Staging liver fibrosis and cirrhosis using non-invasive tests in people with chronic hepatitis B to inform WHO 2024 guidelines: a systematic review and meta-analysis

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See Comment page 280

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Summary

Background Non-invasive tests (aspartate aminotransferase-to-platelet ratio index [APRI] and transient elastography [FibroScan]) were recommended in the 2015 WHO guidelines to guide treatment decisions in people with chronic hepatitis B. We updated the systematic review and meta-analysis that informed the 2015 guidelines to inform new cutoffs for non-invasive tests for the diagnosis of significant fibrosis and cirrhosis for the 2024 WHO guidelines for chronic hepatitis B.

Methods We searched PubMed (MEDLINE), Embase, and Science Citation Index Expanded (Web of Science) for studies published in any language between Jan 1, 2014, and Feb 15, 2023. We included all studies that reported cross-sectional data on the staging of fibrosis or cirrhosis with APRI, Fibrosis-4 (FIB-4), and FibroScan compared with liver biopsy as the reference standard in people with chronic hepatitis B. We excluded studies in which the maximum interval between liver biopsy and non-invasive fibrosis test was more than 6 months; that reported on fewer than ten patients with advanced fibrosis or cirrhosis; that were done exclusively in children; and did not report diagnostic accuracy across our prespecified ranges of test cutoffs. The results of this updated search were collated with the meta-analysis that informed the 2015 guidelines. Outcomes of interest were the sensitivity and specificity of non-invasive tests using defined index test cutoffs for detecting significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) based on the METAVIR staging system. We performed meta-analyses using a bivariate random-effects model.

Findings Of 19 933 records identified by our search strategy, 195 were eligible for our systematic review and combined with the 69 studies from the previous meta-analysis to total 264. Two studies were at low risk of bias, 31 studies had unclear risk of bias, and 231 studies had a high risk of bias. Of these 264, 211 studies with 61 665 patients were used in the meta-analysis. For the diagnosis of significant fibrosis (≥F2), sensitivity and specificity were 72·9% (95% CI 70·2–75·5) and 64·7% (95% CI 61·0–68·2) for the APRI low cutoff (>0·3 to 0·7), 30·5% (23·7–38·3) and 92·3% (89·3–94·6) for the APRI high cutoff (>1·3 to 1·7), and 75·1% (72·2–77·7) and 79·3% (76·2–82·2) for FibroScan (>6·0 to 8·0 kPa), respectively. For the diagnosis of cirrhosis (F4), sensitivity and specificity were 59·4% (53·2–65·2) and 73·9% (70·1–77·4) for the APRI low cutoff (>0·8 to 1·2), 30·2% (24·2–36·9) and 88·2% (85·4–90·6) for the APRI high cutoff (>1·8 to 2·2), and 82·6% (77·8–86·5) and 89·0% (86·3–91·2) for FibroScan (>11·0 to 14·0 kPa), respectively. Using a hypothetical population of 1000 unselected patients with chronic hepatitis B with a 25% prevalence of significant fibrosis (≥F2), the APRI low cutoff for significant fibrosis (≥F2) would result in 262 (26·2%) false positives but only 68 (6·8%) false negatives. The FibroScan cutoff would result in 158 (15·8%) false positives and 63 (6·3%) false negatives. In a population with a 5% prevalence of cirrhosis (F4), the APRI low cutoff for cirrhosis (F4) would result in 247 (24·7%) false positives and 21 (2·1%) false negatives and the FibroScan cutoff would result in 105 (10·5%) false positives and nine (0·9%) false negatives.

Interpretation These findings have informed new thresholds of APRI and FibroScan for diagnosis of significant fibrosis and cirrhosis in the 2024 WHO guidelines on chronic hepatitis B, with an APRI score greater than 0·5 or a FibroScan value greater than 7·0 kPa considered to identify most adults with significant fibrosis (≥F2) and an APRI score greater than 1·0 or a FibroScan value greater than 12·5 kPa to identify most adults with cirrhosis (F4). These patients are a priority for antiviral treatment.

Funding WHO.

Introduction

Hepatitis B virus (HBV) infection is a major public health problem and cause of chronic liver disease that leads to approximately 1·1 million deaths annually, mainly due to cirrhosis and liver cancer.[1] In 2022, WHO estimated that 254 million people were chronically infected and living with chronic hepatitis B, with a disproportionately high burden in low-income and

Research in context

Evidence before this study

Non-invasive tests (aspartate aminotransferase-to-platelet ratio index [APRI] and transient elastography [FibroScan]) were recommended in the 2015 WHO guidelines on treatment decisions in people with chronic hepatitis B. The guidelines were based on a systematic review and meta-analysis that comprised 69 studies and recommended an APRI cutoff of greater than 2 for the diagnosis of cirrhosis. The rationale was to prioritise the reduction of false-positive results, and therefore treatment, in patients who did not have cirrhosis, given the high cost and low availability of antiviral treatment. We undertook an updated systematic review and meta-analysis to inform new cutoffs for non-invasive tests for the diagnosis of significant fibrosis and cirrhosis for the 2024 WHO global guidelines for the care and treatment of people with chronic hepatitis B. We searched PubMed (MEDLINE), Embase, and Science Citation Index Expanded (Web of Science) for studies published between Jan 1, 2014, and Feb 15, 2023, in any language. We included all studies that reported cross-sectional data on the staging of fibrosis of the index test or tests (APRI, Fibrosis-4 [FIB-4], and transient elastography [FibroScan]) compared with a reference standard of liver biopsy in people with chronic hepatitis B. We excluded studies in which the maximum interval between liver biopsy and the non-invasive fibrosis test was more than 6 months; that reported on fewer than ten patients with advanced fibrosis or cirrhosis; that exclusively were done in children; and did not report diagnostic accuracy across our prespecified ranges of test cutoffs. Search terms included "hepatitis B", "elastography", "FIB4", and "APRI", among others. The results of the updated search were collated with the meta-analysis that informed the 2015 guidelines. 264 potentially eligible studies were identified, of which 211 were included in the meta-analysis.

Added value of this study

This updated systematic review and meta-analysis provides the most comprehensive data on the diagnostic accuracy of APRI, FIB-4 and FibroScan for staging liver fibrosis and cirrhosis in patients with chronic hepatitis B. Based on these results, an APRI score greater than 0·5 or a FibroScan value greater than 7·0 kPa for significant fibrosis and an APRI score greater than 1·0 or a FibroScan value greater than 12·5 kPa for cirrhosis were recommended by WHO as key criteria for prioritising initiation of antiviral therapy in resource-limited settings. These cutoffs prioritise the minimisation of false-negative results and accept a higher number of false positives. Assuming a 25% baseline prevalence of significant fibrosis (≥F2), the APRI cutoff will result in around 26·2% of unselected, treated patients not having significant fibrosis (false positives), but will only miss around 6·8% of patients with significant fibrosis (false negatives). An APRI score greater than 0·5 or a FibroScan value of greater than 7·0 kPa will identify most adults with significant fibrosis (≥F2) and an APRI score greater than 1·0 or a FibroScan value of greater than 12·5 kPa will identify most adults with cirrhosis (F4).

Implications of all the available evidence

These findings were used to inform decisions on testing and treatment of people with chronic hepatitis B at a large scale, taking into consideration a combination of factors, including diagnostic accuracy, availability, cost, and number and potential consequences of false-positive and false-negative results. These findings could be used as a blueprint for the use of non-invasive tests in other conditions and settings.

middle-income countries (LMICs).[1] The spectrum of liver disease in people with chronic hepatitis B ranges from minimal fibrosis to cirrhosis and hepatocellular carcinoma. The natural history of chronic hepatitis B has various phases and is dynamic, requiring lifelong monitoring and, potentially, antiviral treatment. Treatment decisions are based on a combined assessment of the concentration of aminotransferases, HBV viral load, and the degree of fibrosis, necroinflammation, or both.[2]

Liver biopsy was previously considered the gold-standard method to stage liver disease and assess fibrosis, but it is no longer widely used because of its high cost, invasiveness, patient discomfort, risk of complications, and the need for expert histological interpretation. Several non-invasive fibrosis tests based on serum indices (aspartate aminotransferase-to-platelet ratio index [APRI] and Fibrosis-4 [FIB-4]) or ultrasound principles (transient elastography [FibroScan]) are now increasingly used for evaluating and staging liver fibrosis, which reduces the need for liver biopsy among people with an established cause of liver disease.[3] In the literature, sensitivities and specificities of APRI and FIB-4 have been reported at dual cutoffs: a high cutoff with high specificity and a low cutoff with high sensitivity. The high and low cutoff is usually set at 90–95% of specificity and sensitivity, respectively. Depending on the clinical scenario and the disease prevalence, the high or low cutoff is used at the expense of increased false negatives and false positives, respectively. If these cutoffs are combined, then false positives and false negatives are minimised but a number of patients will fall in an indeterminate range (ie, their score will be between the low cutoff and the high cutoff) and will need either further non-invasive testing after a defined period or a liver biopsy.

In 2015, WHO issued the first global guidelines for the prevention, care, and treatment of people with chronic hepatitis B, specifically intended for LMICs.[4] These guidelines prioritised for antiviral treatment patients (older than 30 years, in particular) with persistently abnormal alanine aminotransferase (ALT) and high-level HBV replication (HBV DNA >20 000 IU/mL) or adults,

adolescents, and children with clinical evidence of cirrhosis (or based on an APRI score >2·0 in adults), regardless of ALT or HBV DNA. The APRI cutoff used for the diagnosis of cirrhosis had a high specificity of 89% (95% CI 81–94) but a low sensitivity of 35% (95% CI 22–49) and was based on a systematic review and meta-analysis that was performed specifically to inform these guidelines.[4] The choice of this high cutoff was to reduce false-positive results and therefore treatment in patients who did not have cirrhosis, considering the high cost and low availability of antiviral treatment. However, it was recognised that at least 50% of those who had cirrhosis would be missed by such a high cutoff. The cost and availability of antiviral treatment have now improved and focus has shifted to diagnosing patients at lesser fibrosis stages and expanding treatment, because this could prevent the progression to cirrhosis and complications.

We undertook an updated systematic review and meta-analysis to inform new cutoffs for non-invasive tests for the diagnosis of significant fibrosis and cirrhosis for the 2024 WHO global guidelines for the care and treatment of people with chronic hepatitis B.[5] We aimed to compare the diagnostic accuracy of APRI, FIB-4, and transient elastography against liver biopsy in the diagnosis and staging of liver fibrosis and cirrhosis in people with chronic hepatitis B, and to synthesise the accuracy where possible. These tests were chosen because of their potential for ready access and use in LMICs.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we compared the diagnostic accuracy of non-invasive fibrosis tests (APRI, FIB-4, and transient elastography [performed with FibroScan]) for diagnosing and staging liver fibrosis among adults, adolescents, and children with chronic hepatitis B versus liver biopsy as the reference standard. The study followed a predefined protocol that was submitted to WHO before initiation of the work (appendix pp 1–9).

See Online for appendix

We searched PubMed (MEDLINE), Embase, and Science Citation Index Expanded (Web of Science) for studies published between Jan 1, 2014, and Feb 15, 2023. We did not search BIOSIS, the Cochrane Central Register of Controlled Trials, Lilacs, and CINAHL as stated in our original protocol due to time constraints in delivering the results, and also based on the fact that no additional studies were identified in these databases in the 2015 meta-analysis.[4] The search strategy is shown in the appendix (pp 10–12). We also reviewed the reference lists of included studies and systematic reviews, and we contacted researchers of studies we identified in sub-Saharan Africa for unpublished available data. Potentially eligible studies that were not written in English were translated with use of Google Translate or by coauthors or other people who knew the language. The results of the updated searches were collated with the results of the meta-analysis that informed the 2015 guidelines,[4] which used the same search strategy to search for studies published between Jan 1, 1988, and May 30, 2014. We included all studies that reported cross-sectional data (based on either prospective or retrospective cohort studies) on the staging of fibrosis by the index test or tests compared with a reference standard of liver biopsy and histopathological examination of liver tissue in people of all ages with chronic hepatitis B. The staging and grading of liver biopsy could be performed by various histological scoring systems, such as Ishak, METAVIR, Knodell, and others.[6] For data synthesis and analysis, we transformed the histological scores used in individual studies to METAVIR because METAVIR is the most commonly used histological score (see appendix p 2 for conversion method). We excluded studies from the systematic review in which the maximum interval between the reference standard (liver biopsy) and the non-invasive fibrosis test (index test) was more than 6 months. We also excluded studies that reported on a total of fewer than ten patients with advanced fibrosis or cirrhosis. Although we included studies that reported on children (age <18 years) in our systematic review, we did not include these studies in the meta-analysis because the performance of different non-invasive tests is not well established in this population. We included in the meta-analysis only studies that reported diagnostic accuracy across a narrow range of prespecified cutoffs.

The results retrieved by our search strategy were searched by two researchers (AL and MZ) independently for identification of relevant studies. Disagreements were resolved by a third reviewer (EAT). No restrictions were placed on the language or the publication status (full text *vs* abstract from conference proceedings). Full texts were obtained for the studies that at least one of the reviewers considered relevant. Full-text articles were then used to include or exclude studies for the systematic review. All studies from the same authors were reviewed to ensure that they represented separate cohorts.

Data analysis

Data were extracted by two reviewers (MZ and AL) independently. Any differences in the data extraction were resolved by a third reviewer (EAT). Extracted data included patient demographics and non-invasive test used and cutoffs; a full list of the variables for which data were extracted can be found in the appendix (p 13). True-positive, false-positive, true-negative, and false-negative diagnostic test results, or the data necessary to calculate them, were extracted using the reference standard of liver biopsy. In case of duplicate data, we excluded abstract versions of the records we had full articles of. Extracted data were entered into a Microsoft Excel file created for that purpose.

Outcomes of interest were the sensitivity and specificity of non-invasive tests using defined index test cutoffs for detecting significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) based on the METAVIR staging system.

The quality of studies was assessed independently by two reviewers (AL and MZ) using the QUADAS-2 assessment tool.[7–9] This tool comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first three domains are also assessed in terms of concerns regarding applicability. Signalling questions are included to help judge the risk of bias. The quality criteria that were derived from the QUADAS-2 tool and were assessed are shown in the appendix (pp 15–16).

We calculated the median prevalence for the specific stages of fibrosis in the studies included. We performed separate meta-analyses for low and high APRI and FIB-4 cutoffs whenever such cutoffs were reported and were similar across studies. We opted not to perform a separate meta-analysis for each fibrosis stage-specific cutoff of a non-invasive test used in the studies, but instead performed meta-analyses across narrow ranges of cutoffs. These cutoff ranges were based on the results of our systematic review and were determined to achieve a balance between being narrow enough, clinically meaningful, and include as many studies as possible.

We performed meta-analyses of studies reporting the sensitivity and specificity of each index test (*vs* the liver biopsy standard) for detecting significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) at similar thresholds (APRI ≥F2: >0·3 to 0·7 and >1·3 to 1·7; APRI F4: >0·8 to 1·2 and >1·8 to 2·2; FIB-4 ≥F3: >1·2 to 1·7 and >2·8 to 3·5; FibroScan ≥F2: >6·0 to 8·0 kPa; FibroScan ≥F3: >8·0 to 11·0 kPa; FibroScan F4: >11·0 to 14·0 kPa) using a bivariate random-effects model.[10] The bivariate method is a hierarchical two-level model that takes into consideration both within-study and between-study variability. At the first level, within-study sensitivity and specificity are considered to be binomially distributed. At the second level, between-study variability, the logit-transformed sensitivities and specificities of individual studies are assumed to follow a normal bivariate distribution, also taking into consideration the possible correlation between sensitivity and specificity. Summary sensitivity and specificity and negative and positive likelihood ratios, with their 95% CIs, were obtained from the bivariate model estimates at these specific thresholds. Additionally, a sensitivity analysis was performed by including in the meta-analysis only the studies reporting sensitivity and specificity at the following cutoff values, as reported in the studies that first described these scores: 0·5 and 1·5 for APRI F2;[11] 1·45 and 3·25 for FIB-4 F3;[12] and 1·0 and 2·0 for APRI F4.[11]

Heterogeneity was investigated by including in the bivariate model a categorical covariate term for three predefined sources of heterogeneity. These sources were (1) studies of high versus low methodological quality per QUADAS-2; (2) mean ALT in each study (≤upper limit of normal [ULN], >ULN to ≤3×ULN, and >3×ULN); and (3) different ethnicities (Asia,

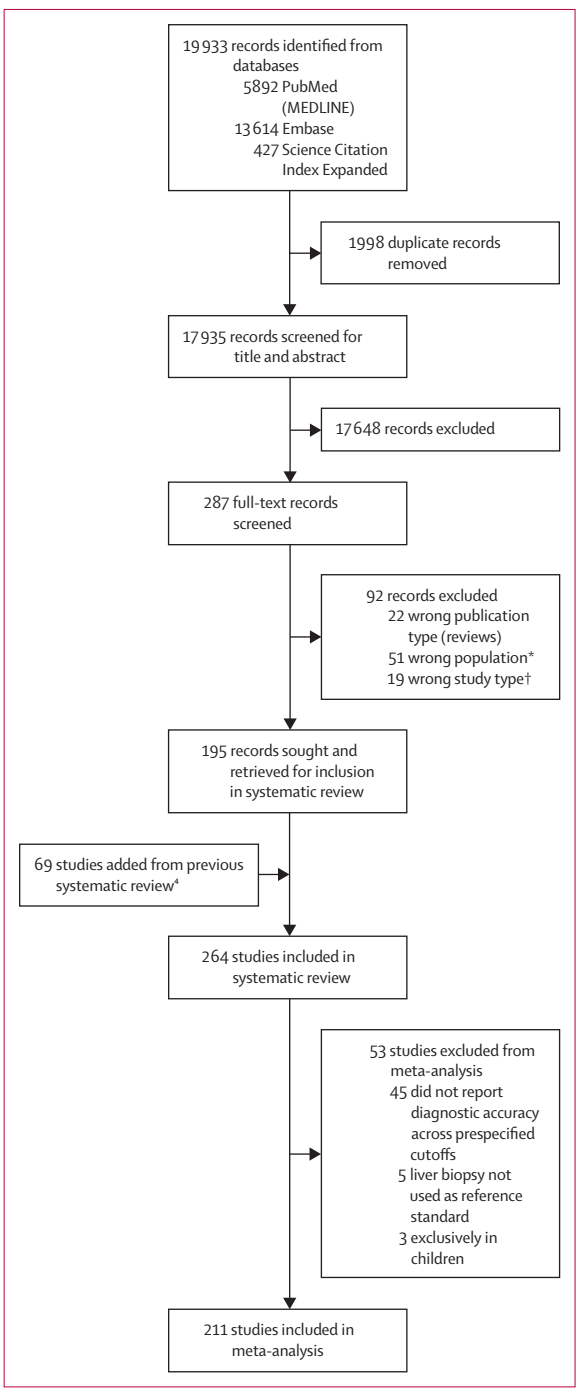


Figure 1: **Study selection**
HBV=hepatitis B virus. *Studies in which patients with liver disease other than HBV-related disease were included and in which there were no specific findings for an HBV cohort. †Studies in which only the prognostic value of non-invasive tests was assessed.

For more on **WHO country classifications** see https://www.who.int/countries

For more on **UN definitions of countries** see https://unstats.un.org/unsd/methodology/m49

sub-Saharan Africa, and other). Specific ethnicity data were challenging to obtain; therefore, ethnicities were proxied by geographical region, according to WHO's regional classification. The Asian group comprised the WHO South-East Asia and Western Pacific regions. Given that the WHO African region comprises an area much larger than sub-Saharan Africa, we instead used the UN definition of the sub-Saharan Africa region. For multicentre studies spanning different regions, these studies were included in the other category. The effect of each single covariate on sensitivity and specificity was assessed by using the likelihood ratio χ^2 test, calculated as the difference in the –2 log likelihood of the models with and without the covariate of interest. We assessed publication bias using funnel plots, testing for symmetry via Deek's test. The METADAS macro[13] and SAS 9.2 statistical software were used for all statistical analyses.

To determine the diagnostic accuracy of testing strategies for significant fibrosis (≥F2) and cirrhosis (F4) in practice in resource-limited settings, the comparative performance of the non-invasive tests was assessed (number of true-positive, false-positive, false-negative, and true-negative results) according to two different hypothetical scenarios. In the first scenario, all patients with positive HBsAg are tested with a non-invasive fibrosis test irrespective of ALT and viral load. A prevalence of 25% for significant fibrosis (≥F2) and of 5% for cirrhosis (F4) was assumed, similar to the previous WHO guidelines, based on expert opinion. In the second scenario, a pre-selection of patients was assumed to be tested based on ALT, viral load, or both—typically an abnormal ALT, an HBV viral load greater than 2000 IU/mL, or both. These are the patients who would typically be considered for a liver biopsy.[2] A prevalence of 52·0% for significant fibrosis (≥F2) and 16·2% for cirrhosis (F4), similar to the median prevalence reported in the studies included in the meta-analysis, was assumed. The cutoffs and assumed prevalences for an analysis of advanced fibrosis (≥F3) can be found in the appendix (pp 17–18).

	Cutoff	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Significant fibrosis (≥F2)						
APRI	>0·3 to 0·7	116	72·9% (70·2–75·5)	64·7% (61·0–68·2)	2·1 (1·9–2·2)	0·4 (0·4–0·5)
APRI	>0·5	45	72·3% (67·5–75·5)	63·7% (57·9–69·1)	2·0 (1·8–2·2)	0·4 (0·4–0·5)
APRI	>1·3 to 1·7	41	30·5% (23·7–38·3)	92·3% (89·3–94·6)	4·0 (3·2–4·9)	0·8 (0·7–0·8)
APRI	>1·5	38	29·4% (22·4–37·5)	92·0% (88·7–94·4)	3·7 (3·0–4·5)	0·8 (0·7–0·8)
FibroScan	>6·0 to 8·0 kPa	53	75·1% (72·2–77·7)	79·3% (76·2–82·2)	3·6 (3·2–4·2)	0·3 (0·3–0·4)
Advanced fibrosis (≥F3)						
FIB-4	>1·2 to 1·7	40	69·1% (64·4–73·5)	70·5% (67·0–73·9)	2·3 (2·2–2·5)	0·4 (0·4–0·5)
FIB-4	>1·45	16	72·6% (67·4–77·2)	66·9% (60·6–72·6)	2·2 (1·9–2·5)	0·4 (0·4–0·5)
FIB-4	>2·8 to 3·5	19	31·1% (24·6–38·5)	94·8% (91·5–96·8)	5·9 (4·2–8·4)	0·7 (0·7–0·8)
FIB-4	>3·25	18	29·6% (23·9–36·1)	95·3% (92·7–97·0)	6·3 (4·5–8·8)	0·7 (0·7–0·8)
FibroScan	>8·0 to 11·0 kPa	51	80·4% (77·1–83·3)	85·2% (82·8–87·3)	5·4 (4·6–6·3)	0·2 (0·2–0·3)
Cirrhosis (F4)						
APRI	>0·8 to 1·2	46	59·4% (53·2–65·2)	73·9% (70·1–77·4)	2·3 (2·1–2·5)	0·6 (0·5–0·6)
APRI	>1·0	26	57·1% (49·9–64·0)	73·5% (69·5–77·1)	2·2 (1·9–2·4)	0·6 (0·5–0·7)
APRI	>1·8 to 2·2	30	30·2% (24·2–36·9)	88·2% (85·4–90·6)	2·6 (2·2–3·0)	0·8 (0·7–0·9)
APRI	>2·0	29	29·3% (23·5–35·8)	88·7% (86·1–90·8)	2·6 (2·2–3·1)	0·8 (0·7–0·9)
FibroScan	>11·0 to 14·0 kPa	37	82·6% (77·8–86·5)	89·0% (86·3–91·2)	7·5 (6·1–9·2)	0·2 (0·2–0·3)

APRI=aspartate aminotransferase-to-platelet ratio index. FIB-4=Fibrosis-4.

Table 1: **Sensitivity and specificity of non-invasive tests for the detection of significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4)**

Role of the funding source

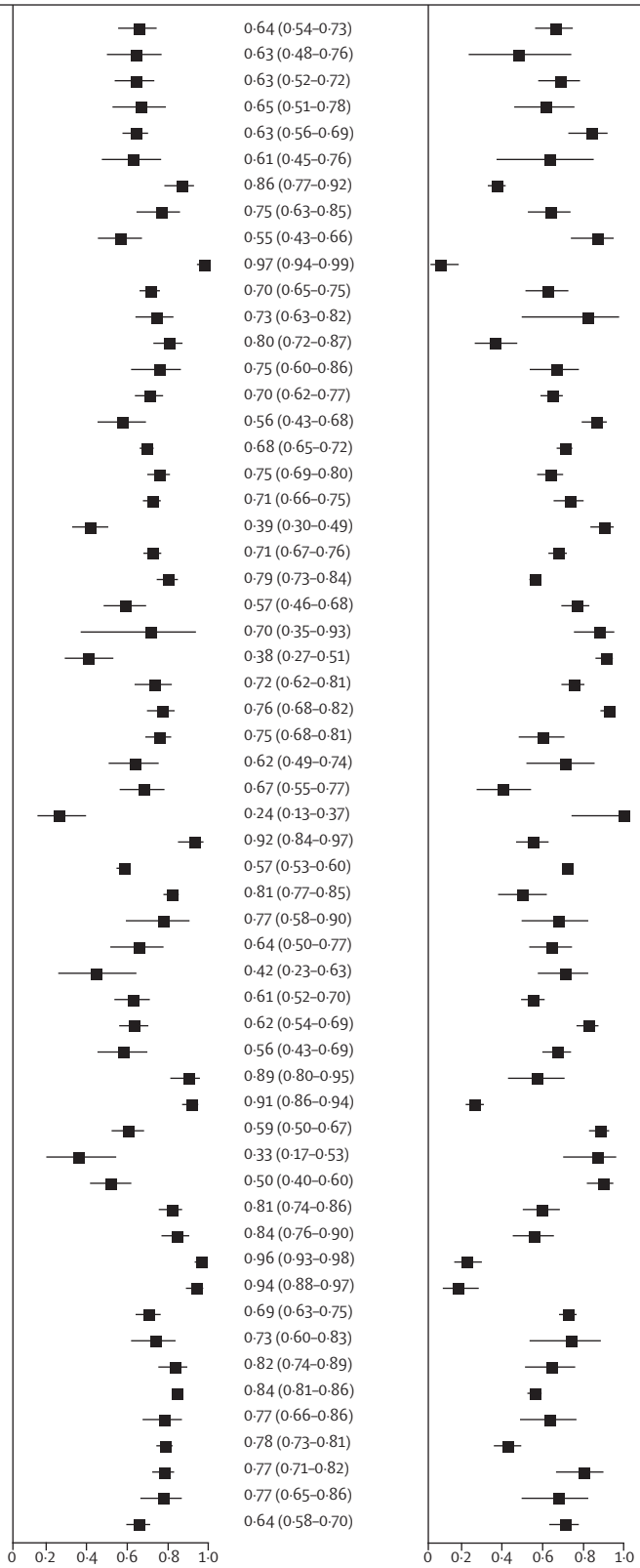
This systematic review and meta-analysis was commissioned and partially funded by WHO. The protocol was approved by WHO and the WHO HBV Guideline Development Group interpreted the data from this meta-analysis to reach a treatment recommendation for patients with chronic hepatitis B. WHO had no role in data collection, data analysis, or writing of the report.

Results

The search strategy retrieved 19 933 studies, of which 19 646 were excluded after review of title and abstract (figure 1). No additional studies were identified by searching the reference lists of retrieved studies. 287 potentially eligible studies were identified, of which 195 were eligible for the systematic review. We did not include data from unpublished studies because they did not use liver biopsy as a comparator for the performance of non-invasive tests. The 195 studies were added to the 69 studies from the previous systematic review that informed the 2015 guidelines,[4] for a total of 264 studies (appendix pp 24–68).[14–277] Five studies reported on the performance of non-invasive fibrosis tests in children (aged 3–9 years).[135,159,181,234,258] One study specifically reported on the performance of non-invasive fibrosis tests in adolescents (aged 10–17 years).[246] 154 studies were done exclusively in Asia,[14,25–27,31–33,35–42,46,49,52–54,57,59,60,66,69,73–84,89–94,96,98,99,101,102,106,107,109–134,137,138,143,147–149,151,158,161,163–165,175–177,179,180,182,183,185–187,189,194,198,199,201,204,206,207,209,211–229,232,237,240,241,243,244,248,249,252–256,260,262–272,274,275,277] seven were done exclusively in sub-Saharan Africa,[23,50,51,104,105,140,196] and the rest were done in various and sometimes multiple countries and geographical regions.

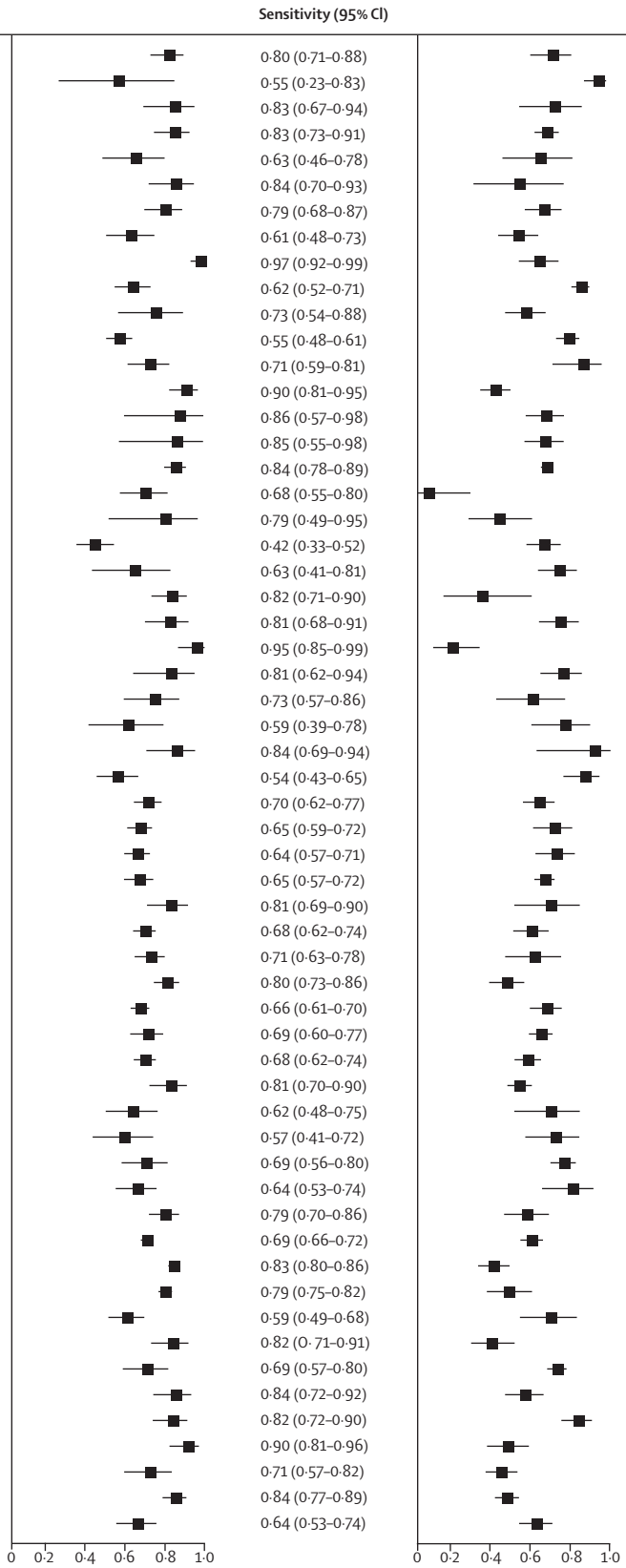
219 studies reported diagnostic accuracy across the predetermined range of cutoffs.[14,17–20,22–33,35–43,45–47,49–55,57,59–62,65–71,73–84,86,89–102,104–134,137–143,145–149,151–156,158–167,169–177,179,180,182,183,185–204,206,207,209,211–229,

	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ayed et al (2018)[18]	64	36	36	67	0·64 (0·54–0·73)	0·65 (0·55–0·74)
Başar et al (2013)[20]	32	8	19	7	0·63 (0·48–0·76)	0·47 (0·21–0·73)
Ben et al (2019)[22]	60	26	36	55	0·63 (0·52–0·72)	0·68 (0·57–0·78)
Boyd et al (2016)[24]	34	17	18	26	0·65 (0·51–0·78)	0·60 (0·44–0·75)
Cao et al (2020)[26]	141	10	84	51	0·63 (0·56–0·69)	0·84 (0·72–0·92)
Castéra et al (2011)[29]	27	6	17	10	0·61 (0·45–0·76)	0·63 (0·35–0·85)
Çelik et al (2020)[30]	80	288	13	158	0·86 (0·77–0·92)	0·35 (0·31–0·40)
Chen et al (2013)[33]	49	31	16	52	0·75 (0·63–0·85)	0·63 (0·51–0·73)
Chen et al (2017)[36]	45	6	37	39	0·55 (0·43–0·66)	0·87 (0·73–0·95)
Chen et al (2018)[37]	181	56	5	4	0·97 (0·94–0·99)	0·07 (0·02–0·16)
Chen et al (2019)[40]	222	32	95	51	0·70 (0·65–0·75)	0·61 (0·50–0·72)
Chen and Jiang (2020)[35]	65	2	24	9	0·73 (0·63–0·82)	0·82 (0·48–0·98)
Chrysanthos et al (2006)[43]	99	53	25	28	0·80 (0·72–0·87)	0·35 (0·24–0·46)
Coskun and Yuksel (2021)[45]	38	21	13	40	0·75 (0·60–0·86)	0·66 (0·52–0·77)
Deng et al (2017), high ALT[49]	118	106	51	185	0·70 (0·62–0·77)	0·64 (0·58–0·69)
Deng et al (2017), normal ALT[49]	38	18	30	110	0·56 (0·43–0·68)	0·86 (0·79–0·91)
Ding et al (2021), training[52]	469	157	217	368	0·68 (0·65–0·72)	0·70 (0·66–0·74)
Ding et al (2021), validation[52]	174	81	59	137	0·75 (0·69–0·80)	0·63 (0·56–0·69)
Ding et al (2021)[53]	285	39	116	103	0·71 (0·66–0·75)	0·73 (0·64–0·80)
Dogan et al (2013)[55]	46	11	71	101	0·39 (0·30–0·49)	0·90 (0·83–0·95)
Dong et al (2018)[60]	286	136	115	271	0·71 (0·67–0·76)	0·67 (0·62–0·71)
Ekin et al (2022)[61]	186	549	49	670	0·79 (0·73–0·84)	0·55 (0·52–0·58)
Eminler et al (2015)[62]	50	36	37	114	0·57 (0·46–0·68)	0·76 (0·68–0·83)
Gümüşay et al (2013)[70]	7	6	3	42	0·70 (0·35–0·93)	0·88 (0·75–0·95)
Güzelbulut et al (2012)[71]	25	17	40	168	0·38 (0·27–0·51)	0·91 (0·86–0·95)
Hongbo et al (2007)[74]	68	58	26	170	0·72 (0·62–0·81)	0·75 (0·68–0·80)
Hu et al (2017)[75]	117	18	37	218	0·76 (0·68–0·82)	0·92 (0·88–0·95)
Huang et al (2017)[80]	135	31	46	44	0·75 (0·68–0·81)	0·59 (0·47–0·70)
Huang et al (2019)[76]	38	9	23	21	0·62 (0·49–0·74)	0·70 (0·51–0·85)
Kavak et al (2022)[86]	48	32	24	20	0·67 (0·55–0·77)	0·38 (0·25–0·53)
Kim et al (2014)[93]	12	0	39	12	0·24 (0·13–0·37)	1·00 (0·74–1·00)
Koksal et al (2016)[95]	73	69	6	80	0·92 (0·84–0·97)	0·54 (0·45–0·62)
Korkmaz et al (2017)[97]	426	505	327	1262	0·57 (0·53–0·60)	0·71 (0·69–0·74)
Lee et al (2016)[101]	335	35	79	33	0·81 (0·77–0·85)	0·49 (0·36–0·61)
Lemoine et al (2016), France[104]	23	11	7	22	0·77 (0·58–0·90)	0·67 (0·48–0·82)
Lemoine et al (2016), The Gambia[104]	34	30	19	52	0·64 (0·50–0·77)	0·63 (0·52–0·74)
Lemoine et al (2016), Senegal[104]	11	16	15	38	0·42 (0·23–0·63)	0·70 (0·56–0·82)
Li et al (2016)[114]	74	129	47	151	0·61 (0·52–0·70)	0·54 (0·48–0·60)
Li et al (2016)[118]	109	35	67	161	0·62 (0·54–0·69)	0·82 (0·76–0·87)
Li et al (2017)[117]	36	58	28	114	0·56 (0·43–0·69)	0·66 (0·59–0·73)
Li et al (2017)[110]	68	22	8	28	0·89 (0·80–0·95)	0·56 (0·41–0·70)
Li et al (2017), older patients[115]	192	264	19	84	0·91 (0·86–0·94)	0·24 (0·20–0·29)
Li et al (2018)[116]	86	20	60	150	0·59 (0·50–0·67)	0·88 (0·82–0·93)
Li et al (2018)[120]	10	4	20	26	0·33 (0·17–0·53)	0·87 (0·69–0·96)
Li et al (2018)[112]	47	10	47	84	0·50 (0·40–0·60)	0·89 (0·81–0·95)
Liao et al (2022), training[123]	148	47	35	66	0·81 (0·74–0·86)	0·58 (0·49–0·68)
Liao et al (2022), validation[123]	98	43	19	51	0·84 (0·76–0·90)	0·54 (0·44–0·65)
Lin et al (2015), training[125]	270	110	12	28	0·96 (0·93–0·98)	0·20 (0·14–0·28)
Lin et al (2015), validation[125]	132	59	9	11	0·94 (0·88–0·97)	0·16 (0·08–0·26)
Liu et al (2011)[127]	149	115	66	293	0·69 (0·63–0·75)	0·72 (0·67–0·76)
Liu et al (2015)[132]	48	7	18	19	0·73 (0·60–0·83)	0·73 (0·52–0·88)
Liu et al (2017)[129]	94	22	20	38	0·82 (0·74–0·89)	0·63 (0·50–0·75)
Liu et al (2018)[126]	1059	339	208	410	0·84 (0·81–0·86)	0·55 (0·51–0·58)
Liu et al (2019)[128]	58	18	17	30	0·77 (0·66–0·86)	0·63 (0·47–0·76)
Liu et al (2022)[131]	321	120	93	83	0·78 (0·73–0·81)	0·41 (0·34–0·48)
Lu et al (2016), training[133]	181	10	54	39	0·77 (0·71–0·82)	0·80 (0·66–0·90)
Lu et al (2016), validation[133]	53	11	16	22	0·77 (0·65–0·86)	0·67 (0·48–0·82)
Lu et al (2020)[134]	163	46	91	108	0·64 (0·58–0·70)	0·70 (0·62–0·77)



(Figure 2 continues on next page)

	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ma et al (2017)[138]	74	24	18	55	0·80 (0·71–0·88)	0·70 (0·58–0·79)
Medhioub et al (2020)[142]	6	6	5	84	0·55 (0·23–0·83)	0·93 (0·86–0·98)
Noguchi et al (2017)[148]	30	10	6	24	0·83 (0·67–0·94)	0·71 (0·53–0·85)
Öznur et al (2021)[152]	60	76	12	154	0·83 (0·73–0·91)	0·67 (0·60–0·73)
Oztas et al (2015)[153]	24	11	14	19	0·63 (0·46–0·78)	0·63 (0·44–0·80)
Park et al (2019)[158]	37	9	7	10	0·84 (0·70–0·93)	0·53 (0·29–0·76)
Raftopoulos et al (2012)[161]	59	36	16	68	0·79 (0·68–0·87)	0·65 (0·55–0·74)
Ren et al (2017)[163]	39	46	25	50	0·61 (0·48–0·73)	0·52 (0·42–0·62)
Salkic et al (2015)[169]	115	34	4	58	0·97 (0·92–0·99)	0·63 (0·52–0·73)
Sanai et al (2017)[170]	70	39	43	214	0·62 (0·52–0·71)	0·85 (0·80–0·89)
Sapmaz et al (2022)[171]	22	41	8	52	0·73 (0·54–0·88)	0·56 (0·45–0·66)
Sayar et al (2020)[172]	121	43	100	153	0·55 (0·48–0·61)	0·78 (0·72–0·84)
Sebastiani et al (2007)[174]	53	5	22	30	0·71 (0·59–0·81)	0·86 (0·70–0·95)
Seto et al (2011)[176]	69	96	8	64	0·90 (0·81–0·95)	0·40 (0·32–0·48)
Sha et al (2019), external validation[177]	12	32	2	63	0·86 (0·57–0·98)	0·66 (0·56–0·76)
Sha et al (2019), internal validation[177]	11	31	2	60	0·85 (0·55–0·98)	0·66 (0·55–0·76)
Sha et al (2019), training[177]	149	285	28	579	0·84 (0·78–0·89)	0·67 (0·64–0·70)
Sheng et al (2022)[180]	41	17	19	1	0·68 (0·55–0·80)	0·06 (0·00–0·27)
Shrivastava et al (2013)[185]	11	22	3	16	0·79 (0·49–0·95)	0·42 (0·26–0·59)
Shukla et al (2020)[186]	45	41	62	78	0·42 (0·33–0·52)	0·66 (0·56–0·74)
Sterling et al (2020)[192]	15	22	9	60	0·63 (0·41–0·81)	0·73 (0·62–0·82)
Tan et al (2017)[194]	63	12	14	6	0·82 (0·71–0·90)	0·33 (0·13–0·59)
Tereshkov et al (2020)[195]	43	20	10	57	0·81 (0·68–0·91)	0·74 (0·63–0·83)
Tseng et al (2018)[198]	53	37	3	8	0·95 (0·85–0·99)	0·18 (0·08–0·32)
Tsuji et al (2020)[199]	22	17	5	52	0·81 (0·62–0·94)	0·75 (0·64–0·85)
Ucar et al (2013)[200]	30	13	11	19	0·73 (0·57–0·86)	0·59 (0·41–0·76)
Udompap et al (2020)[201]	16	8	11	26	0·59 (0·39–0·78)	0·76 (0·59–0·89)
Vasconcelos et al (2020)[202]	32	1	6	11	0·84 (0·69–0·94)	0·92 (0·62–1·00)
Wang et al (2013)[219]	48	8	41	52	0·54 (0·43–0·65)	0·87 (0·75–0·94)
Wang et al (2016)[217]	118	53	51	90	0·70 (0·62–0·77)	0·63 (0·54–0·71)
Wang et al (2017)[213]	146	25	77	60	0·65 (0·59–0·72)	0·71 (0·60–0·80)
Wang et al (2019)[209]	136	23	76	59	0·64 (0·57–0·71)	0·72 (0·61–0·81)
Wang et al (2019)[218]	106	114	57	219	0·65 (0·57–0·72)	0·66 (0·60–0·71)
Wang et al (2019)[207]	48	10	11	22	0·81 (0·69–0·90)	0·69 (0·50–0·84)
Wang et al (2020), training[212]	176	49	83	70	0·68 (0·62–0·74)	0·59 (0·49–0·68)
Wang et al (2020), validation[212]	100	19	41	29	0·71 (0·63–0·78)	0·60 (0·45–0·74)
Wang et al (2021)[215]	126	67	32	57	0·80 (0·73–0·86)	0·46 (0·37–0·55)
Wang et al (2022)[211]	255	45	134	90	0·66 (0·61–0·70)	0·67 (0·58–0·75)
Wang et al (2020)[214]	84	90	37	159	0·69 (0·60–0·77)	0·64 (0·58–0·70)
Wu et al (2012)[225]	184	91	86	121	0·68 (0·62–0·74)	0·57 (0·50–0·64)
Wu et al (2018)[226]	57	119	13	133	0·81 (0·70–0·90)	0·53 (0·46–0·59)
Wu et al (2020)[227]	34	10	21	22	0·62 (0·48–0·75)	0·69 (0·50–0·84)
Xie et al (2022), HBeAg negative[229]	24	13	18	32	0·57 (0·41–0·72)	0·71 (0·56–0·84)
Xie et al (2022), HBeAg positive[229]	44	43	20	134	0·69 (0·56–0·80)	0·76 (0·69–0·82)
Yang et al (2017)[240]	55	8	31	32	0·64 (0·53–0·74)	0·80 (0·64–0·91)
Zeng et al (2016)[249]	92	33	25	43	0·79 (0·70–0·86)	0·57 (0·45–0·68)
Zhang et al (2018)[260]	609	117	273	169	0·69 (0·66–0·72)	0·59 (0·53–0·65)
Zhang et al (2019), training[267]	553	90	112	58	0·83 (0·80–0·86)	0·39 (0·31–0·48)
Zhang et al (2019), validation[267]	432	40	117	36	0·79 (0·75–0·82)	0·47 (0·36–0·59)
Zhong et al (2020)[269]	68	13	48	29	0·59 (0·49–0·68)	0·69 (0·53–0·82)
Zhou et al (2010)[270]	56	48	12	30	0·82 (0· 71–0·91)	0·38 (0·28–0·50)
Zhou et al (2016)[272]	45	90	20	234	0·69 (0·57–0·80)	0·72 (0·67–0·77)
Zhou et al (2021)[271]	52	46	10	57	0·84 (0·72–0·92)	0·55 (0·45–0·65)
Zhu et al (2011)[275]	65	16	14	80	0·82 (0·72–0·90)	0·83 (0·74–0·90)
Zhu et al (2017), external validation[274]	64	47	7	41	0·90 (0·81–0·96)	0·47 (0·36–0·58)
Zhu et al (2017), internal validation[274]	41	84	17	64	0·71 (0·57–0·82)	0·43 (0·35–0·52)
Zhu et al (2017), training[274]	126	140	24	120	0·84 (0·77–0·89)	0·46 (0·40–0·52)
Zou et al (2017)[277]	57	51	32	81	0·64 (0·53–0·74)	0·61 (0·52–0·70)



[232,234,237,240,241,243,244,246,248,249,252–256,260,262–272,274,275,277] Eight studies were subsequently excluded from the meta-analysis; of these, five were excluded because liver biopsy was not used as the reference standard for fibrosis assessment in all of the included patients[50,105,140,166,196] and three were excluded because the study was undertaken only in children.[159,234,246] Therefore, 211 studies with 61 665 patients were included in the meta-analysis.[14,17–20,22–33,35–43,45–47,49,51–55,57,59–62,65–71,73–84,86,89–102,104,106–134,137–139,141–143,145–149,151–156,158,160–165,167,169–177,179,180,182,183,185–195,197–204,206,207,209,211–229,232,237,240,241,243,244,248,249,252–256,260,262–272,274,275,277] A subset of patients from seven studies[23,47,100,145,147,149,260] were receiving antiviral treatment. Because the number was low and the analyses did not report diagnostic accuracies excluding these patients, we chose to include these studies in the analysis.

HIV–hepatitis C virus–hepatitis D virus (HDV) coinfection status was not specified in 34 studies.[18,19,31,35,55,65,67,68,83,93,99,106,107,108,122,138,149,151,154,155,160,171,177,180,182,186,188,190,204,207,241,260,264,274] Four studies[24,47,145,192] included patients with HBV–HIV coinfection, one study[202] included patients with HBV–HDV coinfection, and 172 studies excluded patients with coinfection.[14,17,19,22,23,25–30,32,33,36–43,45,46,49,51–54,57,59–62,66,69–71,73–82,84,86,89–92,94–98,100–102,104,109–121,123–135,137–139,141–143,146–148,152,153,156,158,161–165,167,169,170,172–176,179,183,185,187,189,191,193–195,197–201,203,206,209,211–229,232,237,240,243,244,248,249,252–256,262,263,265–272,275,277]

The sensitivities and specificities of APRI, FIB-4, and transient elastography for fibrosis stages ≥F2, ≥F3, and F4 are summarised in table 1 and in the appendix (pp 139–140). The median prevalence of these fibrosis stages in the included studies was: ≥F2 0·52 (IQR 0·37–0·67), ≥F3 0·30 (0·05–0·54), and F4 0·16 (0·11–0·24).

For the diagnosis of significant fibrosis (≥F2), sensitivity and specificity were 72·9% (95% CI 70·2–75·5) and 64·7% (95% CI 61·0–68·2) for the APRI low cutoff (>0·3 to 0·7), 30·5% (23·7–38·3) and 92·3% (89·3–94·6) for the APRI high cutoff (>1·3 to 1·7), and 75·1% (72·2–77·7) and 79·3% (76·2–82·2) for FibroScan (cutoff >6·0 to 8·0 kPa), respectively.

For the diagnosis of advanced fibrosis (≥F3), sensitivity and specificity were 69·1% (95% CI 64·4–73·5) and 70·5% (95% CI 67·0–73·9) for the low cutoff of FIB-4 (>1·2 to 1·7), 31·1% (24·6–38·5) and 94·8% (91·5–96·8) for the FIB-4 high cutoff (>2·8 to 3·5), and 80·4% (77·1–83·3) and 85·2% (82·8–87·3) for FibroScan (>8·0 to 11·0 kPa), respectively.

For the diagnosis of cirrhosis (F4), the sensitivity and specificity were 59·4% (95% CI 53·2–65·2) and 73·9% (95% CI 70·1–77·4) for the APRI low cutoff (>0·8 to 1·2), 30·2% (24·2–36·9) and 88·2% (85·4–90·6) for the APRI high cutoff (>1·8 to 2·2), and 82·6% (77·8–86·5) and 89·0% (86·3–91·2) for FibroScan (>11·0 to 14·0 kPa), respectively.

Forest plots for the APRI low cutoffs for the diagnosis of significant fibrosis (≥F2) and cirrhosis (F4) are shown in figures 2 and 3, respectively. The rest of the forest plots for the different non-invasive tests across fibrosis stages are presented in the appendix (pp 69–78).

In terms of methodological quality, only two studies were at low risk of bias in all domains of the QUADAS-2 tool,[44,190] whereas 31 studies had an unclear risk of bias and 231 studies had a high risk of bias. Individual study results and summary results across domains are shown in the appendix (pp 89–128). In funnel plots to assess publication bias, some asymmetry was observed in some analyses; however, overall, there was no strong evidence of publication bias (appendix pp 129–134).

In terms of investigating heterogeneity, a subgroup analysis of high versus low methodological quality could not be performed because only two studies were at low risk of bias. In a subgroup analysis of different mean ranges of ALT, APRI had significantly worse sensitivity and better specificity when ALT was less than or equal to the ULN for the low cutoffs for significant fibrosis (≥F2; >0·3 to 0·7) and cirrhosis (F4; >0·8 to 1·2; appendix pp 135–138). There were no reliable significant differences in the diagnostic accuracies of FibroScan and FIB-4 at different mean ranges of ALT. In another subgroup analysis, there were no reliable significant differences in the diagnostic accuracies of the evaluated non-invasive tests between geographical regions (appendix pp 135–138).

We also evaluated the comparative performance of the non-invasive tests in a hypothetical scenario in which the prevalence of significant fibrosis (≥F2) was set at 25% and of cirrhosis (F4) was set at 5%. The classification of 1000 patients using non-invasive tests in this scenario is shown in tables 2 and 3. The classification for advanced fibrosis (≥F3) is shown in the appendix (pp 17–18). This scenario informed the WHO treatment recommendations because it assumed testing of unselected patients. The use of the low APRI cutoff (>0·3 to 0·7) for significant fibrosis (≥F2) in this scenario would result in 26·2% false-positive and 6·8% false-negative results. Use of FibroScan would result in slightly lower false-positive results (15·8%) and a similar rate of false negatives (6·3%). The use of a combined cutoff for APRI would result in 32·6% and 14·7% of the patients being in the indeterminate categories for stages significant fibrosis (≥F2) and cirrhosis (F4), respectively (appendix p 140).

In a second hypothetical scenario, the prevalence of significant fibrosis (≥F2) and cirrhosis (F4) were set at 52·0% and 16·2%, respectively. The classification of 1000 patients using non-invasive tests based on these prevalences and the median prevalence for advanced fibrosis (≥F3) is shown in the appendix (pp 17–18). The use of a combined cutoff for APRI would result in 36·8% and 16·4% of patients being in the indeterminate

Figure 2: **Forest plot for APRI low cutoff (0·3–0·7) in diagnosing significant fibrosis (≥F2)**
ALT=alanine aminotransferase. APRI=aspartate aminotransferase-to-platelet ratio index. FN=false negative. FP=false positive. TN=true negative. TP=true positive.

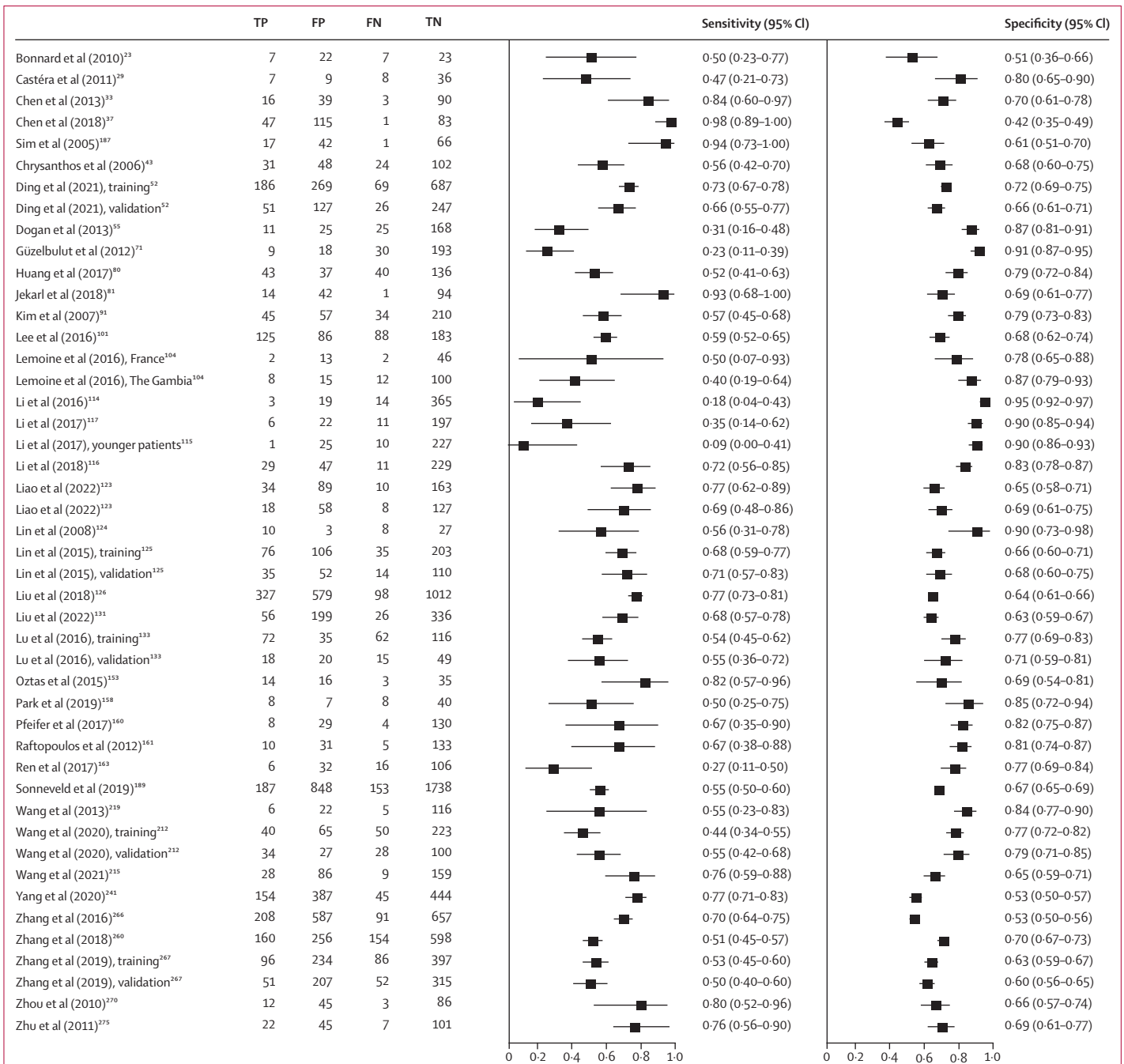


***Figure 3*: Forest plot for APRI low cutoff (0·8–1·2) in diagnosing cirrhosis (F4)**

ALT=alanine aminotransferase. APRI=aspartate aminotransferase-to-platelet ratio index. FN=false negative. FP=false positive. TN=true negative. TP=true positive.

categories for significant fibrosis (≥F2) and cirrhosis (F4), respectively. Further comparisons of APRI and FibroScan for diagnosing significant fibrosis (≥F2) and cirrhosis (F4) for the two different scenarios can be found in the appendix (pp 19–23).

Because the diagnostic accuracies of the narrow ranges did not differ in a statistically significant way from those of the exact cutoffs (APRI ≥F2 0·5 and 1·5, FIB-4 ≥F3 1·45 and 3·25, and APRI F4 1·0 and 2·0; data not shown), single cutoffs were chosen for the WHO guidelines, as well as median FibroScan values (>7·0 kPa for ≥F2, >9·5 kPa for ≥F3, and >12·5 kPa for F4), in order to provide actionable cutoffs for clinical use.

Discussion

In this systematic review and meta-analysis, we show that an APRI cutoff of greater than 0·5 or a FibroScan cutoff of greater than 7·0 kPa identifies most adults with significant fibrosis (≥F2), whereas an APRI cutoff of greater than 1·0 or a FibroScan cutoff of greater than 12·5 kPa identifies the majority of adults with cirrhosis (F4) and in priority need of antiviral therapy. These key findings informed WHO's decisions on new thresholds of APRI and transient elastography for diagnosis of significant fibrosis (≥F2) and cirrhosis (F4). According to the new guidelines, treatment is now recommended for all adults and adolescents (aged ≥12 years) with chronic hepatitis B (including pregnant women and girls and women of reproductive age) with evidence of significant fibrosis (≥F2, based on an APRI score of >0·5 or a transient elastography value of >7 kPa) or evidence of cirrhosis (F4) based on clinical criteria (or an APRI score of >1·0 or a transient elastography value of >12·5 kPa), regardless of HBV DNA or ALT concentrations.

The new 2024 WHO guidelines aimed to simplify and expand treatment indications to promote access to antiviral therapy and therefore to reduce liver-related mortality in resource-limited settings. The focus in these new guidelines is on detecting the presence of significant fibrosis (≥F2), as well as cirrhosis (F4), using non-invasive tests because this is now a priority for treatment eligibility.[5] The 2015 WHO guidelines recommended treatment based on the presence of cirrhosis rather than significant fibrosis, at a much higher APRI threshold of greater than 2·0, because there were strong considerations around the cost and availability of antiviral treatment.[4] It was recognised by WHO subsequently that at least 50% of patients who had cirrhosis would be missed by such a high cutoff. In the selection of new thresholds for non-invasive fibrosis tests, concerns regarding false positives are now much lower than before, given the goals of substantial expansion in treatment eligibility and earlier treatment.

In the updated WHO guidelines, a decision was taken to prioritise the minimisation of false-negative results and accept a higher number of false positives.[5] Therefore, a lower APRI cutoff of greater than 0·5, which has a high sensitivity but moderate specificity, was chosen. As shown in our findings for the narrow ranges, which did not significantly differ from the exact single cutoffs, this strategy will result in around 26·2% of unselected treated patients not having significant cirrhosis (false positives), but will only miss around 6·8% of patients with significant cirrhosis (false negatives), when the baseline prevalence of significant cirrhosis (≥F2) is 25%. An increased baseline prevalence would result in a lower number of false-positive and a higher number of false-negative results. Therefore, the pre-test probability is crucially important when interpreting diagnostic accuracy results of non-invasive tests. This pre-test probability depends on several factors, such as the phase of HBV infection, the age of the patient, and the presence of comorbidities or other risk factors, such as obesity or excessive alcohol use. The use of dual cutoffs for APRI (a low cutoff to rule out and a high cutoff to rule in) would improve diagnostic accuracy but would result in a proportion of patients having indeterminate results, who would therefore need retesting at a later stage, a second non-invasive test, or a liver biopsy. FIB-4, which also consists of widely available variables, was not chosen for the guidelines because it is used for the staging of advanced (≥F3) rather than significant (≥F2) fibrosis and also includes age, which might have resulted in a high number of false-negative results in people younger than 35 years.

Potential harms to consider when choosing thresholds include the possibility of treatment decisions based on either false-positive or false-negative results. A false-negative result would mean that a person with significant fibrosis would not be identified and would be delayed in receiving prompt antiviral treatment that could prevent progression to cirrhosis or decrease the risk of developing hepatocellular carcinoma. A false-positive test result might lead to a patient being treated unnecessarily or prematurely, which would expose them to the inconvenience of long-term treatment, potential drug

	True positive	False positive	False negative	True negative
APRI low cutoff (>0·3 to 0·7)	182 (18·2%)	262 (26·2%)	68 (6·8%)	488 (48·8%)
APRI high cutoff (>1·3 to 1·7)	73 (7·3%)	45 (4·5%)	177 (17·7%)	705 (70·5%)
APRI combined cutoff*	73 (7·3%)	45 (4·5%)	68 (6·8%)	488 (48·8%)
FibroScan (>6·0 to 8·0 kPa)	187 (18·7%)	158 (15·8%)	63 (6·3%)	592 (59·2%)

APRI=aspartate aminotransferase-to-platelet ratio index. *The use of combined cutoffs would mean that 326 people would have indeterminate results and would be unclassified.

Table 2: **Test outcomes of APRI and FibroScan based on a hypothetical population of 1000 patients with a 25% prevalence of significant fibrosis (≥F2; unselected patients with positive HBsAg)**

	True positive	False positive	False negative	True negative
APRI low cutoff (>0·8 to 1·2)	29 (2·9%)	247 (24·7%)	21 (2·1%)	703 (70·3%)
APRI high cutoff (>1·8 to 2·2)	15 (1·5%)	114 (11·4%)	35 (3·5%)	836 (83·6%)
APRI combined cutoff*	15 (1·5%)	114 (11·4%)	21 (2·1%)	703 (70·3%)
FibroScan (>11·0 to 14·0 kPa)	41 (4·1%)	105 (10·5%)	9 (0·9%)	845 (84·5%)

APRI=aspartate aminotransferase-to-platelet ratio index. *The use of combined cutoffs would mean that 147 people would have indeterminate results and would be unclassified.

Table 3: **Test outcomes of APRI and FibroScan based on a hypothetical population of 1000 patients with a 5% prevalence of cirrhosis (F4; unselected patients with positive HBsAg)**

resistance, and a small risk of drug toxicity. Overall, the WHO HBV Guideline Development Group considered that the benefits of using non-invasive tests, with the potential increase in treatment availability, resulting from increased access to non-invasive monitoring, and reduced risk of adverse events from liver biopsy, outweighed these potential harms.

The low cost of blood-based non-invasive tests is a key factor in continuing to recommend APRI as the preferred non-invasive test. The blood tests that are needed to calculate the APRI score are inexpensive (less than a few US$ per test), are routinely available at most health-care facilities in resource-limited settings, and can be undertaken by untrained personnel. Interpreting APRI results is also relatively straightforward. Similarly, transient elastography (FibroScan) is non-invasive, takes less than 10 min to perform, and can be undertaken in outpatient or community settings. Medical, nursing, and other health-care personnel can be easily trained to use FibroScan.

The major strength of this study is that it represents a comprehensive systematic review and meta-analysis following a predefined protocol using the Cochrane methodology. The data were then used by a diverse guideline development group to provide real-world recommendations balancing several factors. Major limitations include the lack of individual patient data and the very small number of studies[23,51] reporting on data from sub-Saharan Africa. We can draw no conclusions about potential differences in diagnostic accuracies in this region compared with other regions. Histological staging was performed using different scores across studies and we converted these to METAVIR for the analysis, which might have introduced bias.

Some other points regarding our systematic review also deserve attention. First, the reported prevalences of significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) do not represent the true prevalences of these stages in unselected patients with chronic hepatitis B. This is because there is a substantial selection bias in which patients with chronic hepatitis B have a liver biopsy, which is based on clinical indication (most often high liver aminotransferases, high viral load, or both). By contrast, inactive carriers are rarely biopsied. Second, the cutoffs for FibroScan for specific fibrosis stages were not predetermined in the vast majority of assessed studies, had considerable variation, and overlapped between fibrosis stages. Because the cutoffs were not predetermined in several FibroScan studies and were rather statistically estimated to correlate in the best way with biopsy results, it is highly probable that summary sensitivity and specificity are overestimated for FibroScan across all fibrosis stages. Third, our finding on the effect of normal ALT on diagnostic accuracy should be interpreted with extreme caution, because we did not have individual patient data available and the analysis was based on mean (or median) ALT values across studies. Finally, a small number of patients in seven of the included studies were receiving antiviral treatment, which might have had an effect on the diagnostic accuracy of the non-invasive tests that were evaluated.

This systematic review also identified several important research gaps. These gaps include the need for further evaluation of the performance of non-invasive tests in under-researched populations, including people with HBV–HIV coinfection, HBV–HDV coinfection, pregnant women, children and adolescents, people with metabolic dysfunction-associated steatotic liver disease,[278] and in populations from sub-Saharan Africa and Latin America. There is a need for studies of the cost-effectiveness of non-invasive tests in resource-limited settings.[279] There is also a need for an evaluation in resource-limited settings of alternative elastography methods, such as acoustic radiation force impulse and shear-wave elastography, which are similar in principle to transient elastography and are incorporated into ultrasound imaging machines.

In conclusion, we present the results of a comprehensive systematic review and meta-analysis on the use of APRI, FIB-4, and FibroScan to stage liver fibrosis and cirrhosis in people with chronic hepatitis B. We also show how these results were used to inform decisions on testing and treatment at a large scale, taking into consideration a combination of factors, including diagnostic accuracy, availability, cost, and number and potential consequences of false-positive and false-negative results. These findings can be used as a blueprint for the use of non-invasive tests in other conditions and settings.

Contributors

AL and MZ: literature search, data extraction, and writing of the original draft. GC: statistical analysis, supervision, and review and editing. PE: conceptualisation and review and editing. EAT: conceptualisation, writing of the original draft, supervision, and review and editing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AL, MZ, GC, and EAT have accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

Extracted data for the systematic review and meta-analysis can be made available after publication, with investigator support, after approval of a proposal with a signed data access agreement. Proposals should be submitted to the corresponding author.

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