

— Original Article (Research reports) —

Prescription Trends and Effectiveness of Anti-influenza Drugs in Osaka, Japan, during the 2022-2023 and 2023-2024 Influenza Seasons

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Abstract

Introduction: Since the beginning of the coronavirus disease 2019 pandemic, there have been limited reports on the clinical outcomes of outpatients with influenza treated with baloxavir or neuraminidase inhibitors (NAIs). This study aimed to investigate the prescription trends and effectiveness of baloxavir and NAIs.

Materials and Methods: This descriptive epidemiological study included data of patients diagnosed with influenza in Osaka Prefecture, Japan, during the 2022-2023 and 2023-2024 seasons who answered a questionnaire via Research Electronic Data Capture.

Results: During the 2022-2023 and 2023-2024 seasons, respectively, we enrolled 73 and 96 patients diagnosed with influenza A at 26 facilities. Oseltamivir was most commonly prescribed (54.8%) in the 2022-2023 season, whereas laninamivir was most commonly prescribed (46.9%) in the 2023-2024 season. Baloxavir was prescribed to 11.0% and 19.8% of patients in the 2022-2023 and 2023-2024 seasons, respectively. The time to fever alleviation did not differ significantly between the baloxavir and NAI groups in either season (2022-2023: $p = 0.47$; 2023-2024: $p = 0.12$). There were no significant differences between groups in new symptoms after drug administration.

Conclusions: No significant differences were observed in the effects of baloxavir or the NAIs on fever.

Keywords

influenza, baloxavir, neuraminidase inhibitors

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Introduction

Influenza is a viral infection that is particularly prevalent in winter worldwide, and the risk of severe illness makes appropriate countermeasures an important issue [1]. After the A(H1N1) influenza pandemic in 2009, two new drugs against influenza infection, laninamivir and peramivir, were released in Japan in 2010. Four varieties of neuraminidase inhibitors (NAIs; oseltamivir, zanamivir, laninamivir, and peramivir) are used for treating influenza in Japan. In addition, a selective inhibitor of the influenza polymerase acidic protein cap-dependent endonuclease, baloxavir marboxil (baloxavir), is a novel anti-influenza drug that suppresses viral growth by inhibiting cap-dependent endonuclease [2]. It was approved for use in Japan in 2018. A randomized study conducted in 2019 reported that the time to clinical recovery

with baloxavir was comparable to that with NAIs in terms of the symptom-improvement effect [3].

Since the beginning of the global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there has been a significant decline in influenza detection in many countries [4]. During the coronavirus disease 2019 (COVID-19) pandemic, influenza sample collection decreased owing to changing priorities, limited funding, and the closure of outpatient clinics, resulting in a decline in both the number of tests performed and positivity rates [5]. The widespread use of hand sanitization and masks and reduced overseas travel due to the COVID-19 pandemic may also have had an impact [4]. There was a significant decline in the number of influenza cases in Japan during the 2020-2021 and 2021-2022 seasons [4]. Since the 2022-2023 season, there have been limited reports on the clinical outcomes

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of outpatients treated with baloxavir or NAIs for influenza [6].

Patients diagnosed with influenza are prescribed baloxavir or an NAI in outpatient clinics, after which they rarely revisit hospitals or clinics. Therefore, it is difficult for doctors to determine the treatment outcomes for these patients. In addition, during the winter season, doctors are too busy to investigate treatment outcomes in detail owing to the large number of patients with viral infections, cardiovascular diseases, or respiratory diseases. Before the COVID-19 pandemic, we conducted a less time-intensive self-reported survey using a postcard questionnaire [7]. To reduce the burden on patients, we decided to conduct surveys utilizing Research Electronic Data Capture (REDCap).

This descriptive epidemiologic study was conducted during the 2022-2023 and 2023-2024 seasons to investigate the prescription trends and effectiveness of baloxavir and NAIs, and to assess the clinical differences between them.

Materials and Methods

Study population and protocol

This multicenter observational study was conducted in Osaka Prefecture, Japan, and involved doctors from 26 facilities, including clinics and general hospitals. Participants were recruited from among outpatients who visited these facilities and were diagnosed with influenza from December 28, 2022, to March 31, 2023, and from November 1, 2023, to March 31, 2024. Doctors provided questionnaires and informed consent documents to the patients diagnosed with influenza. The questionnaire included a “quick-response” code for REDCap and a list of questions. After providing informed consent, the patients completed the questionnaires via REDCap. The questions were as follows: the name of the facilities they visited; their age and sex; if they were tested for influenza; the type of influenza (A or B); if they were tested for COVID-19 and the result; if they had received influenza vaccination in the relevant season; the anti-influenza drug prescribed; past medical history; date of onset; initial symptoms; body temperature before the consultation; body temperature (in the morning and evening) for 5 days, including the date of the patient’s first visit; any new symptoms after drug administration; and whether there was a recurrence of fever.

The duration of the fever was defined as the period from the patient visit until the fever was alleviated for more than 1 day with no relapse thereafter. A decrease in the fever was defined as temperatures under 37.5°C in patients aged <10 years or under 37.0°C in patients aged ≥10 years, as previously described [8-10].

The study protocol was approved by the Ethics Committee of Osaka Metropolitan University (No. 2022-154).

Statistical analyses

Statistical analyses were performed using SPSS (version 28.0; IBM Corp., Armonk, NY, USA). Analyses were conducted separately for the 2022-2023 and 2023-2024 seasons

because the prevalence of influenza subtypes may have differed between seasons and because previous studies also performed analyses on a season-by-season basis [10,11]. Patient characteristics are presented as mean ± standard deviation (SD) for continuous variables and as numbers (percentages) for categorical variables. Pearson’s chi-squared test or Fisher’s exact test was used to assess group differences in the percentage of patients. The log-rank test was used to compare the time from the drug administration until fever alleviation. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

We evaluated the responses of 191 patients during the 2022-2023 and 2023-2024 seasons from 26 facilities, including clinics and general hospitals. In the 2022-2023 season, 97.4% of the patients (76 out of 78) were diagnosed with influenza A, while 2.6% (2 out of 78) had an unknown influenza type. Additionally, 3 patients tested positive for COVID-19. In the 2023-2024 season, 92.0% of the patients (104 out of 113) were diagnosed with influenza A, 5.3% (6 out of 113) were diagnosed with influenza B, and 2.7% (3 out of 113) had an unknown influenza type. Furthermore, 9 patients tested positive for COVID-19.

In this study, the data of patients who tested positive for COVID-19 were excluded from the analysis and only those diagnosed with influenza A were included in the subsequent analysis: 73 patients in the 2022-2023 season and 96 patients in the 2023-2024 season. The baseline characteristics of the patients with influenza A and those prescribed anti-influenza drugs are shown in **Table 1** and **Figure 1**.

In the 2022-2023 season, oseltamivir was the most prescribed anti-influenza drug, accounting for 54.8% of prescriptions. In the 2023-2024 season, laninamivir was the most prescribed, accounting for 46.9%. The proportion of prescriptions for baloxavir showed an increasing trend from 11.0% in the 2022-2023 season to 19.8% in the 2023-2024 season. The baseline characteristics of each patient group who were prescribed an NAI or baloxavir are shown in **Table 2**. In both the 2022-2023 and 2023-2024 seasons, no significant differences were observed in terms of age (0-5 years old, 6-9 years old, and ≥10 years old), vaccination status, or duration from onset to drug administration (≤1 day or not).

Comparison of the duration of the fever

In the 2022-2023 season, the time (mean ± SD) to the alleviation of fever was 1.92 ± 0.54 days in the baloxavir group and 2.31 ± 0.13 days in the NAI group. In the 2023-2024 season, it was 1.92 ± 0.21 days in the baloxavir group and 2.32 ± 0.14 days in the NAI group. In both seasons, There was no significant difference in the duration of fever in either season between the baloxavir and NAI groups (2022-2023: $p = 0.47$; 2023-2024: $p = 0.12$; **Figure 2**).

Table 1. Clinical Characteristics of Patients with Influenza A.

	2022–2023 season				2023–2024 season			
	0-5 years (n = 11)	6-9 years (n = 16)	≥10 years (n = 44)	Total (n = 73)	0-5 years (n = 9)	6-9 years (n = 14)	≥10 years (n = 72)	Total (n = 96)
Age, years	3.8 ± 1.0	7.8 ± 1.0	26.0 ± 17.3	18.5 ± 16.7	4.1 ± 1.2	7.4 ± 1.2	29.5 ± 18.3	23.8 ± 18.8
Sex male, n (%)	6 (54.5)	8 (50.0)	17 (38.6)	33 (45.2)	5 (55.6)	7 (50.0)	29 (40.3)	42 (43.8)
Past medical history, n (%)	1 (9.1)	3 (18.8)	9 (20.5)	14 (19.2)	2 (22.2)	2 (14.3)	14 (19.4)	18 (18.8)
Vaccinated this season, n (%)	5 (45.5)	5 (31.3)	15 (34.1)	26 (35.6)	3 (33.3)	5 (35.7)	18 (25.0)	27 (28.1)
Body temperature, °C	38.8 ± 0.9	39.1 ± 0.7	38.9 ± 0.8	38.9 ± 0.8	38.8 ± 1.2	39.1 ± 0.9	38.5 ± 1.0	38.6 ± 1.0
Time from onset to drug administration, days	0.9 ± 0.8	1.4 ± 2.2	1.0 ± 0.7	1.1 ± 1.2	1.2 ± 0.7	1.2 ± 1.0	1.0 ± 0.9	1.1 ± 0.9
First symptoms (Multiple answers allowed)								
Fever, n (%)	8 (72.7)	15 (93.8)	33 (75.0)	57 (78.1)	8 (88.9)	9 (64.3)	53 (73.6)	71 (74.0)
Cough, n (%)	8 (72.7)	8 (50.0)	24 (54.5)	41 (56.2)	4 (44.4)	8 (57.1)	32 (44.4)	45 (46.9)
Nasal discharge, n (%)	7 (63.6)	3 (18.8)	11 (25.0)	21 (28.8)	4 (44.4)	3 (21.4)	24 (33.3)	32 (33.3)
Sore throat, n (%)	0 (0.0)	2 (12.5)	16 (36.4)	19 (26.0)	1 (11.1)	0 (0.0)	19 (26.4)	21 (21.9)
Headache, n (%)	1 (9.1)	2 (12.5)	13 (29.5)	17 (23.3)	4 (44.4)	6 (42.9)	19 (26.4)	29 (30.2)
Joint pain, n (%)	0 (0.0)	1 (6.3)	14 (31.8)	15 (20.5)	1 (11.1)	0 (0.0)	19 (26.4)	21 (21.9)
Phlegm, n (%)	2 (18.2)	1 (6.3)	4 (9.1)	7 (9.6)	2 (22.2)	1 (7.1)	9 (12.5)	12 (12.5)

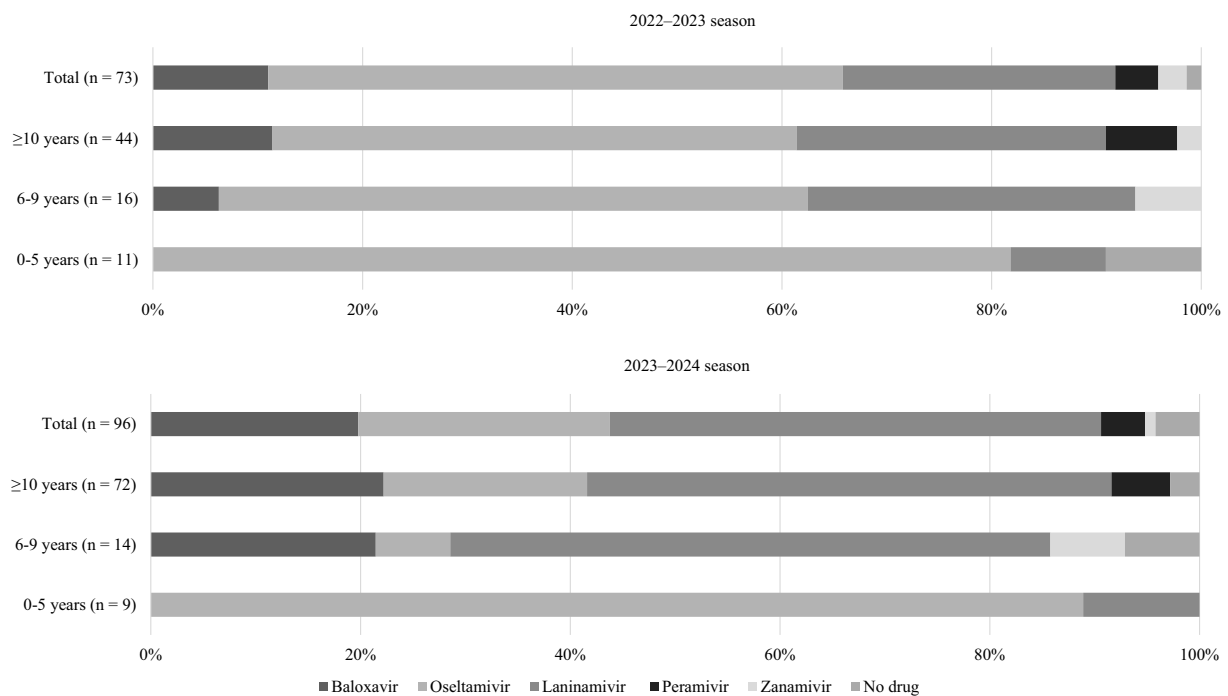


Figure 1. Proportion of patients prescribed anti-influenza drugs during 2022–2023 and 2023–2024 seasons. In the 2022–2023 season, oseltamivir was the most prescribed anti-influenza drug, accounting for 54.8% of prescriptions; in the 2023–2024 season, laninamivir was the most prescribed, accounting for 46.9%. The proportion of prescriptions for baloxavir showed an increasing trend, from 11.0% in the 2022–2023 season to 19.8% in the 2023–2024 season.

New symptoms after drug administration

In both seasons, There were no significant differences between the NAI and baloxavir groups in either season in terms of new symptoms after drug administration (2022–2023: NAI group, 31.7%; baloxavir group, 0%; $p = 0.18$; 2023–2024: NAI group 24.7%; baloxavir group, 10.5%; $p = 0.23$).

Discussion

In this study, we found that oseltamivir was the drug most commonly prescribed for influenza during the 2022–2023 season, whereas laninamivir was the most commonly prescribed during the 2023–2024 season. Baloxavir was prescribed to 11.0% of patients in the 2022–2023 season and to 19.8% in the 2023–2024 season. The time to fever allevia-

Table 2. Comparison of Clinical Parameters between the NAI and Baloxavir Groups.

	2022–2023 season			2023–2024 season		
	NAI (n = 64)	Baloxavir (n = 8)	p-value	NAI (n = 73)	Baloxavir (n = 19)	p-value
0-5 years old, n (%)	10 (15.6)	0 (0.0)	0.58	9 (12.3)	0 (0.0)	0.20
6-9 years old, n (%)	15 (23.4)	1 (12.5)	1.00	10 (13.7)	3 (15.8)	0.73
≥ 10 years old, n (%)	39 (60.9)	5 (62.5)	0.40	54 (74.0)	16 (84.2)	0.55
Vaccinated during the season, n (%)	24 (37.5)	1 (12.5)	0.25	22 (30.1)	4 (21.1)	0.57
Time from onset to drug administration ≤ 1 day, n (%)	46 (79.3)	5 (62.5)	0.37	49 (69.0)	14 (73.7)	0.78
Past medical history, n (%)	12 (18.8)	2 (25.0)	0.65	13 (17.8)	5 (26.3)	0.52

NAI: neuraminidase inhibitor

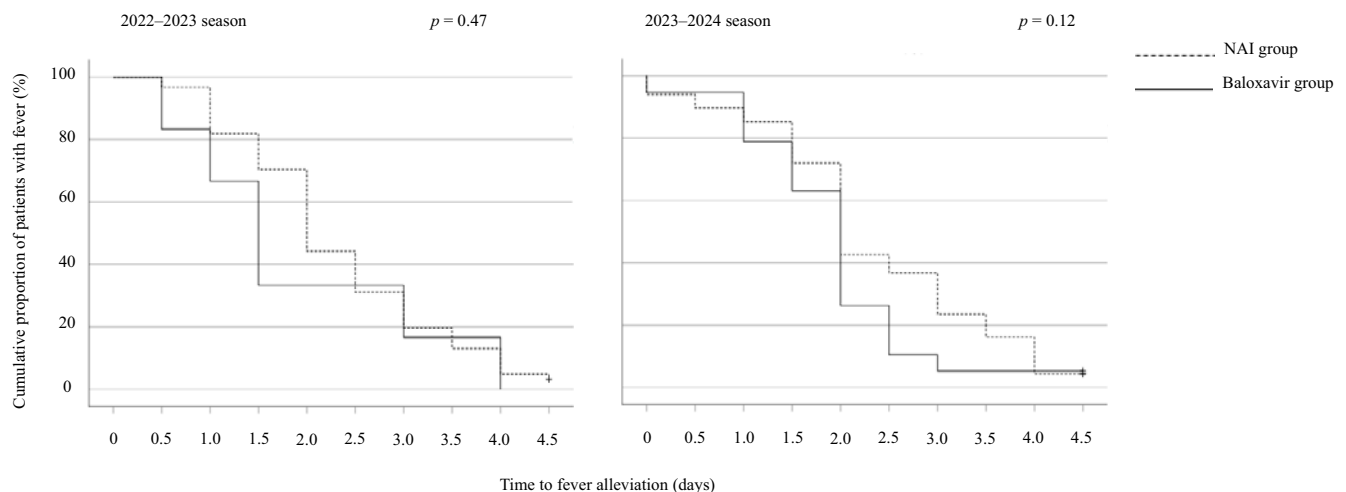


Figure 2. Kaplan-Meier curves of the time to the alleviation of the fever.

The duration of fever did not differ significantly between the baloxiavir and NAI groups. NAI: neuraminidase inhibitor

tion did not differ significantly between the baloxavir and NAI groups in either season.

We previously investigated the prescription trends of four NAIs for 8 years, from the 2010-2011 to the 2017-2018 season [11]. In that investigation, laninamivir was most commonly prescribed to patients aged ≥10 years and oseltamivir was most commonly prescribed to patients aged <10 years. Laninamivir is administered via one-time inhalation and may therefore be associated with a high rate of compliance. However, small children, particularly those aged <3 years, have difficulty inhaling laninamivir [10]. Presumably, the medications were chosen based on the patient's age, drug compliance, and number of doses. In this study, oseltamivir was the drug most commonly prescribed to patients aged ≥10 years as well as to those aged <10 years during the 2022-2023 season. Because coughing can be expected to occur when laninamivir is used as an inhalant, appropriate infection control measures are necessary when providing inhalation guidance in consideration of co-infection with SARS-CoV-2. This background explains why oseltamivir was probably the most prescribed drug, regardless of age. Conversely, in the 2023-2024 season, laninamivir was the drug most commonly prescribed to patients aged ≥10 years and 6-9 years, while oseltamivir was most commonly prescribed to patients aged 0-5 years. We speculate that this change may have been influenced by the stabilization of the COVID-19

pandemic, which made it possible to provide appropriate inhalation guidance.

Baloxavir received regulatory approval in 2018. However, amino acid substitutions at position 38 of the polymerase acidic protein of the influenza virus (PA/I38X) occasionally emerged after baloxavir administration to pediatric and adult patients (23% and 10%, respectively) [12]. The emergence of drug-resistant viruses was reported in the 2018-2019 season [13], and influenza treatment and prevention guidelines in Japan have refrained from actively recommending the drugs. In 2023, the World Health Organization reported that the detection frequencies of influenza viruses with amino acid substitutions associated with reduced drug susceptibility were 0.8% (9/1092) and 0.1% (2/1843) for A(H3N2) and A(H1N1), respectively.

According to the influenza guidelines published by the Japan Pediatric Society in 2022, the use of baloxavir was not recommended for patients under 12 years of age because of the potential for prolonged excretion of viruses with resistant mutations. However, in the influenza guidelines published by the Japan Pediatric Society in 2023, the recommendation was updated: baloxavir is recommended for patients aged 12 years and older, while for those aged 6 to 11 years, careful administration is advised. The changes in these guidelines may be related to the trends in prescription rates observed in this study. In our previous study of the

2018-2019 season, baloxavir was prescribed to 111 out of 295 patients [10]. In the present study, the age group was younger, which may have contributed to a trend towards lower prescription rates compared with the previous study.

In this study, the mean durations of fever in the 2022-2023 season were 1.92 ± 0.54 days in the baloxavir group and 2.31 ± 0.13 days in the NAI group; in the 2023-2024 season, the durations were 1.92 ± 0.21 and 2.32 ± 0.14 days, respectively. There were no significant differences between the baloxavir and NAI groups in either season. Hayden et al. reported that the viral titer was significantly lower on the second day of administration in a baloxavir group than in an oseltamivir group [3]. However, they also reported that the median time to symptom alleviation was similar between their baloxavir and oseltamivir groups during the 2016-2017 season. We previously investigated a total of 295 patients with influenza A during the 2018-2019 season, and the mean duration of fever was significantly shorter in the baloxavir group (1.94 ± 0.09 days) than in the NAI group (2.35 ± 0.08 days) [10]. The antiviral activity of baloxavir may be reflected in the length of the febrile period. In a multicenter study in the 2022-2023 season, the baloxavir group tended to exhibit a shorter median duration of fever (27.0 hours) than the oseltamivir (38.0 hours) and other NAI groups (36.0 hours); however, the difference was not statistically significant [6].

In this study, we assessed only the alleviation of fever, and not the resolution of other symptoms. There was a trend towards a shorter mean duration of fever in the baloxavir group during both seasons, but none of the differences were statistically significant. The mean fever duration after the initial administration of anti-influenza drugs in the 2022-2023 and 2023-2024 seasons was similar to that in the 2018-2019 season [10]. The lack of statistical significance may be partly due to the small number of patients enrolled in this study. Uehara et al. reported that viruses with reduced susceptibility owing to PA/I38X occasionally emerged 3-9 days after baloxavir treatment [14]. The median time to symptom alleviation was 12 hours longer in the group with PA/I38X-substituted viruses than in the group without. Goto et al. reported the virological and clinical effectiveness of baloxavir against A(H3N2) in the 2022-2023 season and suggested a limited clinical influence of post-treatment resistance emergence [6]. Results published by the National Institute of Infectious Diseases estimated the number of influenza cases at 12.005 million in the 2018-2019 season and 4.39 million in the 2023-2024 season. In the 2018-2019 season, AH1pdm09 accounted for 38% and AH3 for 56%, whereas in the 2023-2024 season, AH1pdm09 accounted for 3% and AH3 for 94%. Mutant viruses are primarily detected in A(H3N2) and A(H1N1) [14]. The impact of mutant viruses on overall epidemiology is unknown. In the present study, we were unable to evaluate the emergence of PA/I38X-substituted viruses. However, considering that the number of days to fever resolution was similar to that investigated in the 2018-2019 season, the duration of fever might not have been markedly affected by PA/I38X substitution virus in this study.

This study has some limitations. First, we could not assess the return rate of the questionnaire because we could only confirm the content of the responses through REDCap. Therefore, we could not evaluate the characteristics and course of symptoms of all patients who visited the hospital during the study period. Second, the answers, including the temperatures, were self-reported data, thus limiting reliability. Some elderly patients might not have answered this survey sufficiently compared with younger patients. Therefore, there may be an age-related difference in data reliability. Third, the subtypes of influenza A virus and the emergence of PA/I38X-substituted viruses could not be evaluated. Therefore, further studies are necessary to evaluate the impact of influenza infection with PA/I38X-substituted viruses on the clinical course. Finally, we enrolled consecutive patients diagnosed with influenza A who responded to the questionnaire; however, the number of enrolled participants was too small to adjust for all covariates to estimate the effects of anti-influenza drugs. Further prospective studies with a larger number of participants are necessary to accurately assess the effect of each treatment on the clinical course.

Conclusions

Oseltamivir was the most commonly prescribed drug in the 2022-2023 season, whereas laninamivir was the most commonly prescribed in the 2023-2024 season. Baloxavir was prescribed to 11.0% of the patients in the 2022-2023 season and 19.8% in the 2023-2024 season. The time to fever alleviation did not differ significantly in either season between the baloxavir and NAI groups.

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Hospital, and Yodogawa Christian Hospital.

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Conflicts of Interest: There are no conflicts of interest.

Approval Code: The study protocol was approved by the Ethics Committee of Osaka Metropolitan University (No. 2022-154).

Informed Consent: Informed consent was obtained from all participants through the REDCap.

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