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Preliminary study regarding the predicted body weight-based dexamethasone therapy in patients with COVID-19 pneumonia

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ABSTRACT

Background: The RECOVERY clinical trial reported that 6 mg of dexamethasone once daily for up to 10 days reduces the 28-day mortality in patients with coronavirus disease 2019 (COVID-19) receiving respiratory support. In our clinical setting, a fixed dose of dexamethasone has prompted the question of whether inflammatory modulation effects sufficiently reduce lung injury. Therefore, preliminary verification on the possibility of predicted body weight (PBW)-based dexamethasone therapy was conducted in patients with COVID-19 pneumonia.
Methods: This single-center retrospective study was conducted in a Japanese University Hospital to compare the treatment strategies/management in different periods. Consecutive patients (n = 90) with COVID-19 pneumonia requiring oxygen therapy and were treated with dexamethasone between June 2020 and May 2021 were analyzed. Initially, 60 patients administered a fixed dexamethasone dose of 6.6 mg/day were defined as the conventional group, and then, 30 patients were changed to PBW-based therapy. The 30-day discharged alive rate and duration of oxygen therapy were analyzed using the Kaplan–Meier method and compared using the log-rank test. The multivariable Cox regression was used to evaluate the effects of PBW-based dexamethasone therapy on high-flow nasal cannula (HFNC), noninvasive ventilation (NIV), or mechanical ventilation (MV).
Results: In the PBW-based group, 9, 13, and 8 patients were administered 6.6, 9.9, and 13.2 mg/day of dexamethasone, respectively. Additional respiratory support including HFNC, NIV, or MV was significantly less frequently used in the PBW-based group (P = 0.0046), with significantly greater cumulative incidence of being discharged alive and shorter oxygen demand within 30 days (92 vs. 89%, log-rank P = 0.0094, 90 vs. 92%, log-rank P = 0.0002, respectively). Patients treated with PBW-based therapy significantly decreased the use of additional respiratory support after adjusting for baseline imbalances (adjusted odds ratio, 0.224; 95% confidence interval, 0.062–0.813, P = 0.023). Infection occurred in 13 (21%) and 2 (7%) patients in the conventional and PBW-based groups, respectively (P = 0.082).
Conclusions: In patients with COVID-19 pneumonia requiring oxygen therapy, PBW-based dexamethasone therapy may potentially shorten the length of hospital stay and duration of oxygen therapy and risk of using HFNC, NPPV, or MV without increasing serious adverse events or 30-day mortality.

1. Introduction

Coronavirus disease 2019 (COVID-19), a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still continuously spreading worldwide since December 2019, and a large number of patients have been infected and died due to COVID-19 [1,2]. In 2020, a major randomized clinical trial conducted by the RECOVERY Collaborative Group in the United Kingdom (comprising a total of 2104 and 4321 patients assigned to receive dexamethasone and usual care, respectively) revealed that dexamethasone 6 mg/day for up to 10 days (or until hospital discharge) reduced the mortality in patients with COVID-19 who receive oxygen therapy or invasive mechanical ventilation [3]. Therefore, most countries and facilities have followed the

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List of abbreviations

AGMP	aerosol-generating medical procedures
ARDS	acute respiratory distress syndrome
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
DM	diabetes mellitus
HFNC	high-flow nasal cannula
MV	mechanical ventilation
NIV	noninvasive ventilation
PBW	predicted body weight
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

procedure using dexamethasone, especially for patients with COVID-19 who require oxygen therapy. However, the appropriate dose of dexamethasone or corticosteroid for each patient with COVID-19 (e.g., sex, race, physique, and body mass index (BMI)) remains unclear to date. Although the effectiveness of a higher dexamethasone dose in patients with acute respiratory distress syndrome (ARDS) due to COVID-19 remains controversial, a higher dexamethasone dose might prevent an immune response characterized by a cytokine storm and has been one of the major therapeutic options [4–7].

Predicted body weight (PBW) proposed by the ARDS network is often used to calculate tidal volume in mechanical ventilation (MV) and determine corticosteroid dose in treating patients with ARDS [8,9]. Its formula consists of height and sex and reflects normal lung volume; therefore, being overweight or underweight cannot affect its results [10,11]. Because individuals with obesity were reported to be more at risk for COVID-19 pneumonia and higher hospitalization, intensive care unit admission, and mortality rates, obese patients have more opportunities to be treated by dexamethasone [12]. When considering the dexamethasone dosage to treat COVID-19 pneumonia, the therapeutic dose based on the actual bodyweight may be higher for obese patients, since this dosage could be susceptible to infection or hyperglycemia. In contrast, the dexamethasone dosage would not sufficiently prevent hyperinflammation in underweight patients. PBW-based dexamethasone therapy, which is not dependent on the actual body weight but height and sex, has beneficial potential for COVID-19 therapy.

Herein, a retrospective cohort study was conducted to investigate the efficacy and safety of PBW-based dexamethasone therapy in patients with COVID-19 pneumonia who needed oxygen therapy through comparison with the conventional group.

2. Material and methods

2.1. Ethical approval

All study procedures involving human participants were approved by the Human Ethics Committee of the International University of Health and Welfare (no. 20-Nr-101). This study was designed and conducted following the ethical principles of the 1964 Helsinki Declaration and subsequent amendments. The requirement for informed consent was waived by the ethics committee because this retrospective analysis was limited to the preexisting data collected as the standard of care by respiratory physicians. Data anonymization was followed, and privacy issues were protected.

2.2. Study design and definition

This single-center retrospective study that compares treatment strategy/management in certain different periods included consecutive patients with COVID-19 pneumonia who needed oxygen therapy and were treated with dexamethasone between June 2020 and May 2021 at the International University of Health and Welfare Narita Hospital in Japan. COVID-19 was diagnosed through the detection of SARS-CoV-2 by polymerase chain reaction from a nasopharyngeal swab specimen, and pneumonia was defined as having pulmonary infiltrate on chest computed tomography.

2.3. Administration dose of dexamethasone

Dexamethasone was administered to patients with COVID-19 pneumonia with peripheral capillary oxygen saturation (SpO_2) of $\leq$93% at room temperature at sea level or who needed oxygen therapy. Its administration had been approved before the study by the Ministry of Health, Labour, and Welfare in Japan. Injectable dexamethasone including 4.4 mg as dexamethasone sodium phosphate was also approved at 3.3 mg/vial through the Japanese pharmaceutical regulation. Multiple dexamethasone vials were administered due to clinical implications offered by The Japanese Association of Infectious Diseases, and dosage modification for obese or overweight patients with COVID-19 was also an optional therapy offered by the 2020 Health and Labour Policy Promotion Survey Emerging and Re-emerging Infectious Diseases and Vaccination Policy Promotion Research Project [13,14]. Between June 2020 and March 2021, 6.6 mg/day of dexamethasone was administered to patients with COVID-19 in the conventional dose group. Between April and May 2021, the therapeutic protocol was modified by the pulmonary department, and the dose was changed based on PBW [15]. For clinical implication, the PBW-based dose group was divided into four: males with $\geq$170 cm height (>66 kg at PBW) were administered 13.2 mg/day dexamethasone; males with <170 cm height were administered 9.9 mg/day; females with $\geq$150 cm height were administered 9.9 mg/day; and female with <150 cm height (<43 kg at PBW) were administered 6.6 mg/day. Dexamethasone was intravenously administered once daily for up to 10 days or until hospital discharge in both groups.

2.4. Administration of other drugs

Remdesivir was also administered to patients with COVID-19 pneumonia with SpO_2 of $\leq$93% at room temperature at sea level or who needed oxygen therapy. The study was conducted after the approval of the Ministry of Health, Labour and Welfare in Japan. Off-label use of tocilizumab was approved by the Human Ethics Committee of International University of Health and Welfare Narita Hospital, and written informed consent was obtained. Tocilizumab was also used in some patients (shown in Table 1). During the study period (from April 23), baricitinib was approved for COVID-19 pneumonia by the Ministry of Health, Labour, and Welfare in Japan. Patients treated with baricitinib were not included in this study population.

2.5. Data collection

The following information was collected from medical records: age, sex, BMI, comorbidities, laboratory data on the day of starting dexamethasone or latest data before the initiation, previous treatment, the dose and timing of dexamethasone therapy, and clinical outcomes. The clinical outcome included the following adverse events: hyperglycemia or infection, re-administration of corticosteroids, need for additional respiratory support including high-flow nasal cannula therapy (HFNC), noninvasive ventilation (NIV) and mechanical ventilation (MV), 30-day mortality, length of hospital stay, and duration of oxygen therapy.

2.5. Statistical analysis

Data are expressed as median and interquartile ranges. Baseline characteristics were analyzed using Fisher's exact test or Mann–Whitney *U* test. The analysis included a Cox regression to test significant effects

Table 1
Characteristics and outcomes of patients with conventional and PBW-based dexamethasone doses.

	Conventional dose (n = 60)	PBW-based dose (n = 30)	P-value
Baseline characteristics			
Age (years)	66 (54–76)	62 (50–72)	0.16
Male, no (%)	51 (85)	19 (63)	0.03
Body mass index (kg/m^2)	26 (23–28)	25 (23–27)	0.62
Comorbidity, no (%)	50 (83)	24 (80)	0.77
Diabetes mellitus, no (%)	16 (27)	10 (33)	0.62
OHA, no (%)	10 (17)	7 (23)	0.57
Insulin therapy, no (%)	0 (0)	3 (10)	0.035
HTN, HL, or HU, no (%)	31 (52)	10 (33)	0.12
Laboratory data on the day of starting Dex			
Lymphocyte count (/μL)	792 (672–1010)	791 (522–1081)	0.84
C-reactive protein (mg/dL)	10 (6.8–15)	8.6 (5.5–13)	0.20
HbA1c (%)	6.4 (6.1–7.1)	6.5 (6.0–7.3)	0.80
Ferritin (ng/mL)	805 (511–1079)	720 (470–906)	0.18
D dimer (μg/mL)	0.95 (0.70–1.47)	0.83 (0.63–1.39)	0.29
SpO_2/FiO_2 ratio	321 (236–350)	336 (317–343)	0.28
Treatments			
Any pretreatment, no (%)	16 (27)	9 (30)	0.80
Dose of Dex, 6.6, 9.9, and 13.2 (mg), no	60/0/0	9/13/8	
Dex administration period (days)	9 (5–10)	10 (5–10)	0.73
Days to start Dex from onset (days)	8 (5–9)	7 (5–9)	0.55
Days to start Dex from admission (days)	0 (0–2)	0 (0–2)	0.71
Remdesivir, no (%)	46 (77)	24 (80)	0.79
Tocilizumab, no (%)	7 (12)	1 (3)	0.26
Outcome			
Additional OHA, no (%)	7 (12)	3 (10)	1.00
Additional insulin therapy, no (%)	23 (40)	13 (45)	0.65
Adverse events related to Dex, no (%)	13 (21)	2 (7)	0.082
Re-administration of corticosteroids, no (%)	3 (4)	5 (17)	0.11
HFNC, NIV, or MV, no (%)	26 (43)	4 (13)	0.0046
30-Day mortality, no (%)	6 (10)	3 (10)	1.00
Length of hospital stay (days)	14 (11–22)	11 (10–14)	0.023
Length of oxygen therapy (days)	11 (7–16)	6 (4–8)	<0.0001

Dex; dexamethasone, HbA1c; hemoglobin A1c, HFNC; high-flow nasal cannula oxygen therapy, HT; hypertension, HL; hyperlipidemia, HU; hyperuricemia, MV; mechanical ventilation, NIV; noninvasive ventilation, OHA; oral hypoglycemic agent, PBW; predicted body weight.
Data are presented as the median and interquartile ranges for continuous variables and as no. (%) for categorical variables. P-values were calculated using Fisher's exact test or Mann–Whitney *U* test.

on the hazard of using HFNC, NIV, or MV. This approach was selected to adjust for baseline imbalances in variables, such as sex, age, BMI, and diabetes mellitus (DM), based on previous reports [16–18]. Cumulative incidence of discharged alive rate and oxygen-free rate within 30 days were analyzed using the Kaplan–Meier method and compared by the log-rank test. Two-tailed P-values of <0.05 were considered significant. All analyses were performed using the JMP pro 13.2.0 (SAS Institute Inc. Cary, NC, USA).

3. Results

During the study period, 96 hospitalized patients who needed oxygen therapy due to COVID-19 pneumonia were administered dexamethasone. Three patients treated with oral dexamethasone in each group were excluded, and 90 patients administered intravenous dexamethasone were analyzed. Of these, 60 patients were administered dexamethasone at a fixed dose of 6.6 mg in the conventional-dose group, and 30 patients were at a dose defined based on PBW (Fig. 1).

Baseline characteristics of patients are shown in Table 1. The number of male patients in the PBW-based dose group was significantly smaller than those in the conventional-dose group (85 vs. 63%, P = 0.03). Three patients in PBW-based group were administered insulin therapy (10 vs. 0%, P = 0.035). Twenty-three patients (40%) needed additional insulin therapy in the conventional-dose group and 13 (45%) in the PBW-based dose group (P = 0.65). Diabetic ketoacidosis or hyperosmolar hyperglycemic state was not reported in both groups; however, infection occurred in 13 (21%) patients, namely, bacterial pneumonia (n = 11), urinary tract infection (n = 1), and catheter-related bloodstream infection (n = 1), in the conventional group and 2 patients (7%) had pneumonia (n = 1) and soft-tissue infection (n = 1) in PBW-based group (P = 0.082).

In the PBW-based dose group, 9, 13, and 8 patients were administered 6.6, 9.9, and 13.2 mg/day of dexamethasone, respectively. Remdesivir was not administered due to its short supply in 20 patients. Twenty-five patients (28%) were included in several clinical trials as pretreatment (e.g., favipiravir); however, these trials were terminated due to worsened respiratory condition, and dexamethasone therapy was initiated for meeting the criteria.

The use of additional respiratory support including HFNC, NIV, or MV was significantly less frequently in the PBW-based group (P = 0.0046). The length of hospital stay and duration of oxygen therapy were significantly shorter in the PBW-based group (14 vs. 11 days, P = 0.023, 11 vs. 6 days, P < 0.0001, respectively).

The PBW-based dose group had significantly greater cumulative incidence of being discharged alive from the hospital and shorter oxygen demand within 30 days (92 vs. 89%, log-rank P = 0.0094, 90 vs. 92%, log-rank P = 0.0002, respectively) (Figs. 2 and 3).

Patients treated with PBW-based dexamethasone therapy significantly reduced the use of additional respiratory support after adjusting baseline imbalances (adjusted odds ratio, 0.224; 95% confidence interval [CI], 0.062–0.813, P = 0.023) (Table 2). BMI and male sex were significantly associated with its increased use (adjusted odds ratio, 1.325; 95% CI, 1.086–1.616, P = 0.0024, adjusted odds ratio, 8.447; 95% CI, 1.248–57.172, P = 0.029, respectively) (Table 2).

4. Discussion

In this historical cohort study for patients with COVID-19 pneumonia who needed oxygen therapy, the PBW-based dexamethasone dose group had significantly lesser use of additional respiratory support and shorter hospital stay and oxygen demand without increasing the mortality or adverse events compared to the conventional dose group. To our knowledge, the utility and safety of dexamethasone therapy with dosing according to PBW in patients with COVID-19 pneumonia have not been investigated.

The efficacy of corticosteroid therapy at the dose using mg/kg based on the actual bodyweight was controversial [19]. Indeed, obesity and DM often recognized in overweight patients are the risks of severe COVID-19 according to previous reports, and hyperglycemia and infection are the major concerns related to the administration of corticosteroids [16,17,20]. Indeed, not only cytokine storm but also multiple mechanisms including respiratory dysfunction, pro-thrombotic environment, blocked autophagy, and fat deposition due to obesity are contributing to the poor prognosis of obese patients with COVID-19 [12,21]. From these points of view, corticosteroid dosages estimated based on the actual bodyweight might be higher for patients with higher BMI and leads to poor outcomes.

Although the pharmacokinetics of dexamethasone in patients with COVID-19 is unclear or corticosteroid therapy for other viruses such as severe acute respiratory syndrome and Middle East respiratory syndrome was controversial, our study revealed that the maximum dose escalation of dexamethasone to 13.2 mg/day according to PBW might

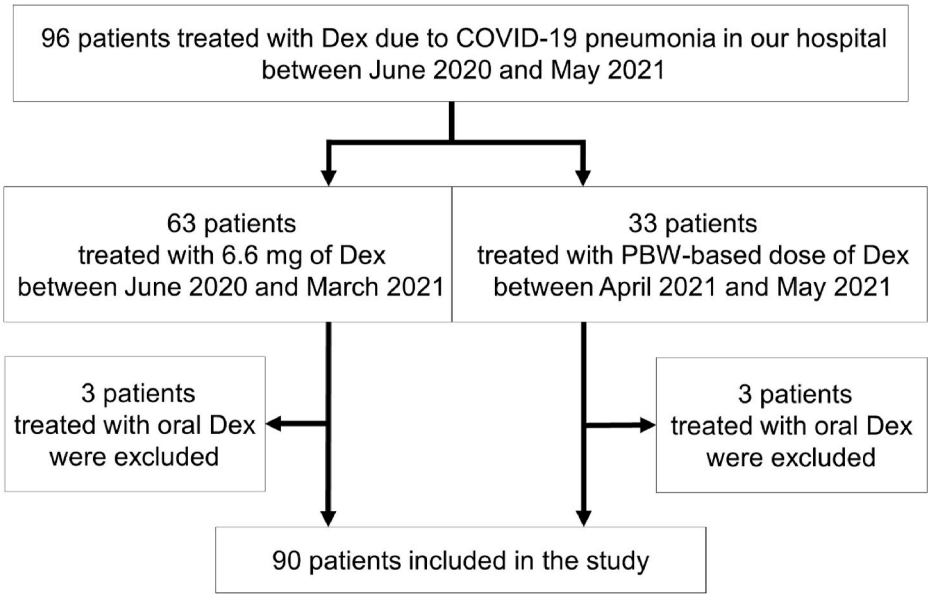

Fig. 1. Study flow chart.
Of the 96 patients treated with dexamethasone during the study period, we excluded 3 from each group, leaving a final sample size of 90. Sixty patients were treated with 6.6 mg/day of dexamethasone, and 30 patients had the predicted body weight based on its dose.
Dex; dexamethasone, PBW; predicted body weight.

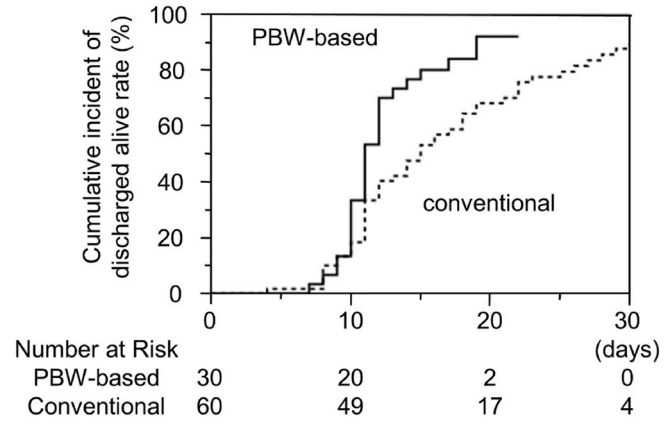

Fig. 2. Cumulative incidence of discharged alive rate between the PBW-based dexamethasone and conventional groups
P = 0.0094
P-values were calculated using the log-rank test.
PBW; predicted body weight

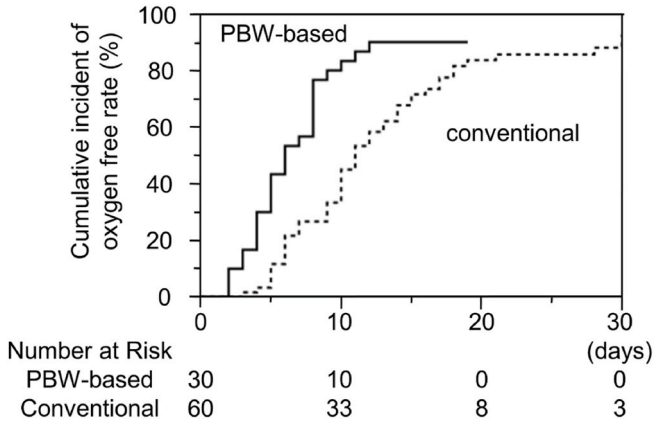

Fig. 3. Cumulative incidence of oxygen-free rate between the PBW-based dexamethasone and conventional groups
P = 0.0002
P-values were calculated using the log-rank test.
PBW; predicted body weight

have beneficial therapeutic potential in patients with COVID-19 pneumonia [22].

The present study revealed that PBW-based dose dexamethasone was associated with less frequent use of additional respiratory support and shorter length of hospital stay and oxygen demand. The course of COVID-19 has been divided into three phases, which are early infection, pulmonary phase, and hyperinflammation phase, including ARDS. Hypoxemia requiring oxygen therapy in the pulmonary phase is a result of host hyperinflammatory response after viral response phase in the early infection [23]. Indeed, glucocorticoid agents are well known to be useful in stopping the inflammatory storm, which is contributed to the excessive activation of immune cells in response to viral infection, if used at the appropriate time during the disease course [24,25]. Therefore, we believe that sufficient but not excessive amount of dexamethasone should be administered in the hypoxic stage demanding oxygen therapy to properly control the initial host inflammation and to prevent proceeding to the next stage with severe respiratory failure and ARDS and that PBW-based dose dexamethasone may be one of the therapeutic options for COVID-19.

Using additional respiratory support including HFNC and NIV in patients with COVID-19 could be aerosol-generating medical procedures (AGMP) and have a potential of transmission to healthcare workers. As a treatment principle, patients with COVID-19 undergoing AGMP should be admitted to a negative pressure room or single-patient room [26]. Shorter oxygen demand and hospital stay are required especially during

Table 2
Association between the PBW-based dexamethasone therapy and decreased use of HFNC, NIV, or MV.

	Odds ratio (95% CI)	P-value
Age	1.042 (0.990–1.097)	0.10
Diabetes mellitus	1.048 (0.334–3.285)	0.94
Body mass index	1.325 (1.086–1.616)	0.0024
Male	8.447 (1.248–57.172)	0.029
PBW-based Dex therapy	0.224 (0.062–0.813)	0.023

CI; confidence interval, Dex; dexamethasone, HFNC; high-flow nasal cannula oxygen therapy, MV; mechanical ventilation, NIV; noninvasive ventilation, PBW; predicted body weight.
P-values were calculated using multivariate logistic regression analysis.

the pandemic to maintain both human and material resources [27]. Therefore, reduction of the risk for additional respiratory support is very useful in a real-world situation.

Finally, it should be noted that our study had a small sample size and was limited because of its retrospective design. Our study population was small because, according to Our World in Data, the number of cumulative confirmed COVID-19 cases in Japan (0.8 million) by the end of May 2021 was much smaller than that of the United Kingdom (4.5 million) or the United States (33 million), and the inclusion of more patients during the study period was difficult [28]. Second, some patients might have variants of SARS-CoV-2, and the participants could not be homogeneous. Third, 25 patients have included drug clinical trials before administering dexamethasone in this study, because no therapy has established the effectiveness of treatment in patients who do not need oxygen therapy in Japan. Fourth, we compared the data on the SpO_2/FiO_2 ratio instead of the PaO_2/FiO_2 ratio as indicator of respiratory failure because oxygen therapy was recommended for patients with $SpO_2 \leq 93\%$ in room air according to the Japanese clinical management guideline for COVID-19. Indeed, most patients were treated in the inpatient ward, not in the intensive care unit, and Japan experienced a state of emergency several times because of small healthcare capacity. Therefore, obtaining data on arterial blood gas for each patient was difficult. Further large-scale studies must be conducted to confirm the findings of the present study because the number of patients enrolled was small, which could affect the results.

5. Conclusions

In patients with COVID-19 pneumonia who require oxygen therapy, PBW-based dexamethasone therapy may shorten the length of hospital stay and duration of oxygen therapy and risk of using additional respiratory support, including HFNC, NPPV, or MV, without increasing serious adverse events or 30-day mortality. However, randomized controlled studies with PBW-based dose dexamethasone are required to confirm its effect.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

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Authors' contributions

YH, YI, JT, and KTa contributed to the study concept and design. YS, YT, YI, KK, TK, HT, TKi, YTa, and KTu contributed to the data curation and investigation of patients. YH, YI, and JT examined the enrolled patients in the hospital. YH, YI, and JT performed the statistical analyses. All authors have read and approved the final manuscript.

CRediT authorship contribution statement

Yuri Isaka: ConceptualizationConceptulization, Formal analysis, Conceptulization and design, Analysis. **Yasutaka Hirasawa:** ConceptualizationConceptulization, Formal analysis, Conceptulization and design, Analysis. **Jiro Terada:** Conceptulization and design, Analysis. **Jiro Terada:** Conceptualization, Formal analysis. **Yu Shionoya:** Data curation, Investigation. **Yuichiro Takeshita:** Data curation, Investigation. **Toru Kinouchi:** Data curation, Investigation. **Ken Koshikawa:** Data curation, Investigation. **Hiroshi Tajima:** Data curation, Investigation. **Taku Kinoshita:** Data curation, Investigation. **Yuji Tada:** Data curation, Investigation. **Koichiro Tatsumi:** Supervision. **Kenji Tsushima:** Supervision.

Declaration of competing interest

The authors declare that they have no competing interests.

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