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STUDY PROTOCOL

Prospective and multicenter study on clinical-biological factors predictive of chronic colon diverticulitis: DICRO Trial

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Abstract

Purpose This manuscript presents the protocol for a prospective, multicenter study aimed at identifying prognostic factors for the recurrence of diverticulitis. The design, methodology, and analysis plan are detailed, providing a comprehensive framework for evaluating clinical endpoints and intervention outcomes in patients with diverticulitis.

Methods Clinical, observational, prospective, and multicenter study of patients diagnosed with acute diverticulitis in the Emergency Department (ED) of 5 Spanish hospitals. The inclusion criteria were patients with acute diverticulitis who did not require emergency surgery. A 2-year follow-up will be carried out. The main objective is the description of prognostic factors of new episodes of acute diverticulitis and the creation of a therapeutic algorithm to select patients who could benefit from early elective surgery. Secondary endpoints are descriptive analyses of quality of life at different periods to establish the evolution of the disease and to correlate symptoms with systemic and local inflammatory markers; and sub-analysis of immunosuppressed patients to assess disease virulence.

Conclusion Determination of a marker predictive of recurrent disease or chronic inflammation would be of benefit in developing a good treatment strategy. One group that would particularly benefit is immunosuppressed patients.

Trial registration ClinicalTrials.gov Identifier: NCT04407793.

Keywords Acute diverticulitis · Chronic diverticulitis · Recurrence · Diverticulitis treatment · Fecal calprotectin

Background

Diverticular disease of the colon significantly impacts the healthcare system due to its prevalence and morbidity. Although many individuals with diverticula remain asymptomatic, the prevalence of the condition appears to increase with age, affecting an estimated 5–25% of those in their 50 s and 50–60% of individuals over 80 years old [1]. The spectrum of diverticular disease varies from symptomatic uncomplicated diverticular disease (SUDD) to symptomatic complicated forms. Specifically, phlegmonous diverticulitis is classified as uncomplicated and accounts for approximately 70% of acute diverticulitis cases, highlighting the varied progression of the disease. Identifying at-risk patients in the early uncomplicated stages is crucial to prevent complications and administer appropriate medical or surgical interventions [2]. Approximately 25% of patients who experience diverticulitis will have recurrent episodes after initial conservative management [3], while around 33% may continue to suffer from symptoms such as abdominal pain or changes in bowel habits, which pose significant social and economic challenges [4, 5].

The management of diverticular disease remains controversial. Recent European guidelines [6] have introduced new treatment protocols for acute diverticulitis, including non-antibiotic strategies [2, 6]. There is a trend towards outpatient treatment for diverticulitis, with fewer patients requiring emergency surgery and increased utilization of elective laparoscopic surgery [7, 8]. However, debates continue regarding the best approach for treating patients who experience recurrent acute diverticulitis or persistent symptoms following acute episodes. Existing studies on the

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management of these patients are limited, varied, and often retrospective.

Traditionally, the recommendation has been to consider colonic resection after a second episode of acute diverticulitis due to the higher likelihood of poor response to medical treatment in subsequent episodes, which can increase morbidity and mortality [9]. Quality of life is a critical factor for monitoring these patients; data suggest that 40% of those treated conservatively for diverticulitis may ultimately require surgery due to complications or lingering symptoms [10, 11]. Researchers postulate the existence of chronic latent inflammation that may disrupt intestinal motility and cause visceral hypersensitivity, which could lead to frequent gastrointestinal symptoms or exacerbated diverticulitis episodes. Studies indicate that between 6.8 and 27.7% of patients treated conservatively for acute diverticulitis may need surgical intervention due to recurrent episodes or persistent abdominal issues, especially within the first year of follow-up [8, 12].

During follow-up, the main reason cited for elective colectomy is recurrent diverticulitis or ongoing abdominal pain adversely affecting patient quality of life. In certain cases, initial antibiotic treatments may fail, resulting in subacute or chronic diverticulitis [9]. Distinguishing between unresolved persistent diverticulitis and true recurrence is often challenging [13]. Recurrent diverticulitis is typically defined as three or more episodes exhibiting clinical signs within a 2-year timeframe, with a necessary symptom-free interval of at least 3 months between episodes to qualify as a recurrence [11]. Selecting the right candidates and timing for elective surgery poses significant challenges, especially for patients with persistent abdominal pain resembling irritable bowel syndrome (IBS). Differentiating IBS from symptoms following diverticulitis is critical since IBS is a functional disorder that should not generally be addressed with surgical intervention. It is worth noting that 25% of patients continue to experience functional symptoms and/or abdominal pain following elective sigmoidectomy, with IBS present in 14% of these cases [14].

Immunosuppressed individuals who experience acute diverticulitis require special consideration due to typically more aggressive presentations compared to immunocompetent patients, including a higher incidence of perforation [6]. Among post-transplant patients, acute diverticulitis occurs in 1.7% of cases, with a complicated presentation in 40%. In contrast, the rate of complicated diverticulitis in immunocompetent patients is between 10 and 15% [15]. Patients using chronic corticosteroids for over 3 months face a heightened risk for urgent surgery and recurrence, particularly within the first year after the initial diverticulitis episode [6, 16]. Within the immunocompromised cohort, there is ongoing debate about the optimal therapeutic strategy, whether it be elective sigmoidectomy or clinical observation [18]. Recent European guidelines indicate that elective surgery following a single acute diverticulitis episode is also unwarranted in these patients due to similar complications and mortality rates observed whether following one or multiple episodes. Furthermore, surgical risks tend to be elevated among immunocompromised patients, necessitating individualized evaluations [18].

Chronic diverticulitis, initially recognized by the ESCP group, is characterized by thickening of the colonic wall and persistent inflammation of the mucosa [2]. This condition can significantly affect a patient's quality of life, leading to ongoing abdominal symptoms such as pain and bloating, as well as alterations in bowel habits. A key challenge is the limited understanding of the chronic nature of diverticular disease, compounded by a lack of studies that effectively demonstrate this chronic inflammatory state. Identifying these factors is essential for developing optimal therapeutic strategies.

Endoscopy offers a valuable method for directly assessing the condition of the colonic mucosa, including its lesions, extent, and severity. This approach allows for the objective evaluation of organic disease, helping to differentiate it from functional disorders [19]. The degree of mucosal involvement is directly linked to disease activity and serves as a crucial diagnostic tool. Furthermore, insights gained from endoscopic findings can aid in predicting the risk of recurrence, a capability that has been well-established in the context of inflammatory bowel disease (IBD).

However, literature concerning predictors of recurrence and chronic diverticulitis remains sparse [20]. Notably, when comparing diverticular disease and IBD, both conditions demonstrate that active inflammation during acute phases correlates with the migration of neutrophils and leukocytes to the intestinal area. Certain neutrophil proteins, measurable in feces, serve as valuable biomarkers, indicating local gastrointestinal inflammation [21]. Fecal markers, particularly calprotectin, are non-invasive tests with high sensitivity and specificity for detecting such inflammation. Calprotectin, released by neutrophils, provides a measurable indication of inflammatory activity, thereby distinguishing true inflammation from functional bowel alterations [22, 23]. Interestingly, patients exhibiting a longer extent of colonic involvement tend to have elevated levels of fecal calprotectin, which may correlate with an increased risk of recurrence [24]. While an increase in fecal calprotectin has been noted during follow-up of patients with acute diverticulitis [20, 22], current evidence does not support its role as a reliable predictor of recurrence or its connection to worsening persistent abdominal symptoms. Therefore, the primary aim of this project is to identify potential prognostic factors for the recurrence of acute diverticulitis, including fecal calprotectin and to develop a therapeutic algorithm that can guide clinical practice and improve patient outcomes.

Methods/design

This is a clinical, observational, multicenter, prospective trial involving patients, diagnosed with acute diverticulitis in the emergency department (ED) of the participating hospitals, who meet the inclusion and exclusion criteria of the study. Patients will be followed for a minimum of 2 years.

The primary endpoint of this study is to confirm fecal calprotectin such as prognostic factor of acute diverticulitis recurrence and its association with symptomatic diverticular chronic disease.

Secondary endpoints include (1) exploring the relationship between systemic and local inflammatory markers and both recurrence and persistent symptoms following conservatively managed mild or complicated diverticulitis; (2) conducting a sub-analysis of immunosuppressed patients to evaluate disease virulence; (3) assessing the evolution of the disease through quality of life (QoL) questionnaires and correlating patient-reported outcomes with inflammatory markers to validate the chronic diverticulitis profile; and (4) supporting the creation of a diagnostic-therapeutic algorithm to guide treatment strategies and prevent complications such as recurrence, fistulization, and stenosis.

Data collection will be carried out at each center included in the project through an online database. Statistical analysis, presentation of results, discussions, and conclusion drawing will be conducted by the organizing team located at the University Hospital of Bellvitge.

Hypothesis and objectives Due to the lack of consensus on the therapeutic management of patients with recurrent episodes of diverticulitis or persistent symptoms, these individuals are treated at the discretion of each surgeon [8]. It is unclear whether this condition represents a sustained inflammatory response or a functional disorder, and distinguishing between the two is essential for guiding appropriate treatment. The scientific evidence concerning recurrent and chronic diverticulitis is scarce, resulting in an information gap that makes it difficult to determine whether a patient with acute diverticulitis has a high or low probability of recurrence, as well as when it might occur. Vulnerable groups, such as immunosuppressed patients, would particularly benefit from early treatment to prevent more severe episodes [16].

Our hypothesis is that after an episode of acute diverticulitis, a chronic inflammatory process may persist, leading to sustained abdominal symptoms, recurrent acute episodes, and/or chronic complications such as fistulas to neighboring organs and colon stenosis. Certain systemic inflammatory markers, in conjunction with others like fecal calprotectin, may help predict the recurrence of acute episodes and/or chronic abdominal symptoms.

The primary objective of this project is to identify prognostic factors for future episodes of acute diverticulitis and to develop a therapeutic algorithm that can guide the selection of patients who might benefit from early elective surgery. Secondary objectives include conducting a descriptive analysis of quality of life (QoL) across different periods, establishing the evolution of the disease, and correlating symptoms with systemic and local inflammatory markers. A sub-analysis of immunosuppressed patients will also be performed to assess disease virulence.

Study setting and participants All consecutive patients clinically diagnosed with acute diverticulitis of the colon and with radiological confirmation by abdominal CT scan who come to the ED of the participating hospitals will be subjects of this study.

All patients, who meet the inclusion criteria, do not present any exclusion criteria and voluntarily agree to participate in the study after having been visited and diagnosed in the following hospitals will be included: *Hospital Universitari de Bellvitge*, *Hospital de Sant Joan Despí Moisès Broggi*, *Consorci Sanitari Parc Taulí*, *Hospital Universitari Josep Trueta*, and *Hospital Germans Trias i Pujol*. All patients will receive an information sheet and informed consent form. Once the patients are considered eligible and have formulated their questions and/or doubts to the researcher, they will be included. All institutions belong to the Spanish Public Health Care System.

Inclusion criteria

Eligible participants include (i) individuals aged ≥ 18 years; (ii) those with radiological confirmation of acute diverticulitis via a computed tomography (CT) scan; (iii) patients undergoing non-surgical management; and (iv) individuals who have signed an informed consent form. Patients with immunosuppression (IMS) will also be eligible for inclusion. IMS is defined as the presence of conditions that lead to decreased host defenses, including solid organ transplantation, active extracolonic malignancies, cytotoxic chemotherapy, emphysema, arthritis, and other collagen-vascular diseases, pulmonary and congenital fibrosis, or acquired immunodeficiency syndrome. Additionally, patients with a concurrent history of immunosuppressive medication—such as chronic glucocorticoids, azathioprine, cyclosporine, methotrexate, tacrolimus, and anti-tumor necrosis factor agents—will also be included.

Exclusion criteria

(i) Patients who do not provide informed consent will not be eligible to participate in the study; (ii) radiological confirmation of severe diverticulitis requiring urgent surgery during admission (patients with earlier episodes will be included in the study); (iii) radiological suspicion of colon cancer; (iv) pregnancy or breastfeeding; (v) a history of acute diverticulitis in the previous year before the study begins; (vi) a history of inflammatory bowel disease; (vii) cognitive or psychiatric disorders; and (viii) patients with irritable bowel syndrome (Rome IV criteria).

Withdrawal criteria

Exitus is due to causes unrelated to treatment or acute diverticulitis; patient request for withdrawal from the study; discovery of neoplastic colon pathology during follow-up; or requiring emergent or elective surgery for diverticulitis during follow-up.

Informed consent and legal considerations

The trial is conducted in accordance with the Declaration of Helsinki (7 th revision) and the Spanish laws and regulations for biomedical research, with authorization from the Spanish Agency for Drugs and Medical Devices (Agencia Española del Medicamentos y Productos Sanitarios, AMPES). The trial protocol, patient information, and informed consent sheets have been approved by the competent Ethics Committees of all participating trial centers. The trial has been registered at the ClinicalTrials.gov database (NCT04407793.; https://clinicaltrials.gov).

All eligible patients are given an initial verbal description of the proposed study, and interested individuals sign a written informed consent form. During the trial, patients are identified solely by an individual and anonymous identification code. Trial findings are stored in accordance with Spanish data protection law (Law 15/1999 on the protection of personal data) and handled in strict confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized people. All personal information will be processed in accordance with the provisions of Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of digital rights in Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016.

Trial interventions

Patients with acute diverticulitis attending the emergency department (ED) of each participating center, and who meet the inclusion and exclusion criteria, will be enrolled in the study. Baseline data will be collected in the ED: a blood sample will be obtained upon arrival, including tests for C-reactive protein (CRP), albumin, blood counts, and total leukocyte count. Subsequently, the following markers of systemic inflammation will be calculated: the neutrophil–lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, and the Modified Glasgow Prognostic Score. Additionally, SF12 and GIQLI quality of life (QoL) questionnaires will be administered and completed by patients in the ED. Each patient will receive a ScheBo® Quick-Prep BUHLMANN tube, specifically designed for collecting the first stool sample following a diagnosis of diverticulitis. This tube not only ensures optimal storage conditions for the detection of fecal calprotectin but also allows for quick processing and analysis of the sample. The test has been selected for its proven reliability, fast turnaround time, and high sensitivity in detecting inflammation. In addition, the working protocol with this kit is designed to be simple and intuitive with a lower risk of error. This procedural simplicity contributes to the standardization of sample handling and improves reproducibility across different centers.

Patients are instructed to return the tube to the laboratory during their hospital stay or within 7 days of diagnosis, ensuring the sample is kept refrigerated at a temperature between 2 and 8 °C until analysis.

Patients are included in the study in the emergency department (ED) when there is an episode of acute diverticulitis, and there is no exclusion criteria, receiving:

1. *A blood test* (leukocyte count and differential, CRP, and albumin levels)
2. *Fecal calprotectin*: a ScheBo® Quick-Prep BUHLMANN collection kit. Patients are instructed to return the sample within 7 days after the acute episode or during their stay at the hospital.
3. *Quality of life questionnaires (SF-12 and GIQLI)* baseline.

After acute diverticulitis episode, patients are followed up at 3 months, 6 months, 1 year, 18 months, and 2 years at the outpatient clinic (Fig. 1). At each follow-up visit, the following assessments will be performed:

1. *Demographic and clinical data collection*: including age, sex, history of previous episodes of acute diverticulitis and their dates, alcohol, and/or tobacco consumption, physical activity, prior immunosuppression, and any factors that may influence fecal calprotectin values (e.g., medications).
2. *Blood tests*: leukocyte count and differential, CRP, and albumin levels.

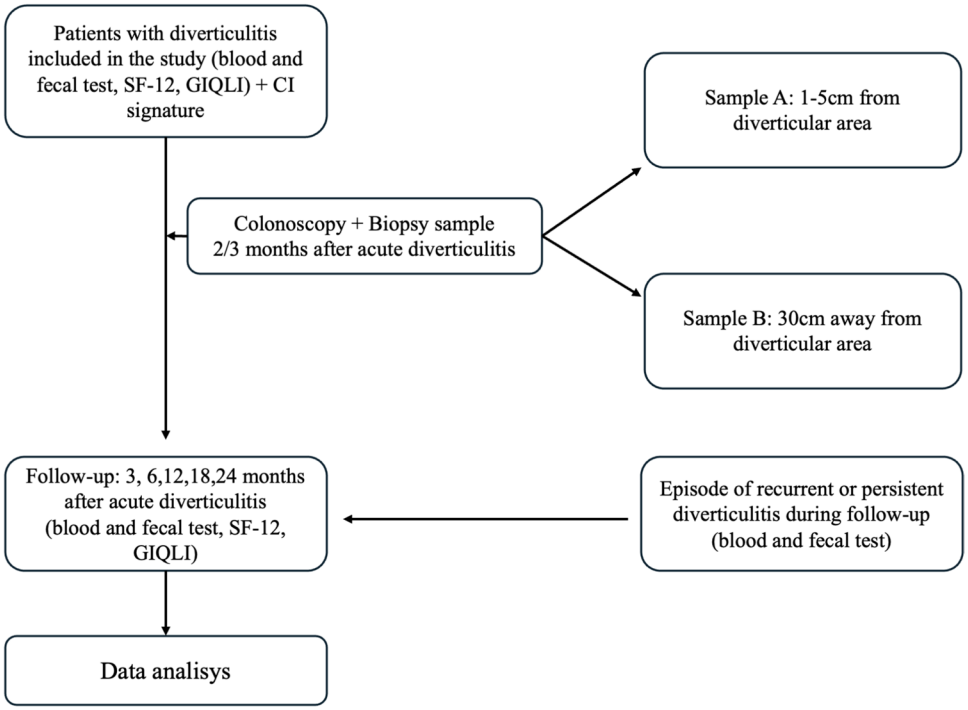

Fig. 1 Follow-up

3. *Fecal calprotectin*: a ScheBo® Quick-Prep BUHLMANN collection kit will be provided at each scheduled visit for stool sample collection.
4. *Quality of life questionnaires (SF-12 and GIQLI)*: will be administered and completed by the patient at each follow-up visit.
5. *Colonoscopy*: will be scheduled between 2 and 3 months after the first episode. During the colonoscopy, mucosal findings will be assessed using the May classification. Biopsies will be obtained from: (A) 1–5 cm of the diverticulum involved during the episode and (B) 30 cm from the area affected by diverticulitis. These samples will be analyzed for local inflammatory markers (e.g., macrophages, mast cells, and eosinophils) to compare patients with recurrent diverticulitis, those with a single episode, and those with chronic diverticulitis.

In the event of a relapse or recurrence during follow-up, a new blood test, and stool collection for fecal calprotectin analysis will be performed in the emergency room or upon hospital admission. Patients experiencing a recurrence will continue to be followed completing the study's follow-up period.

Patients who undergo surgical treatment—whether during follow-up, after several acute diverticular episodes, or chronic symptomatic diverticular disease—are not excluded from the study. Follow-up ends at the time of surgery, but this is not an exclusion criteria. Their data up to the point of surgery will be analyzed.

Each center participating in the study will be responsible for collecting and entering its own data into a centralized database specifically designed for the study. For fecal calprotectin testing, Bellvitge Hospital will coordinate the procurement and periodic distribution of the fecal sample collection kits (ScheBo® Quick-Prep BUHLMANN) to each participating center. Once data from all centers is collected, the final analysis will be conducted by the sponsoring center, Bellvitge Hospital.

Study endpoints

Primary endpoint

Primary endpoint of this study is to confirm fecal calprotectin such as prognostic factor of acute diverticulitis recurrence and its association with symptomatic diverticular chronic disease. These findings will support the development of a diagnostic-therapeutic algorithm to guide clinical decision-making, particularly in identifying patients who could benefit from early elective colonic resection and determining the optimal timing for such interventions.

Secondary endpoints

1. To investigate the relationship between systemic and local inflammatory markers and both the recurrence of acute diverticulitis and the persistence of symptoms

following conservatively treated mild or complicated diverticulitis.
2. To conduct a descriptive analysis of quality of life (QoL) across different time points in order to assess disease progression and correlate patient-reported outcomes with systemic and local inflammatory markers, thereby confirming the existence of chronic diverticulitis.
3. To perform a sub-analysis of immunosuppressed patients in order to evaluate the virulence and clinical course of the disease in this subgroup.
4. To validate a therapeutic algorithm aimed to guide treatment strategies for chronic diverticular disease or patients with multiple acute episodes, at preventing complications such as recurrent acute episodes, fistula formation, and stenosis.

Sample size

The sample size was calculated based on prior data from a cross-sectional study conducted at the Emergency Department of Bellvitge University Hospital in 2017. In that study, 73 patients diagnosed with acute diverticulitis were treated conservatively. At 2 years of follow-up, 21% of these patients experienced a recurrence. Assuming an alpha risk of 0.05, a beta risk of 0.20 (80% power), and a bilateral hypothesis test, and estimating a proportion of 0.90 in the control group, we determined that a total of 500 patients with diverticulitis are required. This sample size also accounts for the inclusion of up to 10 candidate prognostic predictors in multivariable analysis, ensuring sufficient power to detect meaningful associations with recurrence and chronic symptoms.

Statistical analysis

The principal aim is to perform a descriptive analysis and then a multivariate analysis to detect prognostic values for recurrence of new episodes of diverticulitis.

For the study of variables, a comparison of systemic and local inflammatory markers, baseline, and follow-up between patients who relapsed and those who did not during the period was analyzed. Description of prognostic markers of a new acute diverticulitis crisis was done by bivariate and multivariate analysis. Patients' quality of life as measured by QoL questionnaires will be included in the analysis of prognostic factors. Calculation of the ROC curve for the different quantitative variables was also made.

For the statistical comparison of qualitative variables, the chi-square test (or Fisher's exact test when the conditions of application require it) will be used. For the comparative analysis of quantitative variables, the Student's *t*-test or Mann–Whitney *U*-test will be used always after checking the normality of the data distribution. ANOVA and Kruskall-Wallis for more than 2 categories were used, respectively. Variables that have shown a significant association ($p < 0.05$) in the bivariate study or are clinically relevant will be considered, as well as possible confounding factors in multivariate analysis. Survival analysis (Kaplan–Meier and Cox), linear mixed models, cluster analysis and logistic regression will be performed to study the different objectives.

Statistical significance (always bilateral) will be less than or equal to 5% ($p < 0.05$). Statistical analysis will be performed with R version 4.3.

Discussion

Diverticular disease, while generally classified as benign, ranks as one of the most significant gastrointestinal conditions due to its clinical implications and impact on patients' quality of life [9]. The unpredictability of this disease, particularly in patients experiencing mild to moderate diverticulitis, complicates its management. Currently, there is no established consensus for treating patients who face recurrent episodes or persistent symptoms, leading to uncertainty regarding whether these cases represent a sustained inflammatory condition or a functional disorder. This distinction is crucial, as it guides the appropriate management strategies for affected individuals.

A major knowledge gap exists regarding the likelihood of recurrence in patients who experience acute diverticulitis. The inability to predict the likelihood of further episodes not only hampers effective management but also raises concerns about the potential for more severe complications. Additionally, the absence of objective markers to gauge inflammatory activity means that clinicians must rely on subjective evaluations, which can further complicate treatment decisions.

The insights gained from this study could be pivotal in developing standardized treatment protocols for those suffering from chronic diverticular disease. Establishing clear prognostic factors may also aid in recognizing patients at higher risk for more severe disease outcomes, particularly in vulnerable populations like the immunocompromised. Early intervention strategies could possibly mitigate the risks of exacerbated episodes, enhancing the overall quality of care. Furthermore, identifying reliable prognostic markers, such as fecal calprotectin, could revolutionize how we monitor and manage diverticular disease and its potential recurrence. By embedding these findings into clinical practice, we could enhance our understanding of chronic diverticulitis and inspire new, more effective treatment modalities. The anticipated results from this study hold the promise of reshaping existing management strategies, ensuring that patients receive targeted treatment, thereby optimizing health outcomes and reducing the burden associated with this prevalent condition.

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Author contribution We certify that we have participated sufficiently in the work to take public responsibility for the appropriateness of the experimental design and method. The authors warrant that the article is the author's original work and has not been published before.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors declare no competing interests.

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