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ORIGINAL ARTICLE

Defining the Threshold: New Data on the Ability of Capsule Endoscopy to Discriminate the Size of Esophageal Varices

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Abstract
Background Endoscopy (esophagogastroduodenoscopy, EGD) to screen for esophageal varices (EV) is recommended in patients with portal hypertension. Reports indicate that capsule endoscopy (CE) is capable of identifying large/medium varices (L/MV) when the varix comprises more than 25% of the circumference of the field of view.
Aims We evaluated the ability of CE to discriminate the size of EV using this grading scale.
Methods Patients underwent CE and EGD on the same day. A blinded investigator interpreted capsule findings. CE labeled EV as L/MV if $\geq$25% of the lumen circumference was occupied, and small/none for <25%.
Results A total of 37 patients were enrolled in this prospective, observational study at a single tertiary-care academic center. Three CE were excluded due to rapid esophageal transit time or technical malfunction. Using a 25% threshold, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for EC to discriminate L/MV were 23.5%, 88.2%, 66.7%, and 53.6%, respectively ($\kappa = 0.12$). Reducing the threshold to 12.5% resulted in sensitivity, specificity, PPV, and NPV of 88.2%, 64.7%, 71.4%, and 84.6%, respectively ($\kappa = 0.53$). A receiver-operator characteristic (ROC) curve showed a 15% threshold to be optimal in discriminating EV size using CE, resulting in sensitivity, specificity, PPV, and NPV of 76.5%, 82.4%, 81.3%, and 77.8%, respectively ($\kappa = 0.59$).
Conclusions This study indicates that discriminating EV size by the current capsule scale is unreliable. Lowering the grading threshold improved the ability to discriminate EV size by CE. In the proper context, CE is an alternative to EGD to screen for EV.

Keywords Esophageal varices · Gastric varices · Capsule endoscopy · Cirrhosis · Portal hypertension · Surveillance · Screening

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Introduction

Severe upper gastrointestinal bleeding as a complication of portal hypertension develops in 30–40% of cirrhotic patients [1, 2]. The prevalence of esophageal varices in cirrhotic patients has been reported to be as high as 80–90% [3, 4]. A single episode of esophageal variceal bleeding can have a mortality rate as high as 30% [5, 6].

The standard of care in patients with suspected or known cirrhosis is to screen for esophageal varices. Additionally, patients with known varices require periodic surveillance. Varices of small size do not require intervention and should be re-evaluated each year for progression of size. Medium to large varices require medical therapy or band ligation to reduce the risk of future bleeding episodes [9].

Detection of varices by endoscopy is not without complications. Cardiopulmonary complications related to sedation and analgesia are the most common adverse outcomes [7, 8].

Capsule endoscopy is a new mechanism to examine the esophagus without the need for sedation or the potential

complications associated with standard endoscopy [10]. Capsule endoscopy (CE) is performed with less anxiety, pain, and discomfort. The risk for adverse events is more remote with CE, being e.g., retained capsule in a stricture or diverticula, or difficulty swallowing the capsule [11, 12].

A large, prospective multicenter study confirmed the safety and accuracy of CE for evaluation of varices, with sensitivity and specificity of 77% and 86%, respectively [13]. A meta-analysis of seven studies verified that CE has acceptable sensitivity and specificity (85.8% and 80.5%, respectively) in detecting esophageal varices [10, 14–20].

One of the limitations of these studies is the lack of consensus in grading these varices by CE. Grading varices by endoscopy requires distention of the esophagus with air insufflation; CE lacks this component. The largest published study utilized the results of the initial pilot study to use the circumference of the capsule picture frame as a reference point and to grade varices according to the proportion of the circumference occupied by the largest varix present. Small varices occupied less than 25% of the circumference and large varices occupied more than 25% [10, 17]. The second largest study used the conventional EGD grading system for esophageal varices "on the basis of estimated size and convergence of the varices and the presence of red signs" [13].

We report the results of a prospective, pilot study comparing CE with EGD. The primary objective is to identify an association between the grade (size) of esophageal varices seen on PillCam Eso (Given Imaging, Yoqneam, Israel) CE (using the aforementioned circumference grading system) and variceal grade by EGD. The secondary objectives are to determine the accuracy of esophageal CE for detecting signs of risk (i.e., cherry-red spots, hemocystic spots, red wales) and severity of portal gastropathy.

Patients and Methods

This is a prospective, pilot study that evaluated patients who presented for evaluation of known or suspected esophageal varices. It was approved by the Penn State Milton S. Hershey Institutional Review Board (IRB).

Patients had PillCam Eso CE followed immediately by standard esophagogastroduodenoscopy (EGD) for screening of esophageal varices. Inclusion criteria were:

- Males over the age of 18 years, or female over the age of 18 years with a negative preprocedure pregnancy test or of nonreproductive potential
- Inpatient or outpatient
- Able to provide informed consent

Exclusion criteria were:

- Pregnancy
- Presence of a known Zenker's diverticulum
- Swallowing disorder
- Known intestinal diverticulum
- Suspected intestinal obstruction or stricture
- Pseudo-obstruction
- Active variceal bleeding
- Presence of a cardiac pacemaker or implanted electromedical device
- Suspected or known Crohn's disease
- Presence of ileostomy

After informed consent, the patient ingested the PillCam Eso capsule. Participants swallowed the capsule according to the manufacturer's recommended protocol without any sedation or topical anesthetics. Participants drank 100 ml of cold water with ten drops of simethicone. The patient was then placed in supine position. The capsule was ingested with a sip of water, up to 10 ml, including two drops of simethicone. The bed remained at 0° for 2 min, and was then elevated to 30° for 2 min, then to 60° for 1 min. The participants took a sip of water and waited 15 s, then sat upright and had another sip of water, and waited 15 s.

The participants underwent standard EGD immediately thereafter. All endoscopies were performed by one of two board-certified transplant hepatologists at our institution. EGDs were performed with either conscious sedation or general anesthesia. In all cases, the endoscope was inserted under visual control through the mouth to the pharynx with subsequent intubation of the upper esophageal sphincter.

The PillCam Eso capsule was immediately retrieved using a Roth net (US Endoscopy, Mentor, OH). This was done as an extra safety measure as requested by the IRB. If the capsule was unable to be retrieved, participants were instructed regarding monitoring of bowel movement for the passage of the capsule. If, in 2 weeks, patients did not note the passage of the capsule, they had an abdominal X-ray to confirm passage.

After capsule retrieval, EGD was performed in standard fashion.

At completion of the endoscopic procedure, the endoscopist assessed:

- The grade of esophageal varices
- The presence or absence of risk signs
- The severity of portal gastropathy, as defined by the New Italian Endoscopic Club (NIEC) [21]
- The presence or absence of gastric varices
- Stigmata of prior banding
- Whether or not the capsule was able to be removed at the time of endoscopy

Using a minor modification of the Japanese Research Society for Portal Hypertension rules [22, 23], variceal size on endoscopic view was graded as follows:

- F0: No varices
- F1: Small and nontortuous varices that easily flatten with air insufflation
- F2: Medium varices that are enlarged, tortuous, and occupy less than one-third of the lumen
- F3: Large, tortuous varices occupying greater than one-third of the lumen

CE was read by a third, blinded investigator and assessed using the same criteria.

For statistical analysis, EGD was considered the gold standard in all comparisons. Sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) along with 95% confidence intervals (CIs) were calculated for diagnosis of varices in three groups:

1. Presence or absence of EV of any size
2. Differentiation of large or medium varices (L/MV) from small or no varices using a luminal circumference threshold of 25%
3. Differentiation of L/MV from small or no varices using a luminal circumference threshold of 12.5%

The agreement between the capsule and endoscopic results at the different thresholds were assessed using Cohen's kappa coefficient (κ) with 95% CIs.

An exact logistic regression model was fitted to esophageal variceal size (small/none versus large/medium) as defined by EGD, with the luminal circumference percentage occupied from CE as the independent variable. Using the exact logistic regression model, a receiver-operating characteristic (ROC) curve was constructed to evaluate the sensitivity and specificity at each luminal circumference percentage occupied from CE. Youden's J index, defined as [(sensitivity + specificity) − 1], was used to determine the optimal luminal circumference percentage threshold from the ROC curve to discriminate EV size (i.e., small/none versus large/medium).

Results

Between October 1, 2006 and May 31, 2008, 37 participants (28 male, 9 female) were enrolled through a single university-based medical center. Table 1 presents the demographic information of the study population.

EGD was performed without adverse events in all 37 patients. In two patients, no capsule results were obtained due to capsule malfunction and inappropriate connection of the transmitter. In a third patient, the capsule did not remain in the esophagus long enough to provide adequate images. A total of 34 capsule studies were analyzed.

Table 1 Demographic information

Characteristic	Value
Age in years (mean, median, range)	56, 53, 21–78
Sex	
Male	28 (82%)
Female	9 (18%)
Cause of cirrhosis/portal hypertension	
Alcohol	11 (30%)
Nonalcoholic steatohepatitis	8 (22%)
Chronic hepatitis C (HCV)	7 (19%)
Chronic HCV and alcohol	5 (13%)
Miscellaneous*	6 (16%)
MELD (mean, median, range)†	11, 10, 6–33
Child–Pugh class	
A	23 (62.2%)
B	9 (24.3%)
C	5 (13.5%)
Indication for endoscopy	
Surveillance of previously documented varices	19 (51%)
Screening for esophageal varices	18 (49%)

* Includes cryptogenic cirrhosis, Budd–Chiari syndrome, autoimmune hepatitis, and primary sclerosing cholangitis

† Only reported in 28 of the 34 patients who had a model for end-stage liver disease (MELD) score available within 4 months of the study

The sensitivity, specificity, PPV, and NPV for the detection of varices were 54.5%, 66.7%, 95.2%, and 15.4% (Table 2).

The sensitivity, specificity, PPV, and NPV of CE to distinguish L/MV from small or absent varices using a 25% luminal circumference threshold were 23.5%, 88.2%, 66.7%, and 5.36% (Table 3); the κ value was 0.12. Figure 1 illustrates a large varix occupying more than 25% of the CE circumferential field.

The sensitivity, specificity, PPV, and NPV of CE to distinguish L/MV from small or absent varices using a 12.5% luminal circumference threshold were 88.2%, 64.7%, 71.4%, and 84.6% (Table 4); the κ value was 0.53.

Table 5 presents the sensitivity, specificity, PPV, and NPV along with the exact 95% confidence intervals (CIs) at each percentage of luminal circumference from CE specified in our data set. A receiver-operating characteristic (ROC) curve was generated based on the percentage of the luminal circumference from CE predicting medium/large (as opposed to none/small) varices from the endoscopy (gold standard).

The ROC curve (Fig. 2) yielded an estimated area under the curve of 0.79, with an optimal luminal circumference threshold of 15% to discriminate the size of EV using CE (Youden's J index of 0.588). The 15% threshold resulted in

Table 2 CE and the ability to detect the presence of EV

Frequency		Presence of EV on EGD		
		Yes	No	Total
Presence of EV on CE	Yes	20	1	21
	No	11	2	13
Total		31	3	34
Sensitivity % (95% confidence interval)			64.5 (45.4, 80.8)	
Specificity % (95% confidence interval)			66.7 (9.4, 99.2)	
Positive predictive value % (95% confidence interval)			95.2 (76.2, 99.9)	
Negative predictive value % (95% confidence interval)			15.4 (1.9, 45.4)	
Kappa value (95% confidence interval)			0.12 (−0.13, 0.38)	

CE capsule endoscopy; *EV* esophageal varices

Table 3 CE and the ability to distinguish large/medium varices from small or no varices, using 25% luminal circumference threshold

Frequency		Large/medium EV on EGD		
		Yes	No	Total
Large/medium EV on CE	Yes	4	2	6
	No	13	15	28
Total		17	17	34
Sensitivity % (95% confidence interval)			23.5 (6.8, 49.9)	
Specificity % (95% confidence interval)			88.2 (63.6, 98.5)	
Positive predictive value % (95% confidence interval)			66.7 (22.3, 95.7)	
Negative predictive value % (95% confidence interval)			53.6 (33.9, 72.5)	
Kappa value (95% confidence interval)			0.12 (−0.14, 0.37)	

CE capsule endoscopy

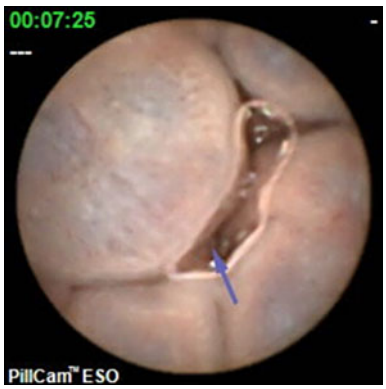

Fig. 1 Large varix occupying more than 25% of the CE circumferential field

a sensitivity, specificity, PPV, and NPV of 76.5% [95% CI: (50.1%, 93.2%)], 82.4% [95% CI: (56.6%, 96.2%)], 81.3% [95% CI: (54.4%, 96.0%)], and 77.8% [95% CI: (52.4%, 93.65)], respectively [$\kappa = 0.59$; 95% CI: (0.32, 0.86)].

The sensitivity, specificity, PPV, and NPV of CE to identify signs of risk on esophageal varices were 50.0%, 85.0%, 70.0%, and 70.8% (Table 6); the κ value was 0.37. The sensitivity, specificity, PPV, and NPV of CE to detect prior banding scars were 25.0%, 92.3%, 50.0%, and 80.0% (Table 7); the κ value was 0.21.

Due to the immediate removal of capsule at EGD, the capsule did not progress to the antrum in 29 of 34 cases. The amount of time in the stomach was insufficient to assess for gastric varices and portal gastropathy in 14 of 34 cases. Accordingly, we cannot address the ability of CE to detect gastric varices or portal gastropathy.

Discussion

Previously, EGD was the only technique available to screen for esophageal varices.

PillCam Eso is an endoscopic capsule specifically designed to assess the esophagus in the outpatient setting with minimal, if any, complications. A recent meta-analysis of seven studies showed an acceptable ability for EC to detect varices, with pooled sensitivity and specificity of 85.8% and 80.5%, respectively [14]. In the current study, CE did not perform as well, with sensitivity and specificity of 64.5% and 66.7%, respectively, for detection of varices.

Intervention with medications or band ligation is only recommended when medium or large varices are identified. Whether or not CE has the ability to differentiate those patients with large/medium varices versus those with small or absent varices will determine whether CE can be an alternative to EGD.

Table 4 CE and the ability to distinguish large/medium varices from small or no varices, using 12.5% luminal circumference threshold

Frequency		Large/medium EV on EGD		
		Yes	No	Total
Large/medium EV on CE	Yes	15	6	21
	No	2	11	13
Total		17	17	34
Sensitivity % (95% confidence interval)			88.2 (63.6, 98.5)	
Specificity % (95% confidence interval)			64.7 (38.3, 85.8)	
Positive predictive value % (95% confidence interval)			71.4 (47.8, 88.7)	
Negative predictive value % (95% confidence interval)			84.6 (54.6, 98.1)	
Kappa value (95% confidence interval)			0.53 (0.25, 0.81)	

CE capsule endoscopy

Table 5 Modeling medium/large varices from endoscopy. independent variable: percentage of luminal circumference from capsule

Percentage of luminal circumference from capsule	Sensitivity (exact 95% CI)	Specificity (exact 95% CI)	PPV (exact 95% CI)	NPV (exact 95% CI)	Youden's *J* index
0	1.000 (0.805, 1.000)	0.000 (0.000, 0.195)	0.500 (0.324, 0.676)		0.000
12.5	0.882 (0.636, 0.985)	0.647 (0.383, 0.858)	0.714 (0.478, 0.887)	0.846 (0.546, 0.981)	0.529
15	0.765 (0.501, 0.932)	0.824 (0.566, 0.962)	0.813 (0.544, 0.960)	0.778 (0.524, 0.936)	0.588
16.5	0.706 (0.440, 0.897)	0.824 (0.566, 0.962)	0.800 (0.519, 0.957)	0.737 (0.488, 0.909)	0.529
18.75	0.647 (0.383, 0.858)	0.824 (0.566, 0.962)	0.786 (0.492, 0.953)	0.700 (0.457, 0.881)	0.471
18.8	0.353 (0.142, 0.617)	0.824 (0.566, 0.962)	0.667 (0.299, 0.925)	0.560 (0.349, 0.756)	0.176
22	0.294 (0.103, 0.560)	0.824 (0.566, 0.962)	0.625 (0.245, 0.915)	0.538 (0.334, 0.734)	0.118
23	0.294 (0.103, 0.560)	0.882 (0.636, 0.985)	0.714 (0.290, 0.963)	0.556 (0.353, 0.745)	0.176
31.25	0.235 (0.068, 0.499)	0.882 (0.636, 0.985)	0.667 (0.223, 0.957)	0.536 (0.339, 0.725)	0.118
31.5	0.235 (0.068, 0.499)	0.941 (0.713, 0.999)	0.800 (0.284, 0.995)	0.552 (0.357, 0.736)	0.176
47.5	0.176 (0.038, 0.434)	0.941 (0.713, 0.999)	0.750 (0.194, 0.994)	0.533 (0.343, 0.717)	0.118
53	0.118 (0.015, 0.364)	0.941 (0.713, 0.999)	0.667 (0.094, 0.992)	0.516 (0.331, 0.698)	0.059
56.25	0.059 (0.001, 0.287)	0.941 (0.713, 0.999)	0.500 (0.013, 0.987)	0.500 (0.319, 0.681)	−0.000
75	0.059 (0.001, 0.287)	1.000 (0.805, 1.000)	1.000 (0.025, 1.000)	0.515 (0.335, 0.692)	0.059

A large, prospective study claimed that CE was an acceptable tool to determine which EV would need primary prophylaxis, with sensitivity, specificity, negative predictive value, and positive predictive value of 77%, 88%, 90%, and 75%, respectively [13]. A weakness of that study is the absence of a specific CE grading system. Another study used the circumference occupied by the largest varix in the capsule picture frame to grade the EV size. CE differentiated large or medium varices from small or no varices with sensitivity, specificity, positive predictive value, and negative predictive value of 78%, 96%, 87%, and 92%, respectively. The authors concluded that capsule endoscopy, "although showing good diagnostic ability, did not reach statistical equivalence to EGD" to differentiate the size of EV [17].

Our study shows CE to be unreliable in distinguishing the size of varices with the 25% threshold. Sensitivity, specificity, PPV, and NPV of 23.5%, 88%, 66.7%, and 53.6%, respectively, were noted. A κ value of 0.12 shows very little agreement between CE and EGD.

Our patient population is comparable to the deFranchis study, with a similar distribution of Child–Pugh A, B, and C patients (A, 62.2% versus 68.8%; B, 24.3% versus 25.4%; C, 13.5% versus 5.8%). Our study benefits from a good distribution in variceal size, with 17 of the 34 patients (50%) having medium or large varices and 17 (50%) having small or no varices.

The incidence of L/MV in our population is greater compared with the other two studies. In Lapalus's study, 35 of 113 (31%) patients had L/MV and 78 patients (69%) had small/absent varices [13]. deFranchis's population of 288 patients had 79 (25%) with L/MV and 209 (75%) with small/absent varices [12]. The greater incidence of larger-sized varices in our study is accounted for by the fact that 51% (19/34) of our patients were having surveillance of known EV. Only 32% (93/195) of the patients in the deFranchis study were being surveyed for known varices.

In clinical practice, the incidence of varices is not as high as in our population. As the sensitivity of CE to detect

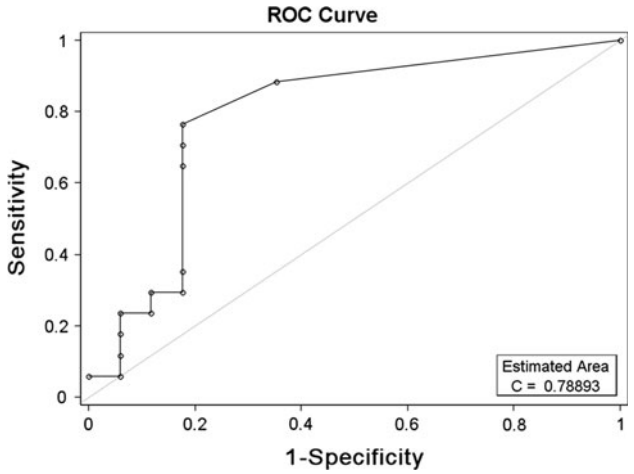

Fig. 2 Receiver-operating characteristic (ROC) curve. An optimal luminal circumference threshold of 15% to discriminate the size of EV using CE is noted (Youden's *J* index of 0.588)

EV of any size in the current study was only 65%, it may be predicted that CE would not perform as well when applied to the general population.

By lowering the luminal circumference threshold to 12.5%, sensitivity, specificity, positive predictive value, and negative predictive value of 88.2%, 64.7%, 71.4%, and 84.6%, respectively, were noted. Decreasing the threshold to 12.5% increases the κ value to 0.53, with moderate agreement between CE and EGD. While these values are still not as high as in previous reports, they are in close agreement with previously published studies.

Using the ROC curve generated from our data set, the threshold for defining a medium or large varix should be reduced to 15% (Youden's *J* index of 0.588).

A weakness of the current study is the fact that it was performed at a single center with a limited number of patients. Our sensitivity and specificity estimates are subject to substantial standard deviation, as shown by the broad 95% confidence intervals in Table 5. Furthermore, there was only one capsule endoscopist; we could therefore not investigate the degree of interobserver agreement in the CE results.

One valid criticism of the study design is that we grouped our patients into two groups: medium/large varices and small/no varices. Ideally, the ability of CE to distinguish EV should be stratified into three groups: (1) high-risk varices requiring prophylaxis, (2) small varices at risk of progression, and (3) no varices. The small population size precluded this subanalysis.

Another limitation of the study's small sample size is the inability to perform subgroup analysis of the performance of CE in patients who previously had variceal banding. CE may not be a reliable tool for this group, as banding can produce a variety of mucosal changes that can

Table 6 CE and the ability to identify variceal signs of risk

Frequency		Signs of risk present on EGD		
		Yes	No	Total
Signs of risk present on CE	Yes	7	3	10
	No	7	17	24
Total		14	20	34
Sensitivity % (95% confidence interval)			50.0 (23.0, 77.0)	
Specificity % (95% confidence interval)			85.0 (62.1, 96.8)	
Positive predictive value % (95% confidence interval)			70.0 (34.8, 93.3)	
Negative predictive value % (95% confidence interval)			70.8 (48.9, 87.4)	
Kappa value (95% confidence interval)			0.37 (0.05, 0.68)	

CE capsule endoscopy

Variceal signs of risk: red wales (longitudinal red streaks on varices), hematocystic spots (raised discrete red spots overlying varices that resemble "blood blisters") or cherry-red spots (discrete cherry-red-colored spots that are flat and overlie varices)

Table 7 CE and the ability to identify banding scars

Frequency		Scars present on EGD		
		Yes	No	Total
Scars present on CE	Yes	2	2	4
	No	6	24	30
Total		8	26	34
Sensitivity % (95% confidence interval)			25.0 (3.2, 65.1)	
Specificity % (95% confidence interval)			92.3 (74.9, 99.1)	
Positive predictive value % (95% confidence interval)			50.0 (6.8, 93.2)	
Negative predictive value % (95% confidence interval)			80.0 (61.4, 92.3)	
Kappa value (95% confidence interval)			0.21 (−0.16, 0.58)	

CE capsule endoscopy

hinder identification of varices and stigmata. Furthermore, previously banded patients may be managed differently (i.e., are varices of sufficient size to warrant repeat banding and/or sclerotherapy?). Due to the small population size, we were unable to look at these data. This is an area for further investigation.

We did not record the esophageal transit time for each capsule. This data would be useful to have. Rapid transit times would have a direct effect on the ability of the capsule to grade varices accurately. If we had documented rapid transit times, this might explain the lower sensitivity and specificity in our study compared with aforementioned papers.

The IRB made the request that we retrieve the capsule as an extra safety precaution, given the fears regarding capsule retention. As EGD immediately followed capsule ingestion, we could not analyze in any meaningful way gastric evidence of portal hypertension (e.g., gastric varices or portal gastropathy) or gastric antral varices. While this information would not change the conclusions of this paper, it would be interesting to note whether or not CE has the ability to detect these stigmata of cirrhosis.

We did not assess patients' perceptions regarding CE and EGD, nor did we investigate which procedure the patient would rather undergo again. However, no patient had any difficulties swallowing the capsule, and no complications occurred with either procedure.

In conclusion, this study shows that CE is an unreliable tool to distinguish the size of esophageal varices using a threshold of 25% of the luminal circumference of the CE field. However, reducing this threshold to 12.5% results in moderate agreement between CE and EGD. For the select patient population who are not willing or not suitable for EGD, CE offers a reasonable alternative.

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