

Red Cell Distribution Width to Platelet Ratio is Not Inferior than Aspartate Aminotransferase to Platelet Ratio Index Score in Predicting Liver Fibrosis in Chronic Hepatitis B Patients at Sanglah General Hospital Denpasar

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ABSTRACT

Background: Red cell distribution width to platelet ratio (RPR) is known to be associated with a degree of liver fibrosis in patients with hepatitis B. This study aims to compare the under curve area, sensitivity, specificity, positive predictive value, and negative predictive value between RPR and aspartate aminotransferase to platelet ratio index (APRI) score with degree of fibrosis.

Method: This study is a retrospective study, data taken from medical records of all chronic hepatitis B patients examined by Fibroscan at Sanglah General Hospital Denpasar, Bali from January 2016 to February 2018.

Results: Ninety eight (98) patients with chronic hepatitis B, 81 patients were recovered after exclusion of patients with chronic kidney disease, malignancy, and dengue haemorrhagic fever (DHF). In receiver operating characteristic (ROC) analysis, obtained area under the ROC curve (AUC) at RPR of 0.816, and at APRI score 0.797. In RPR with cut off 0.066 the sensitivity was 76.9%, specificity 78.6%, PPV 79.5%, NPV 73.8%. While APRI score with cut off 0.85 got 69.2% sensitivity, specificity 76.2%, positive predictive value (PPV) 73.0%, and negative predictive value (NPV) 72.7%. According to Kappa test, we found kappa coefficient 0.653 ($p < 0.05$).

Conclusion: In predicting severe liver fibrosis in chronic hepatitis B patients, RPR is not inferior than APRI score, and may be used as a diagnostic marker, with 65.3% conformity.

Keywords: aspartate aminotransferase to platelet ratio index (APRI) score, red cell distribution width to platelet ratio (RPR), Chronic hepatitis B, liver fibrosis

ABSTRAK

Latar belakang: Red cell distribution width to platelet ratio (RPR) diketahui terkait dengan tingkat fibrosis hati pada pasien dengan hepatitis B. Penelitian ini bertujuan untuk membandingkan area under curve (AUC), sensitivitas, spesifisitas, nilai prediksi positif, dan nilai prediksi negatif antara RPR dan skor aspartate aminotransferase to platelet ratio index (APRI) dalam memprediksi derajat fibrosis.

Metode: Penelitian ini merupakan studi retrospektif, data yang diambil dari rekam medis semua pasien hepatitis B kronis yang diperiksa menggunakan Fibroscan di Rumah Sakit Sanglah General Denpasar, Bali mulai Januari 2016 sampai Februari 2018.

Hasil: Sembilan puluh delapan (98) pasien dengan hepatitis B kronis, 81 pasien diambil sebagai sampel setelah dieksklusi pasien dengan penyakit ginjal kronis, keganasan, dan demam berdarah dengue (DBD). Dalam analisis receiver operating characteristic (ROC) diperoleh AUC di RPR sebesar 0,816, dan pada skor APRI 0,797. Apabila RPR dipakai cut off 0,066 sensitivitasnya adalah 76,9%, spesifisitas 78,6%, positive predictive value (PPV) 79,5%, negative predictive value (NPV) 73,8%. Sedangkan skor APRI dengan cut off 0,85 mendapat sensitivitas 69,2%, spesifisitas 76,2%, PPV 73,0%, dan NPV 72,7%. Pada uji Kappa, kami menemukan koefisien kappa 0,653 ($p < 0,05$).

Simpulan: Dalam memprediksi fibrosis hati yang parah pada pasien hepatitis B kronis, RPR tidak lebih inferior dibandingkan skor APRI, dan dapat digunakan sebagai penanda diagnostik, dengan kesesuaian 65,3%.

Kata kunci: skor aspartate aminotransferase to platelet ratio index (APRI), red cell distribution width to platelet ratio (RPR), hepatitis B kronis, fibrosis hati

INTRODUCTION

Liver fibrosis is a chronic complication of hepatitis B infection. This condition remains silent until the patient falls to decompensated cirrhosis, which is the third leading cause of death after cardiovascular disease and cancer.¹ Early detection is very important in the management of chronic hepatitis B, in order to determine therapy and also improves prognosis.² Histopathological examination of liver tissue is still a gold standard of the diagnosis of fibrosis and cirrhosis of the liver. However, this method is an invasive procedure and tends to be abandoned lately. Various non-invasive methods were developed as an attempt to replace liver biopsy tests, such as ultrasonography, transient elastography (TE), and biochemical markers, such as aspartate aminotransferase to platelet ratio index (APRI), gamma glutamyl transpeptidase to platelet ratio (GPR), and fibrosis-4 (FIB-4).³

According to the World Health Organization (WHO) guidelines in 2015, APRI has recommended as a non-invasive method to predict liver cirrhosis in areas with limited resources, whereas TE is recommended in areas with adequate facilities.² APRI with a value of ≥ 2 has been validated to detect liver cirrhosis. While TE is an examination using low frequency shear waves to assess liver stiffness.^{4,5} Red cell distribution width to platelet ratio (RPR) is currently under investigation because it is thought to be associated with a degree of liver fibrosis. The RPR was first proposed by Chen et al in 2013, a prediction model consisting of red cell distribution width (RDW) and platelet components known to be associated with a degree of liver fibrosis in a multivariate analysis.⁶ In another study, RPR can also predict liver fibrosis in Primary Biliary Cirrhosis populations with 46.7% sensitivity and 96.4%

specificity.⁷ In terms of cost, RPR is cheaper than APRI because it only requires one panel of routine blood examination. However, its performance when compared with APRI is still not much studied. In this study we will investigate the accuracy of diagnosis of liver fibrosis by using RPR and APRI and compare the two methods.

METHOD

This study was conducted retrospectively, from January 2016 to February 2018. Data were taken from medical record and Fibroscan register Sanglah General Hospital Bali which fulfilled the inclusion criteria ; all chronic hepatitis B patients aged > 12 years with HBsAg positivity for 6 months or more, who came to Sanglah General Hospital and performed Fibroscan examination. Exclusion criteria in this study were the presence of HIV and hepatitis C coinfection, hepatocellular carcinoma (HCC), chronic renal disease, idiopathic thrombocytopenia purpura and dengue hemorrhagic fever.

In subjects meeting the inclusion criteria, RPR and APRI were evaluated with medical record tracking, and compared with Fibroscan examination results. RDW, platelet, aspartate aminotransferase (AST), and Fibroscan data were taken at the same or the longest period within 30 days. RPR is calculated by the formula = $RDW(\%)/Plt(10^9/L)$, whereas APRI = $AST(ULN) \times 100/Plt(10^9/L)$. Fibroscan examination results were classified into 2 groups; mild-moderate fibrosis (metavir F0-2) and severe fibrosis (metavir F3-4). Then the data was analysed using receiver operating characteristic (ROC) curve to determine the area under the ROC curve (AUC), cut-off point, sensitivity, specificity, positive

predictive value (PPV), and negative predictive value (NPV) between APRI and RPR. There were also Kappa tests to determine the suitability between RPR and APRI in diagnosing severe fibrosis. Analysis was performed using SPSS Statistics version 23 (IBM Corporation, New York, NY).

RESULTS

In January 2016 up to February 2018 there were 98 chronic hepatitis B patients examined by Fibroscan. After exclusion of patients with chronic kidney disease, malignancy, and DHF, 81 samples were obtained in the study. The subjects consisted of 59 men and 22 women, aged 15-72 years with an average age of 43 years. The results of Fibroscan examination were 42 persons with mild-moderate fibrosis (metavir F0-2) and 39 severe fibrosis (metavir F3-4). The average RDW value of the study subjects was $13.78\% \pm 2.69$. The average platelet count was $187.429/\text{mm}^3 \pm 101.601$. The ratio of RDW/platelet obtained an average of 0.16 ± 0.45 .

Table 1. Characteristic of the subjects

Variables	n = 81
Sex, n (%)	
Male	59 (72,8)
Female	22 (27,2)
Age (years)	43 ± 12,36*
Fibroscan result, n (%)	
F0	23 (28,4)
F1	15 (18,5)
F2	4 (4,9)
F3	4 (4,9)
F4	35 (43,2)
Aspartate aminotransferase (AST)	41,70 (8,80 – 532,10)**
Platelet	187,43 ± 101,60*
Red cell distribution width (RDW)	12,76 (11,22 – 24,92)**
AST to Platelet Ratio Index (APRI) score	0,72 (0,1 – 28,6)**
RDW to platelet ratio (RPR)	0,06 (0,03 – 4,09)**

*mean, SD; **median, minimum-maximum

In ROC analysis in Figure 1, we can see that both RPR and APRI curves are on the left side of the diagonal line. The AUC of RPR in predicting severe fibrosis was found 0,816 ($p < 0,05$) which tends to be no different than APRI with AUC 0,797 ($p < 0,05$) (Figure 2). In RPR with the cut off 0.063 the sensitivity was 76.9%, specificity 78.6%, PPV 79.5%, NPV 73.8% for predicting severe liver fibrosis. While APRI with the cut off 0.85 obtained 69.2% sensitivity, specificity 76.2%, PPV 73.0%, and NPV 72.7%. Furthermore, in Kappa test, the coefficient of Kappa 0.653 ($p < 0.05$) as shown in Figure 3, which means the match between RPR and APRI in predicting severe fibrosis is 65.3%.

DISCUSSION

Some non-invasive markers to assess the degree of liver fibrosis in chronic hepatitis B patients are widely proposed and validated.³ This is due to the importance of in the use of non-invasive blood markers such as APRI, GRP, FIB-4, or RPR for determining treatment and prognosis in limited area setting. APRI was first proposed by Wai et al in 2003 to predict liver fibrosis and cirrhosis in chronic hepatitis C patients.⁸ This simple examination is preferred because it is cheap and easy to apply especially as an early screening of cirrhosis in areas with limited resources. Then several studies on its use in chronic hepatitis B infection were done, until finally APRI had recommended its use by WHO in 2015. However, when compared with other non-invasive markers, APRI is more inferior than the markers FIB-4 and GPR.³

A study conducted by Chen et al in 2013 stated that RDW and platelet levels correlated with the degree of liver fibrosis in chronic hepatitis B patients, which then made a prediction model of RPR.⁶ In another study, there was also an increase in RDW in chronic renal disease, systemic lupus erythematosus (LES), and acute myocardial infarction.⁹ RDW also plays a prognostic factor, which the increase in RDW is positively correlated with cirrhosis based on Child-Pugh score and increased mortality of patients with coronary heart disease, with an unexplained mechanism.^{10,11}

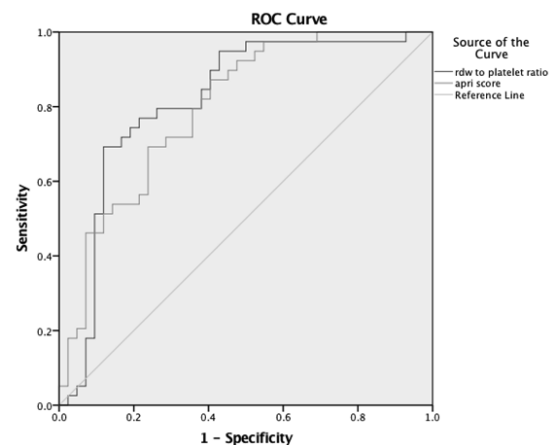


Figure 1. Receiver operating characteristic (ROC) curve

Several previous studies have suggested that RPR is superior to APRI in predicting significant liver fibrosis.^{3,6} Comparing to FIB-4 and GPR, RPR has a comparable AUC in predicting significant fibrosis (metavir $F \geq 2$).³ While in this study obtained AUC of RPR and APRI did not significantly different

Test result variable (s)	Area	Std.error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence interval	
				Lower bound	Upper bound
Red cell distribution width (RDW) to platelet ratio	.816	.050	.000	.717	.914
AST to platelet ratio index (APRI) score	.797	.049	.000	.702	.893

Figure 2. Area under the curve (AUC)

	Value	Standard error ^a	Approximate T ^b	Significance	
Measure of agreement	Kappa	.653	.084	5.886	.000
N of valid cases		81			

^aNot assuming the null hypothesis

^bUsing the asymptotic standard error assuming the null hypothesis

Figure 3. Kappa test result for RDW platelet ratio (RPR) and aminotransferase to platelet ratio index (APRI)

in predicting liver fibrosis in chronic hepatitis B patients. The AUC stated that both APRI and RPR have moderate accuracy in diagnosing severe fibrosis (metavir F3-4). So these two predictive models can both be used as a diagnostic tool.

The differences of sample characteristics, differences of cut off used, and some weaknesses in this study may be the cause of different results obtained from previous research. The weaknesses in this study were retrospective study design, no direct interviews on the subjects, and no histopathological examination of the liver as a gold standard diagnosis of liver fibrosis which allowed less representative results. Evaluation based on HBV DNA and HBeAg virus counts was also not done because of the limited data available. However, RPR is comparable to APRI in predicting severe liver fibrosis in chronic hepatitis B patients and may be used as a non-invasive marker with moderate accuracy.

CONCLUSION

In predicting severe liver fibrosis in chronic hepatitis B patients, RPR is not less inferior than APRI and can be used as one of the non-invasive methods in areas with limited resources.

REFERENCES

1. Nurdjanah S. Sirosis Hati. In: Alwi I, Salim S, Hidayat R, Kurniawan J, Tapahary DL, eds. Penatalaksanaan di bidang Ilmu Penyakit Dalam Panduan Praktik Klinis. 6th ed. Jakarta: Interna Publ 2015.p.1978–83.
2. World Health Organization. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. WHO 2015.p.66.
3. Zhu MY, Zou X, Li Q, Yu DM, Yang ZT, Huang D, et al. A novel non-invasive algorithm for the assessment of liver fibrosis in patients with chronic hepatitis B virus infection. *J Viral Hepat* 2017;1:42–9.
4. Yu JH, Lee J II. Current role of transient elastography in the management of chronic hepatitis B patients. *Ultrasonography* 2017;36:86–94.

5. Castera L, Chan HLY, Afdhal N, Bedozza P, Friedrich-Rust M, Han K-H, et al. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015;63:237–64.
6. Chen B, Ye B, Zhang J, Ying L, Chen Y. RDW to platelet ratio: a novel non-invasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis B. *PLoS One* 2013;8:1–8.
7. Wang H, Xu H, Wang X, Wu R, Gao X, Jin Q, et al. Red blood cell distribution width to platelet ratio is related to histologic severity of primary biliary cirrhosis. *Medicine* 2016;95:e3114.
8. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple non-invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;38:518–26.
9. Xu WS, Qiu XM, Ou Q, Liu C, Lin JP, Chen HJ, et al. Red blood cell distribution width levels correlate with liver fibrosis and inflammation. *Medicine* 2015;94:e612.
10. Hu ZD, Sun Y, Wang Q, Huang Y, Liu X, Ding C, et al. Red blood cell distribution width is a potential prognostic index for liver disease. *Clin Chem Lab Med* 2013;51:1403–8.
11. Chen PC, Sung FC, Chien KL, Hsu HC, Su TC, Lee YT. Red blood cell distribution width and risk of cardiovascular events and mortality in a community cohort in Taiwan. *Am J Epidemiol* 2010;171:214–20.