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The Effectiveness of Noninvasive Biomarkers to Predict Hepatitis B-Related Significant Fibrosis and Cirrhosis: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy

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Abstract

Noninvasive biomarkers have been developed to predict hepatitis B virus (HBV)-related fibrosis owing to the significant limitations of liver biopsy. Those biomarkers were initially derived from evaluation of hepatitis C virus (HCV)-related fibrosis, and their accuracy among HBV-infected patients was under constant debate. A systematic review was conducted on records in PubMed, EMBASE and the Cochrane Library electronic databases, up until April 1st, 2013, in order to systematically assess the effectiveness and accuracy of these biomarkers for predicting HBV-related fibrosis. The questionnaire for quality assessment of diagnostic accuracy studies (QUADAS) was used. Out of 115 articles evaluated for eligibility, 79 studies satisfied the pre-determined inclusion criteria for meta-analysis. Eventually, our final data set for the meta-analysis contained 30 studies. The areas under the SROC curve for APRI, FIB-4, and FibroTest of significant fibrosis were 0.77, 0.75, and 0.84, respectively. For cirrhosis, the areas under the SROC curve for APRI, FIB-4 and FibroTest were 0.75, 0.87, and 0.90, respectively. The heterogeneity of FIB-4 and FibroTest were not statistically significant. The heterogeneity of APRI for detecting significant fibrosis was affected by median age ($P = 0.0211$), and for cirrhosis was affected by etiology ($P = 0.0159$). Based on the analysis we claim that FibroTest has excellent diagnostic accuracy for identification of HBV-related significant fibrosis and cirrhosis. FIB-4 has modest benefits and may be suitable for wider scope implementation.

Introduction

Chronic infection with hepatitis B virus (HBV) is an important global health problem. Approximately 350 million people are chronically infected with hepatitis B virus worldwide, especially in developing countries, 25% of whom will die from long term sequelae, such as cirrhosis, liver failure and hepatocellular carcinoma, resulting in 600,000 to one million deaths annually [1]. Patients who are suffering from significant hepatic inflammation and fibrosis are at high risk of those complications [2]. Assessment of liver significant fibrosis is critical to establishing effective clinical practice. It could be of great help for a doctor to determine patients' suitability and the optimal time for antiviral therapy to achieve the best curative effects as well as to prevent excessive medication [3]. In addition, early prediction of cirrhosis is beneficial to reducing complications in patients with chronic viral hepatitis [4].

Liver biopsy, an invasive technique, is the gold standard for the assessment of fibrosis. It has several disadvantages, such as patients' reluctance, pain, hemoperitoneum, and pneumothorax, etc. [5]. In addition, its accuracy in assessing fibrosis is questionable because of sampling errors and intra- and inter-observer variations [6]. Therefore, many people are beginning to realize the importance of prediction of liver fibrosis by noninvasive biomarkers.

Aspartate aminotransferase-to-platelet ratio index (APRI), the fibrosis index based on the 4 factors (FIB-4) and FibroTest are examples of noninvise biomarkers predicting liver fibrosis based on routinely available clinical parameters [7]. They were initially used in Western populations with hepatitis C virus (HCV) or HCV/human immunodeficiency virus (HIV) co-infection [8] and had good performance. The area under the receiver operating characteristic (AUROC) curve of FibroTest for detecting significant fibrosis peaked out at 0.85 [9], and the AUROC curve of APRI and FIB-4 reached 0.80 [10] and 0.81 [11] respectively. For detecting cirrhosis, FibroTest also has the best result, and its AUROC curve topped out at 0.90 [12]. The AUROC curve of APRI and FIB-4 are 0.83 [13] and 0.89 [14], respectively. These three markers can be considered as "good", even "better" markers, according to the criteria of Deeks JJ [15]. Consequently, the researchers were regularly conducting those markers to predict significant fibrosis and cirrhosis among HBV-infected patients. APRI was first used to predict significant fibrosis or cirrhosis in patients with HBeAg-negative chronic hepatitis B by Chrysanthos et al. [16]. They found APRI was strongly correlated to the

fibrosis. Later FIB-4 and FibroTest were successively used to predict HBV-related fibrosis.

However, due to the fact that those markers were initially derived from evaluation of HCV-related fibrosis, their accuracy for HBV patients was under constant debate among the researchers. Some scholars indicated that all of those noninvasive markers were able to predict significant fibrosis or cirrhosis among HBV patients, and could potentially be used to decrease the number of liver biopsies [7]. Others maintained that those markers were not directly applicable to evaluation of HBV-related fibrosis because of the small AUROC curve [17]. Therefore, we decided to conduct this meta-analysis to assess the pooled performance of these biomarkers for prediction of significant fibrosis and cirrhosis among HBV-infected patients. It could provide the basis for future research and clinical application.

Methods

Literature Search

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] (see Checklist S1 for PRISMA checklist). A protocol (see Text S1) was developed and systematic methods were used to identify relevant studies, assess study eligibility for inclusion, and evaluate study quality. Online database search was completed on PubMed, EMBASE and the Cochrane Library (01/2003-04/2013) for terms including the following: aspartate aminotransfer-ase-to-platelet ratio index, APRI, fibrosis index based on the 4

factors, FIB-4, FibroTest, hepatitis B virus, HBV, Chronic hepatitis B, CHB, fibrosis and cirrhosis (see Text S2 for full search strategies). Additional studies were identified via a manual search for the referenced studies and review articles. EndNote X5 software was used to manage the references.

Selection Criteria

Studies were included if they met the following inclusion criteria: (a) The study evaluated the performance of the APRI and/or FIB-4 and/or FibroTest for the prediction of fibrosis and/or cirrhosis in HBV infected patients. Studies on patients with other etiologies of liver disease were also included if data for HBV-infected patients could be independently extracted. In addition, special populations of HBV patients (e.g., HBV/HIV coinfection, HBV/HCV, and HBV/ hepatitis D virus [HDV]) were also included. (b) Liver biopsy was used to diagnose liver fibrosis as a golden standard. (c) Data could be extracted to construct at least one 2×2 table of test performance, based on some cutoff points of the APRI, FIB-4, and FibroTest for a fibrosis stage. (d) They assessed the diagnostic accuracy for fibrosis stage $F \geq 2$ or $F \geq 4$ according to METAVIR or a comparable staging system. (e) The study included at least 40 patients. Studies of smaller sample sizes were excluded due to concerns on their applicability.

Data Extraction and Quality Assessment

Two reviewers (XYX and RXS) screened the downloaded titles and abstracts against the inclusion criteria. Two reviewers (XYX and HK) independently evaluated study eligibility, graded the
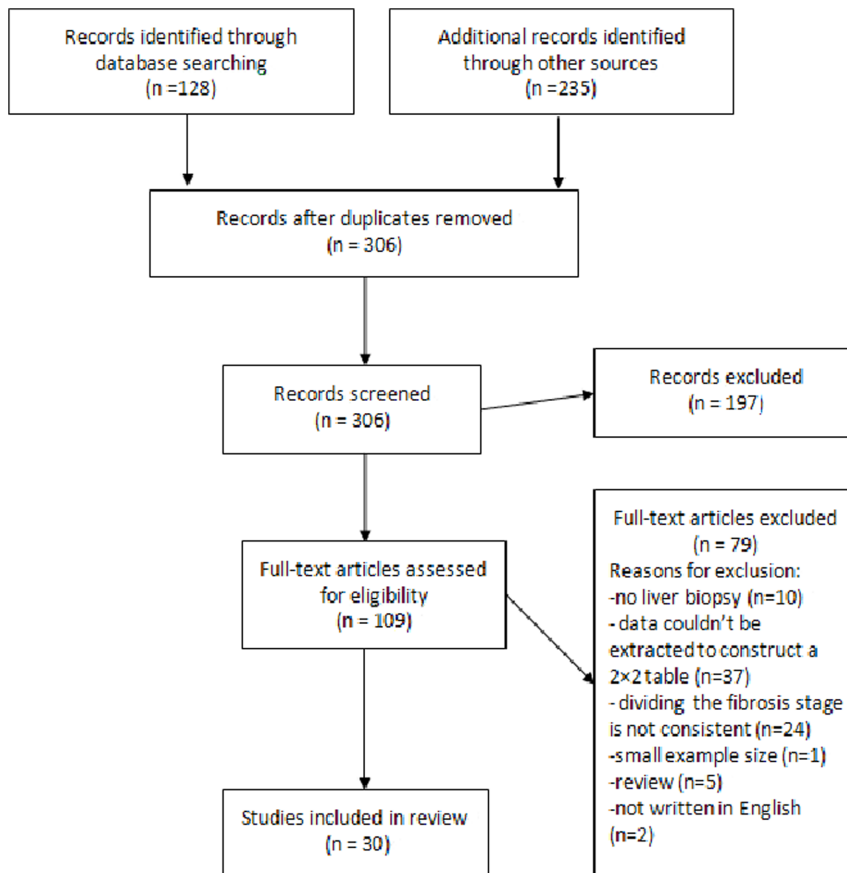

Figure 1. Flow diagram of article selection.
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Table 1. Characteristics of the 31 Studies Included in the Meta-analysis.

Test	Author, Year, Regin	Study/Center Description	N	Interval Between Biopsy&Predictive index	Mean Age (%male)	Etiology	Liver biopsy System	length of liver specimen	Prevalence F2-4/F4	QUADAS Score
APRI	Zhou, 2010, China	Retrospective, 4 centers	146	Same time	35(84%)	HBV	Scheuer	>15 mm	58%,10%	13
APRI	Lin, 2008, TaiWan	Retrospective, one center	48	Unclear	56(83%)	HBV	METAVIR	Unclear	NA,38%	12
APRI	Shin, 2008, Korea	Retrospective, one center	264	Unclear	28(87%)	HBV	METAVIR	22 mm	53%,3%	13
APRI	Kim, 2007, Korea	Retrospective, 2 centers	346	Same time	34(90%)	HBV	Batts Ludwing	Unclear	75%,23%	13
APRI	Chrysanthos, 2005, Greece	Retrospective, one center	205	Same time	51(75%)	HBV(eAg+)	Ishak	≥15 mm	60%,27%	12
APRI	Liu, 2007, China	Retrospective, 2 centers	444	<1 week	30(71%)	HBV	Scheuer	>10 mm	29%,6%	14
APRI	Guzelbulut, 2011, Turkey	Retrospective, one center	250	Unclear	39(58%)	HBV	Ishak	Unclear	26%,16%	11
APRI	Lesmana, 2011, Indonesia	Retrospective, one center	117	Unclear	41(54%)	HBV	METAVIR	≥15 mm	62%,3%	13
FIB-4	Kim, 2009, Korea	Retrospective, one center	668	<2 days	39(66%)	HBV	Batts Ludwing	≥15 mm	79%,34%	12
FIB-4	Zhang, 2010, China	Retrospective, one center	212	Unclear	31(88%)	HBV	Scheuer	20 mm	76%,21%	11
FibroTest	Myers, 2003, France	Retrospective, one center	209	<6 months	39(70%)	HBV+HDV	METAVIR	Unclear	29%,9%	14
FibroTest	Miallhes, 2011, France	Prospective, 2 centers	59	Unclear	43(84%)	HBV+HIV	METAVIR	58%≥15 mm	61%,20%	14
FibroTest	Bottero, 2009, France	Cohort, multicenter	108	<6 months	42(90%)	HBV+HIV/HDV	METAVIR	17.0±7.3 mm	56%,15%	10
FibroTest	Kim, 2012, Korea	Retrospective, one center	194	Same time	47(61%)	HBV	Batts Ludwing	≥20 mm	85%,39%	14
FibroTest	Stibbe, 2011, The Netherlands	Retrospective, one center	48	<6 months	37(73%)	HBV	METAVIR	≥20 mm	46%,10%	12
FibroTest	Park, 2013, Korea	Retrospective, 3 centers	330	Same time	44(61%)	HBV	Batts Ludwing	≥20 mm	80%,24%	13
FibroTest	Gui, 2008, China	Retrospective, one center	100	Same time	35(78%)	HBV	Ishak	≥15 mm	39%,12%	14
FibroTest	Kim, 2012, Korea	Retrospective, one center	170	Same time	45(60%)	HBV	Batts Ludwing	≥20 mm	71%,28%	12
APRI/FIB-4	Seto, 2011, China	Prospective, one center	237	Same time	32(67%)	HBV	Ishak	15–20 mm	32%,2%	13
APRI/FIB-4	Liu, 2012, China	Retrospective, 2 centers	114	Same time	38(80%)	HBV	China hospital	15–20 mm	51%,11%	14
APRI/FIB-4	Zhu, 2011, China	Retrospective, one center	175	<7 days	37(78%)	HBV	METAVIR	>15 mm	45%,17%	14
APRI/FIB-4	Wu, 2010, China	Retrospective, one center	78	Unclear	33(85%)	HBV	METAVIR	18.2±3.4 mm	41%,12%	13
APRI/FIB-4	Wang, 2012, China	Retrospective, one center	231	Same time	34(68%)	HBV	Scheuer	≥15 mm	29%,7%	14
APRI/FIB-4	Ucar, 2013, Turkey	Retrospective, one center	73	Same time	45(64%)	HBV	METAVIR	Unclear	56%,11%	14
APRI/FIB-4	Gumusay, 2011, Turkek	Prospective, one center	58	Unclear	41(57%)	HBV	Ishak	≥20 mm	17%,NA	13
APRI/FIB-4	Basar, 2013, Turkey	Retrospective, one center	76	Same time	45(45%)	HBV	METAVIR	≥10 mm	67%,17%	14
APRI/FIB-4	Wang, 2012, China	Retrospective, multicenter	349	Same time	37(92%)	HBV(eAg-)	Scheuer	≥10 mm	60%,7%	13
APRI/FIB-4	Liu, 2011, china	Retrospective, one center	623	<1 week	32(55%)	HBV	METAVIR	≥10 mm	35%,6%	14
APRI/FT	Sebastiani, 2011, Italy	Retrospective, multicenter	253	Same time	44(73%)	HBV+HDV	METAVIR	Unclear	58%,8%	13
APRI/FT	Sebastiani, 2007, Italy	Retrospective, one center	110	Same time	43(73%)	HBV	METAVIR	≥15 mm	68%,20%	12
APRI/FIB-4/ FibroTest	Bonnard, 2010, France	Prospective, one center	59	Same time	35(69%)	HBV	METAVIR	21±6 mm	70%,24%	14

APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis index based on the 4 factors; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; QUADAS, The quality assessment of diagnostic accuracy studies.

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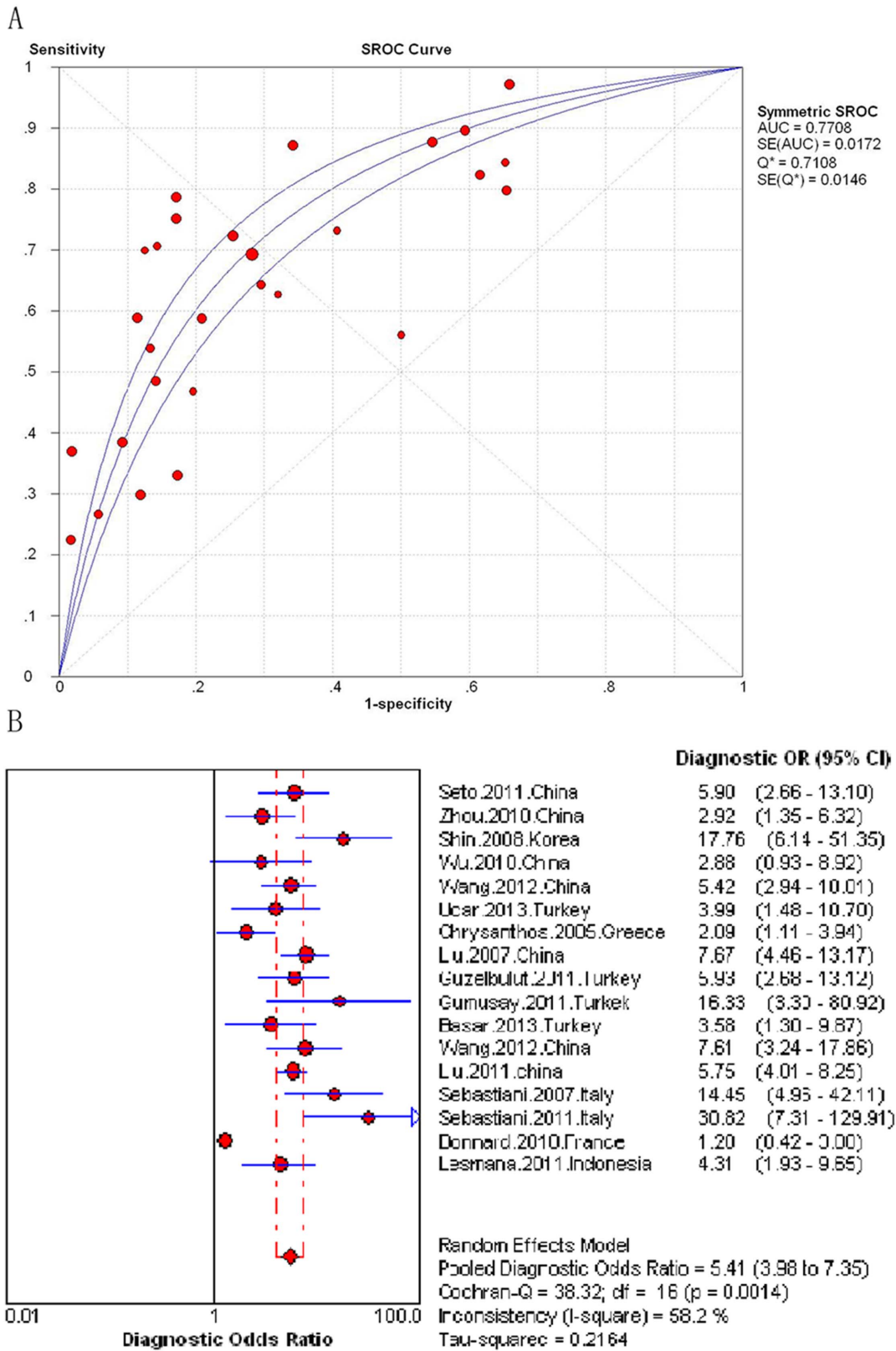
Figure 2. Meta-analysis of Hepatitis B-Related significant fibrosis. (A) SROC curve of the APRI; (B) Diagnostic odds ratio of the APRI.
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Table 2. Diagnostic Accuracy of APRI for the Prediction of Significant Fibrosis in Various Studies.

Author,Year	Cutoff	Sensitivity	Specificity	PPV	NPV	AUROC(95%CI)
Sebastiani, 2011	1.5	36%	98%	96%	53%	0.64(0.58–0.70)
Seto, 2011	0.5	89%	41%	42%	89%	0.71(0.63–0.80)
	1.5	29%	88%	55%	72%	
Bonnard, 2010	1	56%	50%	72%	33%	0.61(0.46–0.76)
Zhou, 2010	0.5	82%	38%	54%	71%	0.72
	1.5	48%	86%	75%	66%	
Shin, 2008	0.5	97%	34%	63%	91%	0.86(0.82–0.91)
	1	87%	66%	75%	82%	
	1.4	78%	83%	84%	77%	
	1.5	75%	83%	83%	74%	
	2	58%	89%	86%	65%	
Wu, 2010	0.5	84%	35%	47%	76%	0.71(0.59–0.83)
	1.5	46%	80%	63%	68%	
Wang, 2012	0.5	58%	79%	54%	82%	0.77(0.71–0.84)
Ucar, 2013	0.54	73%	59%	70%	63%	0.66
Chrysanthos, 2005	0.5	79%	35%	65%	53%	NA
	1.5	33%	83%	75%	45%	
Liu, 2007	0.4	72%	75%	54%	87%	0.77
Guzelbulut, 2011	0.5	87%	45%	36%	91%	0.78(0.72–0.84)
	1.5	38%	91%	60%	81%	
Lesmana, 2011	0.24	64%	70%	78%	54%	0.69(0.60–0.79)
Gumusay, 2011	0.7	70%	87%	54%	93%	0.82
Basar, 2013	0.43	62%	68%	80%	47%	0.67(0.55–0.79)
Wang, 2012	0.5	53%	86%	86%	56%	0.78
	1.5	22%	98%	95%	46%	
Liu, 2011	0.3	69%	71%	56%	82%	0.76(0.73–0.8)
Sebastiani, 2007	0.5	70%	85%	91%	58%	0.72(0.58–0.86)
	1.5	26%	94%	91%	38%	

APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, area under the receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; 95%CI, 95% confidence interval.
doi:10.1371/journal.pone.0100182.t002

study quality, and extracted data from the study. Any disagreements between the reviewers were resolved with detailed discussions between them together with a third reviewer (HBL). The parameters in our literature search included author, year of publication, region, method, patient gender, age, number of patients, underlying chronic liver disease etiology, histological scoring system, average length of liver specimen, time interval between biopsy and laboratory tests, prevalence of the fibrosis stage, as well as cutoff values to identify the fibrosis stage [13].

The quality of included studies was independently appraised by two reviewers (XYX and YHZ) using the quality assessment of diagnostic accuracy studies (QUADAS) questionnaire [19] (see Text S3). It could estimate the internal and external validity of diagnostic accuracy studies used in systematic reviews.

Statistical Analysis and Data Synthesis

We extracted and tabulated the data in a series of 2×2 tables, which included sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at each threshold value. The primary outcome was the identification of significant fibrosis, defined by METAVIR [20], Batts and Ludwig [21], and Scheuer [22] for stages F2 through F4, and Ishak [23] for stages F3 through

F6. This gauge was chosen because significant fibrosis is often considered a threshold for the initiation of antiviral therapy [24]. We also assessed cirrhosis (METAVIR, Batts and Ludwig, and Scheuer F4, and Ishak F5-6). In order to provide clinically meaningful results, the metrics of diagnostic test accuracy were examined.

The SROC curve, generated using linear regression, represents the relationship between the true positive rate and false positive rate across these studies, albeit they may have used different test thresholds [25]. In this analysis, the area under SROC curve was examined according to Moses et al. [26], and each study was weighted with its sample size and with adjustment for the number of thresholds within each study [27].

The diagnostic odds ratio (DOR) describes the odds of a positive test in true disease cases compared with cases of no disease [15]. The summary DOR was calculated using a DerSimonian and Laird random-effects model on a logarithmic scale with a corresponding test of heterogeneity [28]. Because such analyses require a single measure of accuracy for each study and many studies reported multiple test thresholds, we calculate the average DOR among all thresholds for a given study [29]. We also calculated summary sensitivities and specificities using the

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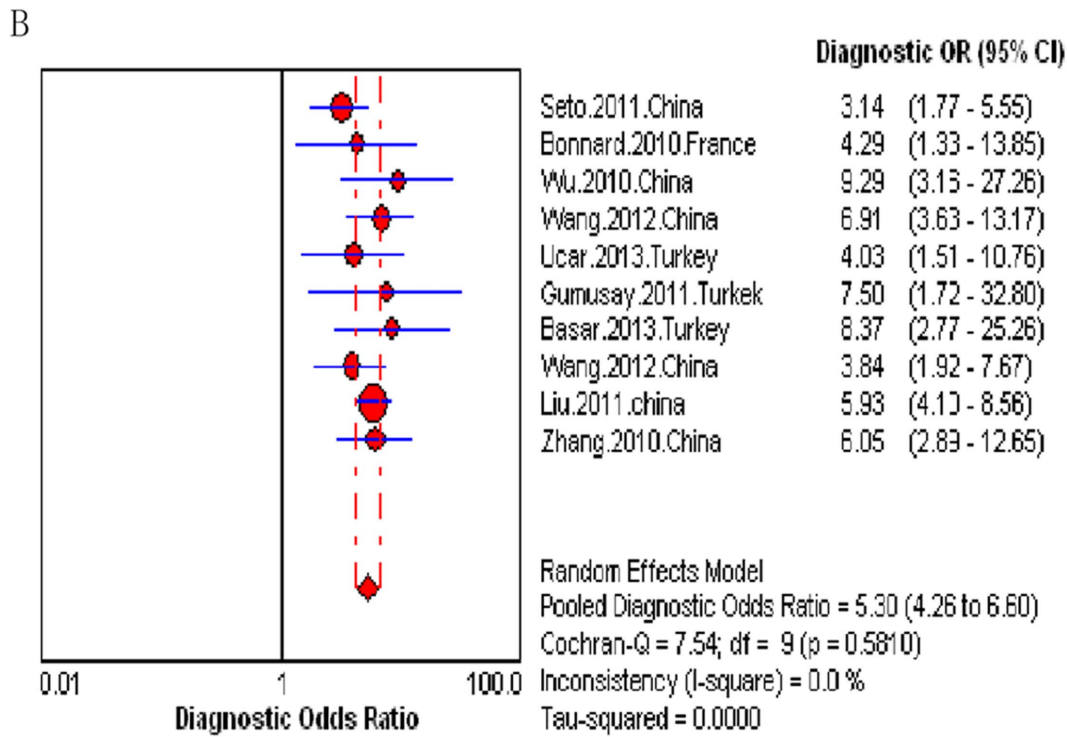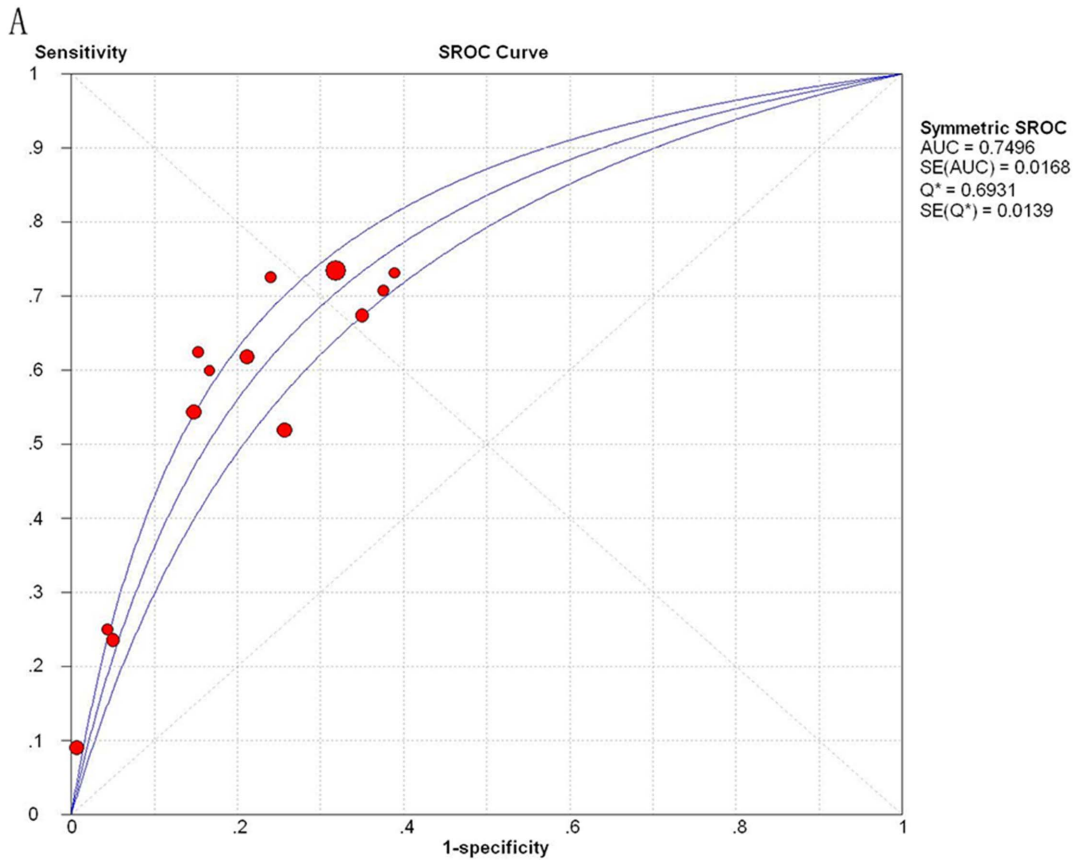
Figure 3. Meta-analysis of Hepatitis B-Related significant fibrosis. (A) SROC curve of the FIB-4; (B) Diagnostic odds ratio of the FIB-4.
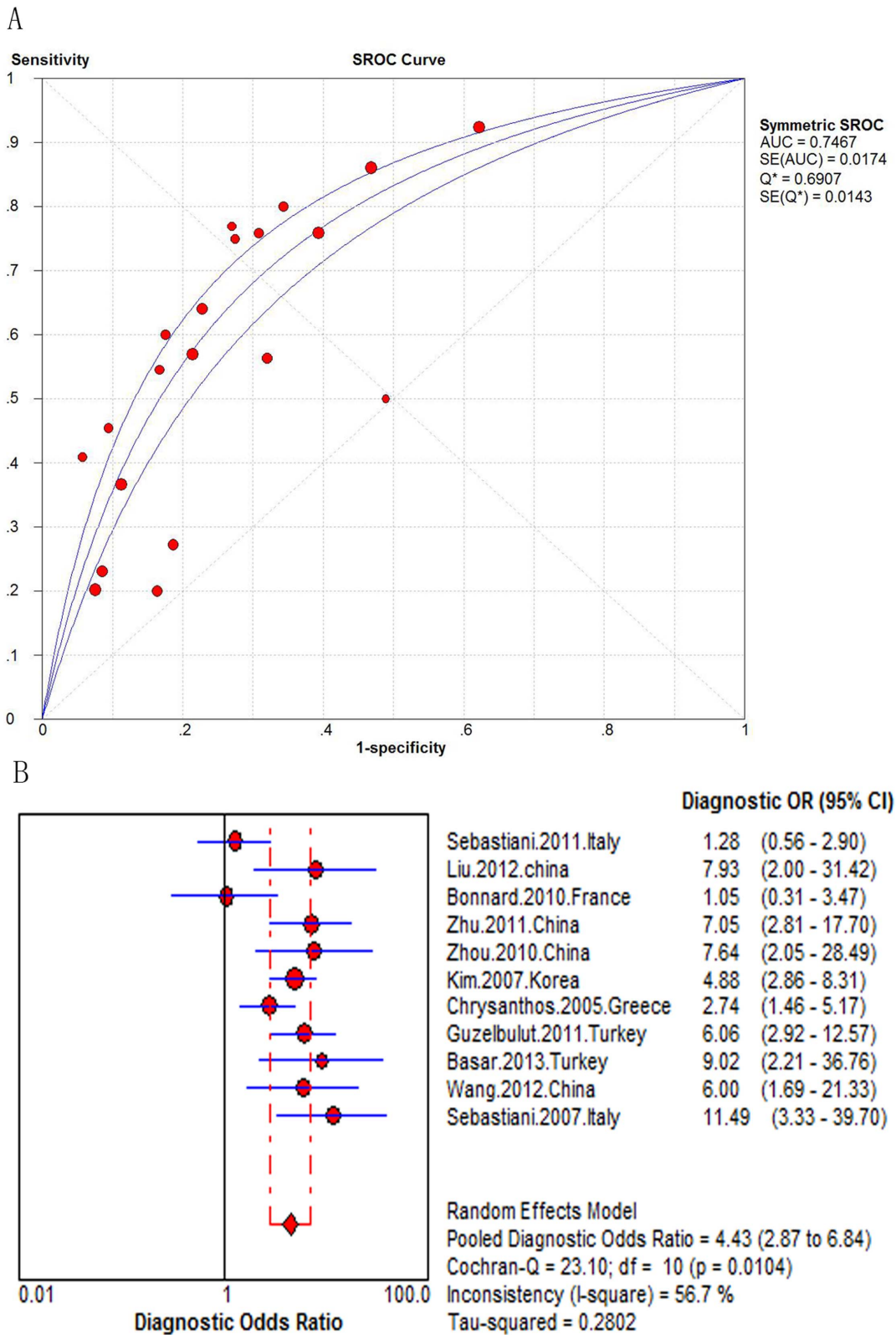doi:10.1371/journal.pone.0100182.g003

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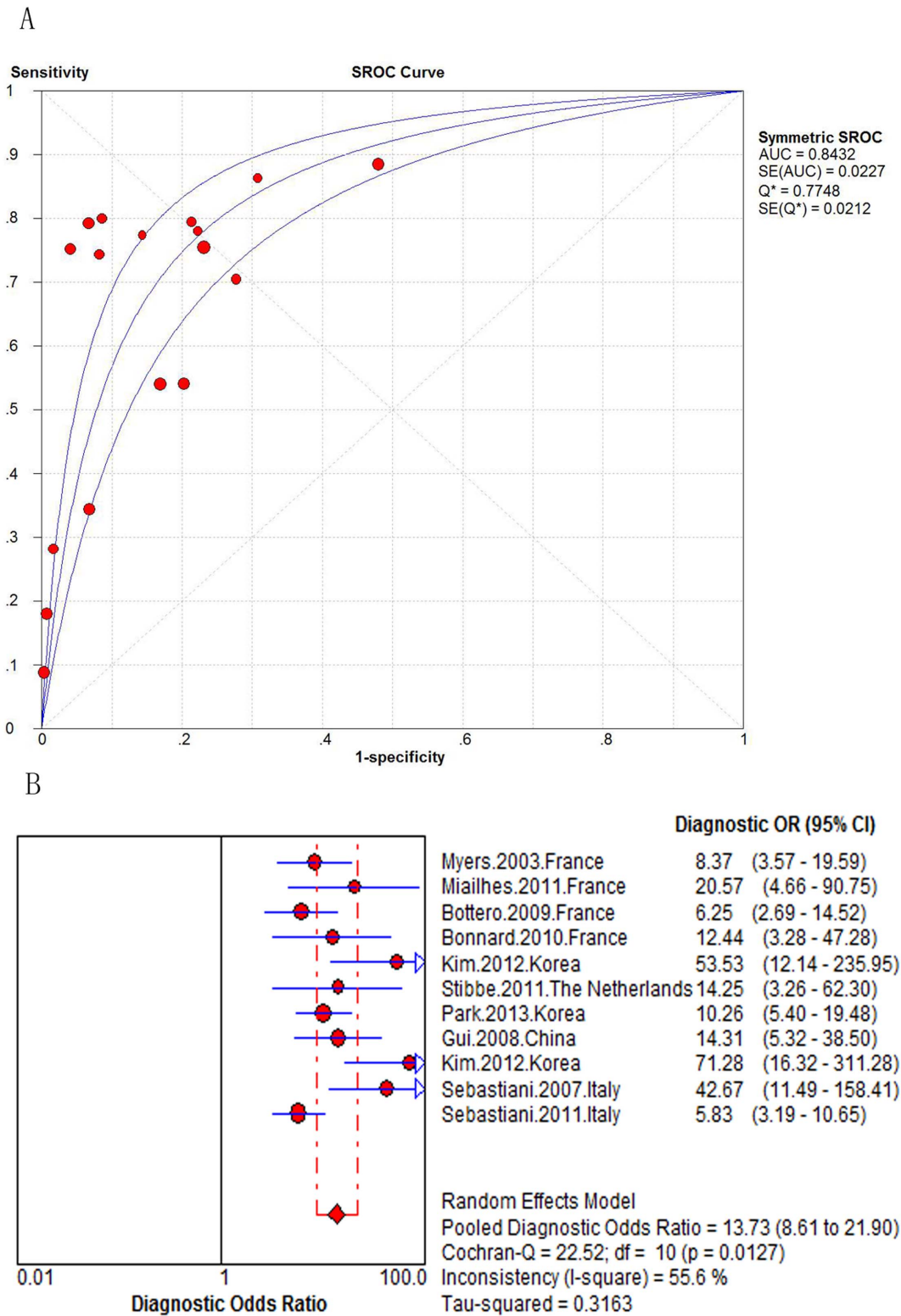
Figure 4. Meta-analysis of Hepatitis B-Related significant fibrosis. (A) SROC curve of the FibroTest; (B) Diagnostic odds ratio of the FibroTest.
doi:10.1371/journal.pone.0100182.g004

bivariate meta-analytic approach [30]. Pairs of sensitivity and specificity for diagnostic thresholds are jointly analyzed, with any correlation that might exist between those two measures taken into account using a random-effects approach.

The heterogeneity (or the lack of homogeneity) of the results between studies was assessed statistically using the Cochran-Q and the quantity I2. I2 value describes the percentage of total variation across studies that is attributable to heterogeneity rather than

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Figure 5. Meta-analysis of Hepatitis B-Related cirrhosis. (A) SROC curve of the APRI; (B) Diagnostic odds ratio of the APRI.
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chance [31]. A meta-regression was conducted to further explore the covariates that may induce heterogeneity, according to the following predefined characteristics: (a) study design (retrospective or prospective); (b) etiology (HBV, HBV[HBeAg negative], or co-infection with other virus); (c) length of liver specimen (≥10 mm, ≥15 mm, ≥20 mm, or not); (d) liver biopsy scoring system

Table 3. Summary Sensitivities and Specificities of the APRI at Different Diagnostic Thresholds for the Prediction of Cirrhosis.

Test Threshold	Number of Studies	SROC	Summary Sensitivity(95%CI)	Summary Specificity(95%CI)
<1.0	5(1,228)	0.76	84% (79%–88%)	54% (51%–58%)
1	6(1,471)	0.76	62% (55%–68%)	75% (72%–77%)
2	6(1,409)	0.79	29% (23%–35%)	89% (87%–91%)

APRI, aspartate aminotransferase-to-platelet ratio index; 95%CI, 95% confidence interval.
doi:10.1371/journal.pone.0100182.t003

(METAVIR, Ishak, Scheuer, Batts and Ludwig, and the Chinese Hospital System); (e) QUADAS score; (f) sample size; (g) median age ($\leq$30, 31–40,41–50, or >50); (h) percentage of males; (i) location of study (Europe or Asia); (j) prevalence of significant fibrosis/cirrhosis.

The potential publication bias was assessed using the Deeks funnel plots (the logarithm of the DOR plotted against

$$1/\sqrt{ESS}$$

) [32].

$$1/\sqrt{ESS}$$

is proportional to the square root of $(1/n1+1/n2)$, where n1 is the number diseased and n2 not diseased. Data analyses were performed using the Meta-Disc software (v. 1.4).

Results

Search Results

The study selection process is presented with a flow chart in Figure 1. 306 studies were retrieved with the described search strategies, of which 196 were excluded following title and abstract screening. The full texts of 110 potentially eligible reports were obtained for further assessment. Of those, 30 papers were included in the review following full-text screening (Table 1); 20 studies were related to the APRI [3,16,17,33–49], 13 studies related to the FIB-4 [3,7,17,39–46,48,50], and 11 studies related to the FibroTest [47–49,51–58].

Characteristics of the Included Studies

In the twenty APRI studies, a total of 4,208 patients (median age 36 yr, 72% male) were included. The overall prevalence of significant fibrosis and cirrhosis were 47% (ranged 17%–70%) and 11% (7%–27%), respectively. The liver biopsy scoring system used to classify the histology varied. 10 studies used a METAVIR score, 4 studies used an Ishak score, 4 studies used a Scheuer score, 1 study used a Batts and Ludwig score, and 1 study used the Chinese Hospital System. Nineteen of these studies (N = 3,955) included HBV-infected patients without comorbid conditions [3,16,17,33–48]. The one remaining study included special populations of patients such as HBV/HDV-coinfected patients (N = 253) [59]. According to the QUADAS scale, eight studies met all 14 requirements of this scale, nine studies met 13, two studies met 12, and one study met 11.

A total of 2,953 patients (median age 36 yr, 70% male) were included in the thirteen studies on FIB-4. The overall prevalence of significant fibrosis and cirrhosis were 53% (ranged 17%–76%) and 15% (11%–34%), respectively. All those studies (N = 2,953) included HBV-infected patients without comorbid conditions. The

liver biopsy scoring system used to classify the histology varied. Six studies used a METAVIR score, three studies used a Scheuer score, two studies used an Ishak score, one study used a Batts and Ludwig score, and one study used the Chinese Hospital System. Seven studies met all 14 requirements of the QUADAS scale, 4 studies met 13, 1 study met 12, and one study met 11.

There were 1,640 patients (median age 42 yr, 69% male) used to assess the performance of FibroTest in eleven studies. The overall prevalence of significant fibrosis and cirrhosis were 63% (ranged 39%–85%) and 20% (8%–39%), respectively. Seven of these studies (N = 1,011) included HBV-infected patients without comorbid conditions [47,48,54–58]. The four remaining studies included special populations with HBV/HDV-coinfected patients (N = 462) [49,51], HBV/HIV-coinfected patients (N = 59) [52], and HBV/HDV/HIV-coinfected patients (N = 108) [53]. According to the Quality Assessment of Diagnostic Accuracy Studies scale, we can see that 5 studies met all 14 requirements of this scale, 2 study met 13, 3 studies met 12, and 1 study met 10.

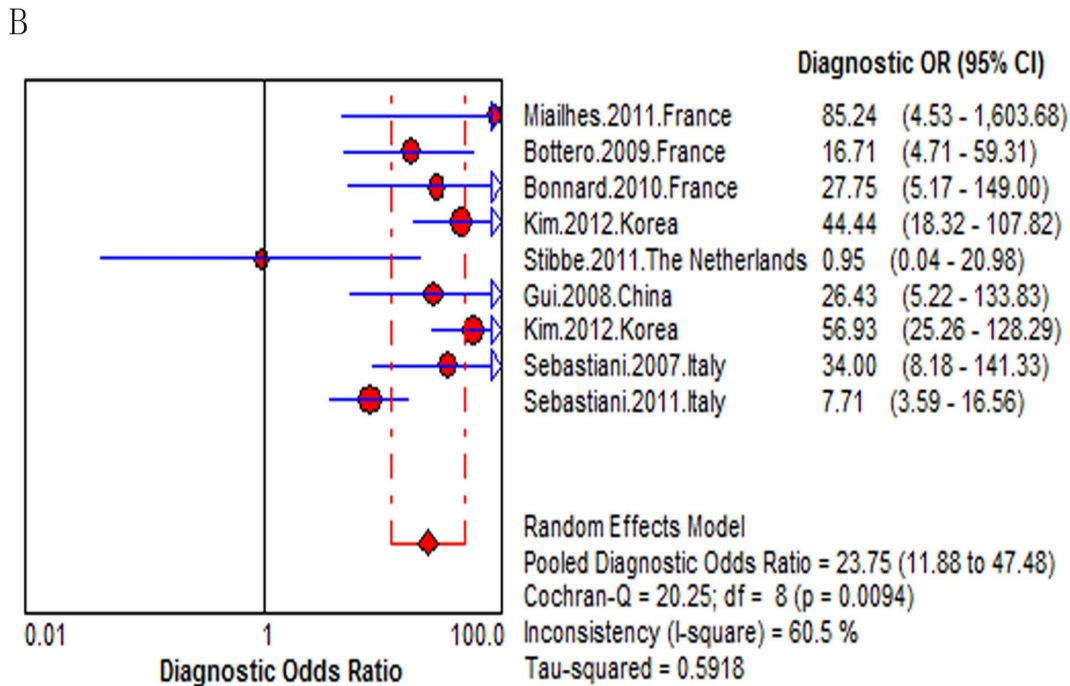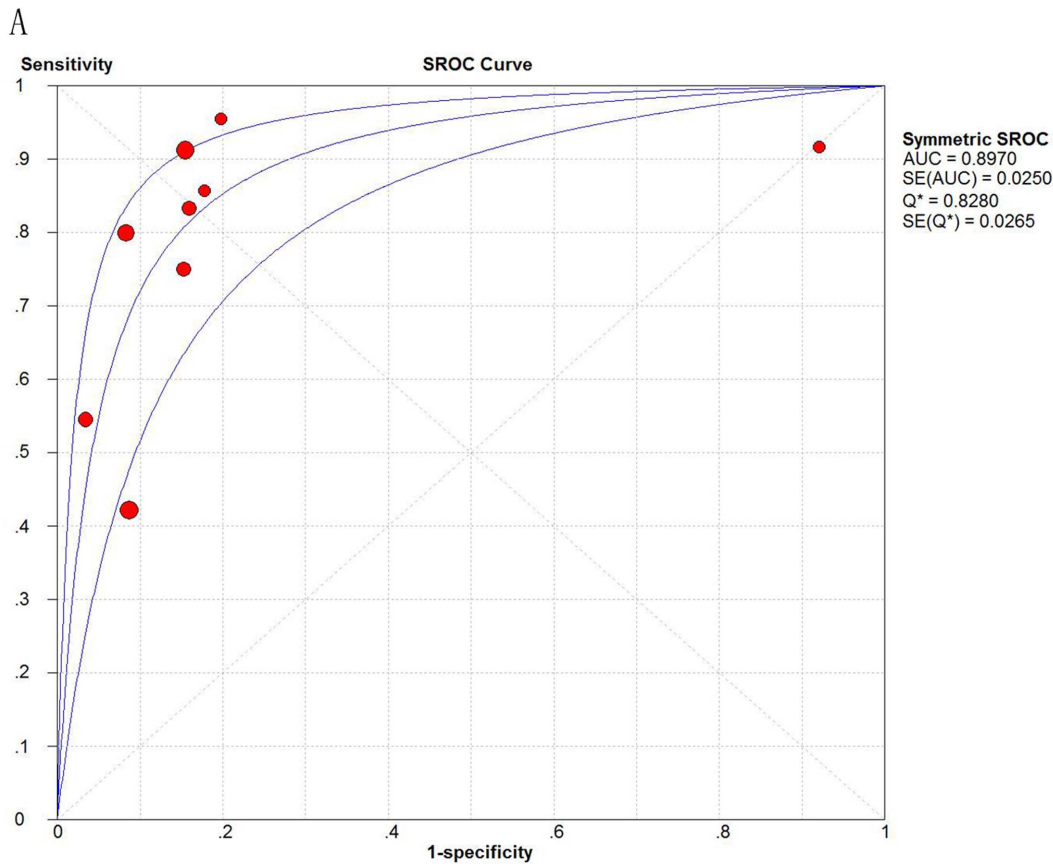### Diagnostic Accuracy for the Prediction of Significant Fibrosis

In the seventeen studies assessing the APRI (N = 3,573), the AUROC curve ranged from 0.61 to 0.86. When combined, the area under the SROC curve was 0.77 08 (SE = 0.0172) (Figure 2A). The Pooled DOR was 5.41 (95% confidence interval [CI] 3.98–7.35) (Figure 2B). The Cochran-Q *and* I^2 value of all measures were 38.32 and 58.2%, indicating significant heterogeneity across the included studies ($P = 0.001$) (Figure 2B). The pooled sensitivities and specificities could not be assessed. Instead, the sensitivities and specificities of the APRI at various diagnostic thresholds in the seventeen studies are listed in Table 2. We used the meta-regression analysis to explore the heterogeneity of the APRI accuracy for detecting significant fibrosis, which was mainly affected by median age ($P = 0.0211$, see Text S4 for meta-regression). There was no significant correlation between other covariates and the DOR.

In the ten studies assessing the FIB-4 for the prediction of significant Fibrosis (N = 1,996), the AUROC curve ranged from 0.69 to 0.77. When combined, the area under the SROC curve was 0.75 (SE = 0.0168) (Figure 3A). The summary DOR was 5.3 (95% CI 4.3–6.6), and the score of Cochran-Q is 7.54 ($P = 0.581$) (Figure 3B). The result from the analysis of the heterogeneity was statistically insignificant. The summary sensitivities and specificities of the FIB-4 were 65.8% (95% CI 62.4%–69.1%) and 73.6% (95% CI 70.8%–76.3%), respectively (Figure S1–S2).

The AUROC curve ranged from 0.69 to 0.90 in the 11 studies assessing the FibroTest (N = 1.640). When combined, the area under the SROC curve was 0.84 (SE = 0.0227) (Figure 4A). The summary DOR was 13.73 (95% CI 8.61–21.90), and the score of Cochran-Q is 22.52, indicating significant heterogeneity across the included studies ($P = 0.0127$) (Figure 4B). We didn't find the cause of the heterogeneity of FibroTest accuracy according to the

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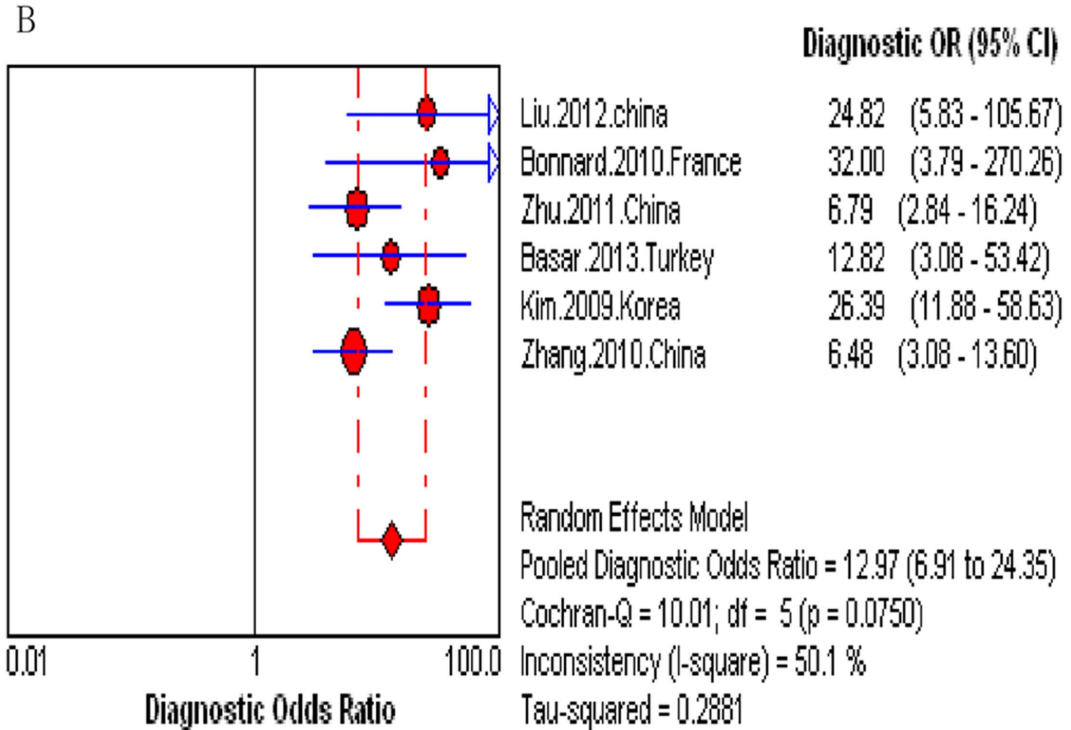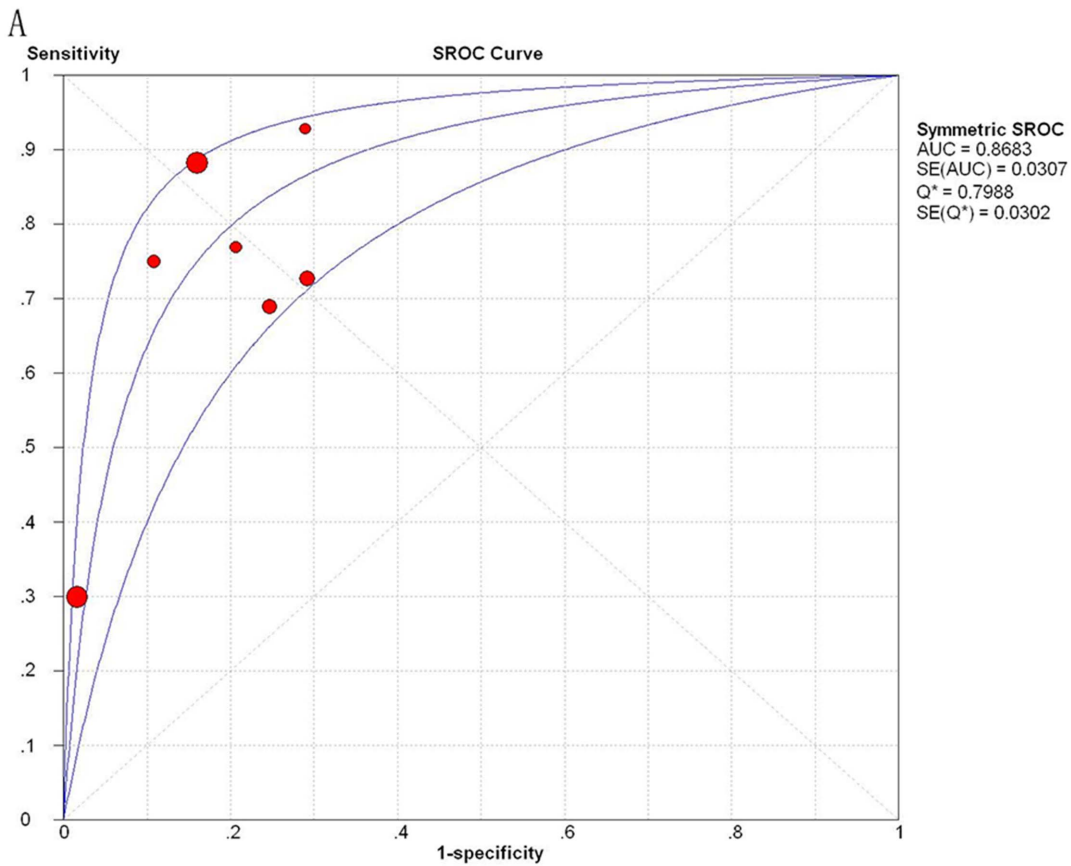
Figure 6. Meta-analysis of Hepatitis B-Related cirrhosis. (A) SROC curve of the FIB-4; (B) Diagnostic odds ratio of the FIB-4.
doi:10.1371/journal.pone.0100182.g006

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Figure 7. Meta-analysis of Hepatitis B-Related cirrhosis. (A) SROC curve of the FibroTest; (B) Diagnostic odds ratio of the FibroTest.
doi:10.1371/journal.pone.0100182.g007

predefined characteristics. But center description might affect heterogeneity beyond the predefined design (See Text S5).

Diagnostic Accuracy for the Prediction of Cirrhosis

There were 11 studies on assessing the APRI for the predication of cirrhosis (N = 2,083). The AUROC curve of these studies ranged from 0.50 to 0.83. When combined, the area under the

Table 4. Diagnostic Accuracy of FibroTest for the Prediction of Significant Fibrosis and Cirrhosis in Various Studies.

Author,Year	Cutoff	Sensitivity	Specificity	PPV	NPV	AUROC(95%CI)
Significant Fibrosis						
Sebastiani, 2011	0.48	54%	83%	81%	57%	0.69(0.63–0.75)
Myers, 2003	0.2	89%	52%	43%	92%	0.78(0.74–0.82)
	0.4	54%	80%	52%	81%	
	0.6	34%	93%	68%	78%	
	0.8	18%	99%	92%	75%	
	1	8%	100%	100%	73%	
Miailhes, 2011	0.38	77%	85%	89%	72%	0.86(0.75–0.96)
Bottero, 2009	0.48	70%	72%	77%	65%	0.77(0.68–0.86)
Bonnard, 2010	0.37	78%	78%	89%	61%	0.79(0.66–0.91)
Kim, 2012	0.32	79%	93%	98%	45%	0.90(0.84–0.97)
Stibbe, 2011	0.31	86%	69%	70%	86%	NA
Park, 2013	0.32	75%	77%	93%	43%	NA
Gui, 2008	0.31	79%	79%	70%	86%	0.84(0.75–0.93)
	0.4	74%	92%	85%	85%	0.84(0.75–0.93)
	0.72	28%	98%	92%	68%	0.84(0.75–0.93)
Kim, 2012	0.31	75%	96%	98%	61%	0.9(0.85–0.94)
Sebastiani, 2007	F2	80%	91%	95%	68%	0.85(0.75–0.95)
Cirrhosis						
Sebastiani, 2011	0.75	42%	91%	51%	88%	0.68(0.63–0.73)
Miailhes, 2011	0.58	100%	81%	56%	100%	0.92(0.85–0.99)
Bottero, 2009	0.73	75%	85%	46%	95%	0.87(0.79–0.94)
Bonnard, 2010	0.5	86%	82%	60%	95%	0.85(0.74–0.96)
Kim, 2012	0.68	80%	92%	87%	87%	0.87(0.82–0.92)
Stibbe, 2011	0.75	100%	7%	11%	100%	NA
Gui, 2008	0.55	83%	84%	42%	97%	0.86(0.71–1.00)
Kim, 2012	0.67	91%	85%	85%	91%	0.88(0.83–0.94)
Sebastiani, 2007	F4	55%	97%	80%	89%	0.76(0.67–0.85)

SROC curve was 0.75 (SE = 0.0174) (Figure 5A). The summary DOR was 4.4 (95% CI 2.9–6.8). The heterogeneity occurred in the meta-analysis for the twelve studies assessing the APRI for the predication of cirrhosis, which was statistically significant (Q = 23.10, $P = 0.01$; $I^2 = 56.7\%$, Figure 5B). However, when we further conducted the meta-analysis at the different thresholds of <1.0, 1.0, and 2.0, we found that the heterogeneity wasn't statistically significant (Figure S3). The summary sensitivity and specificity of the APRI at different diagnostic thresholds are listed in Table 3.

According to the meta-regression analysis, the heterogeneity of APRI accuracy for detecting cirrhosis was mainly affected by etiology ($P = 0.0159$) (See Text S6), whereas the other covariates were not significant. After excluding the only one study which included HBV/HDV-coinfected patients, the pooled DOR was 5.03 (95% CI 3.45–7.35) and heterogeneity was no longer significant (Q = 14.05, $P = 0.1204$; $I^2 = 36.0\%$).(Figure S4) According to the meta-analysis, the pooled sensitivity and specificity were 60.9% (95% CI 55.0–66.6%) and 74.8% (72.4–77.1%), respectively (Figures S5–S6).

The AUROC curve in the six studies assessing the FIB-4 (N = 1,304) ranged from 0.74 to 0.93. When combined, the area

under the SROC curve was 0.87 (SE = 0.0307) (Figure 6A). The summary DOR was 12.97 (95% CI 6.91–24.35) and the score of Cochran-Q is 10.01 ($P = 0.07$) (Figure 6B). The analysis showed that the heterogeneity was statistically insignificant. The summary sensitivities and specificities of the FIB-4 were 44.7% (95% CI 39.4%–50.2%) and 86.6% (95% CI 84.3%–88.7%), respectively (Figures S7–S8).

In the nine studies assessing the FibroTest (N = 1101), the AUROC curve ranged from 0.68 to 0.92. When combined, the area under the SROC curve was 0.90 (SE = 0.0250) (Figure 7A). The summary DOR was 23.75 (95% CI 11.88–47.48) and the score of Cochran-Q is 20.25 ($P = 0.0094$) (Figure 7B). The heterogeneity was statistically significant. The pooled sensitivities and specificities could not be assessed. Instead, the sensitivities and specificities of the FibroTest at various diagnostic thresholds in the nine studies are listed in Table 4.

According to the meta-regression analysis, the heterogeneity of FibroTest accuracy for detecting cirrhosis was mainly affected by sample size ($P = 0.0385$) and median age ($P = 0.0436$) (Text S7), whereas the other covariates were not significant.
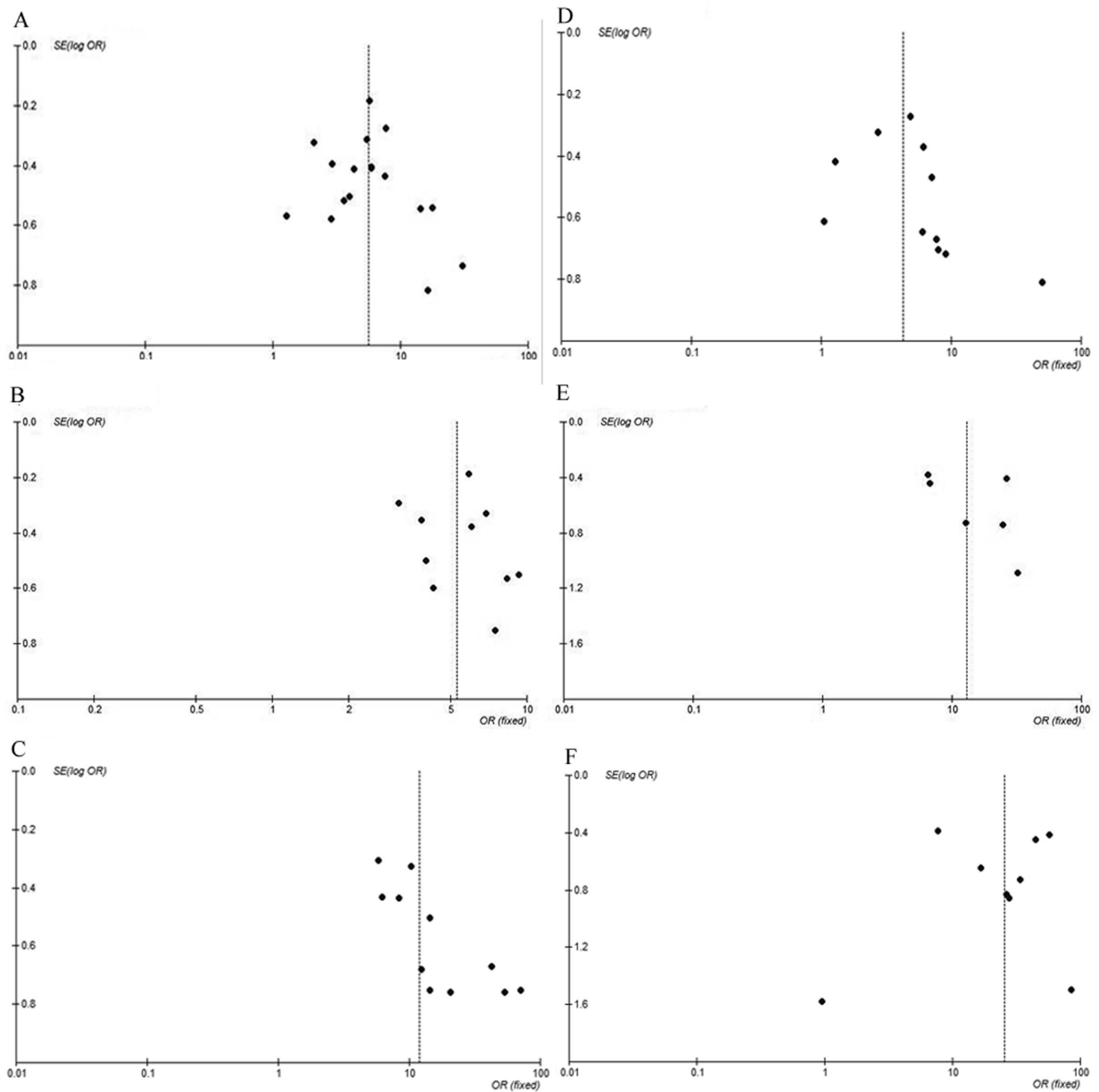
Figure 8. Funnel plot of publication bias. (A) APRI to predict significant fibrosis; (B) FIB-4 to predict significant fibrosis; (C) FibroTest to predict significant fibrosis; (D) APRI to predict cirrhosis; (E)FIB-4 to predict cirrhosis; (F) FibroTest to predict cirrhosis.
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Publication Bias

Funnel plots of these three markers for assessing possible publication bias are illustrated in Figure 8. Mild asymmetry was noted in the funnel plots of the FIB-4 and FibroTest.

Discussion

Liver fibrosis progression is commonly found in HBV-infected patients. Cirrhosis develops in approximately one third of those cases, usually after an extensive period of time during which liver biochemical indices are found to be predominantly or even persistently abnormal [1]. Patients with significant fibrosis or

cirrhosis should be considered for antiviral therapy, which can potentially reverse cirrhosis and reduce complications [60]. Considering the limitations and risks of biopsy, the researchers make persistent efforts in exploring some noninvasive markers in order to more accurately identify patients with significant fibrosis or cirrhosis. APRI, FIB-4 and FibroTest are such noninvasive markers gaining increasing acceptance in clinical practice. Those markers may reduce the need for liver biopsy and may help to monitor the efficacy of treatment [47].

In our systematic review, the diagnostic accuracy of the APRI, FIB-4 and FibroTest for HBV-related significant fibrosis and cirrhosis has been comprehensively evaluated and summarized on

a large scale, and we confirmed the results of many individual studies. Our meta-analysis also included the description of multiple measures of test performance using confirmed meta-analytic techniques and formal assessment for publication bias and heterogeneity, as well as exploratory analysis. All results should be valid and reasonably reliable.

FibroTest had the best result in not only significant fibrosis but also cirrhosis. The area under the SROC curve of FibroTest is bigger and even reaches the standard of "better" on cirrhosis [15], and the summary sensitivity and specificity have reached 84% and 82%, respectively. A meta-analysis about HCV-infected patients showed that the area under the SROC curve of significant fibrosis and cirrhosis are 0.81 and 0.90 [12]. Evidently, the performance of FibroTest in evaluating HBV-related fibrosis is no worse than HCV-related. Therefore, FibroTest could be considered as a better marker in assessing fibrosis and cirrhosis of HBV-infected patients. The FibroTest, however, is calculated with alpha2 macroglobulin, alpha2 globulin (or haptoglobin), gamma globulin, apolipoprotein A1, GGT and total bilirubin [61]. Alpha2 macroglobulin and alpha2 globulin (or haptoglobin) are not routine clinical measurements, and those two indicators are not tested for patients in most hospitals. Furthermore they cost more than conventional indicators. Those factors may bring restrictions to the wider application of the FibroTest in clinical practice.

The calculation method of FIB-4 is simpler than that of FibroTest. The area under the SROC curve of FIB-4 predicting HBV-related significant fibrosis and cirrhosis are 0.75 and 0.87, respectively. FIB-4 also has a better performance of predicting fibrosis [7]. Its test items are easy to obtain in clinical practice, although its predictive results are not as good as FibroTest [11,14]. APRI shows lower diagnostic accuracy than FibroTest and Fib-4 to identify HBV-related significant fibrosis and cirrhosis. It has been introduced to assess HBV-related fibrosis the earliest because of its simple and easy practice. Presently, APRI is widely utilized in identifying the degree of fibrosis and cirrhosis of patients with hepatitis C and hepatitis B, particularly in regions with limited healthcare resources. Some scholars argue that the calculation method of APRI did not consider the factor of spleen size [35]. If patients were grouped by spleen size, the performance of APRI in predicting HBV-related fibrosis would be improved. Our meta-analysis revealed that the area under the SROC curve of APRI was small and the accuracy of the evaluation of HBV-related fibrosis was poor. Our results showed similar performance of APRI for staging of significant fibrosis and cirrhosis [62].

Meta-regression method was convenient and reliable to screen the factors of heterogeneity. The strength of our study is that meta-regression analysis has been used to explore several factors that may be responsible for heterogeneity. Liver biopsy scoring systems and percentage of males emerged from many relevant factors to provide heterogeneity to summary test result on APRI to predict significant fibrosis [62]. On the other hand, etiology of cirrhosis was found to be significantly associated with the heterogeneity on APRI to predict cirrhosis. But the heterogeneity of the meta-analysis of the FIB-4 and FibroTest to predict significant fibrosis and cirrhosis was not statistically significant. FIB-4 and FibroTest to predict fibrosis had better consistency, and summary test results were reasonably reliable.

However, there are several limitations in our systematic review. Firstly, we only focused our analysis on those patients with HBV-related fibrosis, without distinguishing between HBeAg negative and positive cases, or considering the virus replication rate due to the limited number of publications. Secondly, we included studies published in English and Chinese languages only, so the language bias may influence the results to some extent. Lastly, Fibroscan, a widely noninvasive tool, was not considered in this meta-analysis, because our focus was to compare the serum markers calculated by biochemical examination.

In summary, the FibroTest has excellent diagnostic accuracy for the identification of HBV-related significant fibrosis and cirrhosis. But FibroTest is seldom applied in clinical practice as a result of expensive cost. FIB-4, a relatively moderate marker, has better summary diagnostic accuracy and could be measured and calculated relatively easily. Furthermore, APRI shows some limited value in identifying hepatitis B-related significant fibrosis and cirrhosis. All of them have their own advantages and disadvantages. Future studies of novel fibrosis markers are needed to demonstrate improved accuracy and cost-effectiveness compared with those simple, economical, and widely available indeces.

Supporting Information

Figure S1 Sensitivity of FIB-4 detecting significant fibrosis.
(TIF)

Figure S2 Specificity of FIB-4 detecting significant fibrosis.
(TIF)

Figure S3 DOR of APRI cirrhosis (subgroup).
(TIF)

Figure S4 DOR of APRI cirrhosis excluded patients with HBV and HDV coinfected.
(TIF)

Figure S5 Sensitivity of APRI cirrhosis excluded patients with HBV and HDV coinfected.
(TIF)

Figure S6 Specificity of APRI cirrhosis excluded patients with HBV and HDV coinfected.
(TIF)

Figure S7 Sensitivity of Fib-4 detecting cirrhosis.
(TIF)

Figure S8 Specificity of Fib-4 detecting cirrhosis.
(TIF)

Checklist S1 PRISMA checklist of items.
(DOC)

Text S1 Systematic review protocol.
(DOC)

Text S2 Search strategies.
(DOC)

Text S3 Quadas checklist.
(DOC)

Text S4 Meta-regression of APRI detecting significant fibrosis.
(DOC)

Text S5 Meta-regression of FibroTest detecting significant fibrosis.
(RTF)

Text S6 Meta-regression of APRI detecting cirrhosis.
(RTF)

Text S7 Meta-regression of FibroTest detecting cirrhosis.
(RTF)

Author Contributions

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