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Uncovering variation in cholecystitis treatment: protocol and statistical analysis plan for a nationwide observational study – the Dutch Cholecystitis Snapshot Study (Dutch CHESS)

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ABSTRACT

Introduction Cholecystitis is a highly prevalent disease that imposes a substantial burden on the healthcare system. Despite strong underlying evidence, guideline adherence in the treatment of cholecystitis remains low. Moreover, important gaps in knowledge persist that must be addressed to optimise existing guidelines. The primary aim is to assess the nationwide variation in cholecystitis treatment and identify opportunities to improve guideline adherence. Secondary aims include determining the best cystic duct closure method; the best model to predict concomitant choledocholithiasis; the optimal treatment for cholecystitis lasting 7 days or more at diagnosis and the optimal strategy for gallbladder drainage and post-drainage care.

Methods and analysis The Dutch CHESS is a multicentre observational cohort study, including 67 out of 69 Dutch hospitals. From 1 April to 30 September 2024, all patients diagnosed with cholecystitis (Tokyo Guidelines definition) will be prospectively identified. Data on patient characteristics, treatment and outcome (with 6-month follow-up) will be collected to address the primary and secondary aims. For the primary aim, guideline adherence is defined as the percentage of patients who undergo early cholecystectomy for cholecystitis lasting 0–7 days. Current adherence, nationally and for each individual hospital, along with predictors of adherence, will be determined. The adherence of each hospital will be set against the national average and best practices. To further support improvement, the impact of guideline adherence on total hospital stay and morbidity will be determined. Three months after performance feedback to the participating hospitals, the impact on local practice will be assessed through questionnaires. Subgroup analyses and statistical methods for addressing both the primary and secondary aims are predefined in this protocol.

Ethics and dissemination The Medical research Ethics Committees United reviewed the protocol and decided that the Dutch Medical Research Involving Human Subjects Act is not applicable (reference Number: W23.225). Approval was obtained from the institutional review board and board of directors at each participating hospital. Results will be disseminated through peer-reviewed publications and conference presentations.

Study registration number ClinicalTrials.gov, NCT06349863; Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Nationwide coverage ensures comprehensive representation.
⇒ Real-world data with 6-month follow-up, providing insights into actual clinical practices.
⇒ Clinically relevant objectives for a large patient population.
⇒ Observational design, although with a thorough up-front setup and data-analysis plan.

INTRODUCTION

Acute cholecystitis is generally attributable to gallstones, which affect approximately 10–15% of the general population.[1] Its incidence is high and rising, accounting for 5–10% of patients presenting with acute abdominal pain in emergency departments.[2] In the USA, cholecystitis leads to over 200 000 hospital admissions each year, with costs in excess of US$9 billion, annually.[3] Along with cholelithiasis, it is one of the most prevalent and costly gastrointestinal diseases, placing a substantial burden on healthcare resources.[4]

The most effective treatment strategy for acute cholecystitis is an early laparoscopic cholecystectomy in patients fit for surgery. Performing early cholecystectomy reduces overall morbidity, shortens hospital stay and lowers costs compared with delayed cholecystectomy.[1 5] Furthermore, nationwide registry studies from France and Sweden have

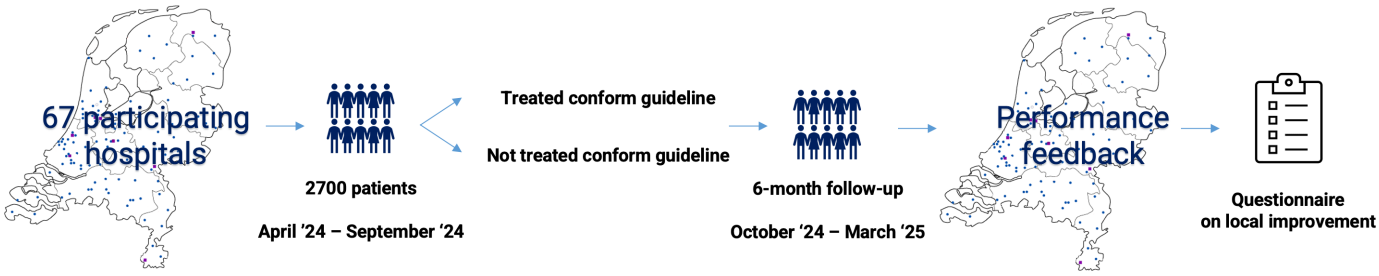

Figure 1 Study design of the Dutch Cholecystitis Snapshot Study.

demonstrated that early cholecystectomy, performed within the first 2–3 days after admission, yields the most favourable outcomes.[6 7] Additionally, routine use of postoperative antibiotic prophylaxis and prophylactic drainage is not indicated.[8 9]

Despite strong underlying evidence, adherence to guidelines in the treatment for cholecystitis remains low. A recent audit in 25 European and North American hospitals found that only 45% of patients with complicated gallstone disease underwent a same-admission cholecystectomy, even though these centres were well-informed of the guidelines. The main causes of guideline deviations were surgeon's preference, logistics and patient characteristics.[10] These findings emphasise the need to identify areas for improvement to enhance guideline adherence, as deviations—given the high incidence of cholecystitis—have a significant impact on the healthcare system.

Addressing knowledge gaps in cholecystitis treatment could further reduce its burden. First, the method of cystic duct closure may significantly affect postoperative bile leakage rates, a complication that is associated with increased healthcare costs and mortality.[11] However, current evidence is limited to mostly retrospective studies not specific to acute cholecystitis.[12] In addition, the frequent presence of elevated liver enzymes and bilirubin in cholecystitis patients often raises suspicion of choledocholithiasis, leading to additional diagnostics and delaying cholecystectomy.[13–15] A prospectively validated triage model could streamline patient management by differentiating those suitable for direct cholecystectomy from those requiring further diagnostics or common bile duct clearance. Further research is also needed to determine the optimal treatment strategy for patients presenting with cholecystitis lasting 7 days or more, as well as the optimal strategy for gallbladder drain placement and post-drainage care.

Therefore, the Dutch Cholecystitis Snapshot Study (Dutch CHESS) will assess the nationwide variation in cholecystitis treatment and identify opportunities for improving adherence to guidelines. In addition, the study will address important gaps in current knowledge. The Dutch CHESS aims to serve as a key driver in improving adherence to and optimisation of guidelines, both within the Netherlands and internationally.

METHODS AND ANALYSIS

Primary objective

The primary objective is to improve guideline adherence in the treatment of cholecystitis in the Netherlands.

Secondary objectives

The predefined four secondary objectives are to determine:

1. The optimal method of cystic duct closure, regarding cystic duct leakages.
2. The optimal model to predict concurrent choledocholithiasis in cholecystitis.
3. The optimal treatment for patients presenting with cholecystitis lasting ≥7 days.
4. The optimal method of gallbladder drainage and optimal post-drainage protocol.

Study design

The Dutch CHESS is a multicentre observational cohort study, registered with ClinicalTrials.gov (NCT06349863). It was designed in accordance with the principles of the Dutch snapshot research collaborative[16] and will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[17] A snapshot study is a resident-led initiative under the supervision of consultants. Its design was proven to be very successful in rapidly generating a population-based overview, providing insight into current clinical practice for common conditions or treatments.[18] All collaborators are allowed to submit post-hoc research questions and, on approval by the snapshot committee, will be provided with anonymised datasets to address them.

The Dutch CHESS will prospectively identify all patients diagnosed with calculous or acalculous cholecystitis from 1 April to 30 September 2024 in the Netherlands (figure 1). Data regarding patient, treatment and outcome characteristics will be extracted by residents from the patient's electronic health record at one week and six months after diagnosis. Possibly, when sufficient funding and support are gathered, the follow-up will extend to two years after admission. Following the end of the inclusion period, a questionnaire will be conducted to gain insight into local protocols, beliefs and organisation.

In order to stimulate guideline adherence, the following steps and actions will be sequentially followed in the data analysis:

Finding where improvement is needed

The Dutch CHESS will assess guideline adherence by determining the proportion of patients with acute calculous cholecystitis (lasting 0–7 days) who receive an early cholecystectomy, as recommended by the Dutch guideline for gallstone disease.[19] Guideline adherence for each hospital will be described anonymously to assess variation between hospitals.

Determining opportunities for improvement

Predictors of guideline non-adherence will be sought, including days of symptoms, comorbidities, sepsis, hospital type and volume, local organisation and protocols. Characteristics of hospitals in the 10th percentile for both the highest and lowest guideline adherence will be identified and compared, with the aim of identifying opportunities for improvement.

Determining potential benefits to guideline adherence

The impact of guideline adherence compared with non-guideline adherence, on complications, index admission hospital stay, hospital stay including readmissions, (non-) planned readmissions, emergency department or outpatient clinic presentations and recurrent biliary disease will be determined. Furthermore, the clinical outcome of hospitals in the highest 10th percentile for guideline adherence (best practices) will be compared with those in the lowest 10th percentile for guideline adherence.

Stimulating local improvement

All participating hospitals will receive their performance, compared to the national average and best-performing hospitals. This will provide insight into local performance and serve as a strong incentive to improve local protocols and practices. After three months, all lead investigators will be questioned as to whether these results changed local practice. Current funding does not permit a formal after-measurement.

Setting

A total of 67 out of 69 Dutch hospital organisations treating calculous cholecystitis will participate. These include seven academic hospitals, 40 teaching hospitals and 20 non-teaching hospitals. Each hospital has a local study team consisting of a principal investigator (consultant) and a co-investigator (resident) who will be responsible for patient inclusion and data extraction.

Study population

All patients aged 18 years or older, diagnosed with acute cholecystitis in a participating hospital, will be included. The location of diagnosis may be the emergency department, the ward during diagnostic admission or the outpatient clinic. Cholecystitis is defined according to the Tokyo Guidelines (TG) 2018 diagnostic criteria for cholecystitis:

1. Local signs of inflammation (Murphy's sign, right upper quadrant pain/mass/tenderness).
2. Systemic signs of inflammation (fever, elevated C reactive protein (CRP), elevated white blood cell count).
3. Imaging findings characteristic of acute cholecystitis.

Patients with a definitive diagnosis (A+one item in B+C) or a suspected diagnosis (A + (one item in B or C)) confirmed by preoperative findings are eligible for inclusion. Both calculous and acalculous cholecystitis will be registered. The only exclusion criterion is cholecystitis secondary to a locoregional malignancy. Subgroups relevant to the primary and secondary objectives will be selected and specified in the according sections.

Data collection

Data will be entered into a predesigned case reporting form within the secure web-based REDCap platform,[20] hosted at St. Antonius Hospital. The complete case reporting form is available on request to the corresponding author. Data to be collected include:

- Patient characteristics: age, body mass index (BMI), history of complicated gallstone disease, American Society of Anaesthesiologists (ASA) physical status classification, comorbidities (cardiovascular, pulmonary, diabetes mellitus, abdominal surgery, liver cirrhosis, malignity, other) and other factors (anticoagulation, immunosuppression, pregnancy).
- Cholecystitis characteristics: TG severity grade, symptom duration, temperature, concomitant gallstone disease (pancreatitis, cholangitis, choledocholithiasis), laboratory findings (CRP, leucocyte count, aspirate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), bilirubin), and imaging findings (eg, common bile duct diameter, cystic duct obstruction stone, abscess, fistula).
- Treatment characteristics: depending on chosen treatment, all characteristics of either choledocholithiasis treatment, cholecystectomy or conservative treatment for cholecystitis will be collected.
- Follow-up: all complications, Clavien-Dindo grading, readmission, visits to emergency department or outpatient clinic, total hospital stay and mortality.

Local investigators will extract these data items from patients' electronic health records at one week and six months after primary diagnosis. The coordinating investigators will execute data quality rules in REDCap to ensure the quality and completeness of data collected. Minimal grouping will be applied to quantitative variables.

Follow-up will be done using the patient's electronic health records. If patients are transferred to other hospitals, for example, due to complications, the outcomes and treatments reported back to the primary hospital will be registered.

Bias

To avoid selection and temporal bias, all hospitals in the Netherlands will include patients diagnosed with cholecystitis in the same period. By prospectively identifying the patients the chance of missing conservatively managed cholecystitis is reduced. Consistency and accuracy of data collection will be ensured by data control and local

audits. Local investigators, comprising both residents and surgeons, have chosen to contribute to this research due to their motivation to improve cholecystitis treatment, ensuring reliable results. However, full monitoring and control of results, as well as blinding, are not feasible. Although a correction will be made for confounding factors, there remains a risk of residual confounding by indication.

Study size

The annual incidence of cholecystitis in the Netherlands is approximately 6000 patients according to the International Classification of Diseases (10th revision) registration.[21] With 69 hospital organisations in the Netherlands, 6 months would result in a total of 3000 patients and a mean of 43 patients per hospital organisation. This number would be sufficient to adequately portray daily practice, even in smaller organisations.

Additionally, a power calculation was performed for the secondary objective with the least frequent outcome: the number of cystic duct leaks between different cystic duct closure methods. To demonstrate a clinically relevant reduction in cystic duct leaks from 3% to 1% when using locking clips or loop closure compared with non-locking clips, a total sample size of 1532 is required (power 80% and alpha 5%).[22] When considering an unequal distribution with a sample size ratio of 2:1, the total required sample size increases to 1824 (power 80% and alpha 5%).

The Dutch CHESS is expected to include 2700 patients, accounting for a 10% missing rate. Of these patients, 80% are expected to undergo a cholecystectomy, either early or delayed, resulting in an estimated number of 2160 cholecystectomies, which is sufficient for this secondary objective.

Predefined statistical analysis plan

General principles

All analyses will be performed after the data entry is completed and data have been cleaned. They will be performed using the latest version of either R or SPSS statistics. Missing data will be imputed with multiple imputation, and selection of patients based on inclusion and exclusion criteria will be made on available data. Categorical variables will be reported as counts with percentages. Comparisons will be made with either the χ^2 or Fisher's exact test, where appropriate. Continuous variables will be reported as means with SD or medians with IQRs. These will be compared using either the student's t-test, Mann-Whitney U-test or analysis of variance, where appropriate.

Primary objective analysis plan

Our goal is to improve guideline adherence in cholecystitis treatment in the Netherlands, with the steps previously described under study design.

To depict current practice in the Netherlands, a flowchart of how patients with calculous cholecystitis are treated and the proportions of patients that undergo early cholecystectomy in each hospital, will be anonymously presented. These proportions will be stratified by days of symptom duration.

To determine the potential benefits of guideline adherence, comparative subgroup analyses will be performed between patients treated conforming to guidelines and those who were not. Patients for whom cholecystectomy is generally deemed contraindicated or impossible will be excluded. These criteria include ASA >3, patient or anaesthetist refusal, concomitant necrotising pancreatitis, symptom duration >7 days at time of diagnosis, inaccessible abdomen or gallbladder fistula.

To account for confounding and clustering by hospital type (academic, teaching, size), generalised mixed models with random effects will be used. This approach allows for the assessment of both fixed and random effects, providing a comprehensive understanding of the variability between hospitals while enabling generalizable inferences about the larger population.

Confounding factors include: age, ASA classification, BMI, TG severity grade, history of biliary disease, history of complicated gallstone disease, cardiovascular disease, pulmonic disease, diabetes, history of abdominal surgery, anticoagulation use, immunosuppression use and liver cirrhosis.

Secondary objectives analysis plan

To determine the optimal method of cystic duct closure, regarding cystic duct leakage

Patients who received either early or delayed laparoscopic cholecystectomy for acute calculous cholecystitis are included. The primary outcome is type A1 postoperative biliary leakage, which corresponds to cystic duct leakage according to the Amsterdam classification.[23] Locking clips or loop closure will be compared with non-locking clips.

A multivariable logistic regression model will be developed, incorporating previously identified confounders as mentioned below.[22] In order to account for clustering by hospital type, a generalised mixed model will be used. This methodology will allow us to determine if any of the different cystic duct closure techniques are associated with the occurrence of postoperative cystic duct leakage.

The potential confounders are ASA classification, history of cholecystitis, preoperative endoscopic retrograde cholangiopancreatography (ERCP)/concomitant biliary disease (pancreatitis/cholangitis/choledocholithiasis), BMI, operating time and immunosuppressants. An interaction term will be used to assess if early or delayed cholecystectomy is an effect modifier. In case the interaction term is significant, a stratified analysis will be performed.

To determine the optimal model to predict concurrent choledocholithiasis in cholecystitis

This secondary objective will be reported in accordance with the TRIPOD+AI statement.[24] All patients diagnosed with acute calculous cholecystitis according to the TG will be included. Patients with pre-existing conditions that

result in bile duct dilation, such as primary sclerosing cholangitis or choledochal cysts, or patients in whom no imaging was performed will be excluded.

The focus of this objective is to predict obstructive choledocholithiasis at the time of diagnosis. Accordingly, the primary outcome is the diagnosis of choledocholithiasis within one week following the diagnosis of cholecystitis. The one-week follow-up period is selected based on the premise that, in the Netherlands, it is unlikely for patients with obstructive stones in the common bile duct at the time of cholecystitis diagnosis to undergo diagnostics after one week. Patients who are diagnosed with choledocholithiasis during evaluation for recurrent symptoms or illness after they initially recovered well are considered to have a new episode.

Choledocholithiasis is defined as the presence of stones or sludge in the common bile duct, visualised either by abdominal ultrasound, CT, endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), ERCP, cholangioscopy or intraoperative cholangiography.

Previously developed prediction models will be tested for accuracy, calculating sensitivity, specificity, positive predicting value (PPV), negative predicting value and area under the curve. These models were found by a systematic literature review as preliminary work for this objective (yet unpublished). The models that will be validated are those proposed by: Chisholm *et al*, Reddy *et al* and Khoury *et al*, as well as the models from the European Society of Gastrointestinal Endoscopy and American Society of Gastrointestinal Endoscopy.[13–15 25 26]

Performance will be considered acceptable if the model's highest risk score (indicating direct ERCP) achieves a PPV of 75%, as deemed acceptable by a survey among gastroenterologists.[27] Additionally, the model should not increase the current diagnostic costs (eg, MRCP, EUS). If neither model demonstrates accurate performance, a new prediction model will be developed using univariable logistic regression and subsequent multivariable logistic regression.

The predictors used in regression will be AST, ALT, ALP, GGT, total bilirubin, common bile duct width (on primary abdominal ultrasound or CT), age, BMI and concomitant complicated gallstone disease (pancreatitis, cholangitis), in line with previous articles.[13–15]

Approximately 5–15% of patients with cholecystitis have concomitant choledocholithiasis.[1] Consequently, the Dutch CHESS will include at least 135 cases of choledocholithiasis (5% of 2700 inclusions). This number is sufficient for developing or validating a model, with nine variables and a minimum event rate of 10 per variable.

A radiologist, resident in radiology or trained PhD candidate will measure initially unmeasured common bile duct widths.

To determine the optimal treatment for patients presenting with cholecystitis lasting ≥7 days

For this objective, all patients with calculous cholecystitis presenting with ≥7 days of symptoms at the time of diagnosis will be included. Patients will be excluded when cholecystectomy is generally deemed contraindicated or impossible as previously described in the primary objective statistical plan. The aim is to compare early cholecystectomy with the alternative strategies, for example, delayed cholecystectomy or conservative treatment without cholecystectomy.

The primary outcome is overall morbidity, defined as any adverse event in the 180 days following diagnosis, as described in the randomised trial of Roulin *et al*.[28] This includes failure of initial conservative treatment requiring emergency cholecystectomy, unplanned readmissions and emergency department presentations, as well as postoperative complications. Patients who receive a delayed cholecystectomy at the end of the follow-up period will be followed for a minimum of 30 days postoperatively.

Secondary outcomes are total hospital stay, recurrence of complicated gallstone disease, re-admissions, presentations at emergency department or outpatient clinic, number of re-interventions and complications that are classified as Clavien-Dindo Grade II or higher. When operated, secondary outcomes also include: operating time, conversions, intraoperative complications, postoperative complications and postoperative hospital stay.

Confounders that will be addressed in the analysis include age, ASA classification, history of cholecystitis, BMI, preoperative ERCP/concomitant biliary disease (pancreatitis/cholangitis/choledocholithiasis), CRP and leucocyte count.

To determine the optimal method of gallbladder drainage and post-drainage protocol

Determining the optimal method of gallbladder drainage

For this objective, all patients treated with gallbladder drainage for calculous cholecystitis will be included. A comparison will be made between the different drainage techniques (in general transperitoneal versus transhepatic drain placement). The primary outcome is the technical and clinical success rate of gallbladder drainage, defined as successful execution of the procedure (drain in gallbladder producing bile or pus), and the resolution of symptoms and inflammation following the procedure (without the need for re-interventions), allowing discharge in good clinical condition, respectively. Secondary outcomes are recurrence of cholecystitis, number of drain dislocations/obstructions/migrations, number of re-interventions (Clavien-Dindo ≥3), complications of drain placement (intra-abdominal bile leakage/bowel perforation/bleeding), re-admissions, presentations at the emergency department or outpatient clinic, time to successful drain removal (without recurrent cholecystitis within 2 weeks), total hospital stay and mortality.

Determining the optimal post-drainage protocol

For this objective, all patients with successful gallbladder drainage will be included. Successful drainage is defined as effective drain placement leading to the resolution of symptoms and inflammation, allowing for hospital

discharge. Time to drain removal, clinical decision for cholecystography and clinical decision after cholecystography will be registered and compared.

The primary outcome is overall morbidity as defined in objective three. Secondary outcomes are number of re-interventions (Clavien-Dindo ≥3), recurrence of cholecystitis, value of cholecystography on clinical decision making, number of drain dislocations/obstructions/migrations, re-admissions, presentations at the emergency department or outpatient clinic, total hospital stay and mortality.

Patient and public involvement

The Dutch CHESS is endorsed by the Dutch Liver Patients Association, which reviewed the protocol and provided suggestions for improvement from the patient's perspective.

Status of the study

The study protocol was submitted to ClinicalTrials.gov on 31 March 2024 (NCT06349863). The inclusion period started as planned on 1 April 2024 and ended on 30 September 2024. As of 18 April 2025, a total of 3689 patients had been included from 67 of 69 hospital organisations treating cholecystitis in the Netherlands. Currently, 3563 of these patients are registered in the REDCap database. The follow-up period concluded at the end of March 2025; however, data entry and cleaning are expected to continue until June 2025. Thereafter, the first analyses will be performed and participating researchers will receive their results set against the national average.

ETHICS AND DISSEMINATION

Ethical aspects and consent

This study will be performed in accordance with the principles of Good Clinical Practice, the Dutch Agreement on Medical Treatment Act and the European General Data Protection Regulation.

The Dutch CHESS will include a large number of patients over a short period, most of whom will be admitted through the emergency department, some with a very brief duration of stay. Obtaining written informed consent from all these patients would pose a substantial risk of participation bias.[29 30] Additionally, due to the large number of patients, it would impede the execution of the study and impose a very high workload on participating surgeons. Therefore, after consulting the legal department of St. Antonius Hospital, an ethical rationale was formulated, explaining why written informed consent will not be requested for the use of patients' data for the Dutch CHESS, in compliance with the Dutch Agreement on Medical Treatment Act (online supplemental file 1).

The Medical research Ethics Committees United reviewed the study protocol and concluded that the Dutch Medical Research Involving Human Subjects Act does not apply. The study is observational, imposes no actions on patients and uses solely routinely collected data from medical records (reference number: W23.225). Furthermore, at every participating hospital, the local institutional research department and the board of directors reviewed and approved the study. As a result of this extensive process, in some hospitals surgeons were required to obtain verbal consent (n=9), while in most hospitals an objection procedure was deemed sufficient (n=58), allowing patients who object to the use of their data to opt out of participation.

Dissemination

All collaborators will receive monthly updates during the study. The results of the Dutch CHESS will be submitted for publication in international peer-reviewed scientific journals, presented at national and international conferences, and each local hospital will receive its own performance set against the nationwide average and best practices.

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Contributors MHGvM, TJW, RCV, KPvL and DB participated to the study conception and design. MHGvM and LG performed the sample size calculations and developed the statistical analysis plan. MHGvM, TJW and LG drafted the manuscript. All authors made critical revisions for important intellectual content and approved the final manuscript for publication. TJW serves as the guarantor of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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