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Original Article

Judicious ending of isolation based on reverse transcription–polymerase chain reaction (RT-PCR) cycle threshold only for patients with coronavirus disease 2019 (COVID-19) requiring in-hospital therapy for longer than 20 days after symptom onset

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ABSTRACT

Background: For patients with coronavirus disease 2019 (COVID-19) requiring hospitalization, extending isolation is warranted. As a cautious protocol, ending isolation based on polymerase chain reaction cycle threshold (Ct) value was introduced for patients requiring therapy for >20 days after symptom onset.

Method: We compared a Ct-based strategy using Smart Gene® between March 2022 and January 2023 with a preceding control period (March 2021 to February 2022) when two consecutive negative reverse transcription–polymerase chain reaction tests using FilmArray® were required for ending isolation. Ct was evaluated on day 21, and ending isolation was permitted in patients with Ct $\geq$ 38. Although patients with Ct 35–37 were transferred to a non-COVID-19 ward, isolation was continued.

Results: The duration of stay on a COVID-19 ward in the Ct group was 9.7 days shorter than that in controls. The cumulative number of tests was 3.7 in controls and 1.2 in the Ct group. There was no nosocomial transmission after ending isolation in either group. The number of days from symptom onset to testing was 20.7 $\pm$ 2.1 in Ct group, and five patients had Ct < 35, nine Ct 35–37, and 71 Ct $\geq$ 38. No patients were moderately or severely immunocompromised. Steroid use was an independent risk factor for prolonged low Ct (odds ratio 9.40, 95% confidence interval 2.31–38.15, p = 0.002)

Conclusions: The efficacy of ending isolation based on Ct values could improve bed utilization without the risk of transmission among patients with COVID-19 requiring therapy for >20 days after symptom onset.

1. Introduction

The isolation of patients with coronavirus disease 2019 (COVID-19) has been recommended to prevent the spread of infection in the hospital [1–4]. Previously, two consecutive negative reverse transcription–polymerase chain reaction (RT-PCR) tests were mandatory for ending isolation [2]. However, patients can have prolonged and sporadic positive PCR test results for longer than 30 days [5], and a positive

Abbreviations: COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription–polymerase chain reaction; Ct, cycle threshold; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CDC, the Centers for Disease Control and Prevention; CRP, C-reactive protein; SD, standard deviation; OR, odds ratio; CI, confidence interval; and HFNC, high-flow nasal canula.

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PCR test does not necessarily mean that the patient is still infectious. Van Kampen et al. [6] reported that the median duration of infectious virus shedding was 8 days, and the rate of the isolation decreased to less than 5% after 15 days. Viral loads above 7 $\log_{10}$ ribonucleic acid (RNA) copies/mL is an independent risk factor for the isolation of infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The cycle threshold (Ct) of RT-PCR is the number of cycles at which fluorescence of the PCR product is detectable over and above the background signal. The Ct value is inversely proportional to the viral load. A systematic review [7] showed that Ct values are significantly lower in specimens producing culturable virus, and the odds of isolating live virus are reduced by 33% for every 1-unit increase in Ct. Singanayagam et al. [8] reported that the probability of culturing virus declines to 8% in samples with Ct values $>$ 35. Among fully vaccinated adults with COVID-19, 46% had negative test results or Ct value $\geq$ 35 in a subsequent RT-PCR by day 6 postdiagnosis, and 84% before day 10 [9]. In the attempt using a test-to-release protocol, fully vaccinated individuals were eligible to return to work once they were fever-free, had improving symptoms for more than 24 h, and after two negative results or Ct values $\geq 35^{10}$. However, the Centers for Disease Control and Prevention (CDC) recommend against the use of test-to release based on Ct evaluation [11]. Factors, including the timing testing or specimen collection and handling, can affect Ct values [12]. A cutoff Ct value is difficult to standardize because of the availability of different SARS-CoV-specific RT-PCR kits with different sensitivities. Additionally, variant-specific characteristics should be considered. Among specimens with culturable virus, Ct values in infection with Omicron are higher than those among individuals infected with other variants [13].

In updated recommendations of the CDC [1], isolation can be discontinued 10 days after symptom onset in patients with moderate illness. Although the CDC has suggested that this may warrant extending the duration of isolation for up to 20 days for patients with severe illness [1], there is insufficient evidence for ending isolation in patients who require prolonged in-hospital therapy. Because of the increase in patients during the Omicron wave in Japan, we changed the rule for ending isolation/precaution from two consecutive negative RT-PCR tests to a Ct-based strategy to promote patient transfer from a dedicated COVID-19 ward to general wards. The main purpose of this study was to evaluate the safety of the Ct-based strategy conducted during the Omicron epidemic wave for patients requiring continued in-hospital therapy for longer than 20 days from symptom onset, and to identify the risk of low Ct values at late stages in the clinical course (suggesting a continued high viral load). As a secondary aim, the duration of isolation/precaution was compared between patients pre- and post-introduction of the Ct-based strategy.

2. Materials and methods

2.1. Study design

The study was approved by the Institutional Review Board of Tokoname City Hospital (No. 2022–03). Patients with COVID-19 who required prolonged in-hospital therapy of more than 20 days after symptom onset were included in this retrospective study. The timing of transfer to a non-COVID-19 ward and ending isolation/precaution in patients admitted to a COVID-19 ward was determined based on the Ct value between March 2022 and January 2023 (Ct group). Before introduction of the Ct-based strategy, two nasopharyngeal samples were collected $\geq$24 h apart, and two consecutive negative results in RT-PCR tests were required for ending isolation between March 2021 and February 2022 (control group). The timing of patient transfer to a non-COVID-19 ward and the number of RT-PCR tests required until the discontinuation of isolation/precaution were compared between patients in the Ct group and those in the control group.

2.2. Criteria for the timing of transfer to a non-COVID-19 ward and ending isolation/precaution for patients in Ct group

The hospital policy regarding the criteria for transfer to general wards and ending isolation/precaution was explained before informed consent was obtained from patients in Ct group. RT-PCR tests were conducted on day 21 and every 5–7 days thereafter until the target Ct value for ending isolation was achieved. With Ct value $\leq$ 34, patients were to remain on the COVID-19 ward. With Ct values between 35 and 37, patients could be transferred to a non-COVID-19 ward; however, isolation/precaution was continued after changing wards. Isolation/precaution was discontinued in patients with Ct values $\geq$ 38. Use of an N95 mask and face shield was mandatory in high-risk procedures including providing patients with meals, bathing, or oral suction treatment in all admitted patients. Different from intra-hospital transfer, patients were discharged when more than 10 days had passed after symptom onset without testing.

2.3. SARS-CoV-2 RNA detection using real-time RT-PCR

Ct values were evaluated using Smart Gene® SARS-CoV-2 (Mizuho Medy Co., Ltd., Tosu City, Saga, Japan), which is a reagent for the detection of SARS-CoV-2 RNA by RT-PCR that uses the quenching probe method [14]. The suspended sample was dripped into the cartridge, which was inserted into the Smart Gene® analyzer (Mizuho Medy Co., Ltd.) for automated RT-PCR analysis. A RT-PCR result was considered "positive" when the Ct value was $\leq$45. In the control period, the FilmArray respiratory panel (RP) 2.1® (bioMérieux, Salt Lake City, Utah, USA) was used for the detection of SARS-CoV-2 RNA.

2.4. Risk factors associated with low Ct value

A low Ct value was defined as less than the median Ct value obtained at the initial RT-PCR. The following variables were evaluated: age $\geq$80 years; male sex; $\leq$two vaccine doses; comorbidities; oxygen supplementation; therapy for COVID-19 including anti-viral drugs, immunosuppressive drugs, steroids, and monoclonal antibody use; co-infection; and C-reactive protein (CRP), D-dimer, and ferritin.

2.5. Statistical analyses

Categorical variables were compared using the chi-squared or Fisher's exact tests. Continuous variables were compared using *t*-tests or Mann–Whitney U tests. Univariate analyses for risk factors associated with low Ct were performed using the chi-square test, and potential confounders were examined via cross-tabulation. Variables selected in the univariate analyses ($p < 0.1$) were subsequently entered into a logistic regression model (odds ratio [OR] and 95% confidence interval [CI]). The level of statistical significance was set at $p < 0.05$. IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA) was used.

3. Results

3.1. The comparison of background characteristics between the Ct group and the control group

The number of patients included in the control was 22, with a rate of 6.3% among 351 COVID-19 patients admitted around the control period. Whereas, 85 of 322 patients (26.4%) were included in the Ct group ($p < 0.001$). Background characteristics are presented in Table 1. Enhanced respiratory support, including high-flow nasal canula (HFNC) oxygen therapy, intubation and mechanical ventilation use, was provided in 40.9% of patients in the control. In contrast, these enhanced respiratory supports were required in only 3.5% of patients in the Ct group ($p < 0.001$). Steroids were used in 72.7% of patients, and

Table 1
Background in control group and cycle threshold (Ct)-based strategy group.

Variables	Control (n = 22)	Ct group (n = 85)	p-value
Age	68.0 ± 12.1	81.8 ± 10.6	<0.001
Male sex	18 (81.8%)	39 (45.9%)	0.003
No vaccination	17/21 (81.0%)	17/84 (20.2%)	<0.001
Oxygen supplementation	17 (77.3%)	47 (55.3%)	0.061
High-flow nasal cannula oxygen	7 (31.8%)	2 (2.4%)	<0.001
Mechanical ventilation	2 (9.1%)	1 (1.2%)	0.107
Anti-viral drugs for COVID-19	20 (90.9%)	50 (58.8%)	0.005
Monoclonal antibody use	2 (9.1%)	3 (3.5%)	0.272
Immunosuppressive drugs	13 (59.1%)	0 (0.0%)	<0.001
Steroids	16 (72.7%)	17 (20.0%)	<0.001
Antibiotic use	4 (18.2%)	40 (47.1%)	0.014
Antifungal use	1 (4.5%)	2 (2.4%)	0.502
Hemodialysis	1 (4.5%)	4 (4.7%)	1.000
Diabetes	8 (36.4%)	22 (25.9%)	0.329
Hypertension	3 (13.6%)	37 (43.5%)	0.012
Other comorbidity	17 (77.3%)	79 (92.9%)	0.046

COVID-19, coronavirus disease 2019.

tocilizumab or baricitinib were used in 59.1% of patients in the control group. In contrast, steroids were used only in 20.0% of patients ($p < 0.001$); no immunosuppressive drugs were used in the Ct group ($p < 0.001$).

In total, 81% of patients in the control group and 20.2% in the Ct group were not immunized by SARS-CoV-2 vaccination ($p < 0.001$). In contrast, a significantly more advanced age and higher rate of comorbidity was demonstrated in the Ct group than the control group. The rate of antibiotic therapy against bacterial co-infection was significantly higher in the Ct group than in controls (47.1% vs. 18.2%, $p = 0.014$). There were no moderately or severely immunocompromised patients in the Ct group, such as those with active treatment for malignancies, hematologic malignancies, solid-organ transplant, high-dose corticosteroid use, or immunosuppressive therapy.

3.2. Efficacy and safety in Ct group compared with controls

A significant difference in the number of days from symptom onset to patient transfer to a non-COVID-19 ward was found between the Ct and the control group (22.3 ± 11.0 vs. 33.2 ± 9.1, $p < 0.001$). The duration of stay on a COVID-19 ward and the duration of isolation/precaution was 9.7 days and 9.0 days shorter in the Ct group, respectively (Table 2). The cumulative number of RT-PCR tests before ending isolation/precaution was 3.7 ± 2.0 in the control group and 1.2 ± 0.4 in the Ct group ($p < 0.001$). Only 11 of 22 patients (50.0%) in the control group could be transferred to a non-COVID-19 ward in initial serial PCR testing, whereas 80 of 85 patients (94.1%) were transferred after the initial test in the Ct group ($p < 0.001$).

The number of days from symptom onset to initial PCR testing was 20.7 ± 2.1 in the Ct group. Tests were conducted with the appropriate timing following the protocol (21 ± 2 days after symptom onset) in 68 patients, with early timing (15–18 days) in 12 patients, and with delayed timing (24–30 days) in five patients (Fig. 1). The initial Ct value was <35 in five patients (5.9%), 35–37 in nine patients (10.6%), 38–40 in 21 patients (24.7%), 41–45 in 17 patients (20.0%), and >45 in 33 patients (38.8%). Among 14 patients with initial Ct values ≤ 37, isolation/precaution was discontinued after a second RT-PCR test in 10 patients (between 22 days and 37 days after symptom onset) and after a third and fourth PCR test in one patient each (31 days and 35 days, respectively). However, two patients were discharged before confirmation of Ct value ≥ 38. Among nine patients with initial Ct values 35–37, seven patients achieved Ct ≥ 38 in a second RT-PCR test and isolation/precaution was discontinued; one patient achieved values ≥ 38 in a third RT-PCR test. The median duration of isolation/precaution on general wards was 6 days. One patient left the hospital without confirmation of a Ct value ≥ 38.

Tests for SARS-CoV-2 were mandatory for patients who shared a room with a patient moved from a COVID-19 ward or medical staff who cared for the patient, if they had fever of undetermined origin or any symptoms related to COVID-19, especially during the first 10 days after ending isolation. Although routine surveillance tests for SARS-CoV-2 were not performed for patients or medical staff without any symptoms on the general wards, nosocomial transmission of SARS-CoV-2 after ending isolation/precaution was not confirmed in the Ct group.

3.3. Analysis of risk factors associated with low Ct for longer than 20 days from symptom onset

Less than the median Ct value 41 in patients with appropriate test timing was defined as low Ct. In addition to 68 patients with initial test with the timing adherent to the protocol (Ct < 41 in 26 patients and Ct ≥ 41 in 42 patients), one patient whose Ct value remained <41 with delayed testing and four patients whose Ct value had increased to ≥41 with earlier testing were included in analysis of the risk factors for low Ct (Fig. 2). In total, we analyzed 27 patients with low Ct among 73 evaluable patients. A significantly higher rate of low Ct was demonstrated in patients with oxygen supplementation (50.0% vs. 21.2%, $p = 0.011$) and those with steroid use (78.6% vs. 27.1%, $p < 0.001$). In addition to these two factors, CRP ≥2.9 mg/dL ($p = 0.071$) was selected for multivariate analysis (Table 3). Because CRP data were unavailable in two patients, 71 patients were included in multivariate analysis (Table 4); steroid use was an independent risk factor for prolonged low Ct (OR 9.40, 95% CI 2.31–38.15, $p = 0.002$). Steroids were continued to treat the primary disease in two patients, and low-dose steroids (orally administered dexamethasone 6 mg or intravenous administration of 6.6 mg) for 10 days were used to treat COVID-19 in 13 patients.

Table 2
Comparison of the timing of initial RT-PCR test and intra-hospital transfer of patients, and duration of stay in the COVID-19 ward between control patients and patients with decision making based on cycle threshold (Ct) value.

Period of the time	Control (n = 22)	Ct group (n = 85)	p-value
Days from symptom onset to initial RT-PCR test for the transfer of patients to non-COVID-19 wards	25.2 ± 5.2	20.7 ± 2.1	<0.001
Days from symptom onset to transfer of patients to non-COVID-19 wards	33.2 ± 9.1	22.3 ± 11.0	<0.001
Duration of stay on the COVID-19 ward (days)	27.6 ± 6.7	17.9 ± 4.5	<0.001
Duration of isolation and precaution (days)	27.6 ± 6.7	18.6 ± 4.8	<0.001

RT-PCR, reverse transcription–polymerase chain reaction; COVID-19, coronavirus disease 2019.

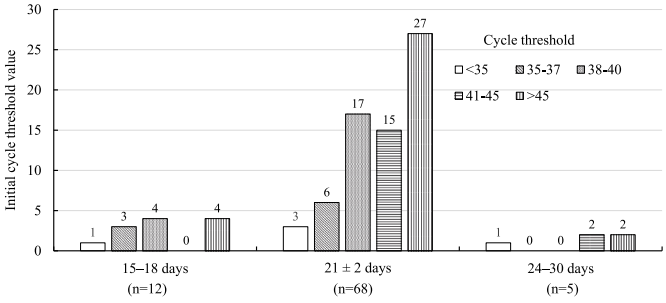

Fig. 1. Initial cycle threshold value according to the timing of reverse transcription–polymerase chain reaction testing. Open bars, cycle threshold (Ct) < 35. Diagonal striped bars, Ct 35–37. Stippled bars, Ct 38–40. Horizontal striped bars, Ct 41–45. Vertical striped bars, Ct > 45.

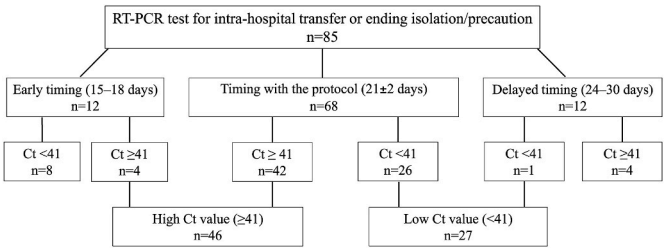

Fig. 2. Flow chart of patient selection process for analyzing risk factors of having a low cycle threshold (Ct) value for more than 20 days after symptom onset.

Table 3
Risk factors of a low cycle threshold (Ct) value for more than 20 days after symptom onset.

Variables	No. of patients with low Ct value (rate)		p-value
	Positive for the factor	Negative for the factor	
Older age (≥80 years)	17/43 (39.5%)	10/30 (33.3%)	0.589
Male sex	11/30 (36.7%)	16/43 (37.2%)	0.962
Cardiovascular disease	8/15 (53.3%)	19/58 (32.8%)	0.141
Cerebral infarction/bleeding	4/20 (20.0%)	23/53 (43.4%)	0.102
Chronic obstructive pulmonary disease	5/12 (41.7%)	22/61 (36.1%)	0.751
Hypertension	9/33 (27.3%)	18/40 (45.0%)	0.118
Diabetes	7/17 (41.2%)	20/56 (35.7%)	0.683
End-stage renal disease	5/9 (55.6%)	22/64 (34.4%)	0.276
≤2 SARS-CoV-2 vaccine doses	11/34 (32.4%)	16/38 (42.1%)	0.393
Oxygen supplementation	20/40 (50.0%)	7/33 (21.2%)	0.011
C-reactive protein ≥ median 2.9 mg/dL	17/35 (48.6%)	10/36 (27.8%)	0.071
D-dimer ≥ median 1.7 μg/mL	16/35 (45.7%)	11/34 (32.4%)	0.256
Ferritin (male >465, female >138 ng/mL)	14/37 (37.8%)	12/27 (44.4%)	0.595
Secondary/concomitant bacterial infection	17/37 (45.9%)	10/36 (27.8%)	0.108
Anti-viral drugs for COVID-19	18/44 (40.9%)	9/29 (31.0%)	0.392
Immunosuppressive drugs	0/1 (0%)	27/72 (37.5%)	1.000
Steroids	11/14 (78.6%)	16/59 (27.1%)	<0.001
Monoclonal antibody use	0/3 (0.0%)	27/70 (38.6%)	0.291

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
COVID-19, coronavirus disease 2019.

Table 4
Multivariate analysis for risk factors of a low cycle threshold (Ct) value for longer than 20 days after symptom onset.

Risk factor	Odds ratio	95% confidence interval	p-value
Steroid use[a]	9.4	2.31 to 38.15	0.002

[a] Steroids were continued for the treatment of primary disease in two patients, and low-dose steroids (dexamethasone 6 mg, oral administration or 6.6 mg, intravenous administration) for 10 days was used in 13 patients.

4. Discussion

The correlation between Ct values and the isolation of viable virus has been studied [15–17]. A Ct value > 30 could be used for ending isolation in clinically improving patients at least 21 days after symptom onset [18]. Jefferson et al. [7] demonstrated that the median Ct value was 26.5 within 7 days after symptom onset, compared with a median of 35.0 at 21 days. The Smart Gene® molecular assay for the detection of SARS-CoV-2 was used in the present study. A significant correlation in Ct value has been demonstrated between the reference real-time RT-PCR (N2 gene) and Smart Gene® assays [14]. A RT-PCR result is considered "positive" with a Ct value ≤ 40 in the reference assay whereas the cutoff Ct value is 45 for a positive result in the Smart Gene® assay. The limit of detection of an RT-PCR test is important to consider in the context of late-stage Ct values and their interpretation. Additionally, the presence of culturable virus despite high Ct values might contribute to the high transmission rates of the Omicron variant [19]. Considering the difference in sensitivity among several RT-PCR and variant-specific differences in viral dynamics, we adopted Ct value ≥ 38 as the cutoff for ending isolation/precaution during the Omicron wave, although values lower than or comparable to 35 were generally used as the cutoff Ct in the test-to release protocol [8,10,15–17]. Isolation/precaution was continued after transfer to a non-COVID-19 ward in patients with Ct values 35–37.

With the Ct-based protocol, isolation/precaution was discontinued at the initial test in 71 patients whereas isolation/precaution was continued after moving to a non-COVID-19 ward in nine patients; changing wards was prohibited in five patients. Most importantly, there was no nosocomial transmission of COVID-19 from transferred patients in the Ct group. After introduction of the Ct-based strategy, the duration of stay in a COVID-19 ward was shortened by approximately 10 days.

Prolonged shedding of viable virus has been demonstrated in severely ill patients and immunocompromised patients [20]. Oxygen supplementation and low-dose steroid use were significant factors for a low Ct remaining longer than 20 days after symptom onset in our study, and steroid use was an independent risk factor in multivariate analysis. In a trial in which patients were randomly assigned to either a methylprednisolone group or control group for treatment, the median time from randomization to SARS-CoV-2 shedding in the methylprednisolone group was significantly longer than that in the control (11 days vs. 8 days) [21]. Cote et al. [18] investigated patients requiring invasive ventilation who received dexamethasone and tocilizumab for COVID-19 caused by the Alpha variant, and five of 10 patients had Ct values < 30 at 21 days or later after symptom onset.

Our study had several limitations. First, the study period in the Ct group coincided with a predominance of the Omicron SARS-CoV-2 variant. Omicron exhibited a shorter duration of PCR positivity and viable virus shedding than Delta [22]. In addition, a higher proportion of patients were immunized against SARS-CoV-2 infection in the Ct group. Virus clearance was faster in vaccinated than in unvaccinated patients [23]. These factors could have affected the duration of isolation in patients with COVID-19 infection. Second, because of the unavailability of Ct values in FilmArray RP 2.1®, which was mainly used for the control group, the Smart Gene® SARS-CoV-2 assay was used for patients in the Ct group. Because different assays have different gene targets and limits of detection, a significant discordance is anticipated between the results obtained using FilmArray RP 2.1® and Smart Gene®. In addition, the cutoff Ct values for ending isolation demonstrated in the present study cannot be equally used in institutions where other RT-PCR assays were adopted. Third, only three patients required invasive ventilation or HFNC therapy in the Ct group. Severe illness in pre-Omicron phase [24] could have a significant impact on Ct values measured in late stages of the clinical course. Fourth, no moderately or severely immunocompromised patients were included in the Ct group. Serial achievement of higher-than-target Ct values at least 24 h apart might be required to discontinue isolation in these patient populations. The CDC recommends isolation for at least 20 days and serial testing prior to ending isolation for moderately or highly immunocompromised patients [1]. Finally, because of a low number of patients (n = 14) with Ct < 38, which was the threshold for discontinuation of isolation in our protocol, this value was not used as the cutoff in the evaluation of risk factors for low Ct. This is why we evaluated the risk of low Ct using less than the median value.

In conclusion, we demonstrated decision making for intra-hospital transfer from a COVID-19 ward and/or ending isolation based on the duration after symptom onset in conjunction with Ct value. Our findings could be useful in guiding the isolation period for patients with COVID-19 who require in-hospital therapy for longer than 20 days after symptom onset to optimize the utilization of beds on COVID-19 wards.

Because there are several issues with Ct evaluation providing a consistent proxy for infectiousness, a Ct-based strategy should not be indicated in patients with a relatively short duration of infection after symptom onset (e.g., 10 days) for discontinuation of isolation and infection control.

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Authorship statement

1. All authors contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
2. All authors drafted the work or revised it critically for important intellectual content.
3. All authors approved the final version of the manuscript to be published.
4. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated.

Authors' contributions

All authors made substantial contributions to the conception of the study. Yoshio Takesue, Yasushi Murakami, and Yasuhiro Nozaki contributed to the study design. Hitoshi Ogashiwa, Takashi Ueda, Kazuhiko Nakajima, Mika Morosawa, and Miki Doi contributed to data acquisition and analysis. Yoshio Takesue and Miyuki Makino contributed to data interpretation. Yoshio Takesue contributed to the drafting of the manuscript. All authors approved the final manuscript.

Declaration of competing interest

None.

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