Cirrhosis is a chronic liver disease that can be caused by almost all progressive liver injuries, such as viral, autoimmune, hereditary, metabolic, and toxin-mediated liver diseases. Esophageal varices (EV) is a frequent complication of cirrhosis. Although the survival rate of cirrhotic patients with bleeding EV has improved because of the progress in variceal hemorrhage management, the inhospital mortality rate still remains at 14.5%. Adequate detection of EV in all patients with liver cirrhosis is required in order to improve the mortality.

Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of varices. Screening with EGD to identify EV in all cirrhotic patients at baseline as well as periodic intervals is recommended by current guidelines. However, the high cost and invasive procedures undercut its acceptance and applicability in patients. Several noninvasive methods, such as capsule endoscopy, computed tomography scan, and Fibrotest, are also frequently used to avoid the unpleasant experience with EGD for many patients.
However, these methods are expensive and/or do not have a high sensitivity or specificity in detecting EV. Thus there is a need to develop and validate noninvasive methods that can accurately diagnose EV.

Transient elastography (TE) is a noninvasive method measuring liver stiffness (LS). Several studies have been conducted in the past few years to evaluate the accuracy of TE (Fibroscan®) for the prediction of EV in cirrhosis. However, the accuracy of TE evaluated by different studies was not consistent, especially in identifying cirrhotic patients with EV from different etiologies. To confirm the foregoing findings, we performed a meta-analysis based on the Grading, Assessment, Development, and Evaluation (GRADE) framework to assess the predictive accuracy of TE, as compared with EGD (the gold standard), for the prediction of EV in cirrhotic patients.

MATERIALS AND METHODS

Literature search
A systematic literature search was performed independently by two reviewers in order to evaluate the predictive accuracy of TE for EV in cirrhotic patients. Studies included were checked by other reviewers, and discrepancies were resolved by discussing with each other. The following search strategy was used: (1) Electronic databases: PubMed, EMBASE, Web of Science, and CENTRAL on The Cochrane Library were searched without time or language restrictions. (2) Terms used were “FibroScan,” “transient elastography,” “stiffness,” and “esophageal varices” [Appendix 1]. After reviewing all titles and abstracts, full-text articles of eligible studies were obtained. The references listed in the papers of every eligible study were reviewed carefully to include studies that met the inclusion criteria. The search strategy was last updated on March 31, 2015.

Inclusion criteria
Studies were considered for inclusion if they met the following criteria: (1) Participants: liver cirrhosis patients (age ≥18 years). (2) Interventions and outcomes: liver stiffness was performed by TE (Fibroscan) for the prediction of EV, and EGD was used as the gold standard. Large EV was defined as EV of Grade II (enlarged, tortuous varices) and Grade III (large, coil-shaped varices). (3) Enough data could be extracted to calculate the true-positive, false-positive, true-negative, and false-negative diagnostic results. (4) Studies with at least 20 patients were included in order to obtain good reliability.

Exclusion criteria
Studies were excluded if (1) TE (Fibroscan) was not used to evaluate LS; (2) EGD was not used as the gold standard for the diagnosis of EV; (3) patients co-infected with HIV or liver carcinoma; (4) there was not enough data to calculate sensitivity or specificity; and (5) studies were reviews, corresponding letters, or abstracts with data that have been published as full-text articles.

Data extraction
Two reviewers carried out the extraction of the following data independently: (1) general characteristics, including the primary author, location, study design, year published, sample size, median age, gender, time period, and etiology of liver cirrhosis; (2) the cutoff value, sensitivity, and specificity to calculate the true-positive, false-positive, true-negative, and false-negative values for the diagnostic performance of TE for EV.

Quality assessment
Two reviewers performed the outcomes’ quality assessment independently using the GRADE framework. The quality of the evidence was rated as high, moderate, low, or very low. Discrepancies were resolved by discussion among the two reviewers and the other three authors.

Statistical analysis
Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CI) were calculated and used to evaluate the diagnostic accuracy of TE for EV. Data analysis was conducted by using the “midas” program of Stata 12.0 statistical software package (StataCorp LP, College Station, TX, USA) and a bivariate mixed-effects regression model.

The heterogeneity of all test parameters was examined by Q-statistic test and F index. Heterogeneity was considered significant if $P < 0.10$ ($Q$ statistic) or the $F$ value was 50% and greater. When heterogeneity was detected, we further evaluated the threshold effects by calculating the Spearman’s correlation coefficient between the logit of sensitivity and the logit of (1−specificity). Threshold effects were considered significant if $P < 0.05$. If no threshold effects existed, sources of heterogeneity were analyzed by using subgroup analyses, where we stratified original estimates according to study characteristics (geographical origin, etiology of cirrhosis, blinding, appropriate interval or not, cutoff value, study design, and so on).
RESULTS

A total of 231 potentially relevant articles were found in the preliminary stage through literature search, and 191 articles remained after removing duplicates. Abstracts of the 191 articles were reviewed in detail to exclude 142 articles, which failed to meet the inclusion criteria. We assessed the remaining 49 articles carefully and further excluded 29 of them. Ten of the 29 excluded articles focused on LS for detecting large EV without reporting data of LS for EV; another article evaluating the diagnostic value of LS for EV was excluded because of the absence of areas under receiver operating characteristics curves (AUROC). Finally, 20 studies (including a total of 2530 patients) were included for our meta-analysis. Figure 1 shows the flow diagram of literature search and study selection.

Table 1 outlines the baseline characteristics of the included 20 studies. Twelve studies were performed in European countries, whereas five were performed in China. The other three studies were performed in the USA, Egypt, and India, respectively. The first study started from November 2002 and the last one started from September 2011. The last patients were recruited in October 2012. All patients were diagnosed as cirrhosis, and the diagnosis was based on liver biopsy or clinical judgment except one study, which included patients with liver stiffness suggesting cirrhosis (>12 kPa). The etiology of liver cirrhosis in most studies included a viral etiology, alcohol, NASH, and autoimmune hepatitis. Seven studies only included patients with virus-related cirrhosis.

Liver stiffness for the detection of esophageal varices

Table 2 summarized the results of studies evaluating the performance of LS for detecting the presence of EV. The cutoff value for AUROC ranged from 12.0 to 29.7 kPa. The pooled sensitivity of 20 studies was 0.84 (95% CI, 0.79–0.87), whereas the pooled specificity was 0.68 (95% CI, 0.61–0.73). The PLR and NLR were 2.58 (95% CI, 2.15–3.10) and 0.24 (95% CI, 0.19–0.32), respectively. The DOR was 10.60 (95% CI, 7.20–15.62) and the AUROC was 0.82 (95% CI, 0.79–0.86) [Figures 2 and 3]. However, the heterogeneity between studies was significant (Q = 28.884; P = 0.000; I² = 93.08, 95% CI, 86.90–99.25). We then performed Spearman’s rank correlation to evaluate the threshold effects. The Spearman’s correlation coefficient was 0.079 (P = 0.829), showing no evidence of threshold effects. We further performed several subgroup analyses in order to find the source of heterogeneity. The results are shown in Table 3. Interestingly, for studies only including hepatitis C patients, the pooled sensitivity was 0.83 (95% CI, 0.69–0.91) and the pooled specificity was 0.63 (95% CI, 0.48–0.75) without heterogeneity (I² = 0.00). The heterogeneity was still significant in other subgroups.
Liver stiffness for the detection of large esophageal varices

Ten included studies also evaluated the performance of liver stiffness for the diagnosis of large EV. The results of these studies are shown in Table 4. The cutoff value for AUROC ranged from 14.6 to 38.2 kPa. The pooled sensitivity was 0.84 (95% CI, 0.80–0.88), whereas the pooled specificity was 0.72 (95% CI, 0.65–0.79). The PLR and NLR were 3.02 (95% CI, 2.33–3.90) and 0.22 (95% CI, 0.17–0.29), respectively. The DOR was 13.65 (95% CI, 8.65–21.53) and the AUROC was 0.85 (95% CI, 0.81–0.88). For the heterogeneity test, $Q = 4.817$, $P = 0.045$, and $I^2 = 58.48$. For the five studies only including patients with viral liver cirrhosis, the pooled sensitivity was 0.82 (95% CI, 0.74–0.89), whereas the pooled specificity was 0.77 (95% CI, 0.65–0.85). The PLR and NLR were 3.56 (95% CI, 2.24–5.65) and 0.23 (95% CI, 0.14–0.37), respectively. The DOR was 15.53 (95% CI, 6.44–36.31) and the AUROC was 0.86 (95% CI, 0.82–0.88). For the heterogeneity test, $Q = 1.646$, $P = 0.220$, and $I^2 = 0.00$.

### Table 1: Baseline characteristics of included studies

| Study                | Geographical origin | Type       | Number of patients | Time period                     | Etiology                                         | Age (years) | Gender (male %) |
|----------------------|---------------------|------------|--------------------|---------------------------------|-------------------------------------------------|-------------|-----------------|
| Castéra et al. 2009  | France              | Original   | 66                 | 2003.06-2007.04                | HCV                                             | 54.1±11.8   | 60              |
| Fraquelli et al. 2014| Italy               | Original   | 26                 | 2010.01-2011.12                | HCV, HBV                                        | 52.0±10.1   | 60              |
| Vizzutti et al. 2007 | Italy               | Original   | 46                 | 2005.03-2006.07                | HCV                                            | 55.6±11.7   | 64              |
| Bureau et al. 2008   | France              | Original   | 89                 | 2005.11-2006.10.5              | Alcohol, HBV, HCV, NASH, autoimmune hepatitis, etc. | 55 (45-65)  | 60              |
| Calvaruso et al. 2013| Italy               | Original   | 96                 | 2008.01-2011.3                 | HCV                                            | 60.7±10.5†  | 66.7†           |
| Kazemi et al. 2006   | France              | Original   | 165                | 2002.11-2004.6                 | HCV, HBV, alcohol, etc.                         | 54.2±12.8†† | 70.6††          |
| Stefanescu et al. 2011| Romania            | Original   | 122                | NR                             | HCV, alcohol                                    | 56 (31-76)  | 56.2            |
| Reed et al. 2011     | UK                  | Abstract   | 96                 | NR                             | HCV, alcohol, NASH, autoimmune hepatitis, etc.   | NR          | NR              |
| Li et al. 2014       | China               | Original   | 260                | 2010.01-2011.12                | HBV, HCV, alcohol, autoimmune hepatitis         | 49.4±9.8   | 67.7            |
| Malik et al. 2010    | USA                 | Original   | 124                | NR                             | Mainly HCV (70%)                                | 53±9.0     | 70              |
| Hu et al. 2015       | China               | Original   | 200                | 2007.07-2012.10                | HBV (84%), HCV                                  | 45.1±10.2  | 71              |
| Liu et al. 2013      | China               | Original   | 101                | 2011.05-2012.01                | HBV, HCV, alcohol, autoimmune hepatitis, etc.  | 50.86±12.67 | 64.9            |
| Saad et al. 2013     | Egypt               | Original   | 32                 | 2011.04-2011.10                | HCV                                            | 49.5±4.7†  | NR              |
| Bințintan et al. 2016| Romania            | Original   | 60                 | 2009-2012                      | HBV, HCV, alcohol                               | 57.0±9.99  | 65              |
| Sharma et al. 2013   | India               | Original   | 174                | 2011.09-2012.03                | Alcohol, HBV, HCV, cryptogenic                   | 49.3±11.7  | 88.5            |
| Salzl et al. 2014    | Austria             | Original   | 59                 | 2009.02-2010.04                | Alcohol, HBV, HCV, etc.                         | 58.5 (34-80) | NR              |
| Goldis et al. 2010   | Romania             | Abstract   | 596                | 2007.05-2009.05                | NR                                             | NR         | NR              |
| Wang et al. 2012     | Taiwan, China       | Original   | 46                 | 2008.11-2009.02                | HBV, HBV, alcohol                               | 54±10      | 65.2            |
| Wang et al. 2012     | Taiwan, China       | Original   | 126                | 2008.11-2011.01                | HBV                                            | 54.5±10.1  | 73.8            |
| Augustin et al., 2014| Spain               | Original   | 49                 | 2010.01-2012.04                | Mainly HCV (84%)                                | 56±13      | 45              |

†Patients without EV ‡Patients with small EV §Patients with large EV patients without clinically significant portal hypertension *Patients with clinically significant portal hypertension. HCV: Hepatitis C virus, HBV: Hepatitis B virus. NASH: Nonalcoholic steatohepatitis, EV: Esophageal varices. NR: Not reported
The quality assessment of the outcomes by using the GRADE framework is presented in Table 5. The quality of the evidence for EV and large EV were rated as low because of risk of bias and inconsistency; however, the quality for EV (hepatitis C) and large EV (virus-related cirrhosis) were rated as moderate.

**Sensitivity analysis**

The pooled sensitivity, specificity, PLR, NLR, DOR, and AUROC changed minimally after omission of any individual study, indicating the stability of our results.

**Publication bias**

We performed the Deeks’ funnel plot asymmetry test and found no evidence of significant publication bias ($P = 0.975$).

**DISCUSSION**

About 80%–90% of patients with cirrhosis may develop EV during their lifetime, 30%–40% of which may suffer severe upper gastrointestinal bleeding. Therefore, screening for EV in patients with cirrhosis is strongly recommended across guidelines. EGD is currently considered as the gold standard for assessing EV. However, the low cost effectiveness and tolerance of EGD should be taken into account, which calls for new tools that are noninvasive and more economical.

In this meta-analysis, we evaluated the diagnostic performance of TE, as a noninvasive tool, for the prediction of EV. We observed that the sensitivity (84%) of TE for EV was good, but the specificity (68%) was moderate. The AUROC was 0.82, indicating a moderately high level of overall accuracy. The DOR was 10.60, indicating that the use of TE was helpful for the detection of EV.

Cirrhotic patients with large EV should be screened more frequently because of the higher risk of bleeding. In our meta-analysis, the diagnostic performance of TE...
for large EV was good with the summary estimates for sensitivity (84%), specificity (72%) and AUROC (0.85), similar to the performance of TE for EV. The DOR was 13.65 and the AUROC was 0.85, indicating a better performance. Encouragingly, when TE was used to detect the presence of large EV in patients with viral liver cirrhosis, the summary estimates for sensitivity and specificity were 82% and 77%, respectively. The AUROC was 0.86 and the heterogeneity was low ($I^2 = 0.00$). The quality of the evidence was rated as moderate by using the GRADE framework, indicating that TE may be more accurate and clinically relevant for detecting large EV in patients with viral cirrhosis.

The heterogeneity of included studies is the main limitation of our meta-analysis. According to our study, we cannot explain the heterogeneity when subgroup analyses were performed for locations or large EV. As for subgroup of hepatitis C patients, the diagnostic performance of TE for detecting the presence of EV was similar to all other patients with a sensitivity of 83% and specificity of 63%; however, the $I^2$ value was 0.00, indicating no significant heterogeneity. Furthermore, the quality of the evidence was rated as moderate by using the GRADE framework. This implies that TE may have a better clinical utility for hepatitis C patients. Several studies also showed that noninvasive predictors performed better in hepatitis C patients.[8,32] Hence, a considerable performance variation between the results of our diagnostic studies may be attributed to the different etiologies.

A study evaluating TE for diagnosing cirrhosis found variations in LS depending on the cause of cirrhosis and suggested that the optimal cutoff may be disease specific.[13] Meanwhile, the presence or development of EV may also be affected by the etiology of cirrhosis. Besides the etiology of cirrhosis, the diagnostic performance of TE can also be influenced by limited operator experience, as well as characteristics of patients (such as obesity, narrow intercostal spaces, and ascites).[34] Therefore, further studies need to be conducted on other disease cohorts to validate TE as a suitable test for EV and to define the optimal liver stiffness cutoffs. Studies on cirrhotic patients with single etiology might be an approach in the foreseeable future.

Combination of TE with other noninvasive methods, such as acoustic radiation force impulse elastography (ARFI), magnetic resonance elastography, and platelet count/spleen diameter ratio[15,17] may provide a better method for the diagnosis of EV than liver TE alone. For example, Fraquelli et al.[13] performed liver TE and spleen TE in combination for detecting EV, which showed a better accuracy than liver TE alone (sensitivity of 91% and specificity of 80% vs sensitivity of 75% and specificity of 47%). Augustin et al.[30] evaluated a sequential screening-diagnostic strategy based on routine clinical data (platelet count, abdominal ultrasonography) and

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| Characteristics | Subgroups | Number of studies | Sensitivity | Specificity | PLR | NLR | DOR | AUROC | Q | P | $I^2$ (%) | CI: Confidence interval |
|----------------|-----------|------------------|-------------|-------------|-----|-----|-----|-------|----|----|-----------|------------------------|
| Geographical origin | European countries | 12 | 0.82 (0.75-0.87) | 0.65 (0.55-0.74) | 2.35 (1.76-3.14) | 0.28 (0.20-0.41) | 0.28 (0.20-0.41) | 0.65 (0.55-0.74) | 8.36 (6.16-11.35) | 0.81 (0.78-0.84) | 0.00 (0.00-100.00) | 90.00 (90.00-90.00) |
| | China | 5 | 0.85 (0.77-0.90) | 0.69 (0.61-0.75) | 2.70 (2.23-3.18) | 0.22 (0.15-0.33) | 0.22 (0.15-0.33) | 0.69 (0.61-0.75) | 7.20 (5.47-9.35) | 0.80 (0.76-0.83) | 0.00 (0.00-100.00) | 90.00 (90.00-90.00) |
| | HCV + HBV | 7 | 0.81 (0.72-0.87) | 0.66 (0.60-0.72) | 2.40 (1.82-3.16) | 0.29 (0.20-0.43) | 0.29 (0.20-0.43) | 0.66 (0.60-0.72) | 7.56 (3.77-15.21) | 0.80 (0.76-0.83) | 0.00 (0.00-100.00) | 90.00 (90.00-90.00) |
| | HCV only | 4 | 0.83 (0.69-0.91) | 0.63 (0.48-0.75) | 2.21 (1.52-3.20) | 0.28 (0.14-0.53) | 0.28 (0.14-0.53) | 0.63 (0.48-0.75) | 7.34 (3.15-17.48) | 0.80 (0.76-0.83) | 0.00 (0.00-100.00) | 90.00 (90.00-90.00) |

HCV: Hepatitis C virus, HBV: Hepatitis B virus, AUROC: Areas under receiver operating characteristic curves, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, DOR: Diagnostic odds ratio, CI: Confidence interval.
Transient elastography for esophageal varices

Table 4: Results of studies evaluating the performance of transient elastography for the presence of large esophageal varices

| Study                  | Cutoff (kPa) | AUROC  | Sensitivity (%) | Specificity (%) | PLR | NLR | DOR |
|------------------------|-------------|--------|-----------------|-----------------|-----|-----|-----|
| Castéra et al., 2009[7]| 30.5        | 0.87   | 77              | 85              | 5.10 | 0.27 | 18.75 |
| Bureau et al., 2008[13]| 29.3        | 0.762  | 81              | 61              | 2.10 | 0.31 | 6.75  |
| Calvaruso et al., 2013[14]| 19.0        | 0.710  | 73              | 56              | 1.65 | 0.48 | 3.41  |
| Kazemi et al., 2006[8]  | 19.0        | 0.83   | 91              | 60              | 2.30 | 0.14 | 16.24 |
| Li et al., 2014[16]    | 30.6        | 0.849  | 83              | 70              | 2.77 | 0.25 | 11.17 |
| Hu et al., 2015[21]    | 25.55       | 0.855  | 84              | 73              | 3.06 | 0.22 | 13.91 |
| Saad et al., 2013[23]  | 38.2        | NR     | 100             | 77              | 3.99 | 0   | 66.82 |
| Bintintan et al., 2015[40]| 28.8        | 0.90   | 88              | 82              | 4.90 | 0.15 | 32.20 |
| Wang et al., 2012[29]  | 14.6        | 0.83   | 89              | 63              | 2.42 | 0.17 | 14.45 |
| Wang et al., 2012[41]  | 21.0        | 0.865  | 77              | 87              | 5.79 | 0.27 | 21.78 |

EV: Esophageal varices, AUROC: Areas under receiver operating characteristics curves, NR: Not reported, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, DOR: Diagnostic odds ratio

Table 5: Outcomes quality assessment by using the grading, assessment, development, and evaluation framework

| Outcome                  | Number of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other consideration | Quality |
|--------------------------|-------------------|--------------|---------------|--------------|-------------|--------------------|---------|
| EV                       | 20                | Serious*     | Serious*      | Not serious  | Not serious  | None               | Low     |
| EV (hepatitis C)         | 4                 | Serious*     | Not serious*  | Not serious  | Not serious  | None               | Moderate |
| Large EV                 | 10                | Serious†     | Not serious†  | Not serious† | Not serious† | None               | Low     |
| Large EV (viral liver cirrhosis) | 5          | Serious*b   | Not serious¹ | Not serious¹ | Not serious¹ | None               | Moderate |

*We downgraded for risk of bias, because there was only 7 of 20 included studies providing sufficient description that endoscopists assessed the presence and size of EV without knowledge of the LS results, while 6 studies described that LS were performed blind to other results. Only 9 studies specifically mentioned the time between endoscopy and LS. **We downgraded for inconsistency, because the heterogeneity between studies was significant (Q=28.884, P=0.000, I²=93.08). *We did not downgrade for other consideration. There was no evidence of significant publication bias (P=0.975). *We downgraded for risk of bias, because there was only 1 study providing sufficient description that endoscopists assessed the presence and size of EV without knowledge of the LS results, while 1 study described that LS were performed blind to other results. All of the 4 studies specifically mentioned the time between endoscopy and LS. **We did not downgrade for inconsistency, because the heterogeneity between studies was significant (Q=1.774, P=0.206, I²=0.00). *We downgraded for risk of bias, because there were only 5 of 10 included studies providing sufficient description that endoscopists assessed the presence and size of EV without knowledge of the LS results, while 3 studies described that LS were performed blind to other results. Only 6 studies specifically mentioned the time between endoscopy and LS, We did not downgrade for inconsistency, because the heterogeneity between studies was significant (Q=4.817, P=0.045, I²=58.48). *We downgraded for risk of bias, because there were only 2 of 5 included studies providing sufficient description that endoscopists assessed the presence and size of EV without knowledge of the LS results, while 1 study described that LS were performed blind to other results. Four studies specifically mentioned the time between endoscopy and LS, We did not downgrade for inconsistency, because the heterogeneity was not statistically significant (Q=1.646, P=0.220, I²=0.00). EV: Esophageal varices, LS: Liver stiffness

TE as a feasible and effective way to identify patients with portal hypertension and EV. It was concluded that patients with low liver stiffness value (<15.6 kPa) and normal platelets/ultrasonography should avoid endoscopy examination, which may be a good method to balance effectiveness and cost. However, the small sample size is the main limitation of this study, requiring large and prospective studies.

CONCLUSIONS

Our meta-analysis indicated that TE could serve as an effective noninvasive screening tool for the prediction of EV, especially in hepatitis C patients, and for the prediction of large EV in patients with virus-related cirrhosis. TE provides a useful adjunct for clinicians in the management of cirrhotic patients. A moderate specificity and different cutoff values should not be obstacles to the application of TE. These limitations might also be a new beginning. Based on our analysis, we suggest that further research on the value of TE for population with single etiology of cirrhosis as well as the development of proper screening-diagnostic strategies should be the “new beginning.”

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Conflicts of interest
There are no conflicts of interest.

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APPENDIX 1

Search strategy
#1. (FibroScan) OR (transient elastography) OR (liver stiffness) OR (spleen stiffness)
#2. (Esophageal varices) OR (oesophageal varices) OR (variceal bleeding) OR (variceal hemorrhage)
#3. (Hepatic venous pressure gradient) OR (portal hypertension)
#4. (Cirrhosis) OR (cirrhotic) OR (fibrosis)
#5. #2 OR #3
#6. #1 AND #4 AND #5