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Original Article

Intensive care burden of COVID-19 in tertiary care hospitals during the first year of outbreak in Kawasaki City, Japan: A retrospective cohort study

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ABSTRACT

Introduction: This study aimed to describe the changes in the intensive care burden of coronavirus disease 2019 (COVID-19) during the first year of outbreak in Japan.

Methods: This retrospective cohort study included COVID-19 patients who received mechanical ventilation (MV) support in two designated hospitals for critical patients in Kawasaki City. We compared the lengths of MV and stay in the intensive care unit (ICU) or high care unit (HCU) according to the three epidemic waves. We calculated in-hospital mortality rates in patients with or without MV.

Results: The median age of the sample was 65.0 years, and 22.7% were women. There were 37, 29, and 62 patients in the first (W1), second (W2), and third waves (W3), respectively. Systemic steroids, remdesivir, and prone positioning were more frequent in W2 and W3. The median length of MV decreased from 18.0 days in W1 to 13.0 days in W3 ($P = 0.019$), and that of ICU/HCU stay decreased from 22.0 days in W1 to 15.5 days in W3 ($P = 0.027$). The peak daily number of patients receiving MV support was higher at 18 patients in W1, compared to 8 and 15 patients in W2 and W3, respectively. The mortality rate was 23.4%, which did not significantly change ($P = 0.467$).

Conclusions: The lengths of MV and ICU/HCU stay per patient decreased over time. Despite an increase in the number of COVID-19 patients who received MV in W3, this study may indicate that the intensive care burden during the study period did not substantially increase.

1. Introduction

Since the identification of the first coronavirus disease 2019 (COVID-19) patient in January 2020, approximately 1.7 million patients in Japan had a confirmed diagnosis of COVID-19, with >17,000 estimated deaths by the end of September 2021 [1]. Fortunately, the number of patients and deaths due to COVID-19 remains smaller in Japan than in most Western countries [2]. However, despite the accumulation of knowledge and experience in infection control for COVID-19, intermittent epidemics continue to occur worldwide, including in Japan [3].

Some COVID-19 patients experience rapid deterioration and require intensive care unit (ICU) treatment and long-term mechanical ventilation support during the clinical course [4,5]. As the number of COVID-19 patients increased, several countries, such as Italy and Brazil, faced a shortage of intensive care resources, including ICU beds and mechanical ventilators, during the early epidemic phase [6,7]. Increasing pressure on critical care capacity was associated with a greater risk of ICU mortality among COVID-19 patients [8], which had been similarly noted in other diseases, such as respiratory and heart diseases [9]. In the US and UK, where a serious outbreak of COVID-19 occurred in the early

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HCU, high care unit; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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epidemic phase, reductions in in-hospital mortality among COVID-19 patients were noted following changes in hospital strategy and clinical processes based on accumulated experience and knowledge and the introduction of effective medications evidenced by randomized controlled trials, during the first several months of the COVID-19 epidemic [10,11].

In Japan, most critically ill patients with COVID-19, especially those who required mechanical ventilation support, have been referred to tertiary care hospitals designated for critical COVID-19 treatment by local governments to efficiently utilize the workforce of trained staff and medical resources (e.g., personal protective equipment and mechanical ventilation machines). Strain in intensive care at these designated tertiary care hospitals could directly increase the risk of mortality and lead to poor prognosis among COVID-19 patients in the entire district. Although intensive care resource use, including the lengths of ICU stay and mechanical ventilation support, has been investigated in Japan [12–14], there is limited knowledge on the changes in intensive care use per patient and in intensive care burden on a district over time due to COVID-19.

Therefore, this study aimed to describe the changes in the intensive care burden of critical COVID-19 patients at the two tertiary care hospitals designated for critical COVID-19 treatment in Kawasaki City during the first year of the COVID-19 outbreak in Japan.

2. Patients and methods

2.1. Study setting and design

Kawasaki City is located between Tokyo and Yokohama City in Japan, with approximately 1.4 million people. There are two secondary medical areas in the city: the northern and southern areas covered approximately 840,000 and 630,000 people, respectively, based on data for 2015. According to the public health center in Kawasaki City, three major waves occurred during the first year of the COVID-19 outbreak. The highest number of COVID-19 patients identified per week was 71 in early April 2020 (first wave), 151 in late July 2020 (second wave), and 1,148 in late December 2020 (third wave) [15]. At the end of February 2021, more than 8,000 COVID-19 patients had been confirmed, including 132 deaths [15].

This retrospective cohort study was conducted in two tertiary care hospitals (i.e., Kawasaki Municipal Hospital and St. Marianna University School of Medicine Hospital), which were the only designated hospitals for critical COVID-19 patients in Kawasaki City at the time of this study. Kawasaki Municipal Hospital is located in the southern medical area, while St. Marianna University School of Medicine Hospital is in the northern medical area of the city. The maximum bed capacities for COVID-19 patients in the Kawasaki Municipal Hospital were four designated beds in the ICU, nine designated beds in high care units (HCU), and 28 other designated beds during the study period. Meanwhile, the St. Marianna University School of Medicine Hospital had 17 available beds in the ICU for COVID-19 patients.

The numbers of COVID-19 patients hospitalized in all designated hospitals in Kawasaki City, regardless of those with or without mechanical ventilation support, were shared every day among all designated hospitals for COVID-19 patients, including the two study facilities for critical patients throughout the study period. Therefore, we confirmed that all COVID-19 patients with mechanical ventilation support in the city were hospitalized in either of the two study facilities.

2.2. Study participants

The first patients with COVID-19 were admitted to these hospitals in March 2020. The study participants included COVID-19 patients aged ≥ 15 years who were hospitalized between March 2020 and February 2021 and received mechanical ventilation during hospitalization. We limited our study to patients with mechanical ventilation support, not all

patients who stayed in ICU/HCU, in order to exclude patients with non-critical COVID-19 but admitted to ICU/HCU. The study participants were followed up until May 31, 2021. As referenced, we also investigated patients hospitalized at either of the study facilities during the study period but did not receive mechanical ventilation support.

2.3. Outcomes

The outcome measures were the lengths of mechanical ventilation and ICU/HCU stay, which were defined as the cumulative days during hospitalization. Thus, for example, when a patient was readmitted to ICU/HCU after discharge from ICU/HCU, we summed up the lengths of each ICU/HCU stay during hospitalization.

2.4. Other measures

Data were collected through a retrospective chart review and included the following: demographics, comorbidities, date of onset, date of laboratory diagnosis, date of admission to the study facilities, date of discharge or transfer to another hospital, the severity of COVID-19 at admission, treatment of COVID-19, including pharmacotherapy, the use of extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy, and all-cause in-hospital mortality. Moreover, the mortality rates in patients with or without mechanical ventilation support were evaluated because the changes in decision making when performing mechanical ventilation support over time might affect the mortality rate in patients who did not receive mechanical ventilation support during the study period.

COVID-19 was diagnosed if they had both of close contact history with COVID-19 patients or typical clinical symptoms and at least one of the following laboratory evidence: polymerase chain reaction testing, quantitative or qualitative antigen testing, or serological testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 severity was classified according to the classification published by the US National Institutes of Health: asymptomatic; mild (any of the various signs and symptoms without shortness of breath, dyspnea, or abnormal chest imaging); moderate (evidence of lower respiratory disease with oxygen saturation (SpO_2) $\geq 94\%$ on room air at sea level), severe ($\text{SpO}_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mmHg, respiratory frequency > 30 breaths/min, or lung infiltrates $> 50\%$), and critical (respiratory failure, septic shock, and/or multiple organ dysfunction) [16]. The severity of patients who required mechanical ventilation support for respiratory failure due to COVID-19 but did not receive mechanical ventilation support due to unavailability of consent for the procedure was defined as critical in this study. ICU beds were defined as deploying with a nurse-patient ratio of 1:2 and HCU beds as deploying with a nurse-patient ratio of 1:4.

According to the epidemic curve of COVID-19 in Japan, the study period was divided into three equal terms: the first wave (March 2020 to June 2020), the second wave (July 2020 to October 2020), and the third wave (November 2020 to February 2021). The study patients were then divided into three groups corresponding to each wave based on admission to the study facilities.

2.5. Statistical analysis

Characteristics of the study patients were compared according to waves using Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables, with the Dunn–Bonferroni post hoc method for two-group comparisons. As a sensitivity analysis, the analyses were repeated only in surviving patients at discharge. SPSS (version 25.0.0, Inc., Chicago, IL, USA) was used to analyze the data, and statistical significance was set at $P < 0.05$.

2.6. Ethical considerations

This study was conducted in compliance with the standards of the Declaration of Helsinki and current ethical guidelines, and the study protocol was approved by the institutional review boards of the Kawasaki Municipal Kawasaki Hospital (approval number 2020-40) and the ethics committee of the St. Marianna University School of Medicine Hospital (approval number 5190). Written informed consent was waived owing to the retrospective nature of the study, and patient data were anonymously analyzed.

3. Results

3.1. Patient characteristics

Among the 505 COVID-19 patients who were admitted to the study facilities during the study period, 128 patients who received mechanical ventilation support during hospitalization were included. The median age of the study population was 65.0 years, and 22.7% were women (Table 1). The numbers of patients in the first, second, and third waves were 37, 29, and 62, respectively. Over time, the patients tended to be older, female, and residents of Kawasaki City. Of the 128 patients, 96 (75.0%) were in a critical stage on admission, and 91 (71.1%) had received mechanical ventilation at or before admission to the study facilities. The median time from admission to the initiation of mechanical ventilation was 2.0 days among 37 patients (28.9%) who had not received mechanical ventilation for the current infection before or at admission. The most prevalent comorbidities were hypertension and diabetes, followed by cardiovascular disease and chronic kidney disease. There were no statistically significant differences in the prevalence of comorbidities between the waves, except for a lower prevalence of cardiovascular disease in the third wave. All patients were discharged by May 31, 2021. The number of patients without mechanical ventilation support in each wave was 41, 107, and 229, respectively. (Table S1).

Table 1 Characteristics of the study participants.

	Total (N = 128)	First wave (n = 37)	Second wave (n = 29)	Third wave (n = 62)	P
Age, years, median (IQR)	65.0 (55.0–74.0)	60.0 (52.0–73.0)	67.0 (55.0–78.0)	67.0 (57.0–74.0)	0.313
Sex, n (%)					
Male	99 (77.3)	33 (89.2)	22 (75.9)	44 (71.0)	0.109
Female	29 (22.7)	4 (10.8)	7 (24.1)	18 (29.0)	
Nationality, n (%)					
Japanese	127 (99.2)	36 (97.3)	29 (100.0)	62 (100.0)	0.290
Foreigner	1 (0.8)	1 (2.7)	0 (0.0)	0 (0.0)	
Residents of Kawasaki City, n (%)	82 (64.1)	21 (56.8)	16 (55.2)	45 (72.6)	0.149
Comorbidities, n (%)					
Hypertension	83 (64.8)	22 (59.5)	17 (58.6)	44 (71.0)	0.371
Cardiovascular disease	20 (15.6)	7 (18.9)	8 (27.6)	5 (8.1)	0.046*
Cerebrovascular disease	13 (10.2)	5 (13.5)	3 (10.3)	5 (8.1)	0.685
Diabetes	66 (51.6)	17 (45.9)	17 (58.6)	32 (52.6)	0.593
Active malignancies	4 (3.1)	2 (5.4)	1 (3.4)	1 (1.6)	0.573
Chronic respiratory disease	16 (12.5)	5 (13.5)	2 (6.9)	9 (14.5)	0.578
Chronic kidney disease	20 (15.6)	2 (5.4)	6 (20.7)	12 (19.4)	0.126
Dialysis	9 (7.0)	1 (2.7)	2 (6.9)	6 (9.7)	0.422
Days from onset to laboratory diagnosis, median (IQR)	5.0 (2.0–7.0)	5.0 (3.0–8.0)	5.0 (2.0–7.3)	3.5 (1.0–6.0)	0.061
Days from onset to admission to study facilities, median (IQR)	7.5 (5.0–10.0)	9.0 (5.0–11.0)	7.0 (5.0–10.0)	7.0 (5.0–9.8)	0.259
Severity of COVID-19 infection on admission, n (%)					
Asymptomatic, mild, or moderate	5 (3.9)	3 (8.1)	1 (3.4)	1 (1.6)	0.129
Severe	27 (21.1)	6 (16.2)	3 (10.3)	18 (29.0)	
Critical	96 (75.0)	28 (75.7)	25 (86.2)	43 (69.4)	
Initiation of mechanical ventilation, n (%)					
Before or upon hospital admission	88 (68.8)	27 (73.0)	23 (79.3)	41 (66.1)	0.415
After hospital admission	40 (31.3)	10 (27.0)	6 (20.7)	21 (33.9)	
Days from hospital admission to initiation of mechanical ventilation, median (IQR)	2.0 (1.0–4.0)	1.0 (1.0–3.0)	1.5 (1.0–2.8)	2.0 (1.0–4.0)	0.264

COVID-19, coronavirus disease 2019; IQR, interquartile range.

*Indicates statistical significance: second vs third waves.

3.2. Clinical management

The proportion of patients administered with antibiotics on admission in the third wave was lower than those in the second waves (Table 2). Remdesivir, systemic corticosteroids, and prone positioning during mechanical ventilation support were more frequently used in the second and third waves than the first wave. ECMO was less frequently

Table 2 Clinical management and mortality.

	Total (N = 128)	First wave (n = 37)	Second wave (n = 29)	Third wave (n = 62)	P
Treatment, n (%)					
Antibiotics on admission	84 (65.6)	27 (73.0)	24 (82.8)	33 (53.2)	0.012**
Remdesivir	71 (55.5)	1 (2.7)	21 (72.4)	49 (79.0)	<0.001****
Systemic steroids (e.g., dexamethasone)	109 (85.2)	18 (48.6)	29 (100.0)	62 (100.0)	<0.001****
Anticoagulants	126 (98.4)	37 (100.0)	28 (96.6)	61 (98.4)	0.553
Continuous renal replacement therapy	18 (14.1)	4 (10.8)	6 (20.7)	8 (12.9)	0.485
ECMO	9 (7.0)	6 (16.2)	1 (3.4)	2 (3.2)	0.035****
Prone positioning	59 (46.1)	10 (27.0)	16 (55.2)	33 (53.2)	0.022****
High-flow nasal cannula oxygen therapy	4 (3.1)	0 (0.0)	0 (0.0)	4 (6.5)	0.111
Mortality, n (%)	30 (23.4)	9 (24.3)	9 (31.0)	12 (19.4)	0.467

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation. Indicates statistical significance: *first vs second waves, ** second vs third waves, and *** first vs third waves.

used in the second and third waves than in the first wave. A high-flow nasal cannula device was used in a few patients before the initiation of mechanical ventilation in the third wave. Almost all patients received anticoagulant therapy during the study period.

3.3. Intensive care use

The length of mechanical ventilation support decreased over time, with a median of 18.0 days, 15.0 days, and 13.0 days in the first, second, and third waves, respectively ($P = 0.019$) (Fig. 1a). Similarly, the length of ICU/HCU stay decreased over time, with a median of 22.0 days, 17.0 days, and 15.5 days in the first, second, and third waves, respectively ($P = 0.027$) (Fig. 1b).

The daily number of patients receiving mechanical ventilation support is shown in Fig. 2. The peak daily number of patients receiving mechanical ventilation support was higher at 18 patients in the first wave (April 21–23, 2020), compared to 8 and 15 patients in the second and third waves, respectively. However, the third wave had the largest number of patients with mechanical ventilation support.

3.4. Mortality

The all-cause mortality rate during hospitalization was 23.4% ($n = 30$), which did not significantly change during the study period ($P = 0.467$) (Table 2). Among the 10 patients who died after 28 days from admission, seven (70%) received mechanical ventilation support until death. The crude mortality rates of 377 COVID-19 patients who were admitted to the study facilities during the same waves and did not receive mechanical ventilation during hospitalization did not significantly increase ($P = 0.319$): 7.3% (3/41), 5.6% (6/107), and 10.5% (24/229) in the first, second, and third waves, respectively.

3.5. Sensitivity analysis

Sensitivity analysis was conducted in 98 patients who received mechanical ventilation support for COVID-19 treatment and survived at discharge (Table S2). The length of mechanical ventilation decreased over time, with a median of 18.0 days, 14.0 days, and 13.0 days in the first, second, and third waves, respectively ($P = 0.041$, Fig. S1a). The length of ICU/HCU stay decreased over time, with a median of 21.0 days, 16.0 days, and 14.5 days in the first, second, and third waves,

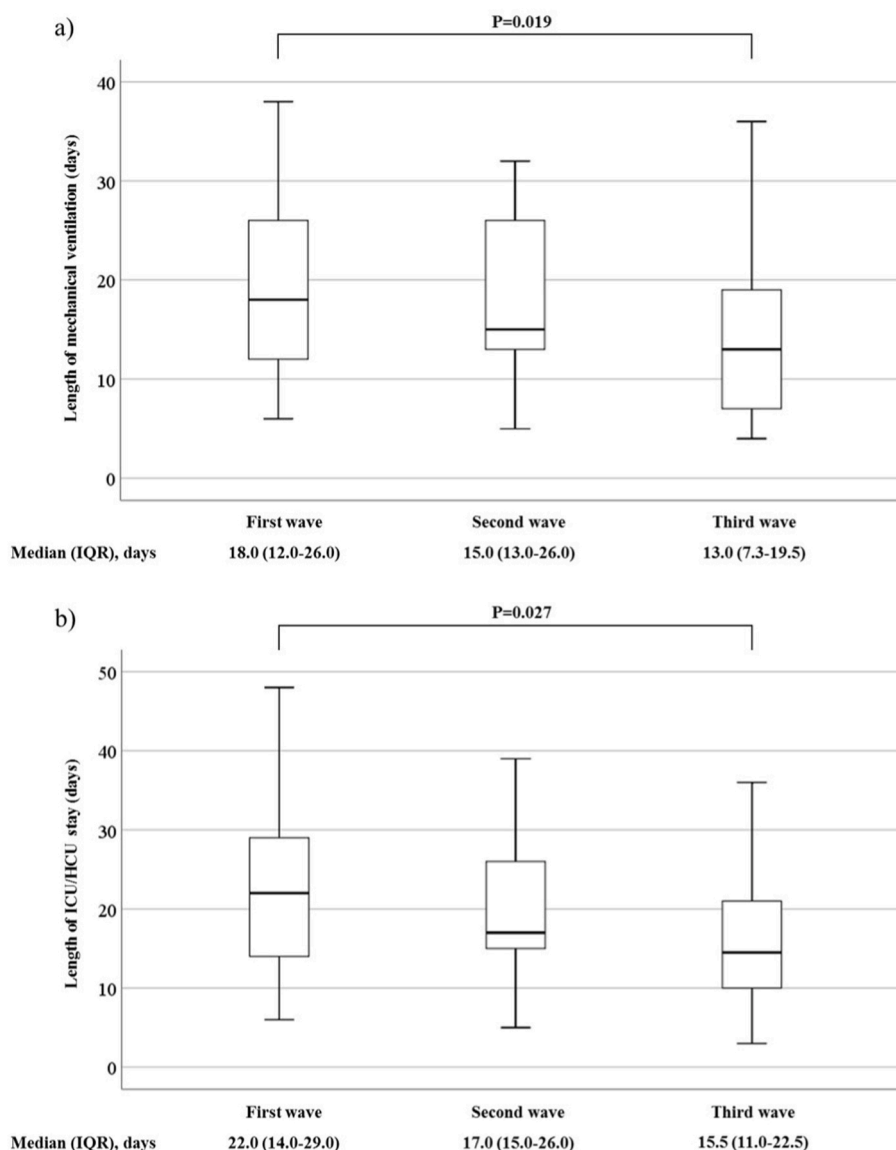


Fig. 1. Lengths of mechanical ventilation and intensive/high care unit stay in each patient included in this study (box plot).

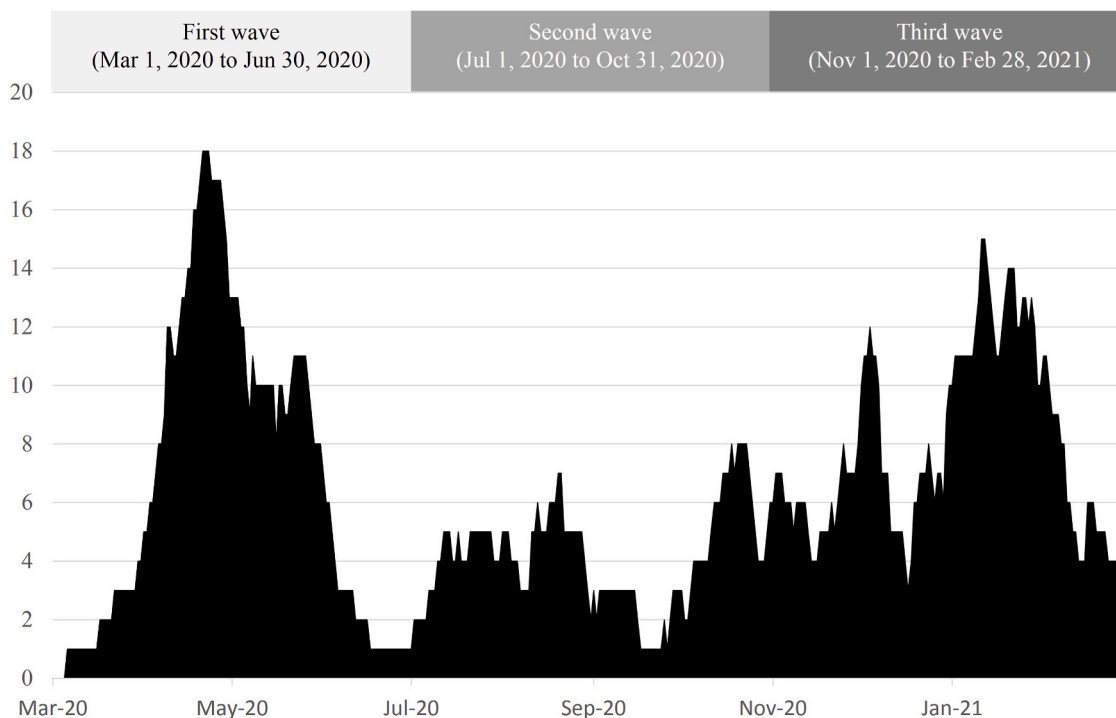


Fig. 2. Daily number of hospitalized COVID-19 patients with mechanical ventilation in the two designated tertiary care hospitals for critical COVID-19.

respectively ($P = 0.058$, Fig. S1b). These results were similar to those obtained from the main analysis.

4. Discussion

We found that the lengths of mechanical ventilation and ICU/HCU stay of critical COVID-19 patients who received mechanical ventilation support in either of the two COVID-19 designated tertiary care hospitals in Kawasaki City during the first year of the COVID-19 outbreak decreased over time. Of note, despite an increase in the number of COVID-19 patients who received mechanical ventilation in the third wave, the daily number of patients with mechanical ventilation peaked in the first wave, which may indicate that the intensive care burden during the study period did not substantially increase. This observation would add new insight into the intensive care burden due to COVID-19 to the findings from previous studies that described clinical courses and management of critical COVID-19 patients, including the lengths of mechanical ventilation and ICU stay, in the early epidemic phase in Japan [12–14]. A more recent study showed that the number of ICU patients peaked in the first wave in Osaka prefecture, which was consistent with our study [17]. Our results may also suggest that the intensive care burden due to an emerging infectious disease like COVID-19 should be predicted based on the latest data because resource use may be dynamically changed partly because of the accumulation of experience and evidence during the early epidemic phase.

One of the strengths of this study was the inclusion of virtually all critical COVID-19 patients with mechanical ventilation support in Kawasaki City; thus, this enabled us to evaluate the intensive care burden in the city. Approximately one-third of the study patients were residents outside the city, suggesting that the two hospitals had enough capacity to accept at least the most critical COVID-19 patients in the city. However, we acknowledge that some Kawasaki City residents with critical COVID-19 might have been admitted to hospitals outside the city.

According to the nationwide inpatient registry in Japan, the median lengths of mechanical ventilation and ICU stay among patients who received mechanical ventilation were 11 days and 13 days, respectively [18], which were both shorter than those found in this study. These

differences may be attributed to the difference in the initiation or termination criteria for mechanical ventilation in each study facility. For example, during the first wave, we avoided using a reservoir mask and high-flow nasal cannula for oxygenation because of concern for aerosol transmission but initiated mechanical ventilation in patients whose SpO_2 levels remained lower than 90% even after the administration of 5 L/min oxygen through the oxygen mask. However, after the accumulation of evidence on the safety of reservoir masks and high-flow nasal cannula devices for COVID-19 patients [19], we changed our practice to place these modalities ahead of mechanical ventilation support in the second to third waves. Thus, earlier application of mechanical ventilation in our hospitals during the first wave may prolong the lengths of mechanical ventilation and ICU/HCU stay, compared to those reported from the registry study. We speculate that the observed decrease in the lengths of mechanical ventilation and ICU/HCU stay during the study period may partly be due to substantial changes implemented in clinical practice and treatment protocol for critical COVID-19 patients during the study period [20]. For example, remdesivir (approved since May 2020 in Japan) and dexamethasone (July 2020) could improve the prognosis of COVID-19 patients [21,22]. Furthermore, prone positioning during mechanical ventilation was proactively implemented in the hospitals during the second and third waves, which could have improved oxygenation [23]. Therefore, we considered that these medications and patient management, including deciding the appropriate timing of initiation or discontinuation of mechanical ventilation by the accumulation of intensive care experience for COVID-19, might have contributed to the shortened lengths of mechanical ventilation and ICU/HCU stay observed between the first and second waves.

It is important to note that the crude mortality rates of study patients with mechanical ventilation and those without remained low and did not significantly increase over the study period. This may be indicative of the absence of strain in intensive care in the study facilities and in the district over the study period. Moreover, we speculated that the selection of patients for mechanical ventilation might be performed appropriately because of no apparent increase in crude mortality rates among those without mechanical ventilation. However, further research with larger sample sizes is needed to verify this finding because we could not

conduct analyses with adjustment for potential confounding factors due to the limited number of study participants. Furthermore, the continuous use of mechanical ventilation until death among patients who died after 28 days from admission may suggest that physicians did not stop their treatment due to a shortage of mechanical ventilation.

This study had two major limitations. Firstly, we could not compare the outcomes after adjustment for demographic and clinical characteristics of the patients because of the small sample size. Secondly, other factors, such as viral genomic variation, which may influence disease severity, may have affected the results of this study [24]. Further studies are required to determine the reasons for the observed changes in the lengths of mechanical ventilation and ICU/HCU stay.

5. Conclusions

Of the COVID-19 patients who received mechanical ventilation support and were admitted to the two tertiary hospitals in Kawasaki City during the first year of the COVID-19 outbreak, the lengths of mechanical ventilation and ICU/HCU stay decreased over time without an apparent increase in the in-hospital mortality rate. Thus, improvements in individual COVID-19 patient management may contribute to the alleviation of the overall intensive care burden despite the increase in the number of patients with critical COVID-19.

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Authorship

TH contributed to the study design, data collection, statistical analysis and interpretation, and drafting of the manuscript. SH contributed to the study design, statistical analysis and interpretation, and critically revised the manuscript for important intellectual content. KN, YS, SY, and AM contributed to data collection, statistical analysis and interpretation, and critically revised the manuscript for important intellectual content. MS and SF contributed to statistical analysis and interpretation, and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication and met the ICMJE authorship criteria.

Declaration of competing interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jiac.2022.01.022>.

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