Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Lin ZH. et al. (2011) Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology*, 53(3):726-736.
Date of Review:	February 23, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☒ **Other: fibrosis, cirrhosis** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **HCV monoinfected and HCV/HIV co-infected patients** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **China** _____ **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	**NO**	**N/A**	**COMMENTS**
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; systematic review to assess the accuracy of aminotransferase-to-platelet ration index (APRI) for the diagnosis of hepatitis C-related fibrosis in HCV monoinfected and HCV/HIV co-infected individuals
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☐	☒	☐	
Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				

Efficacy	☐	☒	☐	
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Search of published articles through electronic databases. Articles were limited to English only.
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☐	☒	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Methodology clearly described
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	Use of APRI may be limited given that FibroTest and FibrooScan have a greater diagnostic accuracy to identify HCV-related fibrosis and cirrhosis
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	APRI is a tool with limited expense and widespread availability
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Hepatology*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Free access from http://onlinelibrary.wiley.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please got to Comments section***	☒	☐	☐	The study was partially supported by grants from the Natural Science Foundation of Shandong Province, China

Other relevant information: _____	☐	☐	☐	

Performance of the Aspartate Aminotransferase-to-Platelet Ratio Index for the Staging of Hepatitis C-Related Fibrosis: An Updated Meta-Analysis

Zhong-Hua Lin,[1,2]* Yong-Ning Xin,[2,3]* Quan-Jiang Dong,[2] Qing Wang,[2] Xiang-Jun Jiang,[2] Shu-Hui Zhan,[2] Ying Sun,[2] and Shi-Ying Xuan[2,3]

The aspartate aminotransferase-to-platelet ratio index (APRI), a tool with limited expense and widespread availability, is a promising noninvasive alternative to liver biopsy for detecting hepatic fibrosis. The objective of this study was to update the 2007 meta-analysis to systematically assess the accuracy of APRI in predicting significant fibrosis, severe fibrosis, and cirrhosis stage in hepatitis C virus (HCV) monoinfected and HCV / human immunodeficiency virus (HIV) coinfected individuals. Studies comparing APRI versus biopsy in HCV patients were identified via a thorough literature search. Areas under summary receiver operating characteristic curves (AUROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to examine the APRI accuracy for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis. Heterogeneity was explored using meta-regression. Twenty-one additional studies were eligible for the update and, in total, 40 studies were included in this review (n = 8,739). The summary AUROC of the APRI for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were 0.77, 0.80, and 0.83, respectively. For significant fibrosis, an APRI threshold of 0.7 was 77% sensitive and 72% specific. For severe fibrosis, a threshold of 1.0 was 61% sensitive and 64% specific. For cirrhosis, a threshold of 1.0 was 76% sensitive and 72% specific. Moreover, we found that the APRI was less accurate for the identification of significant fibrosis, severe fibrosis, and cirrhosis in HIV/HCV coinfected patients. *Conclusion:* Our large meta-analysis suggests that APRI can identify hepatitis C-related fibrosis with a moderate degree of accuracy. Application of this index may decrease the need for staging liver biopsy specimens among chronic hepatitis C patients. (HEPATOLOGY 2011;53:726-736)

Hepatitis C virus (HCV) infection, with an estimated prevalence of more than 170 million worldwide, is a major public healthcare problem.[1] Chronic hepatitis C (CHC) is the most common cause of cirrhosis and hepatocellular carcinoma (HCC), and the leading indication for liver transplantation in the United States and many Western countries. Cirrhosis and its disease-related complications are responsible for more than 40,000 deaths annually in the United States.[2] HCV chronic infection develops into chronic hepatitis in more than 70% of patients and in about 20% of them progresses to cirrhosis and eventually HCC.[3] In HCV monoinfected patients with compensated cirrhosis, the cumulative incidences of HCC, ascites, bleeding, and encephalopathy at 5 and 10 years were 7.8%/7%/2.5%/0% and 28%/20%/5%/2.5%, respectively.[4] Early diagnosis of cirrhosis is important in patients with CHC not only because it prompts screening for HCC and esophageal

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, area under the receiver operating characteristic curve; DOR, diagnostic odds ratio; HCV, hepatitis C virus; NPV, negative predictive value; PPV, positive predictive value; QUADAS, the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews; SROC, summary receiver operating characteristic curves.

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varices, but also because it is the important factor for initiation of treatment in patients with hepatitis C infection.[5]

At present, liver biopsy is still the most commonly used reference standard for the assessment of liver fibrosis. However, it is an invasive method that is associated with patient discomfort and in rare cases with serious complications.[6] In addition, the accuracy of liver biopsy is limited as a result of intra- and interobserver variability and sampling errors.[7] Furthermore, the dynamic process of liver fibrosis resulting from progression and regression cannot be easily quantified by liver biopsy. Therefore, much research has focused on the evaluation of noninvasive methods for the assessment of liver fibrosis. Ideally, such a test should be simple, readily available, inexpensive, and reliable and accurate in predicting liver fibrosis. To date, several laboratory tests and scores have been proposed for the noninvasive prediction of cirrhosis in patients with CHC, including direct biochemical markers of hepatic fibrosis (collagen, hyaluronic acid, laminin, and YKL-40), indirect biochemical markers of hepatic fibrosis (PGA index, Forns' index, Fibrotest, and Hepascore), radiological imaging, and transient elastography. Although several noninvasive direct and indirect serum markers (such as Fibrotest and Hepascore) have exhibited good diagnostic accuracy in some studies, most of these markers require complicated calculations, the use of a specialized set of biochemical markers, and are costly. These limit their application in clinical practice.

Recently, a novel index by combining aspartate aminotransferase (AST)-to-platelet ratio index (APRI) was reported to identify patients with hepatic fibrosis.[8] APRI is an indirect biochemical marker of hepatic fibrosis, based on routine laboratory parameters, reflecting alterations in hepatic function. Since the initial report in 2003 by Wai et al.,[8] an increasing number of studies have evaluated APRI for the diagnosis of liver fibrosis in a multitude of liver diseases with inconsistent results. In 2007, Shaheen and Myers[9] published a meta-analysis that included 4,266 patients to assess the accuracy of APRI in predicting HCV-related significant fibrosis and cirrhosis stage. However, it did not assess the value of APRI in predicting severe fibrosis stage. Furthermore, the results that APRI was more accurate for the identification of cirrhosis in HIV/HCV coinfected patients lacked sufficient data to support it.

In view of the uncertain clinical value of APRI in HCV/HIV coinfection and the limitations of the previous meta-analysis, we conduct an updated systematic review and meta-analysis to comprehensively assess the overall performance of APRI for the diagnosis of hepatitis C-related fibrosis and to analyze the heterogeneity between the available studies to date before its wide application in clinical practice.

Materials and Methods

Search Strategy. The objective of our search was to identify published articles of studies examining the APRI for the prediction of HCV-related fibrosis. An electronic search was completed on PubMed, EMBASE, and the Cochrane Library (01/2003-04/2010) including the following search terms: APRI, AST-to-platelet ratio index, AST, platelet, hepatitis C, and noninvasive fibrosis markers, and serum markers of liver fibrosis.[10] The language was limited to English only. Additional studies were identified via a manual review of the reference lists of identified studies and review articles.

Selection Criteria. Studies were included if they met the following inclusion criteria: (1) The study evaluated the performance of the APRI for the prediction of fibrosis in HCV-infected patients. Studies including patients with other causes of liver disease were included if data for HCV-infected patients could be extracted. (2) Liver biopsy was used as the reference standard for assessing fibrosis. (3) Data could be extracted to allow the construction of at least one 2×2 table of test performance, based on some cutoff point of the APRI for a fibrosis stage; If data were not available in the publication, corresponding authors were contacted to provide supplemental data. (4) They assessed the diagnostic accuracy for fibrosis stage $F\geq2$, $F\geq3$, or $F\geq4$ according to METAVIR or a comparable staging system. (5) The study included at least 30 patients. Smaller studies were excluded because of poor reliability.

Data Extraction and Quality Assessment. Two reviewers (Lin and Xin) independently evaluated study eligibility, graded quality, and extracted outcome data. Disagreements were resolved by consensus. These parameters included study publication year, region, method, patient sex, age, number, author, underlying chronic liver disease etiology, histological scoring system, average liver biopsy length, duration of time between biopsy and performance of APRI, prevalence of the fibrosis stage, as well as cutoff values to identify the fibrosis stage. To assess the quality of the studies included in the meta-analysis, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire was used.[11] This validated tool was designed to assess the internal and external validity of diagnostic accuracy studies included in systematic reviews.

The primary outcome was the identification of significant fibrosis, defined as METAVIR,[12] Batts and Ludwig,[13] or Scheuer[14] stages F2 through F4 or Ishak et al.[15] stages F3 through F6. This outcome was chosen because it is often considered a threshold for the initiation of antiviral therapy.[16] We also examined the identification of severe fibrosis (METAVIR, Batts and Ludwig, or Scheuer F3-4, or Ishak F4-6) and cirrhosis (METAVIR, Batts and Ludwig, or Scheuer F4, or Ishak F5-6).

Statistical Analysis and Data Synthesis. Where data were available, 2×2 tables were constructed to derive sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at each threshold value. To provide clinically meaningful results, three measures of diagnostic test accuracy were used to examine the APRI accuracy for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis: the area under the summary receiver operating characteristic curve (AUROC), summary sensitivities and specificities, and summary PPV and NPV based on the prevalence of fibrosis.

The Meta-Disc software (v. 1.4) and Stata 8.0 (College Station, TX) were used to analyze the reports and tests for sensitivity, specificity, and area under the summary receiver operating characteristic curves (SROC), as well as meta-regression approaches. Studies with a larger sample size and therefore a smaller standard error received more weight when calculating the mean AUROC.[17] The diagnostic odds ratio (DOR) describes the odds of a positive test in disease cases compared with noncases. As these analyses require a single measure of accuracy for each study and many reported multiple APRI thresholds, we calculated the average DOR among all thresholds per study.[18] Because of a priori assumptions about the likelihood for heterogeneity between primary studies, the random-effects model was used for pooled analyses. Wherever zero counts occurred for 2×2 tables, the value of 0.5 was added to all cells containing the value 0 to facilitate analysis. Heterogeneity of accuracy estimates across studies was evaluated using the I^2 statistic, which describes the percentage of the variability in estimates that is due to heterogeneity rather than sampling error (chance). A value >50% may be considered substantial heterogeneity.[19]

A meta-regression technique was used to explore the factors that may induce the heterogeneity, according to the following predefined characteristics: (a) study design (retrospective versus prospective); (b) etiology (HCV versus HCV/HIV); (c) blinded interpretation of APRI and reference standard (yes versus no); (d) liver biopsy length (≥15 mm or not); (e) liver biopsy scoring system (METAVIR, Ishak, Batts Ludwig, and Scheuer); (f) QUADAS score; (g) sample size; (h) median age; (i) percentage of males; (j) location of study (North America, Europe, and other); (k) prevalence of significant fibrosis / severe fibrosis / cirrhosis. To assess possible publication bias, we examined for asymmetry of funnel plots of the accuracy for detecting fibrosis (using the natural logarithm of the DOR) versus the inverse of the square root of the effective sample size.[20]

Results

Search Results. A total of 113 studies were retrieved based on the described search strategies. In all, 57 eligible studies were identified for evaluation. Ultimately, 17 studies were excluded for insufficient data (n = 11), mixed etiology (n = 4), or failure to use biopsy as the reference test (n = 2) (Fig. 1). Thus, our final dataset for the meta-analysis included 40 studies.[8,21-59]

The main features of the studies included in the meta-analyses are shown in Table 1. A total of 8,739 patients (median age, 46 years; 66% male) were included. The overall prevalence of significant fibrosis, severe fibrosis, and cirrhosis were 46% (range, 9%-79%), 28% (range, 9%-59%), and 19% (range, 4%-33%), respectively. The fibrosis staging system used to classify the histology varied. Eighteen studies used a METAVIR score, 12 studies used an Ishak score, six studies used a Batts and Ludwig score, and four studies used a Scheuer score. Thirty studies included HCV monoinfected patients (n = 6,891), and 10 included HIV/HCV coinfected patients (n = 1,848). According to the QUADAS scale, the methodological quality of the included studies was excellent (Table 2).

Diagnostic Accuracy for the Prediction of Significant Fibrosis. Thirty-three studies in 6,259 patients assessed the APRI for the prediction of significant fibrosis. The average prevalence of significant fibrosis in these studies was 46% (range, 9%-79%). When combined, the area under the AUROC was 0.77 (SE = 0.012) (Fig. 2). The summary DOR was 6.19 (5.13-7.49), and heterogeneity was not significant in the analysis of significant fibrosis stage (Q = 54.93, I^2 = 39.9%). The summary sensitivities and specificities of the APRI at various thresholds for the identification of significant fibrosis are listed in Table 3. At the lower threshold of 0.5 recommended by Wai et al., the summary sensitivities and specificities were 74% (95% confidence interval [CI], 73%-76%) and 49% (47%-51%), respectively. At the higher recommended cutoff of 1.5, the summary sensitivities and specificities

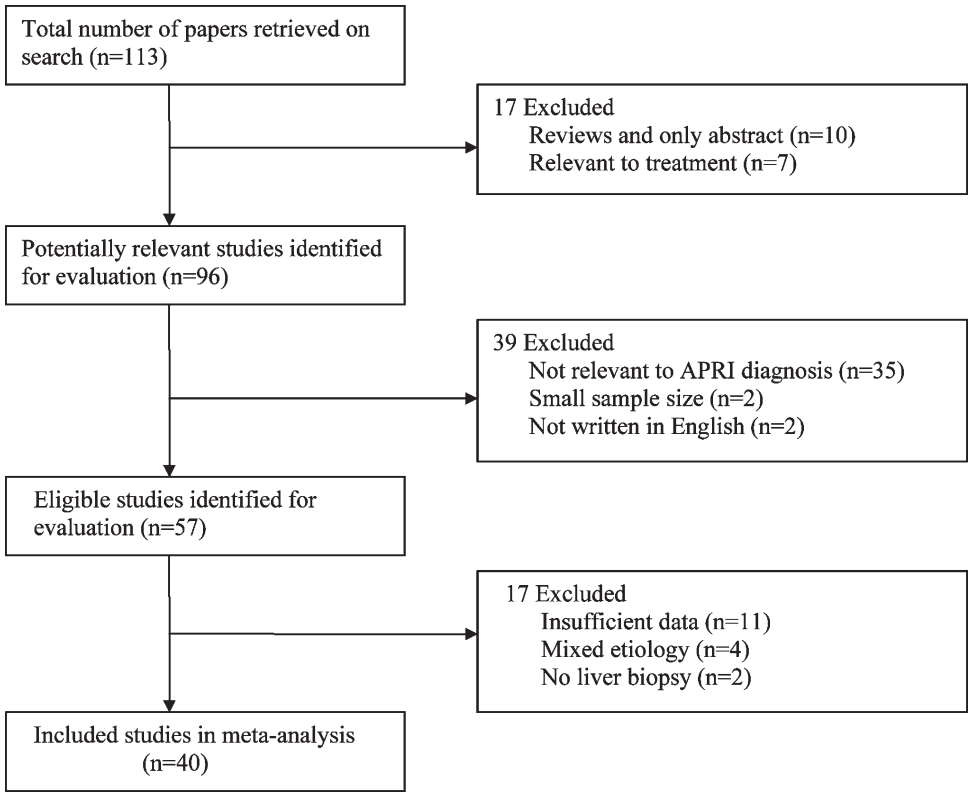

Fig. 1. Flow diagram of study identification.

were 37% (95% CI, 35%-39%) and 93% (91%-94%), respectively. At the optimal threshold of 0.7, the summary sensitivities and specificities were 77% (95% CI, 72%-81%) and 72% (66%-77%), respectively. Based on these values, and assuming a 46% prevalence of significant fibrosis (as observed in the 33 included studies), the estimated PPV and NPV of the 0.5 cutoff were 55% and 69%, respectively. At the 1.5 cutoff, the estimated PPV and NPV were 82% and 63%, respectively. At the 0.7 cutoff, the estimated PPV and NPV were 70% and 79%, respectively.

According to the meta-regression analysis, APRI accuracy for detecting significant fibrosis was affected by blinding ($P = 0.008$), with a mean AUROC of 0.80 for studies in which the pathologists were blinded for blood tests, and 0.74 for studies in which the pathologists were not blinded for blood tests. Part of the heterogeneity was explained by liver biopsy scoring system (AUROC of 0.77 for METAVIR; AUROC of 0.76 for Ishak; AUROC of 0.79 for Batts Ludwig; and AUROC of 0.77 for Scheuer). In addition, the AUROC of APRI for detecting HCV monoinfection and HCV/HIV coinfection-related significant fibrosis were 0.79 and 0.75, respectively. However, this difference was not statistically significant in meta-regression analysis. Moreover, the other covariates were not significant (data not shown). An analysis for funnel plot asymmetry suggested possible publication bias for the prediction of cirrhosis ($P = 0.002$) (Supporting Information Fig. A1).

Diagnostic Accuracy for the Prediction of Severe Fibrosis. Thirteen studies in 4,441 patients assessed the APRI for the prediction of severe fibrosis. The average prevalence of severe fibrosis in these studies was 28% (range, 9%-59%). When combined, the AUROC was 0.80 (SE = 0.023) (Fig. 3). The summary DOR was 2.24 (1.84-2.73), and heterogeneity was not significant in the analysis of severe fibrosis stage ($Q = 5.09$, $I^2 = 0$). The summary sensitivities and specificities of the APRI at various thresholds for the identification of severe fibrosis are listed in Table 3. At the optimal threshold of 1, the summary sensitivities and specificities were 61% (95% CI, 57%-65%) and 64% (61%-66%), respectively. Based on these values, and assuming a 28% prevalence of severe fibrosis (as observed in the 13 included studies), the estimated PPV and NPV of the 1 cutoff were 40% and 81%, respectively.

According to the meta-regression analysis, APRI accuracy for detecting severe fibrosis was not affected by the covariates. In addition, the AUROC of APRI for detecting HCV monoinfection and HCV/HIV coinfection-related severe fibrosis were 0.80 and 0.76, respectively. However, this difference was not statistically significant in meta-regression analysis. According

Table 1. Characteristics of the 40 Studies Included in the Meta-Analysis

	Author, Year, Region	Study/Center Description	N	Interval Between Biopsy & APRI	Median/Mean Age, yr (% male)	Etiology	Liver Biopsy Scoring System	Blind	Liver Biopsy Median Length	Prevalence of Significant Fibrosis, Severe Fibrosis, Cirrhosis	QUADAS Score
1	Cals, 2010, France	Prospective, multicenter	169	≤3 months	41 (65%)	HCV+HIV	METAVIR	Yes	25±12 mm	66%, 33%, 20%	13
2	Macas, 2010, Spain	Retrospective, multicenter	519	Unclear	43 (79%)	HCV+HIV	METAVIR	No	15 (12-20) mm	51%, 26%, 12%	11
3	Boursier, 2009,France	Retrospective, multicenter	1056	≤3 months	46 (60%)	HCV	METAVIR	Yes	21±8 mm	52%, 25%, 11%	13
4	Castera, 2009, France	Retrospective, one center	298	Same time	52 (57%)	HCV	METAVIR	Yes	19.5±7.8 mm	75%, 42%, 23%	14
5	Corradi, 2009, Italy	Retrospective, one center	36	Same time	58 (83%)	HCV	METAVIR	Yes	29 (16-55) mm	36%, 14%, 3%	13
6	Schiavon, 2009,Brazil	Retrospective, one center	102	≤6 months	44 (60%)	HCV	METAVIR	Yes	13.9±3.9 mm	20%, NA, NA	14
7	Tural, 2009, Spain	cohort, one center	324	Unclear	38 (72%)	HCV+HIV	Scheuer	Yes	1.8±0.9 mm	48%, 29%, 6%	12
8	Carvalho-Filho, 2008, Brazil	Retrospective, one center	111	≤6 months	40 (73%)	HCV+HIV	METAVIR	Yes	14.5±4.0 mm	41%, 25%, 18%	14
9	Cheung, 2008, USA	Prospective, multicenter	490	Same time	49 (98%)	HCV	Batts Ludwig	No	Unclear	66%, 38%, 14%	11
10	Dinesen, 2008, Germany	Retrospective, one center	96	Unclear	48 (57%)	HCV	Batts Ludwig	Yes	Unclear	91%, 59%, 28%	11
11	Khan, 2008, Pakistan	Retrospective, one center	120	Unclear	37 (69%)	HCV	METAVIR	Yes	Unclear	54%, 26%, 8%	12
12	Loko, 2008, France	Retrospective, one center	200	Unclear	40 (67%)	HCV+HIV	METAVIR	Yes	15.7±7.5 mm	79%, 36%, 20%	13
13	Paggi, 2008, Italy	Prospective, multicenter	430	Unclear	53 (55%)	HCV	METAVIR	Yes	Unclear	70%, 37%, 20%	13
14	Schiavon, 2008, Brazil	Retrospective, one center	185	≤6 months	45 (64%)	HCV	METAVIR	Yes	13.7±4.9 mm	24%, NA, NA	14
15	Silva, 2008, Brazil	Retrospective, one center	50	≤4 months	50 (68%)	HCV	METAVIR	Yes	Unclear	56%, 36%, 26%	12
16	Trang, 2008, USA	Retrospective, one center	81	≤6 months	47 (84%)	HCV+HIV	Batts Ludwig	No	22.5 mm	61%, 35%, 23%	12
17	Halfon, 2007, France	Retrospective, multicenter	356	≤1 week	45 (53%)	HCV	METAVIR	Yes	22.0±7.1 mm	41%, 15%, 4%	13
18	Leroy, 2007, France	Retrospective, one center	180	Same time	44 (62%)	HCV	METAVIR	No	23 (6-60) mm	51%, 28%, 14%	11
19	Schiavon, 2007, Brazil	Retrospective, one center	203	≤6 months	45 (64%)	HCV	METAVIR	Yes	13.7±4.8 mm	24%, 9%, 3%	14
20	Toniutto, 2007, Italy	Retrospective, one center	102	Same time	56 (61%)	HCV	Ishak	No	Unclear	68%, NA, NA	10
21	Bourliere, 2006, France	Prospective, multicenter	235	Same time	46 (55%)	HCV	METAVIR	Yes	16±7.5 mm	42%, 24%, 7%	13
22	Chrysanthos, 2006, Greece	Retrospective, tertiary center	284	Same time	49 (51%)	HCV	Ishak	Yes	≥15 mm	51%, NA, 20%	14
23	Fabris, 2006, Italy	Prospective, one center	30	Unclear	38 (65%)	HCV	Ishak	Yes	Unclear	13%, NA, NA	11
24	Lieber, 2006, USA	Retrospective multicenter	133	Unclear	46 (97%)	HCV+ alcoholic	Ishak	No	Unclear	44%, NA, NA	9
25	Liu, 2006, Taiwan	Prospective, tertiary center	79	Unclear	43 (35%)	HCV	METAVIR	Yes	19±1 mm	27%, 9%, 0%	12
26	Macias, 2006, Spain	Retrospective, 5 centers	263	≤1 month	37 (84%)	HCV+HIV	Scheuer	Yes	≥15 mm	58%, NA, 15%	13
27	Parise, 2006, Brazil	Prospective, one center	206	≤3 months	47 (56%)	HCV	Batts Ludwig	Yes	Unclear	42%, NA, 21%	12
28	Romera, 2006, Spain	Retrospective, tertiary center	131	Same time	40 (60%)	HCV	Scheuer	No	Unclear	47%, 17%, 12%	10
29	Schneider, 2006, Germany	Prospective, one center	83	Unclear	49 (49%)	HCV	Ishak	No	Unclear	57%, NA, 23%	9
30	Sene, 2006, France	Prospective, tertiary center	138	Median 1 month (range 0.5-3.5)	58 (50%)	HCV	METAVIR	No	67%≥15 mm	47%, NA, 14%	11
31	Snyder, 2006, USA	Retrospective, tertiary center	339	≤4 months	45 (72%)	HCV	Batts Ludwig	No	23±8 mm	49%, 20%, 2%	12
		Prospective, tertiary center	151	Same time	48 (70%)	HCV	Batts Ludwig	Yes	22±8 mm	52%, 33%, 17%	
32	Testa, 2006, Italy	Prospective, tertiary center	75	≤1 day	50 (68%)	HCV	Ishak	Yes	≥15 mm	49%, 20%, NA	13
33	Wilson, 2006, USA	Prospective, multicenter	119	≤45 days	42 (82%)	HCV	Ishak	Yes	11 mm	9%, NA, 0%	13
34	AlMohri, 2005, Canada	Retrospective, 2 centers	46	≤3 months	42 (89%)	HCV+HIV	Batts Ludwig	No	Unclear	72%, 41%, 20%	11
35	Islam, 2005, Sweden	Retrospective, tertiary center	179	Same time	43 (55%)	HCV	Ishak	Yes	≥10 mm	44%, NA, 12%	13
36	Kelleher, 2005, USA	Retrospective, tertiary center	95	Same time	45 (63%)	HCV+HIV	Ishak	Yes	10 mm	27%, 20%, 16%	14
37	Lackner, 2005, Austria	Retrospective, two centers	194	≤1 month	48 (57%)	HCV	Ishak	No	19±8 mm	50%, 26%, 16%	11
38	Nunes, 2005, USA	Prospective, 2 centers	40	≤6 months	47 (77%)	HCV+HIV	Ishak	Yes	15 mm	48%, NA, 33%	13
39	Berg, 2004, Germany	Retrospective, multicenter	484	Unclear	46 (59%)	HCV	Scheuer	No	Unclear	52%, 26%, 13%	10
40	Wai, 2003, USA	Prospective, tertiary center	192	≤4 months	Training: 48 (64%)	HCV	Ishak	Yes	Unclear	47%, NA, 15%	13
		Prospective, tertiary center	78	≤4 months	Validation: 48 (66%)	HCV	Ishak	Yes	Unclear	50%, NA, 17%	

Table 2. Quality Assessment of Included Studies

		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
	Author, Year, Region	Spectrum Composition	Selection Criteria	Appropriate Reference Standard	Disease Progression Bias	Partial Verification Bias	Differential Verification Bias	Incorporation bias	Test execution details	Reference execution details	Test review bias	Diagnostic review bias	Clinical review bias	Intermediate results	Withdrawals
1	Calès, 2010, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
2	Macías, 2010, Spain	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
3	Boursier, 2009, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
4	Castéra, 2009, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Corradi, 2009, Italy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
6	Schiavon, 2009, Brazil	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Tural, 2009, Spain	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
8	Carvalho-Filho, 2008, Brazil	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Cheung, 2008, USA	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
10	Dinesen, 2008, Germany	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
11	Khan, 2008, Pakistan	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Loko, 2008, France	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Paggi, 2008, Italy	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
14	Silva, 2008, Brazil	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
15	Schiavon, 2008, Brazil	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16	Trang, 2008, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
17	Halfon, 2007, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
18	Leroy, 2007, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
19	Schiavon, 2007, Brazil	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20	Toniutto, 2007, Italy	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
21	Bourliere, 2006, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
22	Chrysanthos, 2006, Greece	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23	Fabris, 2006, Italy	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
24	Lieber, 2006, USA	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
25	Liu, 2006, Tiawan	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
26	Macias, 2006, Spain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
27	Parise, 2006, Brazil	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
28	Romera, 2006, Spain	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
29	Schneider, 2006, Germany	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
30	Sene, 2006, France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
31	Snyder, 2006, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
32	Testa, 2006, Italy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
33	Wilson, 2006, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
34	Al- Mohri, 2005, Canada	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
35	Islam, 2005, Sweden	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
36	Kelleher, 2005, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
37	Lackner, 2005, Austria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
38	Nunes, 2005, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
39	Berg, 2004, Germany	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
40	Wai, 2003, USA	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

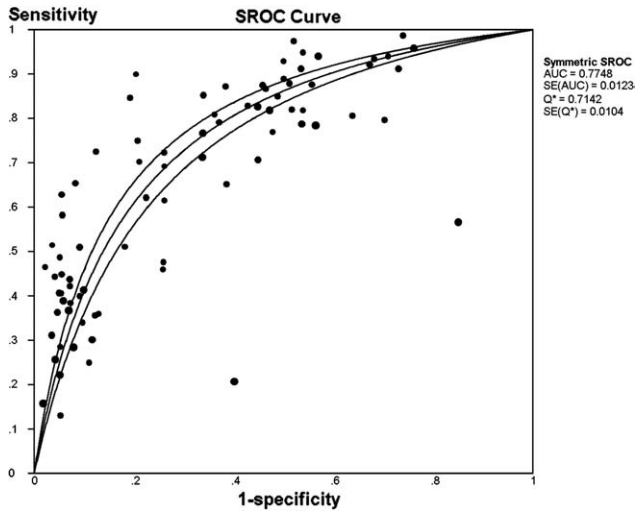

Fig. 2. SROC curve of the APRI for significant fibrosis. AUC, area under the SROC curve. The size of the dots for 1-specificity and sensitivity of the single studies in the ROC space is derived from the respective sample size.

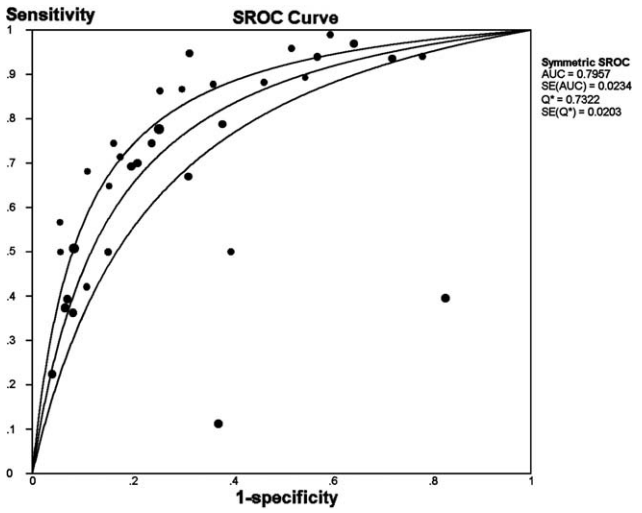

Fig. 3. SROC curve of the APRI for severe fibrosis. AUC, area under the SROC curve. The size of the dots for 1-specificity and sensitivity of the single studies in the ROC space is derived from the respective sample size.

to the regression-based analysis of funnel plot asymmetry, there was no evidence of publication bias ($P = 0.361$) (Supporting Information Fig. A2).

Diagnostic Accuracy for the Prediction of Cirrhosis. Eighteen studies in 4,548 patients assessed the APRI for the prediction of cirrhosis. The average prevalence of cirrhosis in these studies was 19% (range, 4%-33%). When combined, the AUROC was 0.83 (SE = 0.013) (Fig. 4). The summary DOR was 2.19 (1.77-2.72), and heterogeneity was not significant in the analysis of cirrhosis stage ($Q = 3.78$, $I^2 = 0$). At the lower recommended threshold of 1.0, the summary sensitivities and specificities were 76% (95% CI, 71%-80%) and 72% (70%-74%), respectively (Table 3). At the higher recommended cutoff of 2.0, the summary sensitivities and specificities were 46% (95% CI, 41%-51%) and 91% (90%-93%), respectively. Based on these values, and assuming a 19% prevalence of cirrhosis (as observed in the 18 included studies), the estimated PPV and NPV of the 1.0 cutoff were 55% and 69%, respectively. At the 2.0 cutoff, the estimated PPV and NPV were 82% and 63%, respectively.

According to the meta-regression analysis, APRI accuracy for detecting cirrhosis was affected by blinding

Table 3. Summary Sensitivities and Specificities of the APRI at Various Diagnostic Thresholds for Prediction of Significant Fibrosis, Severe Fibrosis and Cirrhosis

Test Threshold	Number of Studies (Patients)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)
Significant Fibrosis			
0.4	5 (836)	0.88 (0.84-0.92)	0.54 (0.50-0.58)
0.5	23 (4,595)	0.74 (0.73-0.76)	0.49 (0.47-0.51)
0.6	3 (531)	0.76 (0.71-0.81)	0.60 (0.54-0.66)
0.7	4 (609)	0.77 (0.72-0.81)	0.72 (0.66-0.77)
1	3 (821)	0.62 (0.58-0.66)	0.45 (0.40-0.51)
1.2	3 (571)	0.48 (0.42-0.54)	0.89 (0.85-0.93)
1.5	23 (4,502)	0.37 (0.35-0.39)	0.93 (0.91-0.94)
<0.5	11 (2,052)	0.89 (0.86-0.91)	0.50 (0.47-0.53)
0.6-1.0	13 (2,424)	0.68 (0.65-0.71)	0.67 (0.65-0.70)
1.1-1.4	6 (1,048)	0.46 (0.42-0.51)	0.89 (0.86-0.91)
>1.5	4 (862)	0.27 (0.23-0.31)	0.95 (0.92-0.97)
Severe Fibrosis			
0.5	5 (1,484)	0.60 (0.55-0.64)	0.43 (0.40-0.46)
1	6 (2,111)	0.61 (0.57-0.65)	0.64 (0.61-0.66)
1.5	4 (1,125)	0.50 (0.44-0.55)	0.87 (0.84-0.89)
2	5 (1,908)	0.36 (0.32-0.40)	0.93 (0.91-0.94)
Cirrhosis			
1	13 (2,636)	0.76 (0.71-0.80)	0.72 (0.70-0.74)
2	11 (2,429)	0.46 (0.41-0.51)	0.91 (0.90-0.93)

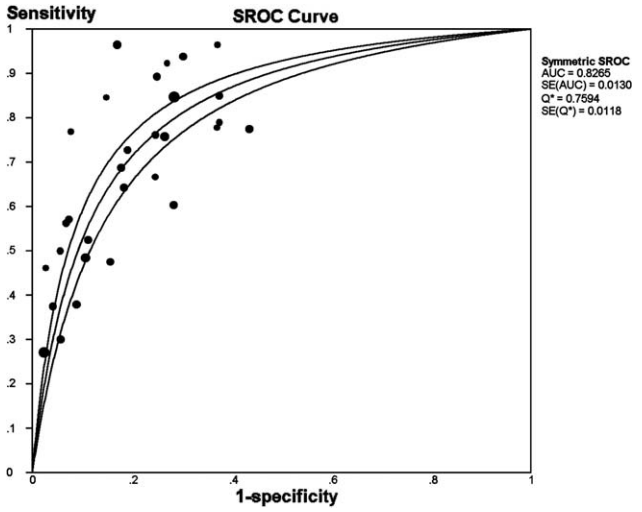

Fig. 4. SROC curve of the APRI for cirrhosis. AUC, area under the SROC curve. The size of the dots for 1-specificity and sensitivity of the single studies in the ROC space is derived from the respective sample size.

($P = 0.001$), with a mean AUROC of 0.83 for studies in which the pathologists were blinded for blood tests, and 0.82 for studies in which the pathologists were not blinded for blood tests. APRI accuracy for detecting cirrhosis was also affected by the research methods ($P = 0.001$), with a mean AUROC of 0.81 for the retrospective studies, and 0.86 for the prospective studies. APRI accuracy for detecting cirrhosis was also affected by quantitative factors, such as QUADAS score ($P = 0.002$), median age ($P = 0.007$), and the prevalence of cirrhosis ($P = 0.002$). Moreover, the AUROC of APRI for detecting HCV monoinfection and HCV/HIV coinfection-related cirrhosis were 0.83 and 0.79, respectively. However, this difference was not statistically significant in meta-regression analysis. The other covariates were not significant (data not shown). According to the regression-based analysis of funnel plot asymmetry, there was no evidence of publication bias ($P = 0.093$) (Supporting Information Fig. A3).

Discussion

Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) resulting from chronic liver diseases. Factors associated with matrix deposition or degradation and some cytokines involved in fibrosis may be used as individual markers or as a combination of markers to generate an algorithm to evaluate the stage of fibrosis. Also, the stage of fibrosis may be predicted using indirect markers such as a single routine laboratory test or multicomponent indirect fibrosis tests. Considering the limitations and risks of biopsy, as well as the improvement of diagnostic accuracy of noninvasive biochemical markers, there is great interest in developing and validating noninvasive methods to detect hepatic fibrosis among patients with chronic liver disease, and liver biopsy should no longer be considered mandatory. APRI is a novel index of liver fibrosis initially validated in patients with CHC, and then in the other common fibrotic liver diseases. It showed great value in detecting liver fibrosis, based on routine laboratory parameters.

In this systematic review and meta-analysis, we identified and evaluated 40 studies from the published literature comparing APRI with liver biopsy for detecting HCV-related fibrosis. Our meta-analysis showed that that the accuracy of the APRI is perhaps less than initially described. In the original Wai et al.[8] study, the AUROC for significant fibrosis and cirrhosis were 0.80 to 0.88 and 0.89 to 0.94, respectively. In our meta-analysis the summary AUROC of the APRI for the diagnosis of significant fibrosis was 0.77. Moreover, the 0.5 threshold was 74% sensitive and 49% specific. Assuming a 46% prevalence of significant fibrosis (as observed in the included studies), this translates into an estimated PPV of 55% and NPV of 69%. On the contrary, a cutoff of 1.5 was more specific (93%) but less sensitive (37%). Assuming a 46% prevalence of significant fibrosis, this translates into an estimated PPV of 82% and NPV of 63%. Optimal cutoff values for APRI were chosen to maximize the sum of sensitivity and specificity, thereby optimizing the diagnostic performance (the sum of true positives and true negatives over the total number of patients). The 0.7 threshold appears promising, maximizing the sum of sensitivity and specificity (sensitivity, 77%; specificity, 72%). Assuming a 46% prevalence of significant fibrosis, this translates into an estimated PPV of 70% and NPV of 79%. With respect to severe fibrosis, the summary AUROC was 0.80. Moreover, the 1.0 threshold was 61% sensitive and 64% specific. Assuming a 28% prevalence of severe fibrosis (as observed in the included studies), this translates into an estimated PPV of 40% and NPV of 81%. With respect to cirrhosis, the summary AUROC was 0.83. Moreover, the 1.0 threshold was 76% sensitive and 72% specific. Assuming a 19% prevalence of severe fibrosis (as observed in the included studies), this translates into an estimated PPV of 55% and NPV of 69%. On the contrary, a cutoff of 2.0 was more specific (91%) but less sensitive (46%). Assuming a 19% prevalence of severe fibrosis, this translates into an estimated PPV of 82% and NPV of 63%.

Compared with the previous meta-analysis,[9] our results showed similar performance of the APRI for the staging of significant fibrosis and cirrhosis. Moreover, APRI tended to show less accurate results for the identification of significant fibrosis, severe fibrosis, and cirrhosis in HIV/HCV coinfected patients than HCV monoinfected patients, which was different from the previous meta-analysis. This finding was in accord with our hypothesis that its accuracy may be diminished in coinfected patients because of HIV-related or antiretroviral-related thrombocytopenia.[60] However, this difference was not statistically significant in meta-regression analysis. A diagnostic tool is defined as perfect if the AUROC is 100%, excellent if the AUROC is greater than 90% and good if the AUROC is greater than 80%. According to these results, APRI can be used in clinical practice as a good tool for the confirmation of severe fibrosis and cirrhosis when other clinical signs and examinations are nondecisive.

Based on these results, APRI shows less value to identify HCV-related fibrosis than some other noninvasive methods. With respect to FibroTest, a meta-analysis

by Shaheen and Myers[9] showed that the AUROC of FibroTest to detect HCV-related significant fibrosis and cirrhosis was 0.81 and 0.90, respectively. With respect to transient elastography, it showed that the AUROC of FibroScan to detect HCV-related significant fibrosis and cirrhosis was 0.83 and 0.95, respectively.[61] Although APRI shows less diagnostic accuracy than FibroTest and FibroScan to identify HCV-related significant fibrosis and cirrhosis, APRI, a tool with limited expense and widespread availability, is still an attractive first-line estimate of liver fibrosis, particularly in regions with limited healthcare resources, where the prevalence of HCV tends to be the highest. According to World Health Organization estimates, over 85% of the 170 million HCV patients worldwide reside outside of the Americas and Europe, the majority in developing countries.

A strength of our review is that meta-regression analyses have been used for exploring factors that may be responsible for heterogeneity. We selected the following predefined characteristics as potential covariates that might contribute heterogeneity: (a) study design (respective versus prospective); (b) etiology (HCV versus HCV/HIV); (c) blinded interpretation of APRI and reference standard (yes versus no); (d) liver biopsy length ($\geq$15 mm or not); (e) liver biopsy scoring system (METAVIR, Ishak, Batts Ludwig, and Scheuer); (f) QUADAS score; (g) sample size; (h) median age; (i) percentage of males; (j) location of study (North America, Europe, and other); (k) prevalence of significant fibrosis/severe fibrosis/cirrhosis. Among patients with significant fibrosis, blinding and liver biopsy scoring systems were found to provide heterogeneity to summary test results. Among patients with severe fibrosis, neither of these variables was found to provide heterogeneity to summary test results. Among patients with cirrhosis, blinding, research methods, QUADAS score, median age, and the prevalence of cirrhosis were found to provide heterogeneity to summary test results. The other advantage of the present study is the large number of studies included, as well as the opportunity to analyze an integrated database. This permitted taking into account the variability factors associated with APRI diagnostic value.

Our systematic review and meta-analysis also have several limitations. One limitation is that we focused our analysis on HCV-infected patients only. The APRI has been used to examine chronic hepatitis B (CHB),[42,62] alcoholic liver disease (ALD),[44] and nonalcoholic fatty liver disease (NAFLD),[63,64] but the published studies suggest reduced accuracy. If the APRI diagnostic value was indeed less in patients with HCV than in patients with the three other frequent fibrotic diseases, it warrants further confirmation. Because there were few published studies related to the above chronic liver diseases-related fibrosis, we restricted our analysis to HCV. Another limitation is that we included English studies only, so the language bias may influence the results to some extent.

In summary, our meta-analysis suggests that the APRI has moderate diagnostic utility for the prediction of fibrosis in HCV-infected patients. Although APRI shows less diagnostic accuracy than some other noninvasive methods, APRI is still the first choice for HCV patients to identify hepatitis C-related fibrosis in regions with limited healthcare resources. Future studies of novel fibrosis markers should demonstrate improved accuracy and cost-effectiveness compared with this simple, economical, and widely available index.

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