Rationale and design for Lowering-hyperuricaemia treatment on cardiovascular outcomes in peritoneal dialysis patients: a prospective, multicentre, double-blind, randomised controlled trial (LUMINA)

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ABSTRACT

Introduction The prevalence of hyperuricaemia in peritoneal dialysis patients is quite high. Studies have demonstrated a correlation between hyperuricaemia and cardiovascular disease and treatment of hyperuricaemia reportedly reduces cardiovascular risk in patients with chronic kidney disease. However, whether hyperuricaemia treatment benefits cardiovascular outcomes in continuous ambulatory peritoneal dialysis (CAPD) patients is not yet known.

Methods and analyses This prospective, multicentre, double-blind, randomised controlled trial was designed to evaluate the effects of hyperuricaemia treatment on cardiovascular event risk in CAPD patients. Based on a power of 80%, with type I error α=0.05, two-sided test and 1:1 parallel control study, considering a dropout rate of 20%, a total of 548 eligible patients are expected to be randomly assigned to either the hyperuricaemia treatment group (febuxostat) or control group (placebo).

Ethics and dissemination This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University and the ethics committees of other participating institutions. Written informed consent will be obtained from potential trial participants or authorised surrogates. The findings of the study will be disseminated through publications in peer-reviewed journals, and presentations at national and international conferences.

Trial registration number NCT03200210. 25 June 2017. The trial was started on 13 July 2017, and is expected to end by 31 December 2022. Till 20 Jan 2020, a total of 548 patients have been recruited.

Protocol version The protocol version number and date are YLT-1604-V2.0 and 15 December 2016.

INTRODUCTION

Background and study rationale

Elevated serum uric acid (SUA) seen in patients with chronic kidney disease (CKD) partly arises from overproduction of purines due to hypercatabolism, as well as reduced excretion of uric acid by the kidneys. It previously was shown that there was a correlation between higher uric acid levels and lower glomerular filtration rate (GFR).1–3 Hyperuricaemia is common in the general population with a prevalence of 13.3%–42.1%.4–6 Based on an epidemiological study in Southern China, the prevalence of hyperuricaemia in the adult population is as high as 31.9%.6 Reduced GFR is seen in patients with CKD and understandably conveys a higher prevalence of hyperuricaemia than in the general population. Our local data revealed that the prevalence of hyperuricaemia at our peritoneal dialysis (PD) centre is 63.1%.6

Many epidemiological and clinical studies have demonstrated a correlation between hyperuricaemia and cardiovascular diseases...
The literature also suggests that hyperuricaemia is associated with other classical cardiovascular risk factors, such as hypertension,16 diabetes mellitus,17 hyperlipidaemia,18 obesity and insulin resistance.19,20 Evidence shows that elevated SUA levels facilitates the oxidation of low-density lipoprotein cholesterol,18 and hyperuricaemia is accompanied by increased free oxygen radical production, which plays a role in inflammation.21 Furthermore, elevated uric acid levels facilitate platelet aggregation, increasing the risk for arterial thrombus formation.22 These features contribute to a higher risk of cardiovascular events.

Treatment of hyperuricaemia reportedly independently reduces renal disease progression in patients with CKD,23 24 and treatment of hyperuricaemia was associated with reduced mortality among haemodialysis patients with no history of CVD in the Dialysis Outcomes and Practice Patterns Study in Japan.25 Additionally, in patients with CKD, treatment of hyperuricaemia has been shown to reduce cardiovascular risk.23 However, whether treatment that lowers uric acid would benefit cardiovascular outcomes in patients with CKD, especially in maintenance dialysis patients, is not yet known.

Objectives
To investigate whether hyperuricaemia-lowering therapy through use of febuxostat reduces the risk of cardiovascular events in continuous ambulatory peritoneal dialysis patients.

Trial design
The study is a prospective, multicentre, double-blind, randomised controlled trial.

METHODS
Study setting
The study is being conducted in mainland China across 24 academic hospitals. A complete list of study sites is given in the acknowledgements.

Inclusion criteria
1. Subjects who are able to understand and have voluntarily signed the informed consent form.
2. Adults aged 18–70 at the time of randomisation.
3. Subjects on PD for longer than 3 months.
4. Subjects with hyperuricaemia defined as follows: women: 6 mg/dL (360 μmol/L) < SUA < 12 mg/dL (720 μmol/L); men: 7 mg/dL (420 μmol/L) < SUA < 12 mg/dL (720 μmol/L).

Exclusion criteria
1. Subjects who have a history of gout.
2. Subjects who have a myocardial infarction, unstable angina, cardiovascular reconstructive surgery (such as a stent or bypass surgery), cerebrovascular accident 12 weeks prior to randomisation or planned cardiovascular reconstructive surgery during the trial.
3. Subjects who have New York stage IV heart failure within 4 weeks prior to screening.
4. Subjects who have previously received kidney transplantation and are currently prescribed immunosuppressive therapy.
5. Subjects who have severe liver disease, such as acute hepatitis, chronic active hepatitis, cirrhosis.
6. Subjects who have alanine aminotransferase (ALT) levels greater than twofolds the upper limit of normal or total bilirubin greater than 1.5 folds the upper limit of normal.
7. Subjects who have experienced severe infections within 4 weeks prior to the screening, such as pneumonia or PD-related peritonitis.
8. Subjects who have had a major surgery within 12 weeks prior to screening or who are not yet fully recovered from surgery.
9. Subjects who have a malignancy.
10. Subjects who report a history of illicit drug use or a regular or daily alcohol consumption of ≥4 alcoholic drinks per day in the 2 years prior to screening.
11. Subjects who are allergic to febuxostat.
12. Subjects who are enrolled in other clinical studies within 4 weeks prior to or at randomisation.
13. Subjects who are currently taking mercaptopurine, azathioprine, vidarabine oromidanosine.
14. Subjects who are taking losartan, fenofibrate, thiazide diuretics or loop diuretics within 4 weeks of randomisation.
15. Subjects who require long-term use of steroids (prednisone < 30 mg/d, or equivalent amount of other steroids and use of < 2 weeks can be enrolled).
16. Subjects who require long-term use of salicylic acid drugs except low-dose aspirin.
17. Fertile, lactating patients who are unwilling or unable to take contraceptives.

Patient and public involvement
We state that neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of our research.

Interventions
Eligible patients will be randomly assigned to the febuxostat treatment group or the placebo control group.

Dose adjustment
Participants are treated with febuxostat/placebo starting at a dose of 20 mg/day, once a day. If SUA does not reach the target level (SUA < 6 mg/dL) or decreases less than 20% at the 4-week visit, the dosage is increased to 40 mg/day once per day. If SUA does not reach target at the 8-week visit, the dosage is increased to 40 mg/day (for those who are at dosage of 20 mg/day) or the dosage is maintained (for those who are at dosage of 40 mg/day) until the end of the study. If at dosage of 40 mg/day and SUA remains > 12 mg/dL for 2 weeks, patients are withdrawn from the study for their safety. If SUA reaches
<3 mg/dL at dose of 40 mg/day, the dose decreased to 20 mg/day, and SUA is checked 2 weeks later. At that time, if SUA is still <3 mg/dL, treatment is stopped for 2 weeks, and SUA is checked again, if SUA still <3 mg/dL, patients are withdrawn from the study. If SUA is ≥3 mg/dL, the 20 mg/day dose is maintained, until SUA is above the target level (≥26 mg/dL), at which point the dose is increased to 40 mg/day.

Criteria for discontinuing or modifying allocated interventions
1. Subjects with continued withdrawal of more than 2 weeks or intermittently stopping more than 1 month.
2. Subjects who experience intolerable side effects.
3. For subjects who have episodes of gout, if SUA remains <6 mg/dL, patients are kept in the trial after acute treatment; however, if SUA ≥6 mg/dL, patient allocation is unblinded, hyperuricaemia is treated, and patients are withdrawn from the trial.
4. Subjects who have no evaluable records available.
5. Subjects who have to use prohibited medications due to illness.
6. Subjects who have ALT, or aspartate aminotransferase (AST) increases to greater than two times of upper limit of normal or elevated bilirubin to more than two times the upper limit of normal that has been persistently elevated for 2 weeks.
7. Subjects who have SUA >12 mg/dL for 2 weeks who are on the maximum treatment dose.
8. Subjects who have SUA <12 mg/dL for 4 weeks who are on the minimal dose of treatment.
9. Subjects who have adverse events and cannot continue the study.
10. Subjects who have unexplained complications.
11. Subjects who become pregnant during treatment.
12. Subjects who have kidney transplantations during the study.
13. If, for safety reasons, the organisers propose to stop the study.
14. If the Ethics Committee decides to discontinue the study.
15. If the research is considered unsuitable for continued further research subjects.

The investigator may terminate a subject’s study participation at any time during the study based on the subject’s best interest. In addition, a subject may discontinue his or her participation at any time during the study.

Strategies to improve adherence to interventions
Participants will be followed up monthly during the first 3 months of the study and every 3 months thereafter until the end of the study. Examinations involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests that include repeated blood counts.

Relevant concomitant care permitted or prohibited during the trial
Medications to treat concomitant conditions are allowed and are recorded at baseline and each follow-up visit. Participants are encouraged to remain on the same dosage of these medications unless advised otherwise by medical professionals. Participants who used diuretics, losartan should be asked to discontinue use for 2 weeks before screening, and patients who used prednisone ≥30 mg/day for more than 2 weeks and other drugs that treat hyperuricaemia other than the assigned trial medications are considered to have dropped out of the trial.

Relevant concomitant care permitted or prohibited during the trial
1. If taking angiotensin-converting enzyme inhibitors/ angiotensin receptor blocker (ACEI/ARB) before the trial, patients can continue but are not to increase the dose during the trial, however, the need to avoid the use of losartan. If patients are not taking ACEI/ARB at the time of enrolment, it is not to be added during the study.
2. If systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg, the dosages of other antihypertension drugs are to be adjusted, except for ACEI/ARB.
3. Lipid-lowering drugs can be used during the study, including statins to treat high cholesterol and fibrates to treat hypertriglyceridaemia primarily to maintain normal cholesterol, triglycerides and low-density lipoprotein levels.
4. Antiglycaemic drugs can be used, such as insulin, to reach target glycaemia control with HbA1c <7.0%.
5. Subjects can use antiplatelet and anticoagulant drugs with low molecular weight heparin (LMWH) preferred.
6. Subjects can use proton pump inhibitors, such as omeprazole, pantoprazole and so on.
7. Subjects can use active vitamin D, calcium and phosphorus lowering drugs.
8. Subjects can use folic acid, diuretics, and other anaemia drugs with target Hb of 100–120 g/L.
9. If diuretics are needed, patients should avoid thiazide diuretics.
10. Avoid long-term use of corticosteroids (subjects using prednisone <30 mg/day, or equivalent number of other hormones with use of <2 weeks can be enrolled).
11. Avoid using allopurinol, benz bromarone, fexbuxostat or probenecid.
12. Avoid long-term use of salicylic acid drugs (except low-dose aspirin), diuretics and losartan.
13. Avoid use of immunosuppressive agents, such as cyclophosphamide, MMF, CsA, FK506, azathioprine, vidarabine, leflunomide, tripterygium glycosides, CD20 antibody and didanosine.

Outcomes
The primary outcome is cardiovascular events comprising cardiovascular mortality and non-fatal cardiovascular
events. Cardiovascular mortality includes death caused by acute myocardial infarction, fatal arrhythmia, sudden death, cardiomyopathy, heart failure and stroke, while non-fatal cardiovascular events include non-fatal acute myocardial infarction, hospital admission for heart failure, unstable angina, atherosclerotic disease requiring hospitalisation (including aneurysm, arterial dissection, arteriosclerosis occlusion), non-fatal stroke, transient ischaemic attack or lower limb ischaemia.

Secondary outcomes include all-cause mortality, cardiovascular mortality and non-fatal cardiovascular events separately.

**Participant timeline**

All participants who are eligible and who have signed the informed consent will be randomised to one of the two treatment groups. A study flowchart is shown in figure 1. Treatment in both groups and follow-up will last for 3 years. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts. Intervals between examinations vary from monthly (start of study) to 3 months (end of study). An overview of examinations is given and obligatory measurements during the trial are shown in table 1.

**Sample size**

According to previous studies, 3-year CVD event-free survival is 55% in untreated patients and 68% in treated patients; therefore, based on a power of 80%, type I error \( \alpha = 0.05 \), two-sided test and 1:1 parallel control study, a sample size of approximately 219 cases is estimated. But considering a 20% drop-out rate due to loss of contact and quitting, this study was designed to recruit 274 patients from each group, for a total of 548 patients. Patients will be randomly assigned into the intervention or control group.

**Recruitment**

Each centre has a routine PD population, and these patients are followed up routinely. Each centre will screen subjects to ensure the target population is achieved (548 subjects) from these patients. The enrolment period will last 24 months. Research assistants and investigators screen participants from routine clinical visits. The enrolment period has ended, and as of 31 December 2019, all patients had been enrolled.

**Allocation**

**Sequence generation**

To ensure that numbers in the intervention and the control groups were equal in each centre, a stratified randomisation method will be used for each centre, and patients will be randomly assigned to one of the two treatment groups at each centre. The allocation sequence was attained using computer-generated random numbers using SAS V.9.2 software.

**Allocation concealment mechanism**

Tablets of febuxostat and placebo will be made and wrapped to appear the same. The allocation sequence was generated using SAS V.9.2 software. When participants were enrolled, investigators randomly distributed an allocation sequence to the participant using SAS V.9.2 software (randomisation number), and study tablet with the corresponding number would be distributed to the participants. During these processes, both trial participants and investigators are blinded to the treatment.

**Implementation**

Investigators randomly distribute an allocation sequence to a given participant using SAS V.9.2 software (randomisation number), and study tablets with the corresponding number are then distributed to the participants.

**Blinding**

**Who will be blinded and how**

After assignment to interventions, trial participants, care providers, outcome assessors and data analysts are blinded. The placebo and febuxostat will be provided in the same tablet and the same packaging (including labels) to protect the blindness, using kit numbers to mark each double-blind treatment. Researchers will obtain the kit number through a random procedure when patients are randomly grouped. At the same time, during treatment and follow-up, patients, researchers and research centre staff are unable to identify to which group the patients were assigned.

**Procedure for unblinding if needed**

Blindness can only be broken only to treat subjects when a need to know which treatment group they are randomly assigned to arises.
Blindness can be broken at any time using the corresponding module of the medical record and/or by calling the sponsor. If blindness is broken, the researcher should record the date, time and cause of the unblind, and report this information (or ‘required relevant information’) on the appropriate page of the case report form (CRF).

When recording causes of unblinding, the researcher must not provide any detailed information related to the nature of the drug in the study. Until the database is closed, the researcher shall not disclose the details of the research drug to the sponsor representative or any staff. In addition, when completing forms, research treatments shall not be disclosed in these tables. After breaking the blinding, the patient must withdraw from the study.

### Data collection methods

All patients who are eligible and who have signed the informed consent will be randomised to one of the two treatment groups. Treatment in both groups and follow-up will last for another 3 years. In the first 3 months at the start of the study, visit intervals will be monthly. After that, visit intervals will be every 3 months until the end of study. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts.
obligatory measurements during the trial in table 1. Baseline characteristics, lab tests and examinations in every visit, adverse events, outcomes and so on will be recorded.

**Plans to promote participant retention and complete follow-up**
Participants will be followed up by monthly clinical visit during the first 3 months of the study and every 3 months thereafter. Research assistants and nurses will follow-up participants outcome data and adverse events, which are reported to the investigators.

**Data management**
A CRF is provided for every study participant, where all information concerning examinations and visits are recorded. Following completion of the form, the original is sent to the trial office, and a carbon copy is retained by the centre. These carbon copies may be required should the original be lost and for comparison of patient data at the end of the study. Study documents are subdivided into five categories: recruiting documents, randomisation documents, patient books (CRFs), correction documents and evaluation documents. The pages of the CRFs will be originals with integrated carbon copies. Following completion of the form, the original will be sent to the trial office, and a carbon copy is retained by the centre. All data will be entered into the database. The database is developed and administered centrally by the responsible personnel at the Institute of Medical Statistics, but data entry maybe achieved in a distributed manner within the trial office. The database will provide online plausibility checks, log files and backup mechanisms. Completeness of patient data has to be verified. This is supported by plausibility checks. Double data entry will be conducted. Documentation of patients will be monitored by the documentation centre. To maintain the time course of the follow-up examinations of the participants, each physician will receive, a list of preferred dates for follow-up examinations after submitting the initial patient documents (recruitment documentation, consent form, medical history and therapy protocol). In the documentation centre, all patient data will be verified for completeness and plausibility. Should patient documents be incomplete, contain mistakes or be ambiguous, the documentation centre will send a correction form (if necessary, with a copy of the incomplete patient documents) to the treating physician. It is required that the treating physician fills in the correction form and returns it to the documentation centre. Execution of each step of statistical analysis (data modification, data transformation, description of the data, statistical tests) must be logged in a protocol by the documentation and statistical centre.

**Statistical methods**
**Statistical methods for primary and secondary outcomes**
Descriptive statistics will be used to analyse the means and distribution between all study variables. The means of the normal distributed variables will be compared with the Student’s t-test, and non-parametric tests (Mann-Whitney U test for continuous and \( \chi^2 \) test for nominal variables) will be used for variables that do not follow a normal distribution. Missing values will be imputed using multiple imputation techniques. Comparisons between groups will be based on types of variables and appropriate methods in analyses. A Kaplan-Meier survival curve will be used to estimate difference in survival rates between the groups, while Log-rank test and multivariable Cox regression will be used to analyse the latter. During data analysis, sensitivity analyses will be conducted by adding an additional covariate in the mixed model to account for rescue medication required during the study.

**Methods for additional analyses**
Not applicable.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data**
Per-protocol population that have protocol adherence between 80% and 120%, no serious violation of the protocol, and no missing data on primary outcomes will be included in the analysis. Multiple imputation will be used to handle missing data.

**Monitoring**
**Composition of the data monitoring committee**
Not applicable. As this study is funded by our university, there is a scientific research department that is independent of the investigators and will act as a monitoring committee, safeguard the interests of trial participants, monitor the primary outcome measures including safety and efficacy and monitor the overall conduct of the trial.

**Interim analyses and stopping guidelines**
Not applicable.

**Harms**
Adverse reactions to febuxostat include liver function damage, allergic reactions such as systemic skin rash, and acute episodes of gout. Study drugs should be stopped if adverse reactions occur and proper treatment should be administered. All adverse events, whether related to study drugs or not, are recorded in detail on the CRFs. When the adverse event is considered not related to study drug, possible reasons are given. Reporting of adverse events should include the following information: name of the adverse event, occurrence time, end time, study drug information (dose, capacity, treatment date and time or time interval), severity of the adverse event, relationship of the adverse event to study drug, treatment of the adverse event and whether it is a serious adverse event. Researchers must track all adverse events until they are resolved or explained by other reasons. Serious adverse events are defined according to globally accepted definitions in the International Conference on Harmonization Guideline for Clinical Safety Data Management. For serious adverse events, researchers should fill out the adverse event report form and report them to the
principal investigators, security commissioner and the Ethics Committee Report and China Food and Drug Administration within 24 hours. Serious adverse events are recorded from the time the patient consent to be in the study through 30 days after study exit.

Auditing
Auditing will be conducted every 6 months; and the process will be independent from investigators and the sponsor. Representatives of the sponsor or its designee must be allowed to visit the study centre periodically to assess the quality of the data and the integrity of the study. Representatives will review study records at the study centre and directly compare these with the source documents, discuss the conduct of the study with the investigator and verify the appropriateness of the conduct of the study. In addition, the study may be evaluated by the sponsor’s internal auditors who must be allowed access to eCRFs, source documents and other study files. The sponsor audit reports will be kept confidential.

The investigator or a designated member of the investigator’s staff must be available at some time during the monitoring visits to review data, resolve any queries, and allow direct access to subjects’ records (eg, medical records, office charts, hospital charts and study-related charts) for source data verification. eCRFs must be completed before each visit and be made available to the sponsor’s representative to ensure that the accuracy and completeness of the eCRF.

ETHICS AND DISSEMINATION
This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University and the ethics committees of other participating institutions. Any amendments to the protocol should be reported to the Medical Ethics Committee.

Investigators will obtain informed consent or assent from potential trial participants or authorised surrogates. Investigators will go through all the participants case histories and lab tests, and screen participants according to inclusion and exclusion criteria. If the potential participant is eligible for the study, the investigator will talk with the participants and their authorised surrogates about the trial, including the time scheme, benefits and risks and so on, to answer questions participants have about the trial. After this, investigators obtained written informed consent from the potential trial participants or their authorised surrogates.

No additional consent provisions for collection or use of participant data and biological specimens in ancillary studies are applicable in this trial.

Confidentiality
All subject information, medical records and laboratory data will be kept confidential. Information and data may be discussed, analysed and reported for the purposes of this clinical study only. However, code numbers will identify subject on the eCRFs and in any reports, to keep the subject’s identity confidential.

Declaration of interests
This work is sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China. All authors declare no conflicts of interest.

Ancillary and post-trial care
Not applicable.

Dissemination policy
Findings will be disseminated through publications in peer-reviewed journals, and presentations at national and international conferences. Authorship eligibility guidelines and any intended use of professional writers, plans of granting public access to the full protocol, participant-level dataset and statistical code are not yet available.

DISCUSSION
Hyperuricaemia is reportedly an independent predictor for cardiovascular outcome in both general and patients with CKD. However, there are limited studies examining the relationship between SUA levels and cardiovascular mortality in patients on maintenance dialysis. A multicentre observational study from China that included 2264 patients on maintenance PD, with a median follow-up of 26.5 months, found that each 1 mg/dL increase in SUA caused a corresponding 12% increased risk of cardiovascular death, and a 5% increase in all-cause mortality. From our centre, each 1 mg/dL increase in SUA in male patients corresponded to increasing the risks of cardiovascular and all-cause mortality by 44% and 33%, respectively.

Lowering SUA was demonstrated to benefit renal outcomes. In the recently published Febuxostat for Cerebral and Cardiorenovascular Events Prevention Study (FREED) study, febuxostat lowered uric acid and delayed the progression of renal dysfunction. However, whether treatment of hyperuricaemia improves cardiovascular outcomes in dialysis patients remains to be explored.

The present Lowering-hyperUricaemia treatment on cardiovascular outcoMes In peritoNeal diAlysis (LUMINA) study is designed to determine this question whether treatment of hyperuricaemia benefits cardiovascular outcomes in PD patients. It will provide evidence for the effect of lowering uric acid on cardiovascular outcomes in PD patients.

The LUMINA study has some limitations. First, we recruit preventative and incidental patients concurrently, which might introduce some bias in baseline characteristics. Second, since centre management capability is not parallel across different centres, centre bias may be present in the study. However, this study also has some strengths. This is a multicentre, randomised, double blind and controlled design with sufficient power to detect a clinically significant difference on the effect of
cardiovascular events between treatment and not treatment of hyperuricaemia in PD patients. To our knowledge, the LUMINA study is the first trial focusing on treatment to reduce hyperuricaemia and its relationship to cardiovascular outcomes in PD patients. Results of this study will provide evidence on whether hyperuricaemia-lowering treatment is of clinically valuable in PD patients.

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Contributors XY is the corresponding author. WC and NH contributed equally to this work. All authors have made substantial contributions to the work. Conceptualization, Funding acquisition, Supervision: XY. Data curation: WC. Formal analysis: OZ and NH. Investigation: NH, WC, HM, XY, LJ and QF. Methodology: NH, WC, QF and JD. Project administration: WC and XY. Resources: XY and JD. Software: NH and OZ. Validation: WC and XY. Visualization, writing - original draft: NH and WC. Writing - review and editing: NH, WC and XY.

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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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