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# Diagnostic performance of APRI, RPR, FIB-4, GPR, AAR, and NLR in assessing the degree of liver fibrosis in patients with chronic hepatitis B



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## ABSTRACT

**Background:** This study aimed to compare the diagnostic performance of aspartate aminotransferase to platelet ratio index (APRI), fibrosis index based on four factors (FIB-4), red cell distribution width to platelet ratio (RPR), gamma-glutamyl transpeptidase to platelet ratio (GPR), aspartate aminotransferase and alanine aminotransferase ratio (AAR), and neutrophil to lymphocyte ratio (NLR) in assessing the degree of liver fibrosis in patients with chronic hepatitis B.

**Methods:** A cross-sectional analytic study was done to analyze the data taken from the medical records of all chronic hepatitis B patients examined using TE at Sanglah Hospital Denpasar, Bali. Receiver operating characteristic (ROC) curve analysis was done to compare the resulting indices of accuracy for each biomarker.

**Results:** From the total of 93 samples, it was found that the number of samples for each degree of fibrosis was 42 (45.16%) F0-1, 17 (18.27%) F2, 7 (7.52%) F3, and 27 (29.03%) F4. Significant differences for each degree of fibrosis ($p<0.005$) were found in APRI, FIB-4, RPR, GPR, and AAR score but not NLR ($p = 0.897$). Higher AUC and indices of accuracy were observed with more severe degree of fibrosis. GPR with the cut-off value of 0.367 for significant fibrosis, 0.559 for severe fibrosis, and 0.698 for cirrhosis had the greatest AUC and diagnostic accuracy.

**Conclusion:** The diagnostic performance of GPR was better than other biomarkers, and the diagnostic accuracy increased along with an increasing degree of fibrosis. Future study on the applicability of GPR alongside APRI and FIB-4 in liver fibrosis assessment is needed.

**Keywords:** Biomarkers, transient elastography, hepatitis B, liver cirrhosis

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## INTRODUCTION

It is estimated that as many as 240 million people worldwide have chronic hepatitis B virus infection, of which 650 thousand mortalities ensued.[1] The liver in individuals with chronic hepatitis B often develops fibrosis, which progresses into cirrhosis and ultimately hepatocellular carcinoma. The presence of liver fibrosis is an indicator of hepatitis B disease progression, hence it constituted an important aspect to determine management and prognosis. Histopathological examination of liver tissue remains the gold standard for diagnosing liver fibrosis. However, several limitations, including its invasive nature, risk of complications, high interobserver variation of histopathological interpretation, sampling error, contraindications, and high cost, have led to the abandonment of this examination and the development of noninvasive methods thereof.[2-3]

Transient elastography (TE) or FibroScan is one of the noninvasive methods recommended for fibrosis assessment, although it is variably available, expensive, and has limited use in obese and ascites cases.[4] Serological markers such as aspartate aminotransferase to platelet ratio index (APRI), fibrosis index based on four factors (FIB-4), red cell distribution width (RDW) to platelet ratio (RPR), gamma-glutamyl transpeptidase (GGT) to platelet ratio (GPR), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ratio (AAR), and neutrophil to lymphocyte ratio (NLR) are being extensively studied to serve as noninvasive modalities that are easy, inexpensive, and generally available in limited facilities settings.[5-7] This study aims to determine the diagnostic performance of APRI, FIB-4, GPR, RPR, AAR, and NLR in assessing fibrosis in patients with chronic hepatitis B.

## METHODS

This analytic cross-sectional study utilized the data obtained retrospectively from medical records and FibroScan registry at Sanglah Hospital Denpasar from January 2016 to February 2017 and January 2018 to June 2019. The inclusion criteria was all

chronic hepatitis B patients aged over 18 years with positive HBsAg examination for six months or longer who underwent FibroScan examination. The exclusion criteria was positive human immunodeficiency virus (HIV) infection status, hepatitis C coinfection, dengue hemorrhagic fever, malignancy, hematological disorders, chronic kidney disease, autoimmune disease, decompensated liver cirrhosis, and other hepatobiliary diseases.

The required data was acquired by tracing medical records for laboratory and FibroScan examinations. Serological test results were obtained within 30 days of FibroScan examination commencement. FibroScan examination results were grouped based on Metavir Score into F0-F1 (2.5-7.0 kPa), F2 (7.1-9.5 kPa), F3 (9.6-12.5 KPa), and F4 (>12.5 kPa).[8] Furthermore, the degree of liver fibrosis was grouped into several groups, viz significant fibrosis or ≥F2 (F0-1 vs. F2-4), severe fibrosis or ≥F3 (F0-2 vs. F3-4), and the cirrhosis group or F4 (F0-3 vs. F4).

The AAR score was calculated by dividing AST (IU/L) by ALT (IU/L).[9] The GPR score was calculated using the formula: (GGT [IU/L] / upper limit of normal GGT) / platelet ($10^9$/L) x 100. (10) The APRI score was derived from the formula: (AST [IU/L] / upper limit of normal AST) / platelet ($10^9$/L) x 100. (1) The FIB-4 score was calculated by the following equation: (age [years] x AST [IU/L]) / (platelet [$10^9$/L] x (ALT [IU/L])$^{1/2}$).[1] The NLR score was calculated by dividing neutrophils ($10^9$/L) by lymphocytes ($10^9$/L). (5) The RPR score is calculated using the formula: RDW (%) / platelet ($10^9$/L).[11]

The data obtained were then processed statistically using IBM SPSS® version 25. The baseline characteristics were analyzed descriptively and presented in appropriate central tendency and dispersion. Comparative analysis was done to seek for markers with a significant difference in each fibrosis degree. Finally, the receiver operating characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC), sensitivity, and specificity of the optimal cut-off value.

**Table 1. Baseline characteristics**

| Characteristics | Chronic Hepatitis B (N=93) |
|---|---|
| Age (years) | 41.95±13.61 |
| Gender, n (%) | |
| Male | 68 (73.11) |
| Female | 25 (26.89) |
| ALT (IU/L) | 48.60 (24.65-207.6) |
| AST (IU/L) | 33.60 (22.70-63.10) |
| GGT (IU/L) | 72.67±102.55 |
| Platelet ($10^3$µ/L) | 231.47±111.85 |
| Neutrophil ($10^3$µ/L) | 4.68±2.62 |
| Lymphocyte ($10^3$µ/L) | 4.38±20.96 |
| RDW (%) | 13.43±2.44 |
| FibroScan (kPa) | 7.9 (5.35-16.30) |
| Degree of Fibrosis, n (%) | |
| F0-F1 | 42 (45.16) |
| F2 | 17 (18.27) |
| F3 | 7 (7.52) |
| F4 | 27 (29.03) |
| APRI | 0.599 (0.327-2.095) |
| FIB-4 | 1.247 (0.655-3.309) |
| RPR | 0.061 (0.045-0.100) |
| GPR | 0.817 (0.508-1.310) |
| AAR | 0.817 (0.508-1.310) |
| NLR | 1.948 (1.433-3.069) |

## RESULTS

A total of 93 samples met the eligibility criteria and was included in the analysis. Study subjects consisted of mostly males (73.11%), with a mean age of 41.95±13.61 years (Table 1). Significant fibrosis was the majority finding (63.43%) with the median FibroScan value of 7.9 (5.35-16.30) kPa.

The data on biomarkers of interest was not normally distributed; hence the Kruskal Wallis test was performed to assess the relationship between APRI, FIB-4, GPR, RPR, AAR, and NLR with the degree of fibrosis (F0-1, F2, F3, F4). All markers with significant differences within the individual degree of fibrosis ($p<0.005$), except for NLR ($p = 0.897$), proceeded for further analysis. The values for all six biomarkers studied (Figure 1-6) showed the tendency to increase proportionally with increasing fibrosis degree.

ROC curve analysis of selected markers was performed to evaluate their performance in identifying each fibrosis group (significant fibrosis, severe fibrosis, cirrhosis). Higher AUC, sensitivity, and specificity were observed with more severe fibrosis degree (Table 2, Figure 7-9). GPR had the greatest AUC throughout the fibrosis degrees.

The indices of accuracy for optimal cut-off values were presented in Table 3 to compare their diagnostic performance. The AAR cut-off value for significant fibrosis was not included since the ROC curve analysis did not yield a significant result ($p=0.217$). GPR had the greatest overall indices of accuracy for significant fibrosis and cirrhosis, while FIB-4 outperformed the other markers in identifying severe fibrosis.

## DISCUSSION

Several noninvasive markers for assessing the degree of liver fibrosis in chronic hepatitis B are being studied and validated for use. The criteria that must be met by these markers are: cheap, easy,

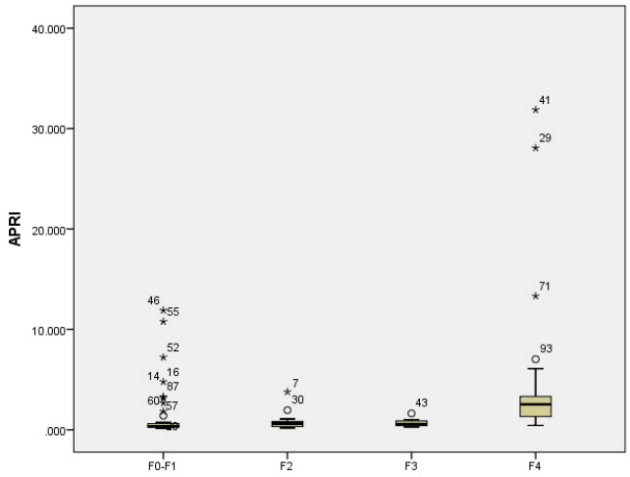


**Figure 1.** The distribution of APRI values for each degree of fibrosis

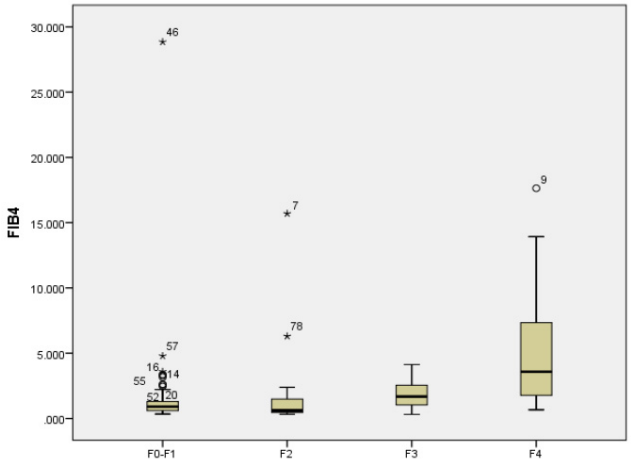


**Figure 2.** The distribution of FIB-4 values for each degree of fibrosis

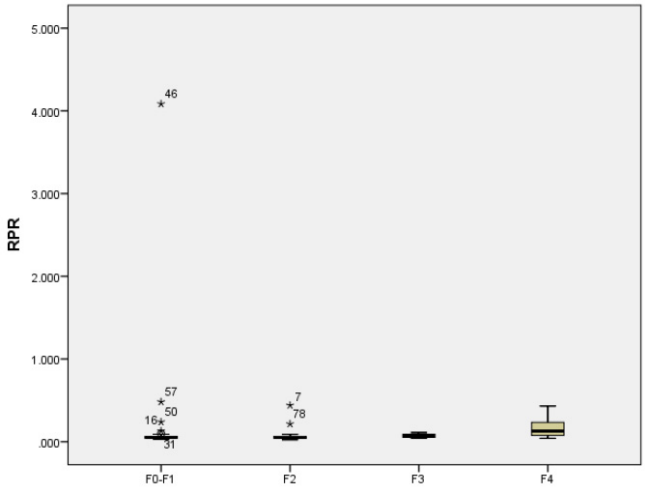


**Figure 3.** The distribution of RPR values for each degree of fibrosis

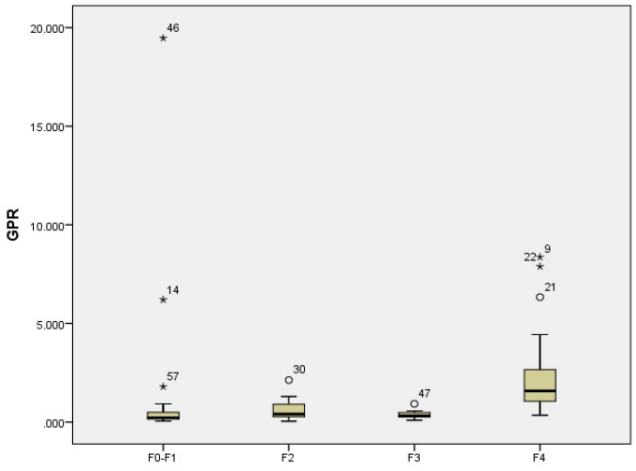


**Figure 4.** The distribution of GPR values for each degree of fibrosis

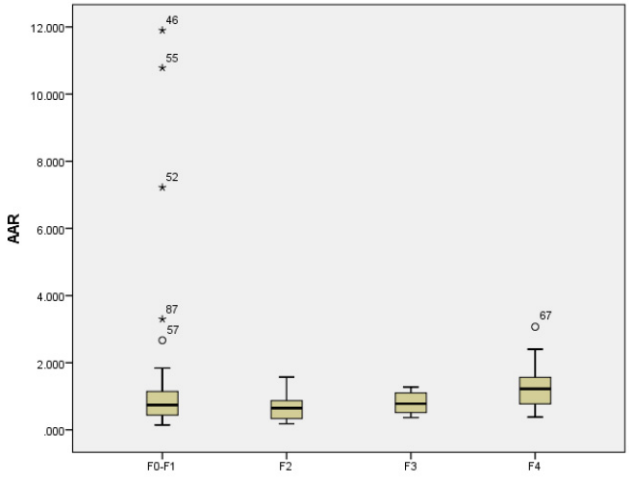


**Figure 5.** Distribution of AAR values at each degree of fibrosis

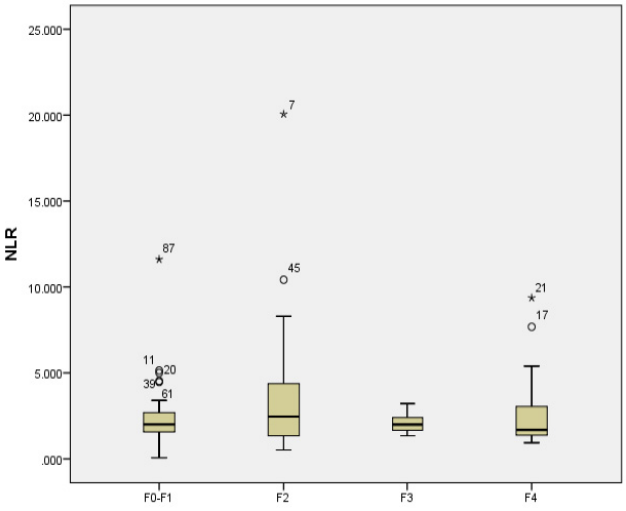


**Figure 6.** Distribution of NLR values in each degree of fibrosis


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**Table 2.** **Performance of different biomarkers in assessing the degree of fibrosis**

| Degree of Fibrosis | Biomarkers | Cut-off value | AUC (95%CI) | Sensitivity (%) | Specificity (%) | p |
|---|---|---|---|---|---|---|
| ≥F2 (F0-1 vs. F2-4) | APRI | 0.569 | 0.739 (0.632-0.847) | 70.6 | 71.4 | 0.000 |
| | FIB-4 | 1.143 | 0.699 (0.590-0.807) | 72.5 | 69 | 0.001 |
| | RPR | 0.052 | 0.686 (0.576-0.795) | 70.6 | 57 | 0.002 |
| | GPR | 0.367 | 0.782 (0.684-0.880) | 76.5 | 69 | 0.000 |
| | AAR | 0.617 | 0.575 (0.455-0.694) | 72.5 | 42.9 | 0.217 |
| ≥F3 (F0-2 vs. F3-4) | APRI | 0.765 | 0.797 (0.707-0.887) | 76.5 | 76.3 | 0.000 |
| | FIB-4 | 1.258 | 0.815 (0.724-0.906) | 82.4 | 71.2 | 0.000 |
| | RPR | 0.0635 | 0.791 (0.694-0.887) | 76.5 | 76.3 | 0.000 |
| | GPR | 0.559 | 0.823 (0.734-0.911) | 76.5 | 71.2 | 0.000 |
| | AAR | 0.746 | 0.664 (0.553-0.774) | 70.6 | 54.2 | 0.009 |
| F4 (F0-3 vs. F4) | APRI | 0.765 | 0.845 (0.766-0.924) | 85.2 | 74.2 | 0.000 |
| | FIB-4 | 1.561 | 0.850 (0.770-0.929) | 81.5 | 74.2 | 0.000 |
| | RPR | 0.063 | 0.821 (0.730-0.912) | 81.5 | 72.7 | 0.000 |
| | GPR | 0.698 | 0.902 (0.839-0.965) | 88.9 | 80.3 | 0.000 |
| | AAR | 0.875 | 0.705 (0.595-0.815) | 70.4 | 63.6 | 0.002 |

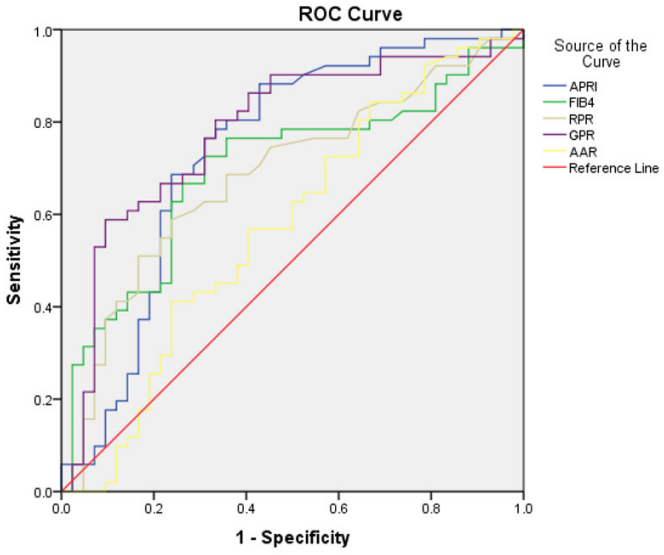


**Figure 7.** ROC curve analysis for significant fibrosis

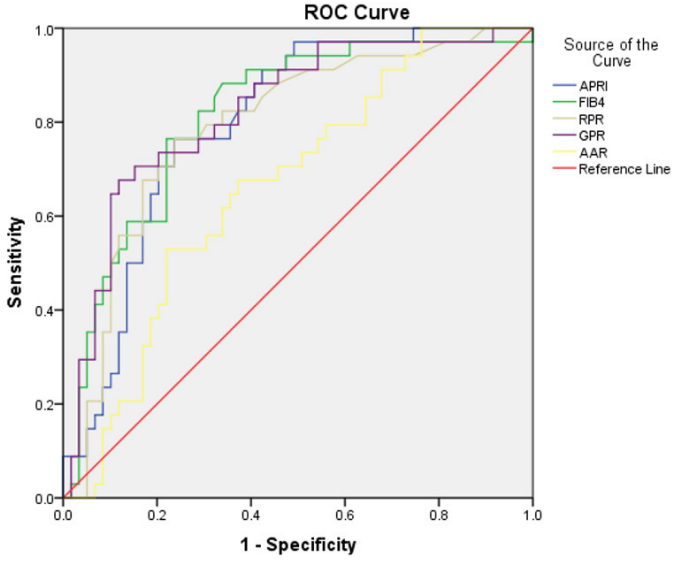


**Figure 8.** ROC curve analysis for severe fibrosis

**Table 3.** **Diagnostic performance of the optimal cut-off values**

| | APRI | FIB-4 | RPR | GPR | AAR |
|---|---|---|---|---|---|
| ≥F2 | | | | | |
| Cut-off value | 0.569 | 1.143 | 0.052 | 0.367 | - |
| Sensitivity | 70% | 72% | 70% | 76% | |
| Specificity | 71% | 69% | 57% | 69% | |
| PPV | 66.7% | 67.4% | 61.5% | 70.7% | |
| NPV | 75% | 74 % | 66.7% | 75% | |
| ≥F3 | | | | | |
| Cut-off value | 0.765 | 1.258 | 0.063 | 0.559 | 0.746 |
| Sensitivity | 76% | 82% | 76% | 76% | 70% |
| Specificity | 76% | 71% | 71% | 71% | 54% |
| PPV | 84.9% | 87.5% | 84% | 84% | 76.1% |
| NPV | 65% | 66.7% | 60.4% | 60.4% | 47% |
| F4 | | | | | |
| Cut-off value | 0.765 | 1.561 | 0.063 | 0.698 | 0.875 |
| Sensitivity | 85% | 81% | 81% | 80% | 70% |
| Specificity | 74% | 74% | 68% | 80% | 63% |
| PPV | 92.4% | 90.7% | 90% | 94.6% | 84% |
| NPV | 57.5% | 56.4% | 51.1% | 64.8% | 44.1% |

NPV: negative predictive value, PPV: positive predictive value.

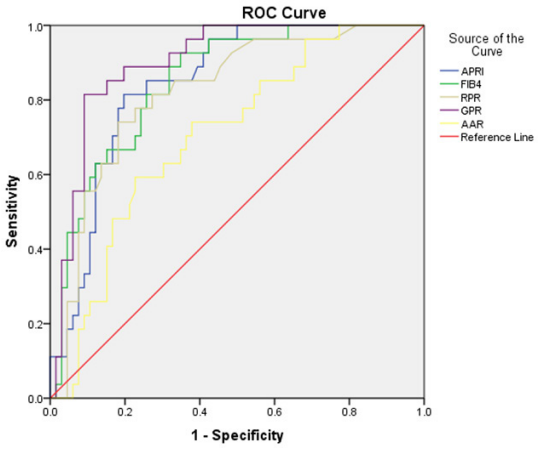


**Figure 9.** ROC curve analysis for cirrhosis

reliable, and accurate in assessing the presence of liver fibrosis. The paramount role of serological markers is especially evident in limited-resource settings.[12-13] APRI and FIB-4 were recommended by WHO to assess liver fibrosis in areas with limited resources, whereas TE was recommended in areas with adequate facilities.[1] However, the moderate performance of these modalities reported in a meta-analysis suggested their supplementary use rather than substitution for biopsy.[14] RPR was also proposed for its good predicting ability[7] comparable to FIB-4 and superior to APRI.[15]

While there was considerable overlap in the range of discriminating ability for all biomarkers included in the analysis, the decision to choose the best modality stood obscured. Consideration of sensitivity and specificity as a discrete index of accuracy is certainly not reasonable, given the comprehensive role expected from the modality of interest in hepatitis B management. Therefore, we pursued the approach of striking a balance between sensitivity and specificity by maximizing their summation. Another approach to consider is determining the optimal cut-off point by maximum AUC, which corresponds to the product of sensitivity and specificity.[16] GPR excelled in terms of AUC with moderate to borderline high diagnostic accuracy. Following the maximum summation approach, GPR emerged as the best predictor for liver fibrosis in significant fibrosis and cirrhosis, but not in severe fibrosis. It was noteworthy that APRI and FIB-4 outperformed GPR in only one particular degree of fibrosis.

In the face of heterogeneous evidence on the predictive role of GPR[17-19], a recent meta-analysis[20] may provide more refined insight on the comparability of current study results. The AUC values in this study were higher than the summary AUC for predicting significant fibrosis (0.733), severe fibrosis (0.777), and cirrhosis (0.796) in the meta-analysis. In contrary to the slight sensitivity predominant tendency of the selected cut-off value in this study, the pooled sensitivity for predicting significant fibrosis (0.49 [0.46-0.52]), severe fibrosis (0.69 [0.66-0.71]), and cirrhosis (0.68 [0.65-0.70]) was lower than that of pooled specificity.

The formulas from which APRI, FIB-4, and GPR score were derived from posed similarity in platelet variable and dissimilarity in liver test parameter variables. APRI and FIB-4 formulas incorporated AST and ALT levels, whilst the GPR formula incorporated GGT level. All of the enzymes have distinct physiology and kinetics, which may partially explain their variability and different application in assessing liver diseases.[21-22] Despite converging to the same endpoint of liver injury and mounting evidence on markers based on these markers, biological explanation for the utility of GGT in this context was lacking. The possibility for a complementary role of GPR score to the recommended APRI and FIB-4 remained arguably viable.

The differences in sample characteristics, fibrosis degree, and opted cut-off values should be taken into account when interpreting study result. The inevitable influence of genetic factors on hepatitis B infection outcome may affect study generalizability.[23]

## CONCLUSION

The diagnostic performance of GPR was better than other biomarkers and the diagnostic accuracy increased along with increasing degree of fibrosis. Future study on the applicability of GPR alongside APRI and FIB-4 in liver fibrosis assessment is needed.

## AUTHOR CONTRIBUTIONS

All authors contributed to the concept, design, definition of intellectual content, literature research, clinical studies, data analysis, manuscript preparation, editing, and review; all authors served as guarantors for this study.

## CONFLICT OF INTEREST

The authors have nothing to disclose.

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Nil.

## ETHICAL CONSIDERATIONS

Written ethical clearance was obtained from the Ethical Committee of Medical Faculty of Udayana University/Sanglah General Hospital and its copy was available to be reviewed by the Editor-in-Chief of this journal.

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