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Clinical characteristics and outcomes of myxedema coma: Analysis of a national inpatient database in Japan



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ABSTRACT

Background: Myxedema coma is a life-threatening and emergency presentation of hypothyroidism. However, the clinical features and outcomes of this condition have been poorly defined because of its rarity.

Methods: We conducted a retrospective observational study of patients diagnosed with myxedema coma from July 2010 through March 2013 using a national inpatient database in Japan. We investigated characteristics, comorbidities, treatments, and in-hospital mortality of patients with myxedema coma.

Results: We identified 149 patients diagnosed with myxedema coma out of approximately 19 million inpatients in the database. The mean (standard deviation) age was 77 (12) years, and two-thirds of the patients were female. The overall proportion of in-hospital mortality among cases was 29.5%. The number of patients was highest in the winter season. Patients treated with steroids, catecholamines, or mechanical ventilation showed higher in-hospital mortality than those without. Variations in type and dosage of thyroid hormone replacement were not associated with in-hospital mortality. The most common comorbidity was cardiovascular diseases (40.3%). The estimated incidence of myxedema coma was 1.08 per million people per year in Japan. Multivariable logistic regression analysis revealed that higher age and use of catecholamines (with or without steroids) were significantly associated with higher in-hospital mortality.

Conclusions: The present study identified the clinical characteristics and outcomes of patients with myxedema coma using a large-scale database. Myxedema coma mortality was independently associated with age and severe conditions requiring treatment with catecholamines.

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Introduction

Myxedema coma, an emergency presentation of hypothyroidism, is well-known to be a life-threatening condition.¹ The occurrence of this disease is rare, with an estimated incidence of 0.22 per million per year in a previous European study.²

Owing to its rarity, the clinical features associated with enhanced survival of this disease remain unclear. Currently, the initial thyroid hormone replacement of intravenous L-thyroxine

(LT4) is regarded as the standard therapy for myxedema coma induced by long-standing severe hypothyroidism.³ L-triiodothyronine (LT3) can be administered simultaneously, depending on coexistent cardiac risk factors.^{3–6} However, any recommendations for the treatment of myxedema coma have merely been based on expert opinions and case reports.^{3–6} In Japan, patients with myxedema coma are treated with enteral LT4, with or without LT3, through a nasogastric tube, while, in many other countries, these treatments are more frequently given intravenously.

In previous small case-series studies, the mortality rates of myxedema coma were 36% (4 of 11 patients), 52% (12 of 23 patients), and 25% (2 of 8 patients).^{2,7,8} However, the factors associated with mortality due to myxedema coma remain uncertain.

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The aims of the present study were (i) to describe the patient characteristics and current clinical treatment practice patterns for myxedema coma, including thyroid hormone replacement therapy; and (ii) to examine the factors affecting in-hospital mortality due to myxedema coma, using a national inpatient database in Japan.

Methods

Data source

The Diagnosis Procedure Combination (DPC) database is a discharge abstract and national administrative claims database for acute-care inpatients in Japan, the details of which have been described elsewhere.^{9–12} Briefly, 1042 hospitals participated in the database and provided data for 6.85 million inpatient admissions in 2012. The attending physicians are required to record the diagnosis of the disease accurately because the diagnostic records are linked to the payment system. The database includes the following data: dates of admission and discharge; patient age and sex; primary and secondary diagnoses, comorbidities at admission, and complications after admission; procedures; medications and devices used; consciousness level at admission, measured with the Japan Coma Scale (JCS); and in-hospital mortality. Diagnoses are recorded using International Classification of Diseases, Tenth Revision (ICD-10) codes and text data in Japanese. The JCS scores are defined as follows¹³: 0, alert consciousness; 1–3, wakefulness without any stimuli; 10–30, arousal by some stimuli; 100–300, coma. JCS and Glasgow Coma Scale assessments are well-correlated.¹⁴ The database does not contain any laboratory data, including serum thyroid hormone levels prior to or during treatment.

Written informed consent was not required because of the anonymous nature of the data. The Institutional Review Board at The University of Tokyo approved the study.

Patient selection and data

From the DPC database, we retrospectively extracted the records for all patients diagnosed with myxedema coma (ICD code: E03.5) from July 1, 2010 through March 31, 2013. We excluded patients with suspected diagnosis of myxedema coma.

We examined patients' age, sex, JCS score at admission, and requirement for mechanical ventilation. Age was categorized into ≤ 69 , 70–79, 80–89, and ≥ 90 years, because this grouping was clinically practical based on previous studies showing that elderly patients with hypothyroidism were more likely to experience myxedema coma.^{2,7,8} We also examined the practice patterns for treating myxedema coma in terms of variation in type and dosage of thyroid hormone replacement therapy (enteral LT4 alone; enteral LT4 combined with LT3; others, comprising no replacement of thyroid hormones or in-hospital preparation of thyroid hormones), and use of steroids (hydrocortisone, prednisolone, methylprednisolone, dexamethasone, and betamethasone) and catecholamines (dopamine, noradrenaline, adrenaline, dobutamine, and isoprenaline). Intravenous administration of thyroid hormones is considered an optimal therapy for patients with myxedema coma, who are unable to take medication orally.^{3–6} In Japan, however, injectable forms of thyroid hormones are not commercially available.¹⁵ Instead, crushed thyroid hormone tablets are enterally administered through a nasogastric tube. Otherwise, injected or suppository forms of thyroid hormones prepared in individual hospitals are used. However, in the DPC database, we could not confirm whether in-hospital preparations of thyroid hormones were used. Therefore, we categorized these unknown patients as "others". The maximal per-day dosage of LT4 was categorized into <100 , 100–199, and ≥ 200 μg , and the maximal

per-day dosage of LT3 was categorized into <20 , 20–49, and ≥ 50 μg . Duration of LT3 treatment was categorized into <7 and ≥ 7 days. Use of steroids and catecholamines was categorized into (i) none, (ii) use of steroids alone, and (iii) use of catecholamines with or without steroids. Duration of steroid and catecholamine treatments were categorized into <7 , 7–13, and ≥ 14 days.

Season at admission was divided into spring (March through May), summer (June through August), autumn (September through November), and winter (December through February). We identified the following comorbidities at admission: cardiovascular diseases, neuromuscular and psychiatric diseases, diabetes mellitus, pneumonia, chronic renal diseases, infections, chronic lung diseases, cerebrovascular diseases, adrenal insufficiency, gastrointestinal and hepatic diseases, trauma, and malignancy. We also identified patients who were newly diagnosed with acute myocardial infarction, angina pectoris, or arrhythmias after admission.

Statistical analyses

We assumed that all patients with myxedema coma were hospitalized. We estimated the incidence of myxedema coma based on bed volume stratification in all acute-care hospitals in Japan and the numbers of beds and myxedema coma patients in the DPC hospitals in 2012. The estimated numbers of myxedema coma patients (Y) were calculated using the following equation:

$$Y = \sum_{i=1}^k N_i \frac{X_i}{n_i}$$

where N is the number of beds in all acute-care hospitals in Japan, n is the number of beds in the DPC hospitals, and X is the observed number of myxedema coma patients in the DPC hospitals in 2012.¹⁶ Because of the rarity of the disease, we calculated their 95% confidence intervals (CI; T_L , T_U) using the method for weighted sums of Poisson parameters.¹⁶ The CIs were calculated using the equation:

$$T_L = Y + (V/X)^{1/2}(X_L - X) \text{ and } T_U = Y + (V/X)^{1/2}(X_U - X)$$

where $X = \sum X_i$, $V = \sum \left(\frac{N_i}{n_i}\right)^2 X_i$, and the corresponding confidence limits X_L and X_U were calculated using the chi-square method.¹⁶ The annual incidence of myxedema coma (number per population per year) was calculated by dividing the estimated number of myxedema coma patients (Y) by the population of Japan in 2012.

In-hospital mortality was compared between the groups using chi-square tests. A multivariable logistic regression analysis was performed to evaluate factors associated with in-hospital mortality. In the multivariable regression model, we included clinically important independent variables (age as a continuous variable, sex, and variation of thyroid hormone replacement) regardless of statistical significance, and candidate independent variables possibly associated with in-hospital mortality ($P < 0.10$ in the chi-square tests). When the ratio of the number of non-survivors to the number of candidate independent variables was small, we selected the more clinically important variables to avoid using too many independent variables with an insufficient sample size. In the category of variation of thyroid hormone replacement, we only included patients who received enteral administration of LT4 alone or LT4 combined with LT3.

All tests were two-tailed, and values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using the SPSS statistical package, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Of approximately 19 million inpatient admissions in the DPC database during the study period, we identified 149 patients who were diagnosed with myxedema coma.

Table 1 shows the characteristics of the patients and the in-hospital mortality in each subgroup. About two-thirds of the 149 patients were female. The mean (standard deviation) age was 77 (12) years. The overall in-hospital mortality was 29.5%. Chi-square tests showed significantly higher in-hospital mortality in patients who used steroids and catecholamines, and in those who required mechanical ventilation. No significant associations with in-hospital mortality were observed for sex, age, seasonality, JCS score at admission, thyroid hormone replacement, or durations of LT3 treatment, steroid use, and catecholamine use. Patients who received LT4 combined with LT3 showed relatively low mortality compared with those who received LT4 alone (18.2% [2 of 11 patients] vs. 30.0% [36 of 120] patients), but the difference was not

significant ($P = 0.66$). Of the patients treated with steroids, 79 received hydrocortisone, 23 received prednisolone, 15 received methylprednisolone, three received dexamethasone, and three received betamethasone. Of the patients treated with catecholamines, 39 received dopamine, 18 received noradrenaline, 11 received adrenaline, 10 received dobutamine, and four received isoprenaline. Among the 50 alert patients (JCS score of 0) at admission in our study, 13 required mechanical ventilation, 25 were treated with steroids, and 11 were treated with catecholamines. Regarding the maximal per-day dosage of LT4, the numbers of patients categorized into the <100, 100–199, and ≥ 200 μg groups were 15, 24, and 10, respectively. Similarly, regarding the maximal per-day dosage of LT3, the numbers of patients categorized into the <20, 20–49, and ≥ 50 μg groups were 0, 1, and 2, respectively.

Table 2 shows the comorbidities at admission. Cardiovascular diseases were the most common comorbidity at admission, followed by neuromuscular and psychiatric diseases, diabetes mellitus, pneumonia, chronic renal diseases, and infections. Diabetes

Table 1
Patient characteristics.

	Overall	Non-survivors	P
Total	149 (100)	44 (100)	
Sex			0.27
Male	51 (34.2)	18 (40.9)	
Female	98 (65.8)	26 (59.1)	
Age, years			0.15
≤ 69	32 (21.5)	4 (9.1)	
70–79	48 (32.2)	16 (36.4)	
80–89	49 (32.9)	16 (36.4)	
≥ 90	20 (13.4)	8 (18.2)	
Japan Coma Scale score at admission			0.13
0 (alert)	50 (33.6)	13 (29.5)	
1–3 (drowsy)	31 (20.8)	5 (11.4)	
10–30 (somnolence)	41 (27.5)	15 (34.1)	
100–300 (coma)	27 (18.1)	11 (25.0)	
Season at admission			0.86
Spring	30 (20.1)	7 (15.9)	
Summer	23 (15.4)	7 (15.9)	
Autumn	27 (18.1)	9 (20.5)	
Winter	69 (46.3)	21 (47.7)	
Thyroid hormone replacement			0.66
Enteral LT4 alone	120 (80.5)	36 (81.8)	
Enteral LT4 and LT3	11 (7.4)	2 (4.5)	
Others	18 (12.1)	6 (13.6)	
Maximal dosage per day of LT4, μg			0.51
<100	36 (24.2)	12 (27.3)	
100–199	55 (36.9)	13 (29.5)	
≥ 200	40 (26.8)	13 (29.5)	
Maximal dosage per day of LT3, μg			0.63
<20	4 (2.7)	1 (2.3)	
20–49	4 (2.7)	1 (2.3)	
≥ 50	3 (2.0)	0 (0)	
Duration of LT3, days			0.66
<7	7 (4.7)	1 (2.3)	
≥ 7	4 (2.7)	1 (2.3)	
Use of steroids and catecholamines			<0.001
None	49 (32.9)	7 (15.9)	
Steroids alone	50 (33.6)	13 (29.5)	
Catecholamines with or without steroids	50 (33.6)	24 (54.5)	
Duration of steroids, days			0.079
<7	37 (24.8)	19 (43.2)	
7–13	19 (12.8)	4 (9.1)	
≥ 14	36 (24.2)	13 (29.5)	
Duration of catecholamines, days			0.47
<7	31 (20.8)	17 (38.6)	
7–13	8 (5.4)	3 (6.8)	
≥ 14	11 (7.4)	4 (9.1)	
Mechanical ventilation			0.008
Yes	39 (26.2)	18 (40.9)	
No	110 (73.8)	26 (59.1)	

Data are shown as n (%). All P values are for chi-square tests.

Table 2
Comorbidities at admission.

	Overall	Non-survivors	P
Total	149 (100)	44 (100)	
Cardiovascular diseases	57 (38.3)	16 (36.4)	0.76
Neuromuscular and psychiatric diseases	29 (19.5)	8 (18.2)	0.80
Diabetes mellitus	25 (16.8)	3 (6.8)	0.035
Pneumonia	19 (12.8)	8 (18.2)	0.20
Chronic renal diseases	14 (9.4)	3 (6.8)	0.49
Infections	13 (8.7)	1 (2.3)	0.07
Chronic lung diseases	12 (8.1)	4 (9.1)	0.76
Cerebrovascular diseases	11 (7.4)	3 (6.8)	0.87
Adrenal insufficiency	10 (6.7)	1 (2.3)	0.16
Gastrointestinal and hepatic diseases	9 (6.0)	4 (9.1)	0.31
Trauma	8 (5.4)	1 (2.3)	0.28
Malignancy	6 (4.0)	2 (4.5)	0.84

Data are shown as n (%). All P values are for chi-square tests.

mellitus was associated with in-hospital mortality. There were no patients with newly-diagnosed acute myocardial infarction or lethal arrhythmia after admission. However, four patients were diagnosed with angina pectoris or non-lethal arrhythmia after admission, comprising one with angina pectoris, one with premature ventricular contraction, one with atrial fibrillation, and one with non-sustained ventricular tachycardia. These four patients were not treated with LT3.

Table 3 shows the estimated numbers of patients with myxedema coma in Japan in 2012. The number of all acute-care beds in Japan (*N*) was 898,166, while the number of beds in the DPC hospitals (*n*) was 370,523. The observed number of myxedema coma patients in the DPC hospitals (*X*) was 56. The overall estimated number of myxedema coma patients in 2012 was calculated to be 138 (95% CI, 96–189). Because the population of Japan was approximately 127.5 million in 2012, the annual incidence of myxedema coma was estimated to be 1.08 (95% CI, 0.75–1.48) persons per million Japanese population per year.

Table 4 shows the results of the multivariable logistic regression analysis. We included a maximum of five factors for the multivariable logistic regression analysis because the number of patients who died was only 44. Consequently, we selected three clinically important independent variables (age as a continuous variable, sex, and variation of thyroid hormone replacement regimen) and two independent variables (requirement for mechanical ventilation and use of steroids and catecholamines [none, steroids alone, or catecholamines with or without steroids]) with values of $P < 0.10$ in the chi-square tests. We did not include diabetes mellitus ($P = 0.035$) as a comorbidity at admission in the multivariable logistic regression model because of the small sample size and unknown hemoglobin A1c levels. Higher age and use of catecholamines (with or without steroids) were significantly associated with higher mortality. There was no difference between patients treated with LT4 alone and LT4 combined with LT3.

Table 3
Estimated number of patients with myxedema coma in Japan in 2012.

Bed volume	Number of acute care hospitals in Japan	Number of DPC hospitals	Number of acute care beds in Japan (<i>Ni</i>)	Number of acute care beds in DPC hospitals (<i>ni</i>)	Number of myxedema coma patients in DPC hospitals (<i>Xi</i>)	Estimated number of all myxedema coma patients in Japan (95% CI) (<i>Yi</i>)
<200	5435	285	307,229	35,966	6	51 (19–112)
200–399	1339	383	249,678	112,005	14	31 (17–52)
400–599	475	244	180,279	118,623	24	37 (23–54)
600–799	155	80	87,208	54,075	8	13 (6–25)
≥800	89	50	73,772	49,854	4	6 (2–15)
Total	7493	1042	898,166	370,523	56	138 (96–189)

CI, confidence interval; DPC, Diagnosis Procedure Combination.

Discussion

We analyzed 149 patients with myxedema coma using a nationwide inpatient database in Japan. The overall in-hospital mortality was 29.5%. The estimated incidence of myxedema coma was 1.08 cases per million people per year. In-hospital mortality was significantly associated with higher age and use of catecholamines (with or without steroids).

The distributions of sex, age, and season at admission were similar to those in a previous study.⁷ Our study confirmed the association between older age and higher mortality, which was also shown in previous studies.^{8,17} A distinct advantage of the present study is the large number of patients with myxedema coma ($n = 149$).

There are no globally validated diagnostic criteria for myxedema coma. This is because establishment of criteria for this illness can be challenging owing to its rarity and sudden onset, thus making it unfeasible to conduct a large, prospective, well-controlled study. The diagnosis of myxedema coma is based on the combination of clinical presentation and laboratory testing. Currently, one study from the United States has reported a diagnostic scoring system for myxedema coma that is useful for earlier recognition of the illness.¹⁸ In Japan, the original diagnostic criteria announced by the Japan Thyroid Association through the internet have been widely adopted. Briefly, the criteria include several elements, such as hypothyroidism, central nervous system failure, hypothermia, hypoventilation, circulatory failure, and hyponatremia. In this study, the diagnosis of myxedema coma was taken from the database and an independent diagnostic scoring system or criteria was not applied. In clinical settings in general, the doctors in an emergency room are not necessarily endocrinologists or thyroidologists, and therefore simple methods to recognize this life-threatening condition and start treatment immediately should be established. In the present study, we were unable to confirm (i) the ability of the attending physicians to identify visual clinical signs and symptoms of myxedema coma, (ii) how many of the suspected patients actually had myxedema coma in the final diagnosis, and (iii) how long it took to reach the diagnosis. However, we will investigate these important clinical questions in future research using a different approach.

Approximately one-third of patients with myxedema coma had a JCS score of 0 (alert) at admission. Previous reports indicated that patients with myxedema coma were difficult to recognize in the early phases because they were not necessarily in a coma, and the name myxedema coma itself can be misleading.^{19–21} Therefore, it may be more appropriate to refer to the condition as myxedema crisis, rather than myxedema coma.⁵ Another possible explanation is that the patients with JCS score of 0 at admission developed myxedema coma after admission, because several studies have reported that some medications, such as anesthetics, sedatives, phenytoin, lithium, amiodarone, and sunitinib, can induce

Table 4
Logistic regression for in-hospital mortality.

	Adjusted odds ratio (95% CI)	P
Age	1.04 (1.00–1.08)	0.049
Sex		
Female	Reference	
Male	0.76 (0.32–1.81)	0.54
Thyroid hormone replacement		
Enteral LT4 alone	Reference	
Enteral LT4 and LT3	0.54 (0.10–2.91)	0.47
Mechanical ventilation	2.11 (0.83–5.35)	0.12
Use of steroids and catecholamines		
None	Reference	
Steroids alone	3.48 (0.87–13.9)	0.078
Catecholamines with or without steroids	6.36 (1.54–26.2)	0.01

CI, confidence interval.

myxedema coma.^{1,3,5} Otherwise, prudent doctors may have promptly treated these patients with potential myxedema coma in the early phases to prevent increasing severity and irreversible outcomes. We consider that it is clinically more important to treat patients with potential myxedema coma aggressively based on clinical impressions, rather than to wait until the patients fall into a comatose state or fulfill the diagnostic criteria for myxedema coma.

Cardiovascular diseases were the most frequent comorbidity at admission in patients with myxedema coma. This may have arisen because hypothyroidism can lead to dyslipidemia, atherosclerosis, myocardial fibrosis, and cardiovascular injury, including heart failure.^{22–24}

The issue of whether myxedema coma should be treated with LT4 alone or a combination of LT4 plus LT3 is controversial.^{3–6} Our data showed that most patients were treated with LT4 alone. The number of patients treated with LT3 was small, and the reasons for this low use of LT3 were not recorded by the treating physicians. A previous report indicated that higher doses of LT3 (≥ 75 $\mu\text{g}/\text{day}$) were associated with fatal outcomes.⁸ In our data, the maximal dosage per day of thyroid hormones did not significantly affect the mortality of myxedema coma. However, because of the small sample size and unknown severity of the myxedema coma, our results could not provide recommendations regarding the optimal dosage of thyroid hormone replacement and whether myxedema coma should be treated by administering LT4 alone or both LT4 and LT3.

It has been reported that rapid increases in serum thyroid hormone concentrations in long-standing hypothyroidism are associated with higher risks of inducing myocardial infarction or arrhythmias.^{20,25} However, in our study, no patients with newly-diagnosed acute myocardial infarction or lethal arrhythmia after thyroid hormone replacement were identified. One possible interpretation of our findings is that the gradual increases in plasma T4 and T3 by enteral administration of thyroid hormones resulted in slower cardiovascular responses compared with intravenous administration.²⁶

The incidence of myxedema coma was estimated to be approximately 1.08 cases per million people per year in Japan. This figure was higher than that in a previous European study (0.22 cases per million per year).²

In previous reports, it has been recommended that patients with myxedema coma should be treated with steroids in stress doses prior to administration of thyroid hormone replacement, until the possibility of coexisting adrenal insufficiency has been excluded.^{3–6} In our study, patients treated with steroids, catecholamines, and mechanical ventilation showed significantly higher mortality rates than patients without these treatments. The results indicate that patients with severe conditions were more likely to receive treatments with steroids, catecholamines, and mechanical ventilation.

Additionally, administration of catecholamines and steroids might have aggravated myxedema coma and increased mortality. This possibility is supported by published evidence that dopamine and steroids can provoke iatrogenic hypothyroidism, namely suppression of thyrotropin secretion and concomitant lower plasma T4 and T3 concentrations.^{27–29} Steroids also reduce peripheral conversion of T4 to T3 and are used to treat thyroid storm.³⁰ Moreover, a previous study showed that the adrenal function to secrete cortisol was not appreciably impaired in patients with hypothyroidism.³¹ In the present study, however, we were unable to confirm the cause-and-effect relationship between use of catecholamines, with or without steroids, and higher mortality in myxedema coma patients because of the retrospective cross-sectional study design. Further studies are needed to determine whether or not patients with myxedema coma should be treated with steroids and/or catecholamines.

Our study has several limitations. First, the recorded diagnoses in an administrative claims database are less well-validated than those in well-planned prospective surveys and are limited by their retrospective nature. We could not confirm the severity of each individual myxedema coma episode or whether the patients fulfilled the diagnostic criteria announced by the Japan Thyroid Association, since we lacked information regarding detailed clinical symptoms or laboratory data in the DPC database. Although previous, small case-series studies showed that the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were the main factors associated with myxedema coma mortality, the DPC database does not include these scores.^{2,7} Second, although the database included approximately 19 million acute-care inpatients in Japan, participation in the DPC system was voluntary for each hospital, and patient selection was not based on a random sampling method. Hence, the generalizability of our results may be limited to DPC hospitals. Third, our results were mainly based on enteral administration of thyroid hormones, although intravenous administration of thyroid hormones is an international standard therapy for patients with myxedema coma. Fourth, we could not include all potential risk factors for myxedema coma mortality in the multivariable logistic regression analysis because of the small number of non-survivors.^{32,33} Finally, post-discharge mortality information is not available in the DPC database.

In conclusion, this large, retrospective observational study using a national database in Japan showed that the overall in-hospital mortality of myxedema coma was 29.5%. Higher age and use of catecholamines (with or without steroids) were significant predictors of in-hospital mortality in myxedema coma. To our knowledge, the present study is the first to report the estimated incidence, clinical characteristics, and outcomes of myxedema coma using a large-scale national database. A well-

planned, prospective case registration system that includes detailed clinical course information should be established for future research in this field.

Contribution statement

YO and HY are the guarantors of this work and had full access to all of the data in the study, and take responsibility for the integrity of the data and accuracy of the data analysis.

All authors approved the final version of the manuscript.

Study concept and design: YO, HY, and YT.

Acquisition, analysis, or interpretation of data: YO, SO, HY, HM, and YT.

Drafting of the manuscript: YO, SO, and HY.

Critical revision of the manuscript for important intellectual content: HY and YT.

Statistical analysis: YO, SO, and HY.

Administrative, technical, or material support: HY, HM, KF, and YT.

Study supervision: HY, KF, and YT.

Conflicts of interest

None declared.

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