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Randomised controlled trial of early magnetically controlled capsule endoscopy for the prevention of gastrointestinal bleeding in patients at high bleeding risk scheduled for percutaneous coronary intervention: MACE-GPS study protocol

Minghui Li, Rong Liu, Yongjian Wu

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Department of Cardiology, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

Correspondence to
Dr Yongjian Wu;
yongjianwu_fuwai@sina.com

ABSTRACT

Introduction Limited data are available regarding the decision-making process for preventing gastrointestinal bleeding in patients at high risk of bleeding scheduled for percutaneous coronary intervention (HBPCI), especially due to the lack of a simple, accurate and sensitive methods for gastrointestinal injury detection. This randomised trial aims to assess the effects of early magnetically controlled capsule endoscopy (MCE) in patients with HBPCI for the prevention of gastrointestinal bleeding compared with conventional management.

Methods and analysis The Magnetic-Assisted Capsule Endoscopy Gastrointestinal bleeding Protection Strategy (MACE-GPS) is a multicentre, open-label, randomised controlled trial. Patients admitted for HBPCI will be randomised and placed into two study groups. In the early MCE group, 1228 patients will undergo MCE following admission to the hospital. If necessary, these patients may further undergo a multidisciplinary approach to determine treatment based on the MCE findings. A total of 1228 patients in the control group will undergo conventional treatment based on the attending cardiologist's interpretation of their clinical presentations. The primary end point is the incidence of gastrointestinal bleeding within 12 months of enrolment.

Ethics and dissemination The MACE-GPS trial has been approved by the ethics committees of all participating sites. Participant recruitment began in April 2023 and will be completed in April 2025, and the 1-year follow-up will be completed in April 2026. The study results will be disseminated through conference presentations and peer-reviewed publications.

Trial registration number ChiCTR2300070025.

STRENGHTS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, open-label, randomised controlled trial with a sufficient sample size and follow-up.
⇒ This is the first large-scale randomised trial to evaluate the impact of early magnetically controlled capsule endoscopy in patients with high bleeding risk scheduled for percutaneous coronary intervention to prevent of gastrointestinal bleeding.
⇒ Due to the nature of the intervention, subjects, investigators and study site staff will not be blinded to the study group assignments.
⇒ It is unclear whether these findings could be generalised to all guidelines-identified individuals at a high risk of bleeding.

INTRODUCTION

Advanced antiplatelet and antithrombotic medications improve outcomes by achieving a significant reduction in ischaemic outcomes in patients with coronary artery disease undergoing percutaneous coronary interventions (PCI).[1 2] However, bleeding and bleeding-related complications after PCI negatively affect clinical outcomes,[3–5] particularly in patients at high risk of bleeding.[6] The most frequent bleeding site is the gastrointestinal tract.[7] The OPT-PEACE (Optimal antiplatelet therapy for prevention of gastrointestinal injury evaluated by ANKON magnetically controlled capsule endoscopy) study reported a 23% incidence of gastric ulcers in a population with low-risk bleeding undergoing PCI.[8] Furthermore, earlier investigations using standard gastroscopy found that gastrointestinal mucosal damage ranged from 30% to 70% in patients at a high risk of bleeding or with gastrointestinal symptoms who were receiving antiplatelet medication.[9–12] Although the benefits of preventing gastrointestinal bleeding are being increasingly recognised and appear promising for improving PCI outcomes, there is still no conclusion as to whether early identification of gastrointestinal conditions in patients at

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high bleeding risk scheduled for PCI (HBPCI) improves patient outcomes.

Previous studies have examined the predictors of gastrointestinal bleeding or have developed predictive instruments for estimating the bleeding risk in patients with coronary artery disease undergoing PCI,[13] however, several issues have been raised. First, patients with high bleeding risk undergoing PCI, including those of advanced age or with renal insufficiency, are often excluded from these trials but constitute a significant percentage of patients undergoing PCI in routine clinical practice.[14 15] Second, despite the fact that many bleeding avoidance strategies have been established in clinical practice, there is limited understanding of how to best implement bleeding risk models in clinical practice.[16–18] Third, current risk scores are insufficient for identifying gastrointestinal injuries and bleeding sites, despite earlier research showing variations and prognostic relevance between upper and lower gastrointestinal bleeding.[19–21] Therefore, there is an urgent need for an accurate, safe and objective assessment approach to assess the digestive tract of patients with HBPCI.

Magnetically controlled capsule endoscopy (MCE) is a novel medical procedure that has revolutionised gastrointestinal diagnostics by providing a minimally invasive, painless and effective visual inspection of the stomach and entire small intestine. Advantage of MCE include it being easy to implement and that it does not require the discontinuation of antiplatelet drugs. Previous studies have demonstrated satisfactory specificity and sensitivity for detecting focal lesions of the gastrointestinal tract using MCE.[22–24] Notably, no studies have been conducted to determine whether treatment strategies based on early MCE testing can prevent the development of gastrointestinal bleeding.

Therefore, we propose the hypothesis that, for patients with HBPCI, early MCE assessment may help guide individualised treatment decision-making to prevent gastrointestinal bleeding. We will perform a multicentre, open-label, randomised controlled trial to test this hypothesis.

METHODS AND ANALYSIS

Patient and public involvement

No patients or members of the general public are engaged in the study's design, recruitment or execution.

Trial design

The Magnetic-Assisted Capsule Endoscopy Gastrointestinal bleeding Protection Strategy (MACE-GPS) trial is a multicentre, open-label, randomised controlled trial conducted across 22 hospitals in China; the list of research units is shown in online supplemental table S1. The objective of this study is to test whether there are statistically significant differences between the standard treatment of HBPCI and deployment of an MCE as the first test, followed by a multidisciplinary approach for the prevention of gastrointestinal bleeding, if needed. Box 1 lists the inclusion and exclusion criteria, and figure 1 summarises the study design. The outcome will be assessed by an independent clinical events committee, which will be blinded to patients' allocation. Endoscopic images will be analysed in an independent core laboratory. An independent data and safety monitoring board (DSMB) will review the safety data at regular intervals, including efficacy rates and serious adverse events throughout the study. If there are concerns regarding the safety of the participants, the DSMB will make recommendations to the trial executive committee regarding continuing, stopping or modifying the trial. This study conforms to the Declaration of Helsinki and has been approved by the Human Research Ethics Committees of the participating hospitals. This study is registered in the Chinese Clinical Trials Registry (ChiCTR2300070025; https://www.chictr.org.cn). Participant recruitment began in April 2023 and is expected to finish in April 2025, and the 1-year follow-up will be completed in April 2026.

Box 1 Inclusion and exclusion criteria of the MACE-GPS (Magnetic-Assisted Capsule Endoscopy Gastrointestinal bleeding Protection Strategy) trial

Inclusion criteria

1. Eligible patients were aged 18 years, undergoing cardiac catheterisation±percutaneous coronary intervention (PCI) for either chronic coronary syndrome or acute coronary syndrome with negative cardiac biomarkers (with a positive exercise electrocardiography or at least one severe (≥70%) coronary artery stenosis diagnosed by invasive coronary angiography or coronary artery CT angiography).
2. In addition to meeting the main inclusion criteria, subjects had to fulfil at least one of the following inclusion criteria:
   - Age ≥75 years.
   - History of peptic ulcer.
   - History of gastrointestinal bleeding.
   - Haemoglobin <110 g/L.
   - Moderate, severe or end-stage chronic kidney disease, estimated glomerular filtration rate <60 mL/min/1.73 m^2.
   - Anticipated use of long-term oral anticoagulation.
   - Liver cirrhosis with portal hypertension.
   - Active malignancy (excluding non-melanoma skin cancer) within the past 12 months.

Exclusion criteria

1. Patients need emergency PCI.
2. Patients with cardiogenic shock.
3. Patients with previous gastrointestinal or colonic surgery.
4. Coronary angiography confirmed coronary lesions not suitable for general percutaneous intervention.
5. Patients with left ventricular ejection fraction ≤35%.
6. Malignant tumours of the colon and rectum.
7. Platelet count <100×10^9/L.
8. Severe haematological disorders.
9. Cerebral haemorrhage or subarachnoid haemorrhage.
10. History of bowel obstruction, bowel diverticulum.
11. Patients with pacemakers, cochlear implants, insulin pumps.

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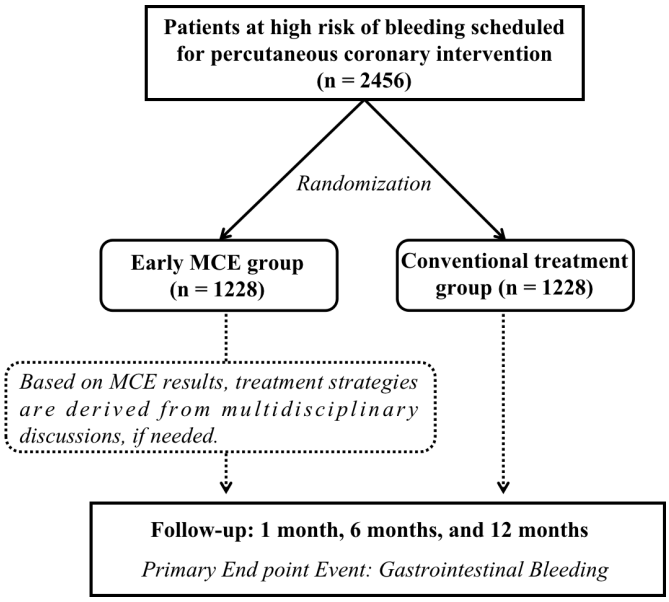

Figure 1 Trial design and flow chart. MCE, magnetically controlled capsule endoscopy.

Study population

Patients with a high risk of bleeding who are admitted to the participating research centres and are scheduled for PCI will be considered for enrolment. The designation of the high-risk population is based on previous research and clinical consensus on risk factors for gastrointestinal bleeding.[6 25–27] The detailed inclusion and exclusion criteria are listed in box 1. Briefly, patients are eligible to be included in this study if they are at least 18 years old and scheduled for PCI for either chronic coronary syndrome or acute coronary syndrome with negative cardiac biomarkers (with a positive exercise electrocardiography or at least one severe (≥70%) coronary artery stenosis diagnosed by invasive coronary angiography or coronary artery CT angiography).

Randomisation and follow-up

Patients who conform to the inclusion criteria and sign the informed consent form will be randomly assigned to either the 'early MCE group' or the 'conventional treatment group' by the researcher or a research assistant using a computerised block randomisation schedule stratified by site. All patients in the 'early MCE group' will undergo MCE prior to PCI.

Data, including demographic information, family and medical histories, laboratory examinations and presenting symptoms, will be obtained from electronic medical records during hospitalisation. After randomisation, the participants in both study groups will be followed up at 1, 6 and 12 months (table 1). Additional follow-up visits will be scheduled, if appropriate. To minimise the loss to follow-up, we will strengthen patient education and conduct communication training for follow-up personnel. Clinical follow-up information will be obtained via telephone calls or outpatient records. All this information is linked to the subject's study ID number.

Table 1 Data collection at baseline and follow-up visit

Domain/Visit	Screening	1 month	6 months	12 months
Informed consent form	X			
Demographic information	X			
Age	X			
Sex	X			
Race	X			
Medical history	X			
Physical measures	X			
Blood pressure	X	X	X	X
Heart rate	X	X	X	X
Weight	X			
Height	X			
Waist circumference	X			
Questionnaires	X			
Smoking use	X			
Alcohol use	X			
Medication	X			
Blood analysis	X	X	X	X
Haematology	X	X	X	X
Urine routine	X			
Stool routine and occult blood	X	X	X	X
Blood clotting function	X			
Liver function	X	X	X	X
Renal function	X	X	X	X
Echocardiography	X		X	X
Coronary intervention information	X			
Coronary lesion typing	X			
Number of coronary lesions vessels	X			
Treatment (DES/DCB)	X			
Antiplatelet programmes	X	X	X	X
Medication adherence		X	X	X
Gastrointestinal bleeding events		X	X	X
Outcome events		X	X	X

DCB, drug-coated balloon; DES, drug-eluting stent.

Blinding and unblinding

Due to the nature of the intervention, the participants and study staff will not be blinded to the intervention assignment; however, outcome assessment will be performed by a blinded independent investigator through clinical visits or standardised telephone interviews with patients or their relatives.

Study outcomes and definitions

The primary and secondary outcomes are shown in box 2. The primary outcome is the incidence of gastrointestinal bleeding within 12 months of enrolment, as defined by

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Box 2 Study outcomes

Primary outcome

The incidence of Bleeding Academic Research Consortium (BARC) definition (types 2, 3 and 5) or clinically evident gastrointestinal haemorrhage.

BARC types 2, 3 and 5 bleeding definition:

⇒ Type 2—any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for types 3–5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional; (2) leading to hospitalisation or increased level of care or (3) prompting evaluation.

⇒ Type 3—BARC 3a: overt bleeding plus haemoglobin decrease of 30 to <50 g/L (provided haemoglobin decrease is related to bleeding); transfusion with overt bleeding. BARC 3b: overt bleeding plus haemoglobin decrease <50 g/L (provided haemoglobin decrease is related to bleeding), cardiac tamponade, bleeding requiring surgical intervention for control, bleeding requiring intravenous vasoactive agents. BARC 3c: intracranial haemorrhage confirmed by autopsy, imaging or lumbar puncture; intraocular bleed compromising vision.

⇒ Type 5—BARC 5a: probable fatal bleeding. BARC 5b: definite fatal bleeding (overt or autopsy or imaging confirmation).

Secondary outcome

1. Cardiovascular death:
   - Death caused by acute myocardial ischaemia.
   - Death caused by sudden cardiac death, including unwitnessed death.
   - Death resulting from heart failure.
   - Death caused by stroke.
   - Death caused by cardiovascular procedures.
   - Death resulting from other cardiovascular causes.
   - Death from cardiovascular haemorrhage.
2. Non-fatal myocardial infarction:
   - Peri-procedural Academic Research Consortium-2: absolute rise in cardiac troponin (from baseline) 35 times upper reference limit plus one (or more) of the following criteria: new significant Q waves or equivalent, flow-limiting angiographic complications and new 'substantial' loss of myocardium on imaging.
   - According to the 2018 universal definition: acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit and at least one of the following: symptoms of myocardial ischaemia, new ischaemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology and identification of a coronary thrombus by angiography or autopsy (only for infarctions of atherothrombotic nature).
3. Target vessel revascularisation: any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.
4. Ischaemic stroke:
   - Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord or retina, which persist for <24 hours or until death, with pathology or neuro-imaging evidence that demonstrates either central nervous system (CNS) infarction in the corresponding vascular territory (with or without haemorrhage) or absence of other apparent causes (including haemorrhage), even if no evidence of acute ischaemia in the corresponding vascular territory is detected; with symptoms lasting <24 hours, with pathology or neuro-imaging confirmation of CNS infarction in the corresponding vascular territory.
   - Ischaemic stroke with haemorrhagic conversion.

Continued

the Bleeding Academic Research Consortium (BARC) definition (types 2, 3 and 5)[28] or clinically evident gastrointestinal haemorrhage.[29] The secondary end points are major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction, target vessel revascularisation and ischaemic stroke, according to the Academic Research Consortium's definite or probable criteria.[6]

Procedure

Early MCE group arm

MCE procedure

MCE (Ankon Medical Technologies, Shanghai, China) is a non-invasive, actively controlled system comprising a magnetic navigation control system. The capsule endoscope measures 27×11 mm, weighs 4.8 g and has a permanent spherical magnet. The field-of-view angle of the capsule is 140° from one end, and the viewing distance is 0–30 mm. The activated capsule is swallowed into the gastrointestinal tract, and the state of the gastrointestinal mucosa is continuously recorded at two frames per second. Once inside the gastric cavity, the endoscopic capsule observes all sides of the stomach (the cardia, fundus, angulus, antrum and pylorus) under the guidance of an external magnetic guidance system. The controller allows movements of 2 mm and changes the viewing angle by 3° in a three-dimensional space. More recently, multicentre studies have demonstrated that MCE controlled by a robot magnet achieved 93.4% accuracy in detecting focal lesions in the stomach compared with standard gastroscopy.[24 30]

The MCE assessment was conducted 1 day before PCI. Prior to the MCE examination, the patients will confirm to have not eaten for 10 hours and to have not consumed any coloured liquid or syrup. Patients will be allowed to take their usual medications for up to 2 hours prior to ingesting the capsule. One hour before the examination, the study participants will ingest 10 mL of simethicone (Menarini Group, Florence, Italy) as a defoaming agent to clean the stomach cavity for 40 min, followed by 500–1000 mL of water to fill the stomach cavity to provide a better view.

The participants will also be asked to wear a portable digital recorder for images of the duodenum and small intestine after completing the stomach examination. If the capsule is not excreted, abdominal radiography is

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Table 2 The modified Lanza score to assess gastric mucosal injury

Category	Score
No erosion	0
One to two erosions localised in the gastric antrum, body or bottom	1
Three to five erosions localised in one area of the stomach	2
Erosions localised in 2 different areas of the stomach (total <10 lesions)	3
Gastric ulcer or ≥10 erosions	4

recommended 2 weeks after the examination. An endoscopy is recommended if a capsule is found in the body.

Interventions

The modified Lanza score (MLS) will be used to assess the degree of mucosal injury (table 2).[31] Multidisciplinary discussions will be considered if the MLS >3, severe erosive gastritis, gastric or duodenal ulcers or bleeding are present. The treatment strategy mainly includes: (1) medical treatment preferred to revascularisation; (2) PCI treatment deferred for prior proton-pump inhibitor (PPI) and gastric mucosal protector therapy treatment; (3) PCI deferred to allow for endoscopic/surgical gastrointestinal injury treatment; (4) PCI with a drug-coated balloon (DCB) instead of a drug-eluting stent; (5) coronary artery bypass graft (CABG) preferred to PCI; (6) shorter/less intense antithrombotic regimen after PCI. For example, if a patient with stable angina has severe gastric erosion or MLS >3, oral PPI and gastric mucosa protective agents can be administered for 2 months, followed by PCI treatment. During PCI, depending on the coronary lesion, DCB dilation is given if the non-left main lesion has <30% residual stenosis after predilation and there is no type C or higher entrapment, otherwise, stenting is given. In the case of severe triple coronary lesions or combined left main lesions with complex lesions, CABG should be considered. If the patient is unstable, the treatment plan is determined by the operator based on the clinical situation and the coronary angiography results. If the MCE reveals suspicious gastrointestinal malignant tumours, it is recommended that after intensive drug therapy, electrogastroscopy and biopsy be performed. Two senior attending physicians should independently determine the treatment plan based on the above suggestions if a change in strategy is required during implementation depending on the MCE results. When treatment recommendations are inconsistent, multidisciplinary teams develop treatment plans at each site, including experts from cardiology, interventional cardiology, cardiac surgery, endoscopy and gastroenterology, in accordance with institutional practice guidelines.[32–35] To ensure patient safety, the study allowed physician to decide whether to adjust the treatment of patients according to their clinical situation.

Helicobacter pylori (HP) infection will be confirmed using the rapid urea breath test. HP eradication therapy is allowed, but not mandatory, at the physician's discretion.

Conventional treatment arm

In the control group, patients will be managed according to the clinicians' routine diagnosis and treatment. The treatment protocols are based on the decisions of cardiovascular physicians and followed the patients' characteristics, current national and international clinical trials or guidelines.[33 36 37] In addition, patients should be evaluated by a multidisciplinary team if necessary.

Sample size determination and adjustment

To determine the sample size, we planned the study as a superiority trial and estimated the probability of gastrointestinal bleeding in the early MCE arm to be twice as low as that in the conventional treatment arm. According to previous literature, the incidence of gastrointestinal bleeding was 5%; therefore, we used experience from previous studies to guide the estimation of effects.[38] Sample size calculations and power analyses were performed using the log-rank Freedman test. The power analysis revealed that in order for this effect size to be detected (80% chance) as significant at the 5% level and considering a loss to follow-up of 10%, a sample of at least 2284 patients (1142 per group) would be required. Secondary analysis for the MACE end point assumed an equal incidence in these groups using a non-inferiority test with a 5% significance level, a non-inferiority margin equal to 20% of the control group and an 80% power to reject the null hypothesis. Considering a loss to follow-up of 10% into account, at least 2456 participants were included in this trial.

Statistical analysis

Patient characteristics and demographics will be described as means with SDs or as proportions. The Student's t-test or the Mann-Whitney U test will be used for continuous variables, and the χ^2 or Fisher's exact test for binary variables. The primary statistical analyses will be conducted according to the 'intention-to-treat' principle. Interim analysis will be performed after the enrolment of 50% of the target study population. Kaplan-Meier survival analysis with a log-rank test will be performed to compare the cumulative incidence of gastrointestinal bleeding between the two groups over time. A Cox proportional hazard analysis will be performed to assess the 'early MCE group' versus 'conventional treatment group' risk for the occurrence of gastrointestinal bleeding over time. The results will be described using HRs and 95% CIs with the associated p value. Statistical significance is set at p<0.05. Statistical analyses will be performed using the

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statistical package R V.4.2.0 (R Foundation for Statistical Computing; http://www.r-project.org).

Data management

All clinical data from individual participants will be de-identified and assigned study numbers. The number of studies serves as a link between the data and the subjects' identifiable information. An Electronic Data Capture System online encrypted database will be used to store the datasets. The database will only be accessed by the primary investigator and research assistants.

ETHICS AND DISSEMINATION

The study was registered in the Chinese Clinical Trial Registry (see online supplemental table S2). The study protocol (V.2.0, dated 5 January 2023), participant information sheets and consent forms (see online supplemental material S3), relevant materials and the ethical aspects of this trial have been reviewed and approved by the ethics committees of Fuwai Hospital and all study centres (no. 2022-1897). Study physicians will be trained to inform eligible patients about the research and obtain written informed consent from those who decide to participate. The findings of the trial will be published in peer-reviewed journals and communicated to the media and the general public.

The primary objective of this study is to verify the effectiveness and feasibility of treatment plan adjustments based on early capsule endoscopy to prevent gastrointestinal bleeding in patients with HBPCI. In addition, the trial will provide data on the source of gastrointestinal bleeding among patients with HBPCI, which is a significant unmet medical need in this patient population.

Despite its potential strengths, this trial may be associated with some limitations. First, given that the aim of this trial is to prevent gastrointestinal bleeding, the definition of patients with HBPCI is not entirely in accordance with the current guidelines. Therefore, the inclusion criteria for this study were developed in conjunction with published guidelines and risk factors for gastrointestinal bleeding. As a result, the study's future findings cannot be properly extended to all guideline-identified people who are at a high risk of bleeding. Second, there are no evidence-based treatment options specifically for patients with HBPCI with MCE results. Although we established a core multidisciplinary consulting committee to provide six suggestions for the management of these individuals, the clinical variety may not be completely appropriate. However, we believe that our study will provide more evidence on the clinical impact of these variants and will foster the development of consensus population-specific guidelines for clinical management. Third, because the MCE is not widely used worldwide, the applicability of this study may be limited.

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Contributors YW conceptualised the study and is the principal investigator and grant holder. ML, RL and YW made significant contributions to designing the study. RL and YW contributed to developing the screening procedures. RL and YW were responsible for the power calculations and statistical analysis plan. ML and RL were responsible for creating the first draft of this manuscript. YW approved the final draft of this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD
Yongjian Wu http://orcid.org/0009-0001-6042-437X

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