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Clinical risk analysis of postoperative delirium in elderly patients undergoing thoracic and abdominal surgery: study protocol of a single-centre observational cohort study

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ABSTRACT

Introduction Postoperative delirium (POD) acts as a common complication in older patients after surgery, accompanied by longer recovery time, prolonged hospital stay, increased hospitalisation costs, etc. Therefore, it is urgent to reduce POD by implementing some intervention strategies. Early identification of associated risk factors was regarded as an effective method to lower the incidence of POD. Currently, the incidence and risk factors of POD have been widely investigated in orthopaedic and cardiac surgery, while remain scarce in thoracic and abdominal surgery. We will perform an observational cohort study to explore the incidence and potential risk variables of POD in thoracic and abdominal surgery, mainly focusing on some prognostic indicators including age-adjusted Charlson Comorbidity Index (ACCI), Prognostic Nutrition Index (PNI) and Fibrinogen to Albumin Ratio (FAR). In addition, we will further develop a predictive model based on related data to provide a novel method for preventing POD.

Methods and analysis A single-centre observational study is conducted among patients aged ≥60 years old undergoing thoracic and abdominal surgery from 28 February 2022 to 31 December 2022. The patients will be divided into POD group and non-POD group following the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Related variables mainly including ACCI, PNI and FAR will be analysed by univariate and multivariate logistic regression analyses. Besides, a predictive model will be established according to associated risk factors, and the receiver operating characteristic curve will be used to further evaluate the accuracy of the predictive model.

Ethics and dissemination The study has been approved by the Medical Ethics Committee of Hebei General Hospital (approval number 2022021) and will intend to be published in peer-reviewed journals.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2200057126).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main advantages of this study are to highlight the connection between postoperative delirium (POD) and some prognostic factors, such as Charlson Comorbidity Index, Prognostic Nutrition Index and Fibrinogen to Albumin Ratio, and to establish a predictive model to better prevent POD.
⇒ The overall design of this protocol is rigorous and the sample size is sufficient. Multicollinearity diagnosis is used to test the collinearity among variables, and binary regression analysis is applied to screen out the risk factors for POD.
⇒ The range of surgical types is wide and the collected data are rich and comprehensive.
⇒ Owing to the exclusion of patients with preoperative communication difficulties, the bias of sample selection cannot be avoided.
⇒ The duration of evaluating delirium is only within 3 days after surgery, which might underestimate its incidence.

BACKGROUND

Nowadays, due to improvements in anaesthetic and surgical techniques, the number of the geriatric patients undergoing surgery is increasing.[1] Thoracic and abdominal surgery accounted for 54.8% of all surgeries among the elderly in China.[2] Meanwhile, it was reported that the incidences of postoperative complications in elderly patients undergoing thoracic and abdominal surgery range from 12% to 47% and from 13% to 39%, respectively, which might bring great challenges for postoperative recovery.[3 4] As one of the most common and serious complications after surgery in geriatric patients, postoperative delirium (POD) is an acute organic brain syndrome with fluctuation in conscious level, decline in cognitive function and sleep–awakening cycle disorder within 3–5 days after surgery.[5] The incidence of POD is dramatically different among various types of surgery. A meta-analysis indicated that the prevalence of POD ranged from 4.1% to 54.9% in cardiac surgery.[6] In addition, approximately 8.2% of orthopaedic patients were reported

to develop delirium after surgery.[7] POD often causes a variety of poor outcomes, such as prolonged hospital stay, and increased morbidity and mortality, which increase economic burden of patients and become a severe social problem.[8 9] Unfortunately, the pathophysiological mechanism of POD is still obscure to date. It is widely considered that the interaction of multiple factors is involved in the occurrence of POD, such as advanced age, comorbidities, fragility and others.[10] Since 30%–40% cases can be prevented,[11] it might play a significant role in reducing POD by analysing and dealing with the related risk factors.

Charlson Comorbidity Index (CCI) has proven its correlation with POD, which was first proposed by Charlson including 19 well-defined medical conditions namely cerebrovascular, neurological and cardiac disease, etc.[12 13] Age-adjusted CCI (ACCI), a new prognostic index by weighting age and CCI score, is associated with long-term survival rate and mortality in a variety of diseases.[14 15] Moreover, a previous study demonstrated that ACCI can predict postoperative complications in orthopaedic surgery, such as arrhythmia, stroke, delirium, etc.[16] However, the direct relationship between ACCI and POD in thoracic and abdominal surgery has not been investigated. Besides, some nutrition-related indicators, such as Prognostic Nutrition Index (PNI) and Fibrinogen to Albumin Ratio (FAR), were well established as predictive factors of long-term prognosis,[17 18] and PNI was regarded as an independent risk factor for POD in orthopaedic surgery.[19] However, the correlation between PNI and POD is controversial in the elderly following thoracic and abdominal surgery.[20 21] Therefore, whether PNI can predict POD needs to be further confirmed. Also, a study evidenced that FAR was positively correlated with POD in elderly subjects after total joint arthroplasty.[22] Nonetheless, the efficiency of FAR as a predictive factor for POD after thoracic and abdominal surgery has not been explored.

Given this context, we aim to explore the related risk factors for POD by conducting an observational analysis, primarily focusing on some prognostic factors, including ACCI, PNI and FAR. Furthermore, we will develop a predictive model based on related data to provide appropriate measures for preventing POD in elderly people after thoracic and abdominal surgery.

METHODS AND ANALYSIS

Study design

The protocol of this study is a single-centre observational cohort study and conforms to the Strengthening the Reporting of Observational Studies in Epidemiology. Patients will be divided into two parallel groups: POD group and non-POD group according to outcome indicators (figure 1). The study will be performed in Hebei General Hospital and will continue for 10 months. Data collection will start from the collection of the first patient until the last one finishes the follow-up (figure 2), and this study is still in process.

Study participants and recruitment

Elderly patients scheduled for thoracic and abdominal surgery undergoing general anaesthesia will be screened for eligibility the day before surgery. The participants meeting the eligibility criteria will be recruited in Hebei General Hospital from 28 February 2022 to 31 December 2022.

Inclusion criteria

- Age ≥60 years old, regardless of gender and nationality, American Society of Anesthesiologists (ASA) grade I~III.
- Surgery types as follows:
  - Thoracic (eg, lung nodule resection, mediastinal tumour resection, etc).
  - Gastrointestinal (eg, colorectal resection, radical gastrectomy, herniorrhaphy, etc).
  - Urinary (eg, urinary calculi lithotripsy, bladder cancer resection, nephrectomy, etc).
  - Hepatobiliary (eg, hepatectomy, pancreaticoduodenectomy, cholecystectomy, etc).
- Accept general anaesthesia.
- Consent to participate in this study and sign the informed consent form.
- Complete case data and scheduled operation.

Exclusion criteria

- Patients refuse to sign the informed consent.
- Preoperative albumin infusion.
- Enter intensive care unit after surgery.
- Lack of cooperation or communication abilities as following conditions:
  - Allolalia.
  - Dysaudia.
  - Coma.
- Epilepsy.
- Parkinson's disease.
- Take dopamine drugs (levodopa, dopamine agonists).
- In a severe condition.
  - ASA grade ≥IV.
- Emergency operation.
- Patients are unable to read Chinese.

Discharge criteria

- Withdraw from the study at any time.
- Loss of the data.
- Violations of test procedures.

Data collection

General baseline data

The following characteristics are considered as potential variables to result in POD, which can be acquired from the case data, including age, gender, educational level, body mass index, ASA grade, smoking and alcohol consumption history, arrhythmia, hypertension, coronary heart disease, related therapeutic drugs such as β-receptor blocker, statins, hydragogue, Ca^{2+} channel blocker, ACE inhibitor, steroids and benzodiazepines, preoperative Mini-Mental State Examination Scale (MMSE) scores,

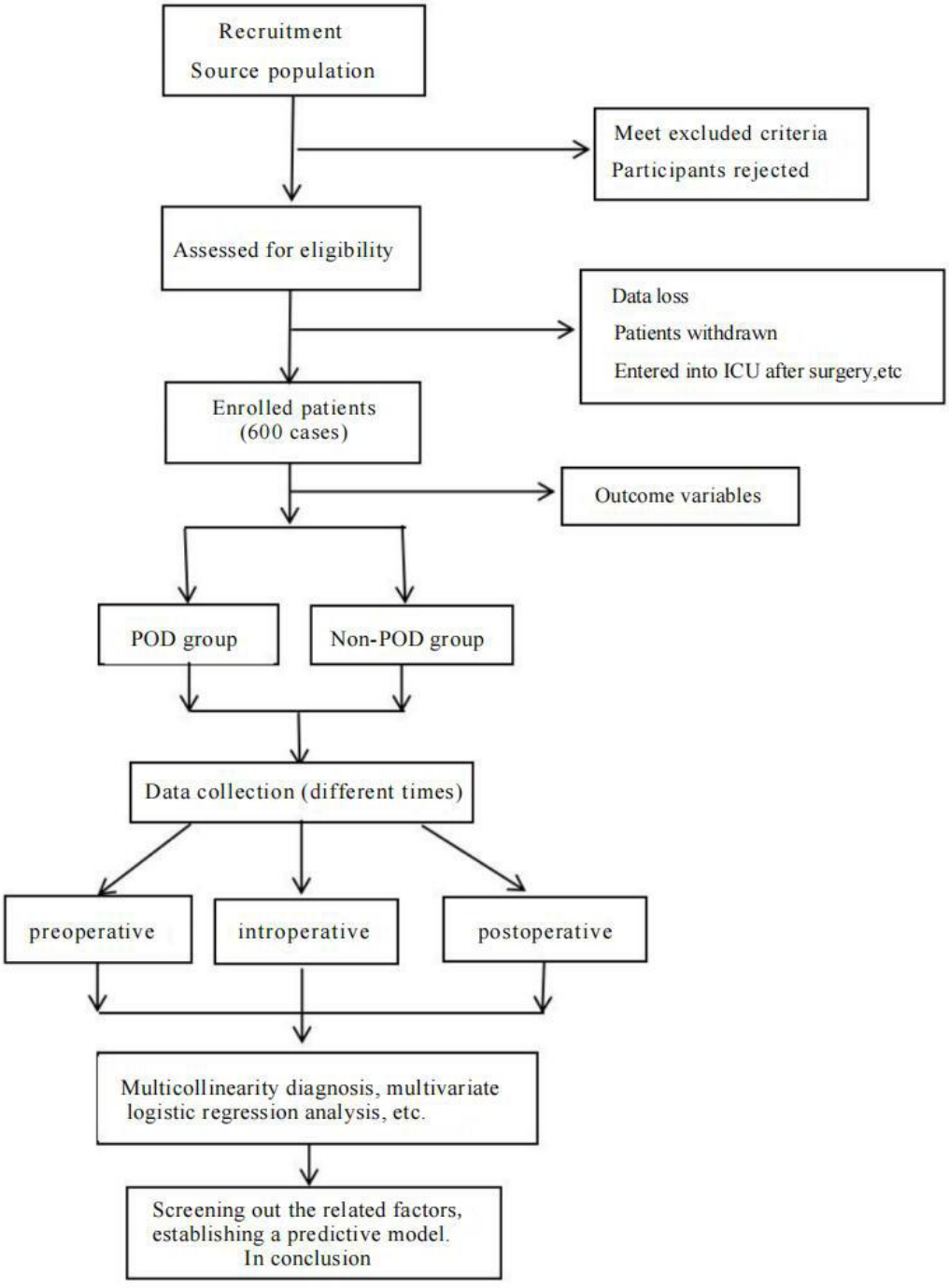

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Figure 1 Consolidated Standards of Reporting Trials diagram for this trial. ICU, intensive care unit; POD, postoperative delirium.

Study period						
	Enrollment	Postoperative days				Close-out
	T0	T1=0	T2=24	T3=48	T4=72[1]	Out of hospital
	Enrollment and filtration					
Enrollment	X					
Eligibility screen	X					
Inform consent	X					
Assessment						
Baseline data (Age, ACCI, MMSE, HADS, etc)	X					
Lab values (serum albumin, FAR, PNI, hemoglobin,etc)	X					
Surgery and anesthesia (the duration of operation and anaesthesia, types of surgery dosages of medications, etc)		X				
DSM-V, VAS, hypoxemia			X	X	X	
In-hospital stay	The first day in hospital					

Figure 2 The total process of the trial. [1]If discharged before the 3-day follow-up, the patients will be contacted by telephone. ACCI, age-adjusted Charlson Comorbidity Index; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; FAR, Fibrinogen to Albumin Ratio; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination Scale; PNI, Prognostic Nutrition Index; T0, day before the operation; T1, day of surgery; T2, postoperative first day; T3, postoperative second day; T4, postoperative third day; VAS, Visual Analogue Scale; X, execution.

Hospital Anxiety and Depression Scale (HADS) scores and ACCI.

Data on the preoperative laboratory

Laboratory data will be attained from the electronic medical record (EMR) the day before surgery, including neutrophil, platelets, total lymphocyte count, white cell count, haemoglobin, serum albumin, creatinine, blood urea nitrogen, calcium, sodium, aspartate transaminase/alanine transaminase (AST/ALT), creatine kinase-MB, uric acid, total cholesterol, blood type, fibrinogen, D-dimer, FAR and PNI. FAR is calculated as fibrinogen divided by serum albumin. PNI is calculated by the following formula: [10×serum albumin value (g/dL)]+[0.005×total lymphocyte count in the peripheral blood (per mm^3)].[20]

Intraoperative and postoperative data on surgery and anaesthesia

The correlated data are collected from the electronic anaesthesia record, mainly consisting of the duration of operation and anaesthesia, surgery types, dosages of medications, including benzodiazepines (midazolam), anticholinergic agents, propofol, opioid drugs (sufentanil and remifentanil) and norepinephrine, blood transfusion, estimated blood loss, minimum body temperature and postoperative analgesia. In addition, hypoxaemia and pain scores are also recorded within the first postoperative 3 days. Postoperative pain is assessed by Visual Analogue Scale.[23] All data will be analysed ultimately by anaesthesiologists and statistical professionals, and all features could be regarded as potential risk factors for POD.

Assessment of preoperative physical and psychological state

HADS is used to assess the anxiety or depression of patients before surgery, which is composed of two subscales including anxiety and depression, with seven problems, respectively. When total score of each scale is ≥8 points, anxiety or depression can be diagnosed.[24]

Table 1 Age-adjusted Charlson Comorbidity Index

Item	Points
One point for each of the following diagnoses: 1. Myocardial infarction 2. Congestive heart failure 3. Peripheral vascular disease 4. Cerebrovascular disease 5. Dementia 6. Chronic obstructive pulmonary disease 7. Connective tissue disease 8. Digestive ulcer disease 9. Diabetes (ordinary type, 1 point; 2 points with other organ damages)	
Two points for each of the following diagnoses: ► Moderate or severe chronic kidney disease ► Hemiplegic paralysis ► Leukaemia ► Malignant lymphadenoma	
Three points for each of the following diagnoses: ► Liver disease (mild, 1 point; moderate or severe, 3 points)	
Six points for each of the following diagnoses: ► Solid tumour (no transfer, 2 points; transfer, 6 points) ► AIDS	
Age: add 1 point per 10 years over 40 years <50, 0 point; 50–59, 1 point; 60–69, 2 points; 70–79, 3 points; ≥80, 4 points	

Table 2 Mini-Mental State Examination Scale

Time	T0	T1=0	T2=24	T3=48	T4=72*
Orientation (10 points)	×				
	10 items, 1 item represents 1 point				
Memory (3 points)	×				
	3 items, 1 item represents 1 point				
Attention computation (5 points)	×				
	5 items, 1 item represents 1 point				
Recall (3 points)	×				
	3 items, 1 item represents 1 point				
Language (9 points)	×				
	9 items, 1 item represents 1 point				

*If discharged before the 3-day follow-up, the patients will be contacted by telephone.
×, execution; T0, day before the operation; T1, day of surgery; T2, postoperative first day; T3, postoperative second day; T4, postoperative third day.

Evaluation and definition of comorbidities are performed prior to surgery. ACCI is calculated by total points based on comorbidities and age, where a higher score indicates a poorer health condition.[15] Since age of all enrolled patients is beyond 60 years old, ACCI score is not less than 2 points (table 1).

Neurocognitive assessments and follow-up

MMSE, a common assessment tool for mental state, is adopted to evaluate the preoperative mental condition, which includes 30 lists of cognitive decline symptoms such as orientation, memory, language, attention, computation and recall. One point will be lost once each of the following symptoms occurs within the allotted time: if the question cannot be answered, if the answer is wrong or the patient is unable to complete the required task. The total score is 30 points. Patients with no less than 27 points have no suspicion of cognitive decline, a score of 26 is recognised as a threshold and cognitive impairment is determined when total MMSE score is less than 24 (table 2).[25]

POD will be evaluated following the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (2013), based on observations from four aspects: (1) consciousness disorder and reduced ability to sustain, focus or shift attention; (2) cognitive changes that cannot be better interpreted as established, pre-existing or evolving dementia; (3) this disturbance develops over a short period of time (hours to days) and fluctuates throughout the day; (4) the evidence from the physical examination, clinical history or laboratory findings indicates disturbance caused by a direct physiological consequence of medication use, an intoxicating substance, a general medical condition or more than one cause. The assessment of POD will be performed daily (in the evening) during the postoperative first 3 days by an experienced anaesthesiologist trained in psychiatry department and blinded to the study protocol.[26] Patients discharged within 3 days can be followed up by telephone. The patients will be finally classified into non-POD group and POD group in accordance with the diagnostic criteria.[26]

Outcomes

The primary outcomes are incidence and the related risk factors of POD following thoracic and abdominal surgery. Additionally, a predictive model is established using potential variables, such as ACCI, PNI, FAR, etc.

Data management and monitoring

A monitoring committee will be established to control the accuracy of data in this study. A member of the study team will be appointed to monitor EMR constantly. Patients' demographic, clinical and perioperative data need to be checked by two researchers. A researcher will review the medical records of all included patients and collect perioperative data. Meanwhile, the sample of 5% of all patients will be randomly selected by another researcher, who will independently confirm the accuracy of the collected data. If any discrepancy occurs, it will be decided by the third researcher. The statistical professionals are responsible for drawing up the statistical analysis plan, establishing the database, and using the SPSS V.25.0 statistical system to analyse

the results through communications with the main researchers.

Sample size

The sample size is calculated based on the incidence of POD. Some previous studies reported the incidence of POD in thoracic and abdominal surgery. One study showed that 23 of 432 patients (5.32%) undergoing thoracic surgery developed POD.[27] Another study indicated that the prevalence of POD in abdominal surgery was 7.3%.[20] Based on above studies, we assume that the POD incidence was ≥5%. The minimum limit of logistic regression model for predicting binary outcomes is at least 10 events per variable.[28] Three variables are selected as explanatory variables in this study, and the number of positive outcomes is at least 30. Therefore, we estimate that a recruitment number of 600 or more will ensure sufficient statistical power.

Statistical analyses

All data are expected to be analysed by statistical software SPSS V.25.0 (SPSS Inc., Chicago, IL,United States). On one hand, quantitative data are described as mean and SD ($\bar{x}\pm s$) or as median and IQRs (M (IQR)), which depend on variables' distribution by Shapiro-Wilk test. For continuous variables, independent sample t-test or Mann-Whitney U test is used to compare differences between two groups, as appropriate. On the other hand, categorical variables are represented as number (n) or rate (%), which can be tested by X^2 test or Fisher's test. A two-sided p value of <0.05 is regarded as a statistical significance. Using multicollinearity diagnosis examines the collinearity among variables, and tolerance >0.1 or variance inflation factor <10 demonstrates non-collinearity. When variables exhibit multicollinearity, the arguments with p value of <0.05 by univariate regression analysis are subjected to stepwise forward multivariate logistic regression analysis, thus controlling the confounding bias and screening out related risk factors for POD. Additionally, as primary explanatory variables, FAR, ACCI and PNI should be taken into regression analysis, regardless of the p value. The effects of related variables are indicated as the OR with 95% CI and the p values, which are considered statistically different if p value is <0.05, and the results are presented by forest plots. In addition, Hosmer and Lemeshow's goodness-of-fit test is conducted to check the fit of the logistic regression model. The delirium prediction index is calculated by regression coefficients of parameters (β) included in the multivariate model. Delirium index=$\beta_1\times R_1+\beta_2\times R_2+\beta_3\times R_3+\ldots+\beta_n\times R_n$ (β: regression coefficients of parameters; R: related risk factors for POD; n: number). Furthermore, the receiver operating characteristic curve is applied as a descriptive tool to further evaluate the accuracy of the predictive index and its components in predicting POD in terms of the area under the curve, the sensitivity and the cut-off value.

Patient and public involvement

Patients do not participate in the design and implementation of the study. Once the results are available, they will be simplified using plain language and then sent to the parents/guardians.

Ethics and dissemination

The study has been approved by the Medical Ethics Committee of Hebei General Hospital (approval number 2022021) and will intend to be published in peer-reviewed journals.

DISCUSSION

POD is one of the serious complications that usually occurs in geriatric patients undergoing thoracic and abdominal surgery. It ultimately leads to various adverse consequences, which timely require prevention, diagnosis and treatment.[8 9] Early identification of its related risk factors might be of great importance to POD prevention. This study primarily aims to analyse the relationship between POD and some prognostic factors, including ACCI, PNI and FAR. We hypothesise that three related variables might have a certain role in predicting POD.

As we all know, advanced age is recognised as an independent risk factor for POD.[29] What is more, a study indicated that CCI ≥2 was closely associated with POD.[13] ACCI is a wide comorbidity scoring system by integrating CCI and age, which is commonly used to predict the prognosis in patients with cancer.[15] Some studies demonstrated a higher score of ACCI could contribute to higher morbidity and worse survival rates.[14 30] Additionally, a study presented ACCI can predict POD among geriatric patients following orthopaedic surgery.[16] Therefore, we speculated that ACCI might have a predictive value in POD following thoracic and abdominal surgery.

It is well-known that malnutrition has been proven to be associated with an increased risk of POD.[31] PNI, an indicator representing patients' nutritional and immune status, is not only verified its association with long-term prognosis,[17] but also involves in the development of POD after non-cardiac surgery.[32] A previous finding indicated that lower PNI could increase the likelihood of developing POD in colorectal surgery.[21] Interestingly, another study noted that there was no association between PNI and POD in abdominal surgery, which might be related to sample size, patient characteristics, types of surgery and diagnostic tools.[20] Hence, the study will further explore the effects of PNI on POD after thoracic and abdominal surgery.

In addition, FAR was identified as a novel marker of predicting malnutrition and was used to assess the prognosis of some patients with cancer after surgery.[18 33] FAR reflects oxidative stress and inflammatory reaction,[34] which are widely speculated to be the possible mechanisms

of POD.[35 36] Hence, FAR might be considered as a predictive factor for POD.

In conclusion, the multiple indicators to predict the prognosis of patients might exert some influence on POD to a certain extent. Therefore, we develop a observational study to validate the association between POD and preoperative indicators, such as ACCI, PNI and FAR. Moreover, a delirium prediction model is established using the related variables, which can be helpful for predicting POD in the elderly following thoracic and abdominal surgery.

Protocol status

The first participant was enrolled on 28 February 2022, and the first version was developed on 20 February 2022. The recruitment will be completed on 31 December 2022. This protocol is the third version which was revised after post-peer review for the following reasons: inaccurate inclusion criteria, unspecific statistical methods, imprecise sample size calculation and inappropriate descriptions. This study is still ongoing.

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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.

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