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Original article

Clinical characteristics of COVID-19 in Osaka, Japan: Comparison of the first–third waves with the fourth wave

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ABSTRACT

Background: The fourth wave of COVID-19 in Osaka Prefecture, Japan, caused a medical crisis. Here, we aim to identify the risk factors for COVID-19 severity and compare patients between the first–third waves and the fourth wave.

Methods: We performed an observational retrospective study of COVID-19 cases at the National Hospital Organization Kinki-Chuo Chest Medical Center.

Results: We identified 404 patients (median age: 71.0 years [interquartile range: 56.0–80.0]), of whom 199 (49.1%) had mild disease, 142 (35.2%) had moderate disease, and 63 (15.6%) had severe disease. The overall mortality rate was 5.4% (22/404). Based on multivariate logistic regression analysis, cardiovascular disease, fever, dyspnea, and several inflammatory biomarkers were independent risk factors for moderate to severe disease. For every 1 mg/dL increase in C-reactive protein, 10 IU/L increase in lactate dehydrogenase, and 100 ng/mL increase in ferritin, the risk for moderate to severe disease increased by 18.3%, 12.9%, and 8.9%, respectively. Overall disease severity in the fourth wave was higher than in the first–third waves. However, there was no significant difference in mortality. Because of a shortage of beds, four of the 28 severe patients (14.3%) in the fourth wave could not be transferred to the advanced hospital.

Conclusions: Cardiovascular disease, fever, dyspnea, and several inflammatory biomarkers were risk factors for moderate to severe COVID-19 in our cohort. During the fourth wave,

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, variant of concern; WBC, white blood cell.

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COVID-19 severity worsened, increasing the number of patients who could not be transferred to beds for severe cases, resulting in a medical crisis in Osaka.

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1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection (coronavirus disease 2019, abbreviated as COVID-19) was confirmed in Wuhan, China, in December 2019, and the pandemic has since spread around the world [1]. A clinical characteristic of COVID-19 is its diverse presentation, ranging from asymptomatic to fatal. The risk of severe disease and mortality may differ based on population, period, and region. For example, there were differences in the number of patients per wave of infections even in cities with similar population sizes. Severity and mortality also differed between waves in Osaka [2], and in Sapporo patient characteristics differed between two waves [3].

Osaka Prefecture is the largest metropolitan area in western Japan, with a population of 8.82 million. As of June 2021, it had experienced four waves of infections in the COVID-19 pandemic, in the following periods: January 29 to June 13, 2020; June 14 to October 9, 2020; October 10, 2020 to February 28, 2021; and March 1, 2021 until the time of writing (Fig. 1). The Japanese government declared a state of emergency three times in Osaka Prefecture, on April 7, 2020, January 13, 2021, and April 25, 2021. This declaration called on people in the area to strictly observe prevention measures including refraining from traveling, early closure requests for restaurants, and encouraging remote working. Despite this, the fourth wave briefly caused a medical crisis because beds for severe cases were at maximum capacity, restricting the transfer of some patients to advanced hospitals.

In the present study, we aimed to identify factors influencing COVID-19 severity and assess any differences in COVID-19 patients between the first–third waves and the fourth wave of infections. Finally, we assessed the factors leading to the medical crisis in Osaka.

2. Materials and methods

2.1. Study subjects

We performed a single-center retrospective observational study with patients from the National Hospital Organization Kinki-Chuo Chest Medical Center, a respiratory disease center designed to manage patients with mild to moderate COVID-19 symptoms. If patients' condition turned severe and needed mechanical ventilation, they were transferred to an advanced hospital.

We retrospectively assessed all consecutive COVID-19 patients admitted to the hospital between 1 March 2020 and 8 June 2021. In addition, we compared the clinical patterns of COVID-19 patients between the first–third waves and the fourth wave.

The severity of the COVID-19 infection at admission was defined by the guidelines on the clinical management of patients with COVID-19 and criteria for Osaka prefecture. Mild cases were defined as those not requiring oxygen administration, moderate cases were those who did require oxygen administration, and severe cases were those requiring mechanical ventilation or extracorporeal membrane oxygenation, or those admitted to the intensive care unit (ICU). Disease severity was defined as the most severe condition recorded during hospitalization. The treatment strategy followed the official Japanese guidelines developed by the Ministry of Health, Labour, and Welfare [4].

COVID-19 diagnosis was confirmed by a polymerase chain reaction test or an antigen test for SARS-CoV-2 from saliva, sputum, or nasopharyngeal swabs. The end of the follow-up period was defined as the date of discharge, transfer to the advanced hospital, or death.

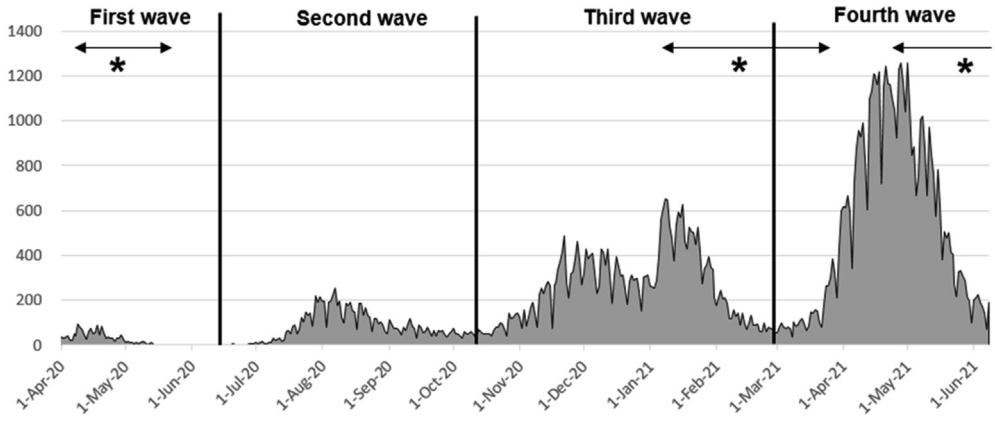

Fig. 1 – Newly diagnosed COVID-19 cases in Osaka Prefecture, Japan [5]. It had experienced four waves of infections in the COVID-19 pandemic. *The state of emergency.

We collected the following data: age, sex, disease severity, presence of infection cluster, smoking history, comorbidities, clinical manifestations, laboratory data at admission, treatment, and outcome. Comorbidities included hypertension, cardiovascular diseases (coronary heart diseases, cerebrovascular diseases, peripheral arterial diseases, and deep vein thromboses), diabetes, dementia, chronic kidney disease, underlying pulmonary conditions, malignant diseases, and connective tissue diseases. Laboratory data included white blood cell (WBC) count, lymphocyte count, C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ferritin, and Krebs von den Lungen-6 (KL-6) at admission. Fever was defined as a measured temperature of 38 °C or greater. We defined a cluster as >5 cases with primary exposure reported at a common event or venue, excluding within-household transmissions.

Publicly available information on the patients was collected from the Osaka prefecture website [5].

This study was approved by the institutional review board of the Kinki-Chuo Chest Medical Center (#795, approval date: 16/JUL/2021). We used an opt-out method that enabled patients and their families to refuse to participate in the study if they wished.

2.2. *Infection control policies of Osaka Prefecture during the first–fourth waves*

The first COVID-19 case in Osaka was detected on January 29, 2020. On April 7, the Japanese government declared a state of emergency, which was lifted on May 21. Daily new cases decreased following the first wave. Although cases had begun to increase again by mid-June 2020, the government did not declare a state of emergency. The third wave began in October 2020. The government declared a state of emergency for the second time on January 7, 2021, after which the cases decreased. However, they began to increase again in April 2021 (Fig. 1). During the fourth wave, Osaka's healthcare system became increasingly overwhelmed, with hospitals running out of beds and ventilators. For example, some patients could not be transferred to the hospital for severe cases. In addition, some mild patients who were still at home or in designated accommodation died when their condition worsened rapidly and they could not be hospitalized.

2.3. *Statistical analysis*

Continuous data are presented as median and interquartile range (IQR), and categorical data are presented as frequencies and proportions. We used Wilcoxon rank-sum tests for nonparametric continuous variables and Pearson's chi-squared tests for categorical variables.

We searched for candidate risk factors for moderate to severe COVID-19 by stratifying the patients based on five categories: patient factors, habits/behaviors, underlying disease, symptoms at admission, and laboratory data. Patient factors were age and sex; habits/behavior was infection from a cluster and smoking history; underlying disease categories were hypertension, cardiovascular diseases, diabetes, dementia, chronic kidney disease, underlying pulmonary conditions, malignant diseases, and connective tissue diseases; symptoms at admission were fever, cough, dyspnea, sputum, fatigue, diarrhea, and anorexia; and laboratory data comprised WBC count, lymphocytes, CRP, D-dimer, albumin, AST, ALT, LDH, ferritin, and KL-6. We used logistic regression analysis to calculate odds ratios (OR) and their 95% confidence intervals (CI). Laboratory test results were converted to clinically useful units and used as explanatory variables; for example, WBC count was expressed as 100/μL.

For our multivariate analyses, we selected covariates according to the modified Disjunctive Cause Criterion, to adjust for confounding factors [6]. As a result, for habits/behavior and underlying disease, we used only patient factors as covariates, whereas for symptoms and laboratory test results at admission, we used all three remaining categories as covariates. In other words, the confounding candidates used to calculate the adjusted ORs were different for each variable. For example, to calculate the OR adjusted for hypertension, we adjusted for the two variables patient characteristics (age and sex), and to calculate the OR adjusted for fever, we adjusted for the following 12 variables: patient characteristics (age and sex), patient habits and behaviors (infection from a cluster and smoking history), and underlying disease (hypertension, cardiovascular diseases, diabetes, dementia, chronic kidney disease, underlying pulmonary conditions, malignant diseases, connective tissue diseases). All *P*-values were two-sided and a *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata/MP version 16.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. *Characteristics and clinical features of COVID-19 patients*

We identified 404 COVID-19 patients (Table 1). The median age of the patients was 71.0 years (IQR: 56.0–80.0), with 342 (59.9%) males and 162 (40.1%) females. Of these, 46 (11.4%) had been infected from a cluster. With respect to case severity, 199 patients (49.1%) had mild disease, 142 (35.2%) had moderate disease, and 63 (15.6%) had severe disease. The most common comorbidities were hypertension (176, 43.6%), diabetes (91, 22.5%), and underlying pulmonary condition (86, 21.3%). Of 86 patients with underlying pulmonary condition, 65 had chronic obstructive pulmonary disease (COPD), ten had asthma, six had interstitial lung diseases, two had asthma and COPD overlap, two had lung cancer, and one patient had pneumoconiosis. After excluding missing data, the median duration from onset to hospitalization in 388 patients was 6 days (IQR: 4–8), with no significant differences observed by severity of the disease. Remdesivir in addition to systemic corticosteroids was the most commonly administered treatment for moderate and severe patients. Tocilizumab or baricitinib were used in cases of suspected cytokine release syndrome. The overall mortality rate was 5.4% (22/404).

We identified risk factors for acute respiratory failure requiring oxygenation (namely, moderate and severe cases) (Table 2). The univariate logistic regression analysis showed

Table 1 – Characteristics of patients with COVID-19 (N = 404).

	Total (N = 404)	Mild (N = 199)	Moderate (N = 142)	Severe/Death (N = 63)
Patient characteristics				
Age, years	71.0 (56.0–80.0)	72.0 (55.0–82.0)	69.0 (56.3–78.0)	71.0 (61.0–82.5)
Sex, female (%)	162 (40.1%)	89 (44.7%)	55 (38.7%)	18 (28.6%)
Patient habits and behaviors				
Infection from a cluster	46 (11.4%)	34 (17.1%)	9 (6.3%)	3 (4.8%)
Smoking history (current- or ex-smoker)	133 (32.9%)	54 (27.1%)	45 (31.7%)	34 (54.0%)
Underlying disease				
Hypertension	176 (43.6%)	90 (45.2%)	63 (44.4%)	23 (36.5%)
Cardiovascular disease	30 (7.4%)	7 (3.5%)	16 (11.3%)	7 (11.1%)
Diabetes	91 (22.5%)	39 (19.6%)	37 (26.1%)	15 (23.8%)
Dementia	79 (19.6%)	52 (26.1%)	16 (11.3%)	11 (17.5%)
Chronic kidney disease[a]	31 (7.7%)	12 (6.0%)	8 (5.6%)	11 (17.5%)
Underlying pulmonary condition	86 (21.3%)	38 (19.1%)	32 (22.5%)	16 (25.4%)
Malignant disease	24 (5.9%)	8 (4.0%)	9 (6.3%)	7 (11.1%)
Connective tissue disease	12 (3.0%)	6 (3.0%)	4 (2.8%)	2 (3.2%)
Symptoms at admission				
Fever	350 (86.6%)	161 (80.9%)	128 (90.1%)	61 (96.8%)
Cough	175 (43.3%)	80 (40.2%)	69 (48.6%)	26 (41.3%)
Dyspnea	218 (54.0%)	81 (40.7%)	93 (65.5%)	44 (69.8%)
Sputum	38 (9.4%)	14 (7.0%)	19 (13.4%)	5 (7.9%)
Fatigue	132 (32.7%)	66 (33.2%)	45 (31.7%)	21 (33.3%)
Diarrhea	18 (4.5%)	7 (3.5%)	10 (7.0%)	1 (1.6%)
Anorexia	74 (18.3%)	34 (17.1%)	28 (19.7%)	12 (19.0%)
Laboratory data at admission				
WBC count (/μL)	5,600 (4,300–7,300)	5,200 (4,100–6,500)	6,100 (4,525–7,900)	6,000 (4,800–8,450)
Lymphocytes (/μL)	900 (700–1,200)	1,000 (750–1,200)	800 (600–1,175)	800 (6,000–1,100)
CRP (mg/dL)	5.7 (2.3–10.5)	3.1 (1.2–6.6)	8.0 (4.0–12.4)	10.6 (6.9–15.0)
D-dimer (μg/mL)	1.3 (1.0–1.9)	1.1 (0.8–1.6)	1.4 (1.1–2.0)	1.7 (1.3–3.2)
Albumin (g/dL)	3.5 (3.2–3.9)	3.7 (3.3–4.1)	3.4 (3.0–3.6)	3.3 (3.1–3.7)
AST (IU/L)	38.0 (27.0–58.0)	29.0 (23.0–40.0)	44.0 (32.0–63.0)	54.5 (35.5–71.3)
ALT (IU/L)	27.0 (16.0–46.0)	21.0 (14.0–36.0)	32.5 (20.0–65.5)	34.0 (22.0–56.0)
LDH (IU/L)	313.0 (237.5–408.0)	250.0 (206.5–317.5)	364.5 (301.8–449.0)	427.0 (339.0–529.5)
Ferritin (ng/mL)	576.7 (247.1–1013.0)	337.5 (144.1–728.8)	743.0 (391.9–1430.1)	851.7 (663.6–1531.0)
KL-6 (U/mL)	336.1 (211.0–384.0)	248.0 (190.0–328.0)	317.0 (232.5–412.5)	405.0 (289.0–619.0)
Oxygen therapy[b]	205 (50.3%)	0 (0%)	142 (100%)	63 (100%)
Conventional oxygen therapy	205 (50.3%)	0 (0%)	142 (100%)	63 (100%)
High-flow nasal cannula	68 (16.9%)	0 (0%)	16 (11.3%)	52 (82.3%)
Mechanical ventilation	44 (11.3%)	0 (0%)	0 (0%)	44 (71.0%)
Treatment regimen				
Favipiravir	117 (30.1%)	83 (41.7%)	21 (14.8%)	13 (21.0%)
Remdesivir	233 (57.8%)	75 (37.7%)	111 (78.2%)	47 (72.3%)
Tocilizumab	17 (4.2%)	0	5 (3.5%)	12 (19.0%)
Baricitinib	7 (1.7%)	0	5 (3.5%)	2 (1.6%)
Corticosteroids	265 (66.2%)	79 (39.7%)	130 (91.5%)	56 (88.9%)
Heparin	20 (5.0%)	4 (2.0%)	9 (6.3%)	7 (11.1%)

Data are presented as n (%) or median (interquartile range). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; WBC, white blood cell.

[a] There were no dialysis patients.

[b] Not mutually exclusive.

that infection from a cluster and dementia were associated with significantly lower ORs for moderate to severe disease, at 0.302 and 0.429, respectively. Conversely, smoking, cardiovascular disease, fever, and dyspnea were associated with significantly higher ORs, 1.635, 3.466, 2.788, and 2.935, respectively. All laboratory data except lymphocytes and albumin were significantly associated with moderate to severe disease risk (OR point estimates: 1.010–1.208). However, even though WBC count, albumin, AST, and ALT were statistically significant, their OR point estimates were close to 1 (1.010–1.021).

In our multivariate analyses, smoking was not significant (OR 1.522, $P = 0.070$), but the results for the other variables were similar to those in the univariate analysis. Cardiovascular disease, fever, and dyspnea were associated with significantly higher ORs, 3.722, 2.853, and 2.507, respectively. All laboratory data other than lymphocytes and albumin were significant (OR point estimates: 1.012–1.254). For every 1 mg/dL increase in CRP, 10 IU/L increase in LDH, and 100 ng/mL increase in ferritin, the risk for moderate to severe disease increased by 18.3%, 12.9%, and 8.9%, respectively.

Table 2 – Logistic regression analysis of risk factors for moderate to severe disease.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Patient characteristics[a]						
Age	1.002	0.989–1.014	0.793	–		
Female	0.684	0.458–1.019	0.062	–		
Patient habits and behaviors[b]						
Infection from a cluster	0.302	0.151–0.602	**<0.001**	0.312	0.152–0.639	**<0.001**
Smoking history (current- or ex-smoker)	1.635	1.069–2.502	**0.023**	1.522	0.966–2.397	0.070
Underlying disease[b]						
Hypertension	0.875	0.591–1.297	0.507	0.887	0.592–1.329	0.561
Cardiovascular disease	3.466	1.452–8.274	**0.005**	3.722	1.547–8.957	**0.003**
Diabetes	1.394	0.871–2.232	0.166	1.360	0.847–2.184	0.204
Dementia	0.429	0.257–0.717	**0.001**	0.367	0.210–0.641	**<0.001**
Chronic kidney disease	1.592	0.751–3.372	0.225	1.449	0.668–3.143	0.347
Underlying pulmonary condition	1.295	0.802–2.091	0.290	1.232	0.756–2.007	0.402
Malignant disease	2.021	0.845–4.835	0.114	1.924	0.796–4.651	0.146
Connective tissue disease	0.970	0.307–3.059	0.958	0.974	0.306–3.105	0.965
Symptoms at admission[c]						
Fever	2.788	1.499–5.187	**0.001**	2.853	1.419–5.737	**0.003**
Cough	1.285	0.866–1.906	0.213	1.279	0.815–2.007	0.285
Dyspnea	2.935	1.956–4.403	**<0.001**	2.507	1.590–3.950	**<0.001**
Sputum	1.752	0.879–3.494	0.111	1.527	0.725–3.216	0.266
Fatigue	0.957	0.631–1.450	0.835	1.002	0.629–1.595	0.995
Diarrhea	1.555	0.591–4.096	0.371	1.210	0.427–3.431	0.720
Anorexia	1.176	0.710–1.950	0.529	1.195	0.683–2.088	0.533
Laboratory data at admission[c]						
WBC count (per 100/μL increase)	1.016	1.008–1.024	**<0.001**	1.018	1.009–1.026	**<0.001**
Lymphocytes (per 100/μL increase)	0.970	0.936–1.006	0.103	0.975	0.943–1.007	0.126
CRP (per 1 mg/dL increase)	1.208	1.151–1.268	**<0.001**	1.183	1.125–1.243	**<0.001**
D-dimer (per 1 μg/mL increase)	1.191	1.021–1.389	**0.026**	1.254	1.046–1.505	**0.015**
Albumin (per 1 g/dL increase)	1.006	0.987–1.026	0.523	1.006	0.986–1.027	0.541
AST (per 1 IU/L increase)	1.021	1.012–1.029	**<0.001**	1.021	1.012–1.031	**<0.001**
ALT (per 1 IU/L increase)	1.010	1.004–1.017	**<0.001**	1.012	1.005–1.020	**<0.001**
LDH (per 10 IU/L increase)	1.124	1.096–1.153	**<0.001**	1.129	1.097–1.162	**<0.001**
Ferritin (per 100 ng/mL increase)	1.093	1.058–1.129	**<0.001**	1.089	1.052–1.128	**<0.001**
KL-6 (per 10 U/mL increase)	1.032	1.020–1.045	**<0.001**	1.034	1.020–1.048	**<0.001**

* The multivariate analysis does not present a miscellaneous model with all variables entered simultaneously. Here, we present odds ratios in the model adjusted for the candidates for confounders of each variable. Please refer to "a" and "c" for the details of the candidates for confounders.

**We did not run multivariate analysis for age and sex because no potential confounding variables were able to be identified. However, age and sex were included in all other multivariate analyses as potential confounding variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; OR, odds ratio; WBC, white blood cell. Statistically significant values are in bold.

[a] No multivariate analysis was performed because variables affecting these factors were not measured.

[b] Since the only recorded variables that may have affected these factors, and were candidates for confounders, were the patient characteristics, multivariate analysis was conducted by adding age and sex.

[c] Since the recorded variables that may have affected these factors, and were candidates for confounders, were the patient characteristics, patient habits/behaviors, and underlying disease, multivariate analysis was performed with these variables.

3.2. *The first–third waves vs. the fourth wave*

Overall disease severity in the fourth wave was higher than that in the first–third waves (Table 3). During the fourth wave, the number of mild cases halved, whereas moderate cases doubled. The proportion of moderate cases, particularly those in the 50–80 age group, increased (Fig. 2). With respect to the laboratory data, CRP, AST, LDH, and ferritin were significantly higher in fourth-wave patients than in first–third-wave patients ($P < 0.01$ for all). There were fewer cases of infection from a cluster than in the first–third waves (16.2% vs. 4.3%, $P < 0.01$). There were no fully-vaccinated patients in the present study.

During the fourth wave, remdesivir and systemic corticosteroids were widely used, based on previous efficacy (Table 3) [7,8]. Conversely, favipiravir was used less frequently, because of a lack of effective treatment evidence.

In the prefecture, the waiting list for beds for severe patients briefly reached a maximum of 94 (Fig. 3). Therefore, four of the 28 severe patients (14.3%) in our hospital could not be transferred to the advanced hospital during the fourth wave. These patients received mechanical ventilation for 2, 3, 9, and 12 days, and

Table 3 – Characteristics of patients with COVID-19: the first–third waves vs. the fourth wave (N = 404).

	First–third wave (N = 241)	Fourth wave (N = 163)	P-value[a]
Age, years	73.0 (60.0–83.0)	67.0 (52.0–76.0)	**<0.01**
Sex, female (%)	41.9%	37.4%	0.48
Infection from a cluster	39 (16.2%)	7 (4.3%)	**<0.01**
Severity			**<0.01**
Mild	145 (60.2%)	54 (33.1%)	–
Moderate	61 (25.3%)	81 (49.7%)	–
Severe	35 (14.5%)	28 (17.2%)	–
Laboratory data at admission			
WBC count (/μL)	5,700 (4,400–7,400)	5,500 (4,300–7,100)	0.24
Lymphocytes (/μL)	1,000 (700–1,200)	800 (600–1,100)	0.32
CRP (mg/dL)	4.5 (1.8–9.8)	7.4 (3.0–12.3)	**<0.01**
D-dimer (μg/mL)	1.2 (0.9–2.0)	1.4 (1.1–1.8)	0.22
Albumin (g/dL)	3.5 (3.2–3.9)	3.5 (3.2–3.8)	1.00
AST (IU/L)	34.0 (24.0–48.0)	43.5 (30.3–65.8)	**<0.01**
ALT (IU/L)	22.0 (15.0–42.0)	32.0 (18.3–58.0)	**0.04**
LDH (IU/L)	284.0 (219.0–371.0)	359.0 (272.8–452.5)	**<0.01**
Ferritin (ng/mL)	433.6 (179.4–843.2)	743.0 (386.9–1275.4)	**<0.01**
KL-6 (U/mL)	275.0 (209.0–381.0)	299.0 (222.0–405.0)	0.42
Oxygen therapy[b]	96 (39.8%)	109 (66.9%)	**<0.01**
Conventional oxygen therapy	96 (39.8%)	109 (66.9%)	–
High-flow nasal cannula	40 (16.6%)	28 (17.2%)	–
Mechanical ventilation	26 (10.8%)	18 (11.0%)	–
Treatment regimen			
Favipiravir	106 (44.0%)	11 (6.7%)	**<0.01**
Remdesivir	104 (43.2%)	129 (79.1%)	**<0.01**
Tocilizumab	1 (0.4%)	16 (9.8%)	**<0.01**
Baricitinib	0 (0%)	7 (4.3%)	**<0.01**
Corticosteroids	125 (51.9%)	140 (85.9%)	**<0.01**
Heparin	12 (5.0%)	8 (4.9%)	0.42
Outcome			0.80
Discharge	204 (84.6%)	140 (85.9%)	–
Transfer to the advanced hospital	24 (10.0%)	14 (8.6%)	–
Death	13 (5.4%)	9 (5.5%)	–

Data are presented as n (%) or median (interquartile range).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; WBC, white blood cell. Statistically significant values are in bold.
[a] Pearson's chi-squared test, Wilcoxon rank-sum test.
[b] Not mutually exclusive.

recovered. There was no difference in mortality between the first–third waves and the fourth wave (5.4% vs. 5.5%, $P = 0.80$).

4. Discussion

COVID-19 in patients with underlying medical conditions induced pneumonia with elevated inflammatory biomarkers. In Osaka, we observed many moderate to severe cases in the fourth wave.

We identified several inflammatory biomarkers as independent risk factors for moderate to severe disease. For example, for every 1 mg/dL increase in CRP, the risk for moderate to severe disease increased by 18.3% in our cohort. Similarly, for every 10 IU/L increase in LDH and 100 ng/mL increase in ferritin, the risk increased by 12.9% and 8.9%, respectively. Studies in Kanagawa prefecture [9] also reported that CRP was a risk factor for moderate (requiring >1–4 L/min of oxygen) to severe (requiring >5 L/min of oxygen) disease. In the fourth wave, pneumonia caused by the variant of concern (VOC) resulted in severe inflammation, and many of the cases with high CRP levels suffered respiratory failure.

There were more moderate cases in the fourth wave than in the first–third waves (49.7% vs. 25.3%). However, we observed no significant increase in mortality (5.5% vs. 5.4%). The reasons could be as follows: the COVID-19 prognosis appears to be positive if the patient survives the respiratory failure phase, and evidence for the therapeutic efficacy of treatments such as systemic corticosteroids and remdesivir administration has been accumulating [7,8]. In our study, systemic corticosteroids were administered to the 39.7% of mild cases who exhibited extensive ground-glass shadows in both lungs, since this was projected to result in respiratory failure within a few days. Since patient treatment and outcome after transfer to the advanced hospital was not included in our cohort, it is possible that there was a difference in the actual mortality rate. However, data from Osaka prefecture reported that there was no difference in mortality between the third and fourth waves (2.6% vs. 2.8%; denominator is all SARS-CoV-2 positive subjects) [5], which supports the validity of our data.

In contrast to the first–third waves, the fourth wave saw a rapid increase in cases, and 66.9% of the fourth-wave patients in our cohort experienced acute respiratory failure (moderate to severe). The proportion of patients requiring oxygen

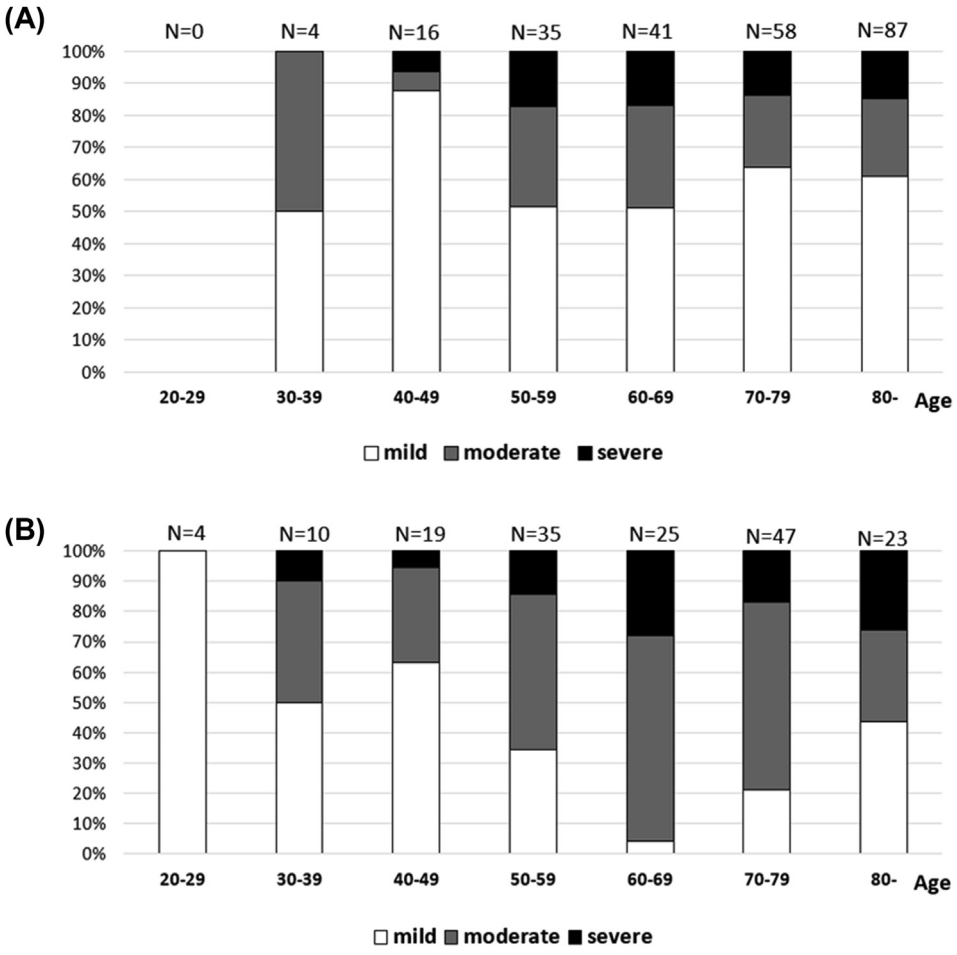

Fig. 2 – Proportion of disease severity by age; (A) first–third waves, (B) fourth wave. The proportion of moderate cases, particularly those in the 50–80 age group, increased.

administration was 1.7 times higher than in the first–third waves. This resulted in a shortage of available medical staff and of beds for severe cases. The number of ICU beds in Osaka Prefecture was originally 618, of which COVID-19 patients occupied an unanticipated 75%. This caused non-COVID-19 medical services, such as emergency medicine and surgery, to halt temporarily. In the prefecture, the waiting list for beds for severe patients briefly reached a maximum of 94 (Fig. 3). Therefore, the fourth COVID-19 wave in Osaka triggered a medical crisis, where mild to moderate cases could no longer be transferred to the advanced hospital after worsening and patients at home or in designated accommodations could not be

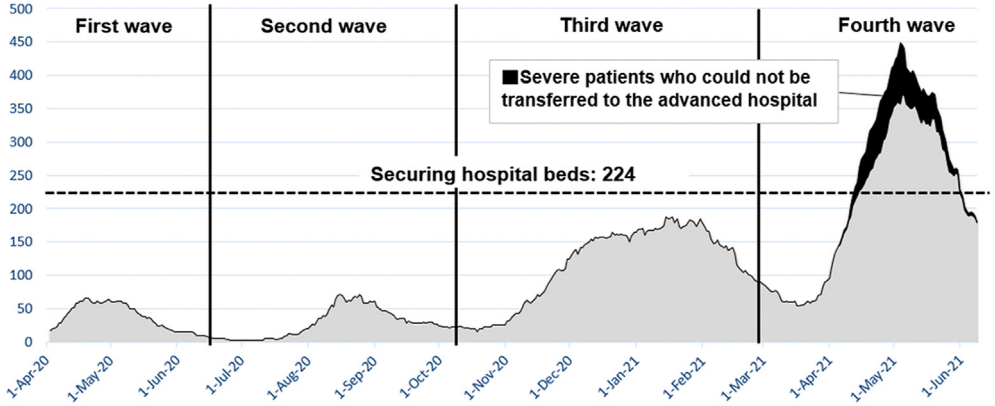

Fig. 3 – Severe COVID-19 cases in Osaka Prefecture [5]. The waiting list for beds for severe patients briefly reached a maximum of 94 and they could not be transferred to the advanced hospital.

admitted to any hospital. The elderly COVID-19 patients had to be cared for in a nursing home. Therefore, there were fewer cases of infection from clusters in the fourth wave than in the first–third waves in our cohort (16.2% vs. 4.3%, $P < 0.01$). This led to some patient deaths at home or nursing home in the fourth wave.

At the end of the third wave, the state of emergency was lifted in Osaka three weeks earlier than in the Tokyo region, where a VOC may have accounted for a rising proportion of new infections. Osaka may have been the epicenter of cases with the alpha VOC (lineage B.1.1.7), which is more infectious and led to more severe disease in the fourth wave. The B.1.1.7 variant accounted for 82% of the positive cases screened by the health center during the fourth wave [4]. Observational studies [10,11] and a retrospective cohort analysis [12] using a large database from the United Kingdom reported that the risk of death associated with the B.1.1.7 variant is 55–64% higher than that of the original strain. In addition, observational studies conducted in Europe [13,14] showed that the B.1.1.7 variant is associated with a higher risk of hospitalization than the conventional strain. In the present study, patients in the fourth wave were more likely to suffer from acute respiratory failure, which may be explained by the B.1.1.7 variant.

Our study has several limitations. First, whether the B.1.1.7 variant of SARS-CoV-2 was responsible for the disease severity in the fourth wave is unclear from our data, because the relevant diagnostic test of variants was not available at our hospital. Second, admission to the beds for mild to moderate cases may have been requested only for much more severe cases in the fourth wave, introducing a potential sampling bias. Third, as mentioned above, since our hospital managed only mild to moderate cases, patient treatment and outcome after transfer to the advanced hospital is not included in the present study, because we used data only from our own hospital. Fourth, this was a single-center study and does not directly reflect overall bed management for COVID-19 in Osaka prefecture. Nevertheless, it can be assumed that, similar to our hospital, several hospitals in Osaka would have experienced a bed shortage for COVID-19 patients.

5. Conclusions

Based on multivariate logistic regression analysis, cardiovascular disease, fever, dyspnea, and several inflammatory biomarkers were risk factors for moderate to severe COVID-19 in our cohort.

During the fourth wave in Osaka prefecture, COVID-19 severity was higher than in the first–third waves, resulting in a medical crisis in which a large number of patients could not be transferred to the advanced hospital for severe cases. At its peak, 20% of severely ill patients were managed at hospitals for mild to moderate cases, resulting in a staffing shortage throughout Osaka. In addition, hospital admissions for patients at home or in designated accommodations were delayed.

In future, emerging infectious diseases may become more common in urban areas in general. Securing hospital beds in the event of widespread diseases that require advanced medical care is a major issue that should be resolved.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

Y.K. contributed to the investigation, data curation, and writing of the original draft. K. Tsuyuguchi contributed to the planning and editing of the article. T.K., S.S., Y.M., A.T., R.S., T.A., K. Tachibana, K.O., and H.M. contributed to the supervision and editing of the article. All authors commented on draft versions and approved the final version.

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