Aspartate Aminotransferase to Platelet Ratio Index and FibroScan for Predicting Liver Fibrosis with Chronic Hepatitis B

Elias Tarigan, Rustam Effendi Yusuf, Leonardo Basa Dairy, Juwita Sembiring, Mabel HM Sihombing, Gontar Alamsyah Siregar, Lukman Hakim Zain
Division of Gastroentero-hepatology, Department of Internal Medicine
Faculty of Medicine, University of Sumatera Utara/Adam Malik Hospital, Medan

ABSTRACT

Background: *Non-invasive test have been constructed and evaluated mainly for binary diagnoses. The accuracy of non-invasive tests such as aspartate aminotransferase to platelet ratio index (APRI) and transient elastography/FibroScan should be evaluated especially in clinical practice. The aim of the study was to evaluate the accuracy of detailed fibrosis classification available for APRI and FibroScan to liver biopsy in chronic hepatitis B patients.*

Method: *A cross sectional study was conducted in 51 patients with chronic hepatitis B. The patients underwent laboratory test, FibroScan and liver biopsy between April 2011 and July 2013 at Adam Malik Hospital, Medan. Liver biopsy was assessed based on the METAVIR score. Area under receiver operating characteristic curve (AUROC) predictive value was used to evaluate the accuracy of APRI and FibroScan. All data were analyzed using SPSS 20.0.*

Results: *APRI versus METAVIR diagnosed severe fibrosis and cirrhosis with sensitivity 40% and specificity 83.9%, positive predictive value (PPV) 61.5%, negative predictive value (NPV) 68.4%, positive likelihood ratio (LR) 2.48 and negative LR 0.72 with diagnostic accuracy 66.7%. The AUROC value was 0.619 (95% CI = 0.446 – 0.715); kappa = 0.255; $p > 0.05$. FibroScan versus METAVIR predictive value with sensitivity 75% and specificity 67.6% were PPV 60%, NPV 67.7%, positive LR 2.31 and negative LR 0.36 with diagnostic accuracy 70.6%. The AUROC value was 0.714 (95% CI = 0.567–0.861); kappa 0.409; $p < 0.05$.*

Conclusion: *FibroScan has better accuracy than APRI for predicting severe fibrosis and cirrhosis in patients with chronic hepatitis B.*

Keywords*: APRI, FibroScan, liver biopsy, chronic hepatitis B*

ABSTRAK

Latar belakang: *Pemeriksaan non-invasif berkembang dan dievaluasi dengan baik terutama untuk diagnosis biner. Keakuratan pemeriksaan aspartate aminotransferase to platelet ratio index (APRI) dan transient elastography/FibroScan perlu dilakukan khususnya dalam praktis klinis. Tujuan penelitian ini adalah untuk menilai keakuratan derajat fibrosis hati berdasarkan APRI dan FibroScan terhadap biopsi hati pada pasien dengan penyakit hepatitis B kronik.*

Metode: *Penelitian potong lintang dilakukan pada 51 pasien dengan penyakit hepatitis B kronik. Dilakukan pemeriksaan laboratorium, FibroScan dan biopsi hati pada masing-masing pasien sejak April 2011 - Juli 2013 di Rumah Sakit Adam Malik, Medan. Seluruh data di analisa untuk menghitung nilai APRI dan FibroScan; biopsi hati dianalisa berdasarkan skor METAVIR. Nilai prediktif AUROC digunakan untuk menilai akurasi APRI dan FibroScan dalam mendiagnosis fibrosis-sirosis kronik. Data dianalisis dengan menggunakan SPSS 20.*

Hasil: *APRI terhadap METAVIR mendiagnosis fibrosis berat dan sirosis dengan sensitivitas 40%, spesifitas 83,9%, nilai prediktif positif (NPP) 61,5%, nilai prediktif negatif (NPN) 68,4%, likelihood ratio (LR) positif 2,48*

dan LR negatif 0,72 dengan akurasi diagnostik 66,7%. Nilai AUROC 0,619 (95% CI = 0,457–0,782); p > 0,05; kappa = 0,255; p > 0,05. Nilai prediktif FibroScan terhadap METAVIR dalam diagnosis fibrosis berat dan sirosis dengan sensitivitas 75% dan spesifitas 67,6% adalah NPP 60%, NPN 67,7%, LR positif 2,31 dan LR negatif 0,36 dengan akurasi diagnostik 70,6%. Nilai AUROC 0,714 (95% CI = 0,567–0,861); kappa = 0,409; p < 0,05.

Simpulan: *Akurasi FibroScan lebih baik dibandingkan dengan APRI dalam memprediksi fibrosis berat - sirosis pada pasien dengan penyakit hepatitis B kronik.*

Kata kunci: *APRI, FibroScan, biopsi hati, hepatitis B kronik*

INTRODUCTION

Early detection of liver fibrosis is essential as a leading point to direct further treatment for patients with chronic viral hepatitis. In those patients, examinations to determine the degree of severity for liver fibrosis have been recommended by the American Association for Study of Liver Disease (AASLD) and European Association for Study of Liver (EASL) in order to recognize those who are at risk for developing chronic liver disease as well as their anti-viral treatment.[1-3]

Liver biopsy is still the gold standard procedure to determine the degree of severity for liver fibrosis in spite of its limitations that have been reported since it is an invasive procedure which may have sampling error, inter- and intra-observer variation and may cause inconvenience for the patients when the procedure should be repeated. As there are many limitations of biopsy procedure, alternative non-invasive procedures are explored in order to determine the accurate and acceptable diagnosis of liver fibrosis. Some simple serum markers have widely reported as the substitutes for assessing liver fibrosis, i.e. aspartate transaminase to alanine transaminase ratio (AAR), aspartate aminotransferase to platelet ratio index (APRI), age platelet count index (API) and many other markers. Among all of the markers, APRI has been extensively used since it is simple and inexpensive.[4-8]

Recently, the measurement of liver stiffness using transient elastrography such as FibroScan has been proven in many studies as an accurate tool for predicting liver fibrosis in patients with chronic hepatitis C. The studies mainly are European studies since the incidence of chronic hepatitis C is relatively high there, but the number of studies on chronic hepatitis B is still limited; while only a few of studies indicate that the assessment using FibroScan has the same quality in predicting liver fibrosis with various etiologies in patients with chronic hepatitis. However, a validation of varied cut off point on some groups of chronic liver disease with different etiologies is necessary before a valid recommendation is issued by FibroScan work out in daily practice.[9-13] Therefore, the aim of the present study was to evaluate the accuracy of FibroScan to diagnose chronic hepatitis B and to compare it with APRI by using liver biopsy as the gold standard procedure.

METHOD

A cross sectional study was conducted in 51 patients at the Division of Gastroentero-hepatology, Department of Internal Medicine, Adam Malik Hospital, Medan between April 2011 and July 2013. The inclusion criteria were patients with chronic hepatitis B, persistent positive hepatitis B surface antigen (HBsAg) results for at least 6 months and elevated alanine transaminase (ALT) serum above normal limit for at least twice in the last 6 months, HBV DNA > 2,000 IU/mL, both male and female patients aged > 18 years and were willing to participate in the study. The exclusion criteria included patients with decompensated liver cirrhosis who were confirmed by clinical examination, laboratory work out and ultrasonography (USG), patients who consumed alcohol > 30 g/day, patients with metabolic liver disease, neoplasm, chronic liver infection other than chronic hepatitis B, patients with cholestatic liver disease, autoimmune hepatitis and patients with HIV/AIDS. The patients underwent FibroScan examination of their right liver lobe and assessed through intercostal plane. The stadium of liver fibrosis is determined based on a defined system on a scale of F0-F4 in FibroScan.

In order to calculate APRI score a serial of examinations was done including laboratory workout for amino transaminase (AST), ALT, platelet counts and USG guided liver biopsy. The biopsy was performed based on METAVIR score. Specimens of liver tissue were examined with 1.4-2 cm length and minimal of 8-10 portal triads. Hematoxillin eosin staining of the liver tissues was also performed without including the data of patients. Liver biopsy was performed in 7

days following the laboratory workout and FibroScan.

The formula to calculate the score was:

$$\text{APRI} = \frac{\text{AST level (U/L) / upper normal limit of AST (U/L)}}{\text{Thrombocyte } (10^9/\text{L})} \times 100$$

The cut-off point of APRI was ≤ 1.50 for mild to severe fibrosis and > 1.50 for severe fibrosis to cirrhosis.[8] The cut-off point for FibroScan was determined according to Ledingen, i.e. F0-2 ≤ 9.3 kPa = mild to moderate fibrosis; F3-4 > 9.3 kPa = severe fibrosis to cirrhosis.[14] For METAVIR score, F0 = no fibrosis; F1 = fibrosis are confined to enlarged portal tract; F2 = the development of periportal septa or portal septa with intact architecture; F3 = fibrosis with architectural distortion (fibrosis septa bridging) but no obvious cirrhosis; F4 = probable or definite cirrhosis.[15]

In order to determine the diagnostic value of APRI and FibroScan, an evaluation was conducted based on the analysis on receiver operating characteristic (ROC) curve and assessing the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA), positive likelihood ratio (LR+) and negative likelihood ratio (LR-), which were calculated based on the cut-off points as mentioned in the original publication. Statistical analysis was performed using SPSS 20.0. The present study was approved by the Research Ethics Committee, Faculty of Medicine, University of Sumatera Utara.

RESULTS

Table 1. Baseline data of the patients

Variable	Hepatitis B n (%)
Patients (n)	51
Sex	
Male	29 (56.9%)
Female	22 (43.1%)
Age (years)	43.5 (SD ± 11.50)*
AST (U/L)	38 (16 - 846)**
ALT (U/L)	62 (10 - 222)**
Thrombocyte (10^9/L)	160 (53 - 421)**
FibroScan (kPa)	4.90 (4.1 - 75)**
APRI score	0.58 (0.17 - 7.49)**
≤ 1.50	38 (74.5%)
> 1.50	13 (25.5%)
FibroScan (kPa)	-
≤ 9.3	26 (51%)
> 9.3	25 (49%)
METAVIR-stage	-
F0 – 2	31 (60.8%)
F3 – 4	20 (39.2%)

*mean, SD; **median, min-max; AST: aspartate transaminase; ALT: alanin transaminase; APRI: aspartate aminotransferase to platelet ratio index

Diagnostic Accuracy of APRI versus METAVIR

Table 2. The predictive value of APRI versus METAVIR for diagnosing severe fibrosis and cirrhosis

Model	Cut off	METAVIR F3 - 4 n = 20	METAVIR F0 - 2 n = 31	Se (%)	Sp	PPV	NPV	LR +	LR -	Acc
APRI	> 1.50 n = 13	8	5	40	83.9	61.5	68.4	2.48	0.72	66.7
	≤ 1.50 n = 38	12	26							

APRI = aspartate aminotransferase to platelet ratio index; Se = sensitivity; Sp = specificity, PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; Acc = accuracy

On Table 2, out of 20 patients with severe fibrosis and cirrhosis based on METAVIR, there were 8 (40%) patients with APRI score > 1.50. The predictive value of APRI versus METAVIR for diagnosing severe fibrosis and cirrhosis with sensitivity 40%, specificity 83.9% were PPV 61.5%, NPV 68.4% LR positive 2.48, LR negative 0.72 with diagnostic accuracy 66.7%, kappa 0.255; p > 0.05. The area value of under receiver operating curve (AUROC) in predicting severe fibrosis and cirrhosis for APRI was 0.619 (95% CI = 0.457 – 0.782) with p > 0.05 (not significant) (Figure 1).

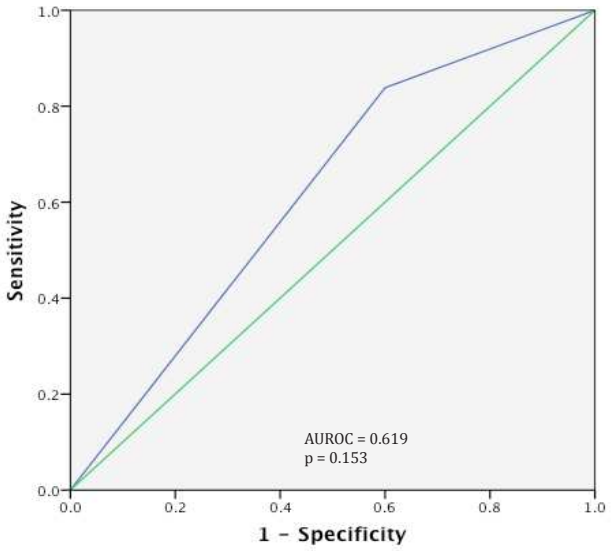

Figure 1. ROC curve of APRI versus METAVIR for predicting severe fibrosis and cirrhosis

Diagnostic Accuracy of FibroScan versus METAVIR

Table 3.The predictive value of FibroScan versus METAVIR for diagnosing severe fibrosis and cirrhosis

Model	Cut off	METAVIR F3 - 4 n = 20	METAVIR F0 - 2 n = 31	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR +	LR -	Acc (%)
Fibro Scan	> 9.3 n = 25	15	10	75	67.6	60	67.7	2.31	0.36	70.6
	≤ 9.3 n = 26	5	21							

Se: sensitivity; Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, LR; likelihood ratio; Acc = accuracy

Table 3 shows that of 20 patients with severe fibrosis and cirrhosis based on METAVIR, there were 15 (75%) patients with the FibroScan value > 9.3 kPa. The predictive value of FibroScan on METAVIR for diagnosing severe fibrosis and cirrhosis with sensitivity 75% and specificity 67.6% were PPV 60%, NPV 67.7% LR positive 2.31, and LR negative 0.36 with diagnostic accuracy 70.6%, kappa 0.409, $p < 0.05$. The AUROC value in predicting severe fibrosis and cirrhosis for FibroScan was 0.714 (95% CI = 0.457–0.782) with $p < 0.05$ (significant) (Figure 2).

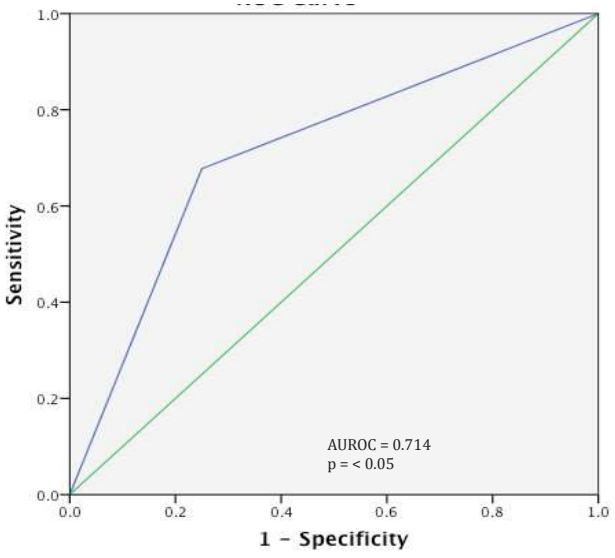

Figure 2. ROC curve of FibroScan and METAVIR for predicting severe fibrosis and cirrhosis

Table 4. AUROC result and accuracy of fibrosis models for predicting severe fibrosis and liver cirrhosis

Model	AUROC	95% CI	p	Kappa	Acc (%)
APRI – METAVIR	0.619	0.457 – 0.782	0.153	0.255	66.7
FibroScan - METAVIR	0.714	0.567 – 0.861	0.001	0.409	70.6

Acc: accuracy; CI: confidence interval

DISCUSSION

APRI scoring system is a relatively inexpensive method and easily performed by clinicians. Many researchers have evaluated the degree of liver fibrosis based on APRI in patients with chronic hepatitis C.[7] However, there are only a few of publications for patients with chronic hepatitis B with different values of the cut-off points. A study conducted by Amorin et al in 119 patients with chronic hepatitis B with cut-off point > 1.50 found Se 42%, Sp 94%, PPV 77%, NPV 75%, and AUROC value 0.79 with accuracy 76%.[16] Similar results have also been found in the present study, i.e. with APRI cut-off point > 1.50, we found Se 40%, Sp 83.9%, PPV 61.5%, NPV 68.4%, LR positive 2.48, LR negative 0.36, and AUROC value 0.72 (95% CI = 0.457–0.782) with accuracy 66.7%. The NPV value for predicting severe fibrosis and cirrhosis was higher than PPV and a low value of positive LR was also found. The correlation between APRI and METAVIR was weak and insignificant (kappa 0.255; $p > 0.05$).

Bonnard et al who conducted a study in 50 patients with chronic hepatitis B and using a cut-off point 1.2 found Se 50%, Sp 51%, PPV 23%, NPV 75%, and AUROC value 0.50.[17] Some studies showed that with a cut-off point more than 1.50, the AUROC value was > 0.70, which means that APRI has moderate accuracy in predicting the degree of severe liver fibrosis and cirrhosis. Jin et al from China evaluated 9 studies in their meta-analysis (n = 1,798) on the diagnostic accuracy of APRI in patients with chronic hepatitis B and showed that the significant prevalence for fibrosis was 53.1% and for cirrhosis was 13.5%. When the cut-off point for APRI was 1.5, they found Se 49% and Sp 84%. Cirrhosis was determined when the cut-off for APRI was 1.0–1.5 with Se 54% and Sp 87%. When the cut-off point for APRI was 2.0, they found Se 28% and Sp 87%. The meta-analysis concluded that the value of APRI for significant identification of fibrosis and cirrhosis in patients with chronic hepatitis B was low.[18]

Some researchers conclude that APRI is not accurate in predicting significant fibrosis and cirrhosis in patients with chronic hepatitis B with varied AUROC value, PPV and NPV. Wai et al were the first who reported APRI for patients with chronic hepatitis B and showed that the AUROC value of APRI for predicting significant fibrosis and cirrhosis were 0.673 and 0.626. They concluded that in their study APRI was not accurate for predicting significant fibrosis and cirrhosis.[19] Furthermore, Sebastiani et al also showed that the AUROC value of APRI for predicting significant fibrosis and cirrhosis were 0.72 and 0.64. The NPV was higher than PPV for predicting cirrhosis.[20] The predictive value of FibroScan in the present study with cut-off point > 9.4 kPa versus METAVIR for diagnosis of severe fibrosis and cirrhosis were Se 75%, Sp 67.6%, PPV 60%, NPV 67.7%, LR positive 2.31 and LR negative 0.36 with diagnostic accuracy 70.6%. Diagnostic performance of FibroScan was then evaluated by assessing the AUROC value for predicting severe liver fibrosis and cirrhosis. The AUROC value for FibroScan was 0.714 (95% CI = 0.567–0.861) with $p < 0.05$ (kappa 0.409; $p < 0.05$). Similar study was also conducted by Sporea et al who

studied 140 patients with chronic hepatitis B and 317 patients with chronic hepatitis. An evaluation of severe fibrosis was performed for both groups.[21]

Mean value of liver stiffness for chronic hepatitis B was the same with chronic hepatitis C, i.e. F1 = 6.5 ± 1.9 kPa vs. 5.8 ± 2.1 kPa (p = 0.0889); F2 = 7.1 ± 2 kPa vs. 6.9 ± 2.5 kPa (p = 0.3369); F3 = 9.1 ± 3.6 kPa vs. 9.9 ± 5 kPa (p = 0.7038); F4 = 19.8 ± 8.6 kPa vs. 17.3 ± 6.1 kPa (p = 0.6574). There was a significant correlation of FibroScan versus METAVIR between those with chronic hepatitis C and B (Spearman r = 0.578; p < 0.0001; r = 0.408, p < 0.0001). AUROC value for severe fibrosis in chronic hepatitis B with cut-off point of 8.8 kPa was 0.753; Se 53% with Sp 85%, PPV 86% and NPV 82%. While for chronic hepatitis C with cut-off point 8.6 kPa the AUROC value was 0.797 with Se 62%, Sp 81%, PPV 71%, NPV 75% and when the values for hepatitis B and C were combined with cut-off point of 8.7, the AUROC value was 0.786 with Se 60%, Sp 83%, PPV 68%, NPV 77%. They concluded that there was no statistical difference regarding on the mean value of liver stiffness between those with chronic hepatitis B and C with an equal degree of liver fibrosis.[21] Vigano et al who studied 217 patients with chronic hepatitis B with cut-off point for FibroScan of 8.7 kPa in predicting severe fibrosis found Se 64%, Sp 92%; while in predicting cirrhosis with cut-off point of 9.4 kPa, they found Se 100% and Sp 82%.[22] The main difference of all the above-mentioned studies is the use of different and undetermined cut-off point for examination based on FibroScan. In which Ziol et al studied patients with chronic hepatitis B and they conclude that FibroScan can be included in a category with level of evidence of 2B.[10]

APRI was firstly introduced by Wai et al for predicting liver fibrosis in chronic hepatitis C with AUROC value of 0.80 (95% CI = 0.74–0.87).[8] The comparison of diagnostic accuracy of FibroScan versus APRI for identifying the degree of severe liver fibrosis and cirrhosis was performed since APRI could be easily calculated from the results of routine blood test in patients with chronic viral hepatitis. Moreover, they also evaluated how APRI in patients with chronic hepatitis B has important role as the non-invasive method as well as a follow-up tool following the treatment. APRI can be performed for all patients; while FibroScan cannot be done for certain patients, particularly for patients with obesity and a narrow intercostal space as the transducer cannot be placed on the skin.

In the present study, FibroScan is more superior to APRI for diagnosis of severe liver fibrosis and cirrhosis with higher values of AUROC, sensitivity and specificity, as well as higher degree of accuracy. The measurement of liver stiffness by FibroScan would assess the liver tissue with diameter of 1 cm^2 and 4 cm length. The volume of this tissue is 100x greater than the tissues obtained for liver biopsy with fast examination (< 5 minutes) and easily performed for patients treated at the outpatient clinic. Moreover, the results are rapidly obtained with an independent operator.[23]

The drawbacks of the present study are: (1) The readings of liver tissue was not confirmed by other pathologist, which according to the literature, there can be 20% intra- and inter-observer differences for evaluation of staging.[6] Likewise, for FibroScan, there is 2% of intra- and inter-observer differences;[24] (2) The length of liver biopsy tissue may also have role in the interpretation of liver fibrosis. The mean length of liver tissue specimens in the present study is 15 mm; while the length suggested by Bedossa et al is 25 mm;[25] (3) The cut-off point was estimated from other investigator; (4) Small sample size.

CONCLUSION

The present study indicates that FibroScan is more accurate than APRI for evaluating the degree of severe fibrosis and cirrhosis in liver biopsy of patients with chronic hepatitis B. The APRI examination is more simple and cheaper for evaluating the degree of liver fibrosis.

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Correspondence:
Elias Tarigan
Division of Gastroentero-hepatology
Department of Internal Medicine
Adam Malik Hospital
Jl. Bunga Lau No. 17 Medan Indonesia
Phone/Facsimile: +62-61-8363009
E-mail: eliastarigan28@yahoo.com