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[Diagnostic Test Accuracy Review]

Capsule endoscopy for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis

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ABSTRACT

Background

Current guidelines recommend performance of oesophago-gastro-duodenoscopy at the time of diagnosis of hepatic cirrhosis to screen for oesophageal varices. These guidelines require people to undergo an unpleasant invasive procedure repeatedly with its attendant risks, despite the fact that half of the people do not have identifiable oesophageal varices 10 years after the initial diagnosis of cirrhosis. Video capsule endoscopy is a non-invasive test proposed as an alternative method for the diagnosis of oesophageal varices.

Objectives

To determine the diagnostic accuracy of capsule endoscopy for the diagnosis of oesophageal varices in children or adults with chronic liver disease or portal vein thrombosis, irrespective of the aetiology. To investigate the accuracy of capsule endoscopy as triage or replacement of oesophago-gastro-duodenoscopy.

Search methods

We searched the Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register (October 2013), MEDLINE (Ovid SP) (1950 to October 2013), EMBASE (Ovid SP) (1980 to October 2013), ACP Journal Club (Ovid SP) (1991 to October 2013), Database of Abstracts of Reviews of Effects (DARE) (Ovid SP) (third quarter), Health Technology Assessment (HTA) (Ovid SP) (third quarter), NHS Economic Evaluation Database (NHSEED) (Ovid SP) (third quarter), and Science Citation Index Expanded (SCI-EXPANDED) (ISI Web of Knowledge) (1955 to October 2013). We applied no language or document type restrictions.

Selection criteria

Studies that evaluated the diagnostic accuracy of capsule endoscopy for the diagnosis of oesophageal varices using oesophago-gastro-duodenoscopy as the reference standard in children or adults of any age, with chronic liver disease or portal vein thrombosis.

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Data collection and analysis

We followed the available guidelines provided in the *Cochrane Handbook for Diagnostic Test of Accuracy Reviews.* We calculated the pooled estimates of sensitivity and specificity using the bivariate model due to the absence of a negative correlation in the receiver operating characteristic (ROC) space and of a threshold effect.

Main results

The search identified 16 eligible studies, in which only adults with cirrhosis were included. In one study, people with portal thrombosis were also included. We classified most of the studies at high risk of bias for the 'Participants selection' and the 'Flow and timing' domains. One study assessed the accuracy of capsule endoscopy for the diagnosis of large (high-risk) oesophageal varices. In the remaining15 studies that assessed the accuracy of capsule endoscopy for the diagnosis of oesophageal varices of any size in people with cirrhosis, 936 participants were included; the pooled estimate of sensitivity was 84.8% (95% confidence interval (CI) 77.3% to 90.2%) and of specificity 84.3% (95% CI 73.1% to 91.4%). Eight of these studies included people with suspected varices or people with already diagnosed or even treated varices, or both, introducing a selection bias. Seven studies including only people with suspected but unknown varices were at low risk of bias; the pooled estimate of sensitivity was 79.7% (95% CI 73.1% to 85.0%) and of specificity 86.1% (95% CI 64.5% to 95.5%). Six studies assessed the diagnostic accuracy of capsule endoscopy for the diagnosis of large oesophageal varices, associated with a higher risk of bleeding; the pooled sensitivity was 73.7% (95% CI 52.4% to 87.7%) and of specificity 90.5% (95% CI 84.1% to 94.4%). Two studies also evaluated the presence of red marks, which are another marker of high risk of bleeding; the estimates of sensitivity and specificity varied widely. Two studies obtained similar results with the use of a modified device as index test (string capsule). Due to the absence of data, we could not perform all planned subgroup analyses. Interobserver agreement in the interpretation of capsule endoscopy results and any adverse event attributable to capsule endoscopy were poorly assessed and reported. Only four studies evaluated the interobserver agreement in the interpretation of capsule endoscopy results: the concordance was moderate. The participants' preferences for capsule endoscopy or oesophago-gastro-duodenoscopy were reported differently but seemed in favour of capsule endoscopy in nine of 10 studies. In 10 studies, participants reported some minor discomfort on swallowing the capsule. Only one study identified other significant adverse events, including impaction of the capsule due to previously unidentified oesophageal strictures in two participants. No adverse events were reported as a consequence of the reference standard.

Authors' conclusions

We cannot support the use of capsule endoscopy as a triage test in adults with cirrhosis, administered before oesophago-gastro-duodenoscopy, despite the low incidence of adverse events and participant reports of being better tolerated. Thus, we cannot conclude that oesophago-gastro-duodenoscopy can be replaced by capsule endoscopy for the detection of oesophageal varices in adults with cirrhosis. We found no data assessing capsule endoscopy in children and in people with portal thrombosis.

PLAIN LANGUAGE SUMMARY

Capsule endoscopy for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis

Background

In cases of hepatic cirrhosis, whatever the cause, the changes in the structure of, and blood flow within, the liver increase the pressure in the portal vein (called portal vein hypertension), which is the vein that drains blood from the bowels to the liver. Portal hypertension induces dilation (opening) of veins within the wall of the oesophagus (food pipe or gullet), which often rupture (break) with severe bleeding. Thus, when liver cirrhosis is diagnosed, an oesophago-gastro-duodenoscopy (OGD) is recommended to detect the presence of oesophageal varices (areas of abnormal dilation of veins). During OGD, a small camera on the end of a tube is inserted down the oesophagus from the mouth. This relays pictures back to a screen. The presence of large varices or of red-coloured signs on even small varices identifies high risk of rupture and bleeding. If high-risk varices are found, treatment with beta-blockers is effective in reducing the risk of bleeding. Capsule endoscopy is a less invasive test than OGD as participants have only to swallow a small device that is able to produce images of the oesophageal walls and could be able to detect the presence of dilated veins.

Study characteristics

We searched scientific databases for clinical studies comparing OGD to capsule endoscopy and reporting the size and appearance of varices in children or adults with chronic liver disease or portal vein thrombosis (narrowing of the portal vein). The evidence is current to October 2013.

Key results

We found 16 studies assessing the ability of capsule endoscopy to diagnose the presence of varices and grade the risk of bleeding and comparing it with OGD in adults with cirrhosis. Capsule endoscopy, even if more acceptable to participants, cannot replace OGD for the detection of oesophageal varices as about 15% are left undetected and 15% are not confirmed by endoscopy. Even the accuracy in detecting large varices or red marks on varices was very lower than endoscopy. Hence, in conclusion, capsule endoscopy is not sufficiently accurate to replace OGD for the detection of oesophageal varices in cirrhotic participants.

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Quality of the evidence

In nine of the sixteen studies there were problems concerning participant selection and incompleteness of reported data which impair accuracy estimates and the transferability of the results.

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Summary of findings 1. Performance of capsule endoscopy for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis

Population: adults with chronic liver disease with no previous gastrointestinal haemorrhage. There were no children or people with portal vein thrombosis in the included studies.

Index test: capsule endoscopy (PillCam ESO, Given Imaging, Israel); 2 studies used string wireless capsule endoscopy (M2A Capsule, Given Imaging, Israel). 2 studies did not specify which device was used (Groce 2007; Frenette 2008), and 1 study used PillCam SB/SB2 a device planned for intestinal exploration not dedicated to the oesophagus (Aoyama 2014).

Target condition: presence of any oesophageal varices or the presence of medium/large oesophageal varices.

Reference standard: oesophago-gastro-duodenoscopy.

Studies included: 16 studies.

15 studies considered "any oesophageal varices" as target disease, while 1 study considered only "large oesophageal varices."

Overall, for 6 studies data were available for the target condition "large oesophageal varices."

All the studies were prospectively cross-sectional designed.

				Pooled estimates (95% CI)					Consequences in a cohort of 100 participants [1]		
Target disease	**Analysis**	**Included studies N**	**Included individuals n**	**Disease prevalence Median (range)**	**Sensitivity**	**Specificity**	**LR+**	**LR-**	**Assumed prevalence %**	**Potentially missed cases n**	**Overtreated participants n**
Any oesophageal varices	All the studies	15	936	72% (43% to 95%)	84.8% (77.3% to 90.2%)	84.3% (73.1% to 91.4%)	5.4 (3.1 to 9.5)	0.18 (0.12 to 0.27)	63%	10	6
									72%	11	4
Any oesophageal varices	Subgroup: string capsule	2	130	82.5% (82% to 83%)	90.0% (72.4% to 96.9%)	86.9% (30.7% to 99.0%)	6.9 (0.61 to 77.8)	0.11 (0.03 to 0.44)	82.5%[2]	8	2

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Any oesophageal varices	Subgroup: standard capsule	13	806	71% (43% to 95%)	83.9% (75.3% to 90.0%)	84.5% (71.8% to 92.1%)	5.4 (2.9 to 10.1)	0.19 (0.12 to 0.30)	63% 72%	10 12	6 4
Any oesophageal varices	Sensitivity analysis: QUADAS-2 'patients selection' domain - only studies at low risk of bias	7	396	63% (43% to 82%)	79.7% (73.1% to 85.0%)	86.1% (64.5% to 95.5%)	5.8 (2.1 to 16.1)	0.24 (0.18 to 0.31)	63%	13	5
Any oesophageal varices	Only full-text studies	11	849	79% (60% to 95%)	82.6% (75.4% to 88.0%)	88.0% (73.9% to 95.0%)	6.9 (3.0 to 16.0)	0.20 (0.14 to 0.29)	63% 72%	11 13	4 3
Any oesophageal varices	Sensitivity analysis: QUADAS-2 'flow and timing' domain - only studies at low risk of bias	9	687	71% (43% to 95%)	85.8% (75.5% to 92.2%)	82.5% (62.2% to 93.1%)	4.9 (2.1 to 11.4)	0.17 (0.1 to 0.30)	63% 72%	9 10	6 5
Medium/large oesophageal varices	All the studies	6	537	37% (27% to 50%)	73.7% (52.4% to 87.7%)	90.5% (84.1% to 94.4%)	7.7 (4.2 to 14.2)	0.29 (0.14 to 0.58)	37% [2]	10	6
Red marks	All the studies	3	150	48% (41% to 77%)	47%, 94%, 82% [3]	89%, 60%, 86% [3]	4.3, 2.4, 5.9 [3]	0.59, 0.10, 0.21 [3]	-	-	-

CI: confidence interval; LR-: negative likelihood ratio; LR+: positive likelihood ratio; n: number of participants; N: number of studies.

[1]Two scenarios were considered: median prevalence of the seven studies at low risk of bias according to QUADAS2 item 'Patients selection' (63%); median prevalence of all the 15 studies (72%).

[2]Only one scenario with specific group prevalence was considered.

[3]Point estimates reported in the three studies.

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BACKGROUND

Portal hypertension commonly accompanies advanced liver disease and often gives rise to life-threatening complications, including haemorrhage from oesophageal and gastrointestinal varices. The prevalence of cirrhosis in high-income countries ranges between 0.4% and 1.1% (Bellentani 1994; Quinn 1997); up to two-thirds of people with cirrhosis develop gastro-oesophageal varices (Garceau 1963; Jensen 2002). The prevalence of gastro-oesophageal varices in people with cirrhosis increases by nearly 5% per year (Merli 2003). Gastro-oesophageal varices are an extension of oesophageal varices, and isolated gastric varices occurring in the absence of oesophageal varices are rare and usually associated with splenic vein thrombosis (Garcia-Tsao 2007).

As varices grow larger, they become more likely to rupture and bleed (Lebrec 1980; NIEC 1988). Haemorrhage from ruptured oesophageal varices is one of the most common causes of gastrointestinal bleeding and the most common cause of death in people with cirrhosis (D'Amico 2006; Garcia-Tsao 2007). Studies by the Northern Italian Endoscopic Club have shown that the frequency of bleeding from large varices is 50% to 53% over two years compared to 5% to 18% from small varices (NIEC 1988; Zoli 1996). Up to 30% of the initial bleeding episodes are fatal, and bleeding recurs in 70% of the survivors (Graham 1981; NIEC 1988; Sharara 2001; D'Amico 2003; Bambha 2008). However, primary prophylaxis with non-selective beta-blockers or endoscopic variceal banding lowers the incidence of first variceal haemorrhage, especially of medium-to-large varices (Garcia-Tsao 2008; Gluud 2012).

The American Association for the Study of the Liver Diseases recommend that medium-sized varices and large varices be managed in the same way (Garcia-Tsao 2007). The guidelines recommend oesophago-gastro-duodenoscopy for screening for oesophageal varices "at the diagnosis of hepatic cirrhosis" (Garcia-Tsao 2007). However, the point prevalence of oesophageal varices requiring prophylaxis is about 15% to 25%, such that the majority of people undergoing screening oesophago-gastro-duodenoscopy either do not have varices or have varices that do not require treatment. Moreover, oesophago-gastro-duodenoscopy is an invasive procedure that requires sedation and is potentially associated with serious, even if rare, complications (Silvis 1976; Cotton 2006). Therefore, there is a need to develop a cost-effective triage pathway to select people who will benefit from oesophago-gastro-duodenoscopy screening.

A non-invasive test could play the role of a triage test if able to detect people with very low probability of having oesophageal varices accurately and hence reduce the use of endoscopy, reserving it only for people with positive results. A non-invasive test may even be more accurate than the reference standard, that is, oesophago-gastro-duodenoscopy, and in such a case, it could replace the reference standard. However, for a non-invasive test to replace oesophago-gastro-duodenoscopy as the preferred diagnostic test for varices, it should accurately demonstrate the presence of varices and also provide the other information that can be gained from endoscopy. Importantly, it should be able to predict the risk of variceal bleeding with as much or greater accuracy as oesophago-gastro-duodenoscopy.

Target condition being diagnosed

Oesophageal varices

The presence of oesophageal varices of any size: oesophageal varices are dilated blood vessels within the wall of the oesophagus that develop when resistance to blood flow through the liver is increased, due to cirrhosis or portal vein obstruction. Large oesophageal varices are associated with greater risk of bleeding than varices of smaller size. Red marks (or red colour signs) on varices diagnosed during oesophago-gastro-duodenoscopy have also been associated with increased bleeding risk (Garcia-Tsao 2007; Garcia-Tsao 2008). Medium varices were classified as large varices, as suggested by the American Association for the Study of Liver Diseases (Garcia-Tsao 2007), because the recommendations for management of medium-sized varices are the same as for large varices.

Index test(s)

Capsule endoscopy

Video capsule endoscopy was originally designed for evaluation of small bowel pathology and has now been adapted to evaluate the oesophagus with the development of an oesophageal video capsule that should be able to explore the oesophageal walls and detect the presence of varices and describe their characteristics, such as size and presence of red marks.

Clinical pathway

At the time of diagnosis of hepatic cirrhosis of whatever aetiology, an oesophago-gastro-duodenoscopy is recommended in order to detect the presence of oesophageal varices and to define the risk of their rupture and bleeding. In the case of high-risk varices (large varices or presence of red marks), primary prophylaxis with a non-selective beta-blocker has been demonstrated to be effective and is hence recommended. If oesophago-gastro-duodenoscopy reveals no varices, then a repeated examination is recommended in three years. If low-risk varices are seen (small varices without red marks), then oesophago-gastro-duodenoscopy should be repeated in two years or if hepatic decompensation is present (Child-Pugh score B-C) (Pugh 1973), then oesophago-gastro-duodenoscopy should be repeated in one year (Garcia-Tsao 2007; Garcia-Tsao 2008).

Prior test(s)

The diagnosis of liver cirrhosis is usually based on clinical judgement derived from history, laboratory test, physical examination, imaging, liver histology, or a combination of these. No prior test is recommended in the guidelines before screening with oesophago-gastro-duodenoscopy of oesophageal varices when the diagnosis of cirrhosis is made.

Role of index test(s)

The possible role of capsule endoscopy is to screen people with diagnosis of cirrhosis for the presence of varices, sparing oesophago-gastro-duodenoscopy in people with negative results. Furthermore, capsule endoscopy could even replace oesophago-gastro-duodenoscopy if its accuracy in detecting varices and defining high-risk varices (large varices or presence of red marks) was equal to that of oesophago-gastro-duodenoscopy.

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Alternative test(s)

Some non-invasive tests have been proposed for the diagnosis of oesophageal varices, such as serum markers for liver fibrosis, platelet count, platelet count/spleen size ratio, transient elastography or imaging with ultrasound computer tomography and magnetic resonance. We will examine each of these tests in future planned reviews (Gana 2010a; Gana 2010b; Gana 2010c; Gana 2010d).

Rationale

The effective prevention of the first variceal haemorrhage (primary prophylaxis) in adults with medium or large varices can be achieved using non-selective beta-blockers or endoscopic variceal ligation (D'Amico 1999; Imperiale 2001; Gluud 2007). Therefore, guidelines recommend endoscopy when cirrhosis is present and at intervals thereafter in order to identify people at risk who might benefit from prophylactic treatment. These guidelines require people to undergo an unpleasant invasive procedure with its accompanying risks repeatedly, despite half of people having no identifiable oesophageal varices 10 years after the initial diagnosis of cirrhosis (Grace 1998; Jalan 2000; Adams 2004; Garcia-Tsao 2007; Garcia-Tsao 2008). Oesophago-gastro-duodenoscopy requires appropriate sedation and analgesia (Cotton 2006), and is associated with an overall complication rate of 0.13%, and a mortality rate of 0.004% (Silvis 1976).

Two cost-effectiveness studies suggested avoidance of surveillance oesophago-gastro-duodenoscopy and treatment with non-selective beta-blockers for all people with cirrhosis, irrespective of the presence or size of varices (Saab 2003; Spiegel 2003). A third cost-effectiveness analysis suggested that this non-selective strategy should be reserved only for people with decompensated liver disease (Arguedas 2002). These conflicting cost-effectiveness recommendations do not recognise that non-selective beta-blockers do not prevent the development of oesophageal varices (Groszmann 2005). Therefore, oesophago-gastro-duodenoscopy remains the recommended test for the diagnosis and prognosis of oesophageal varices (Garcia-Tsao 2007; Garcia-Tsao 2008).

In view of the invasive nature and attendant cost of oesophago-gastro-duodenoscopy, an accurate non-invasive test with adequate accuracy could play a role as a screening test. Such a test will assist in triaging people before oesophago-gastro-duodenoscopy and, if varices of sufficient risk of bleeding are present, primary prophylaxis will be recommended in order to prevent variceal haemorrhage. Non-invasive tests for varices, if sufficiently accurate in detecting high-risk varices, could even replace oesophago-gastro-duodenoscopy, which is the preferred test for diagnosing oesophageal varices. This is why we aimed to assess the ability of capsule endoscopy to triage people for oesophago-gastro-duodenoscopy investigation and in addition, if it could replace oesophago-gastro-duodenoscopy.

OBJECTIVES

To determine the diagnostic accuracy of capsule endoscopy for the diagnosis of oesophageal varices in children or adults with chronic liver disease or portal vein thrombosis, irrespective of the aetiology. To investigate the accuracy of capsule endoscopy as triage or replacement of oesophago-gastro-duodenoscopy.

Secondary objectives

To determine the diagnostic accuracy of capsule endoscopy for the diagnosis of medium oesophageal varices, large oesophageal varices, and presence of red marks on the varices.

The following study characteristics, oesophageal varices, paediatric compared to adult participants, chronic liver disease compared to portal vein thrombosis, different stages of liver disease severity, different aetiologies of liver disease (e.g., viral cirrhosis compared with alcoholic cirrhosis; cholestatic compared to non-cholestatic liver disease), prevalence of oesophageal varices in the study group, and co-morbidities, were considered as sources of heterogeneity.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include studies that, irrespective of publication status and language, evaluated the diagnostic accuracy of capsule endoscopy for the diagnosis of oesophageal varices using oesophago-gastro-duodenoscopy as the reference standard. We considered cross-sectional cohort design studies on people with clinical suspicion of portal hypertension as well as participant-control design studies that compared people with oesophageal varices with matched controls (Colli 2014).

We excluded studies in which data were analysed only per varix rather than per participant unless the participant data were made available by study authors.

Participants

Participants could be of any age in whom the presence of oesophageal varices was clinically suspected (screening cohort) based on chronic liver disease or portal vein thrombosis, irrespective of the aetiology and duration of illness. We also considered people with previous history of upper gastrointestinal bleeding or already diagnosed oesophageal varices (surveillance cohort) for our review as these participants are a distinct group in whom the presence of oesophageal varices has a very higher probability than in a screening cohort, and when they participated in the studies, we analysed their data separately.

We excluded studies with people with a previous surgical portal-systemic shunt procedure or insertion of transjugular intrahepatic portal-systemic shunt, previous ligation, or sclerotherapy of oesophageal varices.

Index tests

Capsule endoscopy

The video capsule endoscope is a wireless capsule comprised of a light source, lens, imaging hardware, battery, and a wireless transmitter, designed to investigate the oesophagus. The capsule is swallowed; it moves down the oesophagus via peristalsis. To improve the oesophagus visualisation, the device can be modified by attaching a string to control movement up and down the oesophagus (string capsule). The capsule obtains photographs at high frequency that are transmitted to a recorder, worn on a belt. The photographs are downloaded into a computer and can be viewed individually or as a video.

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There is a variety of classifications reported for oesophageal varices observed with capsule endoscopy, with no current consensus. The reported methods for evaluating the size of the oesophageal varices with capsule endoscopy are frequently identical to oesophago-gastro-duodenoscopy in spite of the lack of air inflation (which is not possible with the capsule endoscopy). To standardise the classification for the purposes of this review, oesophageal varices observed with capsule endoscopy were dichotomised in the following way: absence or presence of varices; and, small compared to medium or large varices. A small varix is said to occupy less than 25% and a medium/large varix to occupy more than 25% of the radius of the lumen of the oesophagus. The description of red marks on the varices follows the criteria used for oesophago-gastro-duodenoscopy: raised cherry-red spots (dilated sub-epithelial veins) and red wale marking (longitudinal dilated veins resembling whip marks).

Target conditions

The presence of any oesophageal varices (independent of size), detected by oesophago-gastro-duodenoscopy. For secondary analyses, the presence of medium or large varices (Garcia-Tsao 2007), and the presence of red marks were considered the target conditions.

Reference standards

Oesophago-gastro-duodenoscopy is the reference standard test for the diagnosis of oesophageal varices in which the presence of varices in the oesophagus is directly observed by endoscopy. The size and appearance of oesophageal varices is graded at the time of endoscopy according to one of the following systems, using the largest varix identified to classify the participant. People with an indication for primary prophylactic therapy are considered to be those whose largest varix is medium or large in size, or with small varices with red marks.

1. The Baveno Consensus system differentiates small from large oesophageal varices (de Franchis 1992). Small varices are defined as varices that flatten with insufflation during endoscopy or that minimally protrude into the oesophageal lumen. Large oesophageal varices are defined as varices that protrude into the oesophageal lumen and touch each other, or that fill at least 50% of the oesophageal lumen.
2. The Japanese Research Society for Portal Hypertension used three grades for variceal size (JSPH 1980). Grade 1 varices collapse with insufflation during endoscopy, grade 2 do not collapse with insufflation and do not occlude the lumen, and grade 3 varices occlude the lumen. Grade 2 varices were considered equivalent to medium, and grade 3 varices equivalent to large for this review.
3. The Japanese classification was revised by the Italian Liver Cirrhosis Project Group (Zoli 1996), which describes variceal size as the percentage of the radius of the oesophageal lumen that is occupied by the largest varix. A small or grade 1 varix is said to occupy less than 25%, a medium or grade 2 varix to occupy 25% to 50%, and a large or grade 3 varix to occupy greater than 50% of the radius of the lumen of the oesophagus.
4. The Cales criteria define varices as small if they flatten with insufflation during endoscopy, medium if they do not flatten with insufflation, and large if they do not flatten with insufflation during endoscopy and are confluent (Cales 1990).

We included studies applying other classifications if adequately described and logically defined.

The presence of red marks is usually noted as present or absent and may also be described according to different classifications. Even small varices with the presence of red marks are classified as 'at high risk of bleeding'.

The interval between the index test and oesophago-gastro-duodenoscopy has to be less than 14 days in order to avoid possible evolution of the target condition. In the case of longer time intervals, we included the study but considered it at risk of bias.

Search methods for identification of studies

Electronic searches

We ran searches in The Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register (October 2013), MEDLINE (Ovid SP) (1950 to October 2013), EMBASE (Ovid SP) (1980 to October 2013), ACP Journal Club (Ovid SP) (1991 to October 2013), Database of Abstracts of Reviews of Effects (DARE) (OvidSP) (third quarter), Health Technology Assessment (HTA) (Ovid SP)(third quarter), NHS Economic Evaluation Database (NHSEED) (Ovid SP) (third quarter), and Science Citation Index Expanded (SCI-EXPANDED) (ISI Web of Knowledge) (1955 to October 2013) (Royle 2003). We applied no language or document type restrictions. We conducted the last search on 21 October 2013.

We used the multipurpose search command for the Ovid SP interface (.mp.) and the topic search command for the ISI Web of Knowledge interface (TS=) to search both text and database subject heading fields. To capture variations in suffix endings, the unlimited truncation symbol '*' was used in both interfaces. Search strategies with the time spans of the searches are listed in Appendix 1.

Searching other resources

We identified additional references by manually searching the references of articles retrieved from the computerised databases and relevant review articles. We contacted experts in the field for unpublished studies. In addition, we handsearched abstract books from the American Association for the Study of Liver Diseases meetings and European Association for the Study of the Liver meetings from 2003 to 2013.

Data collection and analysis

We followed the available guidelines provided in the *Cochrane Handbook for Diagnostic Test Accuracy Reviews* (DTA Handbook 2010).

Selection of studies

We retrieved publications if they were potentially eligible for inclusion based on abstract review. Two review authors (JCG or JY and AC or GC) independently reviewed the publications for eligibility. To be eligible, we assessed each publication to determine if participants met the inclusion criteria. We only included abstracts if sufficient data for 2 x 2 tables were provided for analysis. We resolved any disagreements by consensus between JCG, JY, or AC and GC.

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Data extraction and management

Review authors, working in pairs (JCG and JY or AC and GC) completed a data extraction form for each included study. AC and GC completed the extraction forms of the studies retrieved with the last search (from 2009 to 2013). Each review author independently retrieved the data: in case of discordance, we reached a consensus through discussion.

We retrieved the following study data:

- general information: title, journal, year, publication status, and study design;
- sample size: number of participants meeting the criteria and total number screened;
- baseline characteristics: baseline diagnosis, age, sex, race, disease severity, and concurrent medications used. Severity of liver disease of the studied population may have been considered using the Child-Pugh score (Pugh 1973), and model for end-stage liver disease (MELD) scores in adults (Kamath 2001), and by the Child-Pugh score and paediatric end-stage liver disease (PELD) scores in children (McDiarmid 2002);
- the index test: type of capsule, number and experience of readers, interobserver variation;
- reference standard test: variceal size, type of classification used;
- prevalence of the target disease;
- number of true positive, true negative, false positive, and false negative. These data were extracted for the two target conditions;
- adverse events or complications due to the capsule endoscopy.

We summarised data from each study in 2 x 2 tables (false positive, false negative, true positive, true negative) according to the two target conditions and to pre-defined sub-populations, and entered into Review Manager 5 software (RevMan 2012).

Missing data

We contacted primary authors for missing data by e-mail. In absence of a reply, we sent a second e-mail two weeks later. We also contacted one study author by telephone, but no supplementary data were available (de Franchis 2008).

Assessment of methodological quality

Two review authors independently assessed the risk of bias of the included studies using QUADAS-2 domains (Whiting 2011). A third review author acted as arbitrator in case of disagreements assessing the bias risk of the studies.

We adopted the domains in Appendix 2 to address aspects of study quality involving the participant spectrum, index test, target condition, reference standard, and flow and timing. We considered studies classified as 'yes' to be at low risk of bias. In the remaining two cases of 'no' or 'unclear', we classified the studies as at high risk of bias (Appendix 2). We removed the domain concerning the cut-off values because we had planned to express the results of capsule endoscopy as positive or negative (i.e., varices present or absent). We added a further domain exploring the participant spectrum. We considered a study at low risk of bias if only screening cohorts were included, but at high risk of bias if surveillance cohorts were also included and no separate analysis was available.

Statistical analysis and data synthesis

We presented data graphically using forest plots that show paired sensitivities and specificities for each study, with the corresponding 95% confidence interval (CI). We also plotted data in the receiver operating characteristic (ROC) space for a more thorough visual assessment of the variation of test accuracy between studies.

Since all the studies were expected to use quite similar criteria to define the presence of varices (i.e., the same implicit cut-off), we conducted the meta-analysis using the bivariate model, where the logit transformed sensitivities and specificities were modelled (Reitsma 2005). If the model did not converge, we fitted the hierarchical summary ROC (HSROC) model. For each analysis, we calculated the summary sensitivity and specificity (summary operating point) with their 95% CIs starting from parameter estimates obtained from the bivariate or HSROC models (Reitsma 2005). We calculated positive (LR+) and negative (LR-) likelihood ratios from summary sensitivity and specificity. We assessed the presence of a possible implicit threshold effect through visual inspection of the plot of the studies in the ROC space.

We performed all analyses using statistical software SAS (release 9.2) and macro METADAS (DTA Handbook 2010).

Investigations of heterogeneity

We investigated heterogeneity first by visual inspection of the paired forest plots of sensitivities and specificities. Subsequently, we performed a subgroup analysis, where appropriate, considering some possible sources of heterogeneity. As possible sources of heterogeneity, we considered the criteria to diagnose and characterise oesophageal varices; paediatric compared to adult participants; chronic liver disease compared to portal vein thrombosis; severity of liver disease; different aetiologies of liver disease (e.g., viral cirrhosis compared to alcoholic cirrhosis; cholestatic compared to non-cholestatic liver disease); prevalence of oesophageal varices in the study (higher than 50% compared to lower than 50%); co-morbidities, and type of video capsule (standard compared to string capsule).

Sensitivity analyses

In order to assess the robustness of the results, we undertook several sensitivity analyses to explore the effect of studies at high risk of bias on overall results.

To account for the possible bias introduced by studies with risk of bias, we had planned some sensitivity analyses:

- considering only the studies that were published in full text;
- considering only the studies classified at low risk of bias for each domain of QUADAS-2;
- considering only cross-sectional design studies.

RESULTS

Results of the search

We identified 1836 references through electronic searches of the Cochrane Hepato-Biliary Group Controlled Trial Register (N = 1), *The Cochrane Library* (N = 155), MEDLINE (Ovid SP) (N = 415), EMBASE (Ovid SP) (N = 869), and Science Citation Index Expanded (N = 396). After the exclusion of 587 duplicates, 1249 references remained; we found 1226 to be irrelevant references. Twenty-three references on

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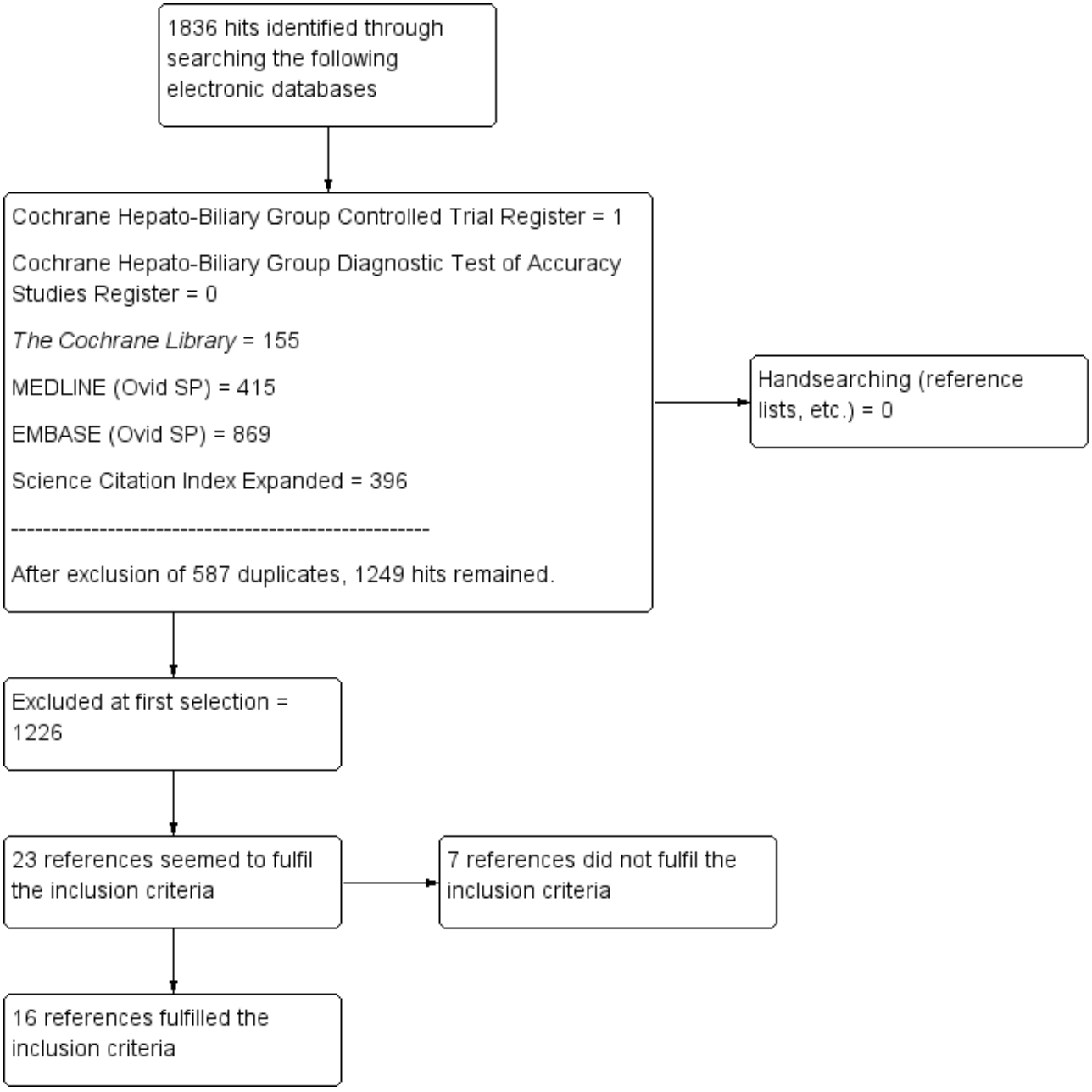
studies seemed to fulfil the inclusion criteria. We excluded seven studies after reading the full text. Finally, we included 16 studies and considered them for data analyses (Figure 1).

Figure 1. Results of the studies search



We included 16 studies in this review, of which 11 evaluated the PillCam ESO (Given Imaging, Israel), two did not specify which device was used (Groce 2007; Frenette 2008), two assessed string capsule in which an M2A capsule endoscope (Given Imaging, Israel) was moved up and down the oesophagus using a string attached to the capsule (Ramirez 2005; Stipho 2012), and one assessed PillCam SB/SB2, a device designed for investigation of the small intestine and not dedicated to the oesophagus (Aoyama 2014). One study assessed the accuracy of capsule endoscopy for the diagnosis of large (high-risk) oesophageal varices (Frenette 2008). The remaining 15 studies assessed the accuracy for the diagnosis of varices of any size. All studies were undertaken in a secondary or tertiary care setting. All studies included only adults with cirrhosis. One study also included people with portal thrombosis (66/288 participants) combining the participant data all together for analysis (de Franchis 2008). We requested data for a separate analysis from the corresponding author, but obtained no further information. Four of the studies were reported in abstract form only (Donnelly 2006; Groce 2007; Gerson 2008; Sharma 2009).

All studies were designed as cross-sectional cohort studies. Seven studies included only people with the suspected, but unknown, presence of oesophageal varices (screening cohort)

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(Lapalus 2006; Groce 2007; Gerson 2008; Lapalus 2009; Sharma 2009; Chavalitdhamrong 2012; Aoyama 2014). This participant sampling was considered as the most appropriate to assess the accuracy of the index test. In the other nine studies, people with antecedent diagnosis of oesophageal varices were also enrolled (surveillance cohort) and the participant data were combined for analysis, likely introducing a selection bias. We requested data for a separate analysis from the corresponding author, but no further information was obtained. Seven studies presented further analyses considering the use of capsule endoscopy to diagnose large oesophageal varices (Summary of findings 1) with or without the presence of red marks; one study assessed only accuracy of capsule endoscopy for the detection of high-risk varices (large varices or small varices with red marks) (Frenette 2008).

Methodological quality of included studies

The evaluation of methodological quality is presented in Figure 2 and Figure 3. We evaluated studies according to QUADAS-2 domains. Two areas were poorly reported by many studies. First, reporting of participant recruitment frequently left some uncertainty about whether those included participants were a representative spectrum of participants in whom the non-invasive diagnosis of varices might be appropriately considered in clinical practice. In fact, even in the studies that included only people with suspected oesophageal varices, the prevalence of the target disease was higher (median 63%; range 43% to 82%) than expected in early cirrhosis (Merli 2003). Large cohort studies reported a lower prevalence of oesophageal varices at the time of diagnosis of cirrhosis, of around 50% (Garcia-Tsao 2008). One study included only people on the waiting list for orthotopic liver transplantation, and thus, it included people with more advanced disease than in other studies (Gerson 2008). Another study enrolled only people defined as affected by end-stage liver disease without any other specification, and found a high prevalence of oesophageal varices (82%); we classified this study as a high-risk study as the participants and the setting did not match the review question (Sharma 2009).

Figure 2. Methodological quality of the 10 included studies.

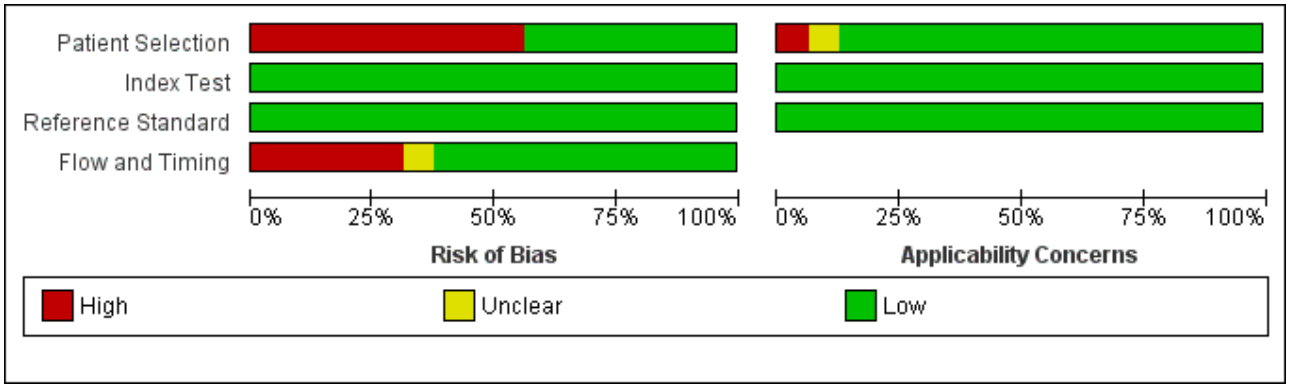

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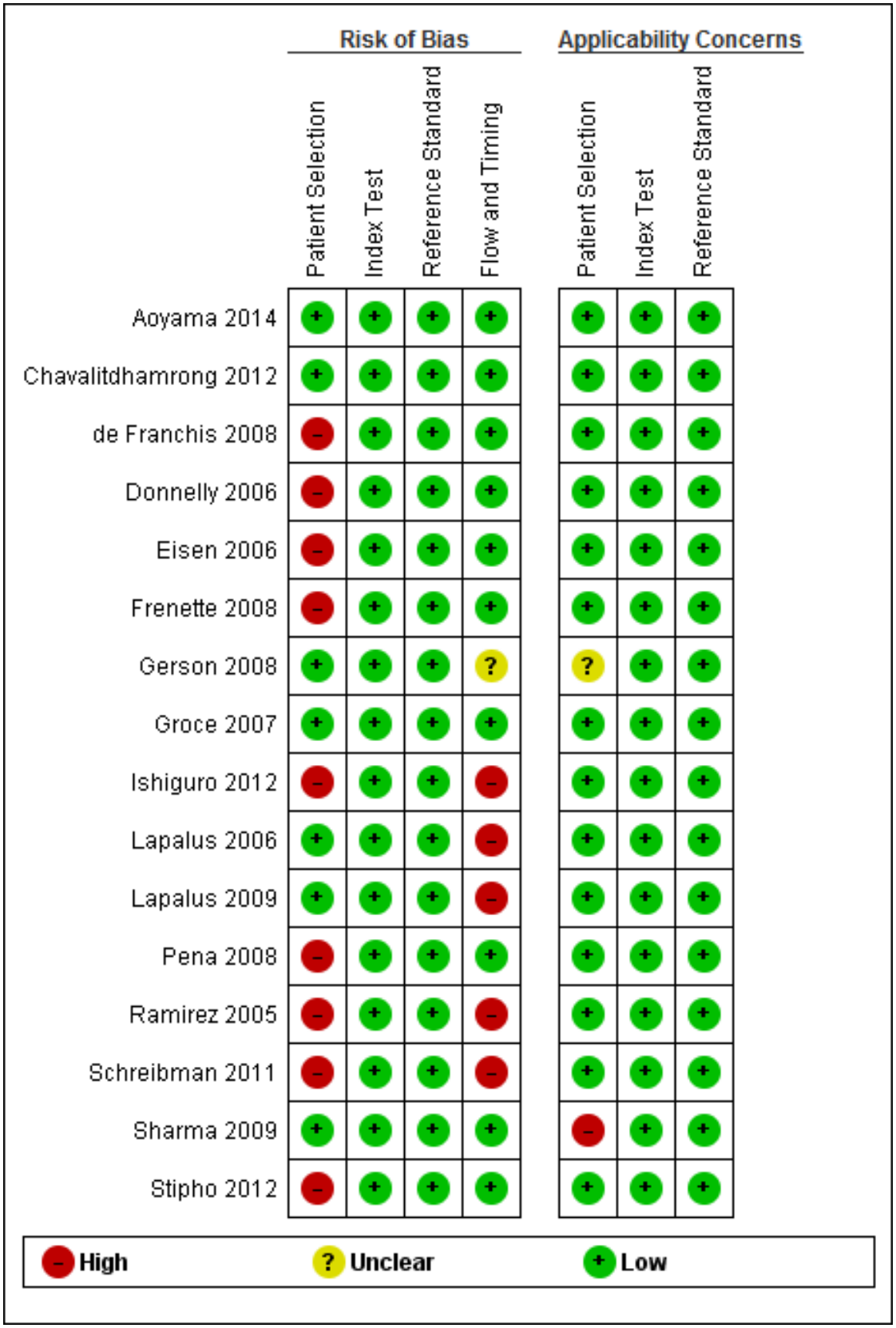
Figure 3. Quality assessment summary: review authors' judgements about each risk of bias item for each included study.



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Nine studies included and analysed together either people with suspected target disease (screening cohort) or people with antecedent diagnosis of oesophageal varices (surveillance cohort). We requested data for separate analysis from the corresponding authors, but received no answers. The inclusion of a different mixture of people with suspected or known varices introduces a spectrum bias that could impair the estimation of diagnostic accuracy in the detection of any size varices. In these studies, the prevalence of oesophageal varices was higher (range 63% to 95%) than that reported in studies that include only a screening cohort.

Data on uninterpretable results of the index test were not always reported and were excluded from the final analysis, thus preventing an 'intention-to-diagnose' analysis. Capsule endoscopy is not always easy for people to swallow and does not always produce adequate images of the oesophagus; these uninterpretable results should be taken into account when estimating the diagnostic accuracy of capsule endoscopy.

Due to the required design characteristics of the studies to be included in this review, we did not expect to find any studies with weakness in the choice of reference standard, partial or differential verification bias, or incorporation bias. None of the studies showed flaws concerning these criteria and only one study reported an unacceptable delay between the index and the reference standard test (Stipho 2012). In all the studies, the interpretation of the capsule endoscopy results were blinded to the results of the reference test, but it was not always stated whether the reference standard (oesophago-gastro-duodenoscopy) results were interpreted without knowing the capsule endoscopy results. One study performed endoscopy immediately after capsule endoscopy, thus preventing the availability of capsule endoscopy information when interpreting the oesophago-gastro-duodenoscopy results (Schreibman 2011). Other studies did not explicitly state this blinding (Ramirez 2005; Gerson 2008; Lapalus 2009; Aoyama 2014), and we interpreted this lack as a reporting flaw that would probably not introduce bias.

Studies did not always report a plan to collect data on adverse events associated with the capsule endoscopy, and such events were only occasionally reported. Finally, only three studies provided interobserver agreement in index test interpretation (Frenette 2008; Gerson 2008; Lapalus 2009).

Findings

Diagnosis of any oesophageal varices

All the studies

Fifteen of the 16 included studies with 936 participants reported accuracy estimates data on the ability of capsule endoscopy to detect varices of any size. Among the 936 included participants, 640 (68.4%) had varices of any size (median 72%; range 43% to 95%).

In 13 studies that provided at least some details of the cause of portal hypertension, people with parenchymal liver disease only were included in 11 studies. In one study, the proportion of people with non-cirrhotic causes of portal hypertension (e.g., portal vein thrombosis or Budd-Chiari syndrome) was less than 23% (de Franchis 2008), and other two studies reported no details (Eisen 2006; Sharma 2009). Specific diseases reflected the common causes of cirrhosis in adults, particularly hepatitis C, alcoholic liver disease, and non-alcoholic fatty liver disease. Four studies did not report any details about the severity of the liver cirrhosis (Child-Pugh classification or MELD score) (Donnelly 2006; Eisen 2006; Groce 2007; Sharma 2009). In one study of 24 participants, the majority (71%) were Child-Pugh score B (Gerson 2008). In the other 10 studies that provided some details of Child-Pugh score, people with compensated cirrhosis were the largest group, but a variable proportion of people with decompensated cirrhosis (class B and C) were also included.

The sensitivity of capsule endoscopy to diagnose oesophageal varices of any size ranged from 65% to 100%, and the specificity from 33% to 100% (Figure 4). The visual inspection of the plot of the studies' results in the ROC space suggested the same implicit cut-off, as the disposition of the study points in the ROC plot (Figure 5) was not consistent with the presence of a threshold effect (i.e., there was not a clear negative correlation between sensitivity and specificity). The bivariate model was fitted and a summary operating point (mean sensitivity and mean specificity) was estimated. The pooled estimates of sensitivity and specificity were 84.8% (95% CI 77.3% to 90.2%) and 84.3% (95% CI 73.1% to 91.4%). The LR+ was 5.4 (95% CI 3.1 to 9.5) and the LR- was 0.18 (95% CI 0.12 to 0.27) (Figure 4; Figure 5).

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Figure 4. Forest plot: Diagnosis of any varices - all the studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aoyama 2014	51	0	20	48	0.72 [0.60, 0.82]	1.00 [0.93, 1.00]
Chavalitdhamrong 2012	36	10	10	9	0.78 [0.64, 0.89]	0.47 [0.24, 0.71]
de Franchis 2008	152	13	28	95	0.84 [0.78, 0.89]	0.88 [0.80, 0.93]
Donnelly 2006	5	2	0	1	1.00 [0.48, 1.00]	0.33 [0.01, 0.91]
Eisen 2006	23	1	0	8	1.00 [0.85, 1.00]	0.89 [0.52, 1.00]
Gerson 2008	9	2	3	10	0.75 [0.43, 0.95]	0.83 [0.52, 0.98]
Groce 2007	7	2	2	10	0.78 [0.40, 0.97]	0.83 [0.52, 0.98]
Ishiguro 2012	21	1	1	5	0.95 [0.77, 1.00]	0.83 [0.36, 1.00]
Lapalus 2006	13	0	3	4	0.81 [0.54, 0.96]	1.00 [0.40, 1.00]
Lapalus 2009	55	6	16	36	0.77 [0.66, 0.87]	0.86 [0.71, 0.95]
Pena 2008	13	0	6	1	0.68 [0.43, 0.87]	1.00 [0.03, 1.00]
Ramirez 2005	24	0	1	5	0.96 [0.80, 1.00]	1.00 [0.48, 1.00]
Schreibman 2011	20	1	11	2	0.65 [0.45, 0.81]	0.67 [0.09, 0.99]
Sharma 2009	28	2	0	4	1.00 [0.88, 1.00]	0.67 [0.22, 0.96]
Stipho 2012	69	5	13	13	0.84 [0.74, 0.91]	0.72 [0.47, 0.90]

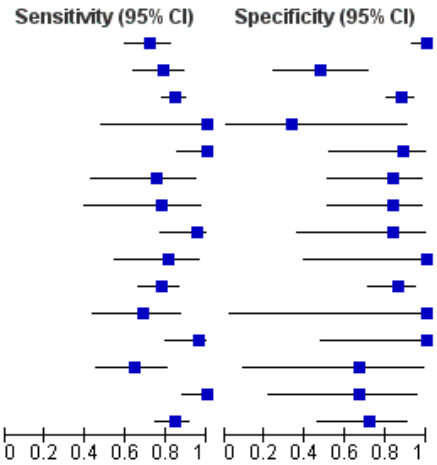

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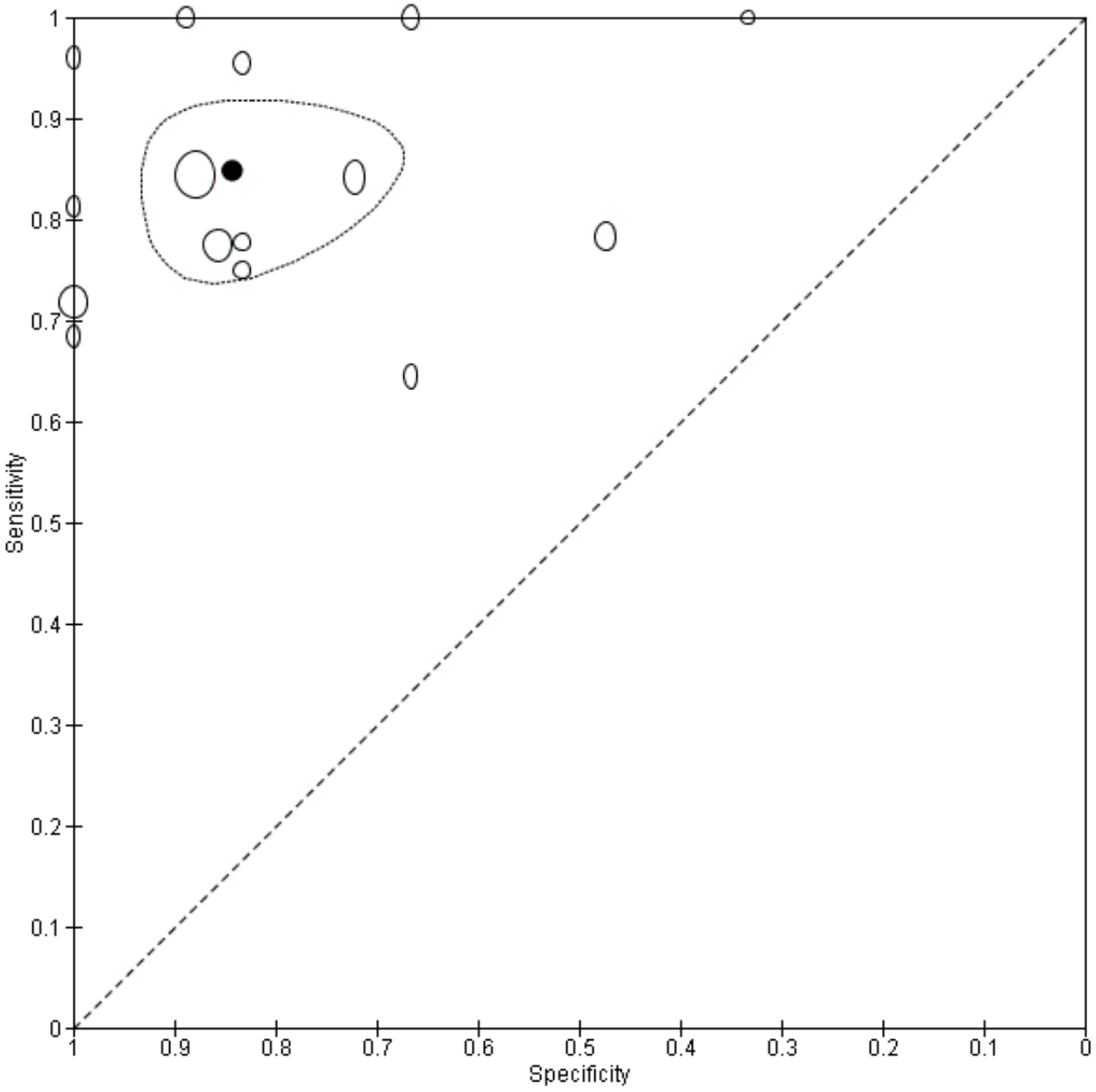
Figure 5. Studies in the receiver operating characteristic (ROC) space: Diagnosis of any varices - all the studies



Using the median prevalence of oesophageal varices in the 15 studies (72%) as a pre-test probability, we obtained a post-test probability of 93% if the test was positive, and a post-test probability of 32% if the test was negative. The prevalence of oesophageal varices of any size in the seven studies at low risk of bias according to the QUADAS-2 'participants selection' domain was 63% (see 'sensitivity analysis' below). Using this value as a pre-test probability, we obtained a post-test probability of 90% if the test was positive, and a post-test probability of 23% if the test was negative.

Subgroup analyses

In the 13 studies (806 participants) that used the ESO standard capsule, the pooled estimate of sensitivity was 83.9% (95% CI 75.3% to 90.0%) and the pooled estimate of specificity was 84.5% (95% CI 71.8% to 92.1%); otherwise in the other two studies with 130 participants that used a modified device (i.e., the string capsule), sensitivity was 90.0% (95% CI 72.4% to 96.9%) and specificity was 86.9% (95% CI 30.7% to 99.0%) (Figure 6; Figure 7). No other planned subgroup analysis was possible. In particular, criteria to diagnose and characterise oesophageal varices were similar among the included studies; no study included children, and people with portal vein thrombosis were included in only one study (de Franchis 2008), but these participants were not analysed separately. No data on co-morbidities were available in any study. Finally, the prevalence of varices was lower than the expected value of 50% in only two studies, both still available in abstract form (Groce 2007; Gerson 2008).

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Figure 6. Forest plot: Diagnosis of any varices - all the studies.

Study	TP	FP	FN	TN	Index Test	Sensitivity (95% CI)	Specificity (95% CI)
Aoyama 2014	51	0	20	48	Capsule endoscopy	0.72 [0.60, 0.82]	1.00 [0.93, 1.00]
Chavalitdhamrong 2012	36	10	10	9	Capsule endoscopy	0.78 [0.64, 0.89]	0.47 [0.24, 0.71]
de Franchis 2008	152	13	28	95	Capsule endoscopy	0.84 [0.78, 0.89]	0.88 [0.80, 0.93]
Donnelly 2006	5	2	0	1	Capsule endoscopy	1.00 [0.48, 1.00]	0.33 [0.01, 0.91]
Eisen 2006	23	1	0	8	Capsule endoscopy	1.00 [0.85, 1.00]	0.89 [0.52, 1.00]
Gerson 2008	9	2	3	10	Capsule endoscopy	0.75 [0.43, 0.95]	0.83 [0.52, 0.98]
Groce 2007	7	2	2	10	Capsule endoscopy	0.78 [0.40, 0.97]	0.83 [0.52, 0.98]
Ishiguro 2012	21	1	1	5	Capsule endoscopy	0.95 [0.77, 1.00]	0.83 [0.36, 1.00]
Lapalus 2006	13	0	3	4	Capsule endoscopy	0.81 [0.54, 0.96]	1.00 [0.40, 1.00]
Lapalus 2009	55	6	16	36	Capsule endoscopy	0.77 [0.66, 0.87]	0.86 [0.71, 0.95]
Pena 2008	13	0	6	1	Capsule endoscopy	0.68 [0.43, 0.87]	1.00 [0.03, 1.00]
Schreibman 2011	20	1	11	2	Capsule endoscopy	0.65 [0.45, 0.81]	0.67 [0.09, 0.99]
Sharma 2009	28	2	0	4	Capsule endoscopy	1.00 [0.88, 1.00]	0.67 [0.22, 0.96]
Ramirez 2005	24	0	1	5	String wireless capsule endoscopy	0.96 [0.80, 1.00]	1.00 [0.48, 1.00]
Stipho 2012	69	5	13	13	String wireless capsule endoscopy	0.84 [0.74, 0.91]	0.72 [0.47, 0.90]

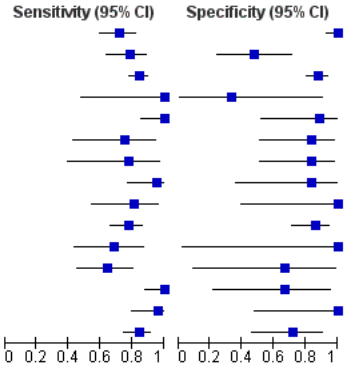

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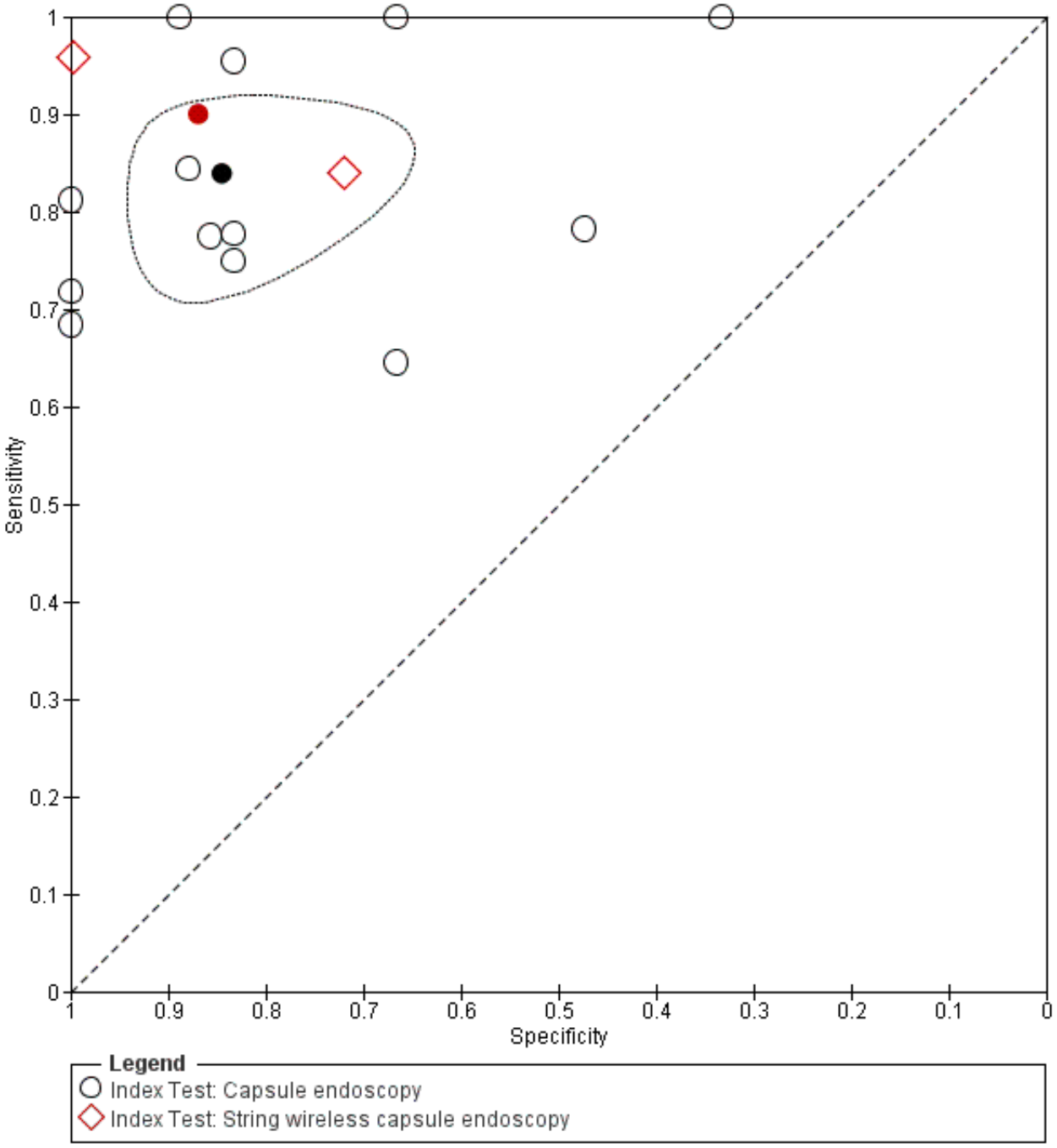
Figure 7. Studies in the receiver operating characteristic (ROC) space: Diagnosis of any varices - all the studies.



Sensitivity analyses

We performed a sensitivity analysis considering only the seven studies with 396 participants at low risk of bias for the QUADAS-2 'participant selection' domain (studies that included only screening cohorts of participants). This showed a pooled sensitivity of 79.7% (95% CI 73.1% to 85.0%), a specificity of 86.1% (95% CI 64.5% to 95.5%), an LR+ of 5.8 (95% CI 2.1 to 16.1) and a LR- of 0.24 (95% CI 0.18 to 0.31) (Figure 8; Figure 9). Using the prevalence of oesophageal varices of any size in these seven studies (63%) as a pre-test probability, we obtained a post-test probability of 91% if the test was positive, and a post-test probability of 29% if the test was negative.

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Figure 8. Forest plot: Diagnosis of any varices - studies at low risk of bias for QUADAS-2 'patient selection' domain.

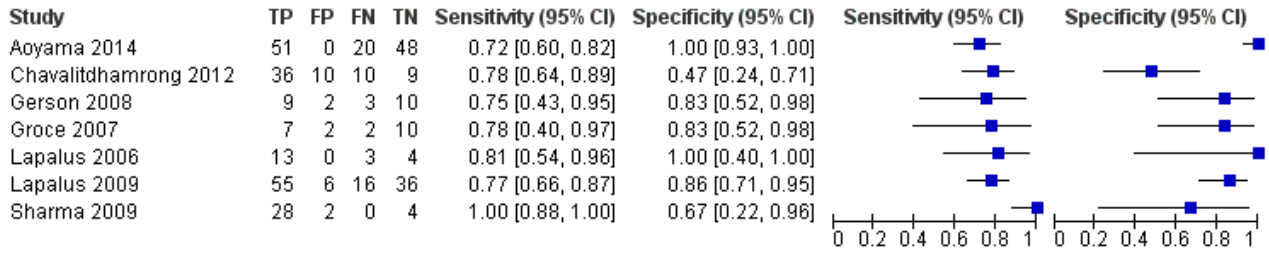
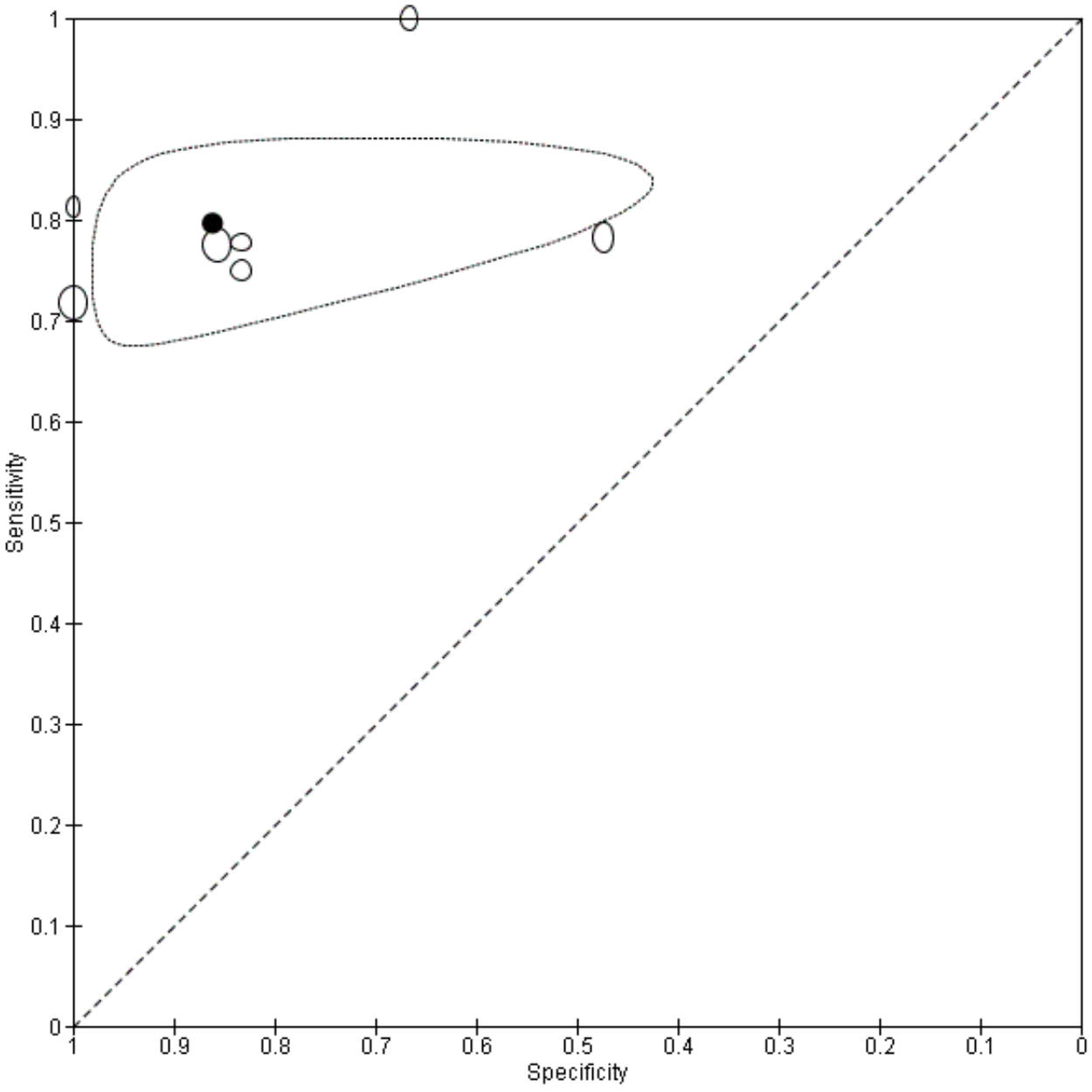


Figure 9. Studies in the receiver operating characteristic (ROC) space: Diagnosis of any varices - studies at low risk of bias for QUADAS-2 'patient selection' domain.



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We performed a second sensitivity analysis considering the nine studies with 687 participants at low risk of bias for the QUADAS-2 'flow and timing' domain. This showed a pooled sensitivity of 85.8% (95% CI 75.5% to 92.2%) and specificity of 82.5% (95% CI 62.2% to 93.1%) (Figure 10; Figure 11).

Figure 10. Forest plot: Diagnosis of any varices - studies at low risk of bias for QUADAS-2 'flow and timing' domain.

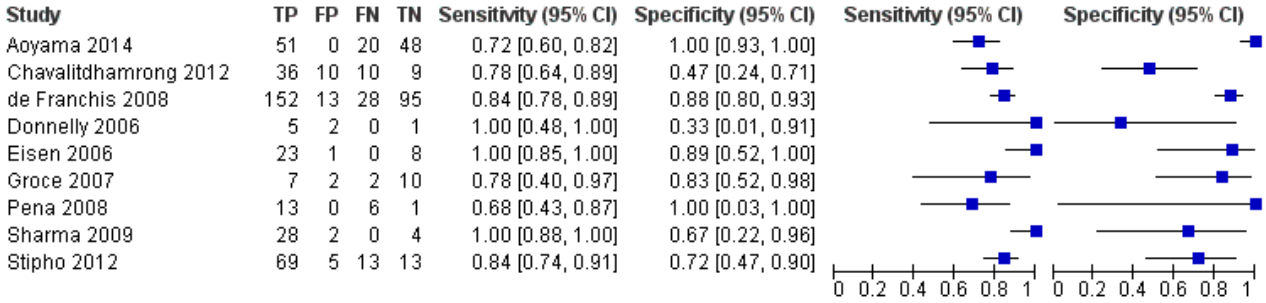

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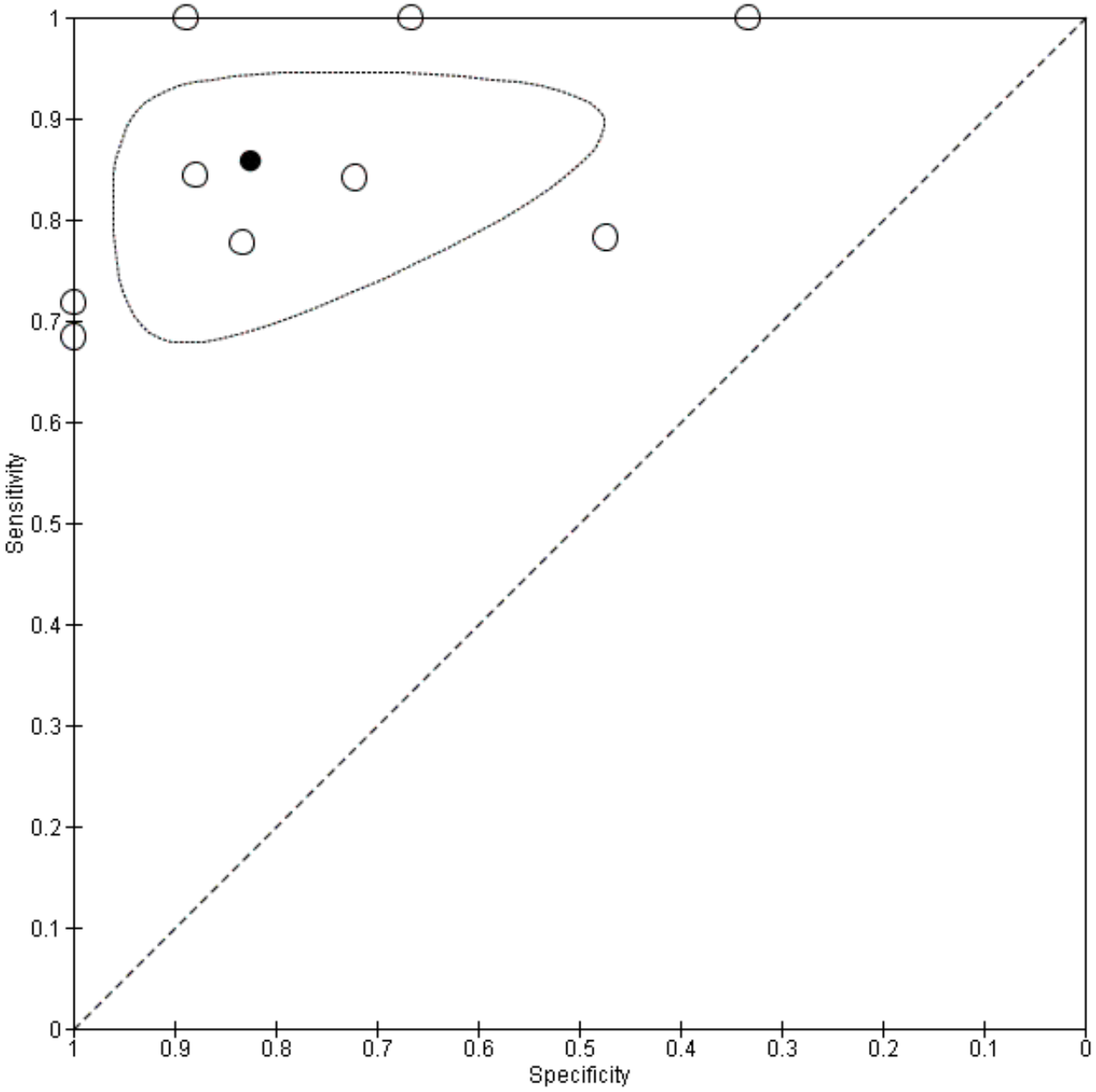
Figure 11. Studies in the receiver operating characteristic (ROC) space: Diagnosis of any varices - studies at low risk of bias for QUADAS-2 'flow and timing' domain.



Finally, when considering the 11 studies with 849 participants alone that were published as full-text articles, the pooled sensitivity was 82.6% (95% CI 75.4% to 88.0%) and the pooled specificity was 88.0% (95% CI 73.9% to 95.0%). LR+ was 6.9 (95% CI 3.0 to 16.0) and LR- was 0.20 (95% CI 0.14 to 0.29) (Figure 12; Figure 13).

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Figure 12. Forest plot: Diagnosis of any varices - only full-text studies.

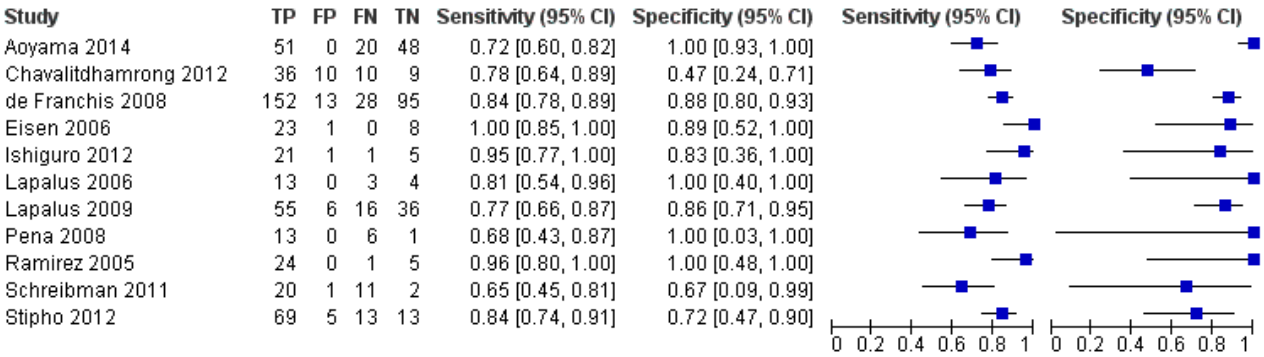

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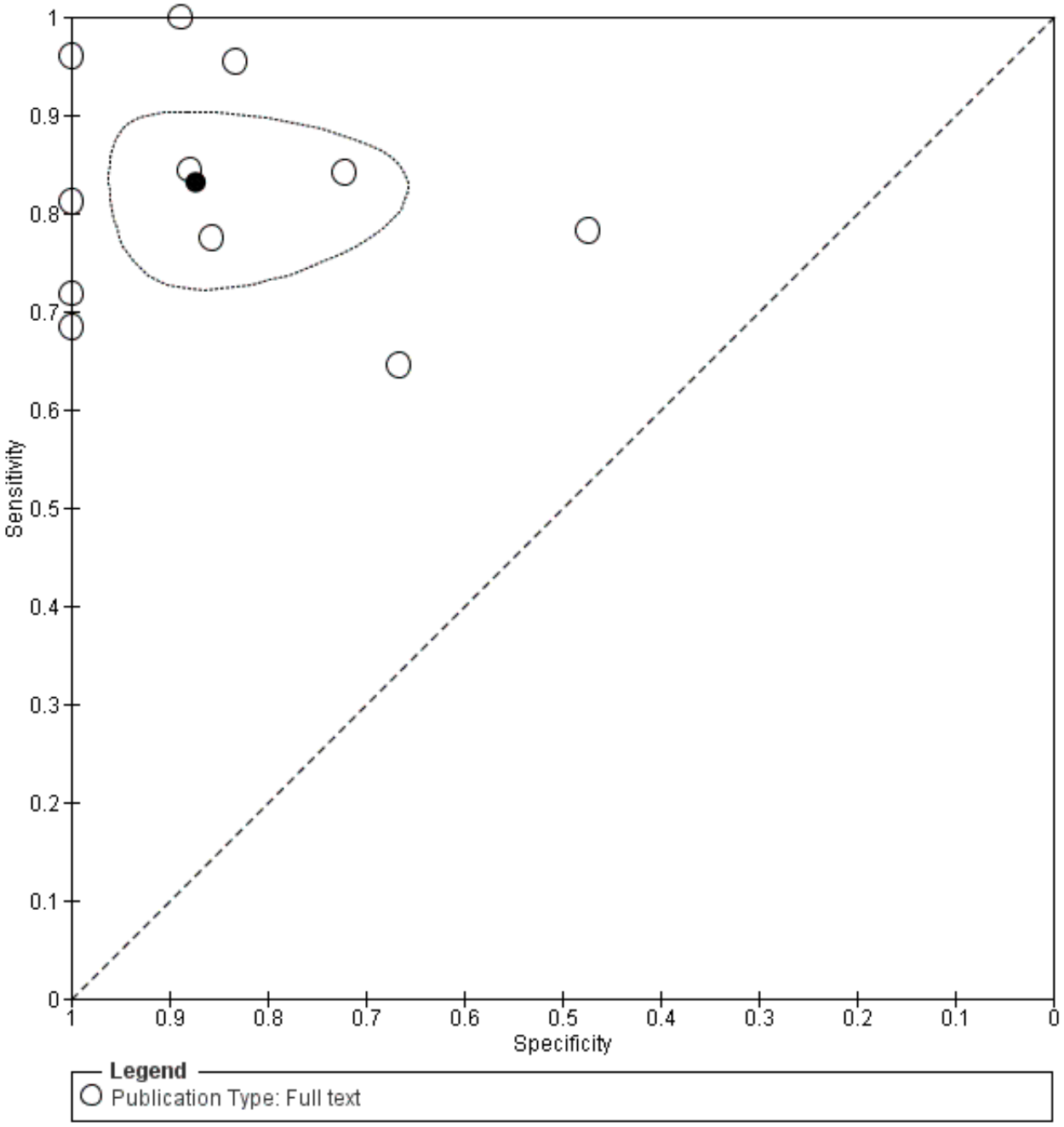
Figure 13. Studies in the receiver operating characteristic (ROC) space: Diagnosis of any varices - only full-text studies.



Diagnosis of medium/large oesophageal varices

Six studies with 537 participants assessed the accuracy of capsule endoscopy for the diagnosis of large oesophageal varices (de Franchis 2008; Frenette 2008; Lapalus 2009; Sharma 2009; Schreibman 2011; Ishiguro 2012). Pooled sensitivity was 73.7% (95% CI 52.4% to 87.7%), pooled specificity was 90.5% (95% CI 84.1% to 94.4%), LR+ was 7.7 (95% CI 4.2 to 14.2) and LR- was 0.29 (95% CI 0.14 to 0.58) (Figure 14; Figure 15). The prevalence of large oesophageal varices in the six studies was 37%. Using this value as a pre-test probability, we obtained a post-test probability of 82% if the test was positive, and a post-test probability of 15% if the test was negative.

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Figure 14. Forest plot: Diagnosis of medium/large varices - all the studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
de Franchis 2008	62	9	17	200	0.78 [0.68, 0.87]	0.96 [0.92, 0.98]
Frenette 2008	11	4	6	19	0.65 [0.38, 0.86]	0.83 [0.61, 0.95]
Ishiguro 2012	12	3	1	12	0.92 [0.64, 1.00]	0.80 [0.52, 0.96]
Lapalus 2009	27	9	8	69	0.77 [0.60, 0.90]	0.88 [0.79, 0.95]
Schreibman 2011	4	2	13	15	0.24 [0.07, 0.50]	0.88 [0.64, 0.99]
Sharma 2009	10	2	1	21	0.91 [0.59, 1.00]	0.91 [0.72, 0.99]

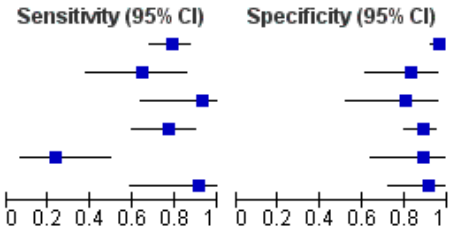
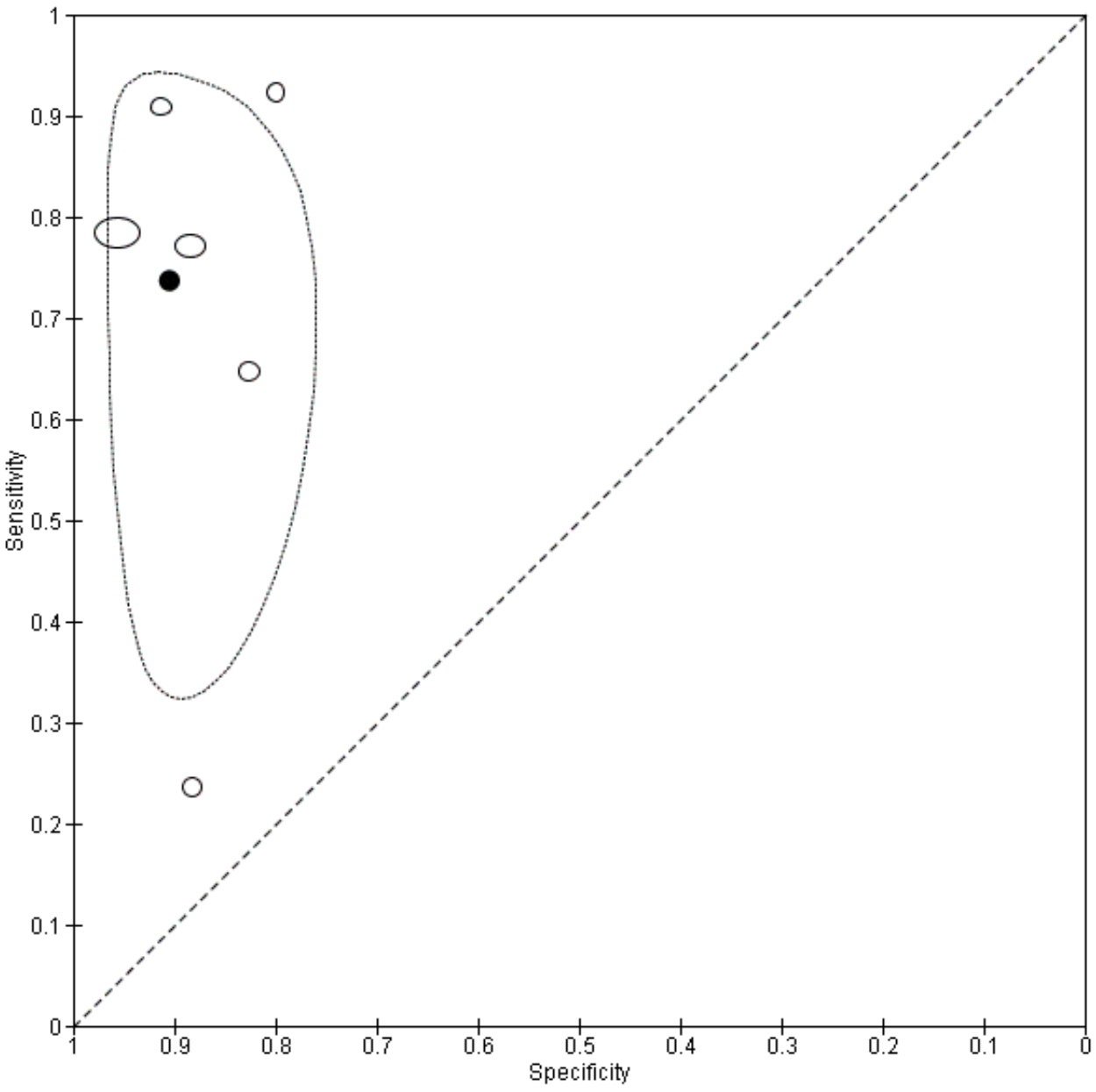


Figure 15. Studies in the receiver operating characteristic (ROC) space: Diagnosis of medium/large varices - all the studies.



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Diagnosis of red marks

Three studies with 150 participants assessed the accuracy of capsule endoscopy for the presence of red marks (Chavalitdhamrong 2012; Ishiguro 2012; Stipho 2012). The statistical model did not converge and, as a consequence, it was not possible to provide a pooled estimate of sensitivity and specificity. We found a large variation of sensitivity (47% to 94%) and specificity (60% to 89%) among the three studies (Figure 16; Figure 17).

Figure 16. Forest plot: Diagnosis of red marks - all the studies.

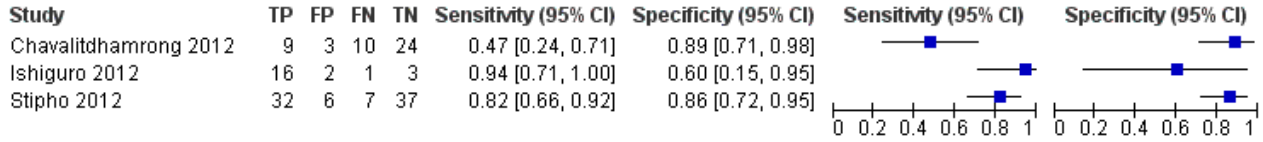
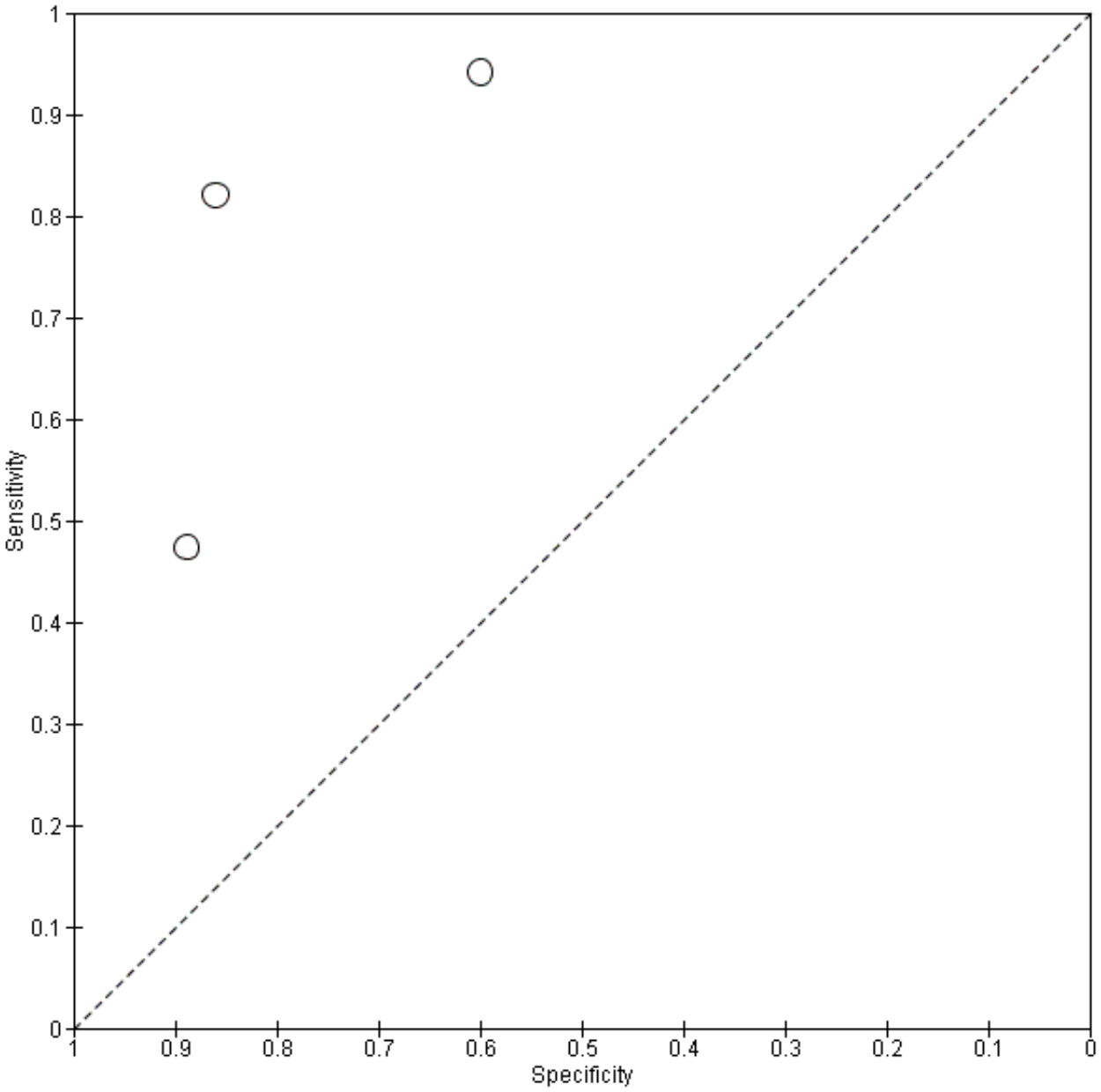


Figure 17. Studies in the receiver operating characteristic (ROC) space: Diagnosis of red marks - all the studies.



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Interobserver agreement

Four studies reported interobserver agreement of capsule endoscopy interpretation (Frenette 2008; Gerson 2008; Lapalus 2009; Chavalitdhamrong 2012). In the study by Gerson 2008, published in abstract form only, the kappa coefficient for agreement between two observers was 0.55 (95% CI 0.31 to 0.79) for the presence of any oesophageal varices, and 0.70 (95% CI 0.31 to 1.0) for the grading of varices. Frenette 2008 reported both interobserver and intraobserver agreement for detection of high-risk varices: kappa = 0.56 and kappa = 0.61 for reader 1 and kappa = 0.41 for reader 2. Lapalus 2009 reported a concordance of 79.4% between observers in the diagnosis of any oesophageal varices (kappa = 0.58), 66.4% for the grading of varices (kappa = 0.79), and 89.7% for the identification of large varices (kappa = 0.32). Chavalitdhamrong 2012 reported an interobserver agreement of kappa = 0.778 ± 0.085 for the detection of any size varices.

Adverse events

In 10 studies, participants reported some minor discomfort on swallowing the capsule (Ramirez 2005; Eisen 2006; Lapalus 2006; Groce 2007; de Franchis 2008; Frenette 2008; Gerson 2008; Pena 2008; Chavalitdhamrong 2012; Stipho 2012). Only one study identified other significant adverse events, including impaction of the capsule due to a previously unidentified oesophageal stricture in two participants (de Franchis 2008). It is interesting to note that this study excluded people with possible oesophageal stenosis or other pathologies that could impair passage of the capsule endoscopy through the oesophagus.

No adverse events were reported as a consequence of the reference standard oesophago-gastro-duodenoscopy.

Participants' preferences

Ten studies planned explicitly to test participants' preferences (Ramirez 2005; Eisen 2006; Lapalus 2006; Groce 2007; de Franchis 2008; Frenette 2008; Gerson 2008; Pena 2008; Chavalitdhamrong 2012; Stipho 2012). Nine studies, using different methodology, reported a preference for capsule endoscopy over oesophago-gastro-duodenoscopy, and one study found no preferences (Pena 2008).

DISCUSSION

Summary of main results

In this review, we aimed to determine the diagnostic accuracy of capsule endoscopy for the diagnosis of oesophageal varices in adults or children with chronic liver disease or portal vein thrombosis, when compared to the reference standard test, oesophago-gastro-duodenoscopy. All of the 16 studies included in the review were undertaken in adults in a secondary care setting, with a 63% median prevalence of varices.

There are two main indications for oesophago-gastro-duodenoscopy in people with cirrhosis, apart from the management of acute gastrointestinal bleeding: screening for oesophageal varices when the diagnosis of cirrhosis, and surveillance of people with known varices and antecedent variceal bleeding or treatment (e.g., endoscopic variceal ligation), or both. In this review, seven studies included only a screening cohort: summary statistics obtained from these studies showed that capsule endoscopy has a low sensitivity leaving more than 20% of varices undetected. Furthermore, about 15% of positive capsule endoscopy results were not confirmed at endoscopy. In these studies, the prevalence of varices ranged from 43% to 82%, and the estimates of accuracy can be considered at low risk of bias for participant selection. Hence, the heterogeneity in the results of these studies arises from sources other than different inclusion criteria. A difference in index test positivity criteria for the definition of the presence of oesophageal varices (implicit cut-off) might play a role. In fact, as shown in Figure 9, the seven studies distribute along the horizontal axis showing a wide specificity variation with an almost fixed sensitivity value, suggesting that differences of an implicit cut-off could only impair the index test specificity without any improvement of the sensitivity. Therefore, it seems unlikely that the sensitivity of capsule endoscopy could be improved enough for it to fulfil its possible role as a screening test before endoscopy adequately.

Eight studies included a mixed population of people with suspected (screening cohorts) and known oesophageal varices (surveillance cohorts). In these studies, the target disease prevalence varied (from 63% to 95%) according to the different proportion of mixing. We considered this mixed participant selection to be at high risk of bias, increasing the proportion of people with the target disease and therefore potentially overestimating the accuracy of the index test. Unfortunately, we were unable to obtain data from the authors of these studies to allow separate analysis of the two participant groups. The pooled estimate of sensitivity was 82.2% (95% CI 76.4% to 86.7%) and of specificity was 85.7% (95% CI 80% to 90%) for these studies.

To investigate whether capsule endoscopy can identify oesophageal varices at high risk of bleeding and thus requiring primary prophylaxis, some studies determined the diagnostic accuracy of capsule endoscopy for large varices. In the six studies that evaluated the accuracy of capsule endoscopy in detecting large varices, the pooled sensitivity was 73.7% (95% CI 52.4% to 87.7%) and specificity was 90.5% (95% CI 84.1% to 94.4%). As shown in Figure 15, a wide variation of the sensitivity was observed with only minimal variations of the specificity. An interpretation might be that any variation of the intrinsic cut-off in the interpretation of capsule endoscopy results could produce wide variation of the sensitivity without changes of the specificity.

Red marks on varices are another criterion of high risk for bleeding, including when associated with small varices that would then be considered for primary prophylactic therapy. Only three studies assessed the role of capsule endoscopy in detecting red marks on varices, showing very wide variations of the estimates of sensitivity and specificity.

Interobserver agreement in the interpretation of capsule endoscopy results and any adverse event attributable to capsule endoscopy were poorly assessed and reported. Participants' preferences for either capsule endoscopy or oesophago-gastro-duodenoscopy were differently evaluated and reported but seemed in favour of capsule endoscopy.

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Strengths and weaknesses of the review

Despite an extensive and thorough search, we retrieved only 16 studies with small sample sizes, of which nine were assessed with high risk of bias due to sub-optimal study design. Most studies assessed whether capsule endoscopy detected the presence of any varices, although the main clinical reason to screen for oesophageal varices is to identify people who are at high risk of bleeding and who may, therefore, benefit from primary prophylactic therapy. Only six studies assessed the accuracy of capsule endoscopy in detecting large varices. The risk of bleeding was not directly measured but instead it was implied from knowledge that larger varices and those with red marks identified by oesophago-gastro-duodenoscopy were more likely to bleed. There is currently no agreed system for reporting the appearance of varices identified by capsule endoscopy. The role of capsule endoscopy in identifying the risk of bleeding has not been studied and may differ from oesophago-gastro-duodenoscopy because there is no ability to examine changes in varices during insufflation of air.

Only six studies reported the proportion of non-evaluable results of the index test and it is not always clear whether this means that no uninterpretable results were observed in the other studies (Lapalus 2006; de Franchis 2008; Gerson 2008; Pena 2008; Chavalitdhamrong 2012; Aoyama 2014). No studies undertook analysis according to 'intention to diagnose'. In the studies that reported uninterpretable results, study participants with uninterpretable results were excluded from the analyses, possibly causing a consequent overestimation of diagnostic accuracy.

Only four studies assessed the interobserver agreement of capsule endoscopy and reported it as moderate or less than moderate.

Another relevant point is that the oesophago-gastro-duodenoscopy reference standard is not perfectly accurate and reproducible (Cales 1989; Bendtsen 1990; Winkfield 2003), impairing a true estimate of the index test accuracy.

The pooled sample is inadequate to explore possible rare adverse events; capsule impaction was observed in two participants from the same study in which oesophageal stenosis and other possible causes of obstruction were among the exclusion criteria (de Franchis 2008).

No studies have yet adequately investigated the use of capsule endoscopy for the diagnosis of oesophageal varices due to portal vein thrombosis or in children. Studies have not investigated any differences in the accuracy of capsule endoscopy for the diagnosis of oesophageal varices in people with different hepatic causes of portal hypertension.

We found only two meta-analyses about this topic (Lu 2009; Guturu 2011). They included seven and nine studies, and the accuracy estimates were similar to the ones we obtained. In both studies, authors concluded that more studies were needed to assess the capsule endoscopy accuracy better. We also retrieved some narrative reviews that also highlighted the need for more data (Ruff 2009; Rondonotti 2010). Finally, a study by White 2009 tried a decision analysis to show that capsule endoscopy was more cost effective than oesophago-gastro-duodenoscopy for the screening of oesophageal varices in people with cirrhosis, even if the differences in cost and effectiveness were small. However, no systematic review of studies was reported, making it difficult to assess the validity of clinical estimates objectively.

Applicability of findings to the review question

The accuracy of capsule endoscopy in detecting the presence of oesophageal varices has been, with the above noted limitations, addressed only in secondary or tertiary care settings and in adults with suspected cirrhosis mainly due to chronic viral hepatitis or alcoholic liver disease. We observed wide variation of the prevalence of the target condition even in studies at low risk of bias for participant selection. The applicability to other specific participant groups, such as those with cholestatic diseases, portal vein thrombosis, or children with liver disease, or in other settings with lower prevalence of the target condition is even more uncertain.

AUTHORS' CONCLUSIONS

Implications for practice

Although current guidelines recommend oesophago-gastro-duodenoscopy to screen for varices in all adults with suspected cirrhosis, there has been poor uptake of this recommendation because oesophago-gastro-duodenoscopy is invasive, unpleasant, and has a low diagnostic yield when applied to all adults with cirrhosis. Therefore, there is a pressing need for a non-invasive test that enables oesophago-gastro-duodenoscopy to be applied to a higher risk patient group. This review shows that capsule endoscopy is more acceptable to patients, but it is not sufficiently accurate to replace endoscopy for the detection of oesophageal varices. Furthermore, its sensitivity does not seem able to support a triage test role before endoscopy in order to spare the number of oesophago-gastro-duodenoscopy examinations.

Implications for research

Larger cross-sectional studies are needed for a more precise estimation of sensitivity and specificity. An agreed system for describing and reporting the appearance of varices identified by capsule endoscopy would support studies that evaluate the role of capsule endoscopy in assessing the risk of variceal bleeding and comparing it with endoscopy for the prediction of bleeding. We totally lack data in paediatric populations and in people with portal thrombosis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aoyama 2014

Study characteristics	
Patient sampling	Cross-sectional cohort (only screening cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 119 participants; 73 men, 46 women; mean age 66.9 years, range 23 to 88 years. **Baseline diagnosis:** clinically or histologically confirmed cirrhosis. Aetiology: 18 HBV; 70 HCV; 13 alcohol; 6 non-alcoholic steatohepatitis; 12 other. **Disease severity:** 56 participants were Child-Pugh score A, 56 participants were Child-Pugh score B, and 7 participants were Child-Pugh score C. **Co-morbidity:** not available. **Geographic location of the study:** Japan. **Inclusion criteria:** clinically or histologically confirmed cirrhosis with suspected bleeding from the small bowel or iron deficiency anaemia with a haemoglobin level of ≤ 12.0 g/dL, or both. **Exclusion criteria:** people with previous treatment for portal hypertension; previous bleeding.
Index tests	**Index test:** PillCam SB/SB2 video capsule (Given Imaging Ltd, Yokneam, Israel) a device planned for intestinal exploration not dedicated to the oesophagus. **Criteria for oesophageal varices:** oesophageal varices appearing as abnormally dilated longitudinal veins in the oesophagus. **Operator:** 2 interpreters, who were unaware of the participants' oesophago-gastro-duodenoscopy results, evaluated the images captured by capsule endoscopy for the presence or absence of oesophageal varices. Diagnoses were reached by consensus. The 2 interpreters had limited experience with oesophageal capsule endoscopy but much experience with capsule endoscopy (> 200 small-bowel examinations) and oesophago-gastro-duodenoscopy (> 3000 examinations).
Target condition and reference standard(s)	**Target condition:** presence of any oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** the Japanese endoscopic classification (JSPH 1980). **Prevalence of the target condition:** 43% (51/119).
Flow and timing	
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** no data on withdrawals were reported. **Side effects or complications:** no side effects or complications were described. **Type of publication:** full text.

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

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Aoyama 2014 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Chavalitdhamrong 2012

Study characteristics

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Chavalitdhamrong 2012 *(Continued)*

Patient sampling	Cross-sectional cohort (only screening cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 65 participants 43 (66.2%) men and 22 (33.8%) women. Mean age 54.6 years (range 35 to 79 years). **Baseline diagnosis:** liver disease. Aetiology: 37 HCV infection, 13 alcoholic liver disease, 5 chronic HBV infection, 4 non-alcoholic steatohepatitis, 3 autoimmune liver disease, 3 primary biliary cirrhosis. **Disease severity:** 27 participants were Child-Pugh score A, 27 participants were Child-Pugh score B, 11 participants were Child-Pugh score C. Mean MELD score of 10.6 and a mean Child-Pugh score of 7.4. **Co-morbidity:** not available. **Geographic location of the study:** USA. **Inclusion criteria:** 1. aged ≥ 18 years and < 86 years at the time of consent; 2. clinically evident or biopsy-confirmed cirrhosis; 3. no previous documented upper gastrointestinal bleeding; 4. no previous endoscopic or radiological treatments for variceal bleeding or ascites; 5. probable life expectancy of ≥ 24 months without liver transplantation and have a MELD score of ≤ 29. Oesophago-gastro-duodenoscopy was scheduled for these participants assuming that they required screening and potentially treatment. **Exclusion criteria:** 1. severe co-morbid illness; 2. cancer with less than a 24-month expected survival or cancer on active treatment with chemotherapy or radiotherapy, or a combination; 3. oesophageal motility disorder, oesophageal stricture, or oesophageal diverticulum, causing dysphagia or requiring dilation; 4. gastrointestinal obstruction or partial obstruction (by history or imaging); 5. symptomatic gastrointestinal stricture or pseudo-obstruction that may prevent passage of the capsule; or 6. potentially reversible portal hypertension such as alcoholic hepatitis, acute viral hepatitis, untreated autoimmune hepatitis or chronic HBV or HCV on viral therapy.
Index tests	**Index test:** capsule endoscopy (PillCam ESO, Given Imaging, Ltd, Yoqneam, Israel). **Criteria for oesophageal varices:** modified Japanese grading system (none, no varices seen; small, the oesophageal varices were small and non-tortuous and not compromising the lumen; medium, the oesophageal varices were tortuous, raised and occupied less than one-third of the distal oesophageal lumen; large, oesophageal varices were large, raised, tortuous, compromising the lumen, and occupied more than one-third of the distal oesophagus). **Operator:** coded capsule images were read by 2 experienced oesophageal capsule endoscopy physicians, blinded to oesophago-gastro-duodenoscopy findings.
Target condition and reference standard(s)	**Target condition:** presence of any oesophageal varices and red marks. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** standard grading for oesophageal varice was used. **Prevalence of the target condition:** 71% (46/65).
Flow and timing	**Completeness of analysis:** 9 participants not included in the analysis. Reasons for not being included in the study were as follows: 2 participants refused to swallow the capsule; 3 participants refused to participate in the oesophageal capsule endoscopy study; 1 participant vomited the capsule out after swallowing it (but had no stricture on oesophago-gastro-duodenoscopy); 3 participants swallowed the capsule but images were not recorded. These 9 participants had oesophago-gastro-duodenoscopy screening, but were not included in this comparative study.
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data were reported. **Side effects or complications:** no side effects or complications were described.

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Chavalitdhamrong 2012 *(Continued)*

Type of publication: full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval be-	Yes		

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Chavalitdhamrong 2012 *(Continued)*

tween index test and reference standard?	
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
	Low

de Franchis 2008

Study characteristics	
Patient sampling	Cross-sectional cohort study (screening cohort + surveillance cohort). Prospective, multicentre study with 11 centres.
Patient characteristics and setting	**Participants:** 288 participants (screening cohort: 195 participants; surveillance cohort: 93 participants); mean 56 years, range 21 to 81 years. Sex: not available. **Baseline diagnosis:** cirrhosis. Aetiology: 20% alcohol, 8.9% HBV, 35.0% HCV, 13.3% alcohol + HBV or HCV cirrhosis, 22.8% other (Budd-Chiari syndrome, portal vein thrombosis, etc.). **Disease severity:** Child-Pugh score A 68.8%; Child-Pugh score B 25.4%; Child-Pugh score C 5.8%. **Co-morbidity:** not available. **Geographical location of the study:** Italy, Spain, USA, and Israel. **Inclusion criteria:** ≥ aged 18 years. Signs/symptoms of portal hypertension, without previous diagnosis of oesophageal varices, with clinical indication for screening endoscopy for the detection of varices, or with prior endoscopic diagnosis of oesophageal varices and indication for surveillance endoscopy. **Exclusion criteria:** dysphagia, Zenker's diverticulum, previous endoscopic treatment of oesophageal varices, known or suspected intestinal obstruction, cardiac pacemakers or other implanted electro-medical devices, pregnancy, planned magnetic resonance imaging examination within 7 days after ingestion of the capsule, prior abdominal surgery of the gastrointestinal tract (other than uncomplicated appendectomy or uncomplicated cholecystectomy), any condition that precluded compliance with study or device instructions (or both), life-threatening conditions and current participation in another clinical study.
Index tests	**Index test:** capsule endoscopy (PillCam ESO, Given Imaging, Ltd., Yoqneam, Israel). **Criteria for oesophageal varices:** small varices occupying < 25% of the circumference and large varices occupying > 25%. **Operator:** experienced capsule endoscopist, blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any oesophageal and large oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Prevalence of the target condition:** 63% (180/288 participants). 79 with large oesophageal varices.

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de Franchis 2008 *(Continued)*

Flow and timing	2 participants were withdrawn from the study. 1 due to "loss of capsule endoscopy recording" and 1 for unsuspected oesophageal stricture.
Comparative	
Notes	**Observer variation:** no data on observer variation reported. **Uninterpretable results:** data were reported. **Side effects or complications:** side effects or complications: overall, 4 (1.4%) adverse events were reported within the study. 1 episode of severe pain occurred with oesophago-gastro-duodenoscopy and improved within 1 week. 3 adverse events occurred with the capsule: 1 episode of diarrhoea that resolved spontaneously within 24 hours, 1 episode of nausea with capsule retention due to an unsuspected oesophageal stricture requiring removal of the capsule by oesophago-gastro-duodenoscopy, and 1 episode of vomiting caused by capsule retention due to an unsuspected oesophageal stricture (the capsule was passed by mouth by vomiting). **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

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de Franchis 2008 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Donnelly 2006

Study characteristics	
Patient sampling	Cross-sectional cohort study (screening cohort + surveillance cohort). Prospective, single-centre study.
Patient characteristics and setting	**Participants:** 8 participants (screening cohort: 4 participants; surveillance cohort: 4 participants); 5 males and 3 females; age not reported. **Baseline diagnosis:** aetiology: 5 alcohol, 1 HCV, 1 non-alcoholic fatty liver disease, 1 primary sclerosing cholangitis. **Disease severity:** not available. **Co-morbidity:** not available. **Geographical location of the study:** UK. **Inclusion criteria:** people with chronic liver disease with suspected or previously documented oesophageal varices. **Exclusion criteria:** not reported.
Index tests	**Index test:** capsule endoscopy (PillCam ESO). **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Operator:** 2 investigators without information about their expertise. Blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any oesophageal varices.

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Donnelly 2006 *(Continued)*

	Reference standard: oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** not reported. **Prevalence of the target condition:** 63% (5/8 participants).
Flow and timing	
Comparative	
Notes	**Observer variation:** data on interobserver variation not reported. **Uninterpretable results:** no data were reported. **Side effects or complications:** no side effects or complications were described. **Type of publication:** abstract.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			

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Donnelly 2006 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Eisen 2006

Study characteristics	
Patient sampling	Cross-sectional cohort study design (screening cohort + surveillance cohort). Prospective, 3-centre study.
Patient characteristics and setting	**Participants:** 32 participants (screening cohort: 10 participants; surveillance cohort: 22 participants) mean age 57.2 ± 8 years. 20 men. **Baseline diagnosis:** not available. **Disease severity:** not available. **Co-morbidity:** not available. **Geographical location of the study:** Italy, Israel, USA. **Inclusion criteria:** aged ≥ 18 years with prior endoscopic confirmation of oesophageal varices or clinically suspect portal hypertension. **Exclusion criteria:** history of current or prior dysphagia; known Zenker's diverticulum; known or suspected intestinal obstruction; pregnancy; history of abdominal surgery of the gastrointestinal tract (other than uncomplicated cholecystectomy or appendectomy); the presence of a cardiac pacemaker or any other implanted electro-medical device; and any condition that precluded compliance with the study or the PillCam ESO instructions (or both).
Index tests	**Index test:** capsule endoscopy (PillCam ESO). **Criteria for oesophageal varices:** the Japanese endoscopic classification (JSPH 1980). **Operator:** no information of the operator expertise or number. Blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** the Japanese endoscopic classification (JSPH 1980). **Operator:** no information of the operator expertise or number. Blinded from the index test. **Prevalence of the target condition:** 72% (23/32 participants).
Flow and timing	
Comparative	

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Eisen 2006 *(Continued)*

Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** no data were reported. **Side effects or complications:** no side effects or complications were described. **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

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Eisen 2006 *(Continued)*

Were all patients included in the analysis?	Yes
	Low

Frenette 2008

Study characteristics	
Patient sampling	Cross-sectional cohort (screening cohort + surveillance cohort) a single tertiary centre.
Patient characteristics and setting	**Participants:** 50 participants (34 men), mean age 58 years, range 25 to 74 years **Baseline diagnosis:** aetiology: 24 HCV, 7 HCV + alcohol, 6 alcohol, 6 non-alcoholic steatohepatitis, 27 other. **Disease severity:** mean MELD1 9.48, range 6 to 23; mean Child-Pugh score 6.8, range 5 to 13). **Co-morbidity:** not available **Geographical location of the study:** USA **Inclusion criteria:** consecutive participants for oesophageal varice screening, i.e., people with clinical or histologically confirmed cirrhosis or for oesophageal varice surveillance, i.e., people who had previously been diagnosed with oesophageal varices via oesophago-gastro-duodenoscopy and were repeating the test to assess for progression of varices. People who had previously undergone banding of oesophageal varices were included in the study if they were stable and had not had a variceal haemorrhage for ≥ 6 months. **Exclusion criteria:** dysphagia, known Zenker's diverticulum, the presence of cardiac pacemaker or other implantable electro-medical devices, pregnancy or a scheduled magnetic resonance imaging within 7 days after capsule ingestion. People also were excluded if they had a history of or risk for intestinal obstruction, including any prior abdominal surgery of the gastrointestinal tract other than uncomplicated cholecystectomy or appendectomy.
Index tests	**Index test:** capsule endoscopy without further specification. **Criteria for oesophageal varices:** high-risk varices according to the North Italian Endoscopic Club (NIEC 1988). **Operator:** capsule endoscopies were read by 2 separate investigators, who were blinded to oesophago-gastro-duodenoscopy findings, patient medical history and reading of the other investigator. Both capsule readers had prior experience in endoscopic evaluation and diagnosis of oesophageal varices. Prior to the study, both readers underwent training as recommended by the capsule manufacturer, consisting of review of a CD ROM and participation in an online course, which included review of 10 cases of capsule endoscopy. Each capsule endoscopy was read twice by each investigator on 2 separate occasions at least 60 days apart. Capsule images were evaluated for the presence and grade of oesophageal varices according to the same scale for oesophago-gastro-duodenoscopy. Intra- and inter-rater were assessed.
Target condition and reference standard(s)	**Target condition:** presence of high-risk or oesophageal varices requiring treatment. **Reference standard:** oesophago-gastro-duodenoscopy on the same day or within 72 hours graded by: F0, no varices; F1, small straight varices; F2, tortuous varices and < 50% of oesophageal radius; F3, large and tortuous varices with or without red spots. Presence or absence of high-risk stigmata, defined as neovascularisation or red or white spots was noted separately. Each observer decided whether treatment was indicated based on presence of F2 or F3 varices or the presence of high-risk stigmata on any size varix. The hepatologists were blinded to the results of the capsule endoscopy, but not to the participant's history or previous endoscopy findings.

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Frenette 2008 *(Continued)*

	Prevalence of the target condition: high-risk varices 34% (17/50 participants); any varices 66% (33/50 participants).
Flow and timing	55 participants were screened to participate in the study. 0 participants withdrawn from the study. 5 participants were not included: 2 participants refused, 1 participant had a history of an oesophageal stricture, 2 participants had history of surgery on the gastrointestinal tract.
Comparative	
Notes	**Observer variation:** data on observer variation were reported (inter-rater agreement kappa = 0.56; intra-rater agreement: kappa = 0.61 for reader 1 and kappa = 0.41 for reader 2). **Uninterpretable results:** data were reported **Side effects or complications:** side effects or complications were described. 5 participants (10%) had a mild amount of difficulty swallowing the capsule, and 4 participants (8%) had a moderate amount of difficulty, 1 of whom had to swallow it in a sitting position. **Type of publication:** full text.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**

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Frenette 2008 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Gerson 2008

Study characteristics	
Patient sampling	Cross-sectional cohort (only screening cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 24 participants. Mean age 52 ± 8.4 years, range 36 to 70 years. 14 (58%) were men. **Baseline diagnosis:** aetiology: 19 (79%) HCV. No other diagnostic information was provided. **Disease severity:** 17 (71%) Child-Pugh score B. No other information was provided. **Co-morbidity:** not available. **Geographical location of the study:** not available. **Inclusion criteria:** people awaiting liver transplantation scheduled for oesophago-gastro-duodenoscopy. **Exclusion criteria:** not available.

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Gerson 2008 *(Continued)*

Index tests	**Index test:** capsule endoscopy (PillCam ESO). **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Operator:** 2 faculty experts, blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Prevalence of the target condition:** 50% (12/24 participants).
Flow and timing	From 39 invited participants to participate, 24 were enrolled. No information about the reasons for the declinations.
Comparative	
Notes	**Observer variation:** data on observer variation were reported (kappa = 0.55). **Uninterpretable results:** data were not reported. **Side effects or complications:** no side effects or complications were described. **Type of publication:** abstract.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			

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Gerson 2008 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

Groce 2007

Study characteristics	
Patient sampling	Cross-sectional cohort (only screening cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 21 participants. No age or sex were provided. **Baseline diagnosis:** cirrhosis. **Disease severity:** not available. **Co-morbidity:** not available. **Geographical location of the study:** not available. **Inclusion criteria:** people with cirrhosis without previous oesophageal varices screening or history of previous gastrointestinal bleeding. **Exclusion criteria:** not available.
Index tests	**Index test:** capsule endoscopies without further specification. **Criteria for oesophageal varices:** not available. **Operator:** no information of the operator expertise or number. Blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** not available. **Prevalence of the target condition:** 43% (9/21 participants)
Flow and timing	1 participant was unable to swallow the capsule and was not included.

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Groce 2007 *(Continued)*

	1 uninterpretable result was reported and classified as false negative.
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data were reported (1 participant with uninterpretable result was included in the analysis). **Side effects or complications:** data on side effects were reported. 13% of participants experienced moderate or severe difficulty swallowing capsule endoscopy and 10% experienced moderate-severe discomfort with the capsule endoscopy. **Type of publication:** abstract.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

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Groce 2007 *(Continued)*

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Ishiguro 2012

Study characteristics	
Patient sampling	Cross-sectional cohort (screening cohort + surveillance cohort); prospective single-centre study
Patient characteristics and setting	**Participants:** 29 participants (19 screening, 10 surveillance). 1 person excluded because the capsule did not reach the oesophago-gastric junction. 9 men, mean age 66 ± 6.6 years. **Baseline diagnosis:** aetiology: 5 HCV, 4 alcohol, 1 primary biliary cirrhosis, 17 hepatocellular carcinoma, 2 other. **Disease severity:** 14 Child-Pugh score A, 14 Child-Pugh score B, 1 Child-Pugh score C. **Inclusion criteria:** aged ≥ 18 years, prior endoscopic confirmation of oesophageal varice and currently under clinical surveillance, or suspected portal hypertension with current endoscopic screening for oesophageal varice. **Exclusion criteria:** history of (or current) dysphagia; known oesophageal diverticulum; known or suspected intestinal obstruction; pregnancy; history of gastrointestinal surgery other than uncomplicated cholecystectomy or appendectomy; having an implanted cardiac pacemaker or any other electro-medical device and any condition that might preclude compliance with the study or the PillCam ESO instructions, or both.
Index tests	**Index test:** endoscopic capsule. PillCam ESO; Given Imaging, Yokneam, Israel. **Criteria for oesophageal varices:** Japanese endoscopic classification system. **Operator:** 3 experienced endoscopists who were blinded to each participant's history, with the exception of liver cirrhosis.
Target condition and reference standard(s)	**Target condition:** presence of any and large oesophageal varices. Presence of red marks. **Reference standard:** oesophago-gastroduo-denoscopy. **Criteria for oesophageal varices:** oesophageal varices were recorded according to the general rules of the Japanese Society for Portal Hypertension. Endoscopic signs predictive of oesophageal varice bleeding comprised moderate or large (F2 or F3) blue varices with marked red signs (RC2 or RC3) on their surface. **Prevalence of the target condition:** 79% (22/28 participants).
Flow and timing	1 participant was not included in the analysis due to uninterpretable result (the capsule did not reach oesophago-gastric junction).
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data were reported. **Side effects or complications:** no side effects or complications were described.

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Ishiguro 2012 *(Continued)*

Type of publication: full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		

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Ishiguro 2012 *(Continued)*

	High

Lapalus 2006

Study characteristics	
Patient sampling	Cross-sectional (only screening cohort); prospective cohort single-centre study. Included both inpatients and outpatients.
Patient characteristics and setting	**Participants:** 21 participants. Mean age 62 years, range 49 to 79 years. Sex: not available. **Baseline diagnosis:** cirrhosis. Aetiology: 5 HCV infection, 15 alcohol, 2 autoimmune hepatitis, 1 non-alcoholic steatohepatitis, 1 haemochromatosis. **Disease severity:** Mean MELD score 10.5 and mean Child-Pugh score 7.3. Child-Pugh score A 62%; Child-Pugh score B 28%; Child-Pugh score C 10%. **Co-morbidity:** not available. **Geographical location of the study:** France **Inclusion criteria:** people with recently diagnosed cirrhosis. **Exclusion criteria:** people aged < 18 years, pregnant, people with known or suspected gastrointestinal obstruction or strictures, people with a cardiac pacemaker or other implanted electro-medical devices, people with swallowing disorders or dysphagia, people who had previously received endoscopic or surgical oesophageal treatment.
Index tests	**Index test:** capsule endoscopy (PillCam ESO). **Criteria for oesophageal varices:** conventional oesophago-gastro-duodenoscopy grading system. **Operator:** 1 experienced capsule endoscopist, blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** not available. **Prevalence of the target condition:** 80% (16/20 participants).
Flow and timing	1 participant was unable to swallow the capsule and was not included in the analysis.
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data were reported. **Side effects or complications:** data on side effects were reported. 10% of participants experienced difficulties in swallowing capsule endoscopy. **Type of publication:** full text.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

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Lapalus 2006 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Lapalus 2009

Study characteristics

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Lapalus 2009 *(Continued)*

Patient sampling	Cross-sectional cohort (only screening cohort); prospective 9-centre study. Included inpatients and outpatients.
Patient characteristics and setting	**Participants:** 120 participants. Mean age 58 years, range 23 to 84 years. 72 (60%) men. However, only 113 participants were analysed (participants who had PillCam ESO). **Baseline diagnosis:** cirrhosis. Aetiology: 17 HCV, 78 alcohol, 14 non-alcoholic steatohepatitis, 9 other causes. **Disease severity:** Child-Pugh score A 48%, Child-Pugh score B 30%, Child-Pugh score C 22%. Mean Child-Pugh score 7.4. Mean MELD score 11.5. Portal hypertension was related to cirrhosis in 113 participants. **Co-morbidity:** not available. **Geographical location of the study:** France. **Inclusion criteria:** people with recently diagnosed cirrhosis. **Exclusion criteria:** aged < 18 years, pregnant, people with known or suspected gastrointestinal obstruction or strictures, people with cardiac pacemaker or other implanted electro-medical devices, people with swallowing disorders or dysphagia, people with previous endoscopic or surgical oesophageal treatment. Representative spectrum? Yes. "Recently diagnosed cirrhosis" and aetiology of liver diseases were described. "All the patients had their procedure performed for screening purpose."
Index tests	**Index test:** capsule endoscopy (PillCam ESO). **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Operator:** 2 independent experienced endoscopists. Blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** any and large oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Prevalence of the target condition:** 63% (71/113 participants).
Flow and timing	Capsule endoscopy procedure was feasible in 113/120 (94%) participants. 7 people were not included in the analysis due to uninterpretable results.
Comparative	
Notes	**Observer variation:** data on observer variation were reported. Kappa for detection of varices = 0.582 in only 107 participants (lost for 6 participants). **Uninterpretable results:** data were reported. **Side effects or complications:** no severe side effects or complications were observed. **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

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Lapalus 2009 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Pena 2008

Study characteristics

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Pena 2008 *(Continued)*

Patient sampling	Cross-sectional cohort (screening cohort + surveillance cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 20 participants (8 for screening; 12 for surveillance, of which 9 previous banding). Mean age 50.7 years, range 34 to 61 years. 14 (70%) men. **Baseline diagnosis:** cirrhosis. Aetiology: 25% HCV; 30% non-alcoholic steatohepatitis; 10% alcoholic; 35% combination. **Disease severity:** mean Child-Pugh score 7.9, range 5 to 12. Mean MELD score 12.9, range 7 to 25. **Co-morbidity:** not available. **Geographical location of the study:** USA. **Inclusion criteria:** aged > 18 years with cirrhosis. **Exclusion criteria:** unable to give informed consent; evidence of active gastrointestinal bleeding, or known or suspected obstruction, stricture or fistula of the gastrointestinal tract; implanted electro-medical devices; difficulty swallowing.
Index tests	**Index test:** capsule endoscopy without any further specification. **Criteria for oesophageal varices:** based on estimation of size: small, medium, large, very large. **Operator:** no previous experience with capsule endoscopy. Blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Prevalence of the target condition:** 95% (19/20 participants).
Flow and timing	13 people declined to participate and 3 were excluded due to inability to obtain consent. Unreliable results: 2 participants who were included in the analysis.
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data were reported. **Side effects or complications:** data on side effects were described. The post-study analogue scale showed a greater level of anxiety before oesophago-gastro-duodenoscopy (mean 2.75/10) versus capsule endoscopy (mean 1.5/10). **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

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Pena 2008 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Ramirez 2005

Study characteristics	
Patient sampling	Cross-sectional cohort (screening cohort + surveillance cohort); prospective single-centre study.

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Ramirez 2005 *(Continued)*

Patient characteristics and setting	**Participants:** 30 participants (11 for screening, 19 for surveillance). Mean age 54.4 years, range 43 to 69 years. 30 (100%) men. Outpatients only. **Baseline diagnosis:** cirrhosis. Aetiology: 14 HCV, 8 alcohol, 7 alcohol + HCV; 1 cryptogenic. **Disease severity:** mean MELD score 12.5; mean Child-Pugh score 6.3. **Co-morbidity:** not available. **Geographical location of the study:** USA. **Inclusion criteria:** cirrhosis. People scheduled for oesophago-gastro-duodenoscopy for screening or surveillance of oesophageal varice. **Exclusion criteria:** not available.
Index tests	**Index test:** string wireless capsule endoscopy (device was modified attaching a string to control movement up and down the oesophagus). **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Operator:** 1 experienced endoscopist, but no information about experience with index test. Blinded from the reference standard.
Target condition and reference standard(s)	**Target condition:** oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** other classification, adequately described and logically defined. **Prevalence of the target condition:** 83% (25/30 participants).
Flow and timing	Reference standard and index test timing: variable. 20 participants were at the same day, 3 within 24 hours, 2 within 14 days, 1 within 1 month, 4 after 1 month.
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** uninterpretable results were not reported. **Side effects or complications:** data on side effects or complications were reported. The string wireless capsule was deemed to be easy or mildly difficult to swallow by 79.3% (23/29) of participants, moderately difficult by 17.2% (5/29), very difficult by 3.5% (1/29). Pulling the string capsule out of the oesophagus caused no or minimal discomfort in 82.8% (24/29) and moderate discomfort in 17.2% (5/29). **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

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Ramirez 2005 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	No		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		High	

Schreibman 2011

Study characteristics	
Patient sampling	Cross-sectional cohort (screening cohort + surveillance cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 37 participants (18 screening, 19 surveillance); 28 male, mean age 56 years (range 21 to 78 years)

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Schreibman 2011 *(Continued)*

	Baseline diagnosis: aetiology: 11 alcohol; 8 non-alcoholic steatohepatitis; 7 HCV; 5 alcohol + HCV; 6 other **Disease severity:** Child-Pugh score A 23; Child-Pugh score B 9; Child-Pugh score C 5. **Co-morbidity:** not available. **Geographical location of the study:** USA. **Inclusion criteria:** men aged > 18 years, or women aged > 18 years with a negative pre-procedure pregnancy test or of non-reproductive potential; inpatient or outpatient; able to provide informed consent. **Exclusion criteria:** 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 electro-medical device; suspected or known Crohn's disease, presence of ileostomy.
Index tests	**Index test:** capsule endoscopy (PillCam ESO) **Criteria for oesophageal varices:** according to the North Italian Endoscopic Club (NIEC 1988). **Operator:** blinded investigator and assessed using the same criteria.
Target condition and reference standard(s)	**Target condition:** any and large oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** as defined by the New Italian Endoscopic Club (NIEC 1988). **Prevalence of the target condition:** 91% (31/34 participants).
Flow and timing	Uninterpretable results: 3 cases not included in the analysis (in 2 participants, no capsule results were obtained due to capsule malfunction and inappropriate connection of the transmitter. In 1 participant, the capsule did not remain in the oesophagus long enough to provide adequate images).
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** 3 cases not included in the analysis. **Side effects or complications:** no side effects or complications were described. **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

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Schreibman 2011 *(Continued)*

Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Sharma 2009

Study characteristics	
Patient sampling	Cross-sectional cohort (only screening cohort); prospective single-centre study.
Patient characteristics and setting	**Participants:** 34 participants with end-stage liver disease. **Baseline diagnosis:** not reported. **Disease severity:** not reported. **Co-morbidity:** not reported. **Geographical location of the study:** not reported.

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Sharma 2009 *(Continued)*

	Inclusion criteria: not reported. **Exclusion criteria:** not reported.
Index tests	**Index test:** oesophageal capsule endoscopy without any further specification. **Criteria for oesophageal varices:** not reported. **Operator:** performed by ESO-trained gastroenterologists.
Target condition and reference standard(s)	**Target condition:** presence of any and large oesophageal varices. **Reference standard:** oesophago-gastro-duodenoscopy. **Criteria for oesophageal varices:** not reported. **Prevalence of the target condition:** 82% (28/34 participants).
Flow and timing	
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data on uninterpretable results were not reported. **Side effects or complications:** no side effects or complications with ESO were described. 4 minor events with oesophago-gastro-duodenoscopy (hypotension, hypoxia, and possible aspiration). **Type of publication:** abstract.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	Yes		
		Low	**High**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			

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Sharma 2009 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Stipho 2012

Study characteristics	
Patient sampling	Cross-sectional cohort (screening cohort + surveillance cohort); perspective single-centre study.
Patient characteristics and setting	**Participants:** 100 participants with cirrhosis (33 screening; 67 surveillance), 99 male; mean age 55.9 years. **Baseline diagnosis:** aetiology HCV alcohol alone or in combination in 91 participants. **Disease severity:** mean Child-Pugh score 5.9; mean MELD 10.8. **Co-morbidity:** not reported. **Geographical location of the study:** USA. **Inclusion criteria:** people with clinically or biopsy-confirmed cirrhosis (or both) scheduled to undergo oesophago-gastro-duodenoscopy for screening or surveillance purposes. **Exclusion criteria:** not reported.
Index tests	**Index test:** capsule endoscopy. String capsule endoscopy was carried out by using the small bowel capsule endoscopy device (PillCam SB; Given Imaging Ltd, Yoqneam, Israel) to which a tethering device consisting of a sleeve and strings was attached. **Criteria for oesophageal varices:** according to the North Italian Endoscopic Club (NIEC 1988). **Operator:** an endoscopist blinded to the oesophago-gastro-duodenoscopy results.
Target condition and reference standard(s)	**Target condition:** presence of any oesophageal varices and red marks. **Reference standard:** oesophago-gastro-duodenoscopy.

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Stipho 2012 *(Continued)*

	Criteria for oesophageal varices: according to the North Italian Endoscopic Club (NIEC 1988). **Prevalence of the target condition:** 82% (82/100 participants).
Flow and timing	
Comparative	
Notes	**Observer variation:** no data on observer variation were reported. **Uninterpretable results:** data on uninterpretable were not reported. **Side effects or complications:** no side effects or complications were described. **Type of publication:** full text.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study enrol only patients with suspected oesophageal varices not until diagnosed?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	**Low**
DOMAIN 4: Flow and Timing			

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Stipho 2012 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

HBV: hepatitis B virus; HCV: hepatitis C virus; MELD: model for end-stage liver disease.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
de Franchis 2005	Full manuscript was added; therefore, we excluded the abstract study.
Delvaux 2008	Aim was not for diagnostic test for oesophageal varices, it was for any oesophageal disease. No 2 x 2 table.
Ganc 2010	Different aim of the study: to detect with endocapsule small bowel lesions in people with portal hypertension due to schistosomiasis.
Ishiguro 2008	Full manuscript was added; therefore, we excluded the abstract study.
Matheus 2006	Only half of the participants have the reference standard test available for comparison of the index test within 1 year. No 2 x 2 table.
Muhammad 2006	Lack of information of the results, including 2 x 2 table, participants characteristics, reference standard, index test, etc.
Wigg 2011	Not possible to extract data for 2 x 2 table.

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Any varices - All the studies	15	936
2 Any varices - only string capsule	2	130
3 Any varices - studies at low risk of bias for QUADAS-2 'patient selection' domain	7	396
4 Any varices - studies at low risk of bias for QUADAS-2 'flow and timing' domain	9	687

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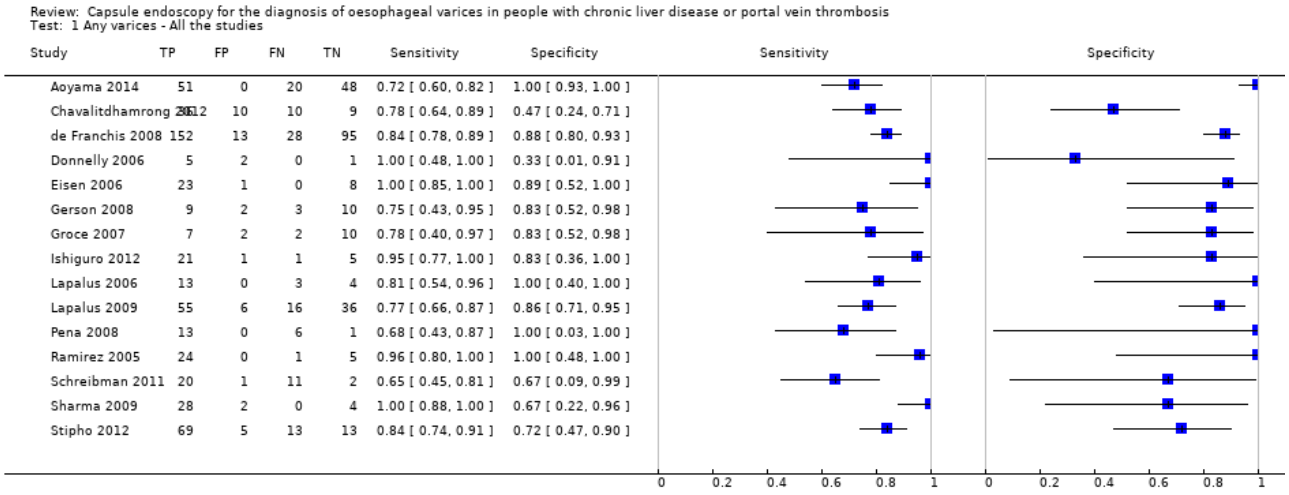
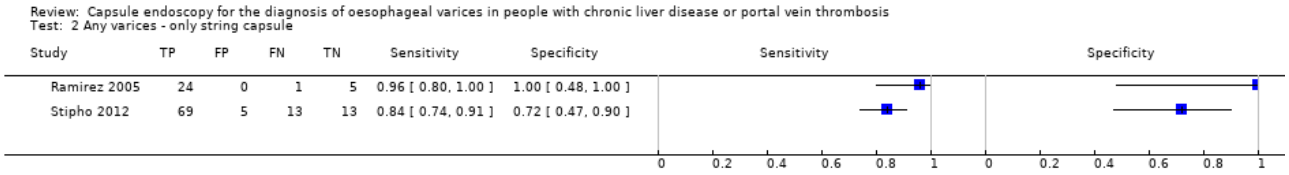
Test	No. of studies	No. of participants
5 Any varices - only full-text studies	11	849
6 Large varices - all the studies	6	537
7 Red marks - all the studies	3	150

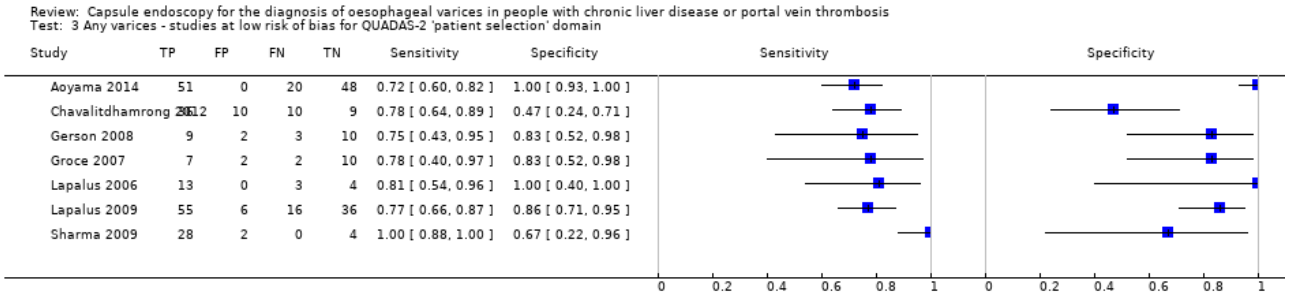
Test 1. Any varices - All the studies.



Test 2. Any varices - only string capsule.



Test 3. Any varices - studies at low risk of bias for QUADAS-2 'patient selection' domain.



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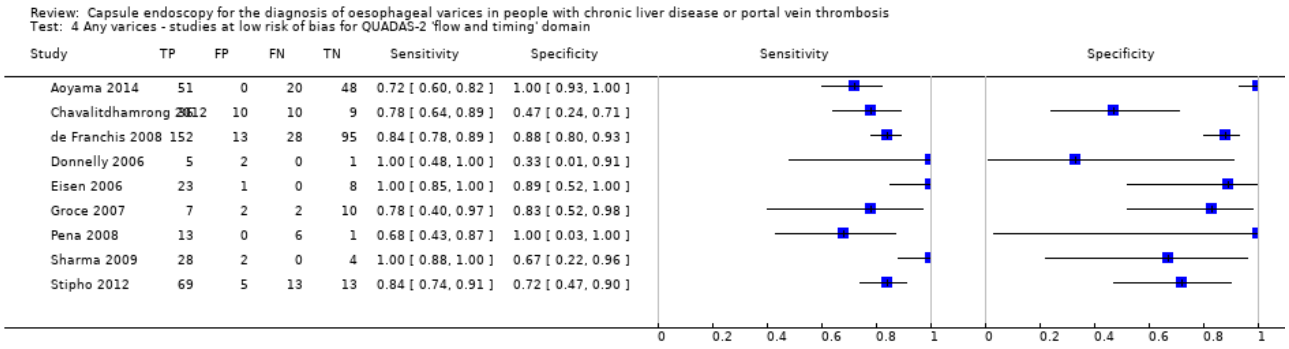
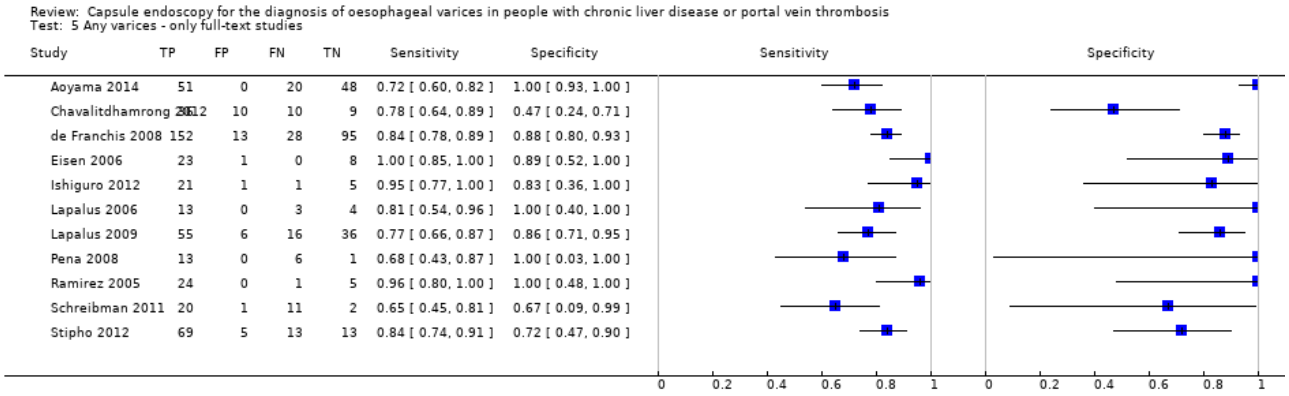
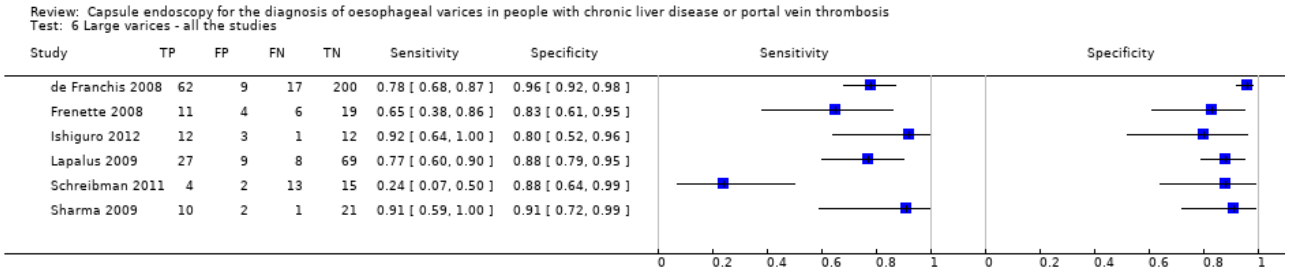
Test 4. Any varices - studies at low risk of bias for QUADAS-2 'flow and timing' domain.



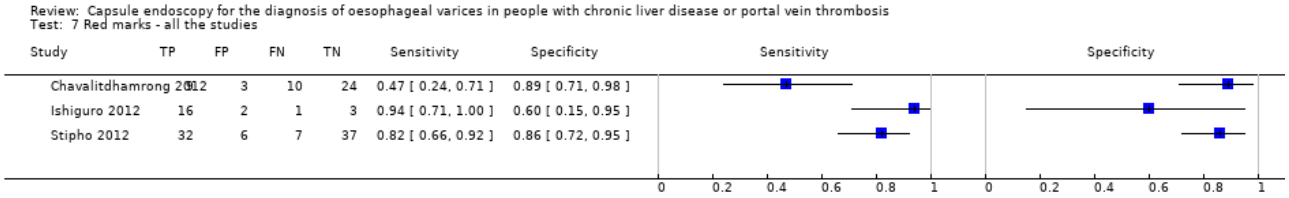
Test 5. Any varices - only full-text studies.



Test 6. Large varices - all the studies.



Test 7. Red marks - all the studies.



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APPENDICES

Appendix 1. Search strategies

Appendix A

Capsule Endoscopy

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register	October 2013	(*esophag* AND vari* AND (capsule* AND (enteroscop* OR endoscop* OR *esophagoscop* or pillcam or endocapsule or microcam or 'video capsule*' or videocapsule*)
MEDLINE (Ovid SP)	1950 to October 2013	#1 (esophag* varic* or esophag* varix or esophago gastric varic* or esophago gastric varix or gastro esophag* varic* or gastro esophag* varix or gastro oesophag* varic* or gastro oesophag* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic* or gastrooesophag* varix or oesophag* varic* or oesophag* varix or oesophago gastric varic* or oesophago gastric varix or paraesophag* varic* or paraesophag* varix or paraoesophag* varic* or paraoesophag* varix or periesophag* varic* or periesophag* varix or perioesophag* varic* or perioesophag* varix).mp. #2 "Esophageal and Gastric Varices"/ #3 2 or 1 #4 (capsule enteroscop* or enteroscop* capsule* or capsule endoscop* or endoscop* capsule* or capsule esophagoscop* or capsule oesophagoscop* or esophag* capsule* or oesophag* capsule* or pillcam or endocapsule or microcam or video capsule* or videocapsule*).mp. #5 4 and 3
EMBASE (Ovid SP)	1980 to October 2013	#1 (esophag* varic* or esophag* varix or esophago gastric varic* or esophago gastric varix or gastro esophag* varic* or gastro esophag* varix or gastro oesophag* varic* or gastro oesophag* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic* or gastrooesophag* varix or oesophag* varic* or oesophag* varix or oesophago gastric varic* or oesophago gastric varix or paraesophag* varic* or paraesophag* varix or paraoesophag* varic* or paraoesophag* varix or periesophag* varic* or periesophag* varix or perioesophag* varic* or perioesophag* varix).mp. #2 "Esophageal and Gastric Varices"/ #3 2 or 1 #4 (capsule enteroscop* or enteroscop* capsule* or capsule endoscop* or endoscop* capsule* or capsule esophagoscop* or capsule oesophagoscop* or esophag* capsule* or oesophag* capsule* or pillcam or endocapsule or microcam or video capsule* or videocapsule*).mp. #5 4 and 3
ACP Journal Club (Ovid SP)	1991 to October 2013	#1 (esophag* varic* or esophag* varix or esophago gastric varic* or esophago gastric varix or gastro esophag* varic* or gastro esophag* varix or gastro oesophag* varic* or gastro oesophag* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic* or gastrooesophag* varix or oesophag* varic* or oesophag* varix or oesophago gastric varic* or oesophago gastric varix or paraesophag* varic* or paraesophag* varix or paraoesophag* varic* or paraoesophag* varix or periesophag* varic* or periesophag* varix or perioesophag* varic* or perioesophag* varix).mp. #2 "Esophageal and Gastric Varices"/ #3 2 or 1

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		#4 (capsule enteroscop* or enteroscop* capsule* or capsule endoscop* or endoscop* capsule* or capsule esophagoscop* or capsule oesophagoscop* or esophag* capsule* or oesophag* capsule* or pillcam or endocapsule or microcam or video capsule* or videocapsule*).mp. #5 4 and 3
Database of Abstracts of Reviews of Effects (DARE) (Ovid SP)	Third quarter 2013	#1 (esophag* varic* or esophag* varix or esophago gastric varic* or esophago gastric varix or gastro esophag* varic* or gastro esophag* varix or gastro oesophag* varic* or gastro oesophag* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic* or gastrooesophag* varix or oesophag* varic* or oesophag* varix or oesophago gastric varic* or oesophago gastric varix or paraesophag* varic* or paraesophag* varix or paraoesophag* varic* or paraoesophag* varix or periesophag* varic* or periesophag* varix or perioesophag* varic* or perioesophag* varix).mp. #2 "Esophageal and Gastric Varices"/ #3 2 or 1 #4 (capsule enteroscop* or enteroscop* capsule* or capsule endoscop* or endoscop* capsule* or capsule esophagoscop* or capsule oesophagoscop* or esophag* capsule* or oesophag* capsule* or pillcam or endocapsule or microcam or video capsule* or videocapsule*).mp. #5 4 and 3
Health Technology Assessment (HTA) (Ovid SP)	Third quarter 2013	#1 (esophag* varic* or esophag* varix or esophago gastric varic* or esophago gastric varix or gastro esophag* varic* or gastro esophag* varix or gastro oesophag* varic* or gastro oesophag* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic* or gastrooesophag* varix or oesophag* varic* or oesophag* varix or oesophago gastric varic* or oesophago gastric varix or paraesophag* varic* or paraesophag* varix or paraoesophag* varic* or paraoesophag* varix or periesophag* varic* or periesophag* varix or perioesophag* varic* or perioesophag* varix).mp. #2 "Esophageal and Gastric Varices"/ #3 2 or 1 #4 (capsule enteroscop* or enteroscop* capsule* or capsule endoscop* or endoscop* capsule* or capsule esophagoscop* or capsule oesophagoscop* or esophag* capsule* or oesophag* capsule* or pillcam or endocapsule or microcam or video capsule* or videocapsule*).mp. #5 4 and 3
NHS Economic Evaluation Database (NHSEED)	Third quarter 2013	#1 (esophag* varic* or esophag* varix or esophago gastric varic* or esophago gastric varix or gastro esophag* varic* or gastro esophag* varix or gastro oesophag* varic* or gastro oesophag* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic* or gastrooesophag* varix or oesophag* varic* or oesophag* varix or oesophago gastric varic* or oesophago gastric varix or paraesophag* varic* or paraesophag* varix or paraoesophag* varic* or paraoesophag* varix or periesophag* varic* or periesophag* varix or perioesophag* varic* or perioesophag* varix).mp. #2 "Esophageal and Gastric Varices"/ #3 2 or 1 #4 (capsule enteroscop* or enteroscop* capsule* or capsule endoscop* or endoscop* capsule* or capsule esophagoscop* or capsule oesophagoscop* or esophag* capsule* or oesophag* capsule* or pillcam or endocapsule or microcam or video capsule* or videocapsule*).mp. #5 4 and 3
Science Citation Index Expanded	1955 to October 2013	#1 TS=(esophag* varic* OR esophag* varix OR esophago gastric varic* OR esophago gastric varix OR gastro esophag* varic* OR gastro esophag* varix OR gastro oesophag* varic* OR gastro oesophag* varix OR gastroesophag* varic* OR gastroesophag* varix OR gastrooesophag* varic* OR gastrooesophag* varix OR oesophag* varic* OR oesophag* varix OR oesophago gastric varic* OR oesophago gastric varix OR paraesophag* varic* OR paraesophag* varix

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OR paraoesophag* varic* OR paraoesophag* varix OR periesophag* varic* OR periesophag* varix OR perioesophag* varic* OR perioesophag* varix)
#2 TS=(capsule enteroscop* OR enteroscop* capsule* OR capsule endoscop* OR endoscop* capsule* OR capsule esophagoscop* OR capsule oesophagoscop* OR esophag* capsule* OR oesophag* capsule* OR pillcam OR endocapsule OR microcam OR video capsule* OR videocapsule*)
#3 #2 AND #1

Appendix 2. QUADAS-2

Domain	1. Participant selection	2. Index test	3. Reference standard	4. Flow and timing
Signalling questions and criteria	Q.1: "*Was a consecutive or random sample of participants enrolled?*" Yes - If the study reports on a consecutive or a random selection of participants. No - if the study reports on another form of selection of participants. Unclear - if the study does not report on how the participants were enrolled. Q.2: "*Was a case-control design avoided?*" Yes - if the case-control design was avoided. No - if the study was a case-control. Unclear - if the study design was not clear. Q.3: "*Did the study avoid inappropriate exclusions*?" Yes - if the study definition of exclusion criteria are appropriate (i.e., concerning the risk of capsule impact) and all exclusions are reported. No - if exclusion criteria are inappropriate and exclusions are not reported. Unclear - if the study does not report causes of exclusions. Q.4: "*Did the study enrol only participants with suspected oe-*	Q.1: "*Were the index test results interpreted without knowledge of the results of the reference standard?*" Yes - if the study reports that the results of the index test were interpreted without the knowledge of the results of the reference standard. No - if the study reports that results of the index test were interpreted with the results of the reference standard. Unclear - if the study does not report information about blinding of the results of the index test and reference standard.	Q.1: "*Is the reference standard likely to correctly classify the target condition?*" Yes - if the reference standard correctly classifies oesophageal varices. No - if there is some doubt if the reference standard classifies oesophageal varices. Unclear - if the study does not report on the reference standard used. Q.2: "*Were the reference standard results interpreted without the knowledge of the results of the index test?*" Yes - if the study reports that the results of the reference standard were interpreted without the knowledge of the results of the index test. No - if the study reports that the results of the reference standard were interpreted with the results of the test index. Unclear - if the study does not report infor-	Q.1: "*Was there an appropriate interval between the index test and the reference standard?*" Yes - if the interval between the index test and the reference standard was less than 14 days; No - if the interval was longer than 14 days; Unclear - if the study does not report the interval between the index test and the reference standard. Q.2: "*Did all participants receive the same reference standard?*" Yes - if the study has only one reference standard for all the participants (OGD with appropriate classification of oesophageal varices). No - if the study has more than one reference standards. Unclear- if the study is not clear about the reference standard used. Q.3 "*Were all participants included in the analysis?"*

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	sophageal varices not until diagnosed?" Yes - if the study enrolled only participants with suspected oesophageal varices not until diagnosed. No - if the study enrolled any participants with already known oesophageal varices. Unclear - if the characteristics of enrolled participants are not adequately defined.		mation about blinding of the results of the reference standard and the index test.	Answer: Yes - if all enrolled participants were included in the analysis (even in the case of uninterpretable index test result). No - if any participant was excluded from the analysis for any reason. Unclear - if it is not clear about the exclusions of participants from the analysis.
Risk of bias	*Could the selection of participants have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" or "Unclear" for at least one signalling question.	*Could the conduct or interpretation of the index test have introduced bias?* Low risk: "Yes" for the signalling question. High risk: "No" or "Unclear" for the signalling question.	*Could the reference standard, its conduct, or its interpretation have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" or "Unclear" for at least one signalling question.	*Could the participant flow have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" or "Unclear" for at least one signalling question.
Concerns about applicability	*Are there concerns that the included participants and setting do not match the review question?* Low concern: the participants included in the review represent the participants in whom the tests is used in clinical practice. High concern: the participants included in the review differ from the participants in whom the tests is used in clinical practice.	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?* High concern: the index test, its conduct or its interpretation of the index test differs from the way it is used in clinical practice. Low concern: the index test, its conduct or its interpretation of the index test does not differ from the way it is used in clinical practice.	*Are there concerns that the target condition as defined by the reference standard does not match the question?*	-

CONTRIBUTIONS OF AUTHORS

AC: completed the search of the studies, data extraction and quality assessment, and drafted parts of the review, provided methodological and statistical analysis, expert hepatology opinion, and reviewed the final version of the manuscript.
JCG: formulated the research question, searched the articles, data extraction and quality assessment, drafted the manuscript, and reviewed the final version of the manuscript.
DT: provided methodological analysis, involved in decision making, and reviewed the final manuscript.

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JY: searched the articles, data extraction and quality assessment, drafted the manuscript, and reviewed the final version of the manuscript.
TAW: search strategies.
SL: formulated the research question, provided hepatology expert opinion, drafted the manuscript, and reviewed the final version of the manuscript.
GC: completed the search of the studies, data extraction and quality assessment, and drafted parts of the manuscript; provided methodological and statistical analysis and reviewed the final version of the manuscript.

DECLARATIONS OF INTEREST

None known.

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  CASL/Schering Victor Feinman Fellowship for the period of one year 2007, for Dr. Juan Cristobal Gana

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to the time elapsed between the protocol and the completed review we had, as recommended, to move from QUADAS to QUADAS-2. Hence, quality assessment and the sensitivity analyses changed accordingly.

INDEX TERMS

Medical Subject Headings (MeSH)

*Capsule Endoscopy; *Portal Vein; Endoscopy, Digestive System; Esophageal and Gastric Varices [*diagnosis]; Liver Diseases [*complications]; Randomized Controlled Trials as Topic; Venous Thrombosis [*complications]

MeSH check words

Adult; Humans

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