median daily ICU occupancy was 50% (36–71%) (Supplemental Material 1: Fig. S1). As of June 28, 2020, six (19%) patients died in the hospital with a median duration from ICU admission of 14 (6–23) days; five (16%) including two with DNI orders died in the ICU and one (3%) died in the stepdown ward after ICU discharge (Table 4). Of the 19 mechanically ventilated patients, three (16%) died in the ICU. The causes of death were cardiac failure (n = 3), respiratory failure (n = 2), and septic shock (n = 1). The detailed characteristics and clinical course of the six deceased patients are presented in Table S1 (Supplemental Material 1). Of 26 surviving patients, 23 discharged from the hospital and three had been discharged from the ICU but remained in the hospital. The median length of ICU

| Characteristics | Study population (n = 32) |
|-----------------|--------------------------|
| ARDS            | 32 (100)                 |
| Sepsis          | 32 (100)                 |
| Septic shock    | 1 (3)                    |
| APACHE II score during first 24 h after ICU admission | 17 (13–21) |
| SOFA score during first 24 h after ICU admission | 6 (3–7) |
| $\text{PaO}_2/\text{FiO}_2$ ratio on ICU admission$^a$ | 150 (115–172) |
| Lowest $\text{PaO}_2/\text{FiO}_2$ ratio during first 3 ICU days$^a$ | 127 (74–159) |
| Laboratory tests |                          |
| White blood cell count, $\times 10^9$/L | 6.6 (4.9–9.0) |
| Lymphocyte count, $\times 10^9$/L$^b$ | 0.6 (0.5–0.9) |
| Platelet, $\times 10^9$/L | 170 (145–252) |
| Aspartate aminotransferase, U/L | 52 (36–93) |
| Alanine aminotransferase, U/L | 27 (18–40) |
| Creatinine, mg/dL | 0.84 (0.64–1.16) |
| C-reactive protein, mg/dL | 13.1 (8.6–18.7) |
| Chest CT findings, no. positive/total no. (%)$^c$ |                          |
| Ground glass opacity | 29/29 (100) |
| Consolidation | 20/29 (69) |
| Bilateral involvement | 28/29 (97) |
| Peripheral distribution | 25/29 (86) |
| Multifocal distribution | 19/29 (66) |
| Diffuse distribution | 10/29 (34) |
| Microbiology tests, no. positive/total no. (%) | | |
| Influenza A/B | 0/21 |
| Mycoplasma | 0/19 |
| Sputum culture$^d$ | 9/18 (50) |
| Blood culture$^e$ | 1/32 (3) |

Data are presented as number (%) or median (interquartile range) unless otherwise noted

$^a$Data available for 31 patients

$^b$Data available for 30 patients

$^c$Chest CT images prior to ICU admission obtained from 29 patients

$^d$Microorganisms identified from sputum cultures included *Staphylococcus aureus* (n = 6), *Streptococcus pneumoniae* (n = 1), *Klebsiella pneumoniae* (n = 1), and *Enterobacter cloacae* complex (n = 1)

$^e$*Escherichia coli* was identified
and hospital stay was 10 (4–19) days and 31 (24–55) days, respectively. The median duration of mechanical ventilation was 14 (8–27) days. Tracheostomy was performed in two patients who were free from mechanical ventilation at ICU discharge. The most common complications during ICU stay were hospital-acquired infections (15 [47%]), acute hepatic injury (14 [44%]), impaired consciousness (14 [44%]), and acute kidney injury (13 out of 30 patients without chronic hemodialysis [43%]) (Supplemental Material 1: Table S2). The patients diagnosed with hospital-acquired infections included 10 with ventilator-associated pneumonia, two with *Clostridioides difficile* infections, one with a blood stream infection, and seven treated with broad-spectrum antibiotics for suspected sepsis or septic shock. For 25 of 26 survivors, the SARS-CoV-2 RT-PCR test was performed twice with a 24-h interval at 4 weeks after symptom onset according to our institutional protocol. Thirteen patients (52%) had negative results on the first set of tests, while the remaining 12 patients required a median of 38 (IQR 32–43) days from symptom onset to achieve two consecutive negative RT-PCR results.

**Discussion**

In this study, we have described the clinical characteristics and outcomes of 32 critically ill patients with COVID-19 and the ICU occupancy in Kobe during the first months of the city’s outbreak. Most patients were men aged ≥ 60 years having normal weight and at least one comorbidity and required invasive mechanical ventilation. The median ICU occupancy was 50% and the case-fatality rate was as low as 19%.

| Table 3 ICU management of patients with COVID-19 |
|-----------------------------------------------|
| Study population *(n = 32)*                   |

| Respiratory support                           | Study population *(n = 32)* |
|-----------------------------------------------|-----------------------------|
| High-flow nasal cannula oxygen therapy        | 0/32                        |
| Non-invasive ventilation*                     | 1/32 (3)                    |
| Invasive mechanical ventilation              | 19/32 (59)                  |
| Neuromuscular blockade                        | 13/19 (68)                  |
| Prone position                                | 4/19 (21)                   |
| Extracorporeal membrane oxygenation*         | 0/19                        |
| Vasconstrictive agents                        | 14/32 (44)                  |
| Inotropic agents                              | 0/32                        |
| Antihypertensive agents                       | 11/32 (34)                  |
| Diuretics                                     | 17/32 (53)                  |
| Renal replacement therapy                     | 7/32 (22)                   |
| Enteral nutrition*                            | 19/32 (59)                  |
| Parenteral nutrition*                         | 1/32 (3)                    |
| Stress ulcer prophylaxis                      | 24/32 (75)                  |
| Venous thromboembolism prophylaxis            | 32/32 (100)                 |
| Therapeutic anticoagulation*                  | 9/32 (28)                   |
| Atrial fibrillation                           | 8/9 (89)                    |
| Renal replacement therapy                     | 6/9 (67)                    |
| Venous thromboembolism                        | 1/9 (11)                    |
| Other pharmacotherapies                       |                             |
| Empiric antibiotics                           | 30/32 (94)                  |
| Favipiravir                                    | 27/32 (84)                  |
| Ciclesonide                                    | 6/32 (19)                   |
| Glucocorticoids                               | 6/32 (19)                   |

Data are presented as number/total number (%) or median (interquartile range). The last follow-up day was June 28, 2020

COVID-19 coronavirus disease 2019, ICU intensive care unit

*Three mechanically ventilated patients and three with do-not intubate orders

| Table 4 Clinical outcomes of patients with COVID-19 admitted to ICU |
|---------------------------------------------------------------|
| Study population *(n = 32)*                                    |

| Study population *(n = 32)*                                    |

| ICU deaths | 5/32 (16) |
| In-hospital deaths* | 6/32 (19) |
| Still in ICU | 0/32 |
| Discharged from ICU but still in hospital | 3/32 (9) |
| Discharged from hospital | 23/32 (72) |
| Duration of ICU stay, days | 10 (4–19) |
| Survivors | 9 (4–16) |
| Non-survivors | 14 (6–23) |
| Duration of hospital stay, days | 31 (24–55) |
| Survivors | 31 (26–65) |
| Non-survivors | 28 (8–46) |
| Duration of invasive mechanical ventilation, days | 14 (8–27) |
| Survivors | 12 (7–27) |
| Non-survivors | 25 (20–36) |
| Tracheostomy | 2/19 (11) |

Data are presented as number/total number (%) or median (interquartile range). The last follow-up day was June 28, 2020

COVID-19 coronavirus disease 2019, ICU intensive care unit

*Three mechanically ventilated patients and three with do-not intubate orders

and hospital stay was 10 (4–19) days and 31 (24–55) days, respectively. The median duration of mechanical ventilation was 14 (8–27) days. Tracheostomy was performed in two patients who were free from mechanical ventilation at ICU discharge. The most common complications during ICU stay were hospital-acquired infections (15 [47%]), acute hepatic injury (14 [44%]), impaired consciousness (14 [44%]), and acute kidney injury (13 out of 30 patients without chronic hemodialysis [43%]) (Supplemental Material 1: Table S2). The patients diagnosed with hospital-acquired infections included 10 with ventilator-associated pneumonia, two with *Clostridioides difficile* infections, one with a blood stream infection, and seven treated with broad-spectrum antibiotics for suspected sepsis or septic shock. For 25 of 26 survivors, the SARS-CoV-2 RT-PCR test was performed twice with a 24-h interval at 4 weeks after symptom onset according to our institutional protocol. Thirteen patients (52%) had negative results on the first set of tests, while the remaining 12 patients required a median of 38 (IQR 32–43) days from symptom onset to achieve two consecutive negative RT-PCR results.
The strength of this study is that we included almost all critically ill patients with COVID-19 admitted to ICUs in the city with a population of 1.5 million and followed all patients at least until ICU discharge. The detailed information about the study population and the ICU capacity during the outbreak will enable policy-makers outside the COVID-19 epicenters to determine the potential need for increasing ICU capacity to prepare for a future influx of critically ill patients with COVID-19.

The demographic data of our cohort were generally consistent with those of the critically ill population in China [3–5, 15], the United States [16–19], Italy [20], and Canada [21], with the exception of patient ethnicity and BMI. The median BMI obtained in our cohort was lower than that [21], with the exception of patient ethnicity and BMI. The patients with COVID-19 in New York City [23] and the city rate. Recently, two large cohort studies of in-hospital reasonable to explore other factors affecting the case-fatality. Among the 32 critically ill patients with laboratory-confirmed COVID-19 admitted to the ICU, the majority were men aged ≥ 60 years having normal weight and at least one comorbidity and required invasive mechanical ventilation. During the first months of the outbreak, the ICU capacity was not strained, and the case-fatality rate was 19%.

**Conclusion**

Among the 32 critically ill patients with laboratory-confirmed COVID-19 admitted to the ICU, the majority were men aged ≥ 60 years having normal weight and at least one comorbidity and required invasive mechanical ventilation. During the first months of the outbreak, the ICU capacity was not strained, and the case-fatality rate was 19%.

**Author contributions** JI, RS, DK, and YM conceptualized the study. JI, DK, KO, SN, YM, MT, and TF contributed to data collection. JI performed data cleaning and statistical analysis, produced the figure, and drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Compliance with ethical standards

Conflict of interest  The authors declare that they have no conflicts of interest.

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