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RESEARCH ARTICLE

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Prolonged corticosteroid therapy and cytomegalovirus infection in patients with severe COVID-19

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Abstract

Systemic corticosteroid therapy is frequently used to treat coronavirus disease 2019 (COVID-19). However, its maximum duration without secondary infections remains unclear. We aimed to evaluate the utility of monitoring cytomegalovirus (CMV) infection in patients with COVID-19 and estimate the maximum duration of systemic corticosteroid therapy without secondary infections. We included 59 patients with severe COVID-19 without CMV infection on admission to the intensive care unit (ICU). All patients received systemic corticosteroid therapy under invasive mechanical ventilation, with examination for plasma CMV-deoxyribonucleic acid (DNA) levels during the ICU stay. We analyzed the correlations among patient characteristics, CMV infection, diseases, and patient mortality. CMV infections were newly identified in 15 (25.4%) patients; moreover, anti-CMV treatment was administered to six (10.2%) patients during the ICU stay. Four (6.8%) patients had secondary infection-related mortality. The cumulative incidences of CMV infection and anti-CMV treatment during the ICU stay were 26.8% (95% confidence interval [CI], 15.8%–39.0%) and 12.3% (95% CI, 4.8%–23.4%), respectively. Furthermore, the median duration of systemic corticosteroid therapy without CMV infection was 15 days (95% CI, 13–16 days). The presence of CMV infection was associated with mortality during the ICU stay ($p = 0.003$). Monitoring plasma CMV-DNA levels could facilitate the detection of secondary CMV infection due to prolonged systemic corticosteroid therapy. The duration of systemic corticosteroid therapy for COVID-19 should be limited.

KEYWORDS

corticosteroids, COVID-19, cytomegalovirus

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), which was first reported in Wuhan City, China, is a major public health burden worldwide.[1] Patients with COVID-19 sometimes present with critical symptoms that cause mortality.[2] In the early phase of COVID-19, specific immune responses stop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reproduction to prevent disease progression. In case this protective immune response is impaired, the virus propagates; moreover, there is massive destruction of the affected tissues. Consequently, the damaged cells induce innate inflammation in the lungs, which is largely mediated by proinflammatory

macrophages and granulocytes. This process leads to acute respiratory distress syndrome (ARDS).[3]

Numerous studies have investigated treatments for improving the outcomes of patients with COVID-19. Systemic corticosteroid therapy is an effective treatment for severe COVID-19 with ARDS.[4,5] It ameliorates COVID-19-induced cytokine storm and improves patient outcomes; however, it can trigger immunosuppression, which causes secondary infections.[6] Additionally, COVID-19 is associated with cytomegalovirus (CMV) reactivation in patients with severe COVID-19.[7,8] Therefore, systemic corticosteroid therapy acts as a double-edged sword in patients with severe COVID-19. Occasionally, the duration of systemic corticosteroid therapy requires extension due to recurrent respiratory failure.[9] However, the association of systemic corticosteroid therapy with CMV infection and patient prognosis remains unclear. We aimed to investigate the correlation of CMV infection with the duration of systemic corticosteroid therapy, to evaluate the utility of monitoring CMV infection in patients with COVID-19, and to estimate the maximum duration of systemic corticosteroid therapy without CMV infection.

2 | METHODS

2.1 | Patients and study design

This retrospective observational study was conducted at Osaka University Hospital (a 1086-bed National University Hospital in Osaka, Japan). Patients with severe COVID-19 were directly admitted via ambulance transport or gathered from other hospitals and treated in the intensive care unit (ICU). Noninvasive ventilation or high-flow nasal cannula oxygen therapy was not administered to avoid aerosolizing virus particles; accordingly, all patients received invasive mechanical ventilation.

All screened patients were adults with COVID-19 (age ≥20 years) who were admitted to Osaka University Hospital between April 1, 2021, and May 31, 2021. We excluded patients with a history of immunodeficiency or CMV infection on admission to the ICU, as well as those with baseline corticosteroid or other immunosuppressant usages before symptom onset. Moreover, we excluded patients with an ICU stay of <7 days to determine the association between prolonged systemic corticosteroid therapy and CMV infection.

All patients were followed until discharge from the ICU, end of the study period (May 31, 2021), or death. To identify factors influencing the incidence of CMV infection, we analyzed the correlations between CMV infection with patient characteristics and laboratory data. Additionally, we evaluated the association of the requirement for anti-CMV treatment with patient prognosis.

The experimental protocol followed the Ethical Guidelines of the Japan Ministries of Health and Labor for Medical and Health Research Involving Human Subjects. This study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Osaka University Hospital (approval number: 21146). An opt-out system was applied to obtain patients' informed consent for a retrospective review, which allowed patients the opportunity to decline participation in the study.

2.2 | Data collection

Information regarding patient characteristics was collected through individual case reviews. Baseline characteristics were obtained for hospital admission. Clinical characteristics included age, sex, body mass index (BMI), comorbidities, and immunosuppressive therapy before ICU admission. Laboratory data included the levels of plasma CMV-deoxyribonucleic acid (DNA), leukocytes, D-dimer, C-reactive protein, lactate dehydrogenase, ferritin, immunoglobulin G (IgG), IgA, and IgM. Furthermore, we monitored CMV infection and diseases that occurred during ICU stay. All-cause mortality during ICU stay was recorded for all patients.

2.3 | COVID-19 diagnosis and treatment

Upon ICU admission, SARS-CoV-2 infection was confirmed through reverse-transcription polymerase chain reaction (RT-PCR) using nasopharyngeal and throat swabs. RT-PCR was conducted using Xpert Xpress SARS-CoV-2 and GeneXpert (Beckman Coulter Inc.). Immunosuppressants and corticosteroid pulse therapy initiated before ICU admission were discontinued. During the ICU stay, 6 mg dexamethasone was administered once daily for 10 days (or until ICU discharge if it occurred sooner).[4] When patients could not be extubated after 10 days of dexamethasone administration due to respiratory failure, ≤6 mg dexamethasone was administered once daily until extubation or death to prevent recurrence of respiratory failure. The dose was tapered to 1–3 mg once daily, if possible.

2.4 | Definition and treatment of CMV disease and infection

CMV infection was diagnosed using real-time PCR to detect viral nucleic acids in plasma.[10] Plasma CMV-DNA levels were quantified by real-time PCR using the Cobas CMV and Cobas 6800 system (Roche Diagnostics Co.), with follow-up measurements at least once per week. CMV-DNAemia was defined as two or more positive results for CMV-DNA in plasma samples.[10] Proven, probable, and possible CMV diseases were defined as described by Ljungman et al.[10] Possible CMV diseases were defined by the presence of CMV in the blood (i.e., CMV-DNAemia), as well as symptoms and/or signs.[10]

Although the absolute cut-off value of plasma CMV-DNA levels for antiviral treatment initiation remains to be established,[11] the cut-off value for CMV-DNAemia is useful for guiding pre-emptive therapy for CMV infection.[12] Accordingly, patients with CMV-DNAemia >200 IU/ml and CMV diseases (including proven, probable, and

possible cases) received 5 mg/kg of intravenous ganciclovir twice daily to prevent disease progression.

2.5 | Statistical analysis

All statistical analyses were performed using EZR version 1.54 (based on R version 4.0.3, R commander version 2.7-1; Jichi Medical University Saitama Medical Center).[13] Mann–Whitney *U* test, Fisher's exact test, and log-rank test were used to compare patient characteristics and laboratory data between patients with and without CMV infection during the ICU stay. The cumulative incidence of CMV infection and diseases was calculated using Gray's method, with discharge from the ICU and death without CMV infection being considered as competing events. Univariate regression analyses were performed to identify factors related to CMV infection. For all analyses, a $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

This study included 59 Japanese patients with severe COVID-19 (Figure 1). The median age (interquartile range) was 60 (56–69) years. Most patients were obese (BMI > 25 kg/m^2, 70.5%); moreover, hypertension (49.2%), diabetes mellitus (32.2%), and dyslipidemia (22.0%) were the most common comorbidities. Systemic corticosteroid therapy was administered to 46 (78.0%) patients before ICU admission. Corticosteroid pulse therapy (250–1000 mg per day for ≤3 days), tocilizumab (400 mg per day, once in 4 weeks), and baricitinib (4 mg once daily for a maximum of 2 weeks) were administered before the transfer from other hospitals and discontinued upon ICU admission. The median duration (95% confidence interval [CI]) of systemic corticosteroid therapy was 15 (13–20) days.

Fifteen (25.4%) patients developed CMV infection during their ICU stay (Table 1). Compared with patients without CMV infection, those with CMV infection showed lower BMI, as well as higher age, duration of systemic corticosteroid therapy and ICU stay, and mortality. On admission, there were higher D-dimer levels in patients with CMV infection than in those without. There were no significant between-group differences in the other laboratory findings (Table 2).

In total, six (40.0%) patients required antiviral treatment for CMV-DNAemia >200 IU/ml (two patients), possible CMV gastrointestinal diseases (two patients), and possible CMV pneumonia (two patients) (Table S1). Four and zero patients with and without CMV infection, respectively, died during the ICU stay ($p = 0.003$). The causes of death included bacterial septic shock (two patients), bacterial pneumonia (one patient), and possible CMV pneumonia (one patient).

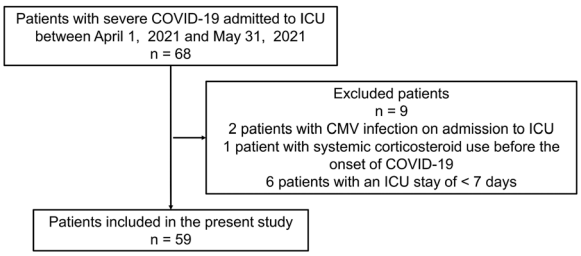

FIGURE 1 Inclusion flowchart. COVID-19, coronavirus disease 2019; CMV, cytomegalovirus; ICU, intensive care unit

3.2 | Analyses of the correlation of systemic corticosteroid therapy with CMV infection and mortality

We calculated the cumulative incidence to analyze the correlation between systemic corticosteroid therapy and CMV infection. The cumulative incidences of CMV infection and anti-CMV treatment during the ICU stay were 26.8% (95% CI, 15.8%–39.0%) and 12.3% (95% CI, 4.8%–23.4%), respectively (Figure 2). Furthermore, the presence of CMV infection ($p = 0.003$) and the requirement for anti-CMV treatment ($p = 0.048$) were associated with all-cause ICU mortality. The median duration of systemic corticosteroid therapy without CMV infection was 15 days (95% CI, 13–16 days). This indicated that prolonged systemic corticosteroid therapy influences the onset of CMV infection and diseases as opportunistic infections.

3.3 | Risk factor analysis for CMV infection during the ICU stay

Logistic regression coefficients were calculated to identify factors related to CMV infection (Table 3). Since patients with CMV infection had a lower BMI than those without, the corticosteroid dose per unit weight could have affected the incidence of CMV infection. In fact, BMI > 25 kg m^{-2} was inversely related to the risk of CMV infection (odds ratio [OR], 0.22; 95% CI, 0.05–0.96; $p = 0.044$). Furthermore, systemic corticosteroid therapy >15 days augmented the risk of CMV infection (OR, 27.1; 95% CI, 3.24–226; $p = 0.002$). However, corticosteroid pulse therapy, tocilizumab, and baricitinib did not significantly affect the incidence of CMV infection. No laboratory findings on ICU admission showed clinical utility in predicting CMV infection. Taken together, prolonged systemic corticosteroid therapy and the higher corticosteroid dose per unit weight were risk factors for CMV-DNAemia.

4 | DISCUSSION

This study monitored plasma CMV-DNA levels and CMV infection in patients with severe COVID-19 who received prolonged systemic corticosteroid therapy during the ICU stay. The incidence of CMV

TABLE 1 Patient characteristics according to CMV infection ($n = 59$)

Parameter	Patients with CMV infection ($n = 15$)	Patients without CMV infection (n = 44)	p value
Age, years	67 (59–73)	60 (54–84)	0.026
Male/female, n	13/2	35/9	0.71
BMI, kg m^{-2}	22.7 (21.5–26.0)	29.4 (25.7–32.4)	<0.001
Comorbidities, *n* (%)	10 (66.7)	31 (70.5)	0.76
Hypertension, *n* (%)	6 (40.0)	23 (52.3)	0.55
Diabetes mellitus, *n* (%)	5 (33.3)	14 (31.8)	>0.99
Dyslipidemia, *n* (%)	4 (26.7)	9 (20.5)	0.72
Use of intensive immunosuppressive treatment before admission, *n* (%)	8 (53.3)	14 (31.8)	0.22
Corticosteroid pulse therapy, *n* (%)	5 (33.3)	8 (18.2)	0.28
Tocilizumab, *n* (%)	3 (20.0)	6 (13.6)	0.68
Baricitinib, *n* (%)	3 (20.0)	3 (6.8)	0.17
Duration of systemic corticosteroid therapy, days	30 (20–41)	13 (11–15)	<0.001
Duration of the ICU stay, days	23 (14–40)	10 (9–12)	<0.001
Mortality in the ICU, *n* (%)	4 (26.7)	0 (0.0)	0.003
CMV disease and infection treated during the ICU stay, *n* (%)	6 (40.0)		
CMV-DNAemia, *n* (%)	2 (13.3)		
Possible CMV gastrointestinal disease, *n* (%)	2 (13.3)		
Possible CMV pneumonia, *n* (%)	2 (13.3)		

Note: Data are presented as median (95% CI) or number (%), as appropriate.

Abbreviations: BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

infection was positively associated with the duration of systemic corticosteroid therapy. Additionally, the presence of CMV infection was associated with the risk of secondary infection-related mortality during the ICU stay. Our findings demonstrated that in patients with severe COVID-19, monitoring plasma CMV-DNA levels might allow sensitive detection of CMV infection. Moreover, prolonged systemic corticosteroid therapy can lead to CMV infection.

In patients with COVID-19, interleukin-2 (IL-2) inhibition decreases the number of $CD8^+$ T-lymphocytes; however, blood IL-6 and IL-10 levels increase.[14] As IL-6 is crucially involved in cytokine storms,[15] abnormal IL-6 levels affect the dysregulated inflammatory response and reflect the COVID-19 severity.[16,17] Therefore, there have been numerous studies regarding the treatment effectiveness for mitigating the immune response and preventing a hyperinflammatory state.[4,18–23] Notably, systemic corticosteroid therapy decreases mortality in patients with severe COVID-19 requiring invasive mechanical ventilation.[4] Moreover, tocilizumab and baricitinib, which is a humanized monoclonal antibody against IL-6 and a selective inhibitor of Janus kinase 1 and 2, are effective against COVID-19.[20,22–24] However, these agents increase the risk of secondary infections in patients with COVID-19.[25] As the association of patient prognoses and CMV infection in patients with COVID-19 remains unclear, we investigated the utility of monitoring CMV infection in patients with severe COVID-19 who received systemic corticosteroid therapy, tocilizumab, and baricitinib.

Our findings indicated that monitoring plasma CMV-DNA levels might contribute to the differentiation of immunosuppressed patients. In immunocompetent patients with critical illness, reactivation from latency, rather than primary infection, is considered to be the cause of CMV infection.[26] Corticosteroids exert immunosuppressive effects mainly by inhibiting the activity of crucial transcriptional regulators of proinflammatory genes and reducing lymphocyte levels.[27] Therefore, exposure to systemic corticosteroids can be a risk factor for bacterial and CMV infection in patients with severe COVID-19.[28,29] This study showed that the presence of CMV infection and the requirement for anti-CMV treatment were associated with all-cause ICU mortality. Since the mortality causes were critical infectious diseases, the presence of CMV disease and infection with

TABLE 2 Laboratory findings on ICU admission in patients with and without CMV infection ($n = 59$)

Parameter	Patients with CMV infection (n = 15)	Patients without CMV infection ($n = 44$)	p value
Hematology (μl)			
Leukocytes	9360 (6250–11 520)	8790 (5850–11 590)	0.83
Neutrophils	8490 (5450–9940)	7510 (5120–10 530)	0.75
Lymphocytes	570 (310–860)	590 (440–870)	0.40
Monocytes	200 (140–390)	240 (150–390)	0.61
Eosinophils	0 (0–0)	0 (0–0)	0.72
Coagulation			
D-dimer, μg/ml	8.08 (1.56–17.92)	1.42 (0.83–2.74)	0.005
Biochemistry			
CRP, mg/dl	7.44 (4.21–12.36)	8.79 (3.42–14.67)	0.77
LDH, U/L	520 (430–860)	474 (355–607)	0.23
Ferritin, U/L	896 (494–1131)	889 (662–1384)	0.50
Serology (mg/dl)			
IgG	1003 (792–1172)	914 (804–995)	0.62
IgA	194 (158–261)	209 (151–317)	0.68
IgM	62 (46–75)	65 (47–81)	0.63

Note: Data are presented as median (IQR), unless otherwise stated.

Abbreviations: CMV, cytomegalovirus; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase.

pre-emptive therapy might be indicative of the preliminary stage of critical secondary infectious diseases. Based on the correlation of patient mortality with the requirement for anti-CMV treatment, the cut-off value of CMV-DNA level for initiating antiviral treatment should be defined sensitively. In contrast to antigenemia, which is a diagnostic tool for CMV infection that is influenced by peripheral blood leukocyte counts, PCR assays can accurately and sensitively

TABLE 3 Risk factor analysis for CMV infection during the ICU stay ($n = 59$)

Parameter	Univariate analysis	
	p value	OR (95% CI)
Duration of systemic corticosteroid therapy > 15 days	0.002	27.1 (3.24–226)
Corticosteroid pulse therapy before ICU admission	0.23	
Tocilizumab use before ICU admission	0.56	
Baricitinib use before ICU admission	0.16	
Age > 65 years	0.10	
Sex (female)	0.54	
BMI > 25 kg m^{-2}	0.044	0.22 (0.05–0.96)
Hypertension	0.41	
Diabetes mellitus	0.91	
Dyslipidemia	0.62	
D-dimer > 2 μg/ml	0.091	

Abbreviations: BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; ICU, intensive care unit; OR, odds ratio.

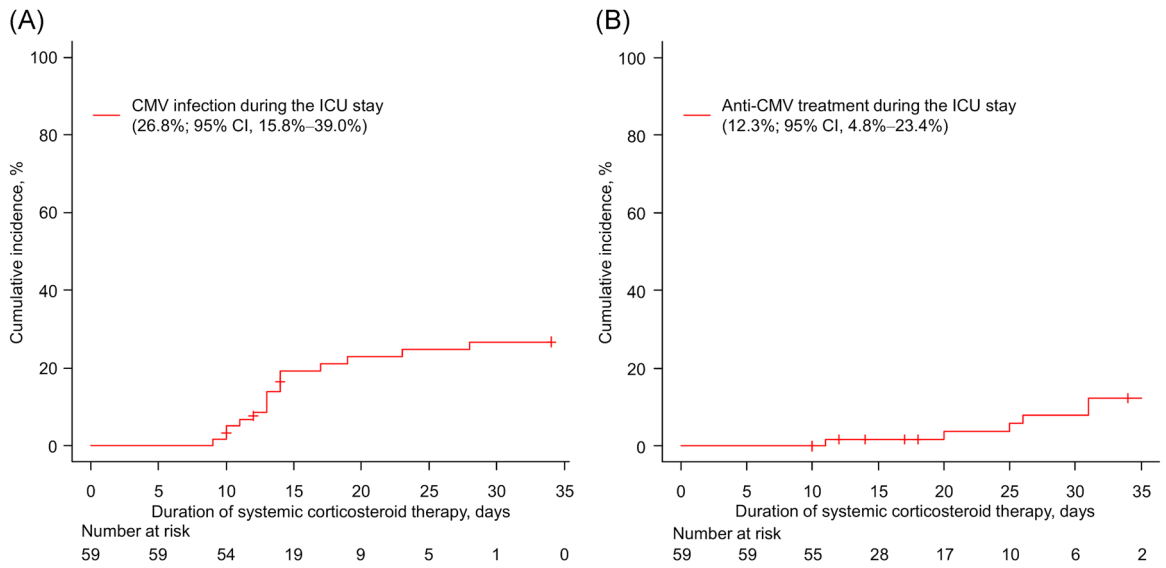

FIGURE 2 Cumulative incidence of CMV infection and disease during the ICU stay ($n = 59$). (A) Cumulative incidence of CMV infection during the ICU stay. (B) Cumulative incidence of CMV disease and infection requiring antiviral treatment during the ICU stay. CMV, cytomegalovirus; ICU, intensive care unit

monitor the progression of CMV infection and diseases, even in patients with severe COVID-19 and subsequent lymphocytopenia.[26,30] Therefore, monitoring plasma CMV-DNA levels is useful for assessing immunosuppression to prevent secondary infection-related mortality.

Extending the duration of systemic corticosteroid therapy might negatively affect the prognosis in patients with severe COVID-19. As aforementioned, systemic corticosteroid therapy can modulate the dysregulated inflammatory response caused by COVID-19 and improve patient outcomes; however, it increases the risk of secondary infection. Short-term corticosteroid pulse therapy consistently reduces mortality and rarely induces secondary infection, even in critically ill patients with COVID-19.[5] However, we experienced a relapse of respiratory failure, despite dexamethasone administration compliant with the RECOVERY trial.[4,9] Therefore, prolonged systemic corticosteroid therapy is considered a treatment option for selected COVID-19 cases.[31] Although we found no correlations between patient mortality and D-dimer levels, previous studies have reported an association with patient prognosis.[32] As shown in Table 2, patients with CMV infection might have presented with more severe COVID-19 on admission than those without. Accordingly, patients with CMV infection might have required extended systemic corticosteroid therapy due to persistent respiratory failure. These findings indicate the need to confirm the maximum duration of systemic corticosteroid therapy without secondary infections. Our findings showed that the median duration of systemic corticosteroid therapy without CMV infection was 15 days. As CMV infection can induce immunosuppression,[33] systemic corticosteroids should be stopped before CMV infection onset in patients with severe COVID-19. Future studies are warranted to assess the safety and appropriate use of immunosuppressive therapy for patients with severe COVID-19.

This study had several limitations. First, this was a single-center small-scale study; moreover, our findings might have been affected by selection bias. To validate our findings, further large-scale studies should implement multivariate analysis. Second, it was difficult to completely differentiate CMV diseases from other infectious diseases given the limited examinations in patients with critical illnesses. Further, possible CMV diseases were diagnosed and treated at the physician's discretion. Selection bias in the anti-CMV treatment initiation might have affected our findings. Finally, although mechanical ventilation is a risk factor for CMV infection,[34] we did not analyze its effect because systemic corticosteroid therapy and mechanical ventilation were discontinued almost simultaneously in most patients. Further studies on the association of mechanical ventilation and systemic corticosteroid therapy with CMV infection, including the interaction between these two factors, are warranted.

In conclusion, this study assessed CMV infection in patients with severe COVID-19 who received systemic corticosteroid therapy and invasive mechanical ventilation. Monitoring plasma CMV-DNA levels could facilitate the prediction of immunosuppression and poor prognosis. As prolonged corticosteroid therapy might increase the risk of CMV infection and diseases, its duration should be limited. Further studies are warranted to investigate the safety and appropriate administration of immunosuppressive therapy for COVID-19.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization and design: Yuji Yamamoto. *Methodology*: Yuji Yamamoto, Takayuki Shiroyama, and Haruhiko Hirata. *Data collection*: Yuji Yamamoto, Kinnosuke Matsumoto, Tomoki Kuge, Midori Yoneda, Makoto Yamamoto, and Akinori Uchiyama. *Writing the original draft*: Yuji Yamamoto. *Supervision*: Yoshito Takeda and Atsushi Kumanogoh. All the authors reviewed and approved the submission of the final manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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