ORIGINAL ARTICLE

Comprehensive Approach to Detect Liver Fibrosis by Indirect Serum Biomarkers

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Abstract

Aim and objective: The diagnostic accuracy of three serum-derived markers—aspartate aminotransferase-to-platelet ratio index (APRI), Fibrosis-4 (FIB-4), and the aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio—was investigated as noninvasive alternatives in this study for assessing liver fibrosis severity and correlating these scores with FibroScan-derived liver stiffness measurements in patients with chronic liver disease (CLD).

Materials and methods: We enrolled 100 adult patients with a confirmed diagnosis of CLD for this cross-sectional analysis at GMC Kota. Consenting patients received clinical evaluations, ultrasound, and biochemical screenings [complete blood count (CBC), liver function tests (LFTs), glucose, and viral serology]. We staged liver stiffness (F0–F4) *via* FibroScan and computed indirect indices, including FIB-4, APRI, and AST/ALT, using validated equations.

Results: The average participant age was 47 years, with males comprising 67% of the study population. FibroScan showed that 73% of patients had F4 fibrosis, followed by F3 (10%), F2 (12%), and F0–F1 (5%). Etiologies included alcohol-related liver disease (34%), hepatitis B (15%), hepatitis C (4%), autoimmune hepatitis (2%), and diabetes-associated nonalcoholic fatty liver disease (NAFLD) (38%). Significant positive correlations were found between liver stiffness and the AST/ALT ratio ($r = 0.658$), APRI ($r = 0.639$), and FIB-4 ($r = 0.444$), all with $p < 0.0001$. Diagnostic thresholds revealed that lower cutoff values (e.g., APRI > 0.5, FIB-4 ≥ 1) had high sensitivity, whereas higher cutoff values (e.g., AST/ALT > 1, APRI ≥ 1, FIB-4 ≥ 3.24) achieved excellent specificity. A stepwise diagnostic approach using these thresholds improved detection accuracy and reduced reliance on liver biopsy.

Significance: The study validates simple, cost-effective biomarkers as reliable tools for fibrosis detection. Their integration into clinical practice may enhance early diagnosis, optimize resource use, and improve outcomes in patients with CLD, especially in low-resource settings.

Keywords: Aspartate aminotransferase-to-platelet ratio index, Fibrosis-4 score, Liver fibrosis, Transient elastography (FibroScan).

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Introduction

Liver fibrosis is a major pathological consequence of sustained liver injury, marked by excessive extracellular matrix (ECM) deposition and progressive architectural distortion of hepatic tissue. The natural history of untreated fibrosis involves a high risk of progression toward cirrhosis and its complications, including hepatocellular carcinoma (HCC) and end-stage liver failure. The global landscape of chronic liver disease (CLD) is heavily impacted by the burden in India; as of 2015, nearly one-fifth (18.3%) of all liver-related fatalities occurred within the country.[1] In 2016, CLDs and cirrhosis were responsible for 2.1% of total deaths in India,[2] with nonalcoholic fatty liver disease (NAFLD) affecting 8–20% of urban populations. Early identification and staging of liver fibrosis are essential to prevent complications and reduce the burden of liver transplantation. Limitations surrounding liver biopsy, primarily its invasive nature and potential complications, have necessitated the shift toward developing reliable, noninvasive assessment tools. This study aims to assess the diagnostic utility of indirect fibrosis markers and their correlation with FibroScan-derived liver stiffness measurements to promote safer, cost-effective fibrosis evaluation.

Materials and Methods

This cross-sectional study was conducted at the Government Medical College and Associated Group of Hospitals, Kota, from ethical approval until December 2024.

Inclusion Criteria

We enrolled patients with established CLD [viral, alcoholic, autoimmune, or nonalcoholic fatty liver disease (NAFLD)] in whom fibrosis or cirrhosis was previously documented *via* imaging [ultrasonography (USG)/FibroScan] or biopsy.

Age >18 years.

Exclusion Criteria

Acute liver diseases or acute liver failure.

Decompensated liver disease with severe complications (e.g., hepatic encephalopathy, variceal bleeding).

Previous liver transplantation or current listing for transplantation.

Significant comorbidities or medical conditions that may interfere with the study or treatment outcomes.

Pregnancy or breastfeeding.

A total of 100 adult subjects with CLD were included, with diagnosis supported by imaging [ultrasonography (USG) or FibroScan] or liver biopsy findings.

Participants were enrolled from inpatient and outpatient settings after informed consent. Clinical evaluation and investigations, including complete blood count (CBC), liver function tests (LFTs), viral markers [hepatitis B virus (HBV), hepatitis C virus (HCV)], glucose, and USG, were conducted. Liver stiffness was measured using FibroScan with patients in a supine position and categorized into fibrosis stages F0–F4 based on kPa values. Blood samples were analyzed for aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, platelets, and glucose. Indirect markers of hepatic fibrosis, including the aspartate aminotransferase-to-platelet ratio index (APRI), AST/ALT ratio, and Fibrosis-4 (FIB-4) index, were computed using established clinical formulas.

Results

Our study group had an average age of 47 years, with a male predominance of 67%, while females comprised 33% of the cohort. A total of 100 patients underwent liver stiffness measurement using FibroScan, which revealed advanced fibrosis (F4) in 73%

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Table 1: Distribution of patients according to liver fibrosis stage

Fibrosis grade	*Count*	*Percentage*
F0-F1 (none to mild)	5	5.00%
F2 (moderate)	12	12.00%
F3 (severe)	10	10.00%
F4 (cirrhosis)	73	73.00%

Table 2: Correlation of serum fibrosis biomarkers with FibroScan-derived liver stiffness measurements

Scores	*Pearson coefficient*	*Pearson p-value*
AST/ALT	0.658	<0.0001
FIB4	0.444	<0.0001
APRI	0.639	<0.0001

of patients, F3 fibrosis in 10%, F2 fibrosis in 12%, and minimal-to-mild fibrosis (F0–F1) in 5% (Table 1). The etiology of CLD varied, with 34% having alcohol-related liver disease, 15% being hepatitis B virus (HBV)-positive, 4% being hepatitis C virus (HCV)-positive, 2% showing an autoimmune association, and 38% having diabetes-associated nonalcoholic fatty liver disease (NAFLD). All three noninvasive indices [APRI, Fibrosis-4 (FIB-4), and the aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio] demonstrated a strong positive correlation with the stage of fibrosis, yielding highly significant results with $p < 0.0001$ (Table 2). Additionally, various cutoff values were assessed for each scoring system, and their respective sensitivity and specificity were calculated to evaluate diagnostic performance (Table 3). A stepwise diagnostic algorithm using these thresholds was applied to enhance diagnostic accuracy and refine the identification of patients with advanced fibrosis (Fig. 1).

Discussion

Our study population spanned an age range of 18–78 years, with a calculated mean of 52.3 ± 12.7 years. A robust correlation emerged between age and fibrosis degree, identifying patient age as a key determinant in the longitudinal progression of CLD within our cohort. Our study was supported by the global meta-analysis by Singh et al.[3] The overall cohort demonstrated a mean age of 55 ± 13 years, which is statistically comparable to the 52.3-year average found in our participants. A similar age was reported in studies by Trifan et al.[4] and Fallatah et al.[5] Similar results of male predominance were reported by Singh et al.,[3] Sherazi et al.,[6] and Alhankawi et al.[7] However, the risk for females increases after menopause, as the loss of estrogen's antifibrotic role contributes to accelerated progression. This underscores the significance of gender-specific surveillance in liver disease management. In our study and all referenced studies, males consistently outnumbered females in terms of both disease prevalence and fibrosis severity.

Table 3: Diagnostic performance of AST/ALT ratio, APRI, and FIB-4 at different cutoff values

Index		*Sensitivity*	*Specificity*
AST/ALT	>0.5	0.989	0
	>1	0.736	1
FIB4	>1	0.989	0.889
	>3.24	0.44	1
APRI	0.5	0.956	0
	1	0.802	0.889

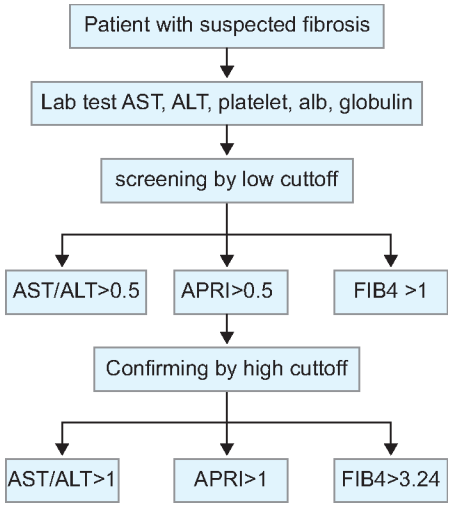

Fig. 1: Stepwise diagnostic algorithm for noninvasive assessment of liver fibrosis using AST/ALT ratio, APRI, and FIB-4

Our results confirm that noninvasive markers, specifically the Fibrosis-4 (FIB-4), APRI, and AST/ALT ratio, closely track with liver stiffness measurements. A comparable relationship was documented by Fallatah et al.,[5] emphasizing the reliability of these markers across different clinical cohorts. A positive statistical association was observed between participant age and the degree of fibrosis; conversely, hepatic stiffness values showed a significant decline as platelet counts increased. The diagnostic performance of these markers is further supported by Alhankawi et al.,[7] who reported significant correlations with FibroScan results for the FIB-4 ($r = 0.472$), APRI ($r = 0.418$), and AST/ALT ratio ($r = 0.219$). Using a 7.5 kPa threshold for significant fibrosis, their study yielded area under the receiver operating characteristic curve (AUROC) values of 0.705, 0.644, and 0.643, respectively, which closely parallel the trends observed in our clinical data.

A study of 1,716 patients by Yen et al.[8] showed a similar correlation of APRI and FIB-4 with fibrosis as our study. Chronic hepatocellular injury, especially due to alcohol or ongoing fibrosis, causes mitochondrial damage and vitamin B6 (pyridoxal phosphate) deficiency, leading to a disproportionately higher release of AST, which selectively reduces ALT activity. The development of thrombocytopenia in patients with advanced hepatic fibrosis is multifactorial. It typically involves impaired thrombopoietin synthesis by the liver, direct bone marrow suppression, and the entrapment of platelets within the spleen, a consequence of portal hypertension-induced splenomegaly. The FIB-4 index effectively reflects fibrosis severity because it integrates key biomarkers of hepatocellular damage, fibrotic progression, and portal hypertension.

Conclusion

Our analysis of 100 patients with CLD demonstrated that simple serum scores correlate well with fibrosis severity. The AST/ALT ratio showed the strongest linear association with FibroScan, followed by APRI and FIB-4. Lower cutoff values improved sensitivity for screening but reduced specificity, highlighting the importance of context-based threshold selection. A stepwise approach, starting with sensitive thresholds and confirming with specific ones, can reduce the need for biopsy, especially in resource-limited settings. Traditional clinical indicators, such as male sex, older age, elevated AST, and thrombocytopenia, also aligned with higher fibrosis stages. Despite their utility, these scores were less accurate at intermediate stages, reinforcing the role of elastography or biopsy in indeterminate cases. As affordable diagnostic adjuncts, the APRI, AST/ALT, and FIB-4 scores remain highly effective for the routine assessment and progression tracking of liver fibrosis.

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