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Evaluation of large esophageal varices in cirrhotic patients by transient elastography: a meta-analysis

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ABSTRACT

Background and purpose: Transient elastography (TE) has been shown to be a valuable tool for the prediction of large esophageal varices. However, the conclusions have not been always consistent throughout the different studies. Therefore, we performed a further meta-analysis in order to evaluate the diagnostic accuracy of transient elastography for the prediction of large esophageal varices.

Methods: We performed a systematic literature search in PubMed, EMBASE, Web of Science, and CENTRAL in The Cochrane Library without time restriction. The strategy we used was "(fibroscan OR transient elastography OR stiffness) AND esophageal varices". Accuracy measures such as pooled sensitivity, specificity, among others, were calculated using Meta-DiSc statistical software.

Results: Twenty studies (2,994 patients) were included in our meta-analysis. The values of pooled sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio were as follows: 0.81 (95% CI, 0.79-0.84), 0.71 (95% CI, 0.69-0.73), 2.63 (95% CI, 2.15-3.23), 0.27 (95% CI, 0.22-0.34) and 10.30 (95% CI, 7.33-

14.47). The area under the receiver operating characteristics curve was 0.83. The Spearman correlation coefficient was 0.246 with a p-value of 0.296, indicating the absence of any significant threshold effects. In our subgroup analysis, the heterogeneity could be partially explained by the geographical origin of the study or etiology; or it could be partially explained blindingly, through the appropriate interval and cut-off value of the liver stiffness (LS).

Conclusions: Transient elastography could be used as a valuable non-invasive screening tool for the prediction of large esophageal varices. However, since LS cut-off values vary throughout the different studies and significant heterogeneity also exists among them, we need more reasonable approaches or flow diagram in order to improve the operability of this technology.

Key words: Transient elastography. Liver stiffness. Esophageal varices. Meta-analysis.

INTRODUCTION

Cirrhosis is the advanced stage of almost all chronic liver diseases. Esophageal varices (EV), which may cause a rupture and variceal hemorrhages, are one of the most dreaded complications of cirrhosis. The rate of patients without varices, that developed varices later on, and the rate of patients with small varices which developed into large varices were 8% per year (1). The risk of first bleeding is related to the size of varices and the severity of red wale marks (2), which emphasizes the importance of screening for large esophageal varices (LEV). Screening for the presence of esophageal varices with esophagogastroduodenoscopy (EGD, the gold standard) in cirrhotic patients is recommended by current guidelines (1). However, the cost of screening with EGD for EV remains too high for patients suffering from cirrhosis, especially for people from under-developed countries. Furthermore, EGD may be unpleasant, of poor compliance, or even risky for some patients. Repeated endoscopic examinations may not be accepted easily by those who are in need of a long-term follow-up. Considering all of the above, an alternative, non-invasive and relatively inexpensive tool is needed in order to predict the presence of LEV.

Several non-invasive methods, such as capsule endoscopy, CT scan and Fibrotest, transientelastography (TE), have been developed to predict EV (3-6). Among them, TE (Fibroscan®) has demonstrated excellent diagnostic accuracy for the staging of liver fibrosis and cirrhosis (7). This non-invasive method has also shown potential value in the prediction of LEV, which will soon have clinical significance throughout the clinical practice. However, the current evidence available is not consistent and it can vary from a good correlation (6,8) to a poor correlation (9). Therefore, we performed a further meta-analysis of all the available studies to assess the diagnostic accuracy of TE (in comparison to EGD) for the prediction of LEV in adult cirrhotic patients.

METHODS

The process of our meta-analysis followed a prior established protocol.

Literature search

We performed a systematic literature search of PubMed, EMBASE, Web of Science, and CENTRAL in the Cochrane Library without time and language restrictions. The search strategy used was "(fibroscan OR transient elastography OR stiffness) AND esophageal varices". The search was conducted independently by three reviewers. All disagreements were resolved by full discussions within the group of researchers or with another author. After reviewing all titles and abstracts, the full-text articles of eligible studies were obtained. The references of each full-text article were also reviewed carefully to include studies that met with the inclusion criteria. The search strategy was last updated on the 31st of March 2015.

Eligibility criteria

1. Participants: liver cirrhosis patients (18 years of age or older) with cirrhosis confirmed by liver biopsy or other clinical/imaging methods.
2. Interventions, comparisons and outcomes: liver stiffness (LS) was performed by TE (Fibroscan) in order to predict LEV and EGD was used as the gold standard.
3. Study: no restriction of research type.

4. Enough data was extracted to be able to calculate the true positive, false positive, true negative and false negative value for diagnostic performance.

5. Esophageal varices were graded according to their size by EGD: grade 0, no varices; grade I, minimal increase of esophageal varices; grade II, enlarged, tortuous varices that occupy less than 1/3 of the lumen; and grade III, large, coil-shaped varices that occupy more than 1/3 of the lumen (10). LEV was defined as EV ≥ grade II.

Exclusion criteria

We excluded those studies that met the following criteria:

1. The participants were not restricted to adult cirrhotic patients.
2. TE (Fibroscan) was not used to evaluate LS.
3. EGD was not used as the gold standard for the diagnosis of LEV.
4. The classification of the gold standard and the diagnostic criteria of liver cirrhosis were not proper.
5. Patients co-infected with HIV were included.
6. Patients with liver carcinoma were included.
7. The documents did not report the necessary data to calculate diagnostic results.
8. Review articles, letters providing no original data, or abstracts with data that have been published as full-text articles.

Data extraction

Two of the three reviewers carried out the extraction of the following data from retrieved studies:

1. General characteristics, including the study design, author, publishing year, geographical origin, sample size, median age, gender, time period, and etiology of liver cirrhosis.
2. The cut-off value, sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) to calculate the true positive, false positive, true negative and false negative values for diagnostic performance of TE for LEV.

Assessment of methodological quality

Three reviewers independently assessed the methodological quality of the relevant studies by using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (11). The QUADAS-2 tool contains four domains: patient selection, index test, reference standard, and flow and timing. The risk of bias was assessed in all four domains and the degree of applicability was assessed in the first three domains (11). All discrepancies were resolved by full discussions within the group of researchers or with another author.

Statistical analysis

We evaluated the threshold effects by calculating the Spearman correlation coefficient between the logit of sensitivity and the logit of (1-specificity). Threshold effects were considered as significant if $p < 0.05$. Pooled sensitivity, specificity, PLR, NLR and diagnostic odds ratio (DOR) were calculated with the corresponding 95% confidence interval (CI). We added 1/2 to all cells of studies containing a count of zero. We also computed the summary receiver operating characteristics curve (SROC) and the area under the receiver operating characteristics curve (AUROC). The heterogeneity of all test parameters was examined with the Q-statistic test and the I^2 index for sensitivity and specificity. Heterogeneity was considered to be significant if $p < 0.10$ (Q statistic) or the I^2 value was 50% or more (12). If available, we conducted subgroup analyses according to the study characteristics (geographical origin, gender, etiology of liver cirrhosis, blind or not, appropriate interval or not, cut-off value, study design, etc.) in order to analyze sources of heterogeneity. All the above statistical analyses were performed by Meta-DiSc statistical software version 1.4 (Hospital Ramón y Cajal, Madrid, Spain).

We used the Deeks' funnel plot asymmetry test to assess publication bias, where a formal test was conducted by a regression of the diagnostic log odds ratio, with $p < 0.10$ for the slope coefficient which indicated significant asymmetry (13). This statistical analysis was conducted using the Stata 12.0 statistical software package (StataCorp LP, College Station, TX, USA).

RESULTS

Following the chosen strategy, we found 231 potentially relevant articles during the preliminary stage. By reviewing the abstracts of all these articles, 180 articles were excluded because they failed to meet the eligibility criteria. In the next round of selection, 31 of the remaining 51 articles were also excluded. Finally, 20 studies (2,994 patients) (6,8,9,14-30) were included for our meta-analysis. Figure 1 shows the flow diagram of literature search and study selection.

Table I outlines the baseline characteristics of the 20 studies included. Ten studies were performed in Western populations (6,8,9,14,18,21,23,26,28,30), while 7 studies were performed in Asian populations (15,16,19,20,22,24,27). The other 3 studies were performed in Africa (Egypt [17,29] and Morocco [25]). The earliest study started patient recruitment in June 2003 (23) and the latest study included patients in February 2013 (29). All patients were diagnosed with liver cirrhosis based on a liver biopsy or clinical judgment. The etiology of liver cirrhosis included virus, alcohol, non-alcoholic steatohepatitis (NASH), and autoimmune hepatitis. Seven studies only included patients with viral liver cirrhosis (8,9,16,17,20,22,29).

We used QUADAS-2 scale to assess the methodological quality of the 20 studies included (Table II). Ten studies did not provide sufficient information to be able to ascertain if the investigators that performed the endoscopy were unaware of the LS value, or vice versa, which put them at risk of review bias (8,9,14,15,18,21,23,24,29,30). The time interval between the performance of EGD and the performance of the TE was too long in 2 studies (28,30) and undefined in 8 studies (8,14,15,20-22,24,25), putting them at risk of disease progression bias.

Liver stiffness for detection of LEV

We evaluated whether the heterogeneity between each study was caused by a threshold effect. The Spearman correlation coefficient between the logit of sensitivity and the logit of (1-specificity) was computed. In our study, the Spearman correlation coefficient was 0.246 with a p-value of 0.296, which indicates the absence of any significant threshold effects.

Table III summarized the results of the studies that assessed the performance of LS to detect the presence of LEV. The cut-off values ranged from 14.5 kPa to 48.0 kPa. The pooled sensitivity of the 20 studies included in the meta-analysis was 0.81 (95% CI, 0.79-0.84), whereas the pooled specificity was 0.71 (95% CI, 0.69-0.73). The PLR and NLR were 2.63 (95% CI, 2.15-3.23) and 0.27 (95% CI, 0.22-0.34), respectively. The DOR was 10.30 (95% CI, 7.33-14.47) and the AUROC was 0.83 (Figs. 2 and 3). We used a random effects model in our meta-analysis because of the significant heterogeneity we observed.

There was considerable heterogeneity across the different studies (I^2 values of pooled sensitivity and specificity were 65% and 89%, respectively). In our study, the absence of significant threshold effects did not contribute to heterogeneity. Thus, several subgroup analyses were performed according to the characteristics of the study. In our subgroup analysis, the heterogeneity could be partially explained by the geographical origin, etiology, blinding, and appropriate interval of the study as well as the cut-off values of LS (Table IV). There was no significant difference in the diagnostic performance of LS based on the analysis of subgroups ($p_{interaction} > 0.05$).

Sensitivity analysis

The pooled sensitivity, specificity, PLR, NLR, DOR and AUROC changed slightly after the omission of any individual study, which indicated the stability of the outcome in our meta-analysis.

Publication bias

We performed the Deeks' funnel plot asymmetry test and there was no evidence of a significant publication bias ($p = 0.313$) (Fig. 4).

DISCUSSION

Esophageal variceal bleeding is a major cause of death in cirrhotic patients. Screening with EGD is recommended, especially for LEV cases, which may require frequent inspections. Liver stiffness by transient elastography correlates with the presence of LEV, although the conclusions from available evidence were not always

consistent. In this meta-analysis, we evaluated the performance of TE for the prediction of LEV and analyzed the source of heterogeneity between the retrieved research documents.

We included 20 individual studies with a total of 2,994 patients in our meta-analysis. The pooled sensitivity (81%) was good, while the specificity (71%) was moderate. Additionally, the overall test performance as evaluated by AUROC (83%) was also good, indicating a relatively high level of diagnostic accuracy for TE, which should be considered as a valuable tool for the prediction of LEV.

We observed a significant heterogeneity among studies. To analyze the origins of heterogeneity, we first evaluated the threshold effects. Despite the fact that the cut-off values of TE to predict LEV were different among studies, the p value for the Spearman correlation coefficient showed no significant threshold effects. Furthermore, subgroup analyses were conducted by stratifying original estimates based on the characteristics of the study.

The cut-off values of AUROC of the 20 studies included in our meta-analysis ranged from 14.5 kPa to 48 kPa. We attributed this variation to the diversity of etiology of the liver cirrhosis considered in the different studies, and the severity of cirrhosis in the recruited patients. Using the value of 27.5 kPa (the median cut-off value) as a line of demarcation between the cut-off values, we found no significant heterogeneity for sensitivity in the "<27.5kPa subgroup", which means that heterogeneity could be partially explained by the different cut-off values.

Pritchett et al. (21) included 211 cirrhotic patients without ascites (Child A) from any underlying liver diseases in their study. They found that the optimal cut-off value for predicting large esophageal varices using transient elastography was disease-specific. We also conducted a subgroup analysis according to the etiology of cirrhosis and found that the heterogeneity of sensitivity and specificity in the "mixed" and "viral" subgroups were both significant, although the I^2 value for specificity in "viral" subgroups was much lower. The etiology of cirrhosis might be one of the causes of heterogeneity, which has not been proved by the available sources.

Furthermore, the geographical origin of the included patients might also have some effects on the final results. A subgroup analysis was conducted in this regard. The I^2

value of sensitivity in 7 studies that were carried out in Asian countries was 0.00, which indicates an absence of heterogeneity. Thus, the geographic origin of patients accounted for the observed heterogeneity in our meta-analysis.

The methodological quality of articles is of the utmost importance for the credibility of meta-analysis conclusions. Here, we used QUADAS-2 tool to assess the methodological quality of the included studies and found that the deficiency of blinding and appropriate time intervals were the main drawbacks in some studies. Furthermore, the lack of blinding during EGD performance may have caused misclassification in diagnosing and grading of varices (31). We therefore conducted a subgroup analysis related to the performance of blinding. In spite of the fact that the heterogeneity of sensitivity and specificity in two subgroups were both significant, the DOR increased by 1/3. Moreover, a subgroup analysis, related to whether an appropriate interval was included, revealed that the heterogeneity for sensitivity in the "appropriate interval" subgroup was not significant, and that the I^2 value for specificity had declined by about 1/3. Both "blinding" and "time interval" subgroup analyses indicated that the methodological quality could be one of the causes of heterogeneity.

Although we identified some causes of heterogeneity via several subgroup analyses, we could not define a "standard" cut-off value, even for single liver cirrhosis etiology. The discrepancy in optimal cut-off values may hinder potential widespread use of TE in clinical practice. The moderate summary specificity may be an additional obstacle. In order to achieve a wider application, such technology needs to be improved and facilitated by more thorough research.

Pritchett et al. (21) reported a NPV of 98% for LEV using a cut-off value of 19.0 kPa in HCV patients, which allowed clinicians to identify when it was unnecessary for certain patients to undergo screening with EGD. In our meta-analysis, we included 5 studies (8,9,17,21,29) that assessed HCV-related cirrhotic patients. The NPVs of the corresponding optimal cut-off value in 5 studies were 98% (Pritchett [21], 19.8 kPa), 94% (Castera [8], 30.5 kPa), 84% (Calvaruso [9], 19.0 kPa), 100% (Saad [17], 38.2 kPa) and 72% (Hassan [29], 22.4 kPa), respectively. The pooled NPV estimate of these 5 studies was 92%. Although the NPV was relatively high, further studies will be

required in the future in order to set the optimal or “standard” exclusion value of TE in HCV-related cirrhotic patients.

Colecchia et al. (32) defined two cut-off values for predicting the presence of EV, one related to the highest PLR to rule in (25.0 kPa with a sensitivity of 56.6% and a specificity of 97.9%) and the other related to the lowest NLR to rule out (16.4 kPa with a sensitivity of 96.2% and a specificity of 59.6%) the target clinical feature. This may be useful for clinical practice as with this method it is possible to identify patients with relatively low and relatively high risk of LEV. Nevertheless, the remaining “average” population would still have to accept EGD. More studies will be required to set reasonable cut-off values for the screening of specific “low risk” or “high risk” patients in the future.

Augustin et al. (33) assessed a sequential screening-diagnostic strategy based on the joint use of routine clinical data (platelet count, abdominal ultrasonography) and TE in order to identify patients with EV. They concluded that patients with a low liver stiffness value (< 13.6 kPa) and normal platelets/ultrasonography were less likely to be exposed to the risk of EV, and, therefore, they could be exempt from endoscopy examination. This indicates that the diagnostic flow diagram for EV can be optimized in order to be more accurate and practical in the clinic. In addition, this flow diagram might act as a good approach to balance costs and benefits.

We should take into account some limitations of this meta-analysis: a) due to the fact that the TE cut-off values to detect LEV in each study were different, it is difficult to determine an accurate diagnostic threshold, which may restrict the clinical application; b) we observed significant heterogeneity and how it is influenced by many factors, such as the experience of operators, patient characteristics, appropriateness of the time interval, etiology of liver disease, etc., and some of these factors are difficult to avoid; and c) liver fibrosis can result in portal hypertension and esophageal varices, but the formation of the latter is influenced by portal hemodynamics, collateral circulation, and so on. As an indirect method to predict LS (34), the results of TE should be explained according to clinical practice and patients characteristics.

In conclusion, our meta-analysis indicates that TE could serve as a valuable non-

invasive screening tool for the prediction of LEV. In spite of the many advantages that it has shown over EGD, the research has not been completed in this regard. Further studies on a "standard" cut-off value for single etiology and specific geographies will be required in the near future and the methodological quality of studies should be strengthened. Meanwhile, more reasonable approaches or diagnostic flow diagrams to specifically screen for "low risk" or "high risk" patients will also be needed if we want to improve the operability of the technology.

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Table I. Baseline characteristics of included studies

Study	*Location*	*Type*	*No. of patients*	*Time period*	*Etiology*	*Patient's age (years)*	*Gender (male %)*	*Study design*
Castera 2009	France	Full text paper	66	2003.06-2007.4	HCV	54.1 ± 11.8	60	Prospective
Bureau 2008	France	Full text paper	86	2005.11-2006.10	Alcohol, HBV, HCV, NASH, autoimmune Hepatitis, mixed, cholestatic disease, miscellaneous	55 (45-65)	60	Prospective
Calvaruso 2013	Italy	Full text paper	96	2008.01-2011.3	HCV	65.1 ± 8.2	72	Prospective
Kazemi 2006	France	Full text paper	165	2002.11-2004.6	HCV, HBV, alcohol, Hemochromatosis, miscellaneous	59.9 ± 11.6	60.0	Retrospective
Li 2014	China	Full text paper	260	2010.01-2011.12	HBV, HCV, alcohol, Autoimmune hepatitis	49.4 ± 9.8	67.7	NR
Hu 2015	China	Full text paper	200	2007.07-2012.10	HBV (84%), HCV	45.1 ± 10.2	71	Prospective

Saad 2013	Egypt	Full text paper	32	2011.04-2011.10	HCV	49.5 ± 4.7[&], 48.9 ± 4.7[#], 55 ± 6.6[$]	NR	NR
Bintintan 2015	Romania	Full text paper	60	2009-2012	HBV, HCV, alcohol	57.03 ± 9.99	65	Prospective
HM Wang 2012	Taiwan, China	Full text paper	46	2008.11-2009.02	HCV, HBV, alcohol	54 ± 10	65.2	Prospective
JH Wang 2012	Taiwan, China	Full text paper	126	2009.11-2011.01	HBV	54.5 ± 10.1	73.8	Prospective
Foucher 2006	France	Full text paper	124	2003.06-2004.09	HCV, HBV, alcohol, mixed, NASH, Hemochromatosis, cholestatic disease, other	50 ± 13	NR	Prospective
Prichett 2011	Canada/Spain/ USA	Full text paper	211	2004.11-2008.07	HCV, HBV, alcohol, other	53.3 ± 1.6[&#] 55.7 ± 2.2[$]	69%[&#]	Prospective
Alam 2012	Bangladesh	Abstract	50	2011.01-2011.12	NR	35.2 ± 11.3	77%[$]	NR
Nguyen-Khac 2010	France	Full text paper	183	2005-2008	HBV, HCV, alcohol, NASH, autoimmune hepatitis, hemochromatosi,	55.4 ± 12.11[&#], 54.22 ± 9.70[$]	64.1%[&#], 65.8[$]	Prospective

					primary sclerosing cholangitis, cryptogenetic			
Chaojin 2013	Thailand	Full text paper	52	2009.01-2009.12	HCV, HBV, alcohol Miscellaneous, NASH	56.3 ± 11.4[&#] 54 ± 14.8[$]	68.4%[&#] 64.3%[$]	Prospective
Azouaoui 2013	Morocco	Abstract	22	2010.01-2010.12	NR	57 ± 13.3	72.7%	Prospective
Sporea 2013	Romania	Full text paper	697	NR	Viral or alcohol	57	57.2%	Retrospective
Chen 2012	China	Full text paper	222	2007.06-2010.08	HBV	42.7 ± 10.1	84.2%	Prospective
Hassan 2014	Egypt	Full text paper	65	2012.01-2013.02	HCV	50.4 ± 6.15	60%	Prospective
Stefannescu 2011	Romania	Full text paper	231	2009.02-2010.08	HCV, alcohol	55.66 ± 9.52	58.4%	Prospective

EV: esophageal varices; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Non-alcoholic steatohepatitis; NR: Not reported;
&: Patients without EV; #: Patients with small EV; $: Patients with large EV.

Table II. Summary of the methodological quality of the 20 studies included in the meta-analysis according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool concerning risk of bias and applicability

	Risk of bias				*Applicability concerns*		
Study	*Patient selection*	*Index test*	*Reference standard*	*FLow risk and timing*	*Patient selection*	*Index test*	*Reference standard*
Castera 2009	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Bureau 2008	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Calvaruso 2013	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Kazemi 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li 2014	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Hu 2015	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Saad 2013	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bintintan 2015	High risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
HM Wang 2012	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Low risk	Unclea	Low risk	Low risk	Low risk	Low risk	Low risk

JH Wang 2012		r risk					
Prichett 2011	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Chen 2012	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Foucher 2006	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Alam 2012	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Nguyen-Khac 2010	Low risk	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk
Chaojin 2013	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Azouaoui 2013	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Sporea 2013	High risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Hassan 2014	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Stefannescu 2011	Low risk	Unclear risk	Low risk	High risk	Low risk	Unclear risk	Unclear risk

Table III. Results of studies evaluating the performance of transient elastography for predicting the presence of large esophageal varices

Study/year	*Cut-off (kPa)*	*AUROC*	*Sensitivity (%)*	*Specificity (%)*	*TP*	*FP*	*FN*	*TN*
Castera 2009	30.5	0.87	77	85	10	8	3	45

Bureau 2008	29.3	0.76	81	61	34	17	8	27
Calvaruso 2013	19.0	0.71	72	55	19	31	7	39
Kazemi 2006	19.0	0.83	91	60	43	47	4	71
Li 2014	30.6	0.85	83	70	57	57	12	134
Hu 2015	25.55	0.86	84	73	58	36	11	95
Saad 2013	38.2	NR	100	77.3	10	5	0	17
Bintintan 2015	28.8	0.90	88	82	28	5	4	23
HM Wang 2012	14.6	0.83	90	63	17	10	2	17
JH Wang 2012	21	0.87	77	87	10	15	3	98
Prichett 2011	19.8	0.76	91	56	72	58	7	74
Chen 2012	17.1	0.73	90.2	43.6	74	79	8	61
Foucher 2006	27.5	0.73	88	53	75	21	10	18
Alam 2012	32.52	0.85	82.6	77.8	19	6	4	21
Nguyen-Khac 2010	48	0.75	73.2	73.2	30	38	11	104
Chaojin 2013	16.2	0.83	85	55	12	17	2	21

Azouaoui 2013	14.5	0.60	69	44	9	5	4	4
Sporea 2013	29.5	0.87	78	87	212	56	61	368
Hassan 2014	22.4	0.80	84	72	27	9	5	24
Stefannescu 2011	38	0.69	55.6	75.3	38	40	30	123

AUROC: Areas under receiver operating characteristics curves; NR: Not reported; TP: True positive; FP: False positive; FN: False negative; TN: True negative.

Table IV. Subgroup analysis reporting the diagnostic test performance characteristics of liver stiffness for the prediction of large esophageal varices

Variable	*Subgroups*	*No. of studies*	*Sensitivity (95% CI)*	I^2	*Specificity (95% CI)*	I^2	*PLR (95% CI)*	*NLR (95% CI)*	*DOR (95% CI)*	*AUROC*
Location	Asian	7	0.85 (0.81-0.89)	0.00	0.67 (0.63-0.71)	0.90	2.68 (1.93-3.72)	0.23 (0.17-0.31)	11.45 (7.88-16.64)	0.87
	European	10	0.79 (0.76-0.82)	0.78	0.74 (0.71-0.76)	0.91	2.64 (1.94-3.58)	0.29 (0.21-0.40)	9.74 (5.70-16.6)	0.82
Etiology	Viral	9	0.87 (0.83-0.91)	0.58	0.65 (0.61-0.68)	0.90	2.62 (1.98-3.45)	0.24 (0.17-0.35)	12.04 (7.01-20.68)	0.84
	Mixed	11	0.79	0.70	0.75	0.88	2.54	0.28	9.97	0.83

			(0.76-0.82)		(0.72-0.77)		(1.89-3.41)	(0.20-0.39)	(5.88-16.89)	
Blinding	Yes	10	0.82 (0.78-0.85)	0.54	0.74 (0.71-0.76)	0.93	2.74 (1.90-3.96)	0.26 (0.22-0.31)	12.08 (7.61-19.17)	0.87
	Not	10	0.81 (0.77-0.84)	0.74	0.68 (0.64-0.71)	0.77	2.40 (1.97-2.81)	0.28 (0.19-0.41)	8.88 (5.74-13.72)	0.81
Interval	appropriate	10	0.85 (0.81-0.88)	0.22	0.67 (0.64-0.70)	0.62	2.44 (2.06-2.89)	0.26 (0.21-0.32)	10.28 (7.20-14.67)	0.83
	Not appropriate	10	0.79 (0.76-0.82)	0.75	0.74 (0.71-0.76)	0.94	2.81 (1.97-4.00)	0.29 (0.21-0.41)	10.03 (5.95-16.90)	0.83
Cut-off value	< 27.5 kPa	10	0.87 (0.83-0.90)	0.19	0.62 (0.59-0.65)	0.87	2.24 (1.81-2.77)	0.25 (0.18-0.33)	9.73 (6.43-14.72)	0.84
	≥ 27.5 kPa	10	0.78 (0.75-0.81)	0.71	0.78 (0.75-0.80)	0.84	3.11 (2.26-4.27)	0.29 (0.21-0.40)	11.13 (6.53-18.96)	0.84

PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio; AUROC: Area under the receiver operating characteristics curve; CI: Confidence interval.

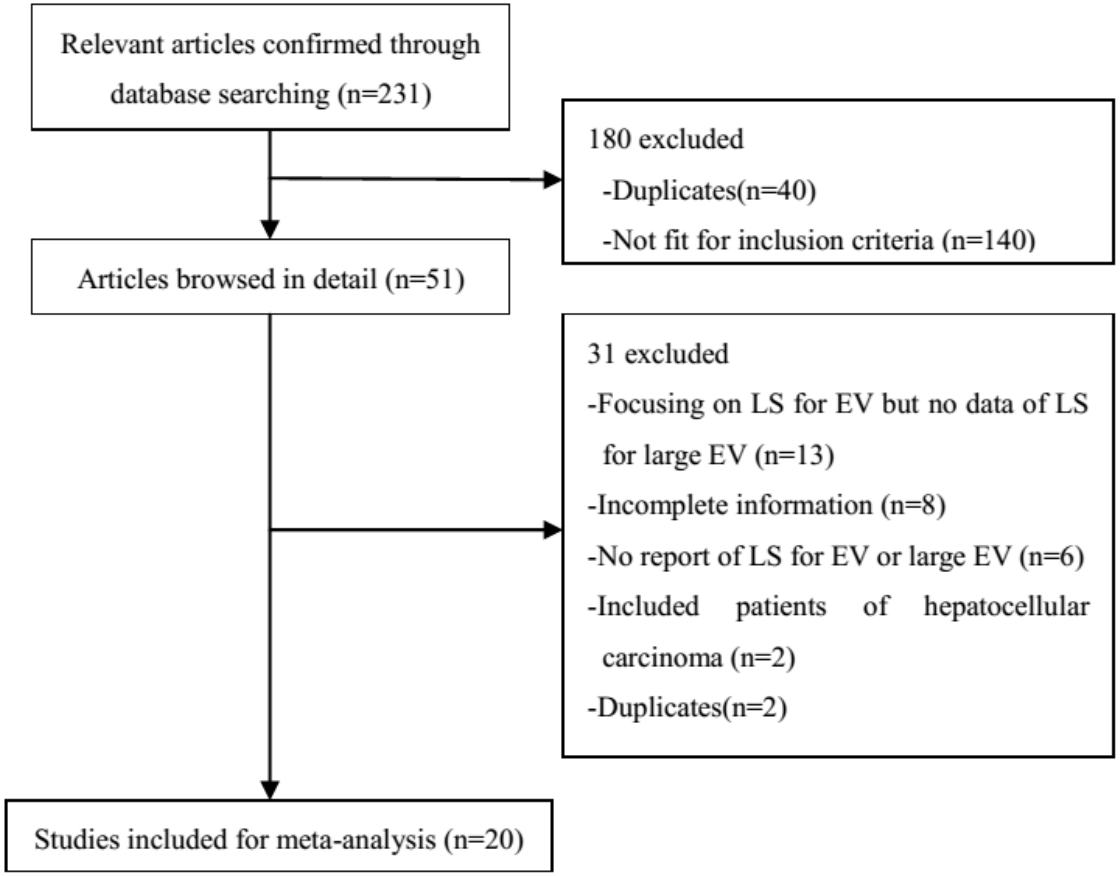
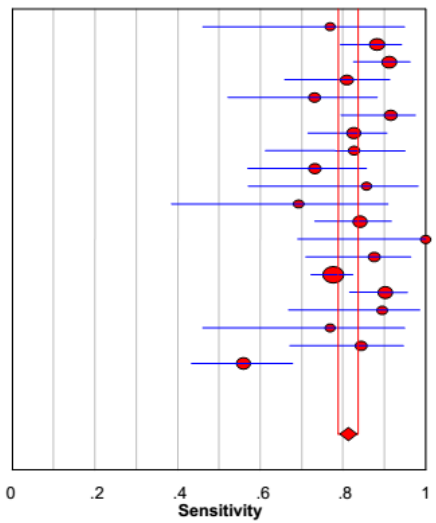


Fig. 1. Flow diagram of the documents retrieved and study selection.

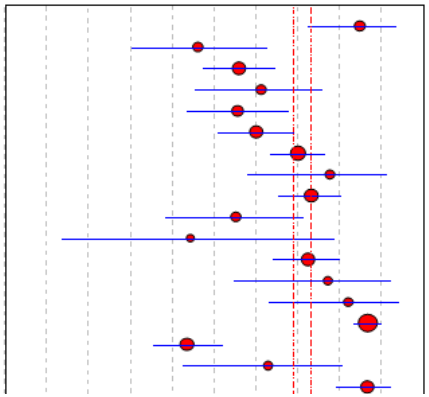
A



	Sensitivity (95% CI)	
Castera	0.77	(0.46 - 0.95)
Foucher	0.88	(0.79 - 0.94)
Prichett	0.91	(0.83 - 0.96)
Bureau	0.81	(0.66 - 0.91)
Calvaruso	0.73	(0.52 - 0.88)
Kazemi	0.91	(0.80 - 0.98)
Li	0.83	(0.72 - 0.91)
Alam	0.83	(0.61 - 0.95)
Nguyen-Khac	0.73	(0.57 - 0.86)
Chaojin	0.86	(0.57 - 0.98)
Azouaoui M.	0.69	(0.39 - 0.91)
Hu	0.84	(0.73 - 0.92)
Saad	1.00	(0.69 - 1.00)
Bintintan	0.88	(0.71 - 0.96)
Sporea	0.78	(0.72 - 0.82)
Chen	0.90	(0.82 - 0.96)
HM Wang	0.89	(0.67 - 0.99)
JH Wang	0.77	(0.46 - 0.95)
Hassan	0.84	(0.67 - 0.95)
stefannescu	0.56	(0.43 - 0.68)

Pooled Sensitivity = 0.81 (0.79 to 0.84)
Chi-square = 54.12; df = 19 (p = 0.0000)
Inconsistency (I-square) = 64.9 %

B



	Specificity (95% CI)	
Castera	0.85	(0.72 - 0.93)
Foucher	0.46	(0.30 - 0.63)
Prichett	0.56	(0.47 - 0.65)
Bureau	0.61	(0.45 - 0.76)
Calvaruso	0.56	(0.43 - 0.68)
Kazemi	0.60	(0.51 - 0.69)
Li	0.70	(0.63 - 0.77)
Alam	0.78	(0.58 - 0.91)
Nguyen-Khac	0.73	(0.65 - 0.80)
Chaojin	0.55	(0.38 - 0.71)
Azouaoui M.	0.44	(0.14 - 0.79)
Hu	0.73	(0.64 - 0.80)
Saad	0.77	(0.55 - 0.92)
Bintintan	0.82	(0.63 - 0.94)
Sporea	0.87	(0.83 - 0.90)
Chen	0.44	(0.35 - 0.52)
HM Wang	0.63	(0.42 - 0.81)
JH Wang	0.87	(0.79 - 0.92)

Fig. 2. Forest plot of transient elastography for predicting large esophageal varices (random effects model: A. Sensitivity. B. Specificity).

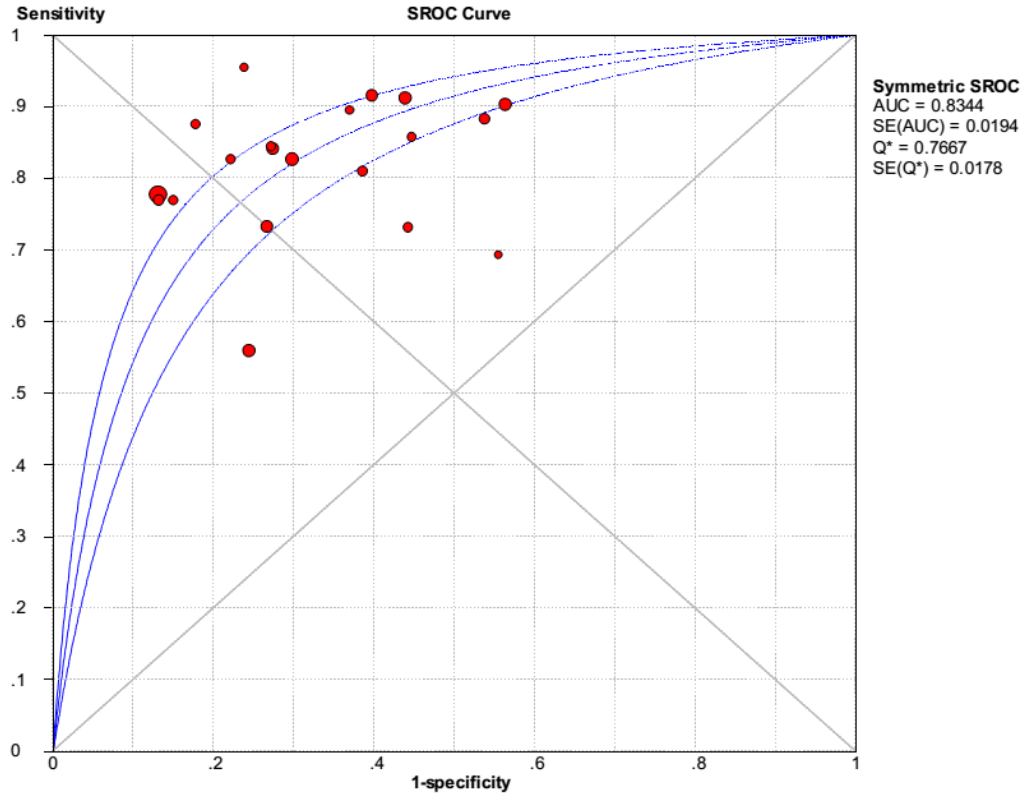


Fig. 3. Summary receiver operating characteristics curve of transient elastography for predicting large esophageal varices (random effects model).

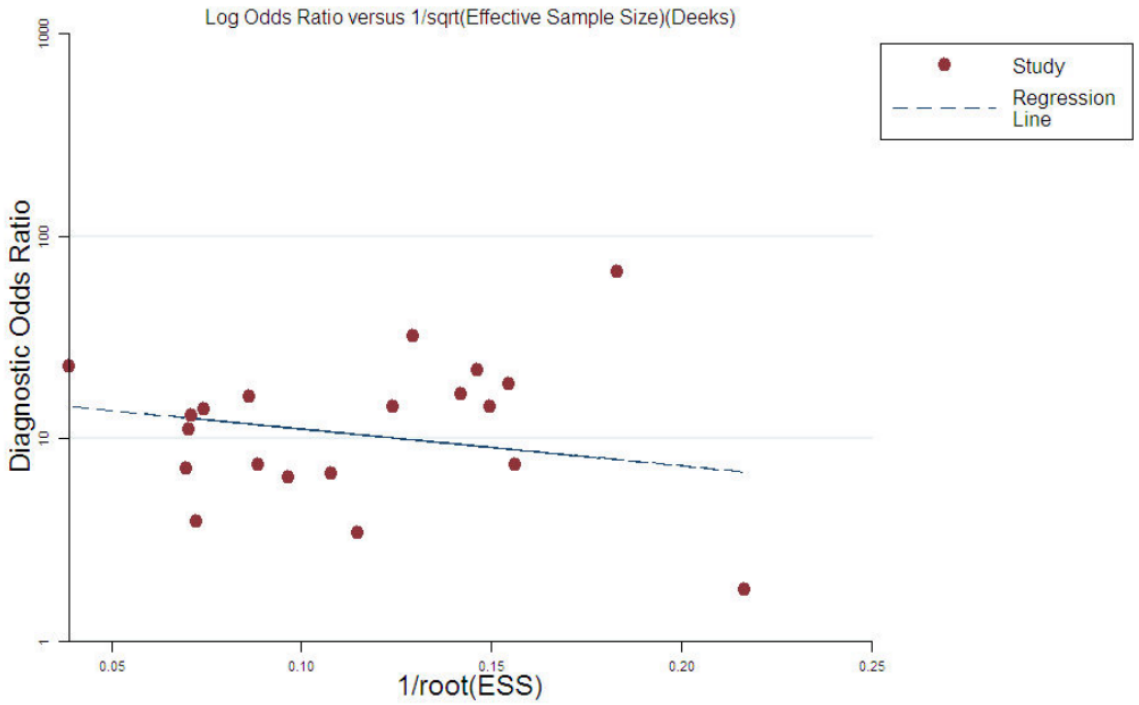


Fig. 4. Deeks' funnel plot asymmetry test of transient elastography for predicting esophageal varices.