Performance of Red Cell Distribution Width-to-Platelet Ratio as a Screening Tool of Liver Fibrosis Based on Transient Elastography in Chronic Hepatitis B Infection

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ABSTRACT

Background: *Identifying liver fibrosis is crucial for initiating antiviral therapy for hepatitis B infection. Liver biopsy is the gold standard for assessing the degree of fibrosis. However, a liver biopsy is an invasive procedure that carries some risks. This study aimed to evaluate the diagnostic capabilities of the red cell distribution width-to-platelet ratio (RPR) and compare its efficacy for determining the degree of fibrosis in patients with chronic hepatitis B infection with that of the aspartate aminotransferase-to-platelet ratio index (APRI) and the Fibrosis-4 index (FIB-4).* ***Methods:*** *This was a retrospective study conducted on patients with chronic hepatitis B infection who had transient elastography results at the Gastroenterology Hepatology Clinic, Dr. Hasan Sadikin General Hospital, Bandung, between January and December 2024. Statistical analysis was performed using receiver operating characteristic curves to determine the diagnostic values and cutoff points of the RPR, APRI, and FIB-4 to detect liver fibrosis based on Transient Elastography in patients with Chronic Hepatitis B infection.* ***Results:*** *A total of 114 patients with chronic hepatitis B infection were included in this study (42 with significant fibrosis and 72 with nonsignificant fibrosis). The area under the curve (AUC) of the RPR was 0.873 ($p < 0.001$) with a cutoff point of >0.0538, whereas the AUCs of the APRI and FIB-4 were 0.833 ($p < 0.001$) and 0.746 ($p < 0.001$), respectively.* ***Conclusion:*** *The RPR has a higher diagnostic performance than the APRI and is superior to the FIB-4 in assessing the degree of fibrosis in patients with chronic hepatitis B infection. The RPR is a simple and cost-effective test and has the potential to be a screening tool for patients with hepatitis B infection.*

Keywords: *hepatitis B, fibrosis, transient elastography, RPR, red cell distribution width.*

INTRODUCTION

Hepatitis B virus (HBV) infection is a significant public health issue globally, with prevalence varying according to geographic region. The prevalence is categorized as high (≥8%), intermediate (2%–7%), or low (<2%). According to the Ministry of Health of the Republic of Indonesia, the prevalence of hepatitis B surface antigen (HBsAg) in Indonesia was 7.1% in 2013, indicating a moderate to high prevalence of HBV infection in Indonesia.[1, 2] Chronic HBV infection can progress to fibrosis, decompensated liver cirrhosis, or even hepatocellular carcinoma if not properly managed.[3]

Determining the severity of fibrosis is crucial for initiating therapy for chronic HBV infection. Liver tissue can be histologically examined using invasive methods, such as liver biopsy, which is considered the gold standard for assessing liver histology. However, this invasive procedure is

associated with many complications, such as pain and hemorrhage.[3] Therefore, various noninvasive methods have been developed. Transient elastography (TE, FibroScan©) is one of the noninvasive methods to assess liver stiffness and determine liver fibrosis. This procedure is simple but has low sensitivity in patients with obesity and ascites.[4] In 2017, the Indonesian Association for the Study of the Liver (Ina-ASL) published guidelines for the management of chronic HBV infection, indicating that therapy should be started in patients with chronic HBV infection with significant fibrosis, defined as liver biopsy with METAVIR score ≥ 2 or Ishak score ≥ 3 or liver stiffness ≥ 8 kPa assessed using TE.[3]

Various laboratory tests have been developed to predict liver fibrosis, such as the aspartate aminotransferase-to-platelet ratio index (APRI), which has been validated for early screening of chronic HBV infection in areas with limited resources, and the Fibrosis-4 index (FIB-4).[5] Additionally, the red cell distribution width (RDW) to platelet ratio (RPR) is associated with liver fibrosis. The RDW reflects the variability in red blood cell volume and is routinely reported in complete blood count tests. Increased RDW is associated with chronic inflammatory conditions, including chronic liver diseases.[6,7] Platelets are an indicator of liver fibrosis in chronic HBV infection.[8,9] Previous studies have shown that the RPR is associated with liver fibrosis in chronic HBV infection.[10-12] Furthermore, the RPR is one of the most easily accessible laboratory tests in daily clinical practice.[11] Therefore, this study aimed to investigate the diagnostic accuracy of the RPR for significant liver fibrosis and compare it with the APRI and FIB-4.

METHODS

This was a diagnostic study of patients with chronic HBV infection conducted at the Gastroenterology and Hepatology Clinic at Hasan Sadikin General Hospital, Bandung, Indonesia, between January and December 2024. Data were collected from the medical records and analyzed. The inclusion criteria were patients with chronic HBV infection, those aged >18 years, those with positive HBsAg test results for a minimum of 6 months, and those who had never undergone hepatitis B therapy. The exclusion criteria were patients with TE data obtained 1 week or more after RDW and platelet examination, those with hepatitis C virus or human immunodeficiency virus coinfection, and those with other comorbidities, such as autoimmune liver disease, cholestatic liver disease, metabolic dysfunction-associated liver disease, haematological disorder, infection, diabetes mellitus, chronic kidney disease, bone disease, hormonal disorder, and pregnancy.

This study has been approved by the Ethical Committee of the Faculty of Medicine, Universitas Padjadjaran, Bandung.

The RPR, APRI, and FIB-4 values were assessed and compared with the TE results. The RPR was calculated as follows: RDW-CV(%)/PLT(10^3/mcL), the APRI was calculated as follows: (AST/ULN) × 100/PLT(10^3/mcL), and the FIB-4 was calculated as follows: age(years) × AST(U/L)/[PLT(10^3/mcL) × ALT ½(U/L)]. The TE results were classified into 2 groups according to the Ina-ASL 2017 guidelines: significant fibrosis (TE ≥ 8 kPa) and nonsignificant fibrosis (TE < 8 kPa). Data were analyzed using the receiver operating characteristic (ROC) curve to determine the area under the curve (AUC), cutoff point, sensitivity, specificity, positive predictive value, and negative predictive value of RPR, APRI, and FIB-4. All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 183 patients diagnosed with chronic HBV infection at the Gastroenterology and Hepatology Clinic, Hasan Sadikin General Hospital, Bandung, Indonesia, between January and December 2024, were enrolled in this study. After applying the exclusion criteria, 114 patients were included in this study. Of the 114 patients, 54 were males, and 60 were females, with a median age of 34 years (range 19–77 years). The median RPR was 0.0504 (range 0.0283–0.0975). The baseline characteristics are shown in **Table 1**.

The median RPR was higher in patients with significant fibrosis than in those with nonsignificant fibrosis (0.0627 vs. 0.0469) ($p < 0.001$). Similarly, the median APRI and FIB-4

Table 1. Baseline Characteristics of Patients with Chronic HBV Infection

Characteristics	N = 114	
	n (%)	Median (min–max)
Age (years)		34 (19–77)
Sex		
Male	54 (47.4)	
Female	60 (52.6)	
RDW (%)		13.0 (11.2–19.5)
Platelet (×10^3 /mcL)		262 (146–441)
RPR		0.0504 (0.028 –0.0975)
APRI		0.253 (0.104–0.799)
FIB-4		0.686 (0.224–2.446)
Liver stiffness measurement (kPa)		5.9 (2.5–25.1)
TE results		
≥ 8 kPa	42 (36.8)	
< 8 kPa	72 (63.2)	

Abbreviations: RDW: red cell distribution width; RPR: red cell distribution width-to-platelet ratio; APRI: aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index

values were higher in patients with significant fibrosis than in those with nonsignificant fibrosis (0.381 vs. 0.214, p < 0.001; 1.032 vs. 0.607, p < 0.001, respectively). **Table 2** shows the associations between the RPR, APRI, and FIB-4 and liver fibrosis.

Table 3 and **Figure 1** show the AUCs and ROC curves of the RPR, APRI, and FIB-4. The diagnostic performance of the RPR and APRI for identifying significant fibrosis was favorable, with AUCs of 0.873 and 0.833, respectively. The FIB-4 was less favorable, with an AUC of 0.745. No significant difference was observed between the APRI and RPR in detecting significant liver fibrosis (p = 0.487). A significant difference was observed between the RPR and FIB-4 in

Table 2. Association between the RPR, APRI, and FIB-4 and Liver Fibrosis

Variable	Liver Fibrosis		*p*-value
	Significant (≥8 kPa) n=42	Nonsignificant (<8 kPa) n=72	
Age (years)	40 (19–77)	32 (19–74)	0.037*
Sex, n (%)			
Male	26 (61.9)	28 (38.9)	0.018*
Female	16 (38.1)	44 (61.1)	
RDW (%)	13.2 (12.0–19.5)	12.9 (11.2–16.4)	0.006*
Platelet (×10^3 /mcL)	223 (146–417)	279 (178–441)	<0.001*
RPR	0.0627 (0.0422–0.0975)	0.0469 (0.0283–0.0781)	<0.001*
APRI	0.381 (0.104–0.799)	0.214 (0.112–0.727)	<0.001*
FIB-4	1.032 (0.267–2.446)	0.607 (0.224–1.758)	<0.001*

Abbreviations: RDW: red cell distribution width; RPR: red cell distribution width-to-platelet ratio; APRI: aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index
*p < 0.05

Table 3. Validity of RPR, APRI, and FIB-4 for the Prediction of Significant Liver Fibrosis

	AUC (95% CI)	SE	*p*-value	Difference between RPR and APRI and FIB-4 *p*-value	Difference between APRI and FIB-4 *p*-value
RPR	0.873 (0.798–0.928)	0.037	**<0.001***		
APRI	0.833 (0.751–0.896)	0.044	**<0.001***	0.487	
FIB-4	0.745 (0.655–0.822)	0.053	**<0.001***	0.048	0.201

Abbreviation: RPR: red cell distribution width-to-platelet ratio; APRI: aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; AUC: area under the curve; SE: standard error; CI: confidence interval
*p < 0.05

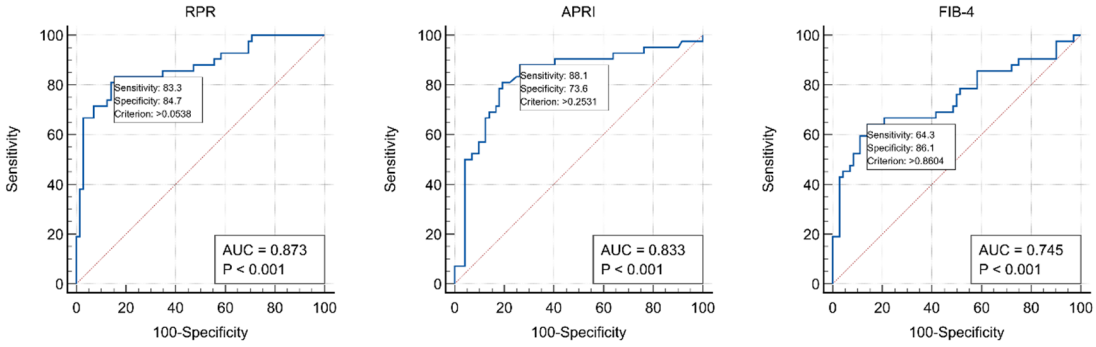

Figure 1. ROC Curves of RPR, APRI, and FIB-4 for the Prediction of Significant Liver Fibrosis

detecting significant liver fibrosis (p = 0.048). However, no significant difference was observed between the APRI and FIB-4 (p = 0.201).

The ideal cutoff point of the RPR for predicting significant liver fibrosis based on the ROC analysis was >0.0538, with sensitivity and specificity of 83.3% and 84.7%, respectively. Regarding the APRI, when the cutoff point was >0.253, the sensitivity and specificity were 88.1% and 73.6%, respectively. Regarding the FIB-4, when the cutoff point was >0.860, the sensitivity and specificity were 64.3% and 86.1%, respectively. According to the World Health Organization (WHO) guidelines, when >0.500 was taken as an ideal cutoff point of the APRI, the sensitivity and specificity were 26.2% and 95.8%, respectively. When >1.450 was taken as the ideal cutoff point of the FIB-4, the sensitivity and specificity were 31.0% and 97.2%, respectively. **Table 4** shows the diagnostic performance of the RPR, APRI, and FIB-4.

DISCUSSION

This study showed that the RPR and APRI had high diagnostic performance in identifying significant fibrosis, whereas the FIB-4 had a moderate diagnostic performance. Regarding the RPR, a cutoff value > 0.0538 provided good accuracy (84.7%), high specificity (84.7%), and high negative predictive value (89.7%), indicating the diagnostic capabilities of the RPR to identify patients with significant fibrosis. Meanwhile, cutoff values for the APRI and FIB-4 of >0.253 and >0.860, respectively, were identified. When adjusting the cutoff value for the APRI to >0.5 according to the WHO guidelines, the APRI showed a decrease in sensitivity (88.1% to 26.2%) and an increase in specificity (73.6% to 95.8%). Similarly, when the cutoff value for the FIB-4 was adjusted to >1.45, the FIB-4 showed a decrease in sensitivity (64.3% to 31.0%) and an increase in specificity (86.1% to 97.2%). This indicates that, at a higher cutoff value, both

Table 4. Diagnostic Performance of the RPR, APRI, and FIB-4 for the Prediction of Significant Liver Fibrosis

	Cut-off	Accuracy (%)	Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR−
RPR	>0.0538	84.2	83.3	84.7	76.1	89.7	5.45	0.20
APRI	>0.253	78.9	88.1	73.6	66.1	91.4	3.34	0.16
	>0.500[a]	71.9	26.2	95.8	78.6	69.0	6.29	0.77
FIB-4	>0.860	78.1	64.3	86.1	73.0	80.5	4.63	0.41
	>1.450[b]	72.8	31.0	97.2	86.7	70.7	11.14	0.71

Abbreviations: RPR: red cell distribution width-to-platelet ratio; APRI: aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; Sn; sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR−: negative likelihood ratio

[a] cut-off value of the APRI recommended by WHO[5]

[b] cut-off value of the FIB-4 recommended by WHO[5]

APRI and FIB-4 show limited use as a screening tool, as it has a high false negative, but may be usable in conditions when the diagnosis of significant fibrosis is ambiguous. These findings are consistent with those reported by Chen et al., who showed that the RPR was comparable with the APRI and FIB-4 in identifying significant fibrosis.[13] However, these findings contradict those reported by Yu et al., who concluded that the APRI had a higher diagnostic value in identifying significant fibrosis than the RPR and FIB-4.[11]

At the time this article was written, the WHO had released updated 2024 guidelines on the management of hepatitis B in response to the stalled global elimination efforts of the virus, especially in countries with limited resources. The guideline emphasizes the simplification of diagnostic and treatment criteria, where significant fibrosis can be identified using an APRI value > 0.5 or liver stiffness > 7.0 kPa, whereas cirrhosis can be diagnosed with an APRI value > 1.0 or liver stiffness > 12.5 kPa.[14] However, these guidelines remain a topic of debate among liver organizations worldwide and have not yet been adopted into national protocols, including those of Indonesia. This indicates that the RPR holds significant potential for the early screening of patients with chronic hepatitis B.

This study has some limitations that may have affected the results. First, this was a retrospective study using data obtained from medical records. Second, this was a single-centre study.

CONCLUSION

The RPR has a remarkable diagnostic performance in identifying significant liver fibrosis in chronic HBV infection compared with the APRI and is superior to the FIB-4. The RPR offers a good balance between sensitivity and specificity and satisfactory predictive values. Besides being cost-effective and easy to administer, the RPR holds promise as an initial screening tool or as part of a more comprehensive diagnostic approach for liver fibrosis, facilitating timely and effective interventions to prevent disease progression.

REFERENCES

1. Muljono D. Epidemiology of hepatitis B and C in the Republic of Indonesia. Euroasian J Hepatogastroenterol. 2017;7(1):55-9.
2. Yano Y, Utsumi T, Lusida MI, et al. Hepatitis B virus infection in Indonesia. World J Gastroenterol. 2015;21(38):10714-20.
3. Rinaldi Lesmana C, Hasan I, Alvani Gani R, et al. National consensus on hepatitis B management. Jakarta: Indonesian Association for the Study of the Liver; 2017.
4. Singh K, Lamba M, Kumar V, et al. A comparative study of novel fibrosis index and other non-invasive serum indices for predicting fibrosis in patients of chronic liver disease. Cureus. 2024;16(7):e63658.
5. WHO Guidelines Approved by the Guidelines Review Committee. Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015.
6. Wang J, Huang R, Yan X, et al. Red blood cell distribution width: a promising index for evaluating the severity and long-term prognosis of hepatitis B virus-related diseases. Dig Liver Dis. 2020;52(4):440-6.
7. Aslam H, Oza F, Ahmed K, et al. The role of red cell distribution width as a prognostic marker in chronic liver disease: a literature review. Int J Mol Sci. 2023;24(4).
8. Lim HI, Cuker A. Thrombocytopenia and liver disease: pathophysiology and periprocedural management. Hematology Am Soc Hematol Educ Program. 2022;2022(1):296-302.
9. Mitchell O, Feldman DM, Diakow M, et al. The pathophysiology of thrombocytopenia in chronic liver disease. Hepat Med. 2016;8:39-50.
10. Chen M, Wu Z, Du Z, et al. Diagnostic accuracy of red blood cell distribution width to platelet ratio for predicting liver fibrosis in patients with chronic hepatitis B: a meta-analysis. Gastroenterol Hepatol. 2022;45(5):361-72.
11. Yu H, Li C, Li M, et al. Optimal use of red cell volume distribution width-to-platelet ratio to exclude cirrhosis in patients with chronic hepatitis B. Liver Res. 2023;7(3):244-51.
12. Cai Y, Liu D, Cui J, et al. Diagnostic accuracy of red blood cell distribution width to platelet ratio for predicting staging liver fibrosis in chronic liver disease patients: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98(14):e15096.
13. Lee HW, Kang W, Kim BK, et al. Red cell volume distribution width-to-platelet ratio in assessment of liver fibrosis in patients with chronic hepatitis B. Liver Int. 2016;36(1):24-30.
14. WHO Guidelines Approved by the Guidelines Review Committee. Guidelines for the prevention, care, and treatment of people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.