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Diagnostic Performance of the Mean Platelet Volume-to-Lymphocyte Ratio as a Hematological Index for Liver Fibrosis in Chronic Hepatitis B: Comparison with APRI and FIB-4

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ABSTRACT: Chronic hepatitis B (CHB) can cause progressive liver fibrosis, but access to non-invasive assessment remains limited in some settings. The mean platelet volume-to-lymphocyte ratio (MPVLR), derived from routine complete blood count parameters, may serve as a potential fibrosis marker. This study evaluated the diagnostic performance of MPVLR for liver fibrosis in CHB compared with the AST-to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4). This cross-sectional study included 250 adults with CHB. Liver stiffness measurements (LSM) obtained by transient elastography served as the reference measure. Significant fibrosis was defined as LSM >7.0 kPa, while LSM ≥9.0 and ≥12.5 kPa were assessed as secondary endpoints. Receiver operating characteristic analysis, DeLong comparisons, and age- and sex-adjusted logistic regression were performed. For LSM >7.0 kPa, the areas under the receiver operating characteristic curve (AUROCs) were 0.606 for MPVLR, 0.725 for APRI, and 0.666 for FIB-4. APRI significantly outperformed MPVLR ($p = 0.013$) and FIB-4 ($p = 0.008$), whereas MPVLR and FIB-4 did not differ significantly ($p = 0.219$). For LSM ≥9.0 and ≥12.5 kPa, MPVLR AUROCs were 0.630 and 0.672, respectively, compared with 0.803 and 0.837 for APRI. MPVLR remained significantly associated with all three endpoints after adjustment for age and sex. In conclusion, MPVLR demonstrated modest discrimination and lower diagnostic performance than APRI and FIB-4. It may serve as a complementary screening marker, but its limited specificity precludes stand-alone use. Further validation in larger prospective cohorts is warranted.

1. INTRODUCTION

Chronic hepatitis B (CHB) continues to be a major global health burden and an important cause of liver-related illness and death. Much of the long-term damage caused by the disease results from persistent hepatic inflammation, which can gradually promote the development and progression of liver fibrosis [1]. As fibrosis advances, the liver may eventually progress to cirrhosis, hepatic decompensation, and other serious complications. For this reason, assessing the extent of fibrosis is an important part of clinical care, helping clinicians estimate disease risk, guide treatment decisions, and determine the need for ongoing surveillance [2]. Liver biopsy has traditionally been considered the reference method for staging hepatic fibrosis. However, its invasive nature, cost, risk of complications, sampling variability, and limited practicality for repeated assessment have encouraged the use of less invasive alternatives. In recent years, non-invasive tests (NITs), including transient

elastography (TE) and serum-based fibrosis indices, have become increasingly useful in clinical practice, offering more convenient and accessible ways to evaluate liver fibrosis without the need for repeated biopsy [3].

Among the serum-based non-invasive tests (NITs), the AST-to-Platelet Ratio Index (APRI) and the Fibrosis-4 index (FIB-4) are among the most commonly used. Both can be calculated using routine laboratory and clinical measurements, making them simple, inexpensive, and practical for everyday clinical use [4]. Their accessibility is particularly valuable in settings where specialized methods of fibrosis assessment are limited or unavailable. Nevertheless, their ability to assess liver fibrosis in patients with CHB is not always consistent and is generally only moderate. Evidence from systematic reviews and WHO-supported assessments has shown considerable variation in their performance across different populations and stages of liver disease [3]. This is especially relevant when distinguishing between intermediate stages of fibrosis, where APRI and FIB-4 may not provide sufficient discrimination. In addition, these indices can be influenced by factors that are not directly related to hepatic fibrosis, such as fluctuations in aminotransferase levels and thrombocytopenia resulting from causes other than fibrosis. Such factors may limit their reliability in some patients with chronic HBV infection [5].

Growing evidence indicates that changes in blood and platelet-related parameters may accompany the progression of chronic liver disease. Among these, mean platelet volume (MPV), a routinely reported platelet index reflecting platelet size and potentially platelet turnover and activation, has been linked to the severity of HBV-related liver disease and hepatic decompensation [6]. The mean platelet volume-to-lymphocyte ratio (MPVLR), which combines MPV with the absolute lymphocyte count, has likewise attracted interest as a simple and inexpensive hematological marker of inflammatory and disease-related changes in both hepatic and non-hepatic conditions. In patients with CHB who underwent liver biopsy, MPVLR demonstrated a modest but statistically significant correlation with the histological fibrosis score ($r = 0.218$; $p = 0.046$) [7]. Similarly, a small cross-sectional study published in 2024 found that the MPV-to-lymphocyte ratio was significantly higher in patients with HBV-related cirrhosis than in those without cirrhosis ($p = 0.001$) [8]. Although these findings are encouraging, they remain limited and provide only an initial rationale for further investigation. In particular, it remains unclear how well MPVLR can distinguish different degrees of liver stiffness in CHB and how its diagnostic performance compares with established non-invasive fibrosis indices such as APRI and FIB-4.

The potential value of MPVLR may be especially relevant in resource-limited settings because it can be calculated entirely from parameters routinely obtained as part of a complete blood count (CBC), without the need for additional or specialized laboratory tests. This makes it an attractive candidate for the initial assessment of liver fibrosis, particularly in settings where access to transient elastography or more specialized biochemical testing is limited.

The potential value of MPVLR may be particularly important in resource-limited settings because it can be calculated directly from routinely available complete blood count (CBC) parameters, without the need for additional or specialized laboratory tests. Against this background, the present study aimed to evaluate and compare MPVLR, APRI, and FIB-4 using predefined FibroScan-based liver stiffness endpoints in 250 adults with CHB. The primary endpoint was significant fibrosis, defined operationally as a liver stiffness measurement (LSM) >7.0 kPa. Secondary analyses examined LSM ≥9.0 kPa and LSM ≥12.5 kPa as markers of higher liver stiffness, corresponding to advanced fibrosis and a cirrhosis-compatible threshold, respectively. We hypothesized that, because MPVLR relies on routinely available CBC parameters, it could provide a practical and low-cost complementary approach to liver fibrosis assessment, particularly in settings where access to specialized fibrosis assessment is limited.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This cross-sectional analytical study was conducted at the Duhok Specialized Laboratory Center in Duhok Province, Kurdistan Region of Iraq, between November 2024 and April 2026. The study focused on evaluating whether the mean platelet volume-to-lymphocyte ratio (MPVLR), a simple hematological parameter derived from routine complete blood count (CBC) results, could help identify liver fibrosis in adults with chronic hepatitis B virus (HBV) infection. Its diagnostic performance was compared with two commonly used non-invasive fibrosis indices, the AST-to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4), using liver stiffness measurement (LSM) obtained by transient elastography (FibroScan) as the reference measure.

The Duhok Specialized Laboratory Center serves as a major diagnostic and reference facility for hematological, immunological and biochemical investigations in Duhok Province. The center routinely receives adults with chronic HBV infection for laboratory evaluation and clinical assessment, providing an appropriate setting for investigating accessible hematological markers of liver fibrosis.

2.2 Participants

Participants were eligible if they were adults aged ≥18 years with confirmed hepatitis B surface antigen (HBsAg) positivity for at least six months. To reduce the influence of conditions that could independently affect liver stiffness, platelet indices, or liver function, participants were excluded if they had: (1) co-infection with hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV); (2) another known chronic liver disease, including autoimmune hepatitis, Wilson disease, or hemochromatosis, or significant alcohol consumption (>30 g/day in men or >20 g/day in women); (3) a hematological or malignant disorder known to affect platelet counts; (4) a recent blood transfusion or acute infection within the preceding three months; or (5) decompensated cirrhosis or hepatocellular carcinoma.

All eligible adults with chronic hepatitis B who met the predefined inclusion criteria and had a valid FibroScan measurement available during the study period were consecutively included in the analysis. This approach allowed the study to capture the available eligible population at the study center without selective sampling. Because the study was based on a fixed-period cohort of eligible participants attending the center, no formal a priori sample-size calculation was performed.

2.3 FibroScan-Based Reference Measure and Operational Endpoints

For the assessment of liver stiffness, liver stiffness measurements (LSM) obtained by transient elastography (FibroScan) were retrospectively retrieved from the participants' medical records. LSM values were recorded in kilopascals (kPa) and analyzed as continuous measurements.

For the primary analysis, significant fibrosis was operationally defined as an LSM >7.0 kPa, based on the 2024 World Health Organization (WHO) guidance for the non-invasive assessment of significant fibrosis in adults with chronic hepatitis B [9].

Advanced fibrosis was evaluated as a secondary exploratory endpoint and was operationally defined as an LSM ≥9.0 kPa. This threshold was selected based on chronic hepatitis B-specific transient elastography data validated against liver biopsy, in which 9.0 kPa was reported as a cutoff for ≥F3 fibrosis [10]. However, because transient elastography does not provide a universally applicable one-to-one correspondence between liver stiffness values and individual histological fibrosis stages across all patients with CHB, the ≥9.0-kPa threshold was considered an operational marker of higher liver stiffness in this study rather than a direct histological designation.

An LSM ≥12.5 kPa was used as a secondary endpoint representing a liver stiffness level compatible with cirrhosis, consistent with WHO guidance [9].

APRI and FIB-4 were calculated independently from the relevant laboratory and demographic variables and were not used to define any of the FibroScan-based reference outcomes.

2.4 Clinical and Laboratory Assessment

Demographic and clinical information, including age, sex, comorbidities, antiviral therapy status, alcohol intake, diabetes mellitus, and hypertension, was recorded for each participant. Liver stiffness measurements (LSM) obtained by transient elastography (FibroScan) were retrieved retrospectively from the participants' medical records and used to assess liver stiffness.

Venous blood samples were collected after an overnight fast. The following laboratory parameters were measured:

- Complete blood count (CBC): including platelet count, mean platelet volume (MPV, fL), and absolute lymphocyte count ($\times 10^9$/L).
- Liver enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with the corresponding upper limits of normal (ULN) documented for the laboratory assays.

Hematological parameters were measured using a Sysmex XN-350 automated hematology analyzer (Sysmex Corp., Kobe, Japan) from venous blood collected in EDTA-containing tubes. To minimize potential preanalytical variation in platelet indices, particularly mean platelet volume (MPV), all samples were processed within 120 minutes of collection in accordance with the laboratory's routine workflow.

2.5 Calculation of Non-Invasive Indices

The following indices were calculated for each participant:

- MPVLR = MPV (fL) / Lymphocyte count ($\times 10^9$/L)
- APRI = (AST / AST ULN × 100) / Platelet count ($\times 10^9$/L) [11].
- FIB-4 = (Age × AST) / (Platelet count × √ALT) [12].

APRI and FIB-4 were calculated from routinely available demographic and laboratory parameters and evaluated as comparator non-invasive fibrosis indices against liver stiffness measurements obtained by transient elastography (FibroScan). Importantly, neither index was used to define the FibroScan-based reference outcomes. MPVLR was evaluated as the candidate hematological biomarker, with its diagnostic performance compared directly with that of APRI and FIB-4 across the predefined liver stiffness endpoints.

APRI and FIB-4 were included as established non-invasive fibrosis indices because both have been widely investigated for the assessment of liver fibrosis in patients with chronic hepatitis B. APRI, in particular, is recognized in the 2024 World Health Organization (WHO) hepatitis B guidelines as an accessible non-invasive approach to fibrosis assessment. Therefore, APRI and FIB-4 were included as comparator measures to provide a clinically relevant comparison with the FibroScan-based reference measure [9].

3. ETHICAL CONSIDERATIONS

The Research Ethics Committee of the Duhok Directorate General of Health, Kurdistan Region of Iraq, examined and approved the study protocol (Approval No. 30102024-9-45). Prior to enrollment, all participants provided written informed consent, and all research procedures adhered to national and institutional ethical standards.

4. STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate, while categorical variables were presented as frequencies and percentages. Participants were primarily categorized according to the FibroScan-based reference definition of significant fibrosis, defined as liver stiffness measurement (LSM) >7.0 kPa. Differences between participants with and without significant fibrosis were assessed using the independent-samples t test or Mann–Whitney U test for continuous variables, as appropriate, and the χ^2 test or Fisher's exact test for categorical variables.

The diagnostic performance of MPVLR, APRI, and FIB-4 for detecting FibroScan-defined significant fibrosis (LSM >7.0 kPa) was assessed using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUROC) and corresponding 95% confidence intervals (CIs) were calculated. Pairwise comparisons of AUROCs were performed using DeLong's method. For each marker, the optimal diagnostic threshold was determined using the Youden J statistic, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at the corresponding optimal threshold. For APRI and FIB-4, diagnostic performance was additionally assessed using prespecified clinically relevant thresholds reported in the literature.

Secondary analyses evaluated the diagnostic performance of MPVLR, APRI, and FIB-4 for advanced fibrosis, operationally defined as LSM ≥9.0 kPa, and for a cirrhosis-compatible liver stiffness endpoint, defined as LSM ≥12.5 kPa. The ≥9.0-kPa threshold was considered exploratory and was selected on the basis of previously published chronic hepatitis B-specific transient elastography studies, whereas the ≥12.5-kPa threshold was consistent with WHO guidance. For each secondary endpoint, AUROC, optimal Youden-derived thresholds, sensitivity, specificity, PPV, and NPV were calculated.

Confidence intervals for diagnostic performance estimates were obtained using stratified bootstrap resampling with 3,000 resamples. Statistical significance was set at $p < 0.05$. All analyses were performed using R software (version 4.3.0), with the pROC, epiR, and caret packages.

5. RESULTS

5.1 Baseline Characteristics

A total of 250 adults with chronic hepatitis B were included in the analysis (Table 1). The mean age of the study cohort was 38.5 ± 10.0 years, and women comprised the majority of participants (84.0%, n = 210). The mean platelet count was 217.3 ± 44.7 $\times 10^9$/L, mean MPV was 9.7 ± 0.8 fL, and mean absolute lymphocyte count was 2.0 ± 0.5 $\times 10^9$/L. Median AST and ALT concentrations were 33.9 U/L (IQR, 25.7–43.8) and 42.7 U/L (IQR, 34.2–51.7), respectively. The median MPVLR, APRI, and FIB-4 values were 4.96 (IQR, 4.14–5.92), 0.39 (IQR, 0.29–0.57), and 0.93 (IQR, 0.64–1.35), respectively.

Based on the prespecified FibroScan reference definition, 119 participants (47.6%) had significant fibrosis, defined as an LSM >7.0 kPa, while 131 (52.4%) had an LSM ≤7.0 kPa. The median LSM was 7.0 kPa (IQR, 5.7–8.5) for the overall cohort. dvanced fibrosis, operationally defined as LSM ≥9.0 kPa, was present in 49 participants (19.6%), while 21 participants (8.4%) had an LSM ≥12.5 kPa, corresponding to the cirrhosis-compatible liver stiffness endpoint.

Participants with LSM >7.0 kPa had significantly lower platelet counts than those with LSM ≤7.0 kPa (200.3 ± 37.2 vs 232.8 ± 45.4 $\times 10^9$/L, $p < 0.001$) and lower lymphocyte counts (1.9 ± 0.5 vs 2.1 ± 0.5 $\times 10^9$/L, $p = 0.004$). MPV was modestly higher among participants with LSM >7.0 kPa (9.8 ± 0.9 vs 9.6 ± 0.8 fL, $p = 0.028$). AST and ALT levels were also higher in the significant-fibrosis group, with median AST values of 39.7 versus 30.3 U/L ($p < 0.001$) and median ALT values of 44.3 versus 41.2 U/L ($p = 0.037$).

Consistent with these hematological and biochemical differences, MPVLR, APRI, and FIB-4 were significantly higher among participants with LSM >7.0 kPa than among those with LSM ≤7.0 kPa. Median MPVLR was 5.11 versus 4.75 ($p = 0.004$), median APRI was 0.47 versus 0.31 ($p < 0.001$), and median FIB-4 was 1.10 versus 0.75 ($p < 0.001$), respectively. Age and sex distributions did not differ significantly between the two groups.

Table 1. Baseline characteristics of the study cohort overall and according to FibroScan-defined significant fibrosis

Characteristic	Overall (n = 250)	LSM ≤7.0 kPa (n = 131)	LSM >7.0 kPa (n = 119)	p-value
Age, years (mean ± SD)	38.5 ± 10.0	38.2 ± 9.7	38.7 ± 10.4	0.685
Female sex, n (%)	210 (84.0)	112 (85.5)	98 (82.4)	0.498
Platelet count, $\times 10^9$/L (mean ± SD)	217.3 ± 44.7	232.8 ± 45.4	200.3 ± 37.2	<0.001
Lymphocyte count, $\times 10^9$/L (mean ± SD)	2.0 ± 0.5	2.1 ± 0.5	1.9 ± 0.5	0.004
MPV, fL (mean ± SD)	9.7 ± 0.8	9.6 ± 0.8	9.8 ± 0.9	0.028
AST, U/L, median (IQR)	33.9 (25.7–43.8)	30.3 (24.2–40.6)	39.7 (29.9–47.6)	<0.001
ALT, U/L, median (IQR)	42.7 (34.2–51.7)	41.2 (33.3–49.8)	44.3 (36.5–54.9)	0.037
MPVLR, median (IQR)	4.96 (4.14–5.92)	4.75 (3.86–5.54)	5.11 (4.29–6.37)	0.004
APRI, median (IQR)	0.39 (0.29–0.57)	0.31 (0.25–0.43)	0.47 (0.37–0.63)	<0.001
FIB-4, median (IQR)	0.93 (0.64–1.35)	0.75 (0.54–1.08)	1.10 (0.81–1.51)	<0.001
LSM, kPa, median (IQR)	7.0 (5.7–8.5)	5.7 (5.0–6.5)	8.6 (7.7–10.8)	<0.001

Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 index; IQR, interquartile range; LSM, liver stiffness measurement; MPV, mean platelet volume; MPVLR, mean platelet volume-to-lymphocyte ratio; SD, standard deviation.

5.2 Diagnostic Performance for Significant Fibrosis

Receiver operating characteristic (ROC) curves for MPVLR, APRI, and FIB-4 in detecting FibroScan-defined significant fibrosis are presented in Figure 1. Significant fibrosis was operationally defined as a liver stiffness measurement (LSM) >7.0 kPa, resulting in 119 of 250 participants (47.6%) meeting the reference criterion. The discriminatory performance of each index was assessed using the area under the ROC curve (AUROC) with corresponding 95% confidence intervals obtained by stratified bootstrap resampling with 3,000 resamples.

MPVLR demonstrated an AUROC of 0.606 (95% CI, 0.536–0.672), with an optimal Youden-derived cutoff of ≥3.608, yielding a sensitivity of 95.8% and specificity of 20.6%. APRI demonstrated the highest discriminatory performance, with an AUROC of 0.725 (95% CI, 0.663–0.784) and an optimal cutoff of ≥0.299, corresponding to a sensitivity of 89.9% and specificity of 47.3%. FIB-4 showed intermediate performance, with an AUROC of 0.666 (95% CI, 0.600–0.731), an optimal cutoff of ≥0.923, sensitivity of 68.1%, and specificity of 64.9%.

At the optimal MPVLR cutoff, the PPV was 52.3% and NPV was 84.4%. For APRI, the corresponding PPV and NPV were 60.8% and 83.8%, respectively, while FIB-4 yielded a PPV of 63.8% and NPV of 69.1%.

At prespecified literature-based thresholds, APRI ≥0.5 yielded a sensitivity of 42.9% and specificity of 79.4%, with a PPV of 65.4% and NPV of 60.5%. APRI ≥1.5 yielded a sensitivity of 0.0% and specificity of 99.2%; only one participant met this threshold. For FIB-4, a threshold of ≥1.45 yielded a sensitivity of 29.4%, specificity of 86.3%, PPV of 66.0%, and NPV of 57.4%.

Pairwise comparisons of AUROCs using DeLong's method showed that APRI significantly outperformed MPVLR (AUROC 0.725 vs 0.606; p = 0.013) and FIB-4 (0.725 vs 0.666; p = 0.008). The difference between FIB-4 and MPVLR was not statistically significant (0.666 vs 0.606; p = 0.219).

Overall, APRI demonstrated the strongest discriminatory performance for FibroScan-defined significant fibrosis, followed by FIB-4, whereas MPVLR showed more modest discrimination. Although MPVLR achieved high sensitivity at its optimal threshold, its low specificity resulted in a substantial number of false-positive classifications. These findings support the potential role of MPVLR as a sensitive screening-oriented adjunct rather than as a standalone confirmatory marker of significant fibrosis.

Table 2. Diagnostic performance of MPVLR, APRI, and FIB-4 for FibroScan-defined significant fibrosis (LSM >7.0 kPa)

Index	AUROC (95% CI)	Optimal cut-off (Youden)	Sensitivity	Specificity	PPV	NPV
MPVLR	0.606 (0.536–0.672)	≥3.608	95.8%	20.6%	52.3%	84.4%
APRI	0.725 (0.663–0.784)	≥0.299	89.9%	47.3%	60.8%	83.8%
FIB-4	0.666 (0.600–0.731)	≥0.923	68.1%	64.9%	63.8%	69.1%

Note: AUROC confidence intervals were estimated using stratified bootstrap resampling (3,000 resamples). Optimal cutoffs were determined using Youden's J statistic. PPV and NPV are dependent on the prevalence of significant fibrosis in the study cohort (47.6%).

Performance at prespecified clinical thresholds

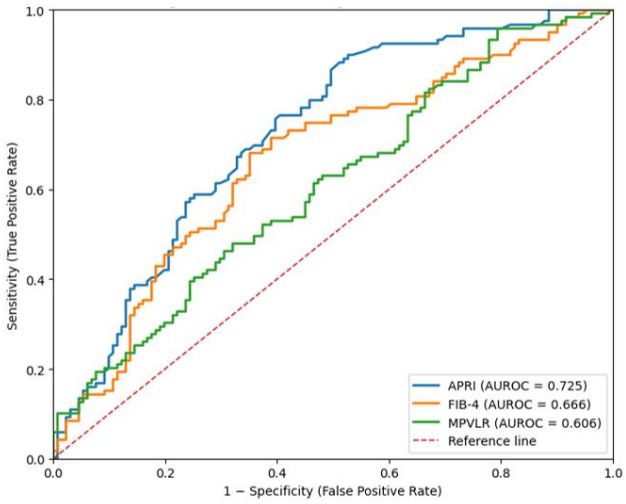
Index / threshold	Sensitivity	Specificity	PPV	NPV
APRI ≥0.5	42.9%	79.4%	65.4%	60.5%
APRI ≥1.5	0.0%	99.2%	0.0%	52.2%
FIB-4 ≥1.45	29.4%	86.3%	66.0%	57.4%

Pairwise AUROC comparison (DeLong's test)

Comparison	ΔAUROC	*p*-value
APRI vs MPVLR	+0.119	0.013
APRI vs FIB-4	+0.059	0.008
FIB-4 vs MPVLR	+0.060	0.219

Note: 95% CIs for AUROC were calculated using stratified bootstrap resampling (3,000 resamples). Optimal cutoffs were determined by maximizing the Youden index (sensitivity + specificity − 1). PPV and NPV are dependent on the prevalence of significant fibrosis in the study cohort (47.6% with LSM >7.0 kPa) and should therefore be interpreted in the context of this study population.

Figure 1. Receiver operating characteristic (ROC) curves for MPVLR, APRI, and FIB-4 in detecting FibroScan-defined significant fibrosis (LSM >7.0 kPa)



Note: ROC curves were generated using liver stiffness measurements obtained by transient elastography in 250 adults with chronic hepatitis B. The AUROC was 0.725 for APRI, 0.666 for FIB-4, and 0.606 for MPVLR. The diagonal line represents no discrimination (AUROC = 0.50). APRI, AST-to-platelet ratio index; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; MPVLR, mean platelet volume-to-lymphocyte ratio.

5.3 Diagnostic Performance for Advanced Fibrosis

For the exploratory detection of FibroScan-defined advanced fibrosis, liver stiffness measurement (LSM) ≥9.0 kPa was used as the reference definition. Forty-nine of 250 participants (19.6%) met this criterion. The diagnostic performance of MPVLR, APRI, and FIB-4 was assessed using receiver operating characteristic (ROC) curve analysis (Figure 2).

MPVLR demonstrated an AUROC of 0.630 (95% CI, 0.541–0.711), compared with 0.803 (95% CI, 0.734–0.864) for APRI and 0.727 (95% CI, 0.648–0.800) for FIB-4. APRI therefore showed the strongest discriminatory performance, followed by FIB-4, whereas MPVLR demonstrated more modest discrimination.

At the optimal Youden-derived cutoff, MPVLR ≥4.263 yielded a sensitivity of 87.8% and specificity of 34.8%, with a PPV of 24.7% and NPV of 92.1%. For APRI, the optimal cutoff of ≥0.57 yielded a sensitivity of 67.3% and specificity of 85.1%, with a PPV of 52.4% and NPV of 91.4%. FIB-4 at an optimal cutoff of ≥0.91 yielded a sensitivity of 81.6%, specificity of 54.7%, PPV of 30.5%, and NPV of 92.4%.

At prespecified literature-based thresholds, APRI ≥1.5 yielded a sensitivity of 0.0% and specificity of 99.5%; only one participant met this threshold. FIB-4 ≥3.25 yielded a sensitivity of 4.1%, specificity of 99.0%, PPV of 50.0%, and NPV of 80.9%, indicating very high specificity but poor sensitivity for the detection of LSM-defined advanced fibrosis.

Pairwise comparison of AUROCs using DeLong's method showed that APRI significantly outperformed MPVLR (0.803 vs 0.630; $p < 0.001$) and FIB-4 (0.803 vs 0.727; $p = 0.006$). The difference between FIB-4 and MPVLR was not statistically significant (0.727 vs 0.630; $p = 0.093$).

Overall, APRI demonstrated the strongest discriminatory performance for FibroScan-defined advanced fibrosis, while MPVLR showed relatively high sensitivity but limited specificity at its optimal threshold. These findings suggest that MPVLR may have greater potential as a screening-oriented adjunct than as a confirmatory marker for advanced fibrosis.

Table 3. Diagnostic performance of MPVLR, APRI, and FIB-4 for FibroScan-defined advanced fibrosis (LSM ≥9.0 kPa)

Index	AUROC (95% CI)	Optimal cut-off (Youden)	Sensitivity	Specificity	PPV	NPV
MPVLR	0.630 (0.541–0.711)	≥4.263	87.8%	34.8%	24.7%	92.1%
APRI	0.803 (0.734–0.864)	≥0.57	67.3%	85.1%	52.4%	91.4%
FIB-4	0.727 (0.648–0.800)	≥0.91	81.6%	54.7%	30.5%	92.4%

Performance at prespecified clinical thresholds

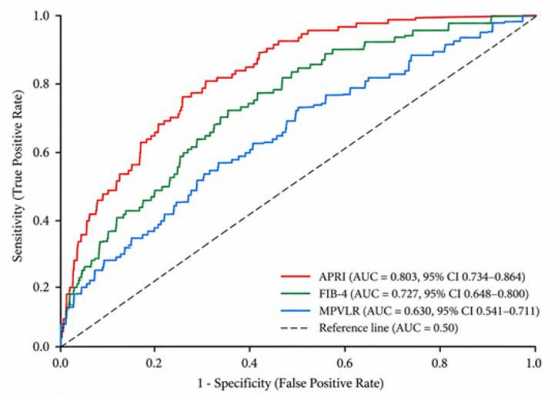
Index / threshold	Sensitivity	Specificity	PPV	NPV
APRI ≥1.5	0.0%	99.5%	0.0%	80.3%
FIB-4 ≥3.25	4.1%	99.0%	50.0%	80.9%

Pairwise AUROC comparison (DeLong's test)

Comparison	ΔAUROC	*p*-value
APRI vs MPVLR	+0.173	<0.001
APRI vs FIB-4	+0.076	0.006
FIB-4 vs MPVLR	+0.097	0.093

Note: AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value. 95% CIs for AUROC were calculated using stratified bootstrap resampling (3,000 resamples). Optimal cutoffs were determined by maximizing the Youden index (sensitivity + specificity − 1). † PPV and NPV are dependent on the prevalence of advanced fibrosis in this cohort (49/250, 19.6%) and should therefore be interpreted in the context of this study population rather than as fixed properties of the test. ‡ Only one participant had an APRI value ≥1.5; therefore, this threshold yielded 0% sensitivity for detecting FibroScan-defined advanced fibrosis.

Figure 2. Receiver operating characteristic (ROC) curves for MPVLR, APRI, and FIB-4 in detecting FibroScan-defined advanced fibrosis (LSM ≥9.0 kPa)



Note: ROC curves were generated using liver stiffness measurements obtained by transient elastography in 250 adults with chronic hepatitis B. Advanced fibrosis was operationally defined as LSM ≥9.0 kPa for this exploratory analysis. The AUROC was 0.803 for APRI, 0.727 for FIB-4, and 0.630 for MPVLR. The diagonal line represents no discrimination (AUROC = 0.50). APRI, AST-to-platelet ratio index; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; MPVLR, mean platelet volume-to-lymphocyte ratio.

5.4 Diagnostic Performance for Cirrhosis-Compatible Liver Stiffness

For the secondary analysis of a cirrhosis-compatible liver stiffness endpoint, an LSM ≥12.5 kPa was used as the reference definition, consistent with the 2024 World Health Organization guidance. Twenty-one of 250 participants (8.4%) met this criterion. The diagnostic performance of MPVLR, APRI, and FIB-4 was assessed using receiver operating characteristic (ROC) curve analysis (Figure 3).

MPVLR demonstrated an AUROC of 0.672 (95% CI, 0.566–0.774), compared with 0.837 (95% CI, 0.739–0.915) for APRI and 0.733 (95% CI, 0.628–0.829) for FIB-4. APRI therefore demonstrated the strongest discriminatory performance, followed by FIB-4 and MPVLR.

At the optimal Youden-derived cutoff, MPVLR ≥4.445 yielded a sensitivity of 95.2% and specificity of 38.0%, with a PPV of 12.3% and NPV of 98.9%. APRI at an optimal cutoff of ≥0.595 yielded a sensitivity of 81.0% and specificity of 83.0%, with a PPV of 30.4% and NPV of 97.9%. FIB-4 at an optimal cutoff of ≥0.754 yielded a sensitivity of 95.2%, specificity of 40.6%, PPV of 12.8%, and NPV of 98.9%.

At the prespecified clinical thresholds, APRI ≥2.0 yielded a sensitivity of 0.0% and specificity of 100.0%, as no participant in the cohort reached this threshold. FIB-4 ≥3.25 yielded a sensitivity of 9.5%, specificity of 99.1%, PPV of 50.0%, and NPV of 92.3%, indicating very high specificity but poor sensitivity for identifying participants with LSM ≥12.5 kPa.

Pairwise comparison of AUROCs using DeLong's method showed that APRI significantly outperformed MPVLR (0.837 vs 0.672; p = 0.010) and FIB-4 (0.837 vs 0.733; p = 0.008). The difference between FIB-4 and MPVLR was not statistically significant (0.733 vs 0.672; p = 0.413). Overall, APRI demonstrated the strongest discrimination for the cirrhosis-compatible liver stiffness endpoint. MPVLR showed high sensitivity at its Youden-derived threshold but limited specificity, resulting in a low PPV. Given the relatively small number of participants with LSM ≥12.5 kPa, these estimates should be interpreted cautiously.

Table 4. Diagnostic performance of MPVLR, APRI, and FIB-4 for a cirrhosis-compatible liver stiffness endpoint (LSM ≥12.5 kPa)

Index	AUROC (95% CI)	Optimal cut-off (Youden)	Sensitivity	Specificity	PPV	NPV

MPVLR	0.672 (0.566–0.774)	≥4.445	95.2%	38.0%	12.3%	98.9%
APRI	0.837 (0.739–0.915)	≥0.595	81.0%	83.0%	30.4%	97.9%
FIB-4	0.733 (0.628–0.829)	≥0.754	95.2%	40.6%	12.8%	98.9%

Performance at prespecified clinical thresholds

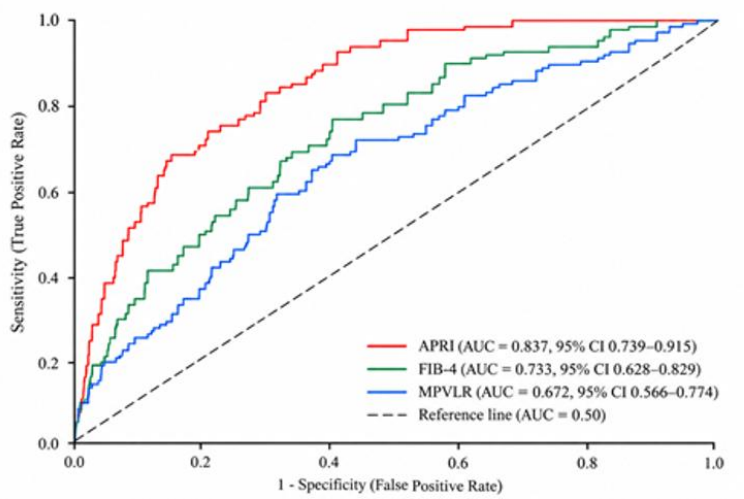
Index / threshold	Sensitivity	Specificity	PPV	NPV
APRI ≥2.0	0.0%	100.0%	N/A	91.6%
FIB-4 ≥3.25	9.5%	99.1%	50.0%	92.3%

Pairwise AUROC comparison (DeLong's test)

Comparison	ΔAUROC	*p*-value
APRI vs MPVLR	+0.165	0.010
APRI vs FIB-4	+0.104	0.008
FIB-4 vs MPVLR	+0.061	0.413

Note: AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value. 95% CIs for AUROC were calculated using stratified bootstrap resampling (3,000 resamples). Optimal cutoffs were determined by maximizing the Youden index (sensitivity + specificity − 1). Given the relatively small number of participants with the cirrhosis-compatible liver stiffness endpoint (LSM ≥12.5 kPa; 21/250, 8.4%), diagnostic performance estimates should be interpreted cautiously. PPV and NPV are prevalence-dependent and should therefore be interpreted in the context of this study population. No participant had an APRI value ≥2.0 (maximum observed value, 1.53); therefore, this threshold yielded 0% sensitivity for detecting LSM ≥12.5 kPa.

Figure 3. Receiver operating characteristic (ROC) curves for MPVLR, APRI, and FIB-4 in detecting a cirrhosis-compatible liver stiffness endpoint (LSM ≥12.5 kPa)



Note: ROC curves were generated using liver stiffness measurements obtained by transient elastography in 250 adults with chronic hepatitis B. Twenty-one participants (8.4%) had LSM ≥12.5 kPa. The AUROC was 0.837 for APRI, 0.733 for FIB-4,

and 0.672 for MPVLR. The diagonal line represents no discrimination (AUROC = 0.50). APRI, AST-to-platelet ratio index; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; MPVLR, mean platelet volume-to-lymphocyte ratio.

5.5 Multivariable Logistic Regression

To assess the associations between the non-invasive indices and FibroScan-based liver stiffness endpoints after adjustment for age and sex, separate multivariable logistic regression models were fitted for MPVLR, APRI, and FIB-4. Each marker was standardized to a z-score, and models were adjusted for age and sex (Table 5).

For significant fibrosis, defined as LSM >7.0 kPa, all three indices remained significantly associated with the outcome after adjustment. A 1-SD increase in MPVLR was associated with 1.59-fold higher odds of significant fibrosis (adjusted OR, 1.59; 95% CI, 1.19–2.14; p = 0.002). The corresponding adjusted ORs were 2.15 (95% CI, 1.56–2.95; p < 0.001) for APRI and 2.02 (95% CI, 1.43–2.85; p < 0.001) for FIB-4.

For dvanced fibrosis, operationally defined as LSM ≥9.0 kPa, MPVLR remained significantly associated with the outcome (adjusted OR, 1.38; 95% CI, 1.03–1.84; p = 0.031). APRI showed a stronger association (adjusted OR, 2.79; 95% CI, 1.95–3.98; p < 0.001), as did FIB-4 (adjusted OR, 2.33; 95% CI, 1.61–3.38; p < 0.001).

For the cirrhosis-compatible liver stiffness endpoint, defined as LSM ≥12.5 kPa, all three markers remained significantly associated with the outcome after adjustment. The adjusted OR was 1.62 (95% CI, 1.13–2.31; p = 0.008) for MPVLR, 2.67 (95% CI, 1.77–4.02; p < 0.001) for APRI, and 2.43 (95% CI, 1.58–3.73; p < 0.001) for FIB-4.

Age was not significantly associated with significant or advanced fibrosis in any of the models. For the cirrhosis-compatible endpoint, age was significantly associated with the outcome only in the FIB-4 model (adjusted OR per year, 0.94; p = 0.039). Sex was not independently associated with any of the three FibroScan-based endpoints in the corresponding models.

Overall, APRI showed the strongest adjusted association with each liver stiffness endpoint, followed by FIB-4, whereas MPVLR demonstrated more modest but statistically significant associations across all three endpoints.

Table 5. Age- and sex-adjusted odds ratios for MPVLR, APRI, and FIB-4 across FibroScan-based liver stiffness endpoints

Endpoint	Marker	Adjusted OR (per 1-SD)	95% CI	*p*-value
LSM >7.0 kPa	**MPVLR**	1.59	1.19–2.14	0.002
	APRI	2.15	1.56–2.95	<0.001
	FIB-4	2.02	1.43–2.85	<0.001
LSM ≥9.0 kPa	**MPVLR**	1.38	1.03–1.84	0.031
	APRI	2.79	1.95–3.98	<0.001
	FIB-4	2.33	1.61–3.38	<0.001
LSM ≥12.5 kPa	**MPVLR**	1.62	1.13–2.31	0.008
	APRI	2.67	1.77–4.02	<0.001
	FIB-4	2.43	1.58–3.73	<0.001

Note: Values are presented as odds ratios (ORs) with 95% confidence intervals (CIs). MPVLR, APRI, and FIB-4 were standardized to z-scores; therefore, ORs represent the change in odds of the specified liver-stiffness endpoint associated with a one-standard-deviation increase in the corresponding index. Separate logistic regression models were fitted for each fibrosis index and each endpoint, with adjustment for age and sex. The primary endpoint was LSM >7.0 kPa, while LSM ≥9.0 kPa and LSM ≥12.5 kPa were evaluated as secondary endpoints. MPVLR, mean platelet volume-to-lymphocyte ratio; APRI, AST-to-Platelet Ratio Index; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; OR, odds ratio; CI, confidence interval.

5.6 Interpretation and Summary

MPVLR is a simple hematological index derived entirely from parameters routinely available as part of a complete blood count. Because it requires no additional biochemical tests or specialized equipment, it is inexpensive and readily accessible, making it a potentially useful marker for the initial assessment of liver fibrosis in patients with chronic hepatitis B. However, the findings of the present study do not support its use as a replacement for established non-invasive fibrosis indices. Across the predefined FibroScan-based endpoints, APRI consistently showed the strongest diagnostic discrimination, FIB-4 demonstrated intermediate performance, and MPVLR provided more modest discrimination.

Key findings include:

- Participants with LSM >7.0 kPa had significantly lower platelet and lymphocyte counts and higher MPV, AST, ALT, MPVLR, APRI, and FIB-4 values than participants with LSM ≤7.0 kPa (Table 1). These cross-sectional differences were consistent with an association between greater liver stiffness and alterations in platelet-, lymphocyte-, and liver enzyme-related parameters, although they do not establish temporal fibrosis progression.
- For significant fibrosis (LSM >7.0 kPa), MPVLR demonstrated modest discrimination (AUROC 0.606, 95% CI 0.536–0.672). APRI showed the strongest performance (AUROC 0.725, 95% CI 0.663–0.784), followed by FIB-4 (AUROC 0.666, 95% CI 0.600–0.731). APRI significantly outperformed both MPVLR and FIB-4 by DeLong's test, whereas the difference between FIB-4 and MPVLR was not statistically significant.
- For advanced fibrosis (LSM ≥9.0 kPa), which was considered an exploratory endpoint, MPVLR showed an AUROC of 0.630 (95% CI 0.541–0.711), compared with 0.803 (95% CI 0.734–0.864) for APRI and 0.727 (95% CI 0.648–0.800) for FIB-4. APRI again demonstrated the strongest discrimination and significantly outperformed both MPVLR and FIB-4, while the difference between MPVLR and FIB-4 was not statistically significant.
- For the cirrhosis-compatible liver stiffness endpoint (LSM ≥12.5 kPa), MPVLR demonstrated an AUROC of 0.672 (95% CI 0.566–0.774), compared with 0.837 (95% CI 0.739–0.915) for APRI and 0.733 (95% CI 0.628–0.829) for FIB-4. APRI again provided the strongest discrimination. Although MPVLR achieved high sensitivity at its Youden-derived threshold, its specificity was limited, resulting in a low PPV. These findings should be interpreted cautiously because only 21 participants (8.4%) met the LSM ≥12.5-kPa criterion.
- Across the three LSM-based endpoints, APRI consistently demonstrated the highest AUROC, followed by FIB-4 and MPVLR. The superiority of APRI over both MPVLR and FIB-4 was statistically significant at each endpoint. In contrast, differences between FIB-4 and MPVLR did not reach statistical significance at any of the three endpoints.
- Despite its more modest discrimination, MPVLR remained significantly associated with all three LSM-based endpoints after adjustment for age and sex. A 1-SD increase in MPVLR was associated with higher odds of LSM >7.0 kPa (adjusted OR 1.59, 95% CI 1.19–2.14), LSM ≥9.0 kPa (adjusted OR 1.38, 95% CI 1.03–1.84), and LSM ≥12.5 kPa (adjusted OR 1.62, 95% CI 1.13–2.31). APRI showed the strongest adjusted associations across all three endpoints.
- At its Youden-derived thresholds, MPVLR showed relatively high sensitivity but limited specificity, particularly for the higher LSM endpoints. This pattern suggests that, if validated in independent cohorts, MPVLR may have greater potential as a screening-oriented marker than as a standalone confirmatory test. However, the present study did not formally evaluate a sequential or combined diagnostic strategy.
- A potential two-step approach in which MPVLR is used for initial screening followed by confirmation with APRI or FIB-4 may be worthy of future investigation. Nevertheless, no sequential or combined-marker analysis, incremental diagnostic analysis, or reclassification analysis was performed in the present study, and therefore no clinical benefit from such an approach can be claimed from these data.

6. DISCUSSION

This study evaluated the diagnostic performance of the mean platelet volume-to-lymphocyte ratio (MPVLR), a simple and low-cost hematological index derived entirely from routinely available complete blood count (CBC) parameters, for the assessment of liver fibrosis in 250 adults with chronic hepatitis B (CHB). Its performance was compared with two established non-invasive fibrosis indices, APRI and FIB-4, using liver stiffness measurements (LSM) obtained by transient elastography as the reference measure. The main finding was that APRI consistently showed the strongest discriminatory performance across all three predefined FibroScan-based endpoints, while FIB-4 demonstrated intermediate performance and MPVLR

showed more modest discrimination. Nevertheless, despite its comparatively lower discriminatory ability, MPVLR remained significantly associated with all three endpoints after adjustment for age and sex and showed relatively high sensitivity at the data-derived thresholds, particularly for the higher liver-stiffness categories.

For significant fibrosis, operationally defined as an LSM >7.0 kPa, MPVLR showed an AUROC of 0.606 (95% CI, 0.536–0.672), compared with 0.725 (95% CI, 0.663–0.784) for APRI and 0.666 (95% CI, 0.600–0.731) for FIB-4. APRI demonstrated significantly better discrimination than both MPVLR and FIB-4, whereas the difference between MPVLR and FIB-4 was not statistically significant. The same overall pattern was seen for the exploratory higher liver-stiffness endpoint of LSM ≥9.0 kPa, with AUROCs of 0.630 for MPVLR, 0.803 for APRI, and 0.727 for FIB-4. At the cirrhosis-compatible threshold of LSM ≥12.5 kPa, APRI again provided the best discrimination (AUROC, 0.837), followed by FIB-4 (0.733) and MPVLR (0.672. Overall, the relative performance of the three indices remained remarkably consistent across the progressively higher liver-stiffness thresholds. APRI showed the most robust discriminatory ability throughout, whereas MPVLR demonstrated a more modest but consistent association with increasing liver stiffness. These findings suggest that, although MPVLR did not perform as well as the established indices, its relationship with liver stiffness was maintained across different levels of disease severity.

The relatively modest AUROC values observed for MPVLR suggest that its ability to distinguish liver fibrosis when used alone is limited, and therefore it should not be regarded as a definitive diagnostic test. Nevertheless, its sensitivity at the data-derived thresholds was notable. MPVLR identified 95.8% of participants with LSM >7.0 kPa, 87.8% of those with LSM ≥9.0 kPa, and 95.2% of those with LSM ≥12.5 kPa. However, these high sensitivities were accompanied by relatively low specificities of 20.6%, 34.8%, and 38.0%, respectively. This combination suggests that MPVLR may be more useful for capturing a large proportion of individuals who meet a liver-stiffness endpoint than for confirming the presence of fibrosis with confidence. The relatively high negative predictive values observed for the advanced and cirrhosis-compatible endpoints are also of potential interest from a rule-out perspective. However, these findings should be interpreted with caution, as predictive values are influenced substantially by the prevalence of the outcome in the study population. This is particularly important for the LSM ≥12.5 kPa endpoint, where only a small proportion of participants met the threshold, making the corresponding predictive estimates less stable.

The biological rationale for examining MPVLR in CHB is reasonable. Lymphocyte counts may reflect changes in immune regulation associated with chronic HBV infection and the progression of liver disease, while MPV may provide information about platelet turnover and activation. By combining these two parameters into a single ratio, MPVLR may capture aspects of these hematological changes that occur alongside chronic liver disease. However, MPV is influenced by several preanalytical and analytical factors, including specimen handling and the time between blood collection and analysis. Therefore, while the observed association between higher MPVLR and greater liver stiffness supports the need for further investigation, MPVLR should not be interpreted as a specific biological marker or surrogate of hepatic fibrosis. Its biological significance will need to be confirmed in future studies using independent reference methods and standardized approaches to sample collection, handling, and analysis.

The present findings are generally in line with earlier studies examining platelet- and lymphocyte-based indices in CHB. Ekmen et al. found a weak but statistically significant correlation between MPVLR and fibrosis score in patients with CHB ($r = 0.218$, $p = 0.046$) [7]. Similarly, a study published in 2024 reported significantly different MPV-to-lymphocyte ratios between patients with CHB who had cirrhosis and those without cirrhosis ($p = 0.001$) [8]. The present study builds on these earlier observations by examining MPVLR across predefined FibroScan-based liver-stiffness endpoints and, importantly, by directly comparing its performance with two established non-invasive indices, APRI and FIB-4. The modest AUROCs observed in the current cohort suggest that MPVLR alone does not provide sufficient discrimination for definitive classification of liver fibrosis. Nevertheless, the consistent association observed across the different liver-stiffness thresholds is noteworthy. Taken together, these findings support further investigation of MPVLR as an accessible hematological marker that could potentially complement established non-invasive approaches rather than replace them.

The consistently stronger performance of APRI in the present cohort is also worth noting. Although APRI was initially developed in the context of hepatitis C, it has subsequently been studied in CHB and has important limitations, particularly because its value can be influenced by aminotransferase activity and platelet count [1,3]. Despite these limitations, APRI showed the highest AUROC at all three LSM-based endpoints in this study and significantly outperformed both MPVLR and

FIB-4 in pairwise comparisons. FIB-4 showed a consistent intermediate performance, with its AUROCs lying between those of APRI and MPVLR across all three endpoints. These findings highlight an important distinction between accessibility and diagnostic performance. A marker that is inexpensive and readily available is not necessarily a better discriminator of liver fibrosis. Rather, the results support the continued use of established non-invasive indices within their appropriate clinical context, while also encouraging the evaluation of simpler hematological markers according to the specific role they are intended to serve—for example, as complementary or screening-oriented tools rather than replacements for established fibrosis assessments.

The results obtained with the prespecified higher clinical thresholds further highlight the difference between sensitivity-oriented detection and specificity-oriented confirmation. In this cohort, APRI ≥1.5 and FIB-4 ≥3.25 provided high specificity but detected relatively few participants with the higher liver-stiffness endpoints. Similarly, the APRI threshold of ≥2.0 was not reached by any participant and therefore did not identify any individual with an LSM ≥12.5 kPa. These findings should not be taken to mean that these established thresholds are inherently ineffective. Rather, their performance depends on the characteristics of the population being studied, the spectrum of disease, the definition of the outcome, and the clinical purpose for which the threshold is used. In the present cohort, which was predominantly composed of participants without cirrhosis, the relatively high fixed thresholds classified only a small number of individuals. This illustrates the important difference between thresholds intended to maximize specificity and data-derived thresholds selected to achieve a more balanced trade-off between sensitivity and specificity. In other words, a threshold designed primarily to rule in advanced disease may behave very differently from one chosen to identify as many potentially affected individuals as possible.

The multivariable analysis provided further support for an association between MPVLR and liver stiffness. After adjustment for age and sex, a one-standard-deviation increase in MPVLR was associated with higher odds of meeting each of the three FibroScan-based endpoints: LSM >7.0 kPa, LSM ≥9.0 kPa, and LSM ≥12.5 kPa. The corresponding associations were consistently stronger for APRI across all three endpoints, which is in keeping with its superior discriminatory performance in the ROC analyses. These findings suggest that the observed relationship between MPVLR and increased liver stiffness was not simply attributable to differences in age or sex within this cohort. However, the regression results should be interpreted as associations rather than evidence of causality or an independent biological mechanism. In addition, because the models were adjusted only for age and sex, it is more accurate to describe the findings as age- and sex-adjusted associations rather than suggesting that MPVLR is an independently established determinant of hepatic fibrosis.

From a practical standpoint, MPVLR is appealing because it can be calculated from parameters routinely reported in a complete blood count (CBC), without the need for an additional biochemical assay. This simplicity may be particularly valuable in resource-limited settings, where access to transient elastography is limited or its routine use is difficult to implement. However, the findings of the present study do not support using MPVLR as a substitute for APRI, FIB-4, or transient elastography. Its modest discriminatory performance and relatively low specificity limit its ability to establish the presence of fibrosis when used on its own. If these findings are confirmed in larger, prospective, and independent cohorts, MPVLR could potentially serve as an inexpensive screening-oriented adjunct, helping to identify individuals who may warrant further assessment of liver fibrosis. Such a role should, however, remain investigational until externally validated. This is particularly important because the present study relied on FibroScan-derived liver stiffness rather than histological confirmation and was conducted at a single center.

7. LIMITATIONS

This study has several limitations that should be considered when interpreting its findings. First, fibrosis assessment was based on liver stiffness measurements (LSM) obtained by transient elastography (FibroScan) rather than liver biopsy. Although transient elastography is a well-established non-invasive method for assessing liver fibrosis, liver biopsy remains the histological reference standard for definitive fibrosis staging. Moreover, liver stiffness can be affected by factors other than fibrosis, including hepatic inflammation, aminotransferase flares, hepatic congestion, cholestasis, and body habitus. Therefore, some degree of misclassification of fibrosis status cannot be excluded. The findings should consequently be interpreted as reflecting the diagnostic performance of the evaluated markers against FibroScan-based non-invasive liver-stiffness definitions, rather than against histologically confirmed fibrosis.

Second, FibroScan measurements were retrospectively retrieved from existing medical records rather than obtained prospectively at the time of blood sampling. As a result, the exact interval between the liver stiffness assessment and CBC collection could not be verified consistently for all participants. Furthermore, detailed FibroScan quality indicators, including the number of valid measurements, success rate, and interquartile range-to-median ratio, were not consistently documented in the available records. Variability in the timing of the measurements, together with incomplete information on measurement quality, may therefore have introduced additional uncertainty into the classification of liver stiffness and, consequently, the diagnostic estimates.

Third, the study was conducted at a single center, which may limit the extent to which the findings can be applied to other populations and clinical settings. Differences in the demographic characteristics of patients, laboratory practices, referral patterns, and the underlying spectrum of CHB disease may influence the performance of the evaluated markers across different settings. Therefore, the findings should be interpreted within the context of the study population, and validation in larger, independent cohorts from different geographic and clinical settings is needed before they can be broadly generalized.

Fourth, the number of participants who met the higher liver-stiffness endpoints was relatively small. Forty-nine participants (19.6%) had an LSM ≥9.0 kPa, while only 21 (8.4%) had an LSM ≥12.5 kPa. The limited number of participants at these thresholds increases the uncertainty surrounding some of the diagnostic estimates, particularly those related to the cirrhosis-compatible endpoint. For this reason, the analyses of LSM ≥9.0 kPa, and especially LSM ≥12.5 kPa, should be considered exploratory. Larger studies with a greater representation of patients with advanced liver disease will be needed to determine whether these findings remain consistent.

Fifth, the multivariable logistic regression models were adjusted for age and sex but did not include all potentially relevant clinical and virological factors. Variables such as HBV DNA level, HBeAg status, antiviral treatment, body mass index, diabetes, and other metabolic or liver-related factors may influence both liver stiffness and hematological parameters. Where these variables were unavailable or incompletely documented, the possibility of residual confounding cannot be excluded. Therefore, the adjusted findings should be interpreted as age- and sex-adjusted associations rather than evidence that the observed relationship between MPVLR and liver stiffness is independent of all other potential confounding factors.

Sixth, MPV is subject to both pre-analytical and analytical variability. Factors such as EDTA-related time-dependent platelet swelling, delays between blood collection and analysis, and differences between automated hematology analyzers can influence MPV measurements. In the present study, CBC parameters were measured using the same automated hematology analyzer, and samples were processed within the predefined time window, helping to reduce, although not completely eliminate, potential measurement variability. Nevertheless, the reproducibility of MPVLR across different laboratories, analyzers, and analytical protocols remains uncertain and should be evaluated in future studies before broader clinical application.

Seventh, the cohort was predominantly female (84.0%), which may limit the generalizability of the findings to populations with a more balanced or male-predominant sex distribution. The distribution of liver stiffness values also indicates that relatively few participants had more advanced disease: 131 participants (52.4%) had LSM ≤7.0 kPa, compared with 49 (19.6%) with LSM ≥9.0 kPa and only 21 (8.4%) with LSM ≥12.5 kPa. As a result, the diagnostic performance estimates may not fully reflect how MPVLR, APRI, or FIB-4 would perform in populations with a substantially higher prevalence of advanced fibrosis or cirrhosis. Further studies including larger and more diverse populations, particularly those with greater representation of advanced liver disease, are therefore warranted.

Finally, the cross-sectional nature of the study limits the conclusions that can be drawn about changes over time. Because MPVLR and liver stiffness were assessed at a single point in the study, it was not possible to determine whether changes in MPVLR correspond to changes in liver stiffness during the course of chronic HBV infection. The study therefore provides evidence of an association and of diagnostic performance at the time of assessment, but it cannot establish whether MPVLR can predict subsequent fibrosis progression or regression, or whether changes in MPVLR reflect response to antiviral treatment. Longitudinal studies with repeated measurements of both MPVLR and liver stiffness will be needed to address these questions.

Future research should build on these findings by using prospectively paired CBC and transient elastography measurements, together with standardized FibroScan quality criteria, to reduce uncertainty related to timing and measurement quality. Larger

and more diverse CHB cohorts would also help determine whether the observed findings are reproducible across different patient populations and clinical settings. Longitudinal follow-up would be particularly valuable for assessing whether changes in MPVLR parallel changes in liver stiffness over time. Where ethically and clinically appropriate, comparison with liver histology or other validated reference methods could further clarify whether MPVLR reflects true hepatic fibrosis rather than changes in liver stiffness alone. uture prospective studies should also examine whether incorporating MPVLR alongside established indices such as APRI or FIB-4 provides meaningful additional diagnostic information. Evaluating combined or sequential testing strategies may help determine whether MPVLR can improve the efficiency of fibrosis assessment while retaining the strengths of currently established non-invasive approaches.

8. CONCLUSION

In this single-center study of 250 adults with chronic hepatitis B, MPVLR showed modest discriminatory ability across the FibroScan-based liver stiffness endpoints, but consistently performed less well than APRI and FIB-4. For significant fibrosis, operationally defined as LSM >7.0 kPa, MPVLR had an AUROC of 0.606, compared with 0.725 for APRI and 0.666 for FIB-4. At the exploratory advanced-fibrosis endpoint of LSM ≥9.0 kPa, the corresponding AUROCs were 0.630, 0.803, and 0.727, respectively. For the cirrhosis-compatible liver stiffness endpoint of LSM ≥12.5 kPa, the AUROCs were 0.672 for MPVLR, 0.837 for APRI, and 0.733 for FIB-4. APRI significantly outperformed MPVLR at all three endpoints, whereas the difference between MPVLR and FIB-4 did not reach statistical significance. Overall, these findings suggest that although MPVLR showed a consistent relationship with increasing liver stiffness, its discriminatory performance was inferior to that of the established indices.

Despite its more modest discriminatory performance, MPVLR remained significantly associated with all three FibroScan-based endpoints after adjustment for age and sex. It also demonstrated relatively high sensitivity at the Youden-derived thresholds, particularly for the advanced and cirrhosis-compatible liver stiffness endpoints. However, its limited specificity reduces its ability to accurately distinguish participants with fibrosis from those without it, making MPVLR unsuitable as a stand-alone tool for definitive fibrosis classification. Its main potential advantage lies in its simplicity and accessibility, as it can be calculated from routinely available complete blood count parameters without the need for additional testing.

Accordingly, MPVLR may be best regarded as a potential complementary or screening-oriented marker rather than a replacement for APRI, FIB-4, or transient elastography. The present study did not formally assess combined-marker models, sequential testing strategies, or the incremental diagnostic value of adding MPVLR to established indices. Therefore, these findings do not provide sufficient evidence to recommend a specific MPVLR-based diagnostic algorithm. Larger, multicenter, prospectively designed studies incorporating standardized FibroScan assessment, more comprehensive clinical and virological data, and longitudinal follow-up are needed to determine whether MPVLR can provide meaningful additional value in the non-invasive assessment of liver fibrosis in CHB.

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AUTHOR CONTRIBUTIONS

Hawar Mohammed Saeed and Najeeb Saeed Rasheed: Supervision, Laboratory Analysis, Data Collection and Curation, and Writing.

Nazik Abdulrahim Abdulkarim: Methodology, Laboratory Analysis and Review of Writing and Editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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