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Original Article

# Temporal trends in clinical characteristics and in-hospital mortality among patients with COVID-19 in Japan for waves 1, 2, and 3: A retrospective cohort study

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## ABSTRACT

**Introduction:** Little information is available on the temporal trends in the clinical epidemiology and in-hospital mortality of patients with coronavirus disease 2019 (COVID-19) in Japan for waves 1, 2, and 3.

**Methods:** A national claims database was used to analyze the time trends in admission, medical procedure, and in-hospital mortality characteristics among patients with COVID-19. Patients who were  $\geq 18$  years and discharged from January 1, 2020 to February 28, 2021 were included.

**Results:** A multilevel logistic regression analysis of 51,252 patients revealed a decline in mortality in waves 2 and 3 (risk-adjusted mortality range = 2.17–4.07%; relative risk reduction = 23–59%; reference month of April 2020 = 5.32%). In the subgroup analysis, a decline in mortality was also observed in patients requiring oxygen support but not mechanical ventilation (risk-adjusted mortality range = 5.98–11.68%; relative risk reduction = 22–60%; reference month of April 2020 = 15.06%). Further adjustments for medical procedure changes in the entire study population revealed a decrease in mortality in waves 2 and 3 (risk-adjusted mortality range = 2.66–4.05%; relative risk reduction = 24–50%).

**Conclusions:** A decline in in-hospital mortality was observed in waves 2 and 3 after adjusting for patient/hospital-level characteristics and medical treatments. The reasons for this decline warrant further research to improve the outcomes of hospitalized patients.

## 1. Introduction

The coronavirus disease 2019 (COVID-19) has caused a global pandemic that has burdened medical systems, societies, and economies [1,2]. Globally, severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) has spread rapidly, resulting in more than 230 million confirmed cases and 4.8 million deaths as of October 4, 2021 [3]. Previous studies that assessed the characteristics of COVID-19 have reported that older age, male sex, obesity, and comorbidities (such as diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease) were associated with a more severe clinical course [4–6]. Furthermore, other studies have reported that in-hospital mortality decreased over time even after adjusting for clinical risk factors [7–11]. Some authors have suggested the reasons for the decline in mortality, such as increased knowledge and experience of the healthcare

providers [8–11]; however, these hypotheses are yet to be proven.

In Japan, from January 16, 2020 (the day on which the first case was confirmed) to October 4, 2021, there were 1.7 million confirmed cases and 17,927 deaths [3]. One study in Japan revealed similar risk factors for severe COVID-19 [12]. Regarding the temporal trends, one study highlighted that patients of the second wave had lower mortality and disease severity and were less likely to have comorbidities than those of the first wave [13]. However, the sample size of these studies was limited, and the trends in in-hospital mortality were not analyzed with risk adjustment. Our aim was to describe the clinical characteristics of hospitalized patients with COVID-19 in Japan and to analyze the temporal trends in in-hospital mortality for the first three waves using a nationwide database with adjustments for patient- and hospital-level characteristics.

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## 2. Patients and methods

### 2.1. Study design and data source

We conducted a retrospective cohort analysis using information from the Diagnosis Procedure Combination (DPC) database governed by the Ministry of Health, Labour and Welfare. The DPC database is an administrative claims database for billing purposes in Japan. Data for research use were submitted from more than 1000 hospitals that cover approximately 40% of all acute-care in-patient beds in Japan. The database contains patient-level data for each admission, such as age, sex, primary diagnosis, other diagnoses on admission, diagnoses given after admission, billing codes for procedures and medications, and discharge status and destination. Diagnoses were recorded according to the International Classification of Diseases, 10th revision (ICD-10). Further details of the DPC database can be found elsewhere [14].

In this study, informed consent was waived because of the anonymous nature of the DPC data. The institutional review board of the Tokyo Medical and Dental University approved this study.

### 2.2. Study population

Patients who were discharged from January 1, 2020 to February 28, 2021 were included. This period included wave 1 (January–May 2020), wave 2 (June–September 2020), and wave 3 (October 2020–February 2021) of the COVID-19 pandemic in Japan. Vaccines for COVID-19 were not available until mid-February 2021, and SARS-CoV-2 variants of concern first emerged in Japan in December 2020 and started to spread in March 2021 [15].

We identified patients with COVID-19 who had ICD-10 codes for COVID-19 (B34.2 or U07.1) as the primary diagnosis. Patients with adjunct codes for suspected cases were regarded as not having COVID-19. Because of different time schedules of data submission, data from university hospitals and national hospitals were not included in this study. Patients who were <18 years were excluded from the study. Records of patients who had multiple hospital admissions during the study period were excluded, except for those at last admission because there was no risk of death in the preceding admissions. Finally, patients with missing data on billing information for medical procedures were excluded.

### 2.3. Outcomes

The primary outcome of interest was in-hospital mortality, which was defined as death at discharge. The secondary outcomes included length of hospital stay, discharge disposition, and total medical cost in US dollars (1 US dollar = 110 Japanese yen).

### 2.4. Statistical analysis

A multilevel logistic regression model was used to investigate the association between in-hospital death and patient-level characteristics, including the month of admission. The admission months were not categorized into waves to observe a more detailed trend within waves as well as thorough out the three waves. January and February 2020 were combined because of the low number of patients in these two months. The covariates for the regression model included age, sex, body mass index (BMI) on admission, the Brinkman index, comorbidities using the Charlson Comorbidity Index (CCI) categories [16], the Japan Coma Scale (JCS) score on admission, the Barthel index on admission, transfer from another hospital, and ambulance use. These covariates were chosen based on known risk factors and clinical knowledge. The JCS score was used to assess the altered mental status on admission [17]. To account for the clinical severity on admission, the following variables were added to the regression model: admission to the intensive care unit (ICU), oxygen support, mechanical ventilation, and vasopressor use

within the first two days of admission.

Additionally, subgroup analysis was conducted according to the severity of the clinical course. Subgroups of patients requiring oxygen support but not mechanical ventilation and patients requiring mechanical ventilation were analyzed with the same variables used in the regression model of the main analysis.

Further, as part of an exploratory analysis to investigate the factors related to the temporal trends in in-hospital mortality, medical procedures, medication use, and case volume during the study period were added to the regression model. The procedures and medications included were ICU admission, antibiotics, antiviral drugs, azithromycin, lopinavir/ritonavir, hydroxychloroquine, oral steroid, intravenous steroid, intravenous or subcutaneous anticoagulant, vasopressor, oxygen support, mechanical ventilation, extracorporeal membrane oxygenation, intermittent renal replacement therapy (IRRT), and continuous renal replacement therapy (CRRT). The case volume, the number of patients admitted during the study period, was categorized as follows, such that each category contained approximately the same number of patients in order to maximize the statistical power:  $\leq 104$ ,  $>104$  and  $\leq 213$ , and  $>213$  patients.

Concerning the month of admission, the adjusted odds ratio (aOR) for in-hospital death was calculated along with the risk-adjusted mortality. April 2020 was set as the reference month for wave 1 to reduce uncertainty because of the low number of cases of the other months. The risk-adjusted mortality was obtained with the *margins* command, which gives the average marginal effect of the month of admission on in-hospital death [18].

Missing values were imputed with multiple imputation by the chained equation [19,20]. Variables that had missing values were considered to be missing at random. Twenty imputation datasets were computed. The imputation procedure was repeated 30 times, and convergence was confirmed visually with a plot displaying the mean and variance of the imputations.

The predictive performance of the regression model was assessed using the C-index and Brier score [21,22]. The adjusted intraclass correlation (ICC) was calculated to evaluate the variance between hospitals, which can be used to justify a multilevel model [23]. A lower ICC indicates low variance among hospitals. The uncertainty of these performance measures was provided with a range of values from each imputation set because it was uncertain whether these measures could be integrated with Rubin's rule [24].

Descriptive statistics are presented as medians and interquartile ranges (IQRs) for continuous variables and as numbers and percentages for categorical variables. All data analyses were performed using R statistical software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). All analyses used two-sided statistical tests, and a *p*-value of  $<0.05$  was considered statistically significant without adjustment for multiple testing. The recommendations of the STROBE guidelines were followed to present our study [25].

## 3. Results

### 3.1. Study population

Across 763 hospitals in Japan between January 1, 2020 and February 28, 2021, a total of 51,252 patients confirmed with COVID-19 were included in this study (Fig. 1). The number of patients with COVID-19 peaked in April 2020, August 2020, and January 2021, and the peak became higher in the later waves (Fig. 2). Table 1 shows an excerpt of the baseline characteristics and temporal trends of these characteristics among the study population and a full version of the characteristics is provided in Supplementary Table S1. The median age of the patients in the total sample was 60 years (IQR = 43–76), and 23,373 (43.7%) patients were female. The proportions of patients requiring oxygen support, mechanical ventilation, or vasopressor use within the first two days of hospital admission was lower in wave 2. The overall in-hospital

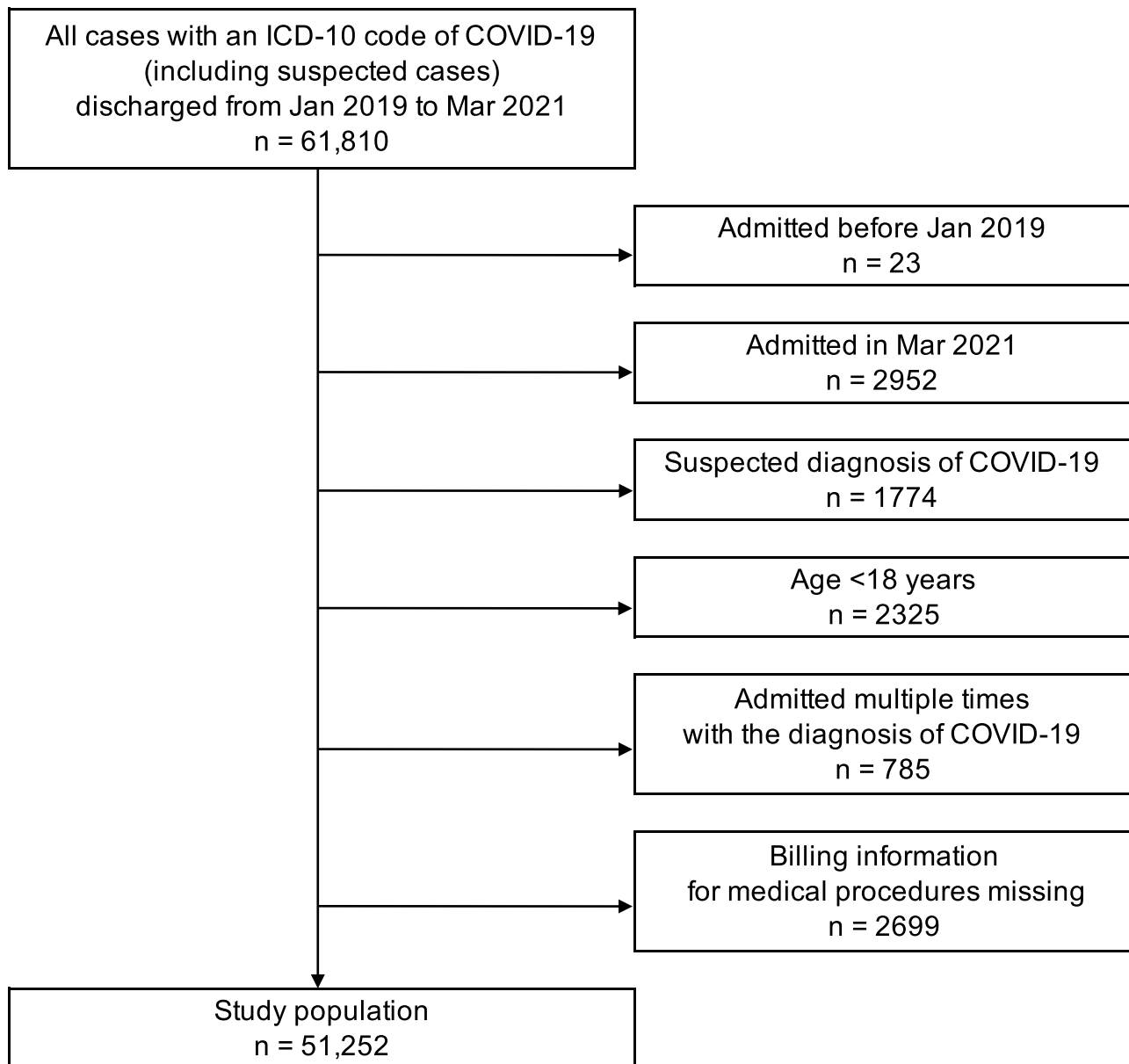


Fig. 1. Study population flow chart  
COVID-19; coronavirus disease 2019, ICD-10; International Classification of Diseases 10th revision.

mortality rate was 5.3%. The monthly trend of in-hospital mortality showed a concave shape with a bottom at wave 2 (Fig. 2). When stratified by sex and age, most of the age groups had a higher in-hospital mortality in wave 1 than in the other waves. A trend similar to that of the entire study population was observed in the subgroup of patients with oxygen support but without mechanical ventilation (Fig. 3). Supplementary Tables S2 and S3 provide the baseline characteristics of the subgroups. Regarding the other outcomes, more patients were discharged, had a shorter length of hospital stay, and had a lower total medical cost in wave 2 (Supplementary Table S1).

Missing values were observed for the following variables: BMI, Brinkman index, Barthel index on admission, transfer from another hospital, and ambulance use. BMI and Brinkman index had the highest percentages of missing values (16.8% and 16.2%, respectively). Convergence was confirmed using the aforementioned plot.

### 3.2. Main analysis

The multilevel logistic regression model revealed that an age of  $\geq 60$  years; male sex; a BMI of  $\geq 30$  or  $< 18.5$  kg/m<sup>2</sup>; a CCI category other than 0; a JCS score other than 0; a Barthel index other than 100; oxygen support, mechanical ventilation, or vasopressor use within the first two days after hospital admission; and March being the admission month were significant risk factors for in-hospital death (Table 2). A reduction in risk-adjusted mortality ranging from 23% to 59% was observed in the months of wave 2 and 3 compared with the in-hospital mortality in April 2020. The C-index, Brier score, and ICC were 0.925 (range = 0.925–0.926), 0.0383 (range = 0.0382–0.0384), and 0.0792 (range = 0.0778–0.0803), respectively.

### 3.3. Subgroup analysis

In the subgroup analysis, patients who needed oxygen support but not mechanical ventilation in the months of waves 2 and 3 had

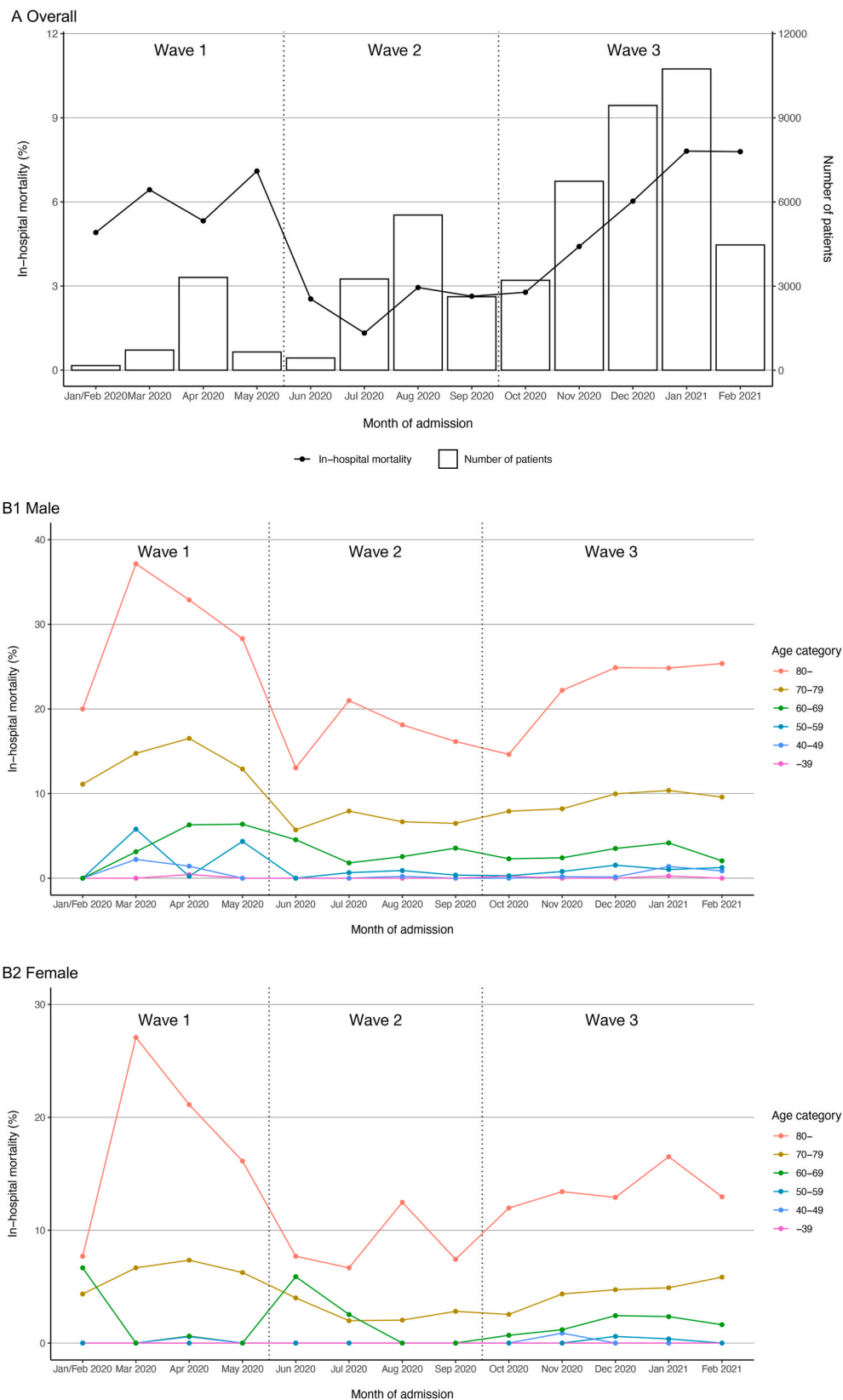


Fig. 2. Monthly trend of in-hospital mortality.

significantly lower aORs for in-hospital mortality, while those who needed mechanical ventilation did not show such a significant trend (Table 3). The risk-adjusted mortality rate of the former subgroup dropped by 22–60% in the months of wave 2 and 3 compared with the

mortality in April 2020. The C-index, Brier score, and ICC in the regression model for the oxygen support subgroup were 0.844 (range = 0.843–0.846), 0.0957 (range = 0.0954–0.0959), and 0.0736 (range = 0.0723–0.0748), and those for the mechanical ventilation subgroup

**Table 1**  
Clinical characteristics and temporal trend.

	Overall	Month of admission												
		Wave 1			Wave 2			Wave 3						
		Jan/Feb 2020	Mar 2020	Apr 2020	May 2020	Jun 2020	Jul 2020	Aug 2020	Sep 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021
Number of patients	51252	163	715	3306	648	433	3250	5531	2618	3204	6736	9440	10742	4466
Baseline characteristics														
Age, yrs, median [IQR]	60 [43, 76]	68 [57, 75]	54 [39, 70]	53 [39, 68]	60 [41, 78]	49 [30, 71]	40 [26, 56]	53 [34, 71]	55 [37, 72]	54 [38, 71]	59 [44, 74]	65 [48, 78]	68 [51, 80]	71 [54, 82]
Female (%)	22373 (43.7)	69 (42.3)	294 (41.1)	1346 (40.7)	322 (49.7)	191 (44.1)	1304 (40.1)	2376 (43.0)	1120 (42.8)	1349 (42.1)	2920 (43.3)	4145 (43.9)	4784 (44.5)	2153 (48.2)
BMI category, kg/m <sup>2</sup> (%)														
≥18.5, <25	24267 (47.3)	61 (37.4)	358 (50.1)	1548 (46.8)	287 (44.3)	212 (49.0)	1689 (52.0)	2680 (48.5)	1257 (48.0)	1535 (47.9)	3209 (47.6)	4413 (46.7)	4961 (46.2)	2057 (46.1)
<18.5	3711 (7.2)	5 (3.1)	37 (5.2)	157 (4.7)	66 (10.2)	52 (12.0)	208 (6.4)	395 (7.1)	187 (7.1)	232 (7.2)	462 (6.9)	686 (7.3)	787 (7.3)	437 (9.8)
≥25, <30	10717 (20.9)	38 (23.3)	145 (20.3)	688 (20.8)	110 (17.0)	70 (16.2)	614 (18.9)	1111 (20.1)	586 (22.4)	720 (22.5)	1404 (20.8)	2037 (21.6)	2273 (21.2)	921 (20.6)
≥30	3956 (7.7)	4 (2.5)	47 (6.6)	243 (7.4)	41 (6.3)	29 (6.7)	222 (6.8)	442 (8.0)	224 (8.6)	265 (8.3)	537 (8.0)	729 (7.7)	851 (7.9)	322 (7.2)
missing	8601 (16.8)	55 (33.7)	128 (17.9)	670 (20.3)	144 (22.2)	70 (16.2)	517 (15.9)	903 (16.3)	364 (13.9)	452 (14.1)	1124 (16.7)	1575 (16.7)	1870 (17.4)	729 (16.3)
Charlson comorbidity index (%)														
0	42708 (83.3)	142 (87.1)	613 (85.7)	2843 (86.0)	508 (78.4)	375 (86.6)	2976 (91.6)	4813 (87.0)	2262 (86.4)	2801 (87.4)	5703 (84.7)	7729 (81.9)	8456 (78.7)	3487 (78.1)
1	3420 (6.7)	8 (4.9)	57 (8.0)	234 (7.1)	52 (8.0)	23 (5.3)	126 (3.9)	322 (5.8)	147 (5.6)	168 (5.2)	471 (7.0)	691 (7.3)	810 (7.5)	311 (7.0)
2	3677 (7.2)	10 (6.1)	30 (4.2)	172 (5.2)	64 (9.9)	30 (6.9)	105 (3.2)	291 (5.3)	154 (5.9)	164 (5.1)	410 (6.1)	718 (7.6)	1056 (9.8)	473 (10.6)
≥3	1447 (2.8)	3 (1.8)	15 (2.1)	57 (1.7)	24 (3.7)	5 (1.2)	43 (1.3)	105 (1.9)	55 (2.1)	71 (2.2)	152 (2.3)	302 (3.2)	420 (3.9)	195 (4.4)
Procedures														
Admitted to the ICU within the first 2 days after hospital admission (%)	4193 (8.2)	10 (6.1)	37 (5.2)	306 (9.3)	83 (12.8)	15 (3.5)	226 (7.0)	428 (7.7)	193 (7.4)	237 (7.4)	522 (7.7)	783 (8.3)	993 (9.2)	360 (8.1)
Oxygen support within the first 2 days after hospital admission (%)	13978 (27.3)	35 (21.5)	144 (20.1)	915 (27.7)	178 (27.5)	67 (15.5)	363 (11.2)	1180 (21.3)	570 (21.8)	658 (20.5)	1607 (23.9)	2749 (29.1)	3909 (36.4)	1603 (35.9)
Mechanical ventilation within the first 2 days after hospital admission (%)	1354 (2.6)	12 (7.4)	31 (4.3)	129 (3.9)	27 (4.2)	9 (2.1)	36 (1.1)	104 (1.9)	38 (1.5)	57 (1.8)	154 (2.3)	286 (3.0)	365 (3.4)	106 (2.4)
Vasopressor use within the first 2 days after hospital admission (%)	953 (1.9)	8 (4.9)	23 (3.2)	91 (2.8)	16 (2.5)	6 (1.4)	20 (0.6)	67 (1.2)	27 (1.0)	31 (1.0)	99 (1.5)	205 (2.2)	267 (2.5)	93 (2.1)
Outcome														
Death at hospital discharge (%)	2704 (5.3)	8 (4.9)	46 (6.4)	176 (5.3)	46 (7.1)	11 (2.5)	43 (1.3)	163 (2.9)	69 (2.6)	89 (2.8)	297 (4.4)	569 (6.0)	839 (7.8)	348 (7.8)

BMI; body mass index, ICU; intensive care unit, IQR; interquartile range, JCS; Japan coma scale, USD; United States dollar.

were 0.794 (range = 0.792–0.795), 0.163 (range = 0.163–0.164), and 0.0989 (range = 0.0946–0.1030), respectively.

### 3.4. Exploratory analysis

The exploratory analysis that added medical procedures, medication use, and case volume to the regression model revealed significantly lower aORs from June 2020 (Table 4). A decline in risk-adjusted mortality rate ranging from 24% to 50% was observed. Case volume of patients with COVID-19 did not have a significant effect on in-hospital death; the aORs for case volume categories >104 & ≤213 and > 213 were 1.14 (95% confidence interval [CI] = 0.95–1.36) and 1.24 (95% CI = 0.999–1.54), respectively. The trends in medical procedures and medication use per month are provided in the Supplementary Table S4 and Supplementary Fig. S1. The proportion of prescribing azithromycin,

antiviral drugs, lopinavir/ritonavir, and hydroxychloroquine decreased in the later months, whereas the administration of oral and intravenous steroids and intravenous or subcutaneous anticoagulants increased from August 2020. The proportion of using vasopressors, CRRT, mechanical ventilation, and extracorporeal membrane oxygenation decreased overall from wave 1, but there was a slight uptick in their use in wave 3. The trend in oxygen support and antibiotic use revealed a concave shape with a bottom in June 2020. Admission to the ICU and use of IRRD did not show specific trends.

## 4. Discussion

Using a national administrative claims database, the data of a total of 51,252 patients with COVID-19 were analyzed to elucidate the patients' clinical characteristics and temporal trends in waves 1, 2, and 3 of the

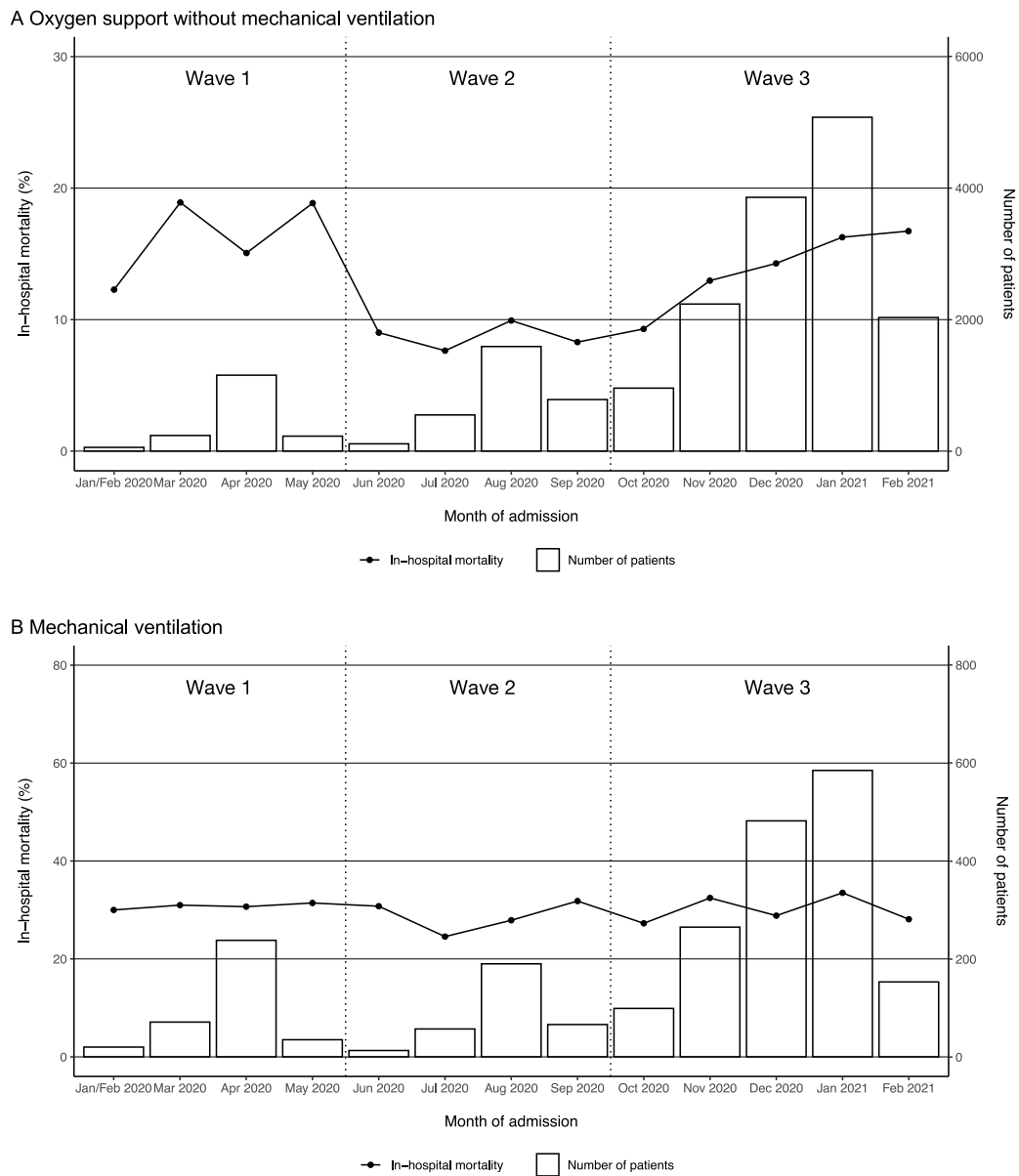


Fig. 3. Monthly trend of in-hospital mortality among subgroups.

pandemic. To date, this is the most extensive cohort study of hospitalized patients with COVID-19 in Japan. Patients who were  $\geq 60$  years, were male, were underweight or obese, had comorbidities, were not alert on admission, and had disabilities presented a risk of in-hospital death. A decline in in-hospital mortality was observed in wave 2. After risk adjustment, a significant decline in mortality was also observed in wave 3.

Previous studies conducted in other countries have reported a much higher mortality among hospitalized patients [4,6–11]. The reason for the difference in mortality is beyond the scope of our study and remains unknown. However, a similar decline in risk-adjusted mortality was observed in a healthcare system that had a relatively low risk of death. The exploratory analysis that additionally controlled for case volume and changes in medical procedures and medication use still showed a lower risk of death in the later months. This means that factors other than those included in the regression model contributed to the improvement in in-hospital mortality. This finding is consistent with that in a previous study that controlled for critical care and respiratory support in addition to baseline clinical characteristics [11]. Case volume did not have a significant effect on in-hospital death. In many diseases

and procedures, it has been reported that increasing case volume levels lead to better outcomes [26]. However, when there is no knowledge or experience of effective interventions, the beneficial effects of increased case volume may not become obvious. The proportion of using several medical procedures and medication included in the regression analysis decreased over time. This may reflect a decline in disease severity or decrease in the choice of treatment with equivocal effects. The proportion of mechanical ventilation, CRRT, and vasopressor use decreased over time, with a slight upward trend in wave 3. This trend may be partly in parallel with the clinical severity of patients. In wave 3, as the number of patients with COVID-19 increased, hospitals were unable to admit all of them. Selected patients who needed extensive treatment were prioritized to be admitted. This may have contributed to the increased severity in wave 3. In contrast, lopinavir/ritonavir and hydroxychloroquine, for example, were found to not be beneficial [27, 28]; therefore, a decrease in their usage may likely reflect a physician's choice. Thus, the exploratory analysis that included procedural variables in the regression model may have further adjusted for clinical severity and the learning effects of physicians in addition to the effect of treatment variables included in the analysis; however, the month of

**Table 2**  
Association between in-hospital mortality and month of admission

Month of admission	Adjusted OR (95% CI)	p	Risk-adjusted mortality, % (95% CI)
April 2020	Reference		5.32 (Reference)
January/February 2020	0.56 (0.24–1.34)	.19	3.04 (0.06–6.02)
March 2020	1.47 (0.97–2.22)	.07	7.28 (5.06–9.49)
May 2020	0.67 (0.45–0.997)	.048	3.64 (2.07–5.22)
June 2020	0.43 (0.21–0.85)	.02	2.17 (0.10–4.24)
July 2020	0.48 (0.33–0.71)	<.001	2.54 (1.19–3.90)
August 2020	0.53 (0.41–0.69)	<.001	2.85 (1.81–3.88)
September 2020	0.44 (0.32–0.61)	<.001	2.26 (1.10–3.42)
October 2020	0.53 (0.39–0.72)	<.001	2.85 (1.69–4.02)
November 2020	0.69 (0.55–0.87)	.002	3.77 (2.76–4.78)
December 2020	0.75 (0.60–0.92)	.007	4.07 (3.12–5.02)
January 2021	0.74 (0.61–0.91)	.005	4.06 (3.13–4.99)
February 2021	0.63 (0.50–0.80)	<.001	3.45 (2.47–4.44)

Covariates	Adjusted OR (95% CI)	p
Age category, yrs	Reference	
≤39	0.16 (0.06–0.39)	<.001
40–49	0.77 (0.47–1.24)	.28
60–69	2.85 (2.08–3.90)	<.001
70–79	7.16 (5.33–9.61)	<.001
80–	17.47 (12.98–23.51)	<.001
Sex	Female	<.001
BMI, kg/m <sup>2</sup>	Reference	
≥18.5, <25	1.18 (1.01–1.38)	.04
<18.5	0.93 (0.80–1.07)	.30
≥25, <30	1.49 (1.18–1.87)	.001
≥30	1.49 (1.18–1.87)	.001
Brinkman index	Reference	
0	1.02 (0.83–1.26)	.82
>0, <400	1.06 (0.91–1.23)	.45
Charlson comorbidity index	Reference	
0	1.34 (1.14–1.58)	<.001
1	1.31 (1.15–1.49)	<.001
2	2.17 (1.84–2.57)	<.001
≥3	Reference	
JCS score on admission	Reference	
0	1.19 (1.05–1.34)	.006
1–3	1.94 (1.55–2.43)	<.001
10–30	3.02 (2.36–3.86)	<.001
100–300	Reference	
Barthel index on admission	Reference	
100 (No disability)	1.52 (1.12–2.07)	.007
90–95 (Mild disability)		

**Table 2 (continued)**

Covariates	Adjusted OR (95% CI)	p
65–85 (Moderate disability)	1.40 (1.10–1.78)	.007
0–60 (Severe disability)	3.02 (2.63–3.47)	<.001
Transfer from another hospital	Yes	1.14 (1.04–1.26)
Ambulance use	Yes	1.35 (1.22–1.50)
Admitted to ICU within the first 2 days after hospital admission	Yes	1.04 (0.88–1.23)
Oxygen support within the first 2 days after hospital admission	Yes	3.28 (2.95–3.64)
Mechanical ventilation within the first 2 days after hospital admission	Yes	1.38 (1.09–1.76)
Vasopressor use within the first 2 days after hospital admission	Yes	1.82 (1.43–2.32)

BMI; body mass index, ICU; intensive care unit, IQR; interquartile range, JCS; Japan coma scale.

admission still had a significant effect on survival. As the admission month itself is unable to improve survival, factors associated with the month of admission, which could not be adjusted for in this analysis, need to be investigated in future studies.

Notably, although a decline in mortality was observed after wave 1, wave 3 had a higher crude in-hospital mortality and risk-adjusted OR than wave 2. This trend of crude in-hospital mortality was also observed in the age group of ≥80 years and in the subgroup receiving oxygen support but not mechanical ventilation. This may indicate that older patients did not choose to be on the ventilator or the choice of mechanical ventilation was limited due to the high number of patients with COVID-19 in wave 3. A change in practice patterns may have partly contributed to these trends.

The study has several strengths. First, it identified risk factors for hospital death and temporal changes in in-hospital mortality among patients with COVID-19 in Japan. Moreover, it further investigated the reasons for these trends. In addition, our study used a nationwide database that reflects a wider range of hospitalized patients with COVID-19 in Japan. Further research is needed to determine the cause of the improved outcome trends. Factors that are present or occur outside the hospital may be keys in improving survival. For instance, improved understanding of the disease by the public may contribute to the avoidance of risky behaviours that could lead to being infected, such as not wearing a face mask [29]. Further, lower viral load can decrease disease severity and mortality [30]. In our study, a decline in mortality was observed in the subgroup of patients who needed oxygen support but not mechanical ventilation, whereas this trend was not obvious among patients who needed mechanical ventilation. This may indicate that a beneficial effect that prevented patients from severe disease progression was present in the later months. In particular, patients who did not agree to receive mechanical ventilation may have benefited from this effect. When patients' disease severities necessitated mechanical ventilation, there were no significant beneficial effects related to the admission month.

However, this study has several limitations. First, since the DPC database is an administrative claims database, clinical information, such as vital signs and laboratory data, was not available. Time from disease onset to hospital admission would also be a significant prognostic factor [13]. These clinical factors could not be adjusted for and might have been accountable for the decline in risk of death in the later waves. Second, the use of novel drugs, such as remdesivir, was not registered in the database because the use of the drugs was approved by the Ministry of Health, Labour and Welfare for emergency and limited use, and its cost was publicly funded. Furthermore, prone positioning does not have



**Table 3**  
Subgroup analysis on the association between in-hospital mortality and month of admission.

Month of admission		Oxygen support without ventilation		Mechanical ventilation			
		Adjusted OR (95% CI)	p	Risk-adjusted mortality, % (95% CI)	Adjusted OR (95% CI)	p	Risk-adjusted mortality, % (95% CI)
April 2020	Reference			15.06 (Reference)	Reference		30.67 (Reference)
January/February 2020	0.41 (0.16–1.05)	.06	6.78 (0.00–13.82)	0.54 (0.17–1.66)	.28	20.13 (2.54–37.72)	
March 2020	1.26 (0.82–1.93)	.30	17.78 (12.54–23.01)	0.80 (0.41–1.56)	.51	26.64 (14.82–38.46)	
May 2020	0.69 (0.45–1.05)	.08	11.09 (6.80–15.38)	0.85 (0.35–2.06)	.71	27.65 (11.77–43.53)	
June 2020	0.37 (0.18–0.78)	.009	5.98 (0.55–11.42)	0.71 (0.18–2.90)	.64	24.69 (0.87–48.51)	
July 2020	0.49 (0.33–0.73)	.001	8.11 (4.48–11.73)	0.55 (0.26–1.20)	.13	20.60 (8.27–32.94)	
August 2020	0.52 (0.40–0.68)	<.001	8.63 (5.94–11.32)	0.69 (0.43–1.12)	.13	24.14 (15.68–32.61)	
September 2020	0.43 (0.31–0.61)	<.001	7.11 (4.05–10.18)	0.95 (0.48–1.85)	.87	29.68 (17.42–41.94)	
October 2020	0.52 (0.38–0.71)	<.001	8.60 (5.57–11.62)	0.78 (0.43–1.41)	.41	26.15 (15.62–36.68)	
November 2020	0.68 (0.53–0.86)	.001	10.93 (8.32–13.54)	0.87 (0.56–1.36)	.54	28.20 (20.20–36.19)	
December 2020	0.70 (0.56–0.87)	.002	11.30 (8.86–13.74)	0.67 (0.45–1.00)	.053	23.76 (16.67–30.84)	
January 2021	0.73 (0.59–0.90)	.004	11.68 (9.30–14.06)	0.86 (0.58–1.25)	.42	27.85 (20.91–34.78)	
February 2021	0.66 (0.52–0.83)	<.001	10.67 (8.11–13.23)	0.59 (0.35–0.99)	.04	21.47 (12.70–30.23)	

OR; odds ratio, CI; confidence interval.

**Table 4**  
Exploratory analysis additionally adjusted with treatment.

Month of admission	Adjusted OR (95% CI)	p	Risk-adjusted mortality, % (95% CI)
April 2020	Reference		5.32 (Reference)
January/February 2020	0.40 (0.15–1.09)	.07	2.43 (0.00–5.04)
March 2020	1.05 (0.66–1.67)	.84	5.51 (3.73–7.29)
May 2020	0.90 (0.57–1.40)	.63	4.92 (3.28–6.55)
June 2020	0.44 (0.21–0.93)	.03	2.68 (0.61–4.76)
July 2020	0.53 (0.34–0.81)	.003	3.18 (1.83–4.54)
August 2020	0.49 (0.37–0.66)	<.001	2.98 (1.99–3.98)
September 2020	0.44 (0.30–0.63)	<.001	2.66 (1.52–3.80)
October 2020	0.47 (0.33–0.67)	<.001	2.86 (1.75–3.98)
November 2020	0.65 (0.49–0.85)	.002	3.82 (2.84–4.79)
December 2020	0.69 (0.53–0.88)	.003	4.00 (3.07–4.92)
January 2021	0.70 (0.54–0.89)	.004	4.05 (3.14–4.96)
February 2021	0.67 (0.51–0.88)	.003	3.92 (2.95–4.89)

OR; odds ratio, CI; confidence interval.

a specific code for billing; hence, it is not recorded in the DPC database. These interventions could not be adjusted for in the exploratory analysis; therefore, they may have been part of the reason for the decline in risk of death in the later waves. Third, although the database covers approximately 40% of acute in-patient beds in Japan and is considered to provide a broader overview of the Japanese population than databases used in previous studies conducted in Japan, different trends may be present among hospitals that did not participate in the DPC payment system because the data are not from a random sample. Hence, they are not representative of hospitals in Japan as a whole. In particular, university hospitals and national hospitals, which were not included during the study period due to logistical reasons, may show different trends. As those hospitals usually encounter more severe patients, the decline in in-hospital mortality may be lower in later months. Furthermore, as the in-hospital mortality in our study population was lower than that

reported in other countries, the results would not be generalizable to other healthcare systems and countries. However, the differences among systems and countries imply that they should be considered while evaluating risk factors, effectiveness of interventions, and outcomes.

In conclusion, we analyzed the characteristics and time trends of hospitalized patients with COVID-19 in Japan using a nationwide administrative database. Risk factors that were similar to those reported in previous studies were identified, and a decrease in risk-adjusted in-hospital mortality was observed in the later months. The effects of other factors on improved hospital outcomes need to be elucidated.

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#### Declaration of competing interests

The authors declare no competing interests.

#### Authorship statement

All authors meet the ICMJE authorship criteria. HE and KL participated in the study design, drafting of the article, analysis and interpretation of data. SW participated in the study design, analysis and interpretation of data, and revision of the article for intellectual content. TO and KF participated in the study design, interpretation of data, and revision of the article for intellectual content. HE, SW, and KL accessed and verified the underlying data. KF had full access to all of the data in the study and takes responsibility for the integrity of the data. All authors read and approved the final manuscript.

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#### Appendix A. Supplementary data

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