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Predictive Role of Non-Invasive Laboratory Markers in Hepatic Fibrosis among Hepatitis B Patients

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ABSTRACT

Introduction: Chronic hepatitis B (CHB) is a major cause of liver fibrosis, which may progress to cirrhosis if undetected. Non-invasive biomarkers such as Gamma-glutamyl Transferase to Albumin Ratio (GAR), Alkaline Phosphatase to Platelet Ratio (APPR), and Alkaline Phosphatase plus Gamma-glutamyl Transferase to Platelet Ratio (AGPR) have shown promise in predicting fibrosis severity, potentially outperforming traditional markers like APRI.
Methods: We conducted a cross-sectional study involving 34 CHB patients at Dr. Sardjito General Hospital, Yogyakarta (October 2022–February 2023). Liver stiffness was assessed using shear wave elastography (SWE) and staged according to the Metavir system (F0–F4). GAR, APPR, and AGPR were calculated from laboratory data. Spearman correlation and linear regression analyses were used to evaluate their association with fibrosis severity.
Result: AGPR showed the strongest correlation with fibrosis stage ($\rho = 0.611$, $p < 0.001$), followed by GAR ($\rho = 0.450$, $p = 0.008$) and APPR ($\rho = 0.384$, $p = 0.026$). All three indices were significant in univariate regression, while the combined model demonstrated improved predictive performance ($R^2 = 0.389$, $p = 0.003$) despite lack of independent significance in multivariate analysis.
Conclusion: GAR, APPR, and AGPR are promising non-invasive biomarkers for assessing liver fibrosis in CHB patients. Their combined use enhances diagnostic accuracy and offers practical benefits, particularly in settings where biopsy is not available.

Keywords: Chronic hepatitis B; Liver fibrosis; Non-invasive biomarkers; GAR; APPR; AGPR

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Introduction

Chronic hepatitis B virus (HBV) infection is one of the most serious global public health challenges, impacting an estimated 254 million people and causing over 1.1 million deaths each year owing to cirrhosis and hepatocellular carcinoma (HCC)[1]. Hepatitis B prevalence is high in Southeast Asia, notably in Indonesia, with national seropositivity rates ranging from 7% to 10%, placing the country in the top ten worldwide in terms of HBV burden[2,3]. According to the Indonesian Ministry of Health, almost 18 million individuals are chronically infected with HBV. Chronic hepatitis B continues to be a major cause of liver disease morbidity in Yogyakarta's Special Region. Hospital-based research at Dr. Sardjito General Hospital found that HBV infection was the leading cause of hepatocellular carcinoma (HCC) in around 48% of cases, with most patients aged 46 to 55 years[4]. Despite this burden, complete screening for liver fibrosis is rare outside of tertiary care facilities, creating a diagnostic gap in early-stage disease diagnosis[5,6].

Liver fibrosis is an important stage in the progression of HBV infection, where more extracellular matrix builds up, potentially causing portal hypertension, liver failure, and HCC[3,7]. While liver biopsy is still the gold standard for detecting fibrosis, it is invasive, expensive, and unsuitable for large-scale or repeated usage[8,9]. To address this, the World Health Organization (WHO) recommends using non-invasive tests like the AST to Platelet Ratio Index (APRI) and the Fibrosis-4 Index (FIB-4) as easier options, particularly in places with limited resources. However, these indexes have a few drawbacks[10,11]. Variable ALT levels during HBV infection reduce APRI's accuracy in diagnosing intermediate fibrosis (F2-F3), limiting its sensitivity to less than 60%[8,9]. FIB-4, although more accurate than APRI in certain cases, might exaggerate fibrosis in older persons owing to the inclusion of age in the calculation, and it may underrepresent cholestatic or synthetic liver dysfunction, limiting its value in early-stage HBV fibrosis[10,12].

Given these constraints, new research has suggested novel HBV-specific laboratory indices that aim to improve diagnostic accuracy[13,14]. Among these, the Gamma-glutamyl Transferase to Albumin Ratio (GAR), Alkaline Phosphatase to Platelet Ratio (APPR), and Alkaline Phosphatase plus GGT to Platelet Ratio (AGPR) have been found to predict liver scarring more accurately, especially in Asian people[15,16]. For example, the AGPR has an area under the receiver operating characteristic curve (AUROC) of 0.83-0.87 for diagnosing severe fibrosis and cirrhosis in patients with chronic HBV, outperforming conventional markers such as APRI and FIB-4 [16]. This measures also consider other liver function factors like ALP, GGT, and albumin, which indicate liver damage, the liver's ability to produce proteins, and high blood pressure in the liver[17,18]. These aspects are often neglected in traditional indices. Their simplicity, consistency, and utilization of regular blood markers make them promising candidates for widespread application, although comparative validation in HBV-endemic areas is limited[15,16].

In the context of Indonesia's high HBV burden and limited access to liver biopsy or elastography at the

primary care level, there is an urgent need to develop additional reliable, low-cost, and HBV-specific non-invasive laboratory indicators that may be incorporated into normal clinical processes. This research, which will take place at Dr. Sardjito General Hospital and Universitas Gadjah Mada (UGM) in Yogyakarta, aims to evaluate how accurately GAR, APPR, and AGPR can predict liver fibrosis stages in patients with chronic hepatitis B. Yogyakarta, located in central Java, confronts comparable public health difficulties to other high-prevalence locations, making it an appropriate environment for investigating alternate fibrosis indicators. The results are likely to help create more context-appropriate diagnostic tools, minimize dependence on invasive procedures, and improve liver disease treatment in resource-constrained settings.

Methods

This observational analytic study with a cross-sectional design was conducted at Dr. Sardjito General Hospital, Yogyakarta, Indonesia, from October 2022 to February 2023. The study involved 34 adult patients diagnosed with chronic hepatitis B (CHB) who met the inclusion criteria of being aged 18 years or older, having a confirmed CHB diagnosis, and providing informed consent to undergo laboratory testing and liver stiffness assessment. Patients with co-infection by other hepatitis viruses (HCV or HDV), other chronic liver diseases, or severe coagulopathy were excluded. Venous blood samples were collected to measure gamma-glutamyl transferase (GGT), albumin, alkaline phosphatase (ALP), and platelet count using automated analyzers. Based on these laboratory values, three non-invasive indices were calculated: the Gamma-glutamyl Transferase to Albumin Ratio (GAR), the Alkaline Phosphatase to Platelet Ratio (APPR), and the Alkaline Phosphatase plus Gamma-glutamyl Transferase to Platelet Ratio (AGPR). Liver stiffness was measured using shear wave elastography (SWE) performed by two trained radiologists following standardized procedures, and fibrosis stages were categorized according to the Metavir scoring system (F0–F4). The median SWE value for each participant was used for staging, and inter-observer agreement was determined using Cohen's kappa coefficient. All laboratory and imaging procedures adhered to internal and external quality control standards.

Statistical analysis was performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation or median (range) as appropriate. Spearman's rank correlation test was used to determine the relationship between GAR, APPR, AGPR, and fibrosis stage, while linear regression analyses were conducted to identify predictors of liver stiffness. A two-tailed p-value of <0.05 was considered statistically significant. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung. Written informed consent was obtained from all participants prior to enrollment, and all procedures were carried out in accordance with the Declaration of Helsinki.

Result

This study included a total of 34 subjects with chronic hepatitis B who underwent laboratory testing and shear wave elastography (SWE) for liver fibrosis assessment. Subject characteristics are presented in **Table 1**. The mean age was 45.12 ± 14.2, with males comprising most participants (61.8%). Laboratory results demonstrated mean values of GAR at 6.88 ± 5.28, APPR at 0.58 ± 0.44, and AGPR at 0.78 ± 0.61, while fibrosis stages were distributed as follows: F0 (26.4%) F1 (5.8%), F2 (41.17%), F3 (17.3%), and F4 (8.8%), based on Metavir scoring.

Table 1. Characteristic Demographic

Variable	Value
Age (years)	45.12 ± 14.2
Body Mass Index (kg/m^2)	23.97 ± 3.9
Diagnosed Duration (years)	6.73 ± 5.32
Sex, n (%)	
Male	21 (62%)
Female	13 (38%)
Symptoms, n (%)	
Fever	3 (9%)
Jaundice	5 (14.7%)
RUQ pain	12 (35%)
Choluric urine	4 (11.7%)
Acholic stool	1 (2.9%)
Comorbidities, n (%)	
Alcohol consumption	0
Autoimmune disease	0
History of cholestasis	0
HIV infection	0
Chronic kidney disease *(or renal failure)*	2 (5.8%)
Hepatitis C virus (HCV) infection	0
Parental history of hepatitis B	9 (26.4%)
Hypertension	5 (14.7%)
Diabetes mellitus	2 (5.8%)
History of malignancy *(or cancer)*	0
Laboratories Examination Finding	
Eritrocyte	4.6 ± 0.92
Haemoglobin	13.37 ± 2.3
Haematocrit	40.51 ± 7.25
MCV	88.44 ± 8.21
MCH	94.77 ± 121.6

MCHC	33.02 ± 0.95
Leukocyte	6.23 ± 1.87
Trombocyte	196.41 ± 72.26
Liver Test Function	
Total Protein	7.55 ± 0.65
Globulin	3.22 ± 0.72
Albumin (g/dL)	4.39 ± 0.65
AST	35.52 ± 16.9
ALT	31.71 ± 14.84
Gamma GT	23.46 ± 13.49
ALP (u/L)	90.29 ± 29.7
Non – Invasive Biomarker	
GAR	6.88 ± 5.28
APPR	0.58 ± 0.44
AGPR	0.78 ± 0.61
Metavir Index (kPa)	7.24 ± 1.67
Liver Fibrosis Grade, n (%)	
F0	9 (26.4%)
F1	2 (5.8%)
F2	14 (41.17%)
F3	6 (17.3%)
F4	3 (8.8%)

Data source: primary data collected from study participants at Dr. Sardjito General Hospital, Yogyakarta (October 2022–February 2023).

A Spearman correlation analysis was conducted to assess the link between non-invasive indicators and liver fibrosis, with the results shown in **Table 2**. Of the three indices, AGPR had the most robust positive connection with liver stiffness (Spearman's $\rho = 0.46$, $p = 0.019$), followed by GAR ($\rho = 0.46$, $p = 0.006$) and APPR ($\rho = 0.29$, $p = 0.092$). These findings suggest a moderate to strong association between these biomarkers and the degree of fibrosis measured by SWE. Further analysis using simple linear regression revealed that all three biomarkers were significant predictors of liver stiffness individually (see **Table 3**). GAR had a B coefficient of 0.144 ($p = 0.011$), APPR had a coefficient of 1.388 ($p = 0.014$), and AGPR demonstrated the highest predictive value with a coefficient of 1.572 ($p < 0.001$), explaining 37.4% of the variance in fibrosis ($R^2 = 0.374$).

Table 2. Spearman Correlation Between Non-Invasive Biomarkers and Liver Fibrosis Stage

Variable	Spearman's rho (ρ)	p – value
GAR	0.46	0.006
APPR	0.29	0.092

AGPR	0.39	0.019

Data source: primary data collected from study participants at Dr. Sardjito General Hospital, Yogyakarta (October 2022–February 2023).

Figure 1 illustrates the receiver operating characteristic (ROC) curves of GAR, APPR, and AGPR for screening significant liver fibrosis (≥F2) in patients with chronic hepatitis B based on shear wave elastography. Among the three non-invasive biomarkers, AGPR demonstrated the highest discriminative ability with an area under the curve (AUC) of 0.67, followed by GAR and APPR, both with an AUC of 0.64. Although the AUC values were within the acceptable range, these findings indicate that GAR, APPR, and AGPR may serve as useful preliminary screening tools to identify patients at higher risk of significant fibrosis, particularly in clinical settings where invasive procedures or advanced imaging modalities are not readily available.

Figure 1. ROC curves of non-invasive laboratory markers for identifying significant liver fibrosis (≥F2).

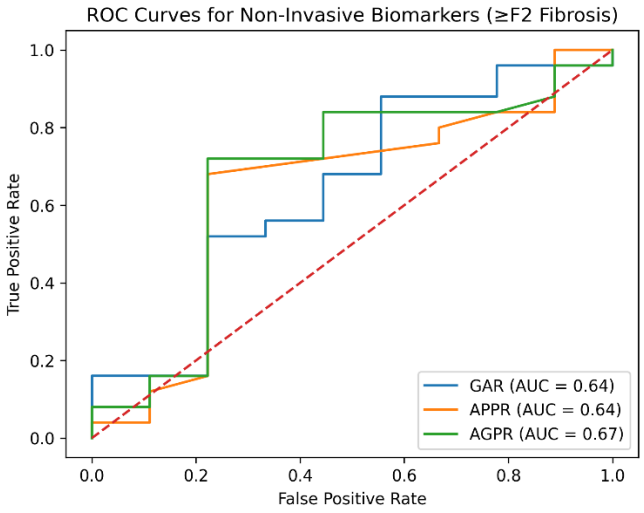

Table 3 summarizes the screening performance of GAR, APPR, and AGPR for identifying significant liver fibrosis (≥F2), including the area under the curve (AUC), optimal cut-off values, sensitivity, and specificity. AGPR showed the highest overall discriminative performance (AUC 0.67) with an optimal cut-off value of 0.44, yielding a sensitivity of 72.0% and specificity of 77.8%. GAR demonstrated the highest sensitivity at 88.0% using a cut-off value of 3.21, albeit with lower specificity (44.4%), suggesting its potential utility as a sensitive screening marker. APPR showed a more balanced screening performance with an AUC of 0.64, sensitivity of 68.0%, and specificity of 77.8% at a cut-off value of 0.36. Overall, these serum-based indices provide a less invasive and easily accessible approach for fibrosis risk stratification rather than definitive diagnosis.

Table 3. Area Under the Curve (AUC) of GAR, APPR, and AGPR for Identifying Significant Liver Fibrosis (≥F2)

Biomarker	AUC	Optimal Cut-off	Sensitivity (%)	Specificity (%)
GAR	0.64	3.21	88.0	44.4
APPR	0.64	0.36	68.0	77.8
AGPR	**0.67**	0.44	72.0	77.8

Discussion

This study assessed the predictive efficacy of three serum-based indices: Gamma-glutamyl Transferase to Albumin Ratio (GAR), Alkaline Phosphatase to Platelet Ratio (APPR), and Alkaline Phosphatase plus Gamma-glutamyl Transferase to Platelet Ratio (AGPR) in evaluating the severity of liver fibrosis in patients with chronic hepatitis B. Although none of the individual biomarkers demonstrated statistical significance in the multivariate linear regression model, their collective predictive strength was notable, with the combined model explaining 38.9% of the variance in fibrosis severity ($R^2 = 0.389$; $p = 0.003$). These findings suggest that the integrated use of multiple biomarkers may offer a more reliable and nuanced approach for non-invasive fibrosis evaluation.

The Spearman correlation analysis confirmed that all three indices had a statistically significant positive correlation with fibrosis stage, with GAR showing the strongest association ($\rho = 0.46$), followed by AGPR and APPR. This supports prior evidence indicating that gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels are not only markers of cholestasis but also correlate with fibrotic progression in chronic liver disease. Albumin and platelet levels, commonly reduced in advanced liver disease, further enhance the discriminatory ability of these composite indices. The significant correlations found in this study are consistent with reports by Pan *et al*. (2022), who demonstrated that APPR could differentiate fibrosis stages in HBV-infected patients, and Li *et al*. (2022), who identified GAR as a prognostic factor in liver and biliary cancers [13,16].

This study supports prior evidence indicating that GGT and ALP levels reflect biliary injury and fibrotic progression, while decreases in albumin and platelets enhance discrimination in composite indices. Notably, Lu *et al*. (2017) reported that GAR significantly outperformed APRI and FIB4 in staging significant fibrosis and cirrhosis in chronic hepatitis B, with areas under the ROC curve (AUROC) of 0.82 vs. 0.70 for APRI and 0.68 for FIB4 [15]. Furthermore, a comparative study of GPR and GAR demonstrated higher AUROCs than APRI in ruling out significant fibrosis (negative predictive value > 93%)(19). While comparisons between GPR and APRI/FIB4 were mixed in some cohorts, GAR displayed consistent superiority over APRI in both training and validation groups.

Although the univariate regression analyses revealed that each biomarker significantly predicted liver stiffness individually, particularly AGPR ($p < 0.001$), none of them retained significance in the multivariate model. This may reflect multicollinearity, where strong intercorrelations between predictors can obscure the independent contribution of each variable. Notably, this does not diminish the clinical utility of the model. Instead, it highlights the value of using a multiparametric approach, a strategy that has been increasingly endorsed in recent hepatology literature [18,20].

The practical appeal of GAR, APPR, and AGPR lies in their use of routine laboratory values, making them cost-effective and widely accessible, especially in low-resource settings. Compared to other established non-invasive fibrosis scoring systems such as APRI, FIB-4, and FibroTest, these indices offer a potentially more liver-specific profile, integrating cholestatic and hepatocellular injury markers with hematologic parameters. Several recent meta-analyses and cohort studies have emphasized the growing role of composite biomarker panels in liver fibrosis screening and monitoring [17,21].

Despite these strengths, our study has several limitations. The sample size was relatively small ($n = 34$), which may limit statistical power, especially for multivariate modeling. Moreover, liver fibrosis staging was based on shear wave elastography (SWE) rather than liver biopsy. While SWE is well-validated and non-invasive, its accuracy may still be affected by inflammation, hepatic congestion, or operator variability[22]. Additionally, potential confounders such as metabolic syndrome components or viral load were not controlled in this model.

Future studies should aim to validate these findings in larger, diverse cohorts and explore the predictive value of GAR, APPR, and AGPR across different etiologies of liver disease, including non-alcoholic fatty liver disease (NAFLD) and hepatitis C. There is also growing interest in combining biochemical indices with machine learning algorithms or imaging biomarkers (e.g., radiomics, elastography features) to enhance diagnostic accuracy and fibrosis stratification.

Conclusion

In patients with chronic hepatitis B, the non-invasive laboratory indices GAR, APPR, and AGPR demonstrated acceptable discriminative ability for screening significant liver fibrosis (≥F2), with AGPR showing the highest performance (AUC 0.67), followed by GAR and APPR (both AUC 0.64). GAR provided high sensitivity (88.0%), supporting its potential role as an initial screening marker, while AGPR and APPR showed more balanced sensitivity and specificity. Given their simplicity, low cost, and reliance on routinely available laboratory parameters, these indices may serve as less invasive adjunctive tools for fibrosis risk stratification, particularly in resource-limited settings where liver biopsy or advanced imaging modalities are not readily accessible. Further validation in larger and more diverse cohorts is warranted.

Conflicts of Interest

There is no conflict of interest.

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