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Original Article

Differences in COVID-19 treatment across Japan: Analysis of the COVID-19 Registry Japan (COVIREGI-JP)

Yusuke Asai [a,b,*], Takahisa Ohashi [c], Keiji Imai [c], Koichi Murata [c], Shinya Tsuzuki [a,b,d], Nobuaki Matsunaga [a], Norio Ohmagari [a,b]

[a] AMR Clinical Reference Center, National Center for Global Health and Medicine, Tokyo, Japan
[b] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan
[c] Pfizer Japan Inc., Tokyo, Japan
[d] Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

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ABSTRACT

Background: This study investigated the differences between metropolitan and non-metropolitan areas in the treatment of hospitalized patients with COVID-19 using data from the nationwide COVID-19 Registry Japan (COVIREGI-JP).

Methods: Data of patients hospitalized for COVID-19 during waves 2–4 (June 1, 2020–June 30, 2021) treated in one of the 800 medical institutions participating in the Registry were extracted. Treatment and treatment outcomes were evaluated in inpatients with moderate 2 and severe disease using propensity score matching performed between metropolitan and non-metropolitan areas.

Results: A total of 32797 patients were identified during epidemic waves 2–4. After matching (wave 2, n = 307; wave 3, n = 913; wave 4, n = 479), the population comprised mostly elderly patients with a median age of ≥65 years (IQR: 52–81 years) and median SpO_2 of 93/94 (IQR: 91%–96%), and the proportion of patients with moderate 2 (SpO_2≤93%/require oxygenation) vs severe disease (ICU admission) ranged from 82.7% to 89.8% vs 10.2% to 17.3% in metropolitan areas vs non-metropolitan areas, respectively, across all epidemic waves. Noninvasive mechanical ventilation was used significantly more in waves 2 and 3 and invasive mechanical ventilation in wave 4 in metropolitan vs non-metropolitan areas, compared with other waves. In wave 2, death as an outcome was significantly higher in metropolitan vs non-metropolitan areas compared with patient discharge to home/transfer.

Conclusion: During the COVID-19 epidemic, starting from wave 2 up until and through wave 4, no clear differences in mortality rates and no regional differences in treatment provision patterns were observed between metropolitan and non-metropolitan areas in Japan.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global public health threat that imposes a large disease burden. COVID-19 is more contagious than other respiratory infections such as influenza and is sometimes fatal to the elderly and those with underlying comorbidities [1–4]. To date, vaccines and therapeutic agents have been developed to treat COVID-19, resulting in decreased mortality and a decreased need for hospitalization. Furthermore, various prevention, diagnosis, and treatment strategies for COVID-19 have been attempted, including changes in the hospitalization criteria and COVID-19 vaccination. Although various treatment strategies were initially used in Japan, including those with unestablished efficacy, new evidence continues to influence the national guidelines and daily clinical care [5,6].

In Japan, the overall case fatality rate of COVID-19 was relatively

Abbreviations: COVID-19, coronavirus disease 2019; COVIREGI-JP, COVID-19 Registry Japan; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; JCRAC, Joint Center for Researchers, Associates and Clinicians; NCGM, National Center for Global Health and Medicine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, peripheral oxygen saturation.

* Corresponding author. AMR Clinical Reference Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo, 162-8655, Japan.
E-mail address: yuasai@ri.ncgm.go.jp (Y. Asai).

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low in the first three waves; however, it was more than twice as high among older patients compared with that in the overall population. In the first wave, the risk of death was the highest after adjusting for age and comorbidities [7]. A content analysis of the first wave in Japan revealed numerous lapses in care, including an unclear evolution of the testing strategy, a sluggish expansion of healthcare system capacity and response in border control, and misunderstanding between risk communication and crisis communication [8]. There is evidence that pharmacotherapy and supportive care for COVID-19 have changed over time in Japan. Epidemiological and clinical characteristics of patients vary widely across age groups [7]. Although guideline-based medical practices and treatments have been implemented, there is a paucity of publications on the regional comparison of treatment practices in Japan [6,7].

A hierarchical Bayesian model analysis demonstrated that the prefecture had a substantial impact on the risk of severe COVID-19 at the time of admission, even after considering the effect of the number of beds separately. The study concluded that a possible association exists between regional heterogeneity and an increased or decreased risk of severe COVID-19 on admission; factors other than the number of beds secured in each prefecture could also be significant during COVID-19 management [9].

This study aimed to investigate the differences in number, severity, treatment, and healthcare provisions of hospitalized patients with COVID-19 between metropolitan and non-metropolitan areas in Japan using data from the nationwide Japanese registry (COVID-19 Registry Japan [COVIREGI-JP]).

2. Materials and methods

2.1. Study design

This observational study evaluated the data of patients hospitalized for COVID-19 (June 1, 2020, to June 30, 2021) using a nationwide Japanese registry (COVIREGI-JP) [10]. Data of all patients with COVID-19 were downloaded for analysis on November 1, 2021, with a total of 800 medical institutions voluntarily participating in the COVID-19 Registry. Data from COVIREGI-JP have been validated in numerous studies [5,11,12].

The characteristics of all patients with COVID-19 were compared between COVID-19 epidemic waves 2 (June 1, 2020, to October 31, 2020), 3 (November 1, 2020, to March 31, 2021), and 4 (April 1, 2021, to June 30, 2021) owing to differing patient characteristics across waves. Data collected during the early epidemic period or wave 1 (January 1, 2020, to May 31, 2020) were excluded because inpatient treatment was not fully established during this wave; thus, the data were not deemed suitable for assessment [13]. The data were further categorized into metropolitan areas (Tokyo, Kanagawa, Osaka, Aichi, Saitama, Chiba, Hyogo, Hokkaido, and Fukuoka) and non-metropolitan areas for comparison (described below). Thereafter, data of patients with moderate 2 and severe disease severity (defined further below) who required hospital admission or inpatient treatment were identified for propensity score matching performed between metropolitan and non-metropolitan areas for epidemic waves 2, 3, and 4.

The study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms, if applicable) were approved by the relevant institutional review boards or independent ethics committees. This study was approved by the National Center for Global Health and Medicine (NCGM) Ethics Review Committee (NCGM-S-004390-00). Informed consent was obtained from the patients using the opt-out method. Standard informed consent from patients was not required because this study used anonymized structured data (legal requirements not applicable, as study data are not subject to privacy laws); however, study information was provided to eligible patients through the Internet or brochures at each participating institution as an opportunity to decline participation by opting out. Information regarding opting out of the study was available on the registry website [10].

2.2. Geographical regions

The data were further categorized into metropolitan and non-metropolitan areas in terms of the cumulative number of positive cases by prefecture and total population. Ranking in terms of the cumulative number of positive cases (as of June 30, 2021) was Tokyo (173,934 persons), followed by Osaka (103,383 persons), Kanagawa (67,391 persons), Aichi prefecture (50,971 persons), Saitama prefecture (46,437 persons), Chiba prefecture (40,303 persons), Hyogo prefecture (40,897 persons), Hokkaido (41,332 persons), and Fukuoka (35,525 persons). The nine prefectures (as of 1 October 2021) of Tokyo (14.010), Kanagawa (9.236), Osaka (8.806), Aichi (7.517), Saitama (7.340), Chiba (6.275), Hyogo (5.432), Hokkaido (5.183), and Fukuoka (5.124) were also the same in the total population ranking by prefecture (population estimates in million) and were thus defined as metropolitan areas. The remaining prefectures were defined as non-metropolitan areas [14,15].

2.3. Data

COVIREGI-JP data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based data capture application hosted at the Joint Center for Researchers, Associates and Clinicians (JCRAC) data center of NCGM [10]. Data were manually entered into the registry by research collaborators at each site, and the JCRAC data center staff performed data management (including data monitoring). After the data sets at the JCRAC data center were fixed as traceable anonymized processed data, the structured data set was provided by NCGM for data analysis. The data sets were managed in the NCGM data analysis room.

Data of all patients with COVID-19 were collected for waves 2, 3, and 4. To evaluate the data for each hospitalization event among patients with moderate 2 and severe disease severity, multiple admissions in a single institute were considered as separate patients.

2.4. Patients

All patients who were positive for SARS-CoV-2 during waves 2–4 were included from COVIREGI-JP data for the comparison of patient characteristics between metropolitan and non-metropolitan areas in epidemic waves 2–4. Among them, patients with moderate 2 or severe disease and who received inpatient treatment were evaluated for differences in the treatment between metropolitan and non-metropolitan areas using propensity score matching.

Patients who refused to participate in the study by opting out and who were transferred from or to other medical institutions (i.e., each hospitalization event in a single institute was counted as one person) were excluded.

2.5. Severity categorization

According to the COVID-19 Medical Practice Guidelines [6], patients were classified into four severity categories: mild, moderate 1, moderate 2, and severe. Signs and symptoms at admission (data obtained in the first 24 h after the initial admission) were extracted from the case report form. Patients who were admitted to the intensive care unit (ICU), including those admitted after a delay of 1 day, were considered to have severe disease; those with peripheral oxygen saturation (SpO_2) of $\leq$93% on room air or those requiring oxygen inhalation with radiologically diagnosed pneumonia were considered to have moderate 2 disease severity; those with SpO_2 between 93% and 96% on room air or those not requiring oxygen inhalation with radiologically diagnosed pneumonia were considered to have moderate 1 disease severity; and those with SpO_2 of $\geq$96% on room air or those not requiring oxygen inhalation

Table 1
Demographics and characteristics of all patients hospitalized for COVID-19 summarized by epidemic waves 2–4 in metropolitan and non-metropolitan areas.

		Wave 2		Wave 3		Wave 4	
Item	Detail	Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas
Number of patients		6946	3801	9188	7542	2429	2891
Sex	Male	4012 (57.8)	2148 (56.5)	4990 (54.3)	4135 (54.8)	1431 (58.9)	1672 (57.8)
	Female	2932 (42.2)	1652 (43.5)	4194 (45.6)	3402 (45.1)	998 (41.1)	1219 (42.2)
	Other	2 (0)	1 (0)	4 (0)	5 (0.1)	0 (0)	0 (0)
Age (years), median (IQR)		49 (30, 68)	47 (28, 65)	68 (49, 80)	59 (42, 74)	60 (46, 75)	57 (41, 72)
Smoking history	Currently smoking	1316 (19)	762 (20.1)	922 (10)	1077 (14.3)	302 (12.4)	582 (20.1)
	Smoking in the past	1305 (18.8)	684 (18.1)	2053 (22.4)	1571 (20.9)	521 (21.4)	544 (18.8)
	Never	3393 (49.0)	1822 (48.2)	4532 (49.4)	3798 (50.4)	1213 (49.9)	1392 (48.1)
	Unknown	913 (13.2)	514 (13.6)	1673 (18.2)	1087 (14.4)	393 (16.2)	373 (12.9)
Alcohol consumption	Daily	646 (9.3)	323 (8.5)	457 (5.0)	442 (5.9)	90 (3.7)	150 (5.2)
	Occasional	2526 (36.5)	1404 (37.1)	2597 (28.3)	2538 (33.7)	739 (30.4)	911 (31.5)
	Never	2285 (33.0)	1304 (34.5)	3867 (42.2)	3093 (41.1)	995 (41.0)	1120 (38.7)
	Unknown	1472 (21.2)	750 (19.8)	2252 (24.6)	1456 (19.3)	605 (24.9)	710 (24.6)
BMI (kg/m^2), median (IQR)		23.1 (20.5, 26.3)	23.1 (20.5, 26.2)	23.4 (20.8, 26.3)	23.4 (20.8, 26.5)	23.8 (21.3, 27)	23.7 (21.2, 26.9)
Body temperature (°C), median (IQR)		36.9 (36.5, 37.5)	36.8 (36.5, 37.4)	37 (36.6, 37.7)	37 (36.6, 37.6)	37.2 (36.7, 38)	37 (36.6, 37.8)
Heart rate (beats/minute), median (IQR)		85 (75, 96)	84 (75, 95)	86 (76, 97)	87 (76, 98)	88 (77, 99)	88 (77, 98)
Respiratory rate (breaths/minute), median (IQR)		18 (16, 20)	18 (16, 20)	18 (16, 20)	18 (16, 20)	20 (16, 23)	18 (16, 21)
AVPU scale	Alert	6637 (98.2)	3605 (98.4)	8584 (95.9)	7118 (97.2)	2322 (96.5)	2772 (98.5)
	Verbal	101 (1.5)	45 (1.2)	307 (3.4)	159 (2.2)	60 (2.5)	33 (1.2)
	Pain	14 (0.2)	8 (0.2)	48 (0.5)	34 (0.5)	10 (0.4)	5 (0.2)
	Unresponsive	10 (0.1)	4 (0.1)	13 (0.1)	12 (0.2)	14 (0.6)	4 (0.1)
SpO_2 (%), median (IQR)		97 (96, 98)	97 (96, 98)	97 (95, 98)	97 (96, 98)	96 (94, 98)	97 (95, 98)
Oxygen support	None (room air)	6435 (99.8)	3556 (99.8)	7745 (99.7)	6761 (99.8)	1671 (99.6)	2544 (99.8)
	Noninvasive oxygen therapy	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	2 (0.1)
	IMV	10 (0.2)	6 (0.2)	21 (0.3)	9 (0.1)	7 (0.4)	4 (0.2)
	ECMO	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Route of noninvasive oxygen	Nasal cannula	336 (75.2)	154 (76.2)	996 (72)	485 (70.7)	441 (59.9)	246 (73.0)
	Face mask	65 (14.5)	30 (14.9)	220 (15.9)	134 (19.5)	137 (18.6)	60 (17.8)
	Reservoir mask	43 (9.6)	12 (5.9)	150 (10.8)	54 (7.9)	143 (19.4)	23 (6.8)
	High-flow oxygen device	3 (0.7)	6 (3.0)	18 (1.3)	13 (1.9)	15 (2.0)	8 (2.4)
X-ray imaging finding	No abnormality	3062 (57.0)	1617 (62.1)	2704 (40.2)	2228 (48.4)	471 (26.9)	703 (42.0)
	Pneumonia	2231 (41.5)	963 (37.0)	3881 (57.7)	2276 (49.5)	1261 (71.9)	943 (56.3)
	Abnormality (excluding pneumonia)	82 (1.5)	24 (0.9)	138 (2.1)	95 (2.1)	21 (1.2)	29 (1.7)
Finding by CT	No abnormality	1475 (31.7)	887 (33.1)	1013 (16.1)	1426 (25.7)	187 (9.9)	536 (23.5)
	Pneumonia	3045 (65.5)	1716 (64.1)	5169 (81.9)	3947 (71.1)	1674 (89)	1676 (73.4)
	Abnormality (excluding pneumonia)	130 (2.8)	73 (2.7)	128 (2.0)	177 (3.2)	19 (1.0)	71 (3.1)
Severity on admission	Mild	3146 (45.6)	1786 (47.4)	2771 (30.3)	2821 (37.8)	457 (18.9)	918 (31.8)
	Moderate 1	2968 (43)	1578 (41.9)	4144 (45.3)	3426 (45.9)	972 (40.2)	1382 (47.8)
	Moderate 2	579 (8.4)	333 (8.8)	1831 (20)	1060 (14.2)	815 (33.7)	509 (17.6)
	Severe	205 (3)	72 (1.9)	403 (4.4)	158 (2.1)	173 (7.2)	80 (2.8)
Days from onset to admission, median (IQR)		4 (2, 7)	4 (2, 6)	4 (2, 7)	3 (2, 6)	5 (3, 8)	4 (2, 6)
Any comorbidity	Yes	3020 (43.5)	1500 (39.5)	6114 (66.5)	4274 (56.7)	1458 (60.0)	1594 (55.1)
Cardiovascular disease	Yes	218 (3.1)	115 (3.0)	564 (6.1)	377 (5.0)	89 (3.7)	87 (3.0)
Peripheral vascular disease	Yes	57 (0.8)	26 (0.7)	201 (2.2)	103 (1.4)	44 (1.8)	24 (0.8)
Cerebrovascular disease	Yes	295 (4.2)	134 (3.5)	800 (8.7)	469 (6.2)	138 (5.7)	156 (5.4)
Paralysis	Yes	76 (1.1)	25 (0.7)	144 (1.6)	99 (1.3)	31 (1.3)	38 (1.3)
Dementia	Yes	379 (5.5)	143 (3.8)	1178 (12.8)	567 (7.5)	187 (7.7)	162 (5.6)
Chronic lung disease	Yes	190 (2.7)	85 (2.2)	407 (4.4)	261 (3.5)	74 (3.0)	93 (3.2)
Bronchial asthma	Yes	381 (5.5)	162 (4.3)	548 (6.0)	363 (4.8)	164 (6.8)	132 (4.6)
Liver disease	Yes	132 (1.9)	69 (1.8)	234 (2.5)	197 (2.6)	73 (3.0)	68 (2.4)
Peptic ulcer	Yes	41 (0.6)	22 (0.6)	67 (0.7)	69 (0.9)	22 (0.9)	11 (0.4)

(*continued on next page*)

Table 1 (*continued*)

Item	Detail	Wave 2		Wave 3		Wave 4	
		Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas
Hypertension	Yes	1580 (22.7)	868 (22.8)	3514 (38.2)	2477 (32.8)	813 (33.5)	938 (32.4)
Hyperlipidemia	Yes	795 (11.4)	410 (10.8)	1629 (17.7)	1222 (16.2)	395 (16.3)	454 (15.7)
Diabetes mellitus	Yes	836 (12.0)	418 (11.0)	1737 (18.9)	1351 (17.9)	451 (18.6)	484 (16.7)
Obesity	Yes	419 (6.0)	147 (3.9)	504 (5.5)	465 (6.2)	168 (6.9)	237 (8.2)
Renal dysfunction/dialysis	Yes	80 (1.2)	43 (1.1)	192 (2.1)	162 (2.1)	41 (1.7)	22 (0.8)
Solid tumor or a metastatic solid tumor	Yes	202 (2.9)	112 (2.9)	497 (5.4)	317 (4.2)	85 (3.5)	69 (2.4)
Leukemia/lymphoma	Yes	26 (0.4)	14 (0.4)	68 (0.7)	53 (0.7)	7 (0.3)	11 (0.4)
Collagen disease	Yes	79 (1.1)	30 (0.8)	138 (1.5)	94 (1.2)	29 (1.2)	30 (1.0)
HIV	Yes	21 (0.3)	3 (0.1)	23 (0.3)	5 (0.1)	6 (0.2)	0 (0)
Immunosuppression	Yes	120 (1.8)	55 (1.5)	210 (2.3)	134 (1.8)	34 (1.4)	47 (1.6)
Neutropenia	Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Use of steroid in the past 1 month	Yes	19 (0.3)	11 (0.3)	51 (0.6)	25 (0.3)	9 (0.4)	6 (0.2)
Chemotherapy in the past 3 months	Yes	46 (0.7)	20 (0.5)	99 (1.1)	73 (1.0)	12 (0.5)	16 (0.6)
Radiotherapy in the past 3 months	Yes	7 (0.1)	6 (0.2)	17 (0.2)	10 (0.1)	2 (0.1)	1 (0)
Solid organ transplantation	Yes	5 (0.1)	8 (0.2)	8 (0.1)	7 (0.1)	1 (0)	2 (0.1)
Immunosuppressant use in the past 3 months	Yes	61 (0.9)	33 (0.9)	98 (1.1)	74 (1.0)	30 (1.2)	27 (0.9)

AVPU, alert, verbal, pain, unresponsive; BMI, body mass index; COVID-19, coronavirus disease 2019; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; IMV, invasive mechanical ventilation; IQR, interquartile range; SpO_2, peripheral oxygen saturation.
"Unknown" represents a check box that was marked in the data set.
Data are presented as n (%), unless specified.
The number of missing values differed for each parameter; therefore, the denominator for calculation of percentages (n [%]) varied from the total number of cases mentioned above in the table (n) to n minus missing data.
Missing data represent unavailability of information.

without radiologically diagnosed pneumonia were considered to have mild disease severity.

2.6. Statistical analysis

For comparison between metropolitan and non-metropolitan areas, patient backgrounds were adjusted using propensity score matching. If more than one type of treatment was administered per patient, each treatment type was counted separately, regardless of whether they were administered concurrently. If one treatment type (e.g., invasive mechanical ventilation [IMV]) was administered more than once during a hospitalization event, it was counted as "1."

Using a 1:1 nearest neighbor matching algorithm with a caliper on the propensity score matching (standardized difference <0.1), adjustments were made for the severity of explanatory variables, days from onset to hospital admission, age (<65 or ≥ 65 years), sex, body mass index (<25 or ≥ 25 kg/m^2), and comorbidities (risk factors for severe COVID-19, including cardiovascular disease, cerebrovascular disease, dementia, chronic respiratory disease, liver disease, hypertension, hyperlipidemia, diabetes mellitus, renal dysfunction/dialysis, solid or metastatic solid tumor, leukemia/lymphoma, and human immunodeficiency virus). The caliper was set to 0.2, and the population ratio (metropolitan areas:non-metropolitan areas) was set to 1:1. Data are summarized as median (interquartile range [IQR]) for continuous variables and number of patients (percentage) for categorical variables. Fisher's exact test was used to compare percentage data. The level of significance was set at $p < 0.05$. Statistical analysis was performed using R software (version 4.0.2). The "matching" package was used for propensity score matching.

3. Results

3.1. Baseline demographics and patient characteristics in patients hospitalized for COVID-19 across all disease severities

A total of 32797 patients with COVID-19 were identified from the COVID-19 Registry during epidemic waves 2–4. The number of patients with COVID-19 was higher in metropolitan areas than in non-metropolitan areas in wave 2 (6946 vs 3801), which increased further in wave 3 (9188 vs 7542); the number of patients was the lowest in wave 4 for both regions (2429 vs 2891). There were more male-to-female patients in both metropolitan and non-metropolitan areas in all three waves.

Compared with wave 2 (41.5% vs 37.0%), the proportion of patients with radiologically confirmed pneumonia was higher in metropolitan areas vs non-metropolitan areas in wave 3 (57.7% vs 49.5%), which increased further in wave 4 (71.9% vs 56.3%).

Wave 2 involved a higher median number of young and middle-aged patients than elderly patients (median [IQR]: metropolitan areas, 49 [30, 68] years; non-metropolitan areas, 47 [28, 65] years) compared with waves 3 (metropolitan areas, 68 [49, 80] years; non-metropolitan areas, 59 [42, 74] years) and 4 (metropolitan areas, 60 [46, 75] years; non-metropolitan areas, 57 [41, 72] years). In wave 2, the median age of the infected patients was 49 and 47 years in metropolitan areas and non-metropolitan areas, respectively, which was 10–20 years lower than the median age in waves 3 and 4. The rate of comorbidity was higher in waves 3 (metropolitan areas vs non-metropolitan areas: 66.5% vs 56.7%) and 4 (60.0% vs 55.1%) than in wave 2 (43.5% vs 39.5%). Specifically, a higher proportion of patients with hypertension, hyperlipidemia, and diabetes mellitus was observed in waves 3 and 4 than in wave 2.

The proportion of patients categorized as severe increased from wave 2 to 4 in metropolitan areas (metropolitan areas vs non-metropolitan areas: wave 2 [3.0% vs 1.9%]; wave 3 [4.4% vs 2.1%]; wave 4 [7.2% vs 2.8%]). The proportion of patients categorized as having moderate 2 disease severity increased from wave 2 to 4 in both metropolitan areas

Table 2
Demographics and characteristics of patients hospitalized for COVID-19 with moderate 2 and severe disease summarized by epidemic waves 2–4 in metropolitan and non-metropolitan areas in the propensity score–matched cohort.

		Wave 2		Wave 3		Wave 4	
Item	Detail	Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas
Number of cases		307	307	913	913	479	479
Sex	Male	208 (67.8)	197 (64.2)	609 (66.7)	606 (66.4)	312 (65.1)	310 (64.7)
	Female	99 (32.2)	110 (35.8)	304 (33.3)	307 (33.6)	167 (34.9)	169 (35.3)
	Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age (years), median (IQR)		66 (53, 76)	68 (55, 78)	72 (57, 81)	71 (59, 81)	65 (52, 76)	65 (54, 76)
Smoking history	Currently smoking	39 (12.7)	28 (9.2)	98 (10.7)	96 (10.5)	63 (13.2)	80 (16.7)
	Smoking in the past	106 (34.6)	112 (36.7)	283 (31)	300 (32.9)	132 (27.6)	128 (26.7)
	Never	118 (38.6)	134 (43.9)	379 (41.6)	373 (40.9)	222 (46.3)	196 (40.9)
	Unknown	43 (14.1)	31 (10.2)	152 (16.7)	143 (15.7)	62 (12.9)	75 (15.7)
Drinking alcohol	Daily	28 (9.1)	24 (7.8)	55 (6.0)	63 (6.9)	23 (4.8)	29 (6.1)
	Occasional	118 (38.4)	121 (39.5)	255 (28)	286 (31.3)	170 (35.5)	149 (31.1)
	Never	97 (31.6)	96 (31.4)	385 (42.2)	348 (38.1)	195 (40.7)	168 (35.1)
	Unknown	64 (20.8)	65 (21.2)	217 (23.8)	216 (23.7)	91 (19)	133 (27.8)
BMI (kg/m^2), median (IQR)		25.1 (22.6, 28.4)	25.1 (22.3, 28.7)	24.4 (21.8, 27.4)	24.3 (21.6, 27.7)	24.8 (22.2, 28.4)	24.8 (22.4, 27.8)
Body temperature (°C), median (IQR)		37.5 (36.8, 38.2)	37.3 (36.7, 38.3)	37.4 (36.8, 38.1)	37.5 (36.9, 38.3)	37.4 (36.8, 38.2)	37.7 (36.9, 38.4)
Heart rate (beats/minute), median (IQR)		91 (81, 102)	89 (78, 101)	89 (79, 101)	90 (80, 103)	88 (78, 99)	90 (78, 101)
Respiratory rate (breaths/minute), median (IQR)		20 (17, 24)	21 (18, 24)	20 (18, 24)	20 (18, 24.5)	20 (16, 24)	20 (18, 24)
AVPU scale	Alert	287 (95.0)	283 (94.6)	836 (93.6)	831 (92.1)	461 (96.8)	456 (97)
	Verbal	14 (4.6)	14 (4.7)	50 (5.6)	57 (6.3)	10 (2.1)	13 (2.8)
	Pain	1 (0.3)	2 (0.7)	6 (0.7)	10 (1.1)	3 (0.6)	0 (0)
	Unresponsive	0 (0)	0 (0)	1 (0.1)	4 (0.4)	2 (0.4)	1 (0.2)
SpO_2, median (IQR)		93 (92, 96)	93 (92, 95)	93 (92, 96)	93 (91, 96)	94 (92, 96)	93 (92, 96)
Oxygen support	None (room air)	124 (98.4)	150 (97.4)	373 (98.9)	389 (97.5)	135 (100)	203 (97.6)
	Noninvasive oxygen therapy	0 (0)	0 (0)	1 (0.3)	1 (0.3)	0 (0)	2 (1.0)
	IMV	2 (1.6)	4 (2.6)	3 (0.8)	9 (2.3)	0 (0)	3 (1.4)
	ECMO	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Route of noninvasive oxygen	Nasal cannula	137 (76.1)	121 (79.6)	386 (72)	364 (71.5)	225 (65.8)	205 (75.6)
	Face mask	25 (13.9)	17 (11.2)	81 (15.1)	101 (19.8)	51 (14.9)	45 (16.6)
	Reservoir mask	16 (8.9)	8 (5.3)	57 (10.6)	33 (6.5)	62 (18.1)	16 (5.9)
	High-flow oxygen device	2 (1.1)	6 (3.9)	12 (2.2)	11 (2.2)	4 (1.2)	5 (1.8)
X-ray imaging finding	No abnormality	31 (12.7)	24 (10)	70 (9.7)	55 (8.3)	30 (7.8)	15 (4.6)
	Pneumonia	211 (86.1)	214 (88.8)	638 (88.1)	586 (88.9)	346 (90.3)	304 (93.3)
	Abnormality (excluding pneumonia)	3 (1.2)	3 (1.2)	16 (2.2)	18 (2.7)	7 (1.8)	7 (2.1)
Finding by CT	No abnormality	7 (2.8)	9 (3.2)	20 (2.6)	28 (3.7)	5 (1.1)	5 (1.2)
	Pneumonia	237 (95.2)	269 (95.1)	728 (95.7)	718 (94)	430 (97.7)	391 (96.5)
	Abnormality (excluding pneumonia)	5 (2.0)	5 (1.8)	13 (1.7)	18 (2.4)	5 (1.1)	9 (2.2)
Severity on admission	Moderate 2	260 (84.7)	254 (82.7)	820 (89.8)	799 (87.5)	416 (86.8)	412 (86)
	Severe	47 (15.3)	53 (17.3)	93 (10.2)	114 (12.5)	63 (13.2)	67 (14)
Days from onset to admission, median (IQR)		6 (3, 8)	5 (3, 8)	5 (3, 8)	5 (2, 8)	6 (4, 8)	6 (3, 8)
Any comorbidity	Yes	235 (76.5)	240 (78.2)	752 (82.4)	728 (79.7)	339 (70.8)	355 (74.1)
Cardiovascular disease	Yes	27 (8.8)	26 (8.5)	86 (9.4)	86 (9.4)	21 (4.4)	23 (4.8)
Peripheral vascular disease	Yes	6 (2.0)	5 (1.6)	32 (3.5)	21 (2.3)	11 (2.3)	7 (1.5)
Cerebrovascular disease	Yes	21 (6.8)	26 (8.5)	103 (11.3)	104 (11.4)	47 (9.8)	45 (9.4)
Paralysis	Yes	3 (1.0)	2 (0.7)	11 (1.2)	19 (2.1)	4 (0.8)	6 (1.3)
Dementia	Yes	17 (5.5)	22 (7.2)	117 (12.8)	107 (11.7)	29 (6.1)	34 (7.1)
Chronic lung disease	Yes	26 (8.5)	27 (8.8)	88 (9.6)	95 (10.4)	23 (4.8)	21 (4.4)
Bronchial asthma	Yes	17 (5.5)	18 (5.9)	52 (5.7)	38 (4.2)	37 (7.7)	31 (6.5)
Liver disease	Yes	10 (3.3)	9 (2.9)	33 (3.6)	23 (2.5)	15 (3.1)	11 (2.3)
Peptic ulcer	Yes	4 (1.3)	5 (1.6)	7 (0.8)	13 (1.4)	5 (1.0)	4 (0.8)

(*continued on next page*)

Table 2 (*continued*)

Item	Detail	Wave 2		Wave 3		Wave 4	
		Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas	Metropolitan areas	Non-metropolitan areas
Hypertension	Yes	154 (50.2)	156 (50.8)	443 (48.5)	449 (49.2)	215 (44.9)	227 (47.4)
Hyperlipidemia	Yes	68 (22.1)	68 (22.1)	217 (23.8)	217 (23.8)	92 (19.2)	98 (20.5)
Diabetes mellitus	Yes	95 (30.9)	93 (30.3)	283 (31)	284 (31.1)	112 (23.4)	121 (25.3)
Obesity	Yes	46 (15.0)	24 (7.8)	85 (9.3)	72 (7.9)	57 (11.9)	52 (10.9)
Renal dysfunction/dialysis	Yes	9 (2.9)	7 (2.3)	24 (2.6)	24 (2.6)	6 (1.3)	5 (1.0)
Solid tumor or a metastatic solid tumor	Yes	14 (4.6)	18 (5.9)	53 (5.8)	49 (5.4)	13 (2.7)	16 (3.3)
Leukemia/lymphoma	Yes	2 (0.7)	1 (0.3)	8 (0.9)	5 (0.5)	0 (0)	0 (0)
Collagen disease	Yes	8 (2.6)	1 (0.3)	16 (1.8)	17 (1.9)	7 (1.5)	8 (1.7)
HIV	Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunosuppression	Yes	12 (4.0)	4 (1.3)	20 (2.3)	22 (2.5)	6 (1.3)	11 (2.3)
Neutropenia	Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Use of steroid in the past 1 month	Yes	3 (1.0)	1 (0.3)	11 (1.2)	7 (0.8)	2 (0.4)	1 (0.2)
Chemotherapy in the past 3 months	Yes	3 (1.0)	3 (1.0)	9 (1)	13 (1.4)	0 (0)	5 (1.0)
Radiotherapy in the past 3 months	Yes	0 (0)	1 (0.3)	1 (0.1)	2 (0.2)	0 (0)	0 (0)
Solid organ transplantation	Yes	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)
Immunosuppressant use in the past 3 months	Yes	8 (2.6)	2 (0.7)	10 (1.1)	12 (1.3)	8 (1.7)	4 (0.8)

AVPU, alert, verbal, pain, unresponsive; BMI, body mass index; COVID-19, coronavirus disease 2019; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; IMV, invasive mechanical ventilation; IQR, interquartile range; SpO_2, peripheral oxygen saturation.
"Unknown" represents a check box that was marked in the data set.
Data are presented as n (%), unless specified.
The number of missing values differed for each parameter; therefore, the denominator for calculation of percentages (n [%]) varied from the total number of cases mentioned above in the table (n) to n minus missing data.
Missing data represent unavailability of information.

and non-metropolitan areas (metropolitan areas vs non-metropolitan areas: wave 2 [8.4% vs 8.8%]; wave 3 [20.0% vs 14.2%]; wave 4 [33.7% vs 17.6%]; Table 1).

3.2. Characteristics of patients from metropolitan areas vs non-metropolitan areas in the propensity score–matched cohort

After propensity score matching (wave 2, n = 307; wave 3, n = 913; wave 4, n = 479), the patient population comprised mostly elderly patients with a median age of ≥65 years (IQR: 52–81 years) and median SpO_2 of 93/94 (IQR: 91–96), and the proportion of patients with moderate 2 vs severe disease ranged from 82.7% to 89.8% vs 10.2% to 17.3% in metropolitan areas vs non-metropolitan areas across all epidemic waves (Table 2). Patients were matched on using propensity score matching between metropolitan areas and non-metropolitan areas, as the standardized mean difference for individual waves was minor, with values at ±0.1 (Fig. 1).

3.3. Treatment and treatment outcomes in metropolitan areas vs non-metropolitan areas among inpatients in the propensity score–matched cohort

The proportion of patients on non-IMV was significantly higher in metropolitan areas than in non-metropolitan areas in waves 2 (6.5% vs 2.6%; p = 0.032) and 3 (3.3% vs 1.6%; p = 0.024). The proportion of patients on IMV was significantly higher in metropolitan areas than in non-metropolitan areas in wave 4 (10.7% vs 5.6%; p = 0.005); no significant difference was observed in the use of extracorporeal membrane oxygenation (ECMO) in metropolitan areas vs non-metropolitan areas across all epidemic waves. However, the proportion of patients on IMV/ECMO was significantly higher in metropolitan areas than in non-metropolitan areas in wave 4 (10.6% vs 5.6%; p = 0.006). The use of prone positioning was significantly higher in non-metropolitan areas than in metropolitan areas in wave 4 (20.5% vs 14.4%; p = 0.017). In the other areas, there was a greater discrepancy between the proportion of patients who needed IMV/ECMO (wave 2, 10.1%; wave 3, 8.9%; wave 4, 5.6%) and ICU stay (wave 2, 20.8%; wave 3, 15.2%; wave 4, 16.9%), compared with metropolitan areas (IMV/ECMO: wave 2, 12.4%; wave 3, 8.5%; wave 4, 10.6%; ICU stay: wave 2, 18.6%; wave 3, 13.8%; wave 4, 18.2%); the proportion of patients who needed IMV/ECMO tended to be less than that of patients who needed ICU stay at each wave. In wave 2, death as an outcome was significantly higher in metropolitan areas than in non-metropolitan areas (9.2% vs 4.9%; p = 0.041) compared with patient discharge to home/transfer (90.8% vs 95.1%); no such difference in death as the outcome was observed in waves 3 and 4. In the metropolitan and non-metropolitan areas, the administration of steroid and remdesivir increased from wave 2 to wave 4 (Table 3).

4. Discussion

This is the first study to report differences in the treatment of patients hospitalized for COVID-19 between metropolitan areas and non-metropolitan areas in Japan using data from the COVIREGI-JP registry [11]. The number of patients with COVID-19 was higher in metropolitan areas than in non-metropolitan areas in wave 2 (6946 vs 3801) and increased further in wave 3 (9188 vs 7542); the patient population then decreased in wave 4 to assume similar numbers between metropolitan areas and non-metropolitan areas (2429 vs 2891). There were more young and middle-aged patients than elderly patients in wave 2 than in waves 3 and 4. The rate of comorbidity was higher in metropolitan areas than in non-metropolitan areas in waves 3 (66.5% vs 56.7%) and 4 (60.0% vs 55.1%) than in wave 2 (43.5% vs 39.5%), which was probably due to the older age of the patients. Specifically, a higher proportion of patients with hypertension, hyperlipidemia, and diabetes mellitus was observed in waves 3 and 4 than in wave 2, which was also probably related to the older age of the patients [7].

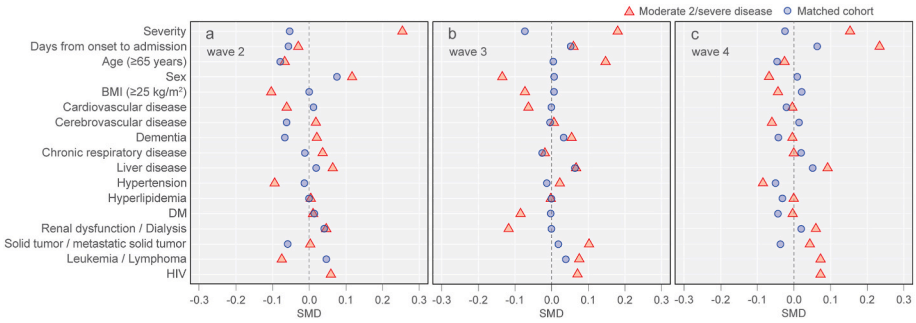

Fig. 1. SMD for (a) wave 2, (b) wave 3, and (c) wave 4 between all patients hospitalized for COVID-19 with moderate 2 or severe disease and the propensity matched cohort with moderate 2 or severe disease.
BMI, body mass index; DM, diabetes mellitus; HIV, human immunodeficiency virus; SMD, standardized mean difference; COVID-19, coronavirus disease-2019.

Patient demographics and clinical characteristics were similar to those reported previously among hospitalized patients with COVID-19 from COVIREGI-JP in Japan [7]. After propensity score matching, the patient population between metropolitan areas and non-metropolitan areas comprised mostly elderly patients aged ≥65 years (IQR: 52–81 years) with a median SpO_2 of 93/94 (IQR: 91–96). No major differences were noted in the proportion of inpatients with severe disease representative of ICU stay/admission across waves 2–4.

In general, ICU capacity is limited in non-metropolitan areas compared with that in metropolitan areas [16]. Our data showed that the use of non-IMV in waves 2 and 3, IMV in wave 4, or IMV/ECMO in wave 4 among inpatients was significantly higher in metropolitan areas than in non-metropolitan areas. Although IMV/ECMO was used less often for moderate 2/severe cases in wave 4 in non-metropolitan areas vs metropolitan areas, the mortality rate was similar, suggesting better healthcare services despite limited available resources in non-metropolitan areas. However, ECMO was more often used in non-metropolitan areas than in metropolitan areas. In addition, the use of prone positioning among inpatients was not significantly different in waves 2 and 3 but was significantly higher in wave 4 in non-metropolitan areas than in metropolitan areas. Furthermore, in non-metropolitan areas, it is possible that patients were admitted to the ICU on a preliminary basis without requiring intensive care. Overall, patients in metropolitan areas were more severely ill and were likely to use ECMO and other ICU/advanced medical care resources. Moreover, it is likely that a limited number of hospitals provided ECMO in non-metropolitan areas. Therefore, despite the differences in the rate of IMV/ECMO and prone positioning in the fourth wave, ECMO is more likely to be used in metropolitan areas, and there might have been a tendency to use prone positioning instead of ECMO in non-metropolitan areas due to the lack of both ECMO and its experience.

Although the proportions of patients admitted to the ICU were similar between waves and across regions, it is possible that non-metropolitan areas vs metropolitan areas may have encountered factors such as differences in the availability of beds [9] that could not be matched based on background characteristics alone. No major difference in mortality was noted between metropolitan areas and other regions. However, in wave 2, death as an outcome in metropolitan areas vs non-metropolitan areas (9.2% vs 4.9%) was significantly higher than patient discharge to home/transfer as the outcome (90.8% vs 95.1%). Mortality rates tended to be similar between metropolitan areas and non-metropolitan areas across waves 3–4, likely because of effective treatment being provided across Japan according to the guidelines [6], without any noticeable gaps in treatment provision across the country.

In non-metropolitan areas, there was a greater discrepancy between the proportion of patients who needed IMV/ECMO and ICU stay than that in metropolitan areas. Moreover, the proportion of patients who needed IMV/ECMO was lesser than that of patients who needed ICU stay, probably because in metropolitan areas, IMV/ECMO use meant ICU stay, whereas in non-metropolitan areas, patients may have been admitted to the ICU just as a preliminary measure for medical treatment.

Steroids were administered to about 60% of cases in the second wave, but this proportion increased in the fourth wave, with more than 80% of patients receiving steroids. Metropolitan and non-metropolitan patients were equally likely to receive effective treatment.

Better outcomes and lower mortality observed in Japan could be related to reduced susceptibility to the pulmonary manifestations of SARS-CoV-2 in the Japanese population [17] and the lack of regional differences in treatment provision patterns, which might be unique to Japan [18,19].

5. Limitations

The regional categorization in this study was metropolitan areas vs non-metropolitan areas, but further regional characteristics in each prefecture were not considered. For example, Kanagawa Prefecture is classified as a metropolitan area but has depopulated areas within the prefecture. While metropolitan and non-metropolitan areas were compared separately, within metropolitan areas, the situation of healthcare provision may differ considerably between areas with easy access to healthcare facilities, such as Tokyo, and even within Hokkaido, such as between Sapporo and other areas. As each hospitalization event was considered as one patient, repeated hospitalization events may have affected the mean/median patient characteristics. As with every database study, the generalizability of the COVIREGI-JP data remains a limitation with regard to the manual input of data and number of patients registered in the database [11]; selection bias due to the persistent epidemic and ever-changing epidemiology of COVID-19, which required continued case registration and data utilization in COVIREGI-JP [11]; possible slow response to improve access to inpatient care for patients with COVID-19 [20]; and data collection in COVIREGI-JP being initiated after the Japan vaccination program started, which may have changed the distribution of severity over time due to vaccine efficacy. It was not possible to evaluate the differences in hospital capacity, such as the number of ICU beds and the availability of ECMO, which may have influenced the treatment and its outcomes, because the COVIREGI-JP data do not provide this information. Therefore, the number of ICUs and ECMOs in each province and the policy of infection control may have an impact on treatment and outcomes and should be investigated in detail.

6. Conclusion

Our results demonstrate that during the early COVID-19 epidemic (wave 2) up until and through wave 4, no clear differences in mortality rates and no regional differences in treatment provision patterns were observed between metropolitan areas and non-metropolitan areas, which might be unique to Japan.

Table 3
Treatment and treatment outcomes during hospitalization summarized by epidemic waves 2–4 and region (metropolitan and non-metropolitan areas) in the propensity score–matched cohort.

		Wave 2			Wave 3			Wave 4		
Item (n [%])	Detail	Metropolitan areas	Non-metropolitan areas	p value	Metropolitan areas	Non-metropolitan areas	p value	Metropolitan areas	Non-metropolitan areas	p value
Number of cases		307	307		913	913		479	479	
Admission to ICU	Yes	57 (18.6)	64 (20.8)	0.543	126 (13.8)	139 (15.2)	0.425	87 (18.2)	81 (16.9)	0.671
Nasal cannula, face mask, or reservoir	Yes	279 (90.9)	277 (90.2)	0.89	834 (91.3)	832 (91.1)	0.934	449 (93.7)	445 (92.9)	0.698
High-flow oxygen device	Yes	33 (10.7)	40 (13)	0.455	127 (13.9)	124 (13.6)	0.839	76 (15.9)	74 (15.4)	0.859
Non-IMV	Yes	20 (6.5)	8 (2.6)	0.032	30 (3.3)	15 (1.6)	0.024	12 (2.5)	12 (2.5)	1
IMV	Yes	38 (12.4)	31 (10.1)	0.443	78 (8.6)	81 (8.9)	0.868	51 (10.7)	27 (5.6)	0.005
ECMO	Yes	4 (1.3)	1 (0.3)	0.373	2 (0.2)	6 (0.7)	0.288	1 (0.2)	4 (0.8)	0.374
IMV/ECMO	Yes	38 (12.4)	31 (10.1)	0.443	78 (8.5)	81 (8.9)	0.868	51 (10.6)	27 (5.6)	0.006
Prone positioning	Yes	26 (8.8)	18 (6.0)	0.214	68 (7.5)	64 (7.0)	0.719	69 (14.4)	98 (20.5)	0.017
Nitric oxide inhalation	Yes	1 (0.3)	0 (0)	0.499	1 (0.1)	0 (0)	0.499	0 (0)	1 (0.2)	1
Tracheotomy	Yes	6 (2.0)	6 (2.0)	1	16 (1.8)	14 (1.5)	0.717	4 (0.8)	5 (1)	1
Neuromuscular blocking agent	Yes	24 (8.1)	19 (6.4)	0.433	51 (5.6)	53 (5.8)	0.92	29 (6.1)	24 (5)	0.484
Vasopressor/inotropic support	Yes	18 (5.9)	12 (3.9)	0.35	45 (4.9)	46 (5)	0.915	23 (4.8)	13 (2.7)	0.092
RRT or dialysis	Yes	11 (3.6)	8 (2.6)	0.642	13 (1.4)	13 (1.4)	1	4 (0.8)	2 (0.4)	0.451
Blood transfusion	Yes	17 (5.5)	11 (3.6)	0.334	27 (3)	31 (3.4)	0.689	17 (3.6)	11 (2.3)	0.258
Immunoglobulin	Yes	3 (1)	3 (1)	1	13 (1.4)	11 (1.2)	0.688	10 (2.1)	3 (0.6)	0.056
Hemodialysis	Yes	6 (2.0)	6 (2.0)	1	11 (1.2)	10 (1.1)	1	2 (0.4)	1 (0.2)	1
CRRT	Yes	6 (2.0)	4 (1.3)	0.752	5 (0.5)	4 (0.4)	1	2 (0.4)	1 (0.2)	1
Peripheral dialysis	Yes	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Favipiravir	Yes	124 (51.0)	143 (58.6)	0.102	272 (38.1)	306 (42)	0.147	129 (29.2)	89 (20.7)	0.004
Remdesivir	Yes	116 (47.9)	108 (44.3)	0.467	385 (53.9)	390 (53.7)	0.958	359 (81.2)	322 (74.9)	0.027
Ciclesonide	Yes	66 (27.2)	61 (25.0)	0.607	79 (11.1)	101 (13.9)	0.111	31 (7)	16 (3.7)	0.035
Steroids (excluding ciclesonide)	Yes	201 (65.5)	190 (61.9)	0.401	743 (81.4)	692 (76)	0.005	412 (86.2)	400 (83.5)	0.279
Tocilizumab	Yes	12 (5)	36 (14.8)	< 0.001	50 (7.0)	76 (10.5)	0.025	77 (17.5)	58 (13.5)	0.112
Nafamostat	Yes	19 (7.9)	35 (14.3)	0.03	24 (3.4)	50 (6.9)	0.003	37 (8.4)	9 (2.1)	< 0.001
Ivermectin	Yes	1 (0.4)	0 (0)	0.498	0 (0)	0 (0)	–	1 (0.2)	1 (0.2)	1
Antibiotics	Yes	119 (38.9)	123 (40.1)	0.804	376 (41.3)	360 (39.6)	0.504	167 (34.9)	119 (24.8)	0.001
Anticoagulants	Yes	119 (38.8)	114 (37.1)	0.739	459 (50.3)	446 (48.8)	0.574	257 (53.7)	248 (51.8)	0.605
Outcome	Discharge to home	211 (69.2)	216 (70.4)	0.192	553 (60.6)	578 (63.3)	0.291	292 (61)	335 (69.9)	0.002
	Transferred to nonmedical facility	2 (0.7)	2 (0.7)		10 (1.1)	7 (0.8)		2 (0.4)	1 (0.2)	
	Transferred to long-term care facility	11 (3.6)	8 (2.6)		57 (6.2)	40 (4.4)		9 (1.9)	18 (3.8)	
	Transferred to medical facility for further treatment or rehabilitation	53 (17.4)	66 (21.5)		190 (20.8)	176 (19.3)		130 (27.1)	86 (18)	
	Death	28 (9.2)	15 (4.9)		103 (11.3)	112 (12.3)		46 (9.6)	39 (8.1)	
Outcome (death)	Discharge/transfer	277 (90.8)	292 (95.1)	0.041	810 (88.7)	801 (87.7)	0.561	433 (90.4)	440 (91.9)	0.496
	Death	28 (9.2)	15 (4.9)		103 (11.3)	112 (12.3)		46 (9.6)	39 (8.1)	

CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; RRT, renal replacement therapy.
Data are presented as n (%), unless specified.
The number of missing values differed for each parameter; therefore, the denominator for calculation of percentages (n [%]) varied from the total number of cases mentioned above in the table (n) to n minus missing data. Missing data represent unavailability of information.

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Authorship statement

All authors meet the ICMJE authorship criteria. YA and TO contributed equally to this manuscript. YA, TO, KI, and KM were responsible for the organization and coordination of the study. YA, ST, and NM were responsible for data analysis. All authors discussed the data and contributed to the writing of the final manuscript. All authors have approved the final version of the manuscript for publication.

Declaration of competing interest

The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: TO, KI, and KM hold stocks and stock options from Pfizer Inc. TO, KI, and KM are full-time employee of Pfizer Japan Inc. ST received payment for supervising medical articles from Gilead Sciences, Inc. YA, NM, and NO have nothing to disclose.

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References

[1] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.

[2] Saito S, Asai Y, Matsunaga N, Hayakawa K, Terada M, Ohtsu H, et al. First and second COVID-19 waves in Japan: a comparison of disease severity and characteristics. J Infect 2021;82:84–123. https://doi.org/10.1016/j.jinf.2020.10.033.

[3] Kucharski AJ, Russell TW, Diamond C, Liu Y, Edmunds J, Funk S, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis 2020;20:553–8. https://doi.org/10.1016/S1473-3099(20)30144-4.

[4] Bai Y, Tao X. Comparison of COVID-19 and influenza characteristics. J Zhejiang Univ - Sci B 2021;22:87–98. https://doi.org/10.1631/jzus.B2000479.

[5] Matsunaga N, Hayakawa K, Terada M, Ohtsu H, Asai Y, Tsuzuki S, et al. Clinical epidemiology of hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan: report of the COVID-19 Registry Japan. Clin Infect Dis 2021;73:e3677–89. https://doi.org/10.1093/cid/ciaa1470.

[6] Clinical Practice Guideline Review Committee. COVID-19 clinical practice guideline ver 8.0. 2022. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00111.html. [Accessed 9 December 2022].

[7] Matsunaga N, Hayakawa K, Asai Y, Tsuzuki S, Terada M, Suzuki S, et al. Clinical characteristics of the first three waves of hospitalised patients with COVID-19 in Japan prior to the widespread use of vaccination: a nationwide observational study. Lancet Reg Health West Pac 2022;22:100421. https://doi.org/10.1016/j.lanwpc.2022.100421.

[8] Shimizu K, Negita M. Lessons learned from Japan's response to the first wave of COVID-19: a content analysis. Healthcare (Basel, Switzerland) 2020;8:426. https://doi.org/10.3390/healthcare8040426.

[9] Tsuzuki S, Asai Y, Matsunaga N, Ishioka H, Akiyama T, Ohmagari N. Impact of regional heterogeneity on the severity of COVID-19. J Infect Chemother 2022;28:554–7. https://doi.org/10.1016/j.jiac.2021.12.032.

[10] National Center for Global Health and Medicine. COVID-19 Registry Japan. https://covid-registry.ncgm.go.jp/. [Accessed 9 December 2022].

[11] Hayakawa K, Asai Y, Matsunaga N, Tsuzuki S, Terada M, Suzuki S, et al. Evaluation of the representativeness of data in the COVID-19 Registry Japan during the first six waves of the epidemic. Glob Health Med 2022;4:204–9. https://doi.org/10.35772/ghm.2022.01033.

[12] Akiyama Y, Morioka S, Asai Y, Sato L, Suzuki S, Saito S, et al. Risk factors associated with asymptomatic hypoxemia among COVID-19 patients: a retrospective study using the nationwide Japanese registry, COVIREGI-JP. J Infect Public Health 2022;15:312–4. https://doi.org/10.1016/j.jiph.2022.01.014.

[13] Ministry of Health, Labour and Welfare. Notification of physicians and veterinarians under the Infectious Diseases Act. https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-shitei-01.html. [Accessed 7 April 2023].

[14] Statistics Bureau. Demographic estimates by the statistical service of the ministry of general affairs (as of october 1, 2021). https://www.stat.go.jp/data/jinsui/2021np/index.html. [Accessed 1 August 2023].

[15] Ministry of Health, Labour and Welfare. New coronavirus infections-cumulative number of positive cases. https://covid19.mhlw.go.jp/extensions/public/index.html. [Accessed 1 August 2023].

[16] JSICM. Views on international comparisons on ICU, etc. https://www.jsicm.org/news/news200510.html. [Accessed 7 April 2023].

[17] Amengual O, Atsumi T. COVID-19 pandemic in Japan. Rheumatol Int 2021;41:1–5. https://doi.org/10.1007/s00296-020-04744-9.

[18] Ministry of Health, Labour and Welfare. Treatment guidelines in the 4.0 edition of the Guide to the Treatment of Novel Coronavirus Infections. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00212.html. [Accessed 7 April 2023].

[19] Ministry of Health, Labour and Welfare. Guideline for medical treatment PDF. 2020. https://www.mhlw.go.jp/content/000702064.pdf [Accessed 9 December 2022].

[20] Nakahara S, Inada H, Ichikawa M, Tomio J. Japan's slow response to improve access to inpatient care for COVID-19 patients. Front Public Health 2021;9:791182. https://doi.org/10.3389/fpubh.2021.791182.