Non-invasive Tests for the Detection of Oesophageal Varices in Compensated Cirrhosis: Systematic Review and Meta-analysis.

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Abstract:	Introduction: Conclusive data on the accuracy and clinical applicability of non-invasive screening tests for oesophageal varices (OV) in patients with compensated cirrhosis remain lacking. We conducted this study to identify currently available tests, estimate their diagnostic performance, and then exemplify how these could be utilized in clinical practice. Materials and methods: A systematic literature search was performed to identify all primary studies which reported accuracy using oesophagogastroduodenoscopy (OGD) as the gold standard. Sources searched included OVID MEDLINE; OVID EMBASE; and The Cochrane

	Library databases for studies published from database inception to March 1st 2017. Results: 21 studies with a total of 2,471 patients were identified. The following tests were evaluated in ≥3 studies: platelet count/spleen diameter ratio (PSR) (n=9), liver stiffness measurement (LSM) (n=5), platelet count (n=5), spleen stiffness measurement (n=3), aspartate aminotransferase to platelet ratio index (n=3). PSR had the highest summary area under the curve for detection of any size OV of 0.85 (95% confidence interval 0.78-0.92). At a cut-off of 909 (n=4 studies) and prevalence rates of 10%, 20%, 30%, 40%, 50% for OV; PSR screening correctly avoided the need for OGD in 70%, 62%, 55%, 47%, and 39% of patients, respectively. Conclusions: PSR appears to be the most accurate and validated non-invasive screening test for OV in patients with compensated cirrhosis. At a cut-off of 909, PSR could be clinically useful to avoid OGDs in a significant proportion of patients and improve the effectiveness of screening for OV.

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Abstract

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Results: 21 studies with a total of 2,471 patients were identified. Several tests were evaluated in ≥3 studies. Platelet count/spleen diameter ratio (PSR) had the highest summary area under the curve for detection of any size OV of 0.85 (95% confidence interval 0.78-0.92). At a cut-off of 909 (n=4 studies) and prevalence rates of 10%, 20%, 30%, 40%, 50% for OV; PSR screening correctly avoided the need for OGD in 70%, 62%, 55%, 47%, and 39% of patients, respectively.

Conclusions: PSR appears to be the most accurate and validated non-invasive screening test for OV in patients with compensated cirrhosis. At a cut-off of 909, PSR could be clinically useful to avoid OGDs in a significant proportion of patients.

Key Summary

- The majority of patients with compensated cirrhosis undergoing invasive screening with oesophagogastroduodenoscopy (OGD) do not have oesophageal varices (OV).
- Several non-invasive tests have been evaluated in this setting with variable results and cut-off values. The value of these tests in clinical practice remains unclear.
- Currently available non-invasive tests for OV specific to patients with compensated cirrhosis are identified and compared.
- Platelet count/spleen diameter ratio (PSR) appears to be the most accurate and validated test for OV in this cohort. At a cut-off of 909, PSR could be clinically utilized to avoid OGDs in a significant proportion of patients.

Introduction

Current guidelines recommend screening all patients diagnosed with liver cirrhosis for oesophageal varices (OV) using oesophagogastroduodenoscopy (OGD) [1]. Present estimates suggest that only 30-40% of patients with compensated cirrhosis have OV at the index OGD [2]. Moreover, the prevalence of medium/large OV in those patients is low at approximately 10% [3]. Therefore, a large proportion of compensated cirrhosis patients currently undergo serial negative OGDs at a significant cost and additional discomfort [4] with potentially marginal clinical benefit[5]. In fact, empirical therapy with non-selective beta blockers was more cost-effective than OGD screening when both strategies were compared to no screening[5]. Thus, the stratification of patients with OV and judicious selction of patients for therapy is an important and common clincial problem.

A large number of studies have evaluated the accuracy of non-invasive serum and imaging biomarkers in predicting the presence of OV. However, both individual studies and meta-analyses have inherent limitations as they are performed on heterogeneous populations with both compensated and decompensated cirrhosis; hence they are subject to high risk of spectrum bias and are challenging to translate into clinical practice [6-8]. Compensated cirrhosis represents a significantly different clinical entity with lower prevalence of OV as well as lower risk of variceal bleeding and death compared to decompensated cirrhosis[9].

The availability of simple, non-invasive tests of liver fibrosis, and advances in radiological imaging will inevitably result in the earlier diagnosis of cirrhosis [10]. This will enrich the number of patients with compensated cirrhosis and having data specific to this population will be imperative in guiding bespoke management strategies. The aims of this study were to: 1) Identify, using a systematic review, non-invasive diagnostic tests that detect OV in compensated cirrhosis; 2) Compare overall diagnostic performance, using meta-analysis, of different diagnostic tests in compensated cirrhosis; and 3) Create a clinical applicability

model to highlight the number of OGDs that could be saved using non-invasive tests at a specified threshold and varying prevalence of OV.

Materials and Methods

This study was conducted according to guidance provided by the Cochrane Collaboration handbook for systematic reviews [11], and following a pre-specified protocol.

Search Strategy

We searched OVID MEDLINE; OVID EMBASE; and The Cochrane Library databases for studies published from database inception to March 1st 2017 for relevant articles evaluating all diagnostic tests for the prediction of OV in patients with compensated cirrhosis. No restrictions were applied to the search algorithm (Supplementary Table 1).

Study selection and outcome measures

Studies were included if:

1) They were performed on adult patients aged 18 years or older.
2) Subjects had proven liver cirrhosis of any aetiology, defined by typical clinical and radiological with or without histological criteria [12].
3) Patients had compensated cirrhosis as defined by Child Pugh A grade, or absence of ascites, encephalopathy, and previous variceal haemorrhage.
4) OGD was used as the reference standard.
5) Sufficient data was provided to allow generation of a 2x2 diagnostic table.

The primary outcome measure was the diagnostic performance of index tests for the detection of any size OV. This was chosen because identification of any OV in patients with compensated cirrhosis results in a change in clinical management, either by reduced interval of surveillance OGD or initiation of primary prophylaxis measures to prevent an index variceal bleed.

Study quality was assessed independently by two investigators (SSS and DH) using the updated version of the quality assessment of diagnostic accuracy studies (QUADAS-2) tool[13].

Statistical analysis

Meta-analyses were performed using the DerSimonian-Laird random effects model [14] to calculate (with 95% confidence intervals [CIs]): pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), DOR, and summary AUC. Summary receiver operating characteristic (SROC) curves were used to compare the overall accuracy of different tests [15].

We aimed to estimate the proportion of OGDs saved by implementing a pre-screening strategy with a non-invasive marker compared to the current practice of universal screening. This clinical applicability was evaluated using the likelihood ratios to calculate post-test probability based on Bayes's theorem [16]. This concept is depicted visually with a Fagan's Bayesian nomogram [16]. Estimates of the pre-test probability of OV were derived from the pooled prevalence across all studies as well as other prevalence rates reported in the literature. The clinical applicability was measured only for tests that are validated in more than one study using the same threshold as identified by our systematic review. Analysis was performed using Meta-DiSc (version 1.4, Ramón y Cajal Hospital, Madrid, Spain) and Stata (version 12.1, College Station, Texas, USA) software packages.

Heterogeneity, subgroup analyses, and publication bias

Heterogeneity was examined both by visual inspection of the forest plots, and by statistical assessment using the chi square and inconsistency (I^2) test. The I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Values of I^2 of 25%, 50% and 75% may be considered to represent low, moderate and high inconsistency [17]. Exploratory subgroup analyses were conducted to investigate sources of heterogeneity. Evidence of publication bias or small study effects was assessed using both

visual inspection of the funnel plot and Deek's asymmetry test [18] whenever there were approximately 10 or more studies included in the meta-analysis [19]. A p-value of <0.10 was suggestive of significant asymmetry and therefore the possible presence of publication bias.

Results

The search strategy identified 5,527 citations which were all screened by reading the title and abstract. We identified 185 potentially eligible articles which were all read in full. 21 studies with a total 2,471 patients with compensated cirrhosis were included in the systematic review [20-40]. Fifteen studies (1,695 patients) [20-33, 39] evaluated similar markers and were also included in the meta-analysis (Figure 1). Details are summarized in Table 1, and 2, respectively. Results of the QUADAS-2 quality assessment are shown in supplementary Table 2.

Diagnostic tests identified

Platelet count/spleen diameter ratio (PSR)

9 studies (n=823 patients) [20-28] evaluated PSR for the diagnosis of any size OV in patients with compensated cirrhosis. The pooled sensitivity and specificity were 0.87 (95%CI 0.83-0.90) and 0.71 (95%CI 0.67-0.75), respectively (Figure 2 and Table 3). The summary AUC was 0.85 (95%CI 0.78-0.92) (supplementary Figure 1). Only one study evaluated the accuracy of PSR for the detection of medium/large OV [28]. There was evidence of significant heterogeneity between studies, and subgroup analyses (supplementary Table 3) identified study location as the only significant source of heterogeneity (DOR: western=8.8 (95%CI 3.8-20.0) vs. non-western=255.9 (95%CI 33.4-1962.4); p=0.0130). No evidence of significant publication bias was detected (p=0.88).

Liver stiffness measurement (LSM)

5 studies (n=553 patients) evaluated the accuracy of LSM by transient elastography (Fibroscan®, Echosens, Paris, France) for the diagnosis of any size OV [26, 28-31]. Variable cut-offs were used (16.4 kPa, 17 kPa, 12 kPa, 13.9 kPa, and 21.5 kPa) (Table 1). The pooled sensitivity and specificity were 0.83 (95%CI 0.77-0.87) and 0.60 (95%CI 0.54-0.65), respectively (Figure 3). The summary AUC was 0.78 (95%CI 0.73-0.83) (supplementary Figure 2). 5 studies (n=664 patients) reported the accuracy of LSM for the diagnosis of medium/large OV [28-32] (Table 3).

Platelet count

3 studies (n=216 patients) evaluated the accuracy of platelets count for the diagnosis of any size OV [25, 29, 31]. Cut-offs analysed were 117, 140, and 221 *10^3/microL (Table 1). The pooled sensitivity, specificity, and summary AUC were 0.65 (95%CI 0.54-0.75), 0.72 (95%CI 0.64-0.79), and 0.76 (95%CI 0.71-0.81), respectively. 4 studies (n=481 patients) evaluated the accuracy of platelets count for the diagnosis of medium/large OV [29, 31-33] (Table 3).

Spleen stiffness measurement (SSM)

3 studies assessed the accuracy of SSM for the detection of any OV (n=422 patients) [26, 28, 39]. The pooled sensitivity, specificity, and summary AUC were 0.88 (95%CI 0.82-0.92), 0.64 (95%CI 0.57-0.70), and 0.66 (95%CI 0.59-0.73), respectively (Table 3). In the study by Takuma et al [39], the acoustic radiation force impulse (ARFI) technique was used for SSM, while the other two studies used the Fibroscan [26, 28]. Two of the three studies above also reported data on accuracy for medium/large OV [28, 39] (Table 1).

Aspartate aminotransferase to platelet ratio index (APRI)

The APRI test was evaluated in 3 studies with regards to the detection of any OV as well as medium/large OV (n=292 patients) [28, 29, 31]. The pooled sensitivity, specificity, and summary AUC for the diagnosis of any OV were 0.69 (95%CI 0.60-0.77), 0.62 (95%CI 0.55-0.70), and

0.77 (95%CI 0.71-0.83), respectively (threshold effect, p<0.001). Data for medium/large OV are shown in Table 3 (threshold effect, p<0.001).

Other tests

Several other non-invasive tests have been evaluated with variable results (Table1).

Clinical applicability model

PSR was the only non-invasive marker that had multiple validation studies at a consistent threshold (4 studies used the 909 cut-off) [20, 21, 23, 27] (supplementary Table 3), hence included in the model. At the 909 cut-off, the pooled sensitivity, specificity, LR+, and LR- for the diagnosis of any size OV were 0.87 (95%CI 0.81-0.92), 0.78 (95%CI 0.73-0.83), 4.0 (95%CI 1.9-7.8), and 0.16 (0.02-0.71), respectively (supplementary Table 3). These values were applied to 5 different hypothetical cohorts with prevalence rates for any size OV at 10%; 20%; 30%; 40%; and 50%. The proportions of correctly saved endoscopies (true negative) were 70%, 62%, 55%, 47%, and 39%, respectively; while the proportions of incorrectly saved endoscopies (false negative) in those 5 cohorts were 1%. 2.5%, 4%, 5%, and 6%, respectively (Figure 4). Results of all Fagan's plots are shown in supplementary Figure 3.

Discussion

Principal findings

This is the first comprehensive systematic review (including 2,471 patients) and meta-analysis (including 1,695 patients) of all non-invasive diagnostic tests for the detection of OV in patients with compensated cirrhosis using the same methodology. The vast majority of studies were published within the last decade which highlights the recent and ongoing search for alternative pathways to improve the effectiveness of screening in this low risk group with cirrhosis. Focusing on tests included in the meta-analysis, PSR was the most frequently evaluated with 9 studies in total [20-28], followed by LSM (5 studies) [26, 28-31], platelet count (5 studies) [25, 29, 31-33], SSM (3 studies) [26, 28, 39], and APRI (3 studies) [28, 29, 31]. For the

diagnosis of any size OV across all cut-offs, PSR had the highest summary AUC compared to other tests (0.85; 95%CI 0.78-0.92), while the accuracy of LSM was higher than platelet count and APRI for the detection of medium/large OV (summary AUC 0.85; 95%CI 0.80-0.90) (Table 3).

Pooled data on the performance of the aforementioned tests represent a global summary of test accuracy based on current literature. However, these values have limited inference and cannot be adopted into clinical practice due to the variation in cut-offs used for each test. We tested PSR at the single 909 threshold, validated by multiple studies, within a clinical applicability model. We demonstrated that a significant proportion of OGDs could be saved ranging from 39% to 70% dependent on the prevalence of OV with a respective range of 50% to 10%. This provides encouraging evidence that existing non-invasive markers could be adopted into clinical practice. Our data suggest that the benefits of PSR become less evident in the context of high prevalence of OV (50% or higher) which is more likely to occur in decompensated cirrhosis[3].

Study strengths and limitations

This systematic review and meta-analysis had several strengths. We only evaluated patients with compensated cirrhosis as defined by the Baveno IV criteria [41]. It is now recognized that the development of diagnostic tests and prognostic models should be specific to each clinical status (compensated vs. decompensated), because treatment aims and outcomes are different in those two groups of patients [41]. Some studies reported data on patients with compensated cirrhosis as a subgroup within the main article. In order not to miss such studies, our search strategy was designed to be inclusive of all patients with cirrhosis regardless of their compensation status; therefore we reviewed a large number (n=185) of manuscripts in full to identify the eligible 21 studies which were included in this review. Moreover, we evaluated all currently available tests in the literature and obtained pooled data for some of the tests using the same methodology, hence, this enables direct

comparisons between the tests' global accuracy to be made rather than relying on indirect comparisons from individual meta-analyses which use different methodologies and inclusion/exclusion criteria. Finally, we presented a tangible outcome measure using a clinical applicability model to estimate the potential reduction in unnecessary screening endoscopies by adopting a non-invasive marker into the OV testing algorithm.

There are also several limitations that need to be considered when interpreting the results. As with most diagnostic accuracy meta-analyses [11], we observed high heterogeneity across studies evaluating PSR, LSM, and SSM. In case of PSR, this could be explained based on the location where the study was performed, but in case of other markers, subgroup analyses were not performed due to the small number of studies available. There may be several possible explanations for heterogeneity including study-, patient-, or test-related factors (supplementary Table 2). Variation in diagnostic thresholds used for the same test could be an important source of heterogeneity. We accounted for this in our analysis and found no evidence of a significant threshold effect in case of PSR, LSM, and SSM studies (p value >0.05 for all analyses), but not in case of platelet count and APRI studies (p<0.001). This may raise doubts regarding the validity of pooling data from studies evaluating the latter two tests, hence these results should be interpreted with caution. Operator bias and inter/intra-observer agreement on the diagnosis of OV are also important factors to consider, hence our primary outcome was presence of any OV (present vs. absent) rather than medium/large OV in order to minimize bias introduced by variability in classification systems used across different studies to define the size of OV.

Implications for clinical practice and areas for future research

Findings from this study have several important implications for clinical practice. We identified the currently available non-invasive markers for the detection of OV and obtained global estimates of their accuracy. Pooled data from this systematic review should be used

in health economic modelling studies to evaluate the cost-effectiveness of different markers in screening for OV.

PSR was found to be the most accurate marker and its potential is enhanced by the fact that its components are readily available in clinical practice as part of standard care (i.e. platelet count and ultrasound). A criticism of PSR is the subjectivity in measurement of spleen bipolar diameter, but studies have shown the latter to be a reliable parameter with excellent reproducibility as measured by both kappa statistic and intra-class correlation coefficient [42, 43].

LSM by transient elastography, was the second most accurate diagnostic test in this study, and has validated diagnostic accuracy for the detection of cirrhosis across mixed aetiologies [44]. The advantage is therefore one test could be used to diagnose cirrhosis and also stratify for OV; however, the precise thresholds for diagnosing OV are yet to be defined [8, 44]. As highlighted by this systematic review, the range of thresholds ranged from 13.9 kPa to 21.5 kPa. Transient elastography requires trained operators and has a small but significant failure rate in 3-5% of patients [45, 46]. Stiffness-based methods have a various proportion of non-valid results, and therefore the actual outcome of the studies that use these methods should incorporate non-valid measurements among the failures of the test.

We demonstrate that adopting PSR at the 909 cut-off into clinical practice can result in a significant (≥55%) saving of unnecessary OGDs in populations with ≤30% prevalence for OV. This will reduce the cost of screening and focus efforts on the remaining patients who require an OGD (PSR test positive) by, for instance, allocating them to more specialist lists operated by endoscopists with expertise in diagnosis and management. The major clinical consequence of misdiagnosis is to fail to detect OV which could bleed in the future. The false negative percentage in compensated cirrhosis was in the range of 1-6% (Figure 4), and it is important to note that not all of these would require prophylaxis with either band ligation or pharmacological therapy in the context of early compensated cirrhosis (i.e. primary

prophylaxis is currently recommended for medium/large OV in this cohort) [1]. In contrast, the percentage of false negative tests will rise in decompensated cirrhosis (as illustrated by the relationship between the incorrectly saved OGDs and prevalence of OV in Figure 4) and the consequences of missing OV will be more significant as mortality and morbidity are higher in this cohort [9]. This gives further credence to the concept of stratifying compensated versus decompensated cirrhosis before applying a diagnostic test for OV.

Conclusions

Several non-invasive markers have been evaluated to screen for OV in patients with compensated cirrhosis. PSR appears to be the most accurate in detecting any size OV compared to other tests. It is also the most frequently studied test with promising clinical applicability. Based on current estimates, initial screening with PSR at a cut-off of 909, can result in correctly saving unnecessary endoscopies in a significant proportion of patients. This benefit is highest and the risk of missing OV is lowest with lower prevalence rates for the target condition in the tested population. Prospective validation studies, including randomized controlled trials, are needed to confirm these findings and assess the impact of these diagnostic interventions on robust end-points such as the number of variceal bleeds or deaths prevented by using one testing strategy compared to another.

Figure Legends

Figure 1. Flow diagram of the search strategy and selection of studies eligible for data analysis. OGD, oesophagogastroduodenoscopy.

Figure 2. Forest plots of studies evaluating the sensitivity (top) and specificity (bottom) of platelet count/spleen diameter ratio for the diagnosis of any size oesophageal varices in patients with compensated cirrhosis. *studies using 909 cut-off.

Figure 3. Forest plots of studies evaluating the sensitivity (top) and specificity (bottom) of liver stiffness measurement by transient elastography for the diagnosis of any size oesophageal varices in patients with compensated cirrhosis.

Figure 4. Bar chart representation of the proportion of endoscopies saved in a cohort of patients with compensated cirrhosis undergoing pre-screening test with PSR at a cut-off of 909. TP, true positive; FP, false positive; FN, false negative; TN, true negative.

*Example calculation: at a prevalence of 30% for OV = 30% with “disease” and 70% with “no disease”, therefore TP = sensitivity (0.87) * prevalence (30%) = 26% and the remaining 4% are FN. Similarly, TN = specificity (0.78) * 1-prevalence (70%) = 55% and the remaining 15% are FP. Hence correctly saved = TN = 55%; incorrectly saved = FN = 4%; and performed = TP + FP = 26% + 15% = 41%. Based on Fagan’s nomogram (top image), the post-test probability of a negative test is 6.4% (6.4% of those who test negative (TN+FN) will have the disease i.e. FN), so FN = 0.064 * (55% + 4%) = 4%.

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Table 1. Characteristics of included studies (n=21).

Author & Year	Country & Design	No. of pts	Marker	Outcome Measure	Cut-off	Se, Sp
Giannini[20] 2003	Italy Retrospective	145	PSR	Any OV	909	100, 71
Giannini[21] 2006	Multicentre [a] Prospective	111	PSR	Any OV	909	79, 73
Camma[22] 2009	Italy Prospective	104	PSR	Any OV	792	83, 60
			HOMA-IR score	Any OV	3.5	61, 76
			Predictive model	Any OV	N/A	75, 75
Agha[23] 2009	Pakistan Prospective	114	PSR	Any OV	909	100, 98
Abu El-Makarem [24] 2011	Egypt Prospective	46	PSR	Any OV	939.7	100, 82
Esmat[25] 2011	Egypt Prospective	20	PSR	Any OV	1574	100, 85
			Platelet count	Any OV	$221*10^3$/microL	86, 54
			Spleen Length	Any OV	12.5 cm	100, 77
Colecchia[26] 2012	Italy Prospective	100	PSR	Any OV	1883	98, 26
			LSM (Fibroscan)	Any OV	16.4 kPa	96, 60
			SSM (Fibroscan)	Any OV	41.3 kPa	98, 66
			LSPS	Any OV	1.32	98, 64
Mangone[27] 2012	Italy Prospective	87	PSR	Any OV	909	58, 66
Calvaruso[28] 2013	Italy Prospective	96	PSR	Any OV	800	74, 70
				Med+ OV	640	73, 65
			LSM (Fibroscan)	Any OV	17 kPa	71, 57
				Med+ OV	19 kPa	72, 55
			Modified SSM [b]	Any OV	50 kPa	65, 61
				Med+ OV	54 kPa	80, 70
			AST:ALT ratio	Any OV	0.8	69, 67
				Med+ OV	1	69, 72
			APRI	Any OV	1.5	67, 52
				Med+ OV	2	60, 56

Wang[29] 2012	Taiwan Prospective	126	LSM (Fibroscan)	Any OV	12 kPa	67, 77
				Med+ OV [c]	21 kPa	77, 87
			Platelet count	Any OV	117*10^3/microL	67, 73
				Med+ OV	110*10^3/microL	85, 72
			APRI	Any OV	0.77	71, 67
				Med+ OV	1.24	85, 81
Kazemi[30] 2006	France Prospective	165	LSM (Fibroscan)	Any OV	13.9 kPa	95, 43
				Med+ OV	19 kPa	90, 60
Castera[31] 2009	France Retrospective	70	LSM (Fibroscan)	Any OV	21.5 kPa	76, 78
				Med+ OV	30.5 kPa	77, 85
			Fibrotest	Any OV	0.78	72, 69
				Med+ OV	0.78	77, 61
			Prothrombin index	Any OV	80%	44, 84
				Med+ OV	80%	62, 82
			AST:ALT ratio	Any OV	1	68, 89
				Med+ OV	1	69, 77
			Lok Index	Any OV	0.6	68, 82
				Med+ OV	0.6	85, 75
			Platelet count	Any OV	140*10^3/microL	56, 76
				Med+ OV	140*10^3/microL	77, 75
			APRI	Any OV	1.3	68, 64
				Med+ OV	1.3	77, 60
Pritchett[32] 2011	Canada Prospective	211	LSM (Fibroscan)	Med+ OV	19.8 kPa	91, 56
			Platelet count	Med+ OV	101*10^3/microL	65, 77
Burton Jr[33] 2007	USA Prospective	74	Platelet count	Med+ OV [d]	80*10^3/microL	100, 87
Emam[34] 2009	Egypt Retrospective	70	Regression Model	Any OV	7	80, 100
				Med+ OV	13	100, 92
Colli[35] 2001	Italy Prospective	50	U/S Doppler [e]	Any OV	0.7	58, 85
			U/S Doppler [f]	Any OV	0.07	79, 23

Berzigotti[36] 2008	Italy Prospective	60	Regression Model	Any OV	-1.02	93, 37
Berzigotti[37] 2013	Italy & Spain Prospective	117 [g]	LSPS	Any OV	3.21	81, 86
			OV Risk Score	Any OV	-0.16	81, 86
Liu[38] 2008	Taiwan Prospective	240 [h]	Duplex Doppler [k]	Any OV	3	89, 93
		143 [i]	Duplex Doppler [k]	Any OV	3	95, 94
		383 [j]	Duplex Doppler [k]	Any OV	3	92, 93
Takuma[39] 2013, Japan	Japan Prospective	226	SSM (ARFI)	Any OV	3.18 m/s	98, 63
				Med+ OV [c]	3.3 m/s	98, 67
Lisotti[40] 2014	Italy Prospective	96	ICG-r15	Any OV	<10%	98, 52
				Any OV	≥22.9%	54, 90
				Med+ OV	<13.3%	100, 42
				Med+ OV	≥22.9%	58, 73

No. of pts, number of patients included in the 2X2 table; OV, oesophageal varices; Se, sensitivity (%); Sp, specificity (%); Med+, medium/large as defined by classification system used in each study; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PSR, platelet count/spleen diameter ratio; SSM, spleen stiffness measurement; LSM, liver stiffness measurement; ARFI, acoustic radiation force impulse; U/S, ultrasound; ICG-r15, indocyanine green 15-minute retention. [a] Italy, Austria, and USA. [b] Fibroscan using a modified software version with a range between 1.5 and 150 kPa. [g] training cohort, data for validation cohort not extractable. [h] Training cohort. [i] Validation cohort. [j] All cohort. [c] included grade I with high-risk stigmata for bleeding or any grade II or III OV. [d] medium or grade 2 varices were classified as small in this study. [e] Renal resistive Index. [f] Portal Congestive Index. [k] Spleno-portal index. **HOMA-IR**, homeostasis model assessment-Insulin resistance = fasting insulin (μU/mL) x fasting glucose (mmol/L) / 22.5); LSPS ratio, liver stiffness measurement x spleen diameter/ platelet count; **APRI**, AST to platelet ratio index = (AST / upper limit of normal) / platelets x 100; **Fibrotest**, = 4.467 x log [α_2-macroglobulin (g/L)] - 1.357 x log [haptoglobin (g/L)] + 1.017 x log [γ-glutamyl transpeptidase (IU/L)] + 0.0281 x [age (in years)] + 1.737 x log [bilirubin (μmol/L)] - 1.184 x [apolipoprotein A1 (g/L)] + 0.301 x sex (female = 0, male = 1) − 5.540; **Prothrombin index**, = (Prothrombin Time Control Plasma/ Prothrombin Time Patient Plasma) x 100. **Lok index**, log odds = -5.56 - 0.0089 x platelets (10^3/mm^3) + 1.26 x (AST/ALT) + 5.27 x INR. **OV risk score**, = - 4.364 + 0.538 x spleen diameter – 0.049 x platelet count – 0.044 x LS + 0.001 x (LS x platelet count).

Table 2. Baseline characteristics of patients included in the systematic review and meta-analysis.

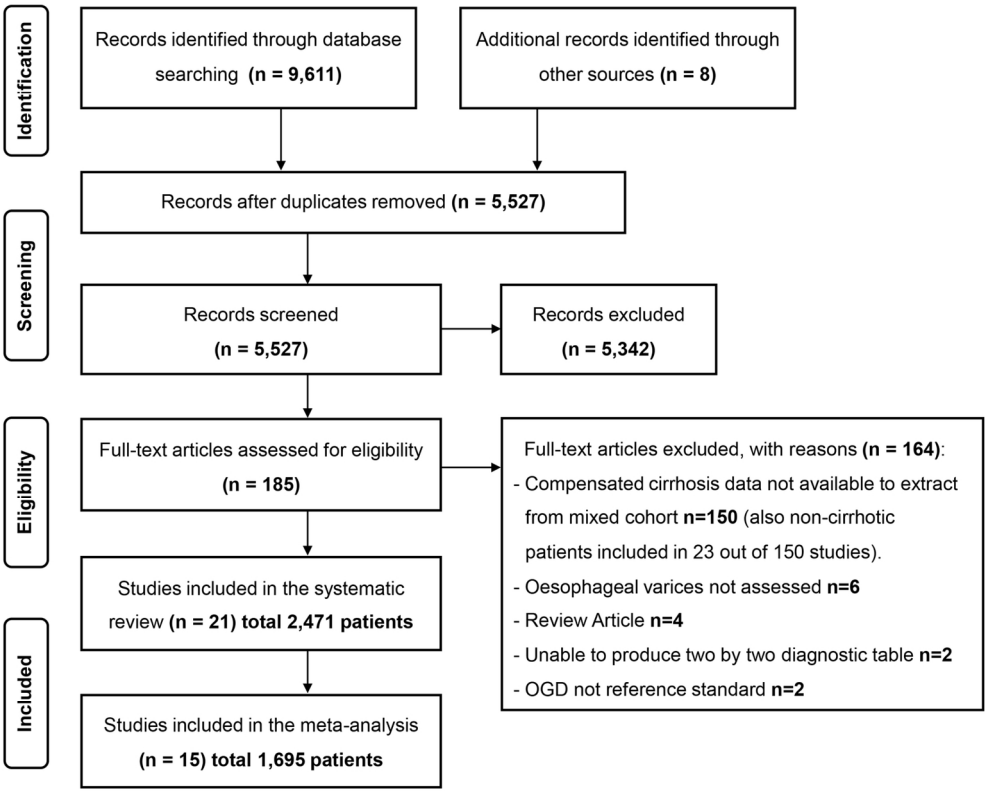
Study author/year	Country	Mean age, y	% male	Etiology % (cause)	Prevalence any OV (med+)
Giannini[20] 2003	Italy	n/s	n/s	n/s	45
Giannini[21] 2006	Multicentre[a]	n/s	n/s	n/s	34
Camma[22] 2009	Italy	61.4	57.7	100 (HCV)	61 (10)
Agha[23] 2009	Pakistan	n/s	n/s	100 (HCV)	26
Abu El-Makarem[24] 2011	Egypt	n/s	n/s	100 (HCV)	30
Esmat[25] 2011	Egypt	n/s	n/s	100 (HCV)	45
Colecchia[26] 2012	Italy	54	71	100 (HCV)	53 (26)
Mangone[27] 2012	Italy	62.8	58.6	63 (HCV), 11 (HBV), 8 (alcohol), 18 (other[b])	36 (10)
Calvaruso[28] 2013	Italy	63.2	69.8	100 (HCV)	56 (27)
Wang[29] 2012	Taiwan	54.5	73.8	100 (HBV)	38 (10)
Kazemi[30] 2006	France	56	67	59 (HCV), 10 (HBV), 22 (alcohol), 9 (other)	45 (29)
Castera[31] 2009	France	54.1	60	100 (HCV)	36 (19)
Pritchett[32] 2011	Canada	53.3	72	73 (HCV), 9 (HBV), 14 (alcohol), 5 (other)	n/s (37)
Burton Jr[33] 2007	USA	n/s	n/s	n/s	56 (9)
Emam[34] 2009	Egypt	43.5	55.7	n/s	64 (29)
Colli[35] 2001	Italy	49.8	76	45 (HCV), 36 (alcohol), 11 (HH), 8 (other)	48
Berzigotti[36] 2008	Italy	60.1	58.3	80 (HCV), 12 (alcohol), 8 (other)	47 (13)
Berzigotti[37] 2013	Italy/Spain	60	70.1	67 (HCV), 9 (HBV), 14 (alcohol), 8 (other)	32 (12)
Liu[38] 2008	Taiwan	59[c]	59.6	55 (HCV), 28 (HBV), 5 (alcohol), 11 (other)	43
		58[d]	63.6	50 (HCV), 36 (HBV), 6 (alcohol), 8 (other)	43
Takuma[39] 2013	Japan	n/s	n/s	n/s	27
Lisotti[40] 2014	Italy	60.3	69.7	59 (HCV), 14 (HBV), 20 (alcohol), 7 (other)	48 (13)

%, percentage; OV, oesophageal varices; med+, medium/large; n/s, not stated; HCV, hepatitis C virus; HBV, hepatitis B virus. [a] Italy, Austria, and USA. [c] Training cohort. [d] Validation cohort. [b] Other includes non-alcoholic fatty liver disease, mixed viral and alcohol, cryptogenic, hereditary hemochromatosis.

Table 3. Random effects meta-analysis results of studies reporting the diagnostic accuracy of currently available markers for the detection of oesophageal varices in patients with compensated cirrhosis.

Test	Outcome	N	Se	I^2	Sp	I^2	LR+	LR-	Summary AUC
PSR	Any OV	9	0.87 (0.83-0.90)	93	0.71 (0.67-0.75)	92	3.1 (1.9-5.2)	0.18 (0.09-0.4)	0.85 (0.78-0.92)
LSM	Any OV	5	0.83 (0.77-0.87)	87	0.60 (0.54-0.65)	88	2.2 (1.6-3.0)	0.28 (0.16-0.5)	0.78 (0.73-0.83)
	Med+ OV	5	0.87 (0.81-0.91)	48	0.67 (0.63-0.71)	91	2.7 (1.9-3.8)	0.25 (0.15-0.4)	0.85 (0.80-0.90)
Platelet count	Any OV	3	0.65 (0.54-0.75)	18	0.72 (0.64-0.79)	12	2.3 (1.7-3.1)	0.50 (0.12-0.3)	0.76 (0.71-0.81)
	Med+ OV	4	0.70 (0.61-0.79)	58	0.77 (0.72-0.81)	50	3.4 (2.5-4.8)	0.37 (0.22-0.6)	0.83 (0.80-0.86)
SSM [a]	Any OV	3	0.88 (0.82-0.92)	95	0.64 (0.57-0.70)	0	2.4 (1.9-3.2)	0.08 (0.0-3.2)	0.66 (0.59-0.73)
APRI	Any OV	3	0.69 (0.60-0.77)	0	0.62 (0.55-0.70)	18	1.8 (1.4-2.3)	0.52 (0.39-0.7)	0.77 (0.71-0.83)
	Med+ OV	3	0.71 (0.57-0.83)	24	0.68 (0.62-0.74)	87	2.2 (1.1-4.4)	0.43 (0.2-0.95)	0.77 (0.53-1.0)

Data presented as values (95% confidence interval). I^2 presented as percentage. N, number of studies; Se, sensitivity; Sp, specificity; LR+, positive likelihood ratio; LR-, negative likelihood ratio; AUC, area under the curve; PSR, platelet count/spleen diameter ratio; LSM, liver stiffness measurement; SSM, spleen stiffness measurement; APRI, aspartate aminotransferase (AST) to platelet ratio index; OV, oesophageal varices; med+, medium/large. [a] One of the three studies used acoustic radiation force impulse (ARFI) technique for SSM[39].



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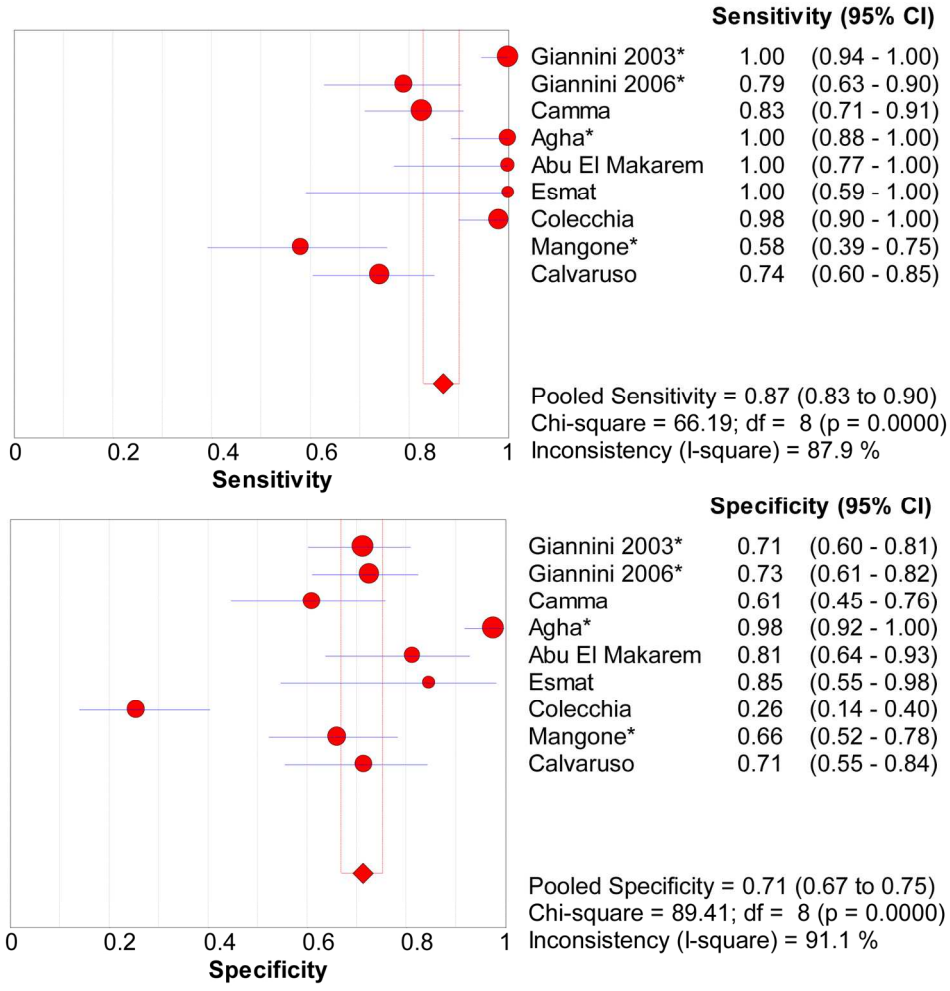

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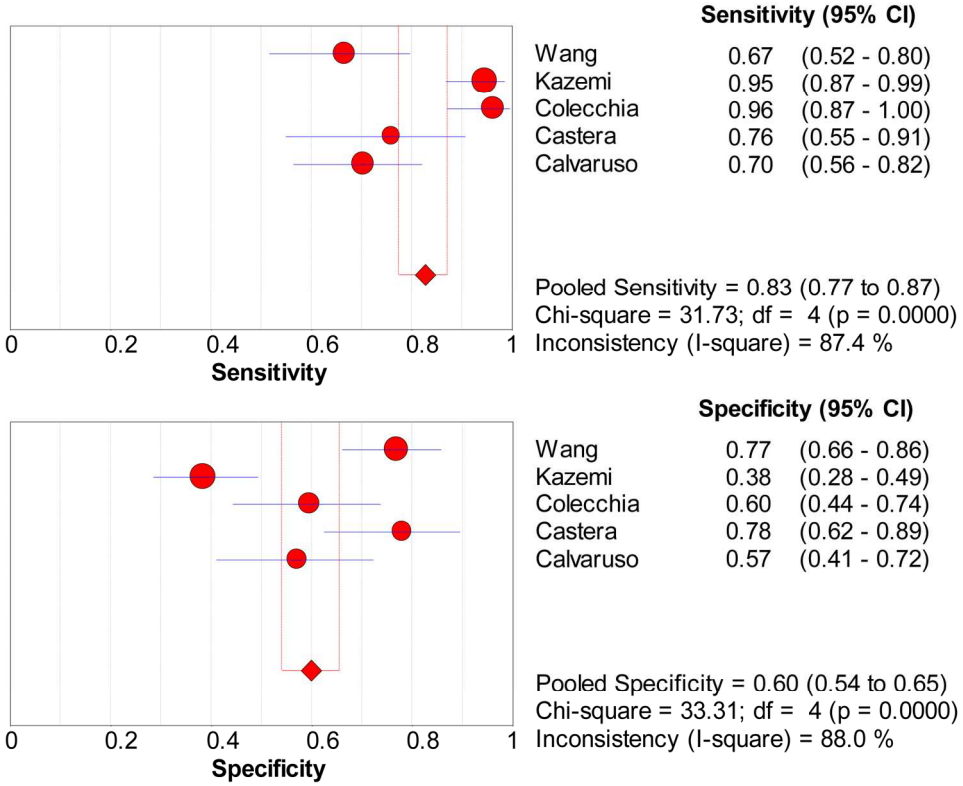

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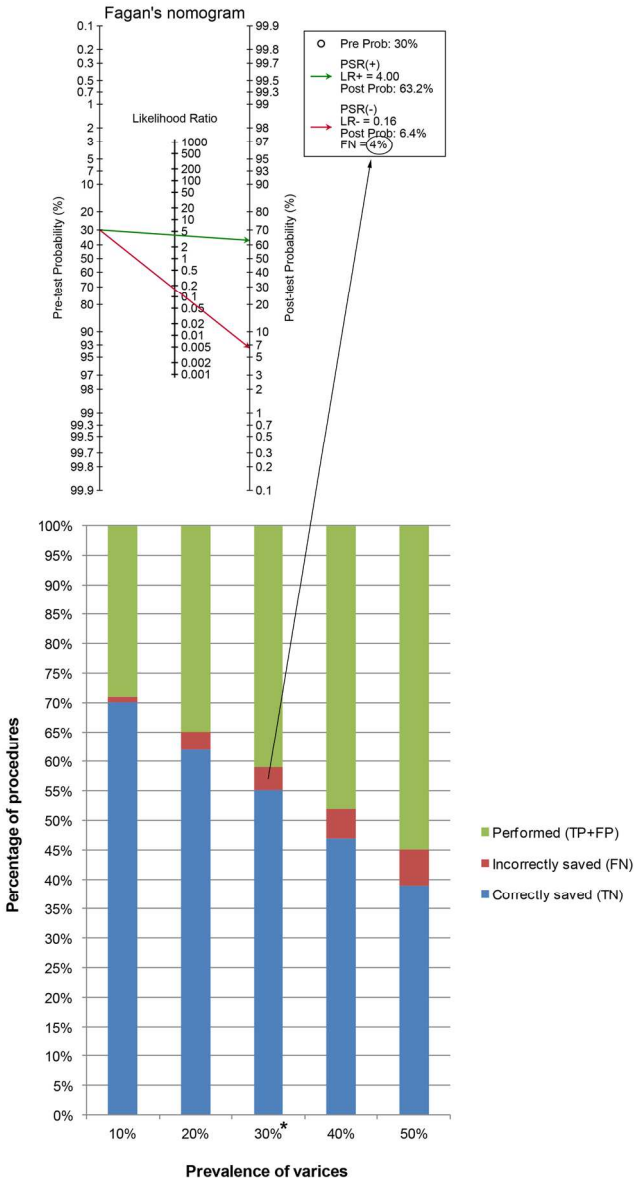

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Supplementary Table 1. Search strategy:

The literature search was performed independently by 2 investigators (SSS and DH), who screened titles and abstracts of all articles identified and excluded those with no relevance to the research question. The full text of all remaining articles was read in full to ensure that they met the inclusion criteria.

Component	Number	Defined Search
Target Condition	#1	exp "Esophageal and Gastric Varices"/
	#2	(Esophag* varic* or esophag* varix or oesophag* varic* or oesophagi* varix or gastroesophag* varic* or gastroesophag* varix or gastrooesophag* varic*or gastrooesophag* varix or gastric varic* or gastric varix)
	#3	(hvpg or hepatic venous pressure gradient or hepat* vein* or hepat* ven*)
	#4	1 or 2 or 3
Index Tests	#5	(AST:ALT ratio or aspartate aminotransferase or alanine aminotransferase or apri or BARD scor* or ELF test* or ELF scor* or enhanced liver fibrosis panel* or fib4 or fib 4 or fibroindex or fibrometer or fibrotest or forns or hepascore or lok index* or lok scor* or nafld fibrosis scor* or platelet* or thrombocyto* or pohl index* or pohl scor* or testa scor* or testa index*)
	#6	(capsule endoscop* or endoscop* capsule or capsule enteroscop* or enteroscop* capsule or pillcam or ct scan* or cat scan* or helical ct* or mri or magnetic resonance imag* or mr angiogra* or magnetic resonance angiogra* or mr elastogra* or magnetic resonance elastogra* or nmr imag* or sple* imag* or sple* enlarg* or sple* stiff* or sple* length* platelet sple* ratio or platelet sple* index or transient elastogr* or fibroscan or liver stiff* or ultraso* or arfi imag*)
	#7	exp Angiogenic Proteins/
	#8	exp Biological Markers/

	#9	exp Diagnostic Imaging/
	#10	5 or 6 or 7 or 8 or 9
	#11	4 and 10

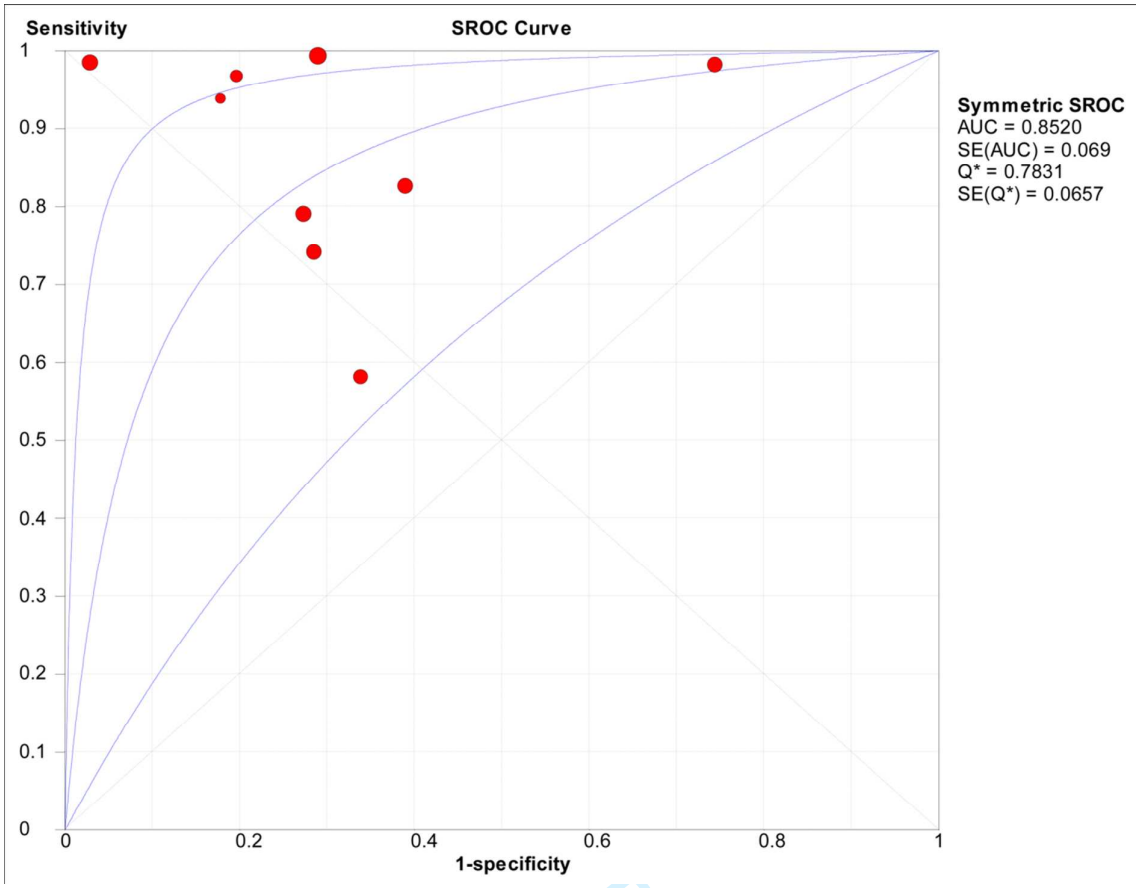
Supplementary Table 2. Quality assessment results using QUADAS-2 tool.

Author Year	Patient selection bias	Index test bias	Reference test bias	Patient flow bias	Patient applicability concerns	Index test applicability concerns	Reference test applicability concerns
Giannini[25] 2003	Unclear	High	Unclear	High	Low	Low	Low
Giannini[26] 2006	High	Low	Low	Low	Low	Low	Low
Camma[27] 2009	Low	High	Low	Low	Low	Low	Low
Agha[28] 2009	Low	Low	Low	Unclear	Unclear	Low	Low
Abu El-Makarem[29] 2011	Low	High	Low	Unclear	Low	Low	Low
Esmat[30] 2011	Unclear	High	High	Unclear	Low	Low	Low
Colecchia[31] 2012	Low	High	Unclear	High	Low	Low	Low
Mangone[32] 2012	Low	Low	Low	Low	Low	Low	Low
Calvaruso[33] 2013	Low	Unclear	Unclear	Low	Low	Low	Low
Wang[34] 2012	Low	Low	Unclear	Unclear	Unclear	Low	Low
Kazemi[35] 2006	Unclear	High	Low	High	Low	Low	Low
Castera[36] 2009	Low	High	High	High	Low	Low	Low
Pritchett[37] 2011	High	High	Unclear	High	Unclear	Unclear	High
Burton Jr[38] 2007	Low	High	High	Unclear	Low	Low	Low
Emam[39] 2009	Unclear	High	Unclear	High	Low	Low	Low
Colli[40] 2001	Low	Low	Low	Low	Low	Low	Low
Berzigotti[41] 2008	Low	High	Unclear	Unclear	Low	Low	Low
Berzigotti[42] 2013	Low	Unclear	Unclear	High	Low	Low	Low
Liu[43] 2008	High	Unclear	Low	Low	Low	Low	Low
Takuma[44] 2013	Low	Low	Low	Low	Low	Low	Low
Lisotti[45] 2014	Low	Unclear	Unclear	Low	Low	Low	Low

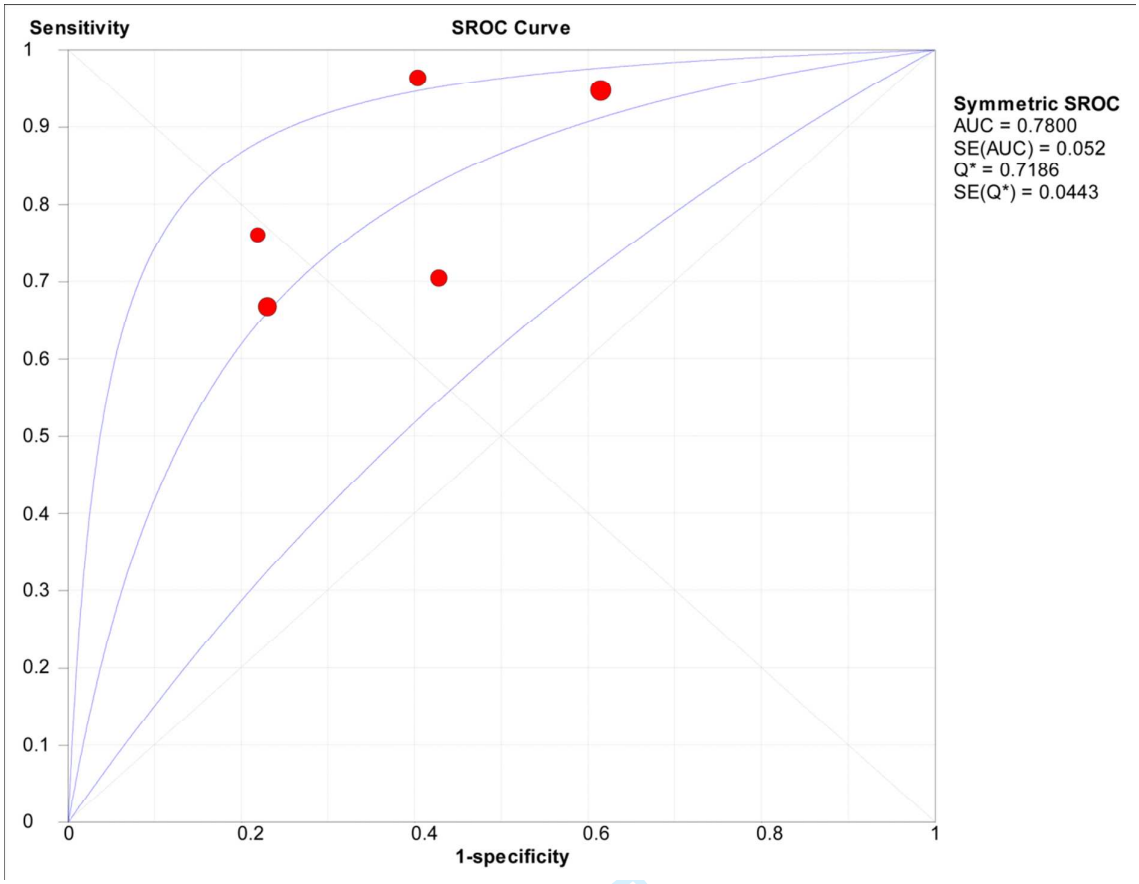
Supplementary Table 3. Subgroup analysis of studies reporting the diagnostic test performance characteristics of platelet count/spleen diameter ratio for the detection of oesophageal varices in patients with compensated cirrhosis.

Variable	Subgroup	N	Sensitivity	I^2	Specificity	I^2	LR+	LR-
Cut-off used	909	4	0.87 (0.81-0.92)	93	0.78 (0.73-0.83)	92	4.0 (1.9-7.8)	0.16 (0.02-0.71)
	Other	5	0.86 (0.81-0.91)	82	0.59 (0.52-0.67)	89	2.6 (1.4-4.7)	0.23 (0.12-0.46)
Aetiology	Viral	6	0.88 (0.83-0.92)	83	0.72 (0.65-0.77)	94	3.8 (1.7-8.6)	0.15 (0.05-0.39)
	Mixed	3	0.84 (0.77-0.90)	94	0.70 (0.64-0.76)	0	2.6 (1.8-3.9)	0.22 (0.05-1.05)
Study location	Western	6	0.85 (0.80-0.88)	90	0.63 (0.58-0.68)	85	2.2 (1.4-3.4)	0.28 (0.15-0.54)
	Other	3	1.0 (0.93-1.0)	0	0.92 (0.86-0.96)	79	9.0 (2.6-31.4)	0.04 (0.008-0.18)
Study design	Prosp	8	0.84 (0.79-0.88)	85	0.71 (0.66-0.76)	92	3.1 (1.8-5.5)	0.25 (0.13-0.47)
	Retro	1	1.0 (0.94-1.0)	NA	0.71 (0.66-0.71)	NA	3.5 (2.8-3.5)	0.00 (0.00-0.09)
***Varices prevalence**	>43%	5	0.89 (0.85-0.93)	89	0.60 (0.54-0.67)	88	2.5 (1.4-4.4)	0.16 (0.05-0.45)
	≤43%	4	0.81 (0.73-0.88)	89	0.81 (0.75-0.86)	91	4.6 (1.9-11.2)	0.18 (0.04-0.76)
Index test bias	High	5	0.94 (0.90-0.97)	82	0.62 (0.55-0.68)	89	2.8 (1.5-5.4)	0.07 (0.01-0.41)
	Unclear or low	4	0.77 (0.70-0.84)	86	0.79 (0.74-0.84)	91	3.7 (1.7-8.0)	0.33 (0.15-0.74)

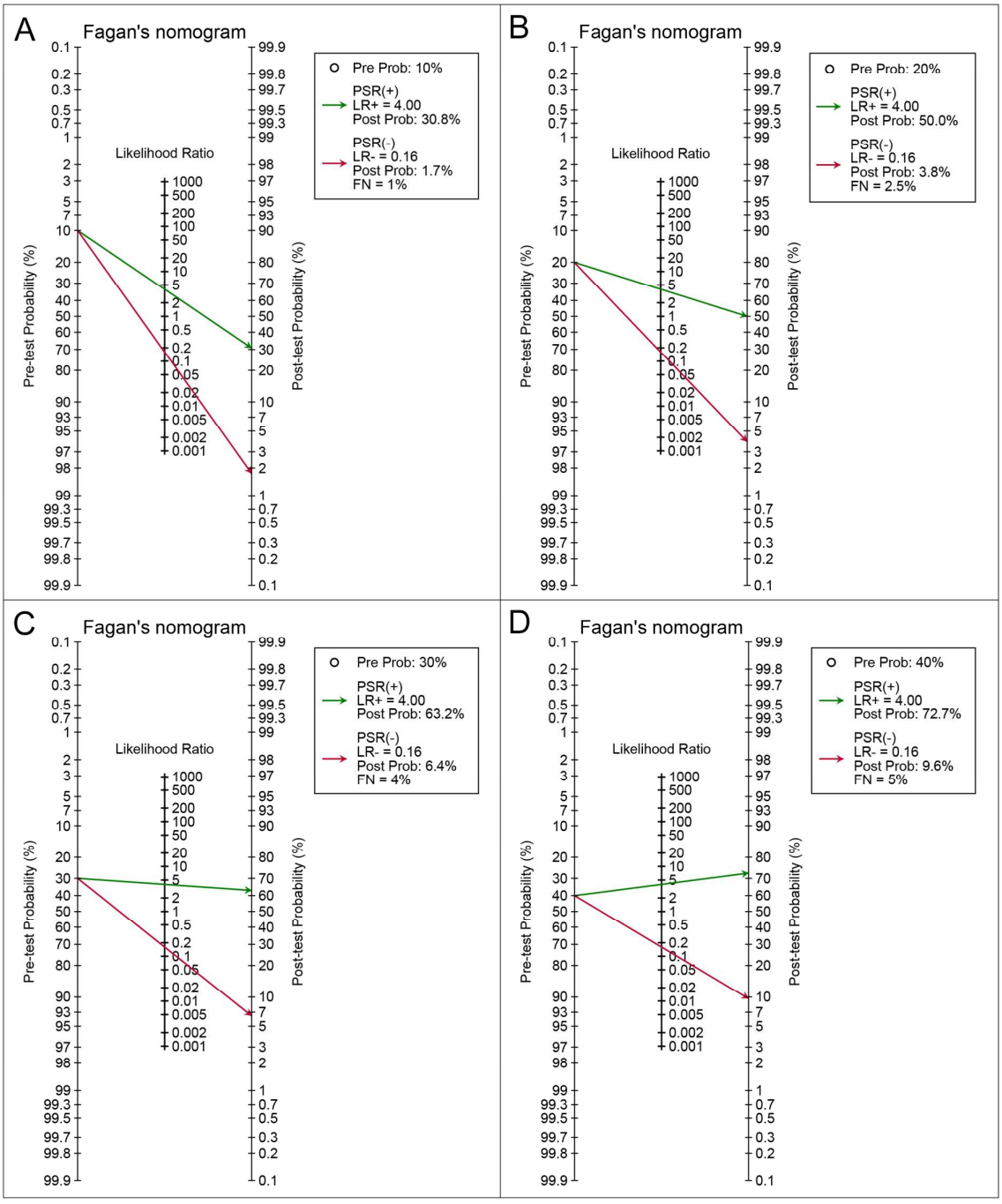
Data presented as values (95% confidence interval). . I^2 presented as percentage. *The pooled prevalence of varices across the eight studies was 0.43. N, number of studies; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio; prosp, prospective; retro, retrospective.



Supplementary Figure 1. Summary receiver operating characteristic (SROC) curve for the eight studies evaluating the diagnostic accuracy of platelet count/spleen diameter ratio for the detection of any size oesophageal varices in patients with compensated cirrhosis.



Supplementary Figure 2. Summary receiver operating characteristic (SROC) curve for the four studies evaluating the diagnostic accuracy of liver stiffness measurement by transient elastography for the detection of any size oesophageal varices in patients with compensated cirrhosis.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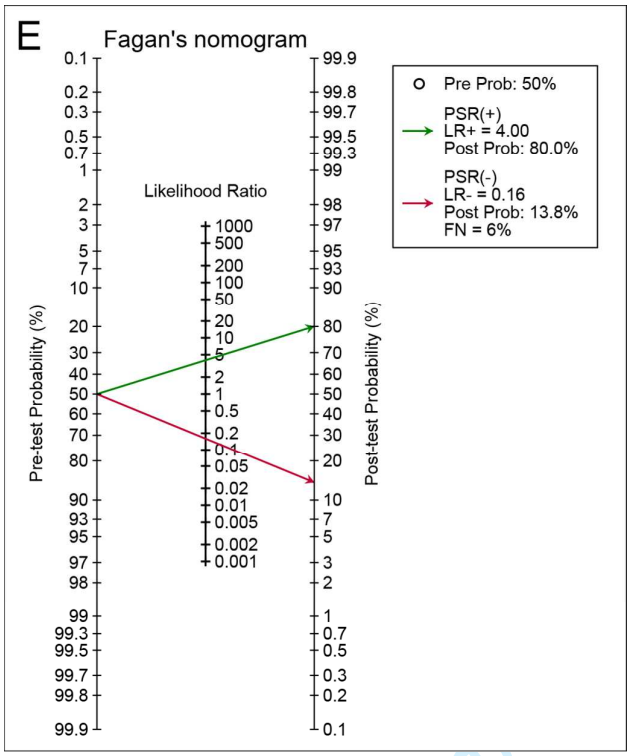
Fagan's nomogram
Likelihood Ratio
Pre-test Probability (%)
Post-test Probability (%)
Pre Prob: 10%
PSR(+)
LR+ = 4.00
Post Prob: 30.8%
PSR(-)
LR- = 0.16
Post Prob: 1.7%
FN = 1%
B
Fagan's nomogram
Likelihood Ratio
Pre-test Probability (%)
Post-test Probability (%)
Pre Prob: 20%
PSR(+)
LR+ = 4.00
Post Prob: 50.0%
PSR(-)
LR- = 0.16
Post Prob: 3.8%
FN = 2.5%
C
Fagan's nomogram
Likelihood Ratio
Pre-test Probability (%)
Post-test Probability (%)
Pre Prob: 30%
PSR(+)
LR+ = 4.00
Post Prob: 63.2%
PSR(-)
LR- = 0.16
Post Prob: 6.4%
FN = 4%
D
Fagan's nomogram
Likelihood Ratio
Pre-test Probability (%)
Post-test Probability (%)
Pre Prob: 40%
PSR(+)
LR+ = 4.00
Post Prob: 72.7%
PSR(-)
LR- = 0.16
Post Prob: 9.6%
FN = 5%



Supplementary Figure 3. Fagan's nomogram calculating the post-test probability of oesophageal varices (OV), based on the pre-test probability (prevalence) using platelet count/spleen diameter ratio (PSR) at a cut-off of 909. (A) At a hypothetically low pre-test probability of 10%, (B) At a pre-test probability of 20% observed in some studies (table 1), (C) At a pre-test probability of OV of 30% observed in most studies (table 1), (D) At a pre-test probability of OV of 40% (pooled prevalence of OV in the 9 studies included), (E) At a high pre-test probability of 50% observed in some studies (table 1).

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