

Comparative study of the usefulness of risk score assessment in the early stages of COVID-19 affected pregnancies: Omicron variant versus previous variants

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Abstract

Aim: To evaluate the utility of the risk score in assessing the current status and prognosis of COVID-19 in pregnancy.

Methods: Seventy-seven cases affected before the Omicron variant epidemic and 50 pregnant cases affected by the Omicron variant were included. The risk score consists of maternal background, current condition, and examination findings. We determined the risk score in the early stages of disease onset.

Results: There were no significant differences in the maternal or gestational ages between the groups. The risk score was significantly lower in the After-Group patients (those affected during the Omicron epoch), while 14.3% of the Before-Group patients (those affected during the pre-Delta and Delta epochs), experienced a worsening of disease after the visit to the center, whereas none of the After-Group patients did. The Before Group's frequency of risk score items was higher among the two groups for "fever for ≥ 48 h," "mild pneumonia image," and "blood tests," whereas "disease onset 14 days after the second vaccination" was increased in After Group. The blood test parameters for platelet count, C-reactive protein, and D-dimer levels were not significantly different between the groups.

Conclusions: The risk score system appeared superior in detecting deteriorating cases. There were no cases of post-illness deterioration in the After-Group, suggesting that cases of the Omicron variant in pregnancy may have had a less severe course compared to that of previous variants. However, there was no significant difference between the groups in terms of a specific blood test evaluation, suggesting the need for a combined evaluation of cases affected during pregnancy.

Key words: COVID-19, Omicron variant, pregnancy, risk scoring, variant of concern.

Introduction

A new type of highly transmissible coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presented at the end of 2019 and

continues to mutate and spread worldwide.¹ Infection with SARS-CoV-2 may be asymptomatic or associated with an acute respiratory illness called coronavirus disease 2019 (COVID-19), which can range from mild to fatal.² Particularly for pregnant women, evaluation

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of the mother and fetus is required, and due to the lack of consensus on how to deliver or treat the patient during infection, medical practice is unclear. COVID-19 morbidity during pregnancy has been associated with a significant increase in maternal morbidity, mortality, and neonatal complications.³ One of the reasons that make it difficult for health care providers to manage the patients is the fact that the frequency of severe disease varies according to the variant of SARS-CoV-2.

The Delta (B.1.617.2) variant of SARS-CoV-2 was observed to have an increased incidence during pregnancy,⁴ especially in pregnant populations with low vaccine acceptance.⁵ Moreover, there are only a few reports on the Omicron variant; therefore, there is no consensus on the appropriate prognostic evaluation and management methods at this stage. Under these circumstances, there is an urgent need to develop a method to accurately assess the prognosis of affected pregnant women based on their condition at the time of infection. Since May 2021, our group has been evaluating all cases of affected pregnancies using a scoring system that we developed. We report the results and usefulness of this scoring system, as well as the management of affected pregnant women.

Methods

This was a retrospective observational, multicenter study. Pregnant women who lived in Mie prefecture affected by COVID-19 between December 2020 and February 2022 were recruited. A positive nasopharyngeal sample polymerase chain reaction test was used as the definitive diagnosis of the COVID-19 disease. The timing of the assignment of the dominant variant was based on the report by Adhikari et al.⁶ as follows: Pre-Delta epoch: May 17, 2020 to June 26, 2021; Delta epoch: June 27, 2021 to December 11, 2021; Omicron epoch: December 12, 2021 to January 29, 2022. The Before Group refers to those affected during the pre-Delta and Delta epochs, and the After Group refers to those affected during the Omicron epoch.

Assessment items

The risk assessment form was developed independently before the risk and severity of the infections in pregnancy were published, and was created and operational in May 2021. The first COVID-19 complicated pregnancy occurred in December 2020 and was included in this study. By the end of April 2021,

17 cases had occurred and all were hospitalized and managed as inpatients.

Since the number of COVID-19 complicated pregnancies was expected to increase in the future the development of risk assessment criteria was required. Therefore, we developed our own risk assessment method.

The risk-scoring assessment items for the severity of the illness at the time of medical examination is shown in Table 1. The risk assessment items were classified into three sections: maternal background information, condition at the time of illness, and examination findings. Each section was scored separately. Each investigator-in-charge (Shoichi Magawa, Yuka Maegawa, Kazuhiro Osato) independently performed the scoring at the facility where the affected pregnant women were examined, and the results were entered into a shared database on a three-point scoring system. If at least one of the three items was

Table 1 Risk scoring sheet

	Score
Maternal background	
Gestational week	
28–36 weeks	3
≥37 weeks	6
Complications	
Obesity (BMI > 30)	2
Diabetes mellitus	2
Respiratory disease	2
Hypertensions	2
Immunosuppressants	3
Condition of the disease	
Fever for more 48 h	2
SpO ₂	
95 ≤ SpO ₂ < 96	2
SpO ₂ < 95	6
Severely ill	2
No symptoms	–1
Disease onset 14 days after second vaccination	–1
Examination findings	
Pneumonia image	
Mild	3
Severe	6
Laboratory findings	3

Note: This is a scoring sheet for use by COVID-19 positive pregnant women. For a score ≥6 or more, we recommend inpatient management. For pregnancies after 37 weeks, hospitalization is recommended even for score <6. One complications item can be selected. Severe pneumonia was defined as bilateral if the two lobes were involved. Positive blood test findings is defined as D-dimer >5 µg/mL or Plt < 100 000/µL or CRP >5 mg/dL. and Abbreviations: BMI, body mass index; CRP: C-reactive proteins; COVID-19: coronavirus disease 2019; Plt: platelet count; SpO₂, saturation of peripheral oxygen.

present, three points were awarded. However, even if 2 ~ 3 items were fulfilled, the added score would remain as 3. Since our risk assessment provides an aggressive recommendation for hospitalization for cases with a score of 6 or higher, they were evaluated as borderline, based on whether they had a score of 6 or higher.

1. Maternal background information included the following assessment items: (1) gestational age 28 to 36 weeks (three points) or 37 weeks or more (six points); (2) obesity with body mass index (BMI) > 30 (two points); (3) preexisting disease (diabetes: two points; chronic respiratory diseases including bronchial stenosis, bronchial asthma, congenital central hypoventilation syndrome, interstitial lung disease, fibrinous dysfunction syndrome, cystic fibrosis, bronchiectasis, chronic lung disease, bronchiolitis obliterans, congenital diaphragmatic hernia, and congenital cystic lung disease: two points; hypertension: two points); (4) use of steroids or immunosuppressive drugs (three points). Pregnancies complicated by cardiac disease were excluded from this category due to the wide variation in the type and severity of cardiac disease in pregnancies complicated by cardiac disease. Pregnancies complicated by cardiac disease were considered on a case-by-case basis and excluded from this study.
2. Current condition included the following assessment items: (5) fever of 38°C or higher for more than 48 h (two points); (6) blood saturation (SpO₂) at rest (<96%: two points; <95%: six points); (7) severity of illness at the time of consultation (two points); (8) no symptoms (minus one point); (9) disease onset 14 days after second vaccination (minus one point).
3. Examination findings included the following assessment items: (10) computed tomography (CT) pneumonia image (mild: three points; severe: six points); (11) blood tests platelet count (Plt), C-reactive protein (CRP), D-dimer abnormalities (three points). Severe pneumonitis was defined as bilateral if the two lobes were involved.⁷ Positive blood test findings were defined as D-dimer >5 µg/mL or Plt <100 000/µL or CRP >5 mg/dL. Cases with a score of 6 or more in both groups were selected, and the information on the percentages and details of the scores were extracted from the electronic medical records and examined.

Patients with a gestational age of 37 weeks or higher were considered to require hospitalization at an appropriate delivery facility and were given a score of 6. Similarly, a patient with a resting blood oxygen saturation of less than 95% was also considered to require hospitalization and was given a score of 6. There is no clear rationale for the minus one, two, and three points. Patients with underlying medical conditions were given two points for each item because of the possibility of multiple items overlapping. Weeks of gestation, immunodeficiency, chest imaging, and blood test findings are objective indicators that may be directly related to worse prognosis in COVID-19, and they were therefore given three points.

Observation protocol

After the patient was confirmed as having COVID-19, we instructed the patient to visit the designated medical institution within 3 days, at their convenience. At the medical institution, blood tests (including Plt, CRP, and D-dimer), a chest CT scan, and SpO₂ were evaluated, and the interviews necessary for a risk assessment were conducted. In principle, inpatient management is recommended, but inpatient care is especially recommended for patients with a risk score ≥6 or gestational age ≥37 weeks. The treatment strategy for mild to moderate COVID-19 at each facility was different. The management policy after hospitalization was as follows:

1. Oxygen administration will be started for patients with SpO₂ < 95.
2. Vital signs, including maternal temperature, SpO₂, and blood pressure, should be measured at least three times a day.
3. Acetaminophen for antipyretic purposes should not be used in routine care.

In addition to the above, anticoagulants, antivirals, and steroids were administered at some facilities.

Patients who did not require inpatient care were managed at home with daily online consultations, performed by an obstetrician certified by the Japanese Society of Obstetrics and Gynecology and qualified to provide online medical care. During home care, the SpO₂ levels and the body temperature were required to be checked, and the subjective symptoms were confirmed by interview. If there was any evidence of worsening pneumonia, such as worsening severity or

respiratory distress, the patient was referred for further medical examination and imaging studies.

The severity of COVID-19 was assessed based on the National Institutes of Health classification.⁸ The method of delivery at the time of illness was not standardized, with vaginal delivery and cesarean section chosen according to the protocols of infection control department of each institution.

Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Mie University Hospital (No.H2021-224). The opt-out proxy method of consent was used for participation in this study.

Statistical evaluation

For the risk score items, the frequency in each group was shown as a percentage. Each item was evaluated using the chi-square test. The Mann–Whitney *U* test was used to compare the maternal background factors, risk scores, and blood test items between the groups. The cases with scores of 6 or more in both

groups were analyzed and evaluated in the same way. Statistical significance was set at $p < 0.05$. SPSS (version 25; IBM Corporation, Armonk, NY) was used for the analysis.

Results

The Before Group consisted of 77 patients and the After Group consisted of 50 patients. Of the 77 patients in the Before Group, 22 were from the pre-Delta epoch and 55 from the Delta epoch.

The maternal background information of the Before Group versus After Group was described, and values given as the means \pm SDs. In the Before Group versus After Group comparison the mean age was 29.10 ± 6.07 versus 27.53 ± 5.53 ($p = 0.198$) years, gestational week 26.09 ± 8.49 versus 25.64 ± 8.83 ($p = 0.841$) weeks, and risk score 4.70 ± 3.67 versus 1.80 ± 2.31 ($p < 0.001$). The number of cases and frequency of occurrence of each item included in the risk score are shown in Table 2. One case with a score that indicated that the patient was severely ill, was not vaccinated.

Table 2 The number of cases and frequency of occurrence of each item included in the risk score

	Before group ($n = 77$)		After group ($n = 50$)		<i>p</i>
	Cases	%	Cases	%	
Maternal background					
Gestational week					
<28 weeks	39	50.6	26	52.0	1.000
28–36 weeks	30	39.0	18	36.0	0.852
≥ 37 weeks	8	10.4	6	12.0	0.779
Complications					
Obesity (BMI > 30)	6	7.8	5	10.0	0.751
Diabetes mellitus	2	2.6	0	2.0	0.519
Respiratory disease	1	1.3	1	2.0	1.000
Hypertensions	1	1.3	2	4.0	0.561
Immunosuppressants	0	0	0	0	
Condition of the disease					
Fever for more 48 h	10	13.0	1	2.0	0.049
SpO ₂					
$95 \leq \text{SpO}_2 < 96$	4	5.2	0	0	0.153
SpO ₂ < 95	1	1.3	0	0	1.000
Severely ill	1	1.3	0	0	1.000
No symptoms	0	0	0	0	
Disease onset 14 days after second vaccination	0	0	11	22.0	<0.001
Examination findings					
Pneumonia image					
Mild	34	44.2	2	4.0	<0.001
Severe	2	2.6	0	0	0.519
Blood tests	19	24.7	2	4.0	0.003

Abbreviations: BMI, body mass index; SpO₂, saturation of peripheral oxygen.

The severity of COVID-19 was as follows: Before Group (mild, 71 cases [92.2%]; moderate, 6 cases [7.8%]; and severe, 0 cases [0%]), After Group (mild, 50 cases [100%]; moderate, 0 cases [0%]; severe, 0 cases [0%]). The percentage of patients whose severity worsened after the visit was 11 (14.3%) in the Before Group and 0 (0%) in the After Group. All worsening cases were in the Before Group and worsened from mild to moderate disease.

Thirty-two cases (41.6%) and five cases (10%) in the Before and After Groups had a score ≥ 6 . In contrast, all the patients with a score ≥ 6 in the After Group had a gestational age ≥ 37 weeks.

The distribution of scores in cases with six or more points in each group is shown in Table 3. All the cases who experienced worsening of COVID-19 after the visit had a score ≥ 6 and belonged to the Before Group.

Blood test findings

There was a significant difference in the percentage of positive blood test risk score items between the groups ($p = 0.003$). At the time of the visit, mean Plt (μL) in the Before Group versus After Group was

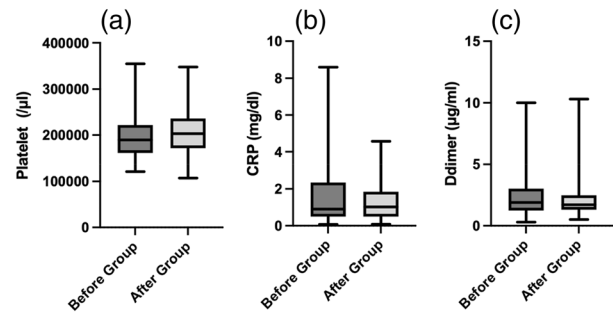


Figure 1 Details of blood tests at the time of visit. The Before Group refers to those who were affected in the pre-Delta and Delta epochs, and the After Group refers to those who were affected in the Omicron epoch. There were no significant differences in the platelet count, C-reactive protein (CRP), and D-dimer levels between the groups.

198 829 \pm 49 800 versus 208 366 \pm 46 856 ($p = 0.424$); CRP levels (mg/dL), 1.62 \pm 1.73 versus 1.33 \pm 1.12 ($p = 0.876$), and D-dimer levels ($\mu\text{g/mL}$), 2.55 \pm 2.10 versus 2.16 \pm 1.77 ($p = 0.427$). There were no significant differences between the two groups (Figure 1).

Table 3 The distribution of scores in cases with 6 or more points in each group

	Before group (N = 32)		After group (N = 5)		p
	Cases	%	Cases	%	
Maternal background					
Gestational week					
<28 weeks	7	21.9	0	0	0.042
28–36 weeks	17	53.1	0	0	<0.001
≥ 37 weeks	8	35.0	5	100	1
Complications					
Obesity (BMI > 30)	2	6.3	0	0	0.519
Diabetes mellitus	0	0	0	0	0.519
Respiratory disease	0	0	0	0	
Hypertensions	0	0	0	0	
Immunosuppressants	0	0	0	0	
Condition of the disease					
Fever for more 48 h	7	21.9	0	0	0.042
SpO ₂					
95 \leq SpO ₂ < 96	2	6.3	0	0	0.519
SpO ₂ < 95	1	3.1	0	0	1
Severely ill	0	0	0	0	1
No symptoms	0	0	0	0	
Disease onset 14 days after second vaccination	0	0	0	0	
Examination findings					
Pneumonia image					
Mild	18	56.3	0	0	<0.001
Severe	2	6.3	0	0	0.519
Blood tests	15	46.9	1	20.0	0.005

Abbreviations: BMI, body mass index; SpO₂, saturation of peripheral oxygen.

Discussion

The key findings of this study were as follows: (1) The After Group had a lower risk score at the time of diagnosis compared to the Before Group, suggesting that the early phase of the disease may be less severe. (2) In the risk score items, the severity of chest imaging and laboratory findings was lower in the After Group compared to the Before Group. However, there were no significant differences between the groups in terms of individual factors, such as the laboratory findings, suggesting that a combined assessment such as a risk score is necessary to evaluate the severity of disease in pregnant patients.

The Omicron variant was designated a variant of concern (VOC) in November 2021 because of its different characteristics from that of the Delta variant. The Omicron variant was the most highly mutated VOC to date and was feared to have an increased infectivity and a partial resistance to immunity to the COVID-19 vaccine.⁹ The Omicron variant has been reported to have a higher infection rate than previous variants because of the spike sequence that affects infectivity.¹⁰ Regarding the severity of the disease, the Omicron variant is considered to be a milder variant compared to other VOCs¹¹; however, more data are needed to confirm the severity of the disease caused by the Omicron variant of SARS-CoV-2.¹²

Considering that 77 cases of the Before Group were recruited in this study in an observation period of about 1 year, while 50 cases were recruited in the After Group in about 1 month, the infectivity of the Omicron variant was clearly indicated.

The risk score assessment used in this study was created at the stage when the epidemic of the new coronavirus began to spread in Japan. Moreover, it was already created before the actual risk factors of COVID-19 patients and the severity of the disease in pregnant women were reported.

The items are divided into three sections to provide background information on the patient, acute-phase disease status, and objective assessment for each case. COVID-19 is a respiratory infection, and obesity and gestational age, which are associated with hypoventilation, may cause worsening of the respiratory disease, as along with various other background factors that may exacerbate respiratory disease or reduce immunity. The focus is a simple, objective assessment of acute disease status. With regards to BMI, obesity has been known to be a risk for severe COVID-19. Additionally, we set the criteria for BMI at 30, considering

the fact that the patient was pregnant. It has been reported that a BMI of >30 has been associated with an increased risk of severe disease.¹³ With regards to age, at the time of development of the risk item, it was assumed that the elderly had an increased risk of serious illness. Recent reports did not indicate an increased risk of mortality in the gestational age of 50 or younger.¹⁴

CT scans and blood tests are used to evaluate chest imaging. A CT is superior to Xp in detecting pneumonia, as well as in detecting early pneumonia in patients with COVID-19. In this study, there was an increased incidence of pneumonia images in the Before Group compared to the After Group in the early stages of disease onset. A CT scan of the chest is important in the diagnosis of COVID-19 in non-pregnant patients, and Huang et al. reported that its diagnostic sensitivity was high or higher and comparable to the polymerase chain reaction (PCR) test, as it enabled detection even in patients who were negative in a reverse-transcription PCR analysis.¹⁵ In addition to this, since the imaging findings also showed the progression of symptoms, they have been used to determine progress and treatment efficacy.¹⁶ The timing of when the cases recruited in this study underwent chest CT is estimated to have been during the early onset period of the disease, which suggested that the chest CT scan was abnormal at a stage before the blood test findings worsened.

The vaccination status may also affect the proportion of cases with an abnormal chest CT. Vaccination has been reported to reduce the incidence of COVID-19 pneumonia.¹⁷ This study also showed fewer cases of pneumonia images in the After Group, but this may have been due to the higher frequency of vaccinations in this group.

Among the blood tests that could be performed at any institution at any time, we focused on the evaluation of inflammation and coagulability. Pregnancy is a hypercoagulable state and further evaluation of hypercoagulability in this setting may allow for evaluation of maternal thrombosis and microthrombus formation in the placenta. In addition to this, viral infections often cause thrombocytopenia¹⁸ and platelets were used as an endpoint to evaluate this and Disseminated Intravascular Coagulation.

On the other hand, there have been reports on the use of immunosuppressive medications, in which it has been reported that being on immunosuppressive medications or being immunosuppressed does not necessarily lead to a worse prognosis in COVID-19.¹⁹⁻²¹

Although such cases were not recruited in the present study, it is necessary to consider their management policy in the future.

Moreover, even though the frequency of the laboratory findings in the risk scores was higher in the Before Group, there were no significant differences in the individual items assessed. Consistent with our original idea, Plt, CRP, and D-dimer levels have been reported to be associated with the prognosis.^{22–24} However, these reports were based on nonpregnant patients and did not mention an obvious cut-off value. In this study, significant differences were found between the two groups for blood test scores, but no significant differences were found for the individual parameters (CRP, D-dimer, and Plt).

Although the risk score provides details of the positive cases for blood test items, two points must be taken into account when considering the cause of this difference: (1) there were no cases with positive platelet items, and (2) there were no cases that met both the positive inflammatory reaction and positive anticoagulation criteria.

Furthermore, the lack of a drop in platelet counts may be attributed to the low frequency of thrombocytopenia associated with COVID-19 infection and the absence of intense inflammation early in the course of COVID-19 disease that would have resulted in DIC.

In reports of nonpregnant cases with COVID-19, thrombocytopenia correlated with the disease severity.²⁵ A retrospective study in China reported thrombocytopenia (<150 000/L) in about 36.2% of patients.²⁶ In our study, we defined thrombocytopenia at 100 000/L or less and found no severe cases. These considerations suggested that our threshold for thrombocytopenia may have been too high.

With regard to the D-dimer levels, in addition to the above reasons, the effect of the number of weeks of gestation should be considered. In this study, we identified 11 cases with positive D-dimer items with the mean number of weeks of gestation being 34.81 weeks. This was above the overall average number of weeks. Previous reports have shown that D-dimer increases during pregnancy as the pregnancy approaches the delivery date.²⁷ In other words, it is possible that many cases have D-dimer values above the threshold due to a mildly elevated inflammatory response associated with COVID-19 disease, plus the factor of the number of gestational weeks.

With respect to an elevated CRP, factors due to the timing of the blood test must also be considered. It is also known that serum inflammatory response markers take some time to peak in response to acute

inflammation.²⁸ The lack of significant differences between groups for blood tests in this study may be also due to the timing of blood tests in this study.

The incidence of pneumonia was higher in the Before Group than in the After Group. COVID-19-associated pneumonia was found to be better detected by CT than by chest radiography,^{29,30} and the use of a CT may have allowed for more sensitive detection and appropriate evaluation.

The results for the worsening cases were significant, as all patients who deteriorated from mild to moderate were in the Before Group and had a risk score of six or higher. This suggested that our scoring system was effective in predicting cases that could progress in severity. At the same time, it raised the issue that conventional assessment methods may be inadequate to evaluate subtle disease progression in pregnant patients. The severity of COVID-19 is assessed primarily using SpO₂ levels and clinical symptoms, with chest imaging studies performed as needed. This method did not specify the timing or the items to be evaluated, and did not take into account factors such as the effects of pregnancy-related decreased ventilation or sleep apnea. In addition, taste symptoms and fatigue were difficult to evaluate objectively or to detect worsening of symptoms.

In the Before group with a risk score of 6 or higher, the following items (28–36 weeks' gestation, fever for more than 48 h, pneumonia image, and blood test) showed an increase from the overall rate.

This suggested that these factors may be involved in the increase in scores and thus in the deterioration of prognosis. It was also suggested that it is important to evaluate COVID-19 during pregnancy from multiple perspectives, comprehensively.

The limitation of this study was the lack of agreement in the treatment methods. This may be because the medications used in different facilities differed. Moreover, the time between the onset of the first symptom and the medical examination was unknown. In addition to objective symptoms such as fever, there are many other symptoms such as abnormality of taste and malaise for which the timing of onset is not clear. Regarding selective bias, when a patient was found to be infected during pregnancy, the prefecture or her family physician notified the physician in charge at Mie University Hospital. The physician in charge of the case then contacted the hospital near the patient's place of residence and ordered an examination and medical interview. Specifically, patients in this study did not voluntarily choose to see a doctor or select a hospital, therefore, we

do not believe that there was any bias in the patient population. However, this system was applicable only to the Mie Prefecture, and there was a bias with regard to the place of residence of the affected patients.

In this study, we assessed the severity of disease using a unique risk score for pregnant women affected by Omicron and earlier strains of SARS-CoV-2. The results showed that the risk score was higher in the group of pregnant women affected by the pre-Omicron variants than in the group of pregnant women affected by the Omicron variant, including those who had worsened since the visit.

The pneumonia image at the time of examination, blood test findings, and vaccination were thought to be strongly related to this result. Birol et al. reported that vaccination during the period of predominance of the Omicron variant resulted in milder symptoms after the onset of COVID-19 and less need for oxygen administration and intensive care than during the period predominance of the other variants.³¹ Vaccination has been reported to have different effects depending not only on the corresponding VOCs, but also on the type of vaccine administered, the frequency, and the time of the previous vaccination.³²

Author contributions

Shoichi Magawa: conceptualization, data curation, formal analysis, investigation, writing – original draft. Masafumi Nii: supervision, writing – review & editing. Shintaro Maki: data curation, supervision. Naosuke Enomoto: data curation, supervision, formal analysis. Sho Takakura: data curation, supervision, resources. Naoko Kusaka: data curation. Yuka Maegawa: data curation, supervision, visualization. Kazuhiro Osato: data curation, supervision, methodology. Hiroaki Tanaka: funding acquisition. Eiji Kondo: supervision. Tomoaki Ikeda: writing – review & editing, project administration, supervision.

Conflict of interest

No interest to disclose.

Data availability statement

Data available on request due to privacy/ethical restrictions. The data that support the findings of this

study are available on request. The data are not publicly available due to privacy or ethical restrictions.

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