Effect of holiday admission on clinical outcome of patients with upper gastrointestinal bleeding: A real-world report from Thailand

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ABSTRACT

Background: Holiday admissions are associated with poorer clinical outcomes compared with non-holiday admissions. However, data remain inconsistent concerning the “holiday effect” for patients with upper gastrointestinal bleeding. This study compared the differences between clinical courses of patients with upper gastrointestinal bleeding who were admitted on holidays and non-holidays in Thailand.

Methods: We retrospectively reviewed the medical records of patients with upper gastrointestinal bleeding confirmed by endoscopy who were admitted on holidays and non-holidays between January 2016 and December 2017. Mortality, medical resource usage, time to endoscopy, and clinical outcomes were compared between the groups.

Results: In total, 132 and 190 patients with upper gastrointestinal bleeding were admitted on holidays and non-holidays, respectively. Baseline characteristics, diagnosis of variceal bleeding, and pre-and post-endoscopic scores were not different between the two groups. Patients admitted on non-holidays were more likely to undergo early endoscopy, within 24 h of hospitalization (78.9% vs. 37.9%, \( p < 0.001 \)), and had a shorter median time to endoscopy (median [interquartile range]: 17 [12–23] vs. 34 [17–56] h, \( p < 0.001 \)) than those admitted on holidays. No significant differences in in-hospital mortality rate, number of blood transfusions, endoscopic interventions, additional interventions (including angioembolization and surgery), and length of stay were observed. Patients admitted on holidays had increased admission costs than those admitted on non-holidays (751 [495–1203] vs. 660 [432–1028] US dollars, \( p = 0.033 \)). After adjusting for confounding factors, holiday admission was a predictor of early endoscopy (adjusted odds ratio 0.159; 95% confidence interval, 0.096–0.264, \( p < 0.001 \)), but was not associated with in-hospital mortality or other clinical outcomes.

Conclusions: Patients with upper gastrointestinal bleeding who were admitted on holidays had a lower rate of early endoscopy, longer time to endoscopy, and higher admission cost than those admitted on non-holidays. Holiday admission was not associated with in-hospital mortality or other clinical outcomes.

1. Introduction

Upper gastrointestinal bleeding (UGIB) is a common problem worldwide. UGIB requires hospital admission, and the mortality rate remains at 5%–10% despite the significant development of both pharmacologic and endoscopic therapy [1, 2]. The management of patients with UGIB involves several processes and coordinated care from initial assessment, resuscitation, and stabilization, to obtain a definitive diagnosis and implementing therapy [3].

Theoretically, outcomes may be worse among patients with UGIB who are hospitalized on holidays. Several explanations have been postulated, such as lower staffing levels and the observation that patients often present with critical conditions on holidays [4, 5]. Endoscopy has become the management and diagnostic procedure of choice for UGIB cases [2]. In general, critically ill patients or those with high-risk scores undergo endoscopy within 24 h of admission [6, 7]. However, endoscopy suites may be unavailable or have limited services during holidays, which may contribute to frequent delays compared with normal working non-holidays [8, 9].
In several countries, previous studies on the outcomes of patients with UGIB based on the “holidays effect” compared with non-holiday admissions have yielded inconsistent results. Some studies have demonstrated higher mortality or adverse events for holiday admissions [10, 11, 12, 13, 14], whereas others did not find differences [15, 16, 17, 18]. Most previous studies on this topic were conducted in developed or high-income countries which may introduce limitations to the generalizability of the findings. Furthermore, the comprehensive data on the effects of holidays on other clinical outcomes and resource utilization for patients with UGIB are limited, especially in middle-income countries (where medical resources are relatively limited). This cohort study aimed to determine the holiday effect on clinical outcomes and medical resource use for patients with UGIB in Thailand.

2. Materials and methods

2.1. Study design and patient population

The present retrospective cohort study was conducted at Hatyai Hospital (a regional tertiary care hospital in southern Thailand) using medical records data from January 2016 to December 2017. The protocol was reviewed and approved by the Institutional Review Board of Hatyai Hospital (protocol number 39/2563) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the anonymization of patient information prior to analysis.

We included patients aged >18 years who were hospitalized because of UGIB symptoms (including hematemesis, coffee ground vomitus, the presence of maroon stool or melena, and hematochezia) and subsequently underwent endoscopy during the admission period. The exclusion criteria consisted of the presence of a UGIB history in the previous 3 months, a final diagnosis of non-UGIB after the endoscopic workup, admission for an elective procedure, or inadequate data for analysis. Holiday admission was defined as admission to the hospital from Friday afternoon 3 p.m. to Monday morning 7 a.m. or during public holidays, whereas non-holidays admission was defined as hospital admission on national office days from Monday to Friday.

All patients were treated as inpatients after initial assessment and hemodynamic stabilization according to the general management practices that are performed in our hospital for patients with UGIB. Pre-endoscopic management, including medications and blood transfusions, and time to endoscopy were determined by each attending gastroenterologist depending on the patient’s condition. Blood transfusion was considered at a hemoglobin level of \(<7\) g/dL or if shock was present \([19, 20]\). In our hospital, the endoscopic center provides on-call, 24 h/day therapeutic endoscopic services and consists of two endoscopists with >5 years of experience and five certified endoscopic nurses. All routine endoscopic sessions were performed between 9 a.m. and 4 p.m. from Monday to Friday. Beyond the normal office hours, patients were offered emergency therapeutic endoscopy if the clinical status was considered critical or a routine endoscopic session the next working day.

For patients with non-variceal UGIB (NVUGIB), endoscopic hemostasis was performed using injection therapy with diluted adrenaline together with a mechanical clip or thermal contact therapy in patients with high-risk lesions according to the Forrest classification \([21]\). Injection monotherapy was not allowed in our hospital \([1]\). Band ligation and cyanoacrylate injections were applied for esophageal and gastric variceal bleeding, respectively \([20, 22]\). If rebleeding occurred, all patients were scheduled for a second endoscopy. Consultation for angioembolization or surgery was performed for patients who failed to achieve endoscopic hemostasis or developed rebleeding despite making two attempts at adequate endoscopic intervention \([1]\). A transjugular, intrahepatic portosystemic stent or balloon-occluded retrograde transvenous obliteration was unavailable in our center.

2.2. Data collection

Patient data from medical records were manually reviewed retrospectively by two independent investigators (C.O. and N.P.), and a third investigator (A.C.) was consulted to resolve discrepancies or disagreements. For each patient, data were collected on age, sex, body mass index, comorbidities, medication usage, clinical manifestations of bleeding, vital signs, laboratory results on the admission date, and final diagnosis (according to endoscopic findings). The severity of UGIB in each patient was assessed according to the Glasgow-Blatchford score (GBS), Rockall score (RS), and AIMS65 score \([23]\). In addition, time to endoscopy, the need for and the number of blood transfusions, treatment (endoscopic/radiologic/surgical), in-hospital rebleeding and mortality, admission period, and costs were recorded.

2.3. Outcomes

The primary outcome was in-hospital mortality, which was defined as any death that developed during the admission period. The secondary outcomes were time to endoscopy, the need for and number of blood transfusions, endoscopic intervention, additional interventions (including angioembolization and surgery), in-hospital rebleeding, length of stay (LOS), and admission cost. The time to endoscopy was defined as the duration between admission and endoscopy. Early and delayed endoscopies were defined when the procedure was performed at \(<24\) and \(>72\) h after admission, respectively. Rebleeding was defined as the presence of new-onset UGIB associated with shock or a >2 g/dL decrease in the hemoglobin level. The presence of shock was indicated by tachycardia (>100 beats/min) or a calculated mean arterial pressure <65 mmHg. The admission cost was determined based on the total cost of the universal health coverage invoice.

2.4. Statistical analysis

Categorical variables were determined using frequency statistics and tested for significant differences using the Pearson chi-square or Fisher’s exact test as appropriate. Student’s-t-test and the Wilcoxon rank-sum test were used to assess significant differences among continuous variables. Univariate logistic regression analysis was used to examine the unadjusted odds ratios (ORs) for the primary and secondary outcomes. Multivariate logistic regression analysis was used to adjust for patient demographic factors, including sex, age, use of non-steroidal anti-inflammatory drugs and antiplatelet therapy, the presence of shock at initial assessment, fresh blood via nasogastric tube, hemoglobin, platelet count, serum creatinine, and GBS \([15]\). Analyses were performed using STATA version 15.1 software (StataCorp LLC, College Station, TX, USA). Statistical significance was set at \(p < 0.05\).

3. Results

3.1. Time of admission and baseline characteristics

A total of 322 patients met the inclusion and exclusion criteria and were included in the analysis. The mean patient age was 61 years, and 73% of them were male. Of the admissions of these patients, 190 (59%) were defined as non-holidays admissions, and 132 (41%) were defined as holiday admissions. There were no significant differences in baseline characteristics or comorbidities related to the time of admission between these two patient groups (Table 1).

3.2. Severity of upper gastrointestinal bleeding at admission

The mean systolic blood pressure did not significantly differ between the two groups. The incidence of fresh blood via nasogastric tube, history of syncope, and shock at the initial assessment were not significantly
different between the groups at the time of admission. Pre- and post-endoscopy risk scores (including GBS, AIMS65, and RS) were not significantly different based on the time of admission (Table 2).

3.3. Endoscopic diagnosis and outcomes

The endoscopic findings, outcomes, and medical utilization are presented in Table 3. The etiology of bleeding based on endoscopy was not significantly different between the two groups, and there were no differences in the incidence of variceal UGIB (VUGIB) and NVUGIB. The time to endoscopy for non-holidays admissions was shorter than that for holiday admissions with a median [interquartile range; IQR] of 17 h [12–23] vs. 34 h [17–56], respectively (p < 0.001). The rate of early endoscopy was higher for patients admitted on the non-holidays (78.9% vs. 37.9%, p < 0.001). However, the rate of delayed endoscopy between the two groups was not significantly different (6.3% vs. 10.6%, p = 0.17) (Table 3).

There were no significant differences between the holiday and non-holiday groups in the need for blood transfusion, additional interventions, rebleeding, or in-hospital mortality based on the time of admission. Furthermore, the number of required red blood cell transfusions and LOS were not significantly different between the groups based on the time of admission. However, the admission costs for patients admitted on holidays was higher than that of patients admitted on non-holidays (median [IQR] = 751 [495–1203] US dollars for holiday admission vs. 600 [432–1028] US dollars for non-holidays admission, p = 0.033).

3.4. Association of holiday admission with outcomes

Patients with UGIB who were admitted on holidays were less likely to undergo endoscopy within 24 h, even after adjusting for confounding factors (adjusted OR, 0.159; 95% confidence interval [CI], 0.096–0.264, p < 0.001) (Table 4). However, holiday admission was not associated with

| Variable | Non-holiday (N = 190) | Holiday (N = 132) | p-value |
|----------|-----------------------|-------------------|---------|
| SD, standard deviation; IQR, interquartile range; UGIB, upper gastrointestinal bleeding.

| Table 1. Baseline demographic data between weekend and holiday admission. |
|-------------------------------------------------|
| Variables                                      | Non-holiday (N = 190) | Holiday (N = 132) | p-value |
| Female sex                                     | 48 (25.3%)             | 38 (28.8%)         | 0.48    |
| Age (years): mean ± SD                         | 61.3 ± 16.8            | 60.5 ± 16.5        | 0.69    |
| Body mass index (kg/m²): mean ± SD             | 23.0 ± 4.8             | 23.1 ± 4.3         | 0.49    |
| History of UGIB                                | 2 (1.1%)               | 2 (1.5%)           | 1.00    |
| Co-morbidity                                   |                       |                   |         |
| None                                           | 100 (52.6%)            | 69 (52.3%)         | 0.95    |
| Hypertension                                   | 59 (31.1%)             | 42 (31.8%)         | 0.88    |
| Diabetic mellitus                              | 39 (20.6%)             | 28 (21.2%)         | 0.63    |
| Dyslipidemia                                    | 18 (9.5%)              | 10 (7.6%)          | 0.55    |
| Ischemic heart disease                         | 6 (3.2%)               | 1 (0.8%)           | 0.25    |
| Renal failure                                   | 16 (8.4%)              | 9 (6.8%)           | 0.60    |
| Cirrhosis                                       | 35 (18.4%)             | 28 (21.2%)         | 0.54    |
| Any malignancies                               | 15 (7.9%)              | 11 (8.3%)          | 0.89    |
| Medication                                      |                       |                   |         |
| Aspirin and/or clopidogrel                      | 12 (6.3%)              | 9 (6.8%)           | 0.86    |
| Warfarin                                        | 5 (2.6%)               | 2 (1.5%)           | 0.70    |
| Non-steroidal anti-inflammatory drug            | 20 (10.5%)             | 15 (11.4%)         | 0.81    |
| Corticosteroid                                  | 1 (0.5%)               | 1 (0.8%)           | 1.00    |
| Proton pump inhibitor                           | 8 (4.2%)               | 6 (4.5%)           | 0.89    |
| Laboratory                                      |                       |                   |         |
| Hemoglobin (g/dL): mean ± SD                   | 8.9 ± 3.4              | 9.0 ± 3.2          | 0.91    |
| Platelet count (x10³/µL): median [IQR]          | 201 [117–287]          | 187.5 [110–266]    | 0.58    |
| Albumin (mg/dL): mean ± SD                     | 3.2 ± 0.8              | 3.1 ± 0.7          | 0.27    |
| International normalized ratio: median [IQR]    | 1.12 [1.05–1.27]       | 1.48 [1.32–1.74]   | 0.91    |
| Blood urea nitrogen (mg/dL): median [IQR]      | 28 [16–52]             | 30 [17–47]         | 0.92    |
| Serum creatinine (mg/dL): median [IQR]         | 1.03 [0.79–1.45]       | 0.97 [0.80–1.31]   | 0.34    |
| SD, standard deviation; IQR, interquartile range.

| Table 2. Measures of the severity of upper gastrointestinal bleeding between weekend and holiday admission. |
|-------------------------------------------------|
| Variables                                      | Non-holiday (N = 190) | Holiday (N = 132) | p-value |
| Fresh blood via nasogastric tube                | 34 (17.9%)             | 35 (26.5%)         | 0.07    |
| History of syncope                              | 62 (32.6%)             | 44 (33.3%)         | 0.90    |
| Systolic blood pressure (mmHg): mean ± SD      | 119.8 ± 27.4           | 120.7 ± 26.1       | 0.77    |
| Shock                                           | 28 (14.7%)             | 16 (12.1%)         | 0.50    |
| Score: median [IQR]                             | 10 [6–13]              | 10 [6–12]          | 0.72    |
| AIMS65                                          | 1 [0–2]                | 1 [0–2]            | 0.72    |
| Rockall score                                   | 3 [2–4]                | 3 [2–4]            | 0.78    |
| SD, standard deviation; IQR, interquartile range.
an increased need for blood transfusions (adjusted OR, 1.445; 95% CI, 0.825–2.532, \(p = 0.19\)), rate of delayed endoscopy (adjusted OR, 1.776; 95% CI, 0.767–4.109, \(p = 0.18\)), endoscopic intervention (adjusted OR, 0.686; 95% CI, 0.393–1.197, \(p = 0.20\)), additional interventions (adjusted OR, 0.624; 95% CI, 0.053–7.336, \(p = 0.62\)), rebleeding (adjusted OR, 2.721; 95% CI, 0.617–12.003, \(p = 0.20\)), or in-hospital mortality (adjusted OR, 1.872; 95% CI, 0.705–4.969, \(p = 0.19\)), when compared to non-holiday admission.

Subgroup evaluation was performed to assess the effect of holiday admission on outcomes in patients with NVUGIB and VUGIB separately using multivariate analysis (Table 4). As observed after examining all UGIB cases, after adjusting for confounders, patients admitted on holidays were less likely to undergo early endoscopy for both NVUGIB (adjusted OR, 0.159; 95% CI, 0.0.089–0.283, \(p < 0.001\)) and VUGIB (adjusted OR, 0.075; 95% CI, 0.019–0.304, \(p < 0.001\)). Among patients with NVUGIB, admission on holidays was not a predictor of the need for blood transfusion (adjusted OR: 1.321; 95% CI, 0.690–2.530, \(p = 0.40\)), rate of delayed endoscopy (adjusted OR, 2.003; 95% CI, 0.723–5.554, \(p = 0.18\)), endoscopic intervention (adjusted OR, 0.750; 95% CI, 0.391–1.436, \(p = 0.39\)), and additional interventions (adjusted OR, 0.624; 95% CI, 0.053–7.336, \(p = 0.71\)), while holiday admission was marginally associated with rebleeding (adjusted OR, 6.809; 95% CI, 0.969–47.854, \(p = 0.054\)), and in-hospital mortality (adjusted OR, 4.268; 95% CI, 0.973–18.723, \(p = 0.054\)). For patients with VUGIB, holiday admission was not an independent predictor of the need for blood transfusion (adjusted OR, 1.768; 95% CI, 0.501–6.241, \(p = 0.88\)), endoscopic intervention (adjusted OR, 0.71), rate of delayed endoscopy (adjusted OR, 1.153; 95% CI, 0.179–7.402, \(p = 0.36\)), rebleeding (adjusted OR, 0.027; 95% CI, 0.000–1.00), or in-hospital mortality (adjusted OR, 0.947; 95% CI, 0.189–4.735, \(p = 0.95\)).
4. Discussion

This cohort study was based on a medium series of patients hospitalized for UGIB and reflects the “real-life” outcome data from a regional tertiary hospital in a middle-income country. Our study demonstrated the following main outcomes: First, there was no significant difference in hospital mortality between patients who were admitted on holidays and non-holidays. Second, patients who were admitted on holidays were likely to have longer wait times for endoscopy, lower rates of early endoscopy, and higher admission costs compared with those who were admitted on non-holidays; there were no significant differences in clinical outcomes or other medical resource usage. Third, after adjusting for confounding factors, holiday admission was associated with early endoscopy but was not associated with in-hospital mortality or other clinical outcomes among patients with overall UGIB, NVUGIB, or VUGIB.

A growing number of health service studies have revealed that increased mortality is associated with hospital admission on holidays, raising concerns regarding the quality of care in emergency situations. Studies have demonstrated that patient care on holidays increases the risk of medical error, resulting in a higher incidence of preventable adverse events [24, 25]. However, data on the impact of this so-called “holiday effect” on patients admitted with UGIB remain inconclusive. Some studies have reported a significantly increased rate of adverse outcomes [5, 13, 14, 26, 27, 28], whereas others failed to demonstrate the holiday effect [15, 16, 17, 18, 29, 30, 31, 32, 33]. However, most previous studies have not distinguished between variceal and non-variceal bleeding. Many differences exist between variceal and non-variceal bleeding, including management and prognosis [23], which may influence the relevance of the results. Recently, a prospective multicenter study conducted in a large Italian population did not reveal any differences in terms of robust clinical outcomes for either NVUGIB or VUGIB patients admitted during the weekend compared to weekdays [34]. Consistently, our results did not indicate a holiday effect on in-hospital mortality or other adverse effects in patients with overall UGIB or when we stratified the patients according to the presence of NVUGIB and VUGIB. The non-significant effect of holiday admission was confirmed following adjustment for confounding factors in the multivariable regression analyses, which is consistent with previous studies [17].

Currently, advances in the treatment of patients with UGIB include improvement of general care, more potent medication, and increased use of dual endoscopic therapy, which result in better outcomes. Shaheen et al. reported that admissions for UGIB during the period from 2000 to 2005 were reduced by 25% compared with those from 1993 to 1999 [5]. Endoscopy performed within 72 h of admission provides a favorable outcome in patients with UGIB, especially by reducing the rebleeding rate. Moreover, early endoscopy, within 24 h of admission, is recommended for critically ill patients or those who are stratified as high-risk patients [6, 7]. Available therapeutic endoscopic services and physicians with endoscopic expertise play a major role in the treatment success rate [1, 7]. A nationwide study of American UGIB admissions conducted by Ananthakrishnan et al. reported similar outcomes for holiday admission among patients who underwent emergency endoscopy and a significantly increased mortality rate among patients who did not undergo endoscopic intervention [35]. Applying these results, the endoscopic unit must be appropriately resourced to provide a 24/7 service 365 days a year with an adequate number of experienced staff [31]. Previous studies have revealed that the holiday effect did not influence outcomes for UGIB patients in centers where full-time therapeutic endoscopic services were available [15, 16, 36].

To best of our knowledge, this is the first study to evaluate the holiday effect on real-world management of UGIB in a middle-income country. Given some of the limitations of using endoscopy for UGIB in our center, the endoscopic unit still provides an on-call, 24 h/day therapeutic endoscopic service. Outside of the normal office hours, emergency endoscopy was performed only for patients who were considered to be critically ill or at an increased risk of death. Those without severe bleeding were scheduled for a routine endoscopy on the next working day. Because of this practice, the waiting time for endoscopy observed in our study was significantly longer in holiday admission and only 37.9% of patients who were admitted on holidays underwent early endoscopy. Although the length of hospital stay (which is a main determinant for admission cost) did not differ between the two groups, there was some difference in cost between patients before and after endoscopy. For example, patients (particularly cases with ongoing bleeding) usually require more intensive monitoring and aggressive resuscitation while waiting for endoscopy than after the endoscopy. After endoscopy, PPI could be a step down for cases with low-risk of rebleeding. This could explain why the longer waiting time for endoscopy would also lead to increased costs during hospitalization [37, 38], which was observed for holiday admissions in our study. To reduce the waiting time for endoscopy and minimize the medical resource use, it is necessary to reduce the gap of endoscopic skills, and efficient and safe care should be implemented regardless of the day of admission.

However, mortality and other clinical outcomes were not affected by the time of admission for patients with either overall UGIB or subgroups of UGIB. These results suggested that effective triage for selecting patients who are at higher risk of death or adverse outcomes and performing necessary emergency endoscopy may be an important aspect in decreasing the holiday effect. Furthermore, this strategy may be considered acceptable when facing holiday admissions in areas with limited medical resources. Recent studies have demonstrated a lack of association between early endoscopy and treatment outcomes in patients with UGIB who have an average risk [39, 40]. To confirm the beneficial effects of early endoscopy on patients with UGIB, future trials with multiple different setting and/or larger population are needed.

Several studies have suggested that patients who were admitted on weekends were more critically ill than those admitted on non-holidays [12, 15, 16]. We did not find significant differences in comorbidities or shock status based on the time of admission. Furthermore, there was no significant difference in age, hemoglobin level, and pre-or post-endoscopy scores depending on the time of admission.

Our study had some limitations. First, this is a single center study, consisting of only Thai patients, and the study results may not apply to other populations. Second, this study was retrospective in nature. All variables were evaluated after medical chart reviews, which may have resulted in misclassification bias along with data that may have been missed. However, errors that may have arisen from the resulting bias were minimized by using two independent reviewers, and a third reviewer made the final decision when discrepancies were found. Third, the study population size was relatively small and may lack statistical power to detect significant differences between the study groups due to type 2 error, especially when considering the rarity of some outcomes. In particular, for NVUGIB, the difference in rebleeding and mortality was not significant but a trend towards a worse outcome for holiday admission was indicated. Fourth, we evaluated the all-cause mortality of the patients. In our opinion, gastrointestinal bleeding-related mortality may have been a more appropriate endpoint; however, this endpoint was challenging to define. Fifth, there was different definition of “holiday” in our study, compared to the study of Ananthakrishnan et al., which could be a confounder for comparing studies on this topic. Sixth, this study did not cover the comparison between the outcome after the working hours in non-holidays and the whole holidays hours. Finally, we did not evaluate the 30-day mortality and rebleeding rates. The LOS in this study was <7 days. Therefore, the hospitalization period may have been too short for accurate interpretations of the differences between the two groups.

5. Conclusions

Patients with UGIB who were admitted on holidays had a lower rate of early endoscopy, longer wait time to endoscopy, and higher admission costs than those who were admitted during non-holidays. Holiday
admission was negatively associated with early endoscopy without association with in-hospital mortality or other clinical outcomes. Our findings may be useful to create appropriate management policies that affect staffing and access to care over the holidays or weekends for patients with UGIB and other patients.

Declarations

Author contribution statement

Arunchai Chang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Chokethawee Ouejiaraphant: Performed the experiments; Analyzed and interpreted the data. Nuttani Pungpipattrakul; Keerati Akarapatima: Performed the experiments. Attapon Rattanasupa: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. Maruthy Phrayakuly: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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