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Research paper

Association of early-onset constipation and diarrhoea with patient outcomes in critically ill ventilated patients: A retrospective observational cohort study

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ABSTRACT

Background: Constipation and diarrhoea are closely related, but few studies have examined them simultaneously.
Objectives: The purpose of this study was to describe patient defecation status after intensive care unit (ICU) admission and determine the association between early-onset constipation and diarrhoea following ICU admission with outcomes for critically ill ventilated patients.
Methods: Patients ventilated for ≥48 h in an ICU were retrospectively investigated, and their defecation status was assessed during the first week after admission. Early-onset constipation and diarrhoea were defined as onset during the first week of ICU admission. The patients were divided into three groups—normal defecation, constipation, and diarrhoea—and multiple comparisons were performed using the Kruskal–Wallis test and the Mann–Whitney U test with Bonferroni adjustment. Additionally, multivariable analysis was performed for mortality and length of stay using the linear and logistic regression models.
Results: Of the 85 critically ill ventilated patients, 47 (55%) experienced early-onset constipation and 12 (14%) experienced early-onset diarrhoea. Patients with normal defecation and diarrhoea increased from the 4th and 5th day of ICU admission. Early-onset diarrhoea was significantly associated with the length of ICU stay (B = 7.534, 95% confidence interval: 0.116–14.951).
Conclusions: Early-onset constipation and diarrhoea were common in critically ill ventilated patients, and early-onset diarrhoea was associated with the length of ICU stay.

1. Introduction

Gastrointestinal (GI) dysmotility is common in critically ill patients, who often develop symptoms such as vomiting, regurgitation, abdominal distension, constipation, and diarrhoea.[1,2] GI motility in critically ill patients can be impaired by many factors, including ischaemia, analgesics, vasoconstrictors, fluid management, and comorbidities such as diabetes.[3] Between 34 and 58% of critically ill patients experience constipation as a result of GI dysmotility.[4] In long-term ventilated patients, adverse symptoms associated with constipation include not only the typical symptoms such as abdominal distension, nausea, and vomiting but also an increased incidence of acquired infections such as ventilator-associated pneumonia and bloodstream infections.[5] A recent meta-analysis reported that constipation was associated with an increased duration of mechanical ventilation (MV) and intensive care unit (ICU) stay in critically ill patients.[6]

Laxatives are commonly used in clinical practice to treat constipation in critically ill patients; however, the above-mentioned meta-analysis further reported that prophylactic laxatives caused significantly more diarrhoea in the intervention group and had no

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effect on patient mortality.[6] Diarrhoea is a common symptom of intestinal inflammation and antibiotic administration in critically ill patients, causing dehydration, electrolyte abnormalities, and incontinence-associated dermatitis and increasing the burden on caregivers.[7] It was also reported that diarrhoea was associated with longer ICU and hospital stays and ICU mortality.[8]

Management of constipation and diarrhoea is limited by minimal guidelines and low-quality evidence.[2,9–11] Prevention of these problems is important; however, as noted above, constipation and diarrhoea are closely related. Many studies focus on either constipation or diarrhoea, and there are few studies that have investigated constipation and diarrhoea simultaneously. Therefore, the purpose of this study was to determine the defecation status during the first week after ICU admission and to clarify the association of early-onset constipation and diarrhoea of ICU admission with the outcome for critically ill patients.

2. Methods

2.1. Setting and patient selection

This study was conducted at the ICU of the University of Tsukuba Hospital, Japan, which has 800 beds. The unit is a 12-bed general ICU with 700–800 patient admissions annually. There was no protocol for interventions for constipation or diarrhoea, and GI peristalsis medications and enemas were administered at the discretion of doctors and nurses.

The participants were selected from all patients who were admitted to the ICU over a 1-year period from April 2018 to March 2019. Inclusion criteria were patients aged over 18 years requiring MV $\geq$ 48 h and in whom MV was induced between 24 h before and 48 h after ICU admission. Exclusion criteria were as follows: after GI surgery and/or colostomy, with GI diseases, bloody stool, readmission, withdrawal from aggressive treatment, and total length of ICU stay <6 days. The reason for the 6-day cut-off point was to match the definition of constipation as described below.

2.2. Data collection

This study design was a retrospective observational cohort study, and patient data were collected from electronic medical records. Age, sex, comorbidities, diseases for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores for illness severity score, body mass index (BMI), defecation status, fluid intake and output, laboratory data, medication data, enteral nutrition (EN) status, new-onset dialysis, duration of ventilation, infection data, and ICU and hospital outcomes were recorded. Fluid overload was defined as a 10% increase in body weight on the second day of admission compared to baseline (the first day of admission or before surgery).[12] Early EN was also recorded as constipation is reported to be associated with late initiation of EN.[4] When EN had been started within 48 h of admission, the patient was considered as being on early EN.[13]

Defecation was assessed by nurses using a semiquantitative tool and was classified as follows: defecation amount as “large, moderate, and small” and properties as “hard, normal, soft, loose, and liquid”.[5] The nurses assessed the combination of defecation amount and properties and recorded them in the electronic medical record (e.g., “large amount of liquid stool”, “moderate amount of loose stool”, “small amount of hard stool”). Constipation was defined as “$\geq$6 days without defecation” from ICU admission.[4,5,14] In accordance with previous studies,[8] diarrhoea was defined as “loose or liquid stools $\geq$3 per day”. Based on previous studies, this study focused on early-onset constipation and diarrhoea defined as occurring during the first week of ICU admission.[4,5,15] According to the above definitions, the participants were divided into three groups (normal defecation, constipation, and diarrhoea) based on their defecation status during the first week in the ICU. The primary outcome was length of ICU stay, and the secondary outcome was 28-day mortality.

2.3. Statistical analysis

Descriptive data were expressed as numbers and percentages, and continuous data were expressed as median and interquartile range. For categorical variables, the χ^2 test or Fisher's exact test was used for comparisons between the three groups and for pairwise comparisons. For continuous variables, the Kruskal–Wallis test was used for comparisons between the three groups and the Mann–Whitney U test was used for pairwise comparisons. Bonferroni adjustment was used for each pairwise comparison. The association of constipation and diarrhoea with patient outcomes was examined using linear and logistic regression analysis. When analysing constipation, diarrhoea was removed to compare constipation with normal defecation, and when analysing diarrhoea, constipation was removed as well. The results are reported as partial regression coefficients (95% confidence interval [CI]) for mortality and odds ratios (95% CI) for the length of stay. Adjustments were made for the following additional covariates that were chosen *a priori*: APACHE II score, fluid overload.[3,16] Differences with p values <0.05 indicated statistical significance. All analyses were conducted with IBM SPSS Statistics for Windows 27 (IBM Corp., Armonk, N.Y., USA).

Because of the retrospective, observational design of this study, sample size was not calculated; however, a post hoc analysis was conducted to assess the robustness of the sample size. Based on the association between constipation and diarrhoea and length of ICU stay in previous studies, the effect size was judged to be medium.[6,8] At a significance level of 5%, a sample size of 85 patients for this study, and a factor number of four in the linear multiple regression analysis, the power was calculated to be 80.3%. This power was considered statistically acceptable. Post hoc analysis was conducted with G*power software 3.1.9.4 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

2.3. Ethics approval

This study was approved by the Institutional Review Board of the University of Tsukuba (Approval #R01-163). Because this study was retrospective in design and used anonymised patient data, informed consent from each patient was waived. All procedures were approved according to the regulations of the University of Tsukuba that equal or exceed the standards set by the Declaration of Helsinki.

3. Results

3.1. Characteristics of patients

During the recruitment period, 703 patients were admitted to the ICU, of whom, 148 were eligible. Of those, 63 patients were excluded and finally 85 patients were available for analysis (Fig. 1). The characteristics of the patients are shown in Supplementary File 1; 55 (65%) were male, mean age was 67 (56–77) years, BMI was 22.6 (20.1–26.5) kg/m^2, the APACHE II score was 27 (22–30), and 38 (45%) had cardiovascular disease.

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3.2. Defecation status after ICU admission

Fig. 2 shows the progress of defecation during the first week of ICU admission. The percentage of patients with normal defecation increased on the 4th day, and the percentage of patients with diarrhoea increased on the 5th day. Normal defecation occurred on day 3 (2–5) in the normal defecation group, and diarrhoea occurred on day 6 (2–6) in the diarrhoea group.

3.3. Comparison of normal defecation, constipation, and diarrhoea

The patients were divided into three groups: 26 (31%) with normal defecation, 47 (55%) with constipation, and 12 (14%) with diarrhoea. There was no significant difference between the three groups at baseline (Table 1). In the medication data, there was a significant difference in propofol doses of 6.9 (1.3–13.1) mg/kg/day in the normal defecation group, 11.4 (1.9–24.3) mg/kg/day in the constipation group, and 1.0 (0.1–6.2) mg/kg/day in the diarrhoea group ($p = 0.015$) (Supplementary File 2); pairwise comparison showed a significant difference between constipation and diarrhoea groups ($p = 0.013$). There was no significant difference between the three groups in EN, new-onset dialysis, MV duration, and infection data, but fluid overload was significantly different in 3 (12%), 19 (40%), and 3 (25%) patients, respectively ($p = 0.032$) (Supplementary File 3), and pairwise comparison was significantly different between the normal defecation group and the constipation group ($p = 0.030$). There was a significant difference in ICU stay of 11 (9–13), 13 (9–21), and 20 (11–28) days ($p = 0.039$), and pairwise comparison showed a significant difference between the normal defecation group and the diarrhoea group ($p = 0.045$) (Supplementary File 4). There was no significant difference between the three groups in mortality (Supplementary File 5).

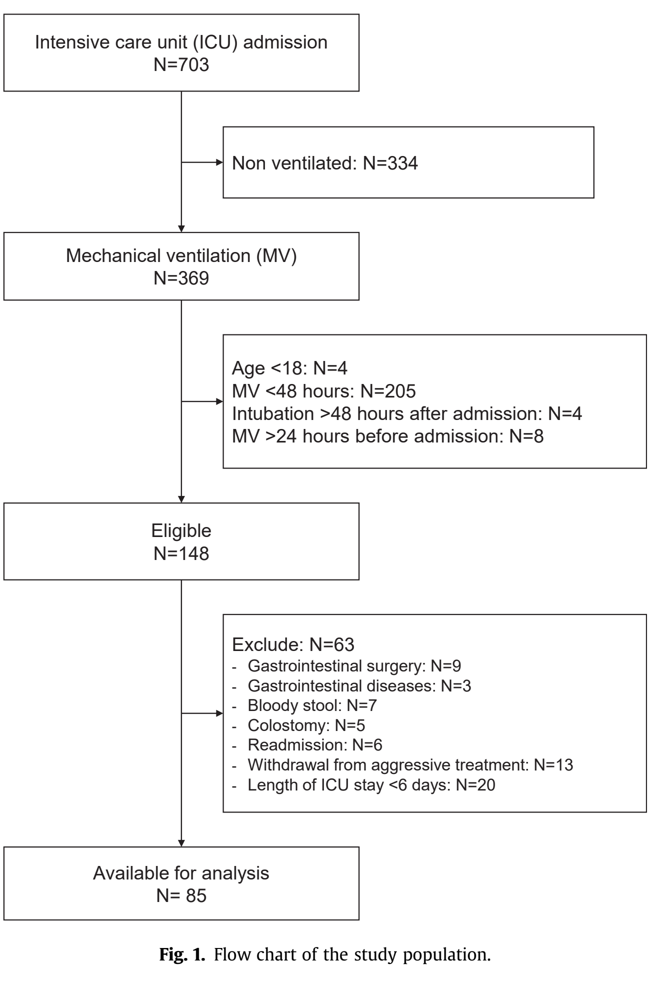

Fig. 1. Flow chart of the study population.

3.4. Association of constipation and diarrhoea with patient outcomes

While constipation was not associated with length of ICU stay ($p = 0.118$) in the multivariable analysis, diarrhoea, in contrast, was (partial regression coefficient [B] = 7.534, 95% CI: 0.116–14.951, $p = 0.047$) (Table 2). Neither constipation nor diarrhoea was associated with mortality ($p = 0.327$; $p = 0.327$, respectively) (Table 3).

4. Discussion

This study had three main findings. First, 55% of critically ill ventilated patients experienced constipation and 14% experienced diarrhoea during the first week of ICU admission. Second, during the first week of ICU admission, the proportion of patients with normal defecation increased from day 4 and the proportion of patients with diarrhoea increased from day 5. Third, neither constipation nor diarrhoea was associated with mortality, but diarrhoea was associated with length of ICU stay.

In previous studies, 34–58% of patients had constipation, which was comparable with the result of this study.[4,5] The incidence of constipation varied among previous studies because of inconsistent definitions of constipation.[6] Many previous studies have used the definition of no defecation ≥3 days. However, in the current study, we defined constipation as no defecation ≥6 days as there is evidence to suggest that this duration without defecation is associated with adverse outcomes.[14]

In a previous study with a large sample size, the incidence of diarrhoea was 13%, which is similar to the results of this study;[17] however, a recent systematic review found a wide range, from 10 to 78%.[6] In addition to the reasons for the different definitions, as described above, this is also attributable to the method of data collection. The longer the number of days for which data are collected, the greater the chance that the patient will experience diarrhoea, and thus the incidence could be higher. However, in our study, the effect was removed by conditioning the event to diarrhoea occurrences during the first week of ICU admission. Future studies of diarrhoea in the ICU should clarify their definitions and data collection methods.

Like the previously mentioned meta-analysis study,[8] diarrhoea was associated with length of ICU stay. The mechanism for this association remains unclear; however, we hypothesise that diarrhoea could cause impaired nutritional intake, electrolyte abnormalities, and dehydration, which may interfere with the critically ill patient's recovery. However, the causal relationship is unclear, and large, well-designed, randomised trials are warranted to clarify the effects of prevention for diarrhoea.

The study carried out by Taito et al highlighted an association between diarrhoea and mortality.[8] This is inconsistent with our findings; however, as mentioned above, many studies do not limit the observation period. Therefore, while late-onset diarrhoea may be relevant, from the results of our study, we can at least say that early-onset diarrhoea was not associated with prognosis.

Constipation was not associated with patient outcomes, but over half of the critically ill patients in our study experienced constipation. Even though EN is started on the third day in many patients, having no defecation ≥6 days is distressing for patients as it can cause bloating, nausea, and vomiting.[18] Taken together, our findings suggest that prevention of both constipation and diarrhoea is essential for critically ill patients. One method of constipation

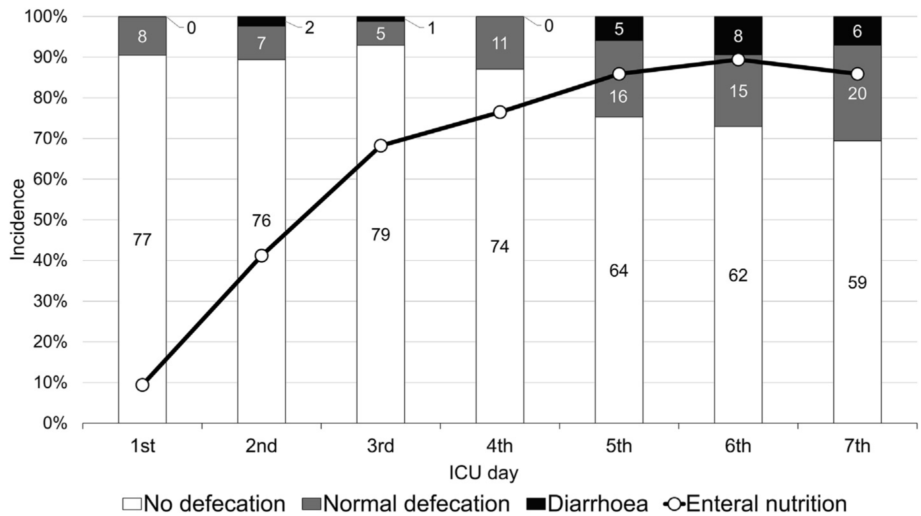

Fig. 2. Temporal trends defecation status after ICU admission. Daily defecation status during the first week of ICU admission is shown as a percentage. White bars indicate no defecation, grey bars indicate normal defecation, black bars indicate diarrhoea, and line graphs indicate enteral nutrition. The proportion of patients with normal defecation increased from day 4, and the number of patients with diarrhoea increased from day 5. ICU, intensive care unit.

Table 1
Comparison of patient background data among the normal defecation, constipation, and diarrhoea groups.

Variables	Normal (n = 26)	Constipation (n = 47)	Diarrhoea (n = 12)	*p* value
Age, median (IQR)	62 (52–79)	67 (57–76)	73 (58–77)	0.658
Male, n (%)	15 (57)	35 (74)	5 (42)	0.070
BMI, mean (SD)	22.0 (20.1–26.1)	23.0 (20.2–27.1)	21.4 (18.7–23.5)	0.319
APACHE II score, median (IQR)	26 (21–34)	27 (21–30)	30 (26–31)	0.214
Disease for ICU admission, n (%)				
Cardiovascular	8 (31)	26 (55)	4 (33)	0.090
Respiratory	6 (23)	6 (13)	5 (42)	0.074
Cardiopulmonary arrest[a]	5 (19)	6 (13)	2 (17)	0.699
Neurology[a]	3 (12)	8 (17)	0 (0)	0.398
Sepsis[a]	2 (8)	1 (2)	0 (0)	0.551
Burn[a]	2 (8)	0 (0)	0 (0)	0.197
Necrotising fasciitis[a]	0 (0)	0 (0)	1 (8)	0.141
Comorbidity, n (%)				
Hypertension	6 (23)	17 (36)	2 (17)	0.290
Diabetes	9 (35)	8 (17)	2 (17)	0.197
Chronic kidney disease	7 (27)	8 (17)	5 (42)	0.177
Cancer[a]	5 (19)	7 (15)	4 (33)	0.333
Autoimmune disease[a]	1 (4)	3 (6)	1 (8)	0.839
Laboratory data, AUC, median (IQR)[b]				
White blood cell	26.0 (22.2–31.2)	21.2 (16.4–30.9)	22.3 (19.2–28.4)	0.175
C-reactive protein	24.18 (20.58 –33.50)	31.82 (21.42 –39.61)	26.77 (15.59 –31.80)	0.170
Albumin	5.0 (4.2–5.8)	5.0 (4.2–5.5)	4.3 (3.6–5.1)	0.200
Creatinine	2.15 (1.25–4.50)	2.12 (1.59–3.91)	4.00 (2.19–8.63)	0.293
Estimated glomerular filtration rate	113.5 (46.6 –192.2)	102.0 (57.4 –156.2)	59.5 (26.5–128.5)	0.329
Total bilirubin	1.5 (1.2–2.5)	2.3 (1.2–4.6)	2.9 (0.8–13.9)	0.139

BMI, body mass index; IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; AUC, area under the curve.
[a] Fisher exact test was performed. All other categorical variables were subjected to the χ^2 test.
[b] The AUC of the laboratory data was calculated from the values at the time of admission, peak, and 1 week later.

and diarrhoea prevention could be a bowel management protocol; however, it has been shown that the use of laxatives for constipated patients increases the risk of diarrhoea occurrence.[6] Symbiotics with dietary fibre and beneficial bacteria have been shown to be effective against diarrhoea and subsequently may be an appropriate therapy worth further consideration.[19] Furthermore, this intervention may be more effective if it is introduced before the fifth day after ICU admission when the occurrence of diarrhoea was observed to increase. If diarrhoea does occur, it is also important to take prompt action against electrolyte abnormalities and dehydration. In particular, appropriate monitoring of laboratory values and early detection of dehydration as well as electrolyte supplementation and fluid management are required.[20]

When investigating constipation or diarrhoea typically, one would divide them directly into two groups representing those with and without occurrence of the event; however, if we compare a group with constipation and a group without constipation, for example, patients with diarrhoea may be included in the group without constipation. Previous studies have not excluded these patients and, as such, the study design might have distorted the results. We were able to eliminate this misclassification bias by dividing the participants into three groups: normal defecation,

Table 2
Multivariable analysis of factors associated with the length of ICU stay.

Variables	B (95% confidence interval)	*p* value
Model 1: Constipation and normal defecation		
Constipation (ref. normal defecation)	6.082 (−1.591 to 13.755)	0.118
APACHE II score	0.313 (−0.170 to 0.796)	0.201
Fluid over	−4.660 (−12.556 to 3.235)	0.243
Propofol dosage	0.230 (−0.041 to 0.501)	0.095
Model 2: Diarrhoea and normal defecation		
Diarrhoea (ref. normal defecation)	7.534 (0.116 to 14.951)	0.047
APACHE II score	0.104 (−0.380 to 0.587)	0.666
Fluid over	9.596 (0.434 to 18.757)	0.041
Propofol dosage	0.059 (−0.291 to 0.410)	0.733

Linear regression analysis was performed with the length of ICU stay as the dependent variable. B is the partial regression coefficient.
ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 3
Multivariable analysis of factors associated with 28-day mortality.

Variables	OR (95% confidence interval)	*p* value
Model 1: Constipation and normal defecation		
Constipation (ref. normal defecation)	2.402 (0.417 to 13.842)	0.327
APACHE II score	1.019 (0.912 to 1.138)	0.741
Fluid over	1.966 (0.195 to 19.809)	0.566
Propofol dosage	1.015 (0.956 to1.078)	0.624
Model 2: Diarrhoea and normal defecation		
Diarrhoea (ref. normal defecation)	2.600 (0.385 to 17.574)	0.327
APACHE II score	1.016 (0.889 to 1.162)	0.812
Fluid over	0.605 (0.045 to 8.170)	0.705
Propofol dosage	1.052 (0.969 to 1.142)	0.230

Logistic regression analysis was performed with 28-day mortality as the dependent variable.
OR, odds ratio; APACHE, Acute Physiology and Chronic Health Evaluation.

constipation, and diarrhoea. Furthermore, this study is novel in that it describes the defecation status during the first week of ICU admission, which has not been done in previous studies.[8] Especially, investigation on the timing of the commencement of diarrhoea is particularly lacking in the literature; thus, our study could be a valuable resource.

This study has several limitations. First, all data were collected retrospectively based on electronic medical records; thus, unrecorded data could be not retrieved. At the facility under observation, information on the administration of injectable drugs was available, but information on the administration of oral drugs was not incorporated into the electronic medical record. Consequently, the use of intestinal peristalsis-promoting drugs, a risk factor for diarrhoea, was unknown and could not be analysed. In addition, the formulation and administration method of EN was based on the judgement of clinicians and as such was varied. To solve these problems, a prospective observation study is necessary; it is difficult, in a retrospective study, to adjust for variables such as GI peristalsis-promoting medications that affect both constipation and diarrhoea. Additionally, a preintervention and postintervention comparative study using EN and bowel management protocols may be necessary to eliminate large variations in interventions to improve GI peristalsis. Second, our findings are limited by the small number of diarrhoea cases; there were 12 patients with early-onset diarrhoea during the 1-year observation period. A multicentre study would be required to increase the sample size and eliminate chance errors. Third, since this study was conducted at a single university hospital, these results may not be generalisable to community hospitals or other institutions. Therefore, to increase the generalisability of the findings, the number of research facilities may need to be increased in future studies. Finally, because the recorded details of the nature and amount of defecation were dependent on the subjective evaluation of the nursing staff, they may have overestimated or underestimated the occurrence or severity of the diarrhoea. We aimed to avoid this by using a semiquantitative tool, but it might be better to introduce a more systematic instrument such as the Bristol Stool Form Scale or King's Stool Chart.[21–23]

5. Conclusions

In critically ill ventilated patients, early-onset constipation and diarrhoea occurred occasionally. In addition, early-onset diarrhoea was associated with the length of ICU stay. However, the causal relationship is unclear; thus, for clarification, larger, well-designed randomised control trials are needed to clarify it.

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CRediT authorship contribution statement

Gen Aikawa: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualisation, Writing original draft.

Akira Ouchi: Conceptualisation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing review and editing.

Hideaki Sakuramoto: Conceptualisation, Formal analysis, Methodology, Supervision, Validation, Writing review and editing.

Hoshino Tetsuya: Funding acquisition, Writing review and editing.

Yuki Enomoto: Formal analysis, Writing review and editing.

Nobutake Shimojo: Supervision, Writing review and editing.

Yoshiaki Inoue: Funding acquisition, Supervision, Writing review and editing.

Conflict of interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in Supplementary File 6.

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Appendix A. Supplementary data

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