Original article

Evaluation of aspartate aminotransferase to platelet ratio index and fibrosis 4 score for selecting patients with chronic hepatitis B to perform liver fibrosis assessment by transient elastography in resource-limited areas

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Background: Liver stiffness measurement operated by transient elastography (TE) becomes a noninvasive method to assess the severity of hepatic fibrosis. However, TE may not be available in resource-limiting areas. Therefore, simple serum biomarker scoring should be evaluated for fibrotic assessment instead of TE.

Objectives: This study aimed to evaluate the diagnostic performance of aspartate. aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores compared with TE in chronic hepatitis B (CHB) patients and determine the optimal cut-off values to select the CHB patients who should be referred to higher-level hospital for TE evaluation.

Methods: We conducted a cross-sectional study including 202 patients with chronic hepatitis B who underwent transient elastography. Using TE as a reference standard, the diagnostic performance of APRI and FIB-4 scores were evaluated.

Results: Both APRI and FIB-4 scores demonstrated a significantly moderate correlation with liver stiffness resulting from TE ($r = 0.667$, $P < 0.001$; and $r = 0.598$, $P < 0.001$, respectively). For evaluation of significant fibrosis, APRI performance was not a significant difference from FIB-4 score as the area under ROC curve (AUROCs) were 0.824 for APRI and 0.780 for FIB-4 score, $P = 0.33$. APRI < 0.25 and FIB-4 < 0.8 demonstrated the better sensitivity in case of ruling out significant fibrosis. APRI ≥ 1.0 and FIB-4 ≥ 1.7 showed the optimal specificity for ruling in significant fibrosis. Regarding cirrhosis, APRI performance was also not a significant difference from FIB-4 score as the AUROCs were 0.921 for APRI and 0.933 for FIB-4 score, $P = 0.78$. APRI < 0.5 and FIB-4 < 1.45 had the optimal sensitivity for exclude cirrhosis. APRI ≥ 1.5 and FIB-4 ≥ 3.25 showed the optimal specificity for diagnosis of cirrhosis.

Conclusion: Both APRI and FIB-4 scores were proved to have impressive diagnostic performance in the prediction of significant fibrosis and cirrhosis. We suggest that these new cut-off levels can determine the optimal strategy to select the right patients to receive the appropriate CHB management.

Keywords: APRI, chronic hepatitis B, FIB-4, liver fibrosis, transient elastography.

Chronic hepatitis B (CHB) is a most common chronic liver disease in Asia, especially Thailand. Recent data estimates 2.2 millions of Thai population infected with CHB.[1] CHB can progress to liver cirrhosis and hepatocellular carcinoma with increasing morbidity and mortality. In many guidelines [2 - 4], determination of significant hepatic fibrosis and cirrhosis can help the physician to initiate CHB treatment, particularly patients whom alanine transaminase (ALT) level does not elevate notably. Moreover, significant liver fibrosis is also an important surrogate marker for the disease's progression. Therefore, the assessment of hepatic fibrotic stage is crucial in modern CHB management. Even though histological evaluation by liver biopsy is the gold

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standard of fibrotic assessment, it is an invasive method with uncommon but potentially life-threatening complications and must be performed by well-trained gastroenterologist.[5] Nowadays, liver stiffness measurement using transient elastography (TE) has become one of the common noninvasive methods to evaluate liver fibrosis. TE has several advantages because of short procedure time, immediate results, and good reproducibility, as well as worldwide validation.[6, 7] Nevertheless, TE had some limitations[8], for examples, unreliable results in some particular patients (ascites, obesity, acute hepatitis, etc.). Additionally, TE requires dedicated device that is costly for many hospital.[8] In Thailand, TE is restricted in university hospitals and some tertiary hospitals. Numerous Thai CHB patients do not receive optimal assessment of liver fibrosis due to the high cost of TE including difficult referral to access TE. Other noninvasive methods should be considered for replacing TE or applying to be a screening tool for select patients allowed to refer for TE evaluation.

Serum biomarker is another current method for liver fibrosis assessment. Aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores are widely accepted for hepatic fibrotic prediction. [6] Meta-analysis demonstrated APRI and FIB-4 had moderate accuracy to identify significant fibrosis and cirrhosis.[9] These scorings are calculated by clinical and simple laboratory values that are routinely investigated in general practice. These scorings are also recommended by World Health Organization (WHO) to be used in resource-limited setting. [10] However, the data regarding the diagnostic performance of APRI and FIB-4 scoring compared with TE in patients with chronic hepatitis B are limited. This study aimed to evaluate the diagnostic performance of APRI and FIB-4 scoring compared with TE in CHB patients and determine the optimal cut-off values to select the CHB patients who should be referred to higher-level hospital for TE evaluation.

Materials and methods

A cross-sectional study was conducted in Phrapokklao hospital, Thailand. We included 202 patients who were diagnosed with chronic hepatitis B who underwent transient elastography by Fibroscan™ (Echosens, France) from 2018 - 2021 and did not receive treatment of chronic hepatitis B at the time of operation. Most of them were referred from the community hospitals where TE is not available. Exclusion criteria were as follows: 1) no available laboratory results of liver tests, complete blood count, and HBV-DNA level within 3 months of TE; 2) patients with coexisting diseases affecting platelet level e.g. immune-mediated thrombocytopenia or hematologic malignancies and aspartate amino-transferase/alanine transaminase (AST/ALT) level e.g. hemolysis or muscle injury; 3) patients with conditions ensuing overestimated liver stiffness measurement i.e. severe hepatitis (AST or ALT > 5 times above upper normal limit (ULN), congestive heart failure, end stage renal disease; 4) patients with current or previous evidence of decompensated cirrhosis; and 5) pregnancy.

Data regarding patients' baseline characteristics (demographic data, laboratory results, hepatitis B viral profile) were retrieved from the electronic medical record program and this study protocol was approved by the hospital research ethic committee (certificate of approval no 061/64).

All laboratory parameters in our study were acquired before initiation of anti-viral therapy in indicated cases. Hence, CHB treatment did not influence the calculation of both serum biomarkers. All transient elastography was evaluated with Fibroscan® (Echosens, France) by three certificated and long-term experienced gastroenterologists and successful TE was defined if three criteria were fulfilled: 1) a number of validated shots of at least 10; 2) a success rate (the ratio of valid shots to the total number of shots) > 70.0%; and, 3) an interquartile range (IQR)/median of liver stiffness < 30.0%. The patients who were undergone TE must be fasted for 6 hours before operation.[11]

Using TE as the reference standard of liver fibrotic measurement, the diagnostic performance of APRI and FIB-4 scores were evaluated. The TE cut-off levels of 7.0 kPa and 12.5 kPa were defined for significant fibrosis ($F \geq 2$) and cirrhosis, respectively. APRI and FIB-4 scores were calculated the formula presented below. [12, 13] The upper normal limit of AST level was 35 U/L. The cut-off values of significant fibrosis and cirrhosis were determined using WHO recommendation: APRI 0.5, 1.5 and FIB-4 1.45 for significant fibrosis as well as APRI 1, 2 and FIB-4 1.45, 3.25 for cirrhosis). [10]

APRI = {[AST (U/L)/AST upper limit of normal (U/L)]/platelet (10^9/L)} x 100

FIB-4 = [age (years) x AST (U/L)]/[platelet (10^9/L)x$ALT^{1/2}$(U/L)]

Statistical analysis

Descriptive statistics was used for patients' baseline characteristics and laboratory results. Quantitative measurements were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) according to their distribution. Categorical variables were shown by numbers and percentages. Spearman's correlation analysis was computed to compare the liver stiffness with APRI and FIB-4 scores. Using TE as the reference standard, the diagnostic performance of APRI and FIB-4 scores were evaluated by the area under the receiver operator characteristic curve (AUROC) and were also reported as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (LR) for each different cut-off values. DeLong's test was used to compare between two ROCs of APRI and FIB-4 for significant fibrosis and cirrhosis. P - value < 0.05 was considered statistically significant.

Results

A total of 202 eligible patients were included in this study. Baseline characteristics of enrolled patients were presented in Table 1. The mean age was 50 years and four-fifths of patients had age ≥ 40 years. Female was the slightly predominant gender and metabolic associated fatty liver was the most common co-liver disease. The majority of chronic hepatitis B in this study was inactive stage (HBV-DNA < 2,000 IU/mL and normal ALT). Conforming to TE criteria, 26.8% of patients had significant fibrosis (F2-3) and 17.8% had cirrhosis.

The APRI and FIB-4 scores demonstrated a significantly moderate correlation with liver stiffness resulting from TE ($r = 0.667$, $P < 0.001$; and $r = 0.598$, $P < 0.001$, respectively).

Table 1. Baseline characteristics of enrolled patients (n = 202).

Characteristics	N (%)
Age, year (mean ± SD)	49.3 ± 11.3
Age group	
25 - 39 year-old	39 (19.3)
40 year-old or more	163 (80.7)
Gender, male	97 (48.0)
Co-liver diseases	
Chronic hepatitis C	4 (2.0)
Chronic alcoholism	15 (7.4)
Metabolic associated fatty liver disease	19 (9.4)
Overweight (BMI ≥ 25 kg/m^2)	68 (33.7)
Liver stiffness, kPa (median, IQR)	6.7 (5.3, 10.2)
Platelet, x10^9/L (median, IQR)	210 (172, 256)
INR (median, IQR)	1.04 (0.98, 1.10)
Albumin level, g/dL (median, IQR)	4.4 (4.2, 4.6)
Total bilirubin level, mg/dL (median, IQR)	0.59 (0.42, 0.79)
ALT level, U/L (median, IQR)	27 (19, 42)
AST level, U/L (median, IQR)	25 (20, 37)
HBeAg positive	36 (17.8)
HBV-DNA level (IU/mL) (median, IQR)	2,805 (137, 409, 500)
Subgroup of patients	
HBV-DNA ≥ 2,000 IU/mL and ALT ≥ 2xULN	26 (13.1)
HBV-DNA ≥ 2,000 IU/mL and ALT < 2xULN	80 (39.6)
HBV-DNA < 2,000 IU/mL and normal ALT	96 (47.5)
Fibrosis stage by TE	
No significant fibrosis (F0 - 1)	112 (55.4)
Significant fibrosis, no cirrhosis (F2 - 3)	54 (26.8)
Cirrhosis (F4)	36 (17.8)

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (LR) at the cut-off points of APRI and FIB-4 scores for predicting significant fibrosis as well as cirrhosis are shown in Table 2 and 3, respectively. An ROC was created for diagnostic performance for APRI and FIB-4 scores in significant fibrosis (Figure 1) and cirrhosis (Figure 2).

Table 2. Diagnostic performances of APRI and FIB-4 scores for predicting significant fibrosis.

Scores	Sensitivity,% (95%CI)	Specificity,% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)
APRI ≥ 0.25	90.0 (81.4, 95.0)	40.2 (31.2, 49.9)	54.7 (46.4, 62.9)	83.3 (70.2, 91.6)	1.50 (1.3, 1.8)	0.25 (0.1, 0.5)
APRI ≥ 0.3	82.2 (72.4, 89.2)	66.1 (56.4, 74.6)	66.1 (56.4, 74.6)	82.2 (72.4, 89.2)	2.42 (1.8, 3.2)	0.27 (0.2, 0.4)
APRI ≥ 0.5	57.8 (46.9, 68.0)	93.8 (87.1, 97.2)	88.1 (76.4, 94.7)	73.4 (65.3, 80.3)	9.24 (4.41, 19.35)	0.45 (0.4, 0.6)
APRI ≥ 1.0	32.2 (23.0, 43.0)	98.2 (93.1, 99.7)	93.5 (77.2, 98.9)	64.3 (56.6, 71.4)	18.04 (4.4, 73.6)	0.69 (0.6, 0.8)
APRI ≥ 1.5	17.8 (10.8, 27.6)	99.1 (94.4, 99.9)	94.1 (69.2, 99.7)	60.0 (52.5, 67.0)	19.91 (2.7, 147.3)	0.83 (0.8, 0.9)
FIB-4 ≥ 0.8	90.0 (81.4, 95.0)	43.8 (34.5, 53.4)	56.3 (47.8, 64.4)	84.5 (72.0, 92.2)	1.60 (1.34, 1.91)	0.23 (0.1, 0.5)
FIB-4 ≥ 1.45	56.7 (45.8, 66.9)	85.7 (77.5, 91.4)	76.1 (63.9, 85.3)	71.1 (62.6, 78.4)	3.97 (2.4, 6.5)	0.51 (0.4, 0.6)
FIB-4 ≥ 1.7	47.8 (37.2, 58.5)	93.8 (87.1, 97.2)	86.0 (72.6, 93.7)	69.1 (61.0, 76.2)	7.64 (3.6, 16.2)	0.56 (0.5, 0.7)
FIB-4 ≥ 3.25	28.9 (20.0, 39.5)	99.1 (94.4, 100.0)	96.3 (79.1, 99.8)	63.4 (55.8, 70.5)	32.36 (4.5, 233.9)	0.72 (0.6, 0.8)

Table 3. Diagnostic performances of APRI and FIB-4 scores for predicting cirrhosis.

Scores	Sensitivity,% (95%CI)	Specificity,% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)
APRI ≥ 0.3	97.2 (83.8, 1.0)	53.6 (45.7, 61.3)	31.3 (23.0, 40.8)	98.9 (59.2, 77.0)	2.10 (1.8, 2.5)	0.05 (0.0, 0.4)
APRI ≥ 0.5	88.9 (73.0, 96.4)	83.7 (77.0, 88.8)	54.2 (40.8, 67.1)	97.2 (92.5, 99.1)	5.47 (3.8, 7.9)	0.1 (0.1, 0.3)
APRI ≥ 1.0	55.6 (38.3, 72.7)	93.4 (88.2, 96.5)	64.5 (45.4, 80.2)	90.6 (85.0, 94.4)	8.4 (4.4, 15.9)	0.5 (0.3, 0.7)
APRI ≥ 1.5	38.9 (23.7, 56.5)	98.2 (94.4, 99.5)	82.4 (55.8, 95.3)	88.1 (82.3, 92.2)	21.5 (6.5, 71.0)	0.6 (0.5, 0.8)
APRI ≥ 2.0	33.3 (19.1, 51.1)	99.4 (96.2, 100.0)	92.3 (62.1, 99.6)	87.3 (81.5, 91.5)	55.3 (7.4, 412.1)	0.7 (0.5, 0.9)
FIB-4 ≥ 0.8	100.0 (88.0, 100.0)	34.9 (27.8, 42.8)	25.0 (18.3, 33.0)	100.0 (92.3, 100.0)	1.54 (1.4, 1.7)	0.0 -
FIB-4 ≥ 1.45	91.7 (76.4, 97.8)	79.5 (72.4, 85.2)	49.3 (36.9, 61.6)	97.8 (93.1, 99.4)	4.5 (3.3, 6.1)	0.1 (0.0, 0.3)
FIB-4 ≥ 3.25	50.0 (33.3, 66.8)	94.6 (89.6, 97.3)	66.7 (46.0, 82.8)	89.7 (84.0, 93.6)	9.2 (4.5, 18.8)	0.5 (0.4, 0.7)

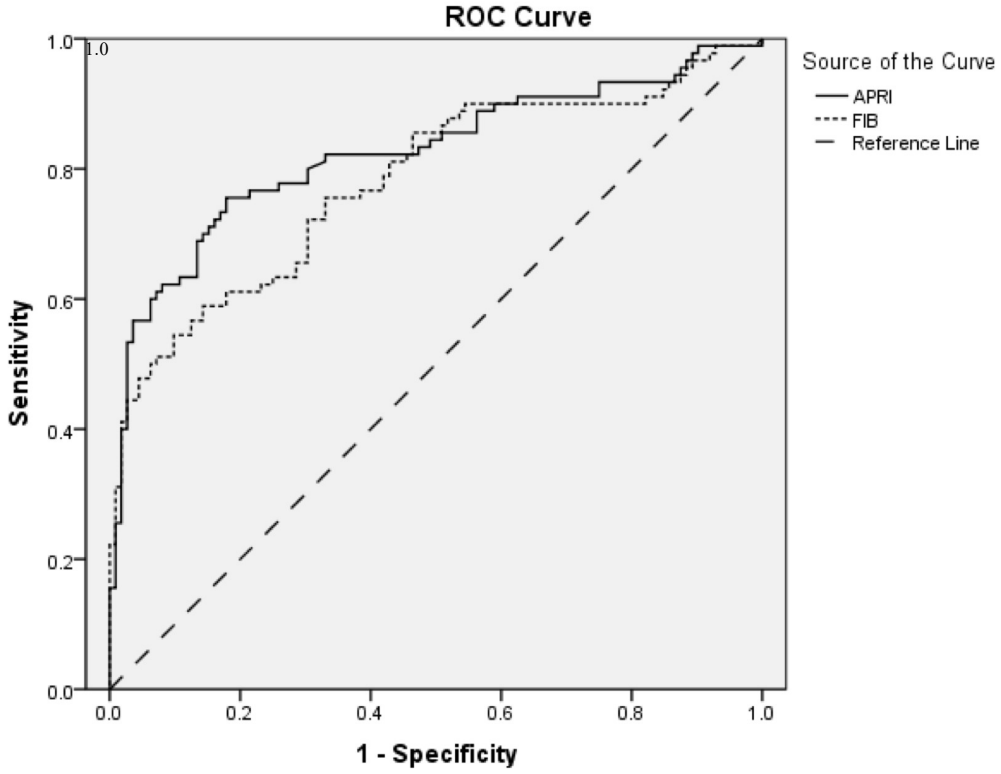

Figure 1. Area under the receiver operator characteristics curve analysis for the diagnosis of significant fibrosis using APRI and FIB-4 scores.

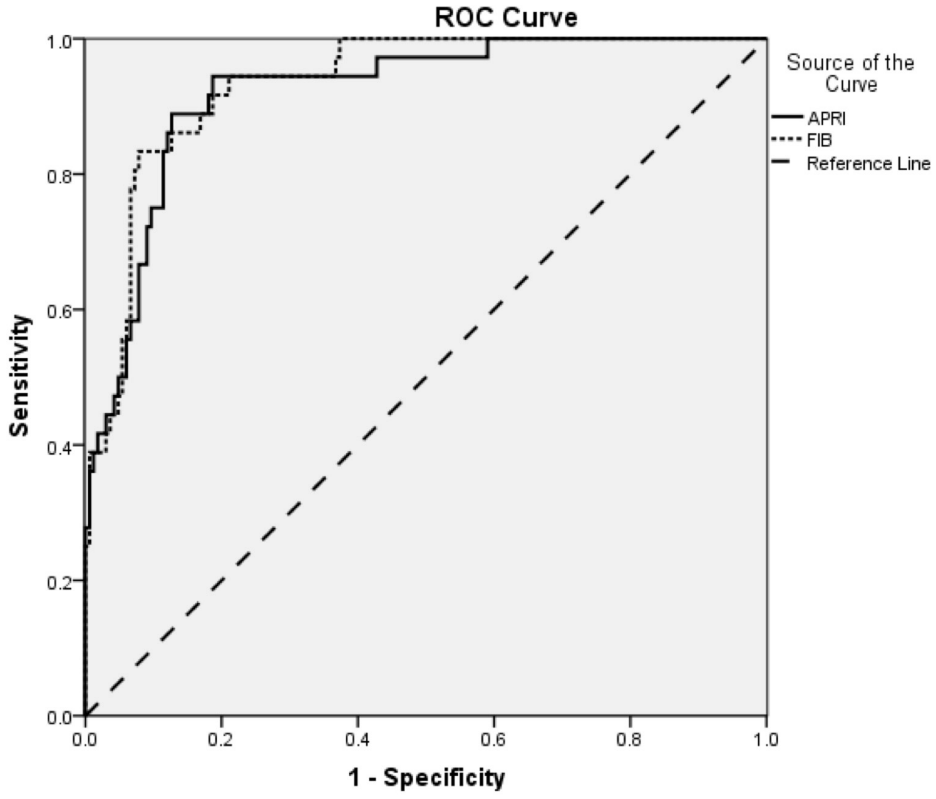

Figure 2. Area under the receiver operator characteristics curve analysis for the diagnosis of cirrhosis using APRI and FIB-4 scores.

Regarding significant fibrosis, APRI performance was not significant difference from FIB-4 score as the AUROCs were 0.824 for APRI (95%CI 0.762, 0.885) and 0.780 for FIB-4 score (95%CI 0.714, 0.847), P = 0.33. An APRI ≥ 0.5 provided high specificity and PPV for predicting significant fibrosis (specificity of 93.8%, PPV of 88.1%) and better specificity and PPV for APRI ≥ 1.0 (specificity 98.2%, PPV 93.5%). Nevertheless, APRI < 0.5 provided low sensitivity (57.8%) and NPV (73.4%) to rule out significant fibrosis. For better sensitivity to rule out significant fibrosis, APRI < 0.25 was the optimal cut-off and provided a sensitivity of 90.0% and NPV of 83.3%. For analysis of FIB-4 score, a FIB-4 ≥ 1.45 showed sensitivity of 56.7% and specificity 85.7%. However, FIB-4 < 0.8 provided better sensitivity (90.0%) and NPV (85.7%) for ruling out significant fibrosis and FIB-4 ≥ 1.7 demonstrated higher specificity (93.8%) and PPV (86.0%) for ruling in significant fibrosis.

Regarding cirrhosis, APRI performance was not significant difference from FIB-4 score as the AUROCs were 0.921 for APRI (95%CI 0.876, 0.966) and 0.933 for FIB-4 score (95%CI 0.896, 0.970), P = 0.78. An APRI ≥ 2.0 showed high specificity and PPV for predicting liver cirrhosis (specificity of 99.4% and PPV of 92.3%). Additionally, APRI ≥ 1.5 had nearby specificity (98.2%) for ruling in cirrhosis. However, the sensitivity of APRI < 1.0 is low to rule out cirrhosis and we found that APRI < 0.5 had better sensitivity (55.3% *vs.* 88.9%, respectively). According to the analysis of FIB-4 score, a FIB-4 < 1.45 showed a sensitivity of 91.7% for excluding cirrhosis and FIB-4 ≥ 3.25 provided 94.6% of specificity for predicting cirrhosis.

Sensitivity and specificity of APRI and FIB-4 scores for predicting significant fibrosis and cirrhosis in each HBeAg status were shown in Table 4 and 5. For ruling out significant fibrosis, APRI < 0.25 and FIB-4 < 0.8 had satisfied sensitivity in both subgroups. Sensitivity of both scores were lower in HBeAg negative subgroup. For predicting significant fibrosis, specificity of APRI ≥ 1.0 and ≥ 1.5 resembled in both subgroups. However, FIB-4 ≥ 1.7 provided higher specificity than FIB-4 ≥ 1.45 in HBeAg negative subgroup but they were not different in HBeAg positive subgroup. In cirrhotic evaluation, APRI < 0.5 and FIB-4 < 0.8 had impressive sensitivity to exclude in both subgroups. About FIB-4 < 1.45, it showed high sensitivity in HBeAg negative subgroup but low sensitivity in HBeAg positive subgroup. For predicting cirrhosis, specificity of APRI ≥ 1.5 and ≥ 2.0 resembled in both subgroups. As well, FIB-4 ≥ 3.25 demonstrated higher specificity than FIB-4 ≥ 1.45 in HBeAg negative subgroup but they were not different in HBeAg positive subgroup.

Table 4. Sensitivity and specificity of APRI and FIB-4 scores for predicting significant fibrosis in HBeAg positive and HBeAg negative subgroups.

Status	**HBeAg positive (n = 36)**		**HBeAg negative (n = 166)**	
Scores	**Sensitivity,% (95%CI)**	**Specificity,% (95%CI)**	**Sensitivity,% (95%CI)**	**Specificity,% (95%CI)**
APRI ≥ 0.25	100.0 (79.1, 100.0)	52.9 (28.5, 76.1)	87.3 (76.8, 93.7)	37.9 (28.3, 48.5)
APRI ≥ 0.5	78.9 (53.9, 93.0)	94.1 (69.2, 99.7)	52.1 (40.0, 64.0)	93.7 (86.2, 97.4)
APRI ≥ 1.0	31.6 (13.6, 56.5)	94.1 (69.2, 99.7)	32.4 (22.0, 44.7)	98.9 (93.4, 99.9)
APRI ≥ 1.5	10.5 (1.8, 34.5)	94.1 (69.2, 99.7)	19.7 (11.5, 31.1)	100.0 (95.2, 100.0)
FIB-4 ≥ 0.8	94.7 (71.9, 99.7)	64.7 (38.6, 84.7)	88.7 (78.5, 94.7)	40.0 (30.2, 50.6)
FIB-4 ≥ 1.45	42.1 (21.1, 66.0)	94.1 (69.2, 99.7)	60.6 (48.2, 71.7)	84.2 (75.0, 90.6)
FIB-4 ≥ 1.7	36.8 (17.2, 61.4)	94.1 (69.2, 89.3)	50.7 (38.7, 62.7)	93.7 (86.2, 97.4)

Table 5. Sensitivity and specificity of APRI and FIB-4 scores for predicting cirrhosis in HBeAg positive and HBeAg negative subgroups.

Status	HBeAg positive (n = 36)		HBeAg negative (n = 166)	
Scores	Sensitivity,% (95%CI)	Specificity,% (95%CI)	Sensitivity,% (95%CI)	Specificity,% (95%CI)
APRI ≥ 0.5	87.5 (46.7, 99.3)	67.9 (47.6, 83.4)	89.3 (70.6, 97.2)	87.0 (80.0, 91.9)
APRI ≥ 1.0	37.5 (10.2, 74.1)	85.7 (66.4, 95.3)	60.7 (40.7, 77.9)	94.5 (89.4, 97.8)
APRI ≥ 1.5	25.0 (4.5, 6.4)	96.4 (79.8, 100.0)	42.9 (25.0, 62.6)	98.6 (94.3, 99.7)
APRI ≥ 2.0	12.5 (0.7, 53.3)	100.0 (0.85, 100.0)	39.2 (22.1, 59.3)	99.2 (87.4, 100.0)
FIB-4 ≥ 0.8	100.0 (59.8, 100.00)	42.9 (25.0, 62.6)	100.0 (85.0, 100.0)	33.3 (21.2, 35.3)
FIB-4 ≥ 1.45	75.0 (35.6, 95.6)	89.3 (70.6, 97.2)	96.4 (80.0, 100.0)	77.5 (69.5, 84.0)
FIB-4 ≥ 3.25	62.5 (25.9, 89.9)	89.3 (70.1, 97.2)	46.4 (28.0, 65.8)	95.7 (90.4, 98.2)

Sensitivity and specificity of APRI and FIB-4 scores for assessing significant fibrosis and cirrhosis in each age subgroup were presented in table 6 and 7. In case of patients with age < 40 years, APRI ≥ 0.5 demonstrated 100.0% of specificity for diagnosis of significant fibrosis. Interestingly, FIB-4 < 0.8 had low sensitivity for excluding significant fibrosis. Both FIB-4 ≥ 1.45 and 1.7 had also 100.0% of specificity for diagnosis of significant fibrosis. There was no patient with age < 40 years diagnosed with cirrhosis, thus sensitivity of APRI and FIB-4 score were not able to be calculated.

Table 6. Comparison of sensitivity and specificity of APRI and FIB-4 scores for predicting significant fibrosis in age < 40 year-old and age 40 year-o ld or more subgroups.

Status	Age < 40 year-old (n = 39)		Age 40 year-old or more (n = 163)	
Scores	Sensitivity,% (95%CI)	Specificity,% (95%CI)	Sensitivity,% (95%CI)	Specificity,% (95%CI)
APRI ≥ 0.25	90.0 (54.1, 0.99)	55.2 (36.0, 99.5)	90.0 (80.7, 95.2)	34.9 (25.0, 46.3)
APRI ≥ 0.5	30.0 (8.1, 64.6)	100.0 (85.4, 100.0)	61.3 (49.7, 71.7)	91.6 (82.9, 96.3)
APRI ≥ 1.0	10.0 (0.5, 45.9)	100.0 (85.4, 100.0)	35.0 (24.9, 46.6)	97.6 (90.8, 99.6)
APRI ≥ 1.5	10.0 (0.5, 45.9)	100.00 (85.4, 100.0)	18.8 (11.2, 29.4)	98.8 (92.5, 99.9)
FIB-4 ≥ 0.8	70.0 (35.4, 92.0)	86.2 (67.4, 95.5)	92.5 (83.8, 96.9)	28.9 (19.7, 40.1)
FIB-4 ≥ 1.45	10.0 (0.5, 45.9)	100.0 (85.4, 100.0)	62.5 (50.9, 72.9)	80.7 (70.3, 88.3)
FIB-4 ≥ 1.7	10.0 (0.5, 45.9)	100.0 (85.4, 100.0)	52.5 (41.1, 63.7)	91.6 (82.9, 96.3)

Table 7. Comparison of sensitivity and specificity of APRI and FIB-4 scores for predicting cirrhosis in age <40 year-old and age 40 year-old or more subgroups.

Status	Age < 40 year-old (n = 39)		Age 40 year-old or more (n = 163)	
Scores	Sensitivity,% (95%CI)	Specificity,% (95%CI)	Sensitivity,% (95%CI)	Specificity,% (95%CI)
APRI ≥ 0.5	NA	92.3 (78.0, 98.0)	88.9 (73.0, 96.4)	81.1 (73.0, 87.2)
APRI ≥ 1.0	NA	97.4 (84.9, 99.9)	55.6 (38.3, 71.7)	92.1 (85.6, 96.0)
APRI ≥ 1.5	NA	97.4 (84.9, 99.9)	38.9 (23.6, 56.8)	98.4 (93.9, 99.7)
APRI ≥ 2.0	NA	97.4 (84.9, 99.9)	33.3 (19.1, 51.1)	100.0 (96.3, 100.0)
FIB-4 ≥ 0.8	NA	71.8 (54.9, 84.5)	100.0 (88.0, 100.0)	23.6 (16.7, 32.1)
FIB-4 ≥ 1.45	NA	97.4 (84.9, 99.9)	91.7 (76.4, 97.8)	74.0 (65.3, 81.2)
FIB-4 ≥ 3.25	NA	100.0 (88.9, 100.0)	50.0 (33.2, 66.8)	92.9 (86.6, 96.5)

Discussion

Hepatic fibrotic degree is crucial parameter in the clinical management of patients with CHB in terms of cirrhotic care (particularly HCC surveillance) and consideration of treatment in significant fibrotic group.[2-4] TE is one of the common tools for fibrotic assessment due to several advantages, the main limitations of TE are high-cost equipment and nonavailability in the general hospital, resulting barriers to optimal assessment of liver fibrosis. Simple serum biomarkers, i.e., APRI and FIB-4 scorings, are recommended to use instead of TE in limited resource areas, although a recent study showed that both scores had slightly lower accuracy than TE to predict significant fibrosis.[14] Nevertheless, simple serum-based scores should be evaluated to properly select CHB patients to refer for further TE assessment.

We found that APRI and FIB-4 performed well and non-significantly different in predicting significant fibrosis and cirrhosis. The results are similar to the AUROC of APRI and FIB-4 scores for significant fibrosis and cirrhosis in the previous meta-analysis using liver biopsy as the gold standard.[9] Additionally, our study supported a moderate positive correlation between two serum-based scores and liver stiffness results from TE. Notably, this correlation was higher than patients with chronic hepatitis C.[15]

From our analysis, there was no single satisfying cut-off level of both APRI and FIB-4 scores for predicting significant fibrosis and cirrhosis. A low cut-off level value which demonstrated high sensitivity should be used for excluding significant fibrosis or cirrhosis as well as a high cut-off level which presented high specificity should be used for the diagnosis of significant fibrosis or cirrhosis. Recent meta-analysis presented APRI and FIB-4 could identify hepatitis B-related significant fibrosis with an acceptable sensitivity (70.0% for APRI of 0.5 and 65.4% for FIB-4 of 1.45.[9] Our study identified new optimal low cut-off and high cut-off levels in patients with chronic hepatitis B. APRI of 0.25 and FIB-4 of 0.8 demonstrated more impressive sensitivity and NPV for ruling out significant fibrosis, compared with low cut-off values from meta-analysis[9] and WHO recommendation[10] (APRI of 0.5 and FIB-4 of 1.45, respectively). For the diagnosis of significant fibrosis, WHO high cut-off level (APRI of 1.5 and FIB-4 of 3.25) yielded very high specificity and PPV in our study. Nevertheless, the new cut-off levels (APRI of 1.0 and FIB-4 of 1.7) presented acceptable high specificity and PPV for predicting significant fibrosis. In the analysis of cirrhosis, both APRI of 0.5 and FIB of 1.45 showed excellent sensitivity for excluding cirrhosis and both of APRI of 1.5 and FIB-4 of 3.25 provided high specificity of cirrhosis. The possible reasons may explain why the cut-off levels differ from previous meta-analysis[9] were as follows: 1) we used TE as the as reference standard while meta-analysis used liver biopsy; 2) baseline characteristics in our study consisted of higher age group, lower

proportion of male, and lower proportion of significant fibrosis; and 3) one-fifth in our study had co-liver diseases whereas meta-analysis had only 6.0%. Aforementioned factors may impact diagnostic performance.

Our study included both HBeAg status and all age groups, especially young patients because we intended to be applicable in real situations that there were different subgroups in clinical practice. According to subgroup analysis, two cut-off level of APRI (1.0 and 1.5) and FIB-4 (1.45 and 1.7) presented similar specificity to establish diagnosis of significant fibrosis in HBeAg positive subgroup. It indicated that we can used the original WHO cut-off in this subgroup. Contrary to HBeAg negative subgroup, our new cut-off level of both scores were distinctly superior. FIB-4 of 0.8 showed disappointed sensitivity for ruling out significant fibrosis in patients with age < 40 year-old. It may explain that age is one of calculated parameters and may influence this score. Nevertheless, number of patients with HBeAg positive or age < 40 year-old were small in our study (about 18.0%). A study with larger number of these subgroups should be conducted to verify these findings.

In terms of clinical application, especially in resource-limited areas, the optimal proposed cut-off level can help the primary physicians to categorize the CHB patients for proper management. A previous study from China confirmed noninvasive test-based algorithm could significantly reduce the need for liver biopsy in CHB patients. [16] The patients calculated APRI < 0.25 or FIB-4 < 0.8 are able to classify nonsignificant liver fibrosis and there is no need to refer them to perform TE. The patients having APRI ≥ 1.0 or FIB-4 ≥ 1.7 can be defined to significant fibrosis and consider to initiate antiviral agents depended on the recent guidelines without waiting for TE result. [2 - 4, 17] For patients with APRI 0.25 - 1.0 and FIB-4 0.8 - 1.7, they should be referred to higher-level hospital for further evaluation by TE. In our study, APRI score and FIB-4 score could avoid the patients to perform TE for 42.6% and 53.5%, respectively. As part of cirrhosis, APRI ≥ 1.5 and FIB-4 ≥ 3.25 could aid the primary doctors to trigger the appropriate care for cirrhosis including HCC surveillance. This strategy can reduce the number of referred CHB patients [18], save the cost for TE assessment and increase the proportion of CHB patients to receive suitable cirrhotic care.

Nonetheless, we acknowledge that there are some limitations to our study. First, the data were collected from a single center, therefore the proposed new cut-off levels are needed to validate in other centers. Second, we determined TE as the reference standard, not the gold standard of liver biopsy. However, liver biopsy for fibrotic evaluation in CHB is not a common practice in Thailand due to many impediments. TE has been validated and accepted in several guidelines.[2 - 4] To minimize the chance of unreliable results, we excluded patients with conditions affecting overestimated liver stiffness measurements and all TE were performed by certificated and long-term experienced gastroenterologists. Third, we collected data retrospectively and there may be some missing data. Lastly, our study did not include the CHB patients who receive anti-viral therapy. Therefore, effects of CHB treatment to TE and both serum biomarkers cannot be explored and their performance in the CHB-treated group needs to be studied.

Conclusion

In conclusion, both APRI and FIB-4 scores were proved to have impressive diagnostic performance in the prediction of significant fibrosis and cirrhosis and showed significantly correlated with TE results. The new optimal cut-off levels were proposed to exclude or confirm each degree of hepatic fibrosis. We suggest that these new cut-off levels can determine the optimal strategy to select the right patients to receive the appropriate CHB management.

Conflicts of interest statement

Each of the authors has completed an ICMJE disclosure form. None of the authors declare any potential or actual relationship, activity, or interest related to the content of this article.

Data sharing statement

The present review is based on the references cited. Further details, opinions, and interpretation are available from the corresponding authors on reasonable request.

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