Diagnostic Accuracy of the Aspartate Aminotransferase-to-Platelet Ratio Index for the Prediction of Hepatitis C–Related Fibrosis: A Systematic Review

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The development of noninvasive markers of liver fibrosis is a clinical and research priority. The aspartate aminotransferase-to-platelet ratio index (APRI) is a promising tool with limited expense and widespread availability. Our objective was to systematically review the performance of the APRI in hepatitis C virus (HCV)–infected patients. Random effects meta-analyses and areas under summary receiver operating characteristic curves (AUC) were examined to characterize APRI accuracy for significant fibrosis (stages 2-4) and cirrhosis. In 22 studies (n = 4,266), the summary AUCs of the APRI for significant fibrosis and cirrhosis were 0.76 [95% confidence interval (CI), 0.74-0.79] and 0.82 (95%CI, 0.79-0.86), respectively. For significant fibrosis, an APRI threshold of 0.5 was 81% sensitive and 50% specific. At a 40% prevalence of significant fibrosis, this threshold had a negative predictive value (NPV) of 80%, but could reduce the necessity of liver biopsy by only 35%. For cirrhosis, a threshold of 1.0 was 76% sensitive and 71% specific. At a 15% cirrhosis prevalence, the NPV of this threshold was 91%. Higher APRI thresholds had suboptimal positive predictive values except in settings with a high prevalence of cirrhosis. APRI accuracy was not affected by the prevalence of advanced fibrosis, or study and biopsy quality. However, the accuracy for cirrhosis was greater in studies including human immunodeficiency virus (HIV)/HCV–co-infected patients. *Conclusion:* The major strength of the APRI is the exclusion of significant HCV-related fibrosis. Future studies of novel markers should demonstrate improved accuracy and cost-effectiveness compared with this economical and widely available index. (HEPATOLOGY 2007;46:912-921.)

Chronic hepatitis C virus (HCV) infection is a major public health problem, affecting an estimated 200 million individuals globally.[1] Although peginterferon and ribavirin treatment leads to a sustained virologic response in more than 50% of patients, only a minority are eligible or have access to therapy.[2] Thus, most are at risk of progressive liver fibrosis, which may lead to cirrhosis and complications including hepatocellular carcinoma and end-stage liver disease.[3] To estimate prognosis and guide management decisions, the accurate staging of hepatic fibrosis is a clinical and research priority. Currently, liver biopsy is the gold standard for this purpose. Unfortunately, this procedure is limited by invasiveness, complications, sampling error, variability in pathological interpretation, and the reluctance of patients to undergo repeated biopsies to monitor disease progression.[4,5] As antifibrotic therapies are developed, the latter will have important practical implications.[6]

Because of these limitations, numerous investigators have examined alternative, noninvasive means of assessing hepatic fibrosis. A promising modality is transient elastography (FibroScan), which employs an ultrasound-based technique to measure the speed of propagation of elastic waves through the liver.[7] Unfortunately, this technology is costly (≈ $90,000 US) and limited to specialized centers. Serum biochemical tests, including direct and indi-

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; AUC, area under the summary receiver operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NPV, negative predictive value; PPV, positive predictive value; SROC, summary receiver operating characteristic.

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rect markers of liver fibrosis, have been the most widely investigated.[8,9] Direct markers such as glycoproteins (for example, hyaluronic acid, laminin, YKL-40), collagens, the matrix metalloproteinases and their inhibitors, and cytokines (for example, transforming growth factor beta) have demonstrated associations with fibrosis, and some have been incorporated into panels available on a proprietary basis (for example, FibroSpect,[10] FibroMeter,[11] Hepascore,[12] the European Liver Fibrosis test[13]). Although these markers are less expensive than liver biopsy, they are still costly and are not available in most clinical settings. On the contrary, indirect markers associated with fibrosis, such as routine biochemistry, platelets, and alpha-2-macroglobulin, are widely available and have been incorporated into composite panels including Forns' index,[14] the Fibrosis Probability Index,[15] and the FibroTest.[16] These tools are largely limited by lack of adequate external validation, difficulty differentiating intermediate fibrosis stages, and in the case of the proprietary indices, expense.[8,9]

In light of the limited availability and high cost of many fibrosis markers, Wai et al. derived and validated the aspartate aminotransferase-to-platelet ratio index [APRI; calculated as aspartate aminotransferase (AST) (U/L)/upper normal $\times$ 100/platelet count (10^9/L)] in a cohort of 270 patients with chronic HCV.[17] This index has the advantage of including only 2 inexpensive laboratory tests, which are performed routinely in all patients. For the identification of significant fibrosis, scores less than 0.5 (on a scale from 0 to 10) had a negative predictive value (NPV) of 86%, whereas scores greater than 1.5 had a positive predictive value (PPV) of 88%. Based on these high predictive values, the authors concluded that the APRI could obviate biopsy in approximately half of patients. Subsequently, numerous studies have attempted to externally validate these findings, but results have been controversial.[11,17,48] Differences in patient populations, including the prevalence of significant fibrosis, and reference ranges for AST, may explain these discrepancies.

Therefore, the objective of this study was to systematically review the diagnostic accuracy of the APRI for the prediction of HCV-related fibrosis. Although other noninvasive fibrosis measures are available,[8,9] we focused on this test because of its widespread availability, limited expense, and numerous studies published to date. We aimed to provide a summary of the existing literature that is applicable to a variety of practice settings and patient populations, and explore reasons behind the heterogeneous results using meta-regression techniques.

Materials and Methods

Search Strategy

The objective of our search was to identify published manuscripts of studies examining the APRI for the prediction of HCV-related fibrosis. An electronic search was completed on Medline, EMBASE, and the Cochrane Library (01/1997-12/2006) including the following search terms: APRI, AST-to-platelet ratio index, AST, platelet, hepatitis C, and fibrosis markers.[18,19] No language limitations were used. Additional studies were identified via a manual review of the reference lists of identified studies and review articles. Studies were deemed eligible 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. Studies including human immunodeficiency virus (HIV)/HCV–co-infected patients were included, but analyzed separately in sensitivity analyses.
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 $\times$ 2 table of test performance.
4. The study included more than 30 patients. Smaller studies were excluded because of poor reliability.

Data Abstraction

Two reviewers independently evaluated study eligibility, graded quality, and extracted outcome data. Disagreements were resolved by consensus. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies score.[20,21] 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,[22] Batts and Ludwig,[23] or Scheuer[24] stages F2 through F4 or Ishak stages F3 through F6.[25] This outcome was chosen because it is often considered a threshold for the initiation of antiviral therapy.[26] We also examined the identification of cirrhosis (METAVIR,[22] Batts and Ludwig,[23] or Scheuer[24] F4, or Ishak F5-6).

Data Synthesis and Analysis

Assessment of Diagnostic Test Accuracy. Data were extracted and tabulated in a series of 2 $\times$ 2 tables allowing the calculation of sensitivity, specificity, PPV, and NPV for each reported test threshold. To provide clinically meaningful results, 3 measures of diagnostic test accuracy were examined: the area under the summary receiver op-

erating characteristic (SROC) curve (AUC), summary diagnostic odds ratios (DORs), and summary sensitivities and specificities.

AUC. Because most of the fibrosis marker literature includes receiver operating characteristic curves, we examined SROC curves according to the method of Moses et al.[27] The SROC curve, generated using linear regression, represents the relationship between the true-positive and false-positive rates across studies, recognizing they may have used different test thresholds.[27,28] In this analysis, each study was weighted by its sample size with adjustment for the number of thresholds within each study.[29] Although typically reported in meta-analyses of diagnostic tests, the area under the SROC curve is limited because it is difficult to translate into clinical practice.

DORs. Summary DORs were calculated using a DerSimonian and Laird random effects model with a corresponding test of heterogeneity.[30] The DOR describes the odds of a positive test in disease cases compared with non-cases.[31,32] Because 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.[33] The disadvantage of the DOR as an outcome parameter is that summary estimates of sensitivity and specificity are not directly available. It is, however, possible to obtain an estimate of sensitivity by specifying a value of specificity, or vice versa.

Summary Sensitivities and Specificities. Because of the limitations in SROC curves and the DOR, we calculated summary sensitivities and specificities using the bivariate meta-analytic approach of Reitsma et al.[34] According to this approach, pairs of sensitivity and specificity for diagnostic thresholds are jointly analyzed, incorporating any correlation that might exist between these measures using a random effects approach.

Sensitivity Analyses

Sensitivity analyses employing random effects meta-regression[35] were conducted to examine the impact of the following factors on APRI performance (natural logarithm of the DOR): (1) sample size; (2) median age; (3) percentage of males; (4) methodological quality; (5) inclusion of HIV/HCV–co-infected patients; (6) prevalence of significant fibrosis/cirrhosis; (7) location of the study (North America, Europe, other); (8) the histopathologic scoring system used; and (9) quality of the reference standard for assessing fibrosis. This was deemed adequate if a study excluded liver biopsies smaller than 15 mm. If sufficient data were not reported in the manuscript, the reference standard was deemed inadequate.

Assessment of Heterogeneity and Publication Bias

Heterogeneity in APRI accuracy between studies was assessed using Cochran's Q-statistic.[36] To assess for possible publication bias, we examined for asymmetry of funnel plots of APRI accuracy versus the inverse of the square root of the effective sample size.[37]

All analyses were performed using Stata 8.2 (Stata Corp., College Station, TX), dr-ROC 2.0 (Diagnostic Research Design & Reporting, Glenside, PA), and SAS 9.1.3 (SAS Institute Inc., Cary, NC) software.

Results

Search Results

Eighty-six studies were identified, including 40 that described the APRI. Thirty-three studies examined the APRI in patients with chronic hepatitis C. Ultimately, 11 studies were excluded for duplication of data (n = 1),[38] insufficient data (n = 5),[11,39-42] small sample size (n = 2),[43,44] or failure to use biopsy as the reference test (n = 3).[45-47] Thus, our final data set for the meta-analysis included 22 studies (Table 1).[17,48-68]

Characteristics of the Included Studies

A total of 4,266 patients (median age, 44 years; 61% male) were included (Table 1). The overall prevalence of significant fibrosis and cirrhosis were 46% (range, 9%-72%) and 14% (0%-33%), respectively. Regarding histopathological classification systems, 11 studies used Ishak, 4 used METAVIR, 4 used Scheuer, and 3 used Batts and Ludwig. Nineteen studies included HCV-monoinfected patients (n = 3,822),[17,20,22-38] and 4 included HIV/HCV–co-infected patients (n = 444).[48-51] Biopsy quality was considered acceptable in only 4 of the 22 studies.[51,53,57,63] According to the Quality Assessment of Diagnostic Accuracy Studies scale, the methodological quality of the included studies was very good. Thirteen studies met all 14 requirements of this scale; 6 studies met 13, and 2 studies met 12.

Diagnostic Accuracy of the APRI for the Prediction of Significant Fibrosis

Nineteen studies in 3,778 patients assessed the APRI for the prediction of significant fibrosis. The average prevalence of significant fibrosis in these studies was 47% (range, 9%-72%). For this outcome, the area under the SROC curve was 0.76 [95% confidence interval (CI) 0.74-0.79; Fig. 1), and the summary DOR was 5.7 (4.3-7.5; Fig. 2). Heterogeneity was significant in this analysis ($Q = 39.38$; $P = 0.004$).

The summary sensitivities and specificities of the APRI at various thresholds for the identification of significant fibrosis are listed in Table 2. At the lower threshold of 0.5

Table 1. Characteristics of the Included Studies

Author, Year, Country	Study/Center Description	n	Interval Between Biopsy & APRI	Median/Mean Age, yr (% male)	Etiology	Liver Biopsy Description	Prevalence Significant Fibrosis (Cirrhosis)	QUADAS Score
Wai, 2003, USA [17]	Prospective, tertiary center	270	≤4 months	Training: 48 (64%) Validation: 48 (66%)	HCV	Unclear	47% (15%); 50% (17%)	13
Berg, 2004, Germany [56]	Retrospective, multicenter	484	Unclear	46 (59%)	HCV	Unclear	52% (13%)	12
Le Calvez, 2004, France [66]	Retrospective, one center	323	Same time	47 (58%)	HCV	≥ 10 mm	41% (13%)	14
Al- Mohri, 2005, Canada [48]	Retrospective, 2 tertiary centers	46	≤ 3 months	42 (89%)	HIV/HCV	Unclear	72% (20%)	13
Romero-Gomez, 2005, Spain [65]	Retrospective, one center	199	Same time	41 (59%)	HCV	Unclear	52% (15%)	13
Islam, 2005, Sweden [54]	Retrospective, tertiary center	179	Same time	43 (55%)	HCV	≥ 10 mm	44% (12%)	14
Kelleher, 2005, USA [49]	Retrospective, tertiary center	95	Same time	45 (63%)	HIV/HCV	> 10 mm and > 5 portal tracts	27% (16%)	14
Lackner, 2005, Austria [67]	Retrospective, two centers	194	≤ 1 month	48 (57%)	HCV	Median 19 ± 8 mm and 11 portal tracts (range 9-16)	50% (16%)	14
Nunes, 2005, USA [50]	Prospective, 2 centers	97	≤ 6 months	47 (67%)	HCV (n = 57); HIV/HCV (n = 40)	Median 14.5 mm for HCV; 15 mm for HIV/ HCV	55% (32%) for HCV; 48% (33%) for HIV/ HCV	14
Bourliere, 2006, France [52]	Prospective, multicenter	235	Same time	46 (55%)	HCV	16 ± 7.5 mm	42% (7%)	14
Chrysanthos, 2006, Greece [53]	Retrospective, tertiary center	284	Same time	49 (51%)	HCV	≥ 15 mm	51% (20%)	14
Lieber, 2006, USA [55]	Retrospective study, multicenter	133	Unclear	46 (97%)	HCV & alcoholic liver disease	Unclear	44% (NA)	13
Liu, 2006, Tiawan [57]	Prospective, tertiary center	79	Unclear	43 (35%)	HCV with normal ALT	19 ± 1 mm	27% (0%)	14
Macias, 2006 Spain[51]	Retrospective, 5 centers	263	≤ 1 month	37 (84%)	HIV/HCV	≥ 15 mm	58% (15%)	14
Parise, 2006, Brazil [58]	Prospective, one center	206	≤ 3 months	47 (56%)	HCV	Unclear	42% (21%)	13
Pavic, 2004, Serbia [68]*	Unclear	143	Unclear	38 (69%)	HCV	Unclear	27% (8%)	Unclear
Romera, 2006, Spain [59]	Retrospective, tertiary center	131	Same time	40 (60%)	HCV	10 ± 2 portal tracts	47% (11%)	14
Schneider, 2006, Germany [60]	Prospective, one center	83	Unclear	49 (49%)	HCV	Unclear	57% (23%)	12
Sene, 2006, France [61]	Prospective, tertiary center	138	Median 1 month (range 0.5-3.5)	58 (50%)	HCV with vasculitis	67% ≥ 15 mm	47% (14%)	13
Snyder, 2006, USA [62]	Retrospective, tertiary center; Prospective, tertiary center	339 151	≤4 months; Same time	45 (72%); 48 (70%)	HCV	23 ± 8 mm; 22 ± 8 mm	49% (2%); 52% (17%)	14
Testa, 2006, Italy [63]	Prospective, tertiary center	75	≤ 1 day	50 (68%)	HCV	≥ 15 mm	49% (12%)	14
Wilson, 2006, USA [64]	Prospective, multicenter	119	≤ 45 days	42 (82.4%)	HCV	Median length 11 mm	9% (0%)	14

*Several details from this manuscript are unclear due to predominant publication in Serbian (some details in English).

recommended by Wai et al.,[17] the summary sensitivity and specificity were 81% (95% CI, 76%-86%) and 50% (47%-52%), respectively. At the higher recommended cutoff of 1.5, the summary sensitivity and specificity were 35% (95% CI, 30%-41%) and 91% (89%-92%), respectively. Based on these values, and assuming a 47% prevalence of significant fibrosis (as observed in the 19 included studies), the estimated PPV and NPV of the 0.5 cutoff

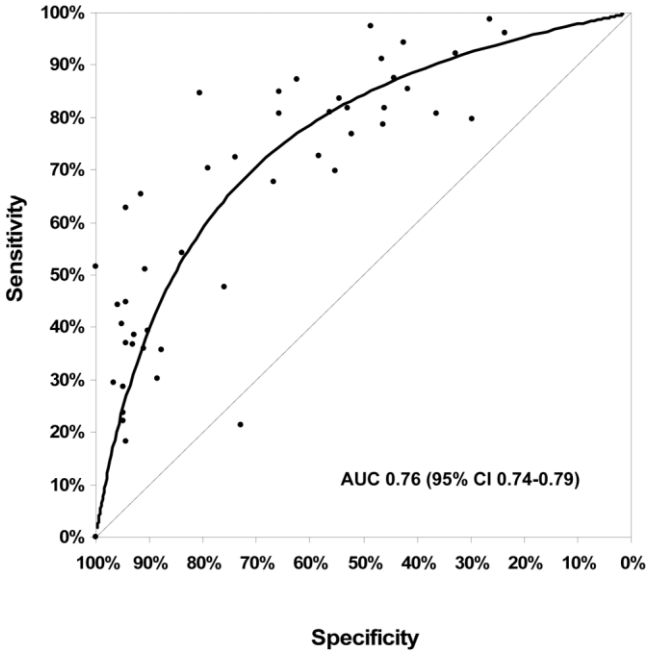

Fig. 1. SROC curve of the APRI for significant fibrosis. AUC, area under the SROC curve.

were 59% and 75%, respectively. At the 1.5 cutoff, the estimated PPV and NPV were 77% and 61%, respectively. The tradeoff between PPV and NPV for these thresholds at variable prevalence rates of significant fibrosis is illustrated in Fig. 3.

According to the meta-regression analysis, APRI accuracy for detecting significant fibrosis was not affected by study-related or patient-related factors. Specifically, sample size ($P = 0.51$), methodological quality ($P = 0.86$), country of origin (P = 0.87), adequacy of biopsy specimens ($P = 0.90$), and histopathological classification ($P = 0.45$) were not significant in this analysis. Similarly, APRI accuracy was not affected by the age of the study population ($P = 0.14$), sex ($P = 0.96$), the prevalence of significant fibrosis ($P = 0.46$), or the inclusion of HIV/HCV–co-infected patients ($P = 0.60$). According to the regression-based analysis of funnel plot asymmetry, there was no evidence of publication bias ($P = 0.67$).

Table 2. Summary Sensitivities and Specificities of the APRI at Various Diagnostic Thresholds for Prediction of Significant Fibrosis and Cirrhosis

Test Threshold and Outcome	Number of Studies (Patients)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)
Significant Fibrosis			
~ 0.4 (0.38-0.42)	4 (717)	86% (54-97%)	54% (49-59%)
0.5	16 (3,277)	81% (76-86%)	50% (47-52%)
0.7	3 (438)	84% (78-88%)	70% (63-76%)
1.0	2 (473)	59% (48-70%)	86% (81-89%)
1.5	15 (3,146)	35% (30-41%)	91% (89-92%)
Cirrhosis			
1.0	9 (2,057)	76% (68-82%)	71% (69-73%)
2.0	8 (1,946)	49% (43-55%)	91% (90-93%)

Abbreviation: CI, confidence interval.

Diagnostic Accuracy of the APRI for the Prediction of Cirrhosis

Twelve studies examined the APRI for the prediction of HCV-related cirrhosis (n = 2,589). The average prevalence of cirrhosis was 15% (range, 7%-33%). For this outcome, the area under the SROC curve was 0.82 (95% CI, 0.79-0.86; Fig. 4), and the summary DOR was 11.3 (7.9-16.0; Fig. 5). Heterogeneity was not significant (Q = 17.45; $P = 0.134$).

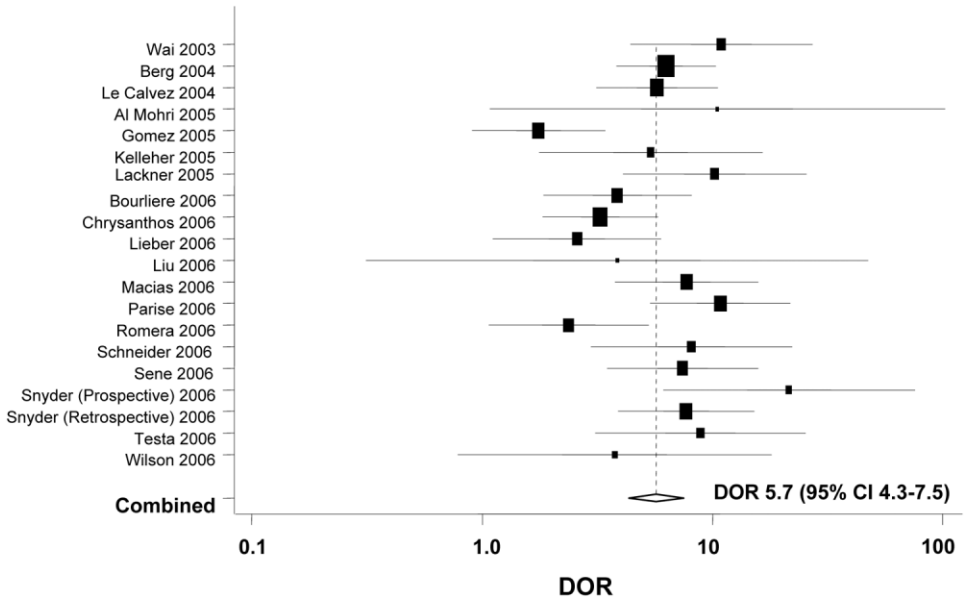

Fig. 2. Diagnostic accuracy of the APRI for significant fibrosis. Heterogeneity was significant in this analysis ($P = 0.004$). Note: x-axis on a logarithmic scale. DOR, diagnostic odds ratio.

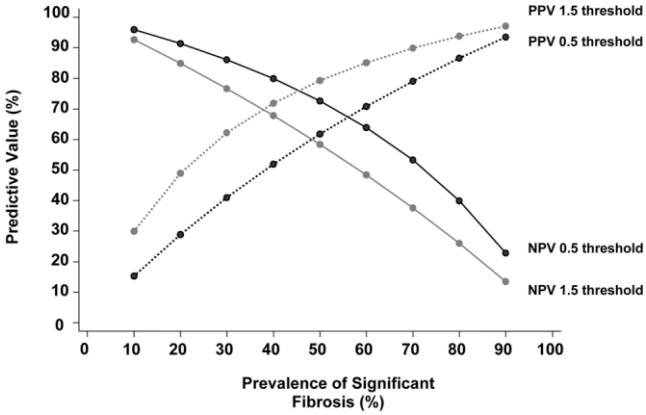

Fig. 3. NPV (solid lines) and PPV (dotted lines) of the APRI for significant fibrosis according to prevalence. Curves are illustrated for the recommended APRI thresholds of 0.5 (black lines) and 1.5 (gray lines).[17]

At the lower recommended threshold of 1.0, the summary sensitivity and specificity were 76% (95% CI 68-82%) and 71% (69-73%), respectively (Table 2). At a more specific threshold of 2.0, these figures were 49% (95% CI 43-55%) and 91% (90-93%), respectively. At the 15% prevalence of cirrhosis observed in the included studies, the estimated PPV and NPV of the 1.0 threshold were 32% and 94%, respectively. At the 2.0 threshold, the estimated PPV and NPV were 50% and 91%, respectively. The inversely proportional relationship between PPV and NPV for these thresholds at variable cirrhosis prevalence rates is illustrated in Fig. 6.

According to the meta-regression analysis, APRI accuracy for the detection of cirrhosis was greater in studies with a higher proportion of males ($P = 0.001$), younger participants ($P = 0.04$), and HIV/HCV–co-infected patients ($P = 0.03$). The DOR for cirrhosis was 44.9 (95% CI, 13.1-153.6) in the 2 studies including HIV/HCV–co-infected patients versus 9.5 (6.9-13.1) in the studies including only HCV-monoinfected participants. The other covariates were not significant (data not shown). An analysis for funnel plot asymmetry suggested possible publication bias for the prediction of cirrhosis ($P < 0.0005$).

Discussion

In this systematic review, we summarize the diagnostic accuracy of the APRI for the prediction of HCV-related fibrosis. In an era in which the number of fibrosis markers is growing rapidly, many clinicians, patients, researchers, and policy makers are confused as to the optimal measure. Because the APRI is based on routinely performed, inexpensive laboratory parameters, it is potentially the ideal tool because most HCV-infected patients reside in regions with limited healthcare resources.[1] Our systematic review suggests that the accuracy of the APRI is perhaps less than initially described. In Wai and colleagues' original study,[17] the AUC for significant fibrosis and cirrhosis in the training and validation cohorts were 0.80 to 0.88 and 0.89 to 0.94, respectively. In our systematic review, the APRI had modest accuracy for significant fibrosis (AUC 0.76; DOR ~6).[69,70] Because these point estimates are difficult to translate into clinical practice, we calculated summary sensitivities and specificities. Moreover, we provide predictive values at varying fibrosis prevalence rates, with the aim of providing practically useful information for clinicians in a variety of practice settings (Figs. 3 and 6). According to these analyses, the primary strength of the APRI is the exclusion of significant fibrosis. Based on our bivariate meta-analysis, the 0.5 threshold was 81% sensitive and 50% specific. Assuming a 47% prevalence of significant fibrosis (as observed in the included studies), this translates into an estimated PPV of 59% and NPV of 75%. Although these predictive values appear suboptimal, the NPV was more acceptable in lower prevalence settings, such as typically observed in community-based cohorts.[64] For example, at a prevalence of 30% to 40%, the estimated NPV ranged from 80% to 86%; at the same time, the PPV did not exceed 52% (Fig. 3). On the contrary, a cutoff of 1.5 was more specific (91%) but less sensitive (35%). The PPV of this threshold did not reach 80% until the prevalence of significant fibrosis exceeded 50%, which is typically observed only in referral centers. Based on these analyses, we suggest that

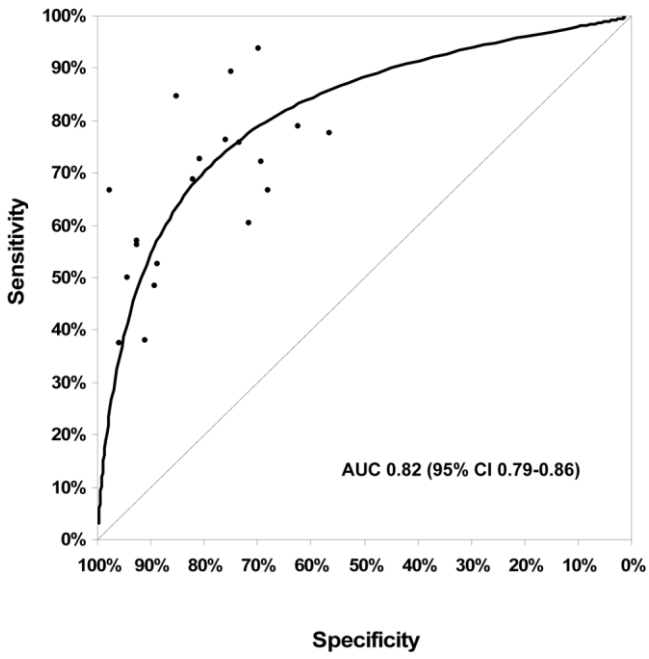

Fig. 4. SROC curve of the APRI for cirrhosis. AUC, area under the SROC curve.

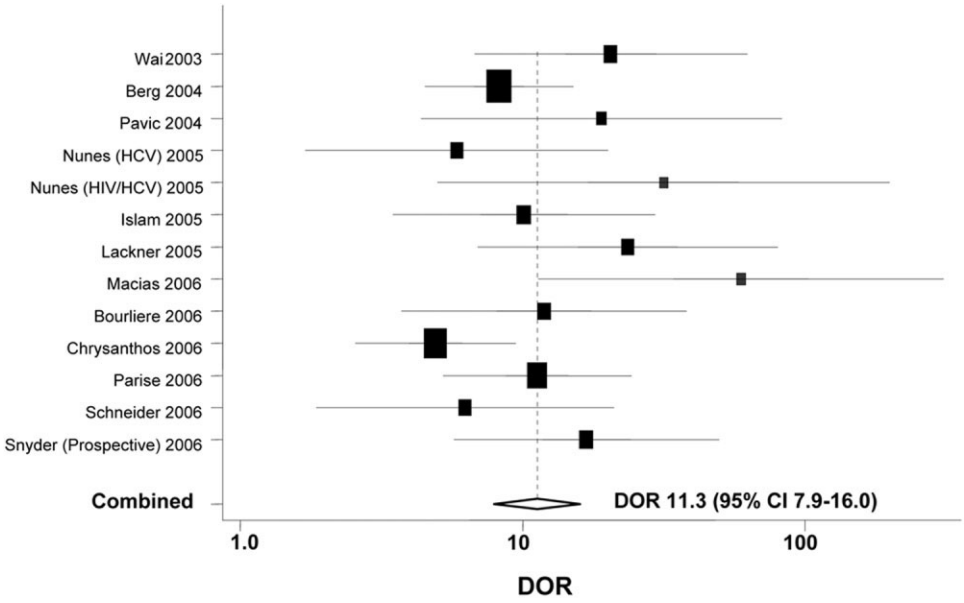

Fig. 5. Diagnostic accuracy of the APRI for cirrhosis. Note: x-axis on a logarithmic scale. DOR, diagnostic odds ratio.

an APRI of 0.5 or less has acceptable accuracy for excluding significant fibrosis in average prevalence settings. In the 16 studies included in this analysis, 35% of patients met this criterion. Thus, at least one third of biopsies could be avoided if this threshold were used to exclude significant fibrosis. On the contrary, higher scores (for example, ≥1.5) have sub-optimal PPV, with the exception of clinical settings with a high prevalence (≥50%) of advanced fibrosis.

Our secondary outcome was the identification of cirrhosis. As expected, the APRI had improved accuracy for this outcome (AUC 0.82; DOR ≈11). Although the APRI cutoff of 1.0 was 76% sensitive and 71% specific, the 2.0 threshold was much more specific (93%) at the expense of reduced sensitivity (49%). Unfortunately, the low PPVs of these thresholds do not allow one to accurately "rule in" cirrhosis. For example, at a cirrhosis prevalence of 15%, as observed in the included studies, the estimated PPV of the 2.0 threshold was only 50% (Fig. 6). The PPV for this threshold did not exceed 80% until the prevalence of cirrhosis was ≥40%. On the contrary, the ability to exclude cirrhosis is excellent. At this prevalence, the 1.0 and 2.0 thresholds had NPVs of 91% and 94%, respectively. In the included studies, 65% of patients had an APRI of 1.0 or less, and 86% had an APRI of 2.0 or less. Therefore, cirrhosis can be excluded in most patients with acceptable accuracy using these thresholds. This finding has important practical implications for the initiation of surveillance programs for gastroesophageal varices and hepatocellular carcinoma without histological data.

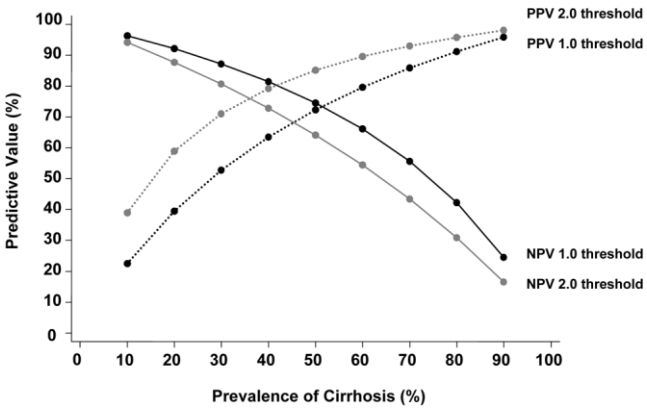

Fig. 6. NPV (solid lines) and PPV (dotted lines) of the APRI for cirrhosis according to prevalence. Curves are illustrated for the recommended APRI thresholds of 1.0 (black lines) and 2.0 (gray lines).[17]

Some of the studies reported APRI thresholds not included in the original description (Table 2).[17] Although we have not focused on these thresholds because of the small number of studies, the 0.7 cutoff appears promising (sensitivity, 84%; specificity, 70% for significant fibrosis). In future studies including the APRI, we would recommend that a wider range of thresholds be reported because this may permit refinement of its use. Also, inclusion of other routinely performed parameters (*e.g.,* gamma glutamyltransferase, alanine aminotransferase, alkaline phosphatase, International Normalized Ratio, bilirubin) may improve its accuracy.

An unresolved issue is a comparison of the APRI with other fibrosis measures. Although we did not address this directly, the AUC of 0.76 that we observed for significant fibrosis is similar to that of the FibroTest in a meta-analysis by Poynard and colleagues (0.79; 95% CI 0.77-0.82).[71] Similarly, in a multicenter comparative study of fibrosis markers,[38] the AUC for significant fibrosis of the

APRI (0.76), FibroTest (0.79), FibroMeter (0.78), and HepaScore (0.76) were not significantly different. With respect to transient elastography, Castera et al. did not find a statistically significant difference between the FibroScan and APRI for METAVIR F2-F4 fibrosis (AUC 0.83 vs. 0.78), although the FibroScan was more accurate for cirrhosis (0.95 vs. 0.83).[40] This largely insignificant difference between the APRI, which is inexpensive and available for all HCV-infected patients, versus other more costly and specialized fibrosis measures underscores 2 important points. First, before the latter tools are widely used, their incremental cost-effectiveness, or the tradeoff between increased accuracy (if there is any) and cost, should be demonstrated.[72] Second, further research must identify novel markers with improved accuracy over conventional measures. These studies should include the APRI as a benchmark for diagnostic performance.

A strength of our review is our analysis for heterogeneity in APRI accuracy, which was significant for the primary outcome. Despite examining 9 patient and study-specific covariates, including study quality, fibrosis stage distribution, and inclusion of HIV/HCV–co-infected patients, we could not explain this finding. Biopsy length, specifically, was not significant in the meta-regression analyses, although this has been reported to affect the accuracy of some fibrosis markers.[38,73,74] Because most of the studies did not exclude suboptimal biopsy specimens (or did not report biopsy characteristics), we would encourage future investigators to be rigorous in their assessment of the quality of liver biopsies, ensuring adequate length and portal tract number.[5] Although these negative findings may reflect a type II error, we hypothesize that they likely relate to "unquantifiable" differences between studies such as the quality of histopathologists, heterogeneous patient populations, and different assays and reference ranges for AST (reported in only 1 of the studies). An individual patient data meta-analysis would be useful to explore these issues. Interestingly, the APRI was more accurate for the identification of cirrhosis in HIV/HCV–co-infected patients. This finding was surprising because we hypothesized that its accuracy may be diminished in co-infected patients because of HIV-related or antiretroviral-related thrombocytopenia.[75] Because this analysis included only 2 studies of co-infected patients, it warrants confirmation.

Our systematic review has several limitations. Although we identified 22 eligible studies including more than 4,200 patients, our funnel plot analysis for cirrhosis suggested the possibility of publication or other small sample size–related biases. This may relate to our inclusion of only published manuscripts. Potentially eligible abstracts were identified, but most did not report sufficient data, and many were subsequently published, often in altered form. Even so, because tests for publication bias have not been fully validated in meta-analyses of diagnostic test accuracy, these findings must be interpreted cautiously.[37] A second limitation is that we have focused our analysis on HCV-infected patients only. The APRI has been examined in hepatitis B, but the few published studies suggest reduced accuracy.[76,77] Therefore, to avoid introducing further heterogeneity, we restricted our analysis to HCV. Ideally, we would have also examined other test characteristics such as cost-effectiveness and impact on clinical outcomes. Because of a scarcity of publications, we could not address these important issues. However, Ngo et al.[47] recently described an association between APRI scores and 5-year survival without HCV-related complications (AUC 0.82). In another study,[46] the APRI 6 months after the end of antiviral therapy was highly predictive of hepatocellular carcinoma development and survival (AUCs 0.87). Finally, we have considered the accuracy of the APRI in isolation, rather than in combination with other measures. As reported by Sebastiani et al.,[39] a stepwise algorithm including the APRI and other markers may improve diagnostic performance. Because of an absence of similar publications, we could not examine this issue.

In summary, our systematic review suggests that the APRI has moderate diagnostic utility for the prediction of fibrosis in HCV-infected patients. Its major role appears to be the exclusion of significant fibrosis and cirrhosis, which can be achieved with acceptable accuracy in at least one third and three quarters of patients, respectively. 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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