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Diagnostic accuracy of magnetically guided capsule endoscopy with a detachable string for detecting oesophagogastric varices in adults with cirrhosis: prospective multicentre study

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ABSTRACT

OBJECTIVE

To evaluate the diagnostic accuracy and safety of using magnetically guided capsule endoscopy with a detachable string (ds-MCE) for detecting and grading oesophagogastric varices in adults with cirrhosis.

DESIGN

Prospective multicentre diagnostic accuracy study.

SETTING

14 medical centres in China.

PARTICIPANTS

607 adults (>18 years) with cirrhosis recruited between 7 January 2021 and 25 August 2022. Participants underwent ds-MCE (index test), followed by oesophagogastroduodenoscopy (OGD, reference test) within 48 hours. The participants were divided into development and validation cohorts in a ratio of 2:1.

MAIN OUTCOME MEASURES

The primary outcomes were the sensitivity and specificity of ds-MCE in detecting oesophagogastric

varices compared with OGD. Secondary outcomes included the sensitivity and specificity of ds-MCE for detecting high risk oesophageal varices and the diagnostic accuracy of ds-MCE for detecting high risk oesophagogastric varices, oesophageal varices, and gastric varices.

RESULTS

ds-MCE and OGD examinations were completed in 582 (95.9%) of the 607 participants. Using OGD as the reference standard, ds-MCE had a sensitivity of 97.5% (95% confidence interval 95.5% to 98.7%) and specificity of 97.8% (94.4% to 99.1%) for detecting oesophagogastric varices (both $P < 0.001$ compared with a prespecified 85% threshold). When using the optimal 18% threshold for luminal circumference of the oesophagus derived from the development cohort ($n = 393$), the sensitivity and specificity of ds-MCE for detecting high risk oesophageal varices in the validation cohort ($n = 189$) were 95.8% (89.7% to 98.4%) and 94.7% (88.2% to 97.7%), respectively. The diagnostic accuracy of ds-MCE for detecting high risk oesophagogastric varices, oesophageal varices, and gastric varices was 96.3% (92.6% to 98.2%), 96.9% (95.2% to 98.0%), and 96.7% (95.0% to 97.9%), respectively. Two serious adverse events occurred with OGD but none with ds-MCE.

CONCLUSION

The findings of this study suggest that ds-MCE is a highly accurate and safe diagnostic tool for detecting and grading oesophagogastric varices and is a promising alternative to OGD for screening and surveillance of oesophagogastric varices in patients with cirrhosis.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03748563.

Introduction

Oesophagogastric varices occur in about half of patients with cirrhosis and are major causes of morbidity and mortality because of the risk of variceal bleeding.¹ To identify people with high risk varices who need prophylactic treatment to prevent variceal bleeding, clinical guidelines recommend oesophagogastroduodenoscopy (OGD) as the standard

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oesophagogastroduodenoscopy (OGD) is used to diagnose oesophagogastric varices in patients with cirrhosis, but it is invasive and involves sedation leading to patient discomfort, poor adherence, and potentially serious complications. Capsule endoscopy is a less invasive test than OGD as patients swallow a small device that produces images of the gastrointestinal tract. Conventional small bowel capsule endoscopy and oesophageal capsule endoscopy, however, are not accurate enough to replace OGD to detect oesophageal or gastric varices.

WHAT THIS STUDY ADDS

In this diagnostic accuracy study of 607 patients with cirrhosis, magnetically controlled capsule endoscopy with a detachable string (ds-MCE) showed high sensitivity and specificity in diagnosing oesophagogastric varices, with OGD as the reference standard. The accuracy of ds-MCE for detecting high risk oesophageal varices was also comparable to OGD. The results indicate ds-MCE is a highly accurate and safe method for detecting and grading oesophagogastric varices, and it is a promising alternative to OGD for screening and surveillance of oesophagogastric varices in patients with cirrhosis.

diagnostic modality for screening and periodic surveillance of oesophagogastric varices.¹⁻³ OGD is an unpleasant invasive procedure, however, which usually necessitates sedation, potentially leading to sedation related complications and low adherence to screening programmes in patients with cirrhosis.⁴ An alternative method to OGD that is minimally invasive and of comparable accuracy is thus needed for detecting and grading oesophagogastric varices in patients with cirrhosis.

Capsule endoscopy, involving the ingestion of a small battery powered device with a camera, has been proposed as a promising minimally invasive diagnostic modality for visualising oesophagogastric varices.⁵⁻⁸ The advantages of capsule endoscopy are that it is minimally invasive, requires no sedation, and is highly acceptable to patients.⁹ Studies have, however, reported that conventional small bowel capsule endoscopy and oesophageal capsule endoscopy are not accurate enough to replace OGD to detect or grade oesophageal varices.^{5 7 9-12} In a multicentre study of 330 participants with cirrhosis, the sensitivity of oesophageal capsule endoscopy to diagnose and correctly stage oesophageal varices was only 76% and 64%, respectively.⁷ Moreover, conventional capsule endoscopy has shown poor accuracy in detecting gastric varices and portal hypertensive gastropathy.^{5 6 13} During oesophageal examination, the image capture rate of conventional capsule endoscopy is insufficient compared to the rapid oesophageal transit time, and the passive movement of the capsule means the transit time cannot be controlled. During gastric examination, the passive movement also prevents complete visualisation of the capacious and non-uniform cavity of the stomach. These limitations preclude conventional capsule endoscopy from providing a complete view of areas with suspected oesophagogastric varices. To date, clinical guidelines do not recommend conventional capsule endoscopy for screening or surveillance of oesophagogastric varices.²

To achieve a complete examination of the oesophagus and stomach using capsule endoscopy, we developed magnetically guided capsule endoscopy with a detachable string (ds-MCE). The capsule can be actively controlled in the oesophagus via the string and in the stomach via magnetic force, and therefore offers a minimally invasive method to detect both oesophageal varices and gastric varices. In addition, the capsule has a long battery life, enabling further evaluation for portal hypertensive enteropathy in the small bowel. Our previous small sample studies showed the feasibility and safety of ds-MCE in healthy volunteers and in patients with compensated cirrhosis.^{14 15} In this paper, we conducted the CENTERS study to further assess the diagnostic accuracy of ds-MCE in detecting and grading oesophagogastric varices in patients with cirrhosis.

Methods

Study design

CENTERS is a prospective multicentre study reported according to the standards for reporting diagnostic accuracy studies.¹⁶ The study was performed at

14 hospitals in China between 7 January 2021 and 25 August 2022. Patients with cirrhosis were consecutively recruited to undergo ds-MCE (index test) first, then OGD (the reference standard) within 48 hours of the first procedure. Certified operators performed the ds-MCE and experienced endoscopists performed the OGD, each blinded to the results of the other test. All participants provided written informed consent. The study protocol and statistical analysis plan are included in the supplementary appendix.

Participants

Eligible patients were those aged at least 18 years with a diagnosis of cirrhosis. Exclusion criteria were dysphagia, Zenker's diverticulum, gastrointestinal obstruction, pregnancy, gastrointestinal bleeding, a cardiac pacemaker or other implanted electromedical device, a life threatening condition, planned magnetic resonance imaging before excretion of the capsule endoscope, participation in another clinical study, and refusal to give informed consent or any condition that precluded compliance with the study. Supplementary method 2.1 lists the inclusion and exclusion criteria.

Study procedures

The ds-MCE examination (index test)

The ds-MCE system (Ankon Technologies, Wuhan, China) consists of a capsule endoscope with a camera for capturing images, a robotic arm with a magnet for guiding the capsule, a data recorder, a computer workstation with software for real time viewing, two joysticks for controlling the orientation of the capsule (see supplementary figure S1),¹⁷⁻²⁰ and a detachable hollow latex string (see supplementary figure S2).¹⁴ The capsule endoscope measures 27×11.8 mm and has a battery life of more than 10 hours and a viewing field of 150 degrees. Images are captured at an adaptive rate of 0.5-6 frames per second, with a resolution of 480×480 pixels. The latex string is 120 cm in length and can be attached to the capsule endoscope at one end and a syringe at the other end.

Figure 1 shows the ds-MCE procedure. Before the examination, participants were asked to fast overnight for 12 hours and to ingest 2.5 g of dimethicone as a defoaming agent 40 minutes before the procedure, followed by 500-1000 mL of water as tolerated before ingestion of the capsule to fill the stomach cavity and aid navigation of the capsule. Participants underwent a standardised gastrointestinal preparation regimen, swallowed the capsule with water, and were not sedated. During examination of the oesophagus, the capsule endoscope was controlled by the string and images were captured at a rate of six frames per second. Once the capsule had reached the gastric cardia by means of the swallowed water, the string was pulled up slowly so that the operator could inspect the oesophagus under real time viewing. This process was repeated at least three times, during which participants drank water to distend the distal oesophagus and to remove saliva and mucous bubbles for better observation. After completion of the examination, the

syringe was used to administer 5 mL of air through the string to detach the capsule and the string was removed via the mouth. At this point the capsule endoscope entered the stomach and was controlled by an external magnetic field during the gastric examination. The procedure was performed twice according to standardised protocol, and the gastric cardia, fundus, body, angulus, antrum, and pylorus were fully examined.¹⁹ On completion of the gastric examination, the capsule endoscope was switched to the mode for examination of the small intestine and allowed to move passively under gastrointestinal peristalsis. In this mode, the frame rate of the capsule

varies because the capsule automatically recognises the velocity at which it is moving and can adjust the camera to capture between 0.5-6 frames per second. At each centre, a dedicated certified operator performed the ds-MCE procedures. Staff at an independent core imaging laboratory reviewed the coded videos of the ds-MCE procedures (see supplementary methods 2.2 and 2.3).

OGD examination (reference standard)

At each centre, experienced endoscopists performed conventional forward viewing OGD within 48 hours after ds-MCE. OGD was conducted with or without

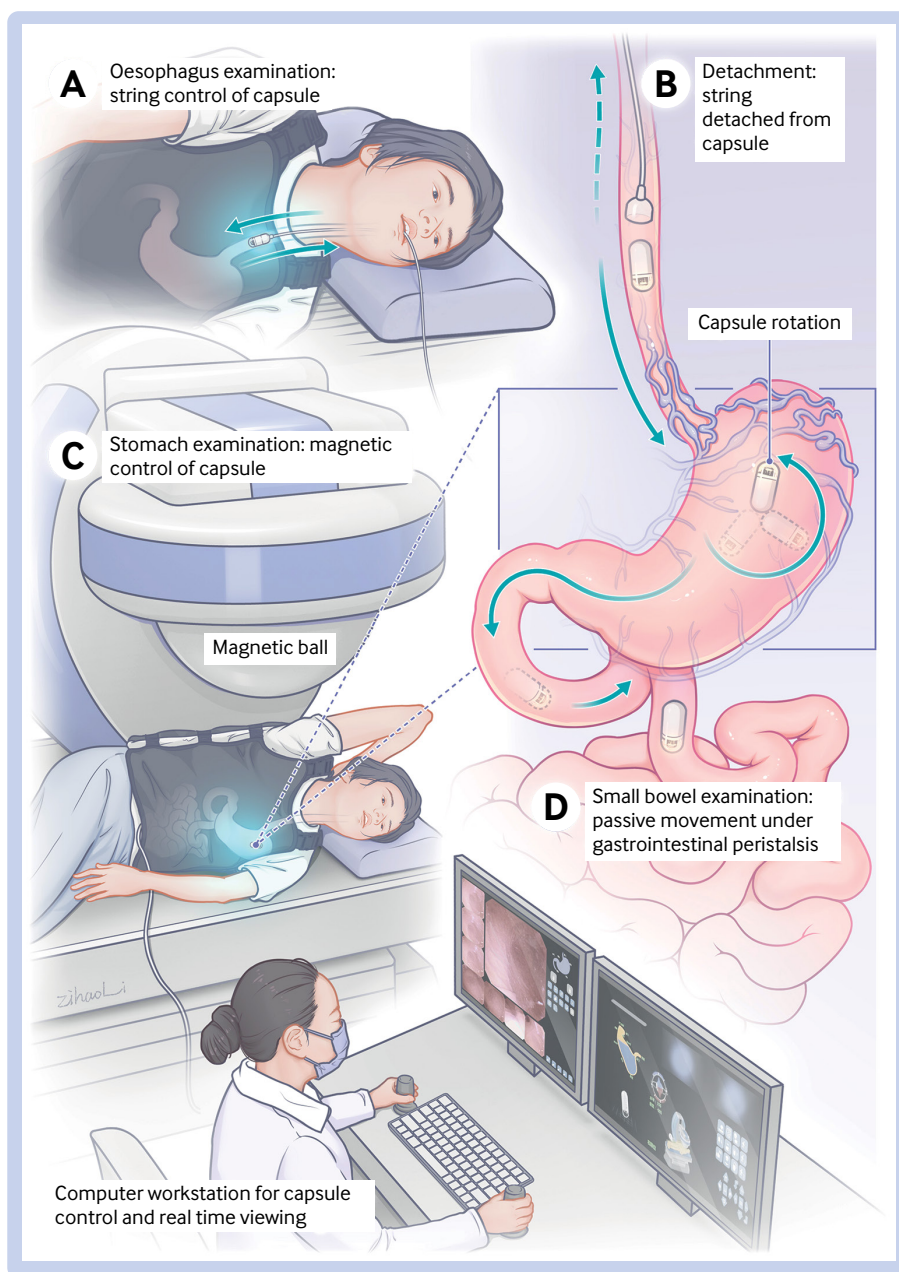


Fig 1 | Magnetically guided capsule endoscopy with a detachable string (ds-MCE). During examination of the oesophagus, the capsule is controlled by a hollow latex string (A); after completion of the oesophageal examination, the string is separated from the capsule by injecting 5 mL of air through the syringe and then removed via the mouth, and the capsule enters the stomach (B); the capsule is then controlled by an external magnetic field during gastric examination (C); then is moved passively under gastrointestinal peristalsis during examination of the small bowel (D)

sedation, according to the centre's standard procedure and preference of the patient. The endoscopist was blinded to results of the preceding ds-MCE. The oesophagus, stomach, and duodenum were examined routinely. The whole examination of each participant was recorded on video and digital images. An independent core imaging laboratory reviewed the coded videos and images of OGD from each centre (see supplementary methods 2.2 and 2.3).

After completion of both examinations, participants were administered a questionnaire on their satisfaction with the procedures. Two weeks after ds-MCE, participants were followed up to confirm excretion of the capsule endoscope. Any adverse events during the study were reported to the investigators and recorded.

Outcomes measures and definitions

The primary outcomes were the sensitivity and specificity of ds-MCE for detecting oesophagogastric varices in patients with cirrhosis, using OGD as the reference standard. The key secondary outcomes were the sensitivity and specificity of ds-MCE in detecting high risk oesophageal varices compared with OGD. Other secondary outcomes included the diagnostic accuracy of ds-MCE in detecting high risk oesophagogastric varices, oesophageal varices, large oesophageal varices, red colour signs of oesophageal varices, gastric varices, cardiofundal gastric varices, and portal hypertensive gastropathy compared with OGD; the findings of portal hypertensive enteropathy in small bowel under ds-MCE; the examination time of ds-MCE and OGD; assessment of patients' satisfaction; and evaluation of safety.

Oesophagogastric varices occur in the oesophagus or stomach. Oesophageal varices detected during OGD were classified as large (diameter ≥ 5 mm) or small according to the Baveno III consensus.²¹ We used the de Franchis method⁵ to grade the size of oesophageal varices detected during ds-MCE according to the percentage of luminal circumference of oesophagus occupied by the largest oesophageal varices (see supplementary figure S3). Oesophageal varices detected during ds-MCE were defined as large when the varix occupied more than the optimal percentage threshold of the luminal circumference of the oesophagus. We defined high risk oesophageal varices as large varices or small varices occurring in the presence of red colour signs.²² Gastric varices in the stomach were classified as gastrooesophageal varices and isolated gastric varices according to Sarin's classification,²³ and cardiofundal gastric varices included type 2 gastrooesophageal varices and type 1 isolated gastric varices. We defined high risk oesophagogastric varices as high risk oesophageal varices or any gastric varices.^{24 25} Patient satisfaction assessments were based on satisfaction scores, with higher scores representing more comfort. Supplementary method 2.4 provides detailed definitions of outcomes.

Statistical analysis

The primary aims of our single arm diagnostic accuracy study were to test whether the sensitivity and

specificity of ds-MCE for detecting oesophagogastric varices would be $>85\%$. With an estimated sensitivity of 90%, specificity of 94%, two sided alpha of 5%, power of 80%, prevalence for oesophagogastric varices of 62%, and dropout rate of 3%, we determined that 591 participants would be needed.²⁶

The diagnostic analyses are based on the results of participants with useable data after ds-MCE and OGD. Using OGD as the reference standard, we assessed the diagnostic accuracy of ds-MCE for detecting oesophagogastric varices, with sensitivity and specificity as the primary outcomes; with the positive predictive value, negative predictive value, and overall diagnostic accuracy of ds-MCE as other measures simultaneously, along with corresponding 95% confidence intervals using Wilson's method, in per patient analysis. We compared the sensitivity and specificity of detecting oesophagogastric varices with the prespecified 85% threshold using the one sample exact test. The diagnostic performance of ds-MCE for detecting oesophageal varices, red colour signs of oesophageal varices, gastric varices, cardiofundal gastric varices, and portal hypertensive gastropathy was assessed using sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy.

In addition, we divided the sample into development and validation cohorts in a ratio of 2:1 according to the temporal order of first-patient-in dates of each centre, such that centres with earlier first-patient-in dates were allocated to the development cohort (seven centres, $n=393$, supplementary table S1) and centres with later first-patient-in dates were allocated to the validation cohort (the remaining seven centres, $n=189$, supplementary table S1). From the development cohort we derived the optimal percentage threshold for luminal circumference of the oesophagus for detecting large oesophageal varices during ds-MCE. We calculated the Youden index, defined as $[(\text{sensitivity} + \text{specificity}) - 1]$, to determine the optimal percentage threshold for oesophageal luminal circumference, rounding down to the nearest whole percentage derived from the development cohort that resulted in the best combination of specificity and sensitivity for detecting large oesophageal varices during ds-MCE. And we internally validated the optimal threshold using the bootstrap method, with 1000 replications. The validation cohort was used to assess the diagnostic accuracy of ds-MCE for detecting high risk oesophageal varices, high risk oesophagogastric varices, and large oesophageal varices on the basis of the optimal threshold, using sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy. P values <0.05 were considered to indicate statistical significance (see supplementary method 2.5).

Patient and public involvement

No patients or members of the public were directly involved in setting the research question or the outcome measures. At the protocol stage, more than

30 patients with cirrhosis were consulted about the ds-MCE procedure. Participants were aware of the purpose and content of this study during recruitment, although they were not involved in the initial design of the trial. Considering the confidentiality of clinical data, patients did not participate in the subsequent reporting of this research. The results were, however, communicated to patients who expressed an interest during clinic visits.

Results

Participants

A total of 607 adults with cirrhosis from 14 centres in China were enrolled into the study between 7 January 2021 and 25 August 2022. Twenty five patients were

excluded—in 17 patients it was not possible to complete the oesophageal and stomach examinations during ds-MCE. Both ds-MCE and OGD examinations were completed in 582 participants (fig 2). These participants were included in the accuracy analysis. Table 1 shows the baseline characteristics of the 582 participants.

Primary outcome

Overall, the findings for oesophagogastric varices were concordant between ds-MCE and OGD in 568 of the 582 participants (97.6%). Results were inconsistent between the two procedures in 14 participants, oesophagogastric varices detected by ds-MCE were not confirmed by OGD in four participants, and ds-MCE failed to detect oesophagogastric varices detected by

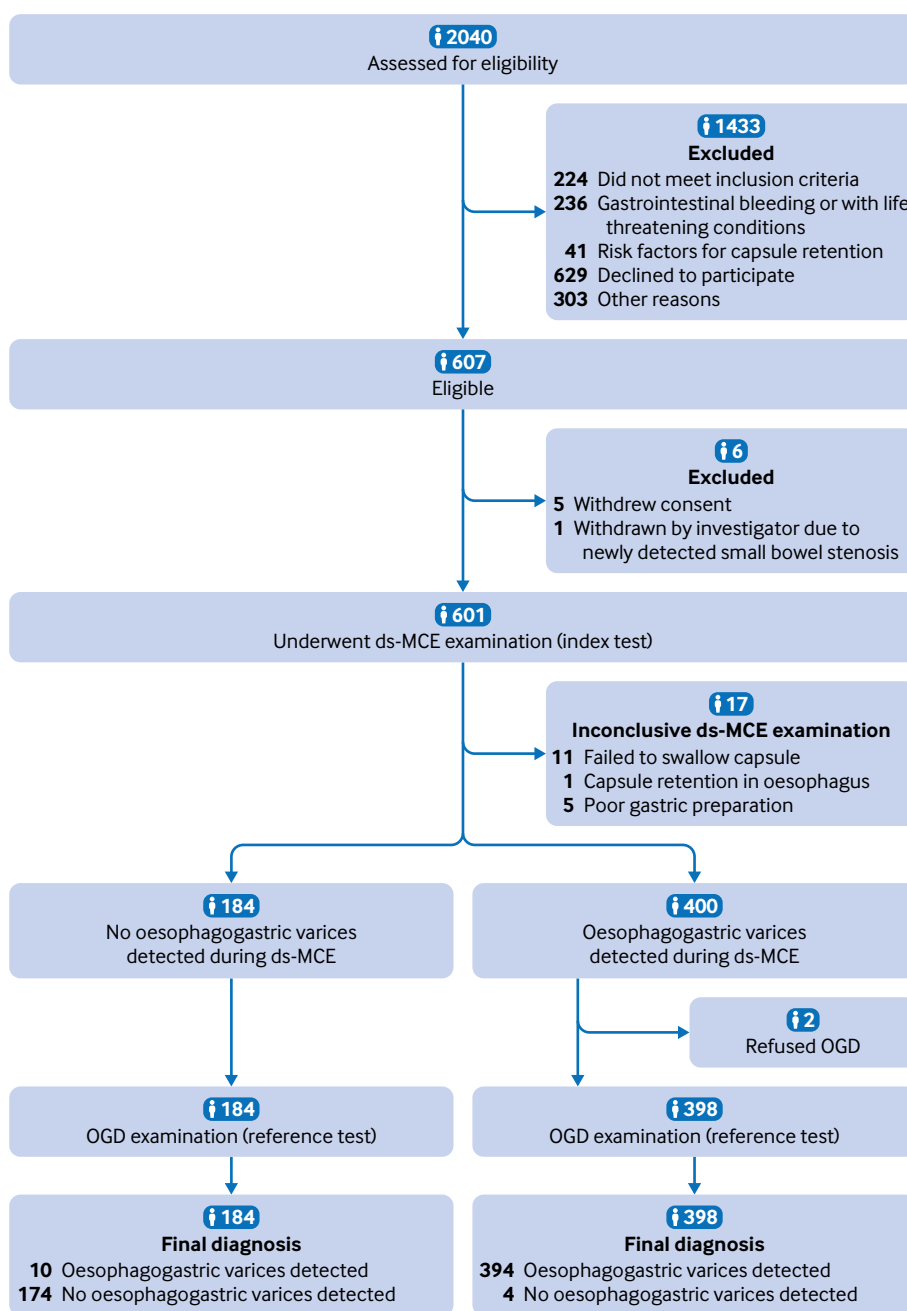


Fig 2 | Flow of participants through study. ds-MCE=magnetically guided capsule endoscopy with a detachable string; OGD=oesophagogastrroduodenoscopy

Table 1 | Baseline characteristics of adults with cirrhosis. Values are number (percentage) unless stated otherwise

Characteristics	Participants (n=582)
Median (IQR) age (years)	55.00 (48.00-64.00)
Sex:	
Male	398 (68.4)
Female	184 (31.6)
Median (IQR) time since cirrhosis diagnosis (years)	2.5 (0.3-6.0)
Cause of cirrhosis:	
Hepatitis B virus infection	340 (58.4)
Hepatitis C virus infection	29 (5.0)
Alcoholic liver disease	61 (10.5)
Autoimmune hepatitis	44 (7.6)
Primary biliary cirrhosis	16 (2.7)
Non-alcoholic steatohepatitis	6 (1.0)
Cryptogenic	60 (10.3)
Other*	26 (4.5)
Median (IQR) Child-Pugh score† (points)	6.0 (5.0-7.0)
Child-Pugh class‡:	
Class A	402 (69.1)
Class B	153 (26.3)
Class C	27 (4.6)
Median (IQR) MELD score§ (points)	9 (7-11)
Median (IQR) laboratory results:	
Platelet count ($\times 10^9/L$)	94 (62-145)
Alanine transaminase (U/L)	25.1 (18-40)
Aspartate aminotransferase (U/L)	31 (24-46.75)
γ -glutamyltransferase (U/L)	38 (22-77)
Total bilirubin ($\mu\text{mol/L}$)	18.55 (13.4-28.55)
Albumin (g/L)	38.75 (33-44.1)
Creatinine ($\mu\text{mol/L}$)	66 (57-78)
Prothrombin time (s)	13.7 (12.7-15.2)
International normalised ratio	1.15 (1.035-1.28)
Decompensated cirrhosis	356 (61.2)
Indication for endoscopy:	
Screening	228 (39.2)
Surveillance	354 (60.8)
Clinical events:	
Ascites	264 (45.4)
History of splenectomy	41 (7.0)
TIPS insertion	39 (6.7)
History of endoscopic variceal treatment	120 (20.6)
History of variceal oesophagogastric bleeding	189 (32.5)

IQR=interquartile range; MELD=model for end stage liver disease; TIPS=transjugular intrahepatic portosystemic shunt.
 *Includes schistosomiasis (n=12), drug induced cirrhosis (n=4), Budd-Chiari syndrome (n=3), co-infection with hepatitis C virus and hepatitis B virus (n=1), hepatitis B infection+alcoholic liver disease (n=5), alcoholic liver disease+schistosomiasis (n=1).
 †Child-Pugh score is a liver reserve function evaluation and scoring system, using five clinical and laboratory measures (total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy) to generate a total score between 5 and 15.
 ‡Class A represents a total Child-Pugh score of 5 to 6, class B a score of 7 to 9, and class C a score of 10 to 15.
 §MELD score measures the severity of liver disease, and is calculated based on serum creatinine and bilirubin levels, international normalised ratio of prothrombin time, and cause of liver disease.

OGD in 10 participants (see supplementary table S3). Using OGD as the reference standard, ds-MCE had a sensitivity of 97.5% (95% confidence interval 95.5% to 98.7%) and specificity of 97.8% (94.4% to 99.1%) for detecting oesophagogastric varices, and both sensitivity and specificity were significantly higher than the prespecified 85% threshold (both $P < 0.001$) (table 2). The positive predictive value and negative predictive value was 99.0% (97.4% to 99.6%) and 94.6% (90.3% to 97.0%), respectively (table 2). Figure 3 shows representative oesophagogastric varices observed during ds-MCE and OGD.

Secondary outcomes

The development cohort included 393 participants from seven centres, and the validation cohort included 189 participants from the remaining seven centres

(see supplementary table S1). Supplementary table S2 presents the clinical characteristics of participants in both cohorts. In the development cohort, the optimal percentage threshold circumference for the oesophageal lumen of ds-MCE in detecting large oesophageal varices was 18.45%, with a Youden's index of 0.95 (see supplementary figure S4). Therefore, we chose a threshold of 18% for discriminating large oesophageal varices during ds-MCE. Using the 18% threshold in the development cohort, internal validation showed a sensitivity of 98.3% (94.9% to 100.0%) and a specificity of 97.6% (93.4% to 99.6%) for detecting large oesophageal varices (see supplementary table S4).

Using the 18% threshold in the validation cohort, the sensitivity and specificity of ds-MCE for detecting high risk oesophageal varices were 95.8%

Table 2 | Diagnostic performance of ds-MCE using oesophagogastroduodenoscopy as reference standard in main analysis for detection of oesophagogastric varices

Outcome	Sensitivity		Specificity		Positive predictive value		Negative predictive value		Diagnostic accuracy	
	% (95% CI)	No/total No	% (95% CI)	No/total No	% (95% CI)	No/total No	% (95% CI)	No/total No	% (95% CI)	No/total No
Primary outcome										
Oesophagogastric varices	97.5 (95.5 to 98.7)	394/404	97.8 (94.4 to 99.1)	174/178	99.0 (97.4 to 99.6)	394/398	94.6 (90.3 to 97.0)	174/184	97.6 (96.0 to 98.6)	568/582
Secondary outcomes										
High risk oesophageal varices*	95.8 (89.7 to 98.4)	91/95	94.7 (88.2 to 97.7)	89/94	94.8 (88.4 to 97.8)	91/96	95.7 (89.5 to 98.3)	89/93	95.2 (91.2 to 97.5)	180/189
High risk oesophagogastric varices*	96.6 (91.5 to 98.7)	112/116	95.9 (88.6 to 98.6)	70/73	97.4 (92.6 to 99.1)	112/115	94.6 (86.9 to 97.9)	70/74	96.3 (92.6 to 98.2)	182/189
Large oesophageal varices*	95.3 (88.5 to 98.2)	81/85	93.3 (86.8 to 96.7)	97/104	92.0 (84.5 to 96.1)	81/88	96.0 (90.3 to 98.5)	97/101	94.2 (89.9 to 96.7)	178/189
Oesophageal varices	96.4 (94.0 to 97.8)	370/384	98.0 (94.9 to 99.2)	194/198	98.9 (97.3 to 99.6)	370/374	93.3 (89.0 to 96.0)	194/208	96.9 (95.2 to 98.0)	564/582
Oesophageal varices with red colour sign	96.1 (92.5 to 98.0)	196/204	97.6 (95.5 to 98.7)	369/378	95.6 (91.9 to 97.7)	196/205	97.9 (95.9 to 98.9)	369/377	97.1 (95.4 to 98.2)	565/582
Gastric varices	96.2 (93.0 to 98.0)	230/239	97.1 (94.7 to 98.4)	333/343	95.8 (92.5 to 97.7)	230/240	97.4 (95.1 to 98.6)	333/342	96.7 (95.0 to 97.9)	563/582
Cardiofundal gastric varices	92.2 (85.8 to 95.8)	106/115	99.6 (98.5 to 99.9)	465/467	98.1 (93.5 to 99.5)	106/108	98.1 (96.4 to 99.0)	465/474	98.1 (96.7 to 98.9)	571/582
Portal hypertensive gastropathy	95.3 (90.9 to 97.6)	161/169	98.3 (96.5 to 99.2)	406/413	95.8 (91.7 to 98.0)	161/168	98.1 (96.2 to 99.0)	406/414	97.4 (95.8 to 98.4)	567/582

CI=confidence interval; ds-MCE=magnetically guided capsule endoscopy with detachable string.

*Based on 18% optimal threshold for oesophageal luminal circumference: in the validation cohort (n=189), a threshold of 18% was applied for discriminating the size of oesophageal varices during ds-MCE. The diagnostic accuracy of ds-MCE for detecting high risk oesophageal varices, high risk oesophagogastric varices, and large oesophageal varices was assessed based on the optimal threshold of 18% in the validation cohort.

(89.7% to 98.4%) and 94.7% (88.2% to 97.7%), respectively (table 2). The diagnostic accuracy of ds-MCE for detecting high risk oesophagogastric varices was 96.3% (92.6% to 98.2%). The sensitivity and specificity of ds-MCE for detecting large oesophageal varices were 95.3% (88.5% to 98.2%) and 93.3% (86.8% to 96.7%), respectively (table 2). Supplementary table S5 presents subgroup analyses of the screening and surveillance populations, and supplementary table S6 presents subgroup analyses of the populations with compensated and decompensated cirrhosis.

Using OGD as the reference standard, the sensitivity and specificity of ds-MCE for detecting oesophageal varices were 96.4% (94.0% to 97.8%) and 98.0% (94.9% to 99.2%), respectively. The sensitivity and specificity of ds-MCE for oesophageal varices with red colour signs were 96.1% (92.5% to 98.0%) and 97.6% (95.5% to 98.7%), respectively (table 2). The

sensitivity and specificity of ds-MCE in detecting gastric varices were, respectively, 96.2% (93.0% to 98.0%) and 97.1% (94.7% to 98.4%), cardiofundal gastric varices were 92.2% (85.8% to 95.8%) and 99.6% (98.5% to 99.9%), and portal hypertensive gastropathy were 95.3% (90.9% to 97.6%) and 98.3% (96.5% to 99.2%).

ds-MCE examination of the small bowel was completed in 510 participants. Supplementary table S7 summarises the detailed findings of portal hypertensive enteropathy. Portal hypertensive enteropathy was found in 333 (65.3%) participants, with spontaneous bleeding in three (0.6%) participants (see supplementary figure S5). Supplementary table S8 shows the durations of ds-MCE and OGD. During ds-MCE, the median examination time for the oesophagus and stomach was 4.74 minutes (interquartile range 3.12 to 7.15 minutes) and 15.78 (8.57 to 23.70) minutes, respectively. The examination time for oesophagus, stomach, and duodenum using OGD was 5.50 (4.50 to 7.00) minutes. The median overall satisfaction score for ds-MCE was higher than for OGD both without sedation (3 v 2), and with sedation (3 v 3) (see supplementary tables S9 and S10, respectively). A total of six (0.99%) adverse events were reported during the study. Two serious adverse events occurred in association with OGD (variceal oesophageal haemorrhage), with both participants requiring hospital admission and endoscopic band ligation. No serious adverse events were associated with ds-MCE, but four adverse events occurred during ds-MCE: capsule retention in the small bowel, with the capsule excreted spontaneously after 23 days (n=1 participant); capsule retention in the oesophagus owing to unexpected oesophageal stenosis, with the capsule pulled out using the string (n=1); syncope mainly due to glucopenia associated

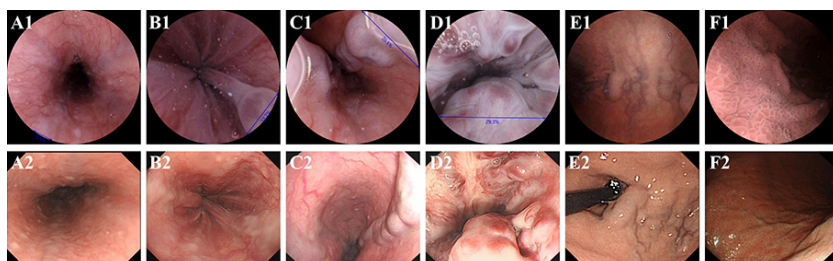


Fig 3 | Representative oesophagogastric varices observed in patients A-F while standing for ds-MCE (panel 1) and OGD (panel 2). Small oesophageal varices (patient A), small oesophageal varices with red colour signs (patient B), large oesophageal varices (patient C), large oesophageal varices with red colour signs (patient D), gastric varices (patient E), and portal hypertensive gastropathy (patient F). ds-MCE=magnetically guided capsule endoscopy with detachable string; OGD=oesophagogastroduodenoscopy

with gastrointestinal preparation (n=1); and rupture and bleeding of haemorrhoids related to small bowel preparation (n=1).

Discussion

In this prospective, multicentre study comparing ds-MCE with the standard reference of OGD among patients with cirrhosis, the results showed that the lower boundary of the 95% confidence interval for the sensitivity and specificity of ds-MCE in detecting oesophagogastric varices were both above the prespecified value of 0.85. This study suggested that ds-MCE has strong discriminative ability to detect oesophagogastric varices owing to technological advances in direct, real time visualisation of oesophagogastric varices under active control. Moreover, ds-MCE showed high accuracy in detecting high risk oesophageal varices in patients both with compensated cirrhosis and with decompensated cirrhosis, which outperformed the non-invasive diagnostic tools of Baveno VII criteria (liver stiffness measurement, spleen stiffness measurement, and platelet count)³ and conventional capsule endoscopy.^{5-9 27 28} In addition, ds-MCE enabled further exploration of the small bowel and thus provided a more comprehensive evaluation of gastrointestinal changes in patients with cirrhosis.

Current guidelines on the management of oesophagogastric varices stress the importance of detecting high risk oesophageal varices to prevent variceal bleeding.^{1 2 29} Three factors need to be identified for oesophageal varices to be classed as high risk: the presence of oesophageal varices, the detection of red colour signs, and the size grading of the oesophageal varices.² ds-MCE showed high diagnostic accuracy in detecting oesophageal varices and red colour signs compared with OGD, which was higher than reported in previous studies on small bowel capsule endoscopy and oesophageal capsule endoscopy.⁵⁻⁹ The absence of a specific grading system for oesophageal varices under capsule endoscopy has been one obstacle to grading the size of oesophageal varices.⁹ The standard grading system for oesophageal varices used during OGD is not applicable to capsule endoscopy because air insufflation is required to fully distend the oesophagus^{2 21 30 31}; a function that capsule endoscopy lacks. Such a difference may in theory impact the grading of oesophageal varices. Previous studies reported a specific oesophageal varices grading system for capsule endoscopy based on the percentage circumference of the oesophageal lumen occupied by the largest oesophageal varices, which showed good correlation with the standard OGD classification.^{5 7 8 28} However, the previously reported luminal circumference thresholds (25%, 1/6, 15%, or 12.5%) for grading oesophageal varices under capsule endoscopy were developed on the basis of small sample sizes and limited oesophageal images, as capsule endoscopy could not capture enough images under passive gastrointestinal movement.^{5 7 8 28} In this large prospective study, ds-MCE provided adequate oesophageal images for each participant to enable

detection of the largest oesophageal varices and the luminal circumference percentage. We therefore developed a new threshold of 18%, and both internal and external validation verified that the new threshold presented high sensitivity and specificity in stratifying large oesophageal varices and high risk oesophageal varices compared with OGD, suggesting ds-MCE is an accurate diagnostic modality to determine prophylactic interventions for oesophageal varices.

For the detection of gastric varices and portal hypertensive gastropathy, the reported oesophageal capsule endoscopy and small bowel capsule endoscopy showed poor diagnostic performance owing to the inability to control the capsule endoscope during gastric examination.^{6 9 32 33} The reported non-invasive tests of the Baveno VI criteria variables had a limited role in predicting the presence of gastric varices or portal hypertensive gastropathy.²⁹ In contrast with these non-invasive diagnostic modalities, ds-MCE is comparable to OGD in being able to detect gastric lesions.^{14 17-19} Notably, in the current study ds-MCE showed robust diagnostic performance for the detection of gastric varices and portal hypertensive gastropathy compared with OGD. Gastric varices were further classified based on Sarin's classification.²³ ds-MCE also showed high accuracy in detecting cardiopulmonary gastric varices, which represent the highest risk of bleeding.²¹ In the current study, the good performance of ds-MCE suggests that, besides detecting oesophageal varices, it is a promising minimally invasive alternative to OGD in detecting gastric varices and portal hypertensive gastropathy.

Portal hypertensive enteropathy is a potential source of gastrointestinal bleeding and may contribute to chronic anaemia.³⁴⁻³⁷ In the current study, ds-MCE enabled the small bowel to be examined, and portal hypertensive enteropathy was detected in 65% of participants with cirrhosis. Importantly, bleeding was observed in the small bowel of three participants. The overall prevalence of portal hypertensive enteropathy was similar to that reported in previous studies on capsule endoscopy.^{34 38 39} The results indicated that ds-MCE is able to recognise small bowel abnormalities and their underlying influence on patients with cirrhosis.

Mild or moderate adverse events specifically associated with ds-MCE occurred in four participants (0.7%). No serious adverse event occurred in association with ds-MCE. Two participants, however, experienced variceal bleeding during OGD examinations and required admission to hospital. In addition, patients' satisfaction with ds-MCE was better than with OGD either with or without sedation, which may improve adherence to the screening and surveillance programme. Taken together, these results highlight that ds-MCE is safe and well tolerated in the detection of oesophagogastric varices without the need for conscious sedation.

Strengths and limitations of this study

We performed a prospective, multicentre study involving a large number of participants with cirrhosis to evaluate the diagnostic value of ds-MCE in

detecting oesophago-gastric varices. The sample size was sufficient to meet our objectives, with suitably narrow confidence intervals. Secondly, we proposed and validated a new capsule endoscopy grading standard for risk stratification of oesophageal varices. Besides, the diagnostic performance of ds-MCE in detecting oesophageal varices and red colour signs of oesophageal varices, gastric varices, and portal hypertensive gastropathy was also validated, providing a more comprehensive evaluation of ds-MCE.

Our study has limitations. Firstly, a small number of participants failed to swallow the capsule endoscope and detachable string. A smaller capsule could overcome this problem.⁴⁰ In addition, ds-MCE takes a longer time to perform than OGD and the cost of the disposable ds-MCE is higher than OGD, whereas ds-MCE does not require preoperative anaesthesia and postoperative recovery and enables a more thorough evaluation of the upper gastrointestinal tract and small bowel. Thus, a cost efficacy analysis is required in future studies. Secondly, most of the participants had cirrhosis related to hepatitis B virus, resulting in unavoidable selection bias. The application value of ds-MCE in other populations requires validation. Thirdly, OGD was always carried out after ds-MCE in this study. This order effect may have influenced the evaluation of patient satisfaction. Fourthly, the size of oesophageal varices was clarified using the oesophageal varices diameter under insufflation of the oesophagus by OGD, whereas the size of oesophageal varices was graded using the luminal circumference percentage grading system during ds-MCE. The effectiveness of this specific grading system and the proposed threshold to detect large oesophageal varices under capsule endoscopy needs to be validated in further studies. Finally, other non-invasive tools, including Baveno VI and VII criteria, were not compared with ds-MCE, and further studies are warranted.

Implications for clinical practice

As the population with cirrhosis increases worldwide, the incidence of oesophago-gastric varices will increase. It is therefore vital to improve the screening and surveillance of oesophago-gastric varices and thus possibly to intervene at an early stage to prevent variceal haemorrhage. Our study has several important implications for clinical practice. Firstly, ds-MCE can be used as a minimally invasive screening tool for detecting oesophago-gastric varices in patients with cirrhosis. As ds-MCE uses direct visualisation, it is able to provide clear images of oesophageal varices, gastric varices, and portal hypertensive gastropathy. Thus, as a screening tool, ds-MCE showed an advantage over other available non-invasive tests, including serum markers, doppler ultrasonography, contrast enhanced ultrasonography, and ultrasound elastography. Secondly, the accurate detection of high risk oesophageal varices during ds-MCE could provide evidence for clinical treatment decisions, which depends on risk stratification for the prevention of variceal bleeding. Therefore, ds-MCE also serves as a

promising surveillance tool for stratification of variceal bleeding risk in patients with cirrhosis. Thirdly, apart from the oesophagus and stomach, ds-MCE can be further used to evaluate small bowel lesions in one process. Finally, ds-MCE is well tolerated, easy to perform, does not require sedation, and is potentially cost effective, and as such is suitable for use in primary, secondary, and tertiary healthcare settings, providing clear potential to optimise the screening and monitoring of oesophago-gastric varices.

Conclusions

This study found that ds-MCE is a highly accurate, safe, and minimally invasive method for detecting and grading oesophago-gastric varices in patients with cirrhosis. Moreover, ds-MCE is a reliable tool to evaluate portal hypertensive gastropathy and small bowel abnormalities during one examination. The better tolerance of patients to ds-MCE may also improve adherence to endoscopic follow-up. Therefore, ds-MCE provides a promising alternative to OGD for screening and surveillance of gastrointestinal lesions in patients with cirrhosis.

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Contributors: XJ, JP, QX, Y-HS, H-HS, CP, and X-LQ contributed equally to the study and are joint first authors. ZL and Z-SL conceived the study. ZL and JP designed the study. XJ, JP, QX, Y-HS, H-HS, CP, Y-YQ, W-BZ, YY, S-QJ, B-SD, SW, YC, D-HX, L-JH, J-ZC, J-FD, XL, TX, WZ, TC, C-HZ, WW, S-JL, Z-YY, FW, LZ, C-ZL, HX, J-XW, BW, YL, XD, L-HQ, Y-QS, HW, Y-FH, H-BB, SZ, LL, Y-HS, X-YW, D-WZ, X-JW, M-DX, HM, C-HH, ZL, X-LZ, S-XH, X-PX, JL, and C-QY conducted the study. XJ and JP drafted the manuscript. ZL, Z-SL, CS, and X-LQ critically revised the manuscript. All authors gave final approval of the manuscript. Z-SL and CS are the co-corresponding authors and can be reached at zhaoshenli@smmu.edu.cn and cristianospada@gmail.com. ZL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: The steering committee of the CENTERS study will consider reasonable requests for the sharing of deidentified individual participant data. Requests should be made to the corresponding author.

The lead author (ZL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this work will be disseminated to the public through the press, social media, and conferences. The lay summaries of the study results will be communicated to study participants and relevant patient groups.

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Supplementary information: Additional information, tables, and figures