ORIGINAL ARTICLE

AST-Platelet Ratio Index as a Predictor of Advanced Liver Fibrosis in Patients with Chronic Hepatitis B Infection

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Abstract:

This cross-sectional study was done to evaluate the significance of serum AST-platelet ratio index (APRI) for diagnosis of severity and extent of liver fibrosis in patients with chronic hepatitis B, and its use in monitoring progress of fibrosis and response to treatment in chronic hepatitis B infection. The study was done on a total of 50 biopsy-diagnosed hepatitis B patients. Every patient was diagnosed clinically and histopathologically. Only pre-treatment biopsies were used for the current study. Fibrosis was scored according to the Scheuer scheme. Random blood samples were drawn. Serum AST concentrations were estimated by Kinetic UV method and blood platelet count was estimated by automated cell counter method. Data were analyzed statistically by Spearman's rank correlation coefficient and binary diagnostic tests using SPSS software version 12. The mean APRI was 0.48 ± 0.28. The values of APRI showed a gradual rise in values with increasing stages of fibrosis. The AUROC for APRI were at 0.09 in mild fibrosis, 0.48 in moderate fibrosis, 0.77 in significant fibrosis, and 0.93 in cirrhosis. So, APRI may be used as a predictor of significant fibrosis and cirrhosis in individuals with chronic hepatitis B infection.

Introduction:

Liver fibrosis is not an independent disease but rather a scarring response that results from chronic injury of any cause including hepatitis B and C, excessive alcohol ingestion, nonalcoholic steatohepatitis, and iron overload among others. Chronic viral hepatitis B and C are the most common causes of liver fibrosis[1].

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Liver biopsy is the gold standard method to assess liver fibrosis in patients with chronic liver disease[2]. However, liver biopsy is an invasive procedure associated with major complications, high costs, and patient/physician reluctance. It has limitations including sampling artifact and inter-individual as well as intra-individual variability in scoring. As a result, simple and reliable non-invasive markers such as blood tests and/or liver imaging modalities that accurately correlate with disease activity and stage are urgently needed to assist in the management of chronic hepatitis B (CHB) patients worldwide and so reduce the need for repeated liver biopsies[3,4].

The ideal noninvasive diagnostic test for hepatic fibrosis is one that is simple, readily available, inexpensive, and accurate. The present study involves the assessment of liver fibrosis using models involving a combination of routine laboratory tests namely serum aspartate aminotransferase-platelet ratio index (APRI). This model has been previously applied in similar studies but the results concerning their diagnostic powers were often conflicting.

The main aim of the current study is to evaluate the efficacy of APRI for diagnosis of severity and extent of fibrosis in patients with chronic hepatitis B, and to evaluate the use of APRI in monitoring progress of fibrosis and response to treatment in chronic hepatitis B infection.

Materials and method:

A cross-sectional study involving a total of 50 biopsy-diagnosed hepatitis B patients was designed in the Department of Biochemistry, Dhaka Medical College, Dhaka, on AST-platelet ratio index (APRI) in patients with liver fibrosis following chronic hepatitis B infection. All patients were treatment-naive, had HBsAg positive for more than six months and HBV DNA level more than 10^5copies/ml prior to entry into the trials, with no evidence of decompensation, metabolic abnormalities, associated co-infection or pregnancy. Each patient was diagnosed clinically and histopathologically. Only pre-treatment biopsies were used for the study. Fibrosis was scored according to the Scheuer scheme. According to the Scheuer scheme, the stage F0 indicates no fibrosis, F1 fibrous portal expansion, F2 portal-portal septa, F3 bridging with distortion, and F4 indicates cirrhosis[5,6]. Random blood samples were drawn. Serum AST concentration was estimated by Kinetic UV method and blood platelet count was done by automated cell counter method. APRI was calculated by the following formula:

AST:platelet ratio index =
[(AST/ULN)/platelet count] X 100

where the platelet count is expressed as 10^9/L and ULN stands for upper limit of normal which was taken as 45 U/L for AST.

Values were expressed as mean ± SD (standard deviation) unless otherwise stated. Relationships among different variables were established by linear correlation (correlation coefficient or 'r'). P value of <0.05 was taken as the level of significance. Data were analyzed statistically by Spearman's rank correlation coefficient and binary diagnostic tests using SPSS software version 12.

Results:

The age range of the patients was 15-47 years and the mean age was 27.4 ± 8.03. Males and females were 37 (74%) and 13 (26%) respectively. The mean APRI was 0.48 ± 0.28, the values ranging from 0.15 to 1.41.

Among the 50 subjects, 4% had fibrosis stage 0, 44% were in stage 1, 4 8% in stage 2, 26% in stage 3, and 18% in stage 4 (Table- I).

Table I: APRI in relation to different stages of fibrosis

Fibrosis stage	Number of patients	APRI (Mean ± SD)
0	02 (4%)	0.27 ± 0.09
1	22 (44%)	0.28 ± 0.07
2	04 (8%)	0.41 ± 0.13
3	13 (26%)	0.81 ± 0.16
4	09 (18%)	0.88 ± 0.30
Total	50	0.48 ± 0.28

The values of APRI showed a gradual rise in values with increasing stages of fibrosis. The mean value of APRI was 0.30 ± 0.09 in mild to moderate fibrosis, and 0.72 ± 0.26 in significant fibrosis and cirrhosis (Table-II).

Table II: APRI in relation to severity of fibrosis and Spearman's rank correlation between them

Fibrosis	Number of subjects	APRI	r value	P value
≤Stage 2 (mild to moderate fibrosis)	28 (56%)	0.30 ± 0.09	0.38	0.046* (<0.05)
>Stage 2 (significant fibrosis and cirrhosis)	12 (44%)	0.72 ± 0.26	0.481	0.023* (<0.05)

* = correlation is significant at the level of 0.05.

Table III shows the correlation of APRI with fibrosis where fibrosis seems to have strong positive correlation with APRI by Spearman's rank (rho) correlation coefficient (r).

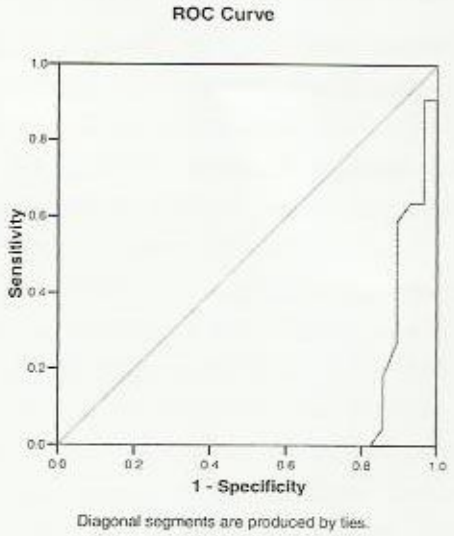
Table-III: Spearman's rank correlation of APRI with stage of fibrosis

Stages of fibrosis	Parameters (Mean ± SD)		r value	P value
	APRI	0.48 ± 0.28	0.829	0.000* (<0.01)

* = correlation is significant at the 0.01 level (2-tailed).

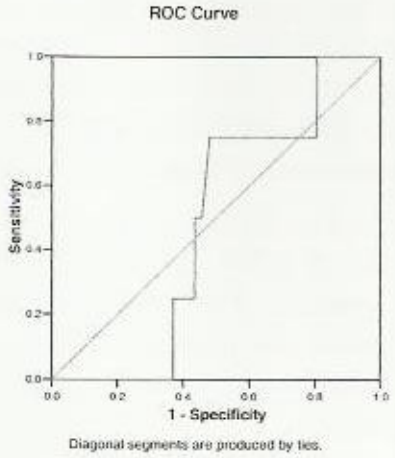
Receiver operating characteristics (ROC) curves were plotted and the areas under the ROC (AUROC) curves were determined to detect the ability of APRI to predict the different stages of hepatic fibrosis. An AUC of 1.0 is characteristic of an ideal test, whereas an AUC of 0.5 or less indicates a test of no diagnostic value.

The AUROC for APRI were at 0.09 in mild fibrosis, 0.48 in moderate fibrosis, 0.77 in significant fibrosis, and 0.93 in cirrhosis (Figures 1-4 and Table-IV). Cut-off predictive probability for APRI was chosen based on the ROC analysis of significant fibrosis and cirrhosis (Figures-3 and 4) to obtain a sensitivity of at least 90% in predicting significant fibrosis. From the ROC curves, three cut-off values, 0.44, 0.50 and 0.56, were chosen for APRI. Diagnostic performance of APRI was measured and compared for the different cut-off values for prediction of advanced fibrosis. At cut-off 0.5, sensitivity was 86%, specificity 96%, positive predictive value (PPV) 95%, negative predictive value (NPV) 90% and accuracy was 92%. Sensitivity (95%) and NPV (96%) were higher for cut-off 0.44, and specificity and PPV were higher (100%) for cut-off 0.56. (Table-V)



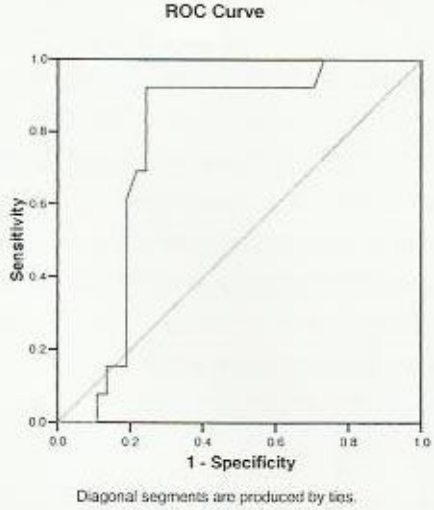
Test result variable(s)	Area under the curve
APRI	.086

Figure-1: ROC curve of using APRI in predicting mild fibrosis (F1) with their areas under the curves.



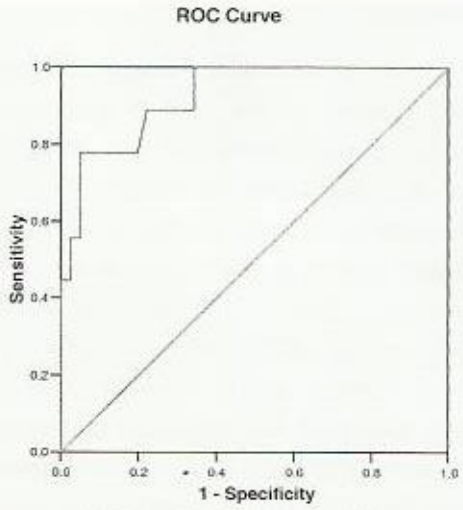
Test result variable(s)	Area under the curve
APRI	.481

Figure-2: ROC curve of using APRI in predicting moderate fibrosis (F2) with their areas under the curves.



Test result variable(s)	Area under the curve
APRI	.767

Figure-3: ROC curve of using APRI in predicting significant fibrosis (F3) with their areas under the curves.



Test result variable(s)	Area under the curve
APRI	.925

Figure-4: ROC curve of using APRI in predicting cirrhosis (F4) with their areas under the curves.

Table-IV: AUROC with 95% CI of APRI in predicting different stages of fibrosis

Stages of fibrosis	AUROC (95% CI) of APRI
1	0.086 (-0.002-0.174)
2	0.481 (0.275-0.687)
3	0.767 (0.628-0.906)
4	0.925 (0.840-1.011)

Table-V: Diagnostic performance of APRI for different cut-off values in predicting significant fibrosis and cirrhosis

Diagnostic tests	Cut-off points		
	0.44	0.50	0.56
Sensitivity (%)	95	86	77
Specificity (%)	93	96	100
PPV (%)	91	95	100
NPV (%)	96	90	85
Accuracy (%)	94	92	90

Discussion:

The ideal noninvasive diagnostic test for hepatic fibrosis is one that is simple, readily available, inexpensive, and accurate. No test meets this definition, although a number of approaches have been proposed and are being evaluated. These include clinical signs, routine laboratory tests, radiological imaging modalities, or quantitative assays of liver function, alone or in combination. Many models based on non-invasive determinations have been developed for liver fibrosis in chronic hepatitis C (CHC) infection and some of them have been tested in chronic hepatitis B (CHB) as well, but their clinical usefulness is still controversial. Liver biopsy is still the gold standard for assessment of fibrosis.

The present study involves the assessment of liver fibrosis using models involving a combination of routine laboratory tests like AST-platelet ratio index (APRI). It has been previously applied in similar studies but the results concerning their diagnostic powers were often conflicting. The results of the current study showed that the APRI is significantly associated with the extent of liver fibrosis in chronic hepatitis B.

Mean APRI was found to be 0.48 ± 0.28 respectively. APRI showed gradual increase with increasing stage of fibrosis. A definite demarcation was found between F2 and F3, on the basis of which the stages were divided into 2 groups, mild or moderate fibrosis being less than or equal to F2 and advanced fibrosis being F3 and above. APRI correlated well with individual stages of fibrosis, particularly advanced fibrosis by Spearman's rank correlation coefficient showing a $p<0.05$. A strong positive correlation was found between APRI and fibrosis stages. On ROC analysis, the AUROC was significant for F3 at 0.77 and F4 at 0.93. Applying a cut-off predictive probability of 0.44, the accuracy of the model was found to be 94% with sensitivity 95%, specificity 93%, PPV 91% and NPV 96% for predicting advanced fibrosis (F3 and F4).

Both platelet count and AST level are routine tests done in CHB and CHC patients in clinical practice. The finding of decreased platelet count and increased AST level with progression of liver fibrosis has been reported in many studies.

While AST had been persistently found to be useful in predicting significant fibrosis in patients with CHC, it is not an independent factor in predicting either significant fibrosis or cirrhosis in patients with CHB[7,8,9]. Elevation of AST with progression of liver fibrosis was believed to be due to reduction in the clearance of AST[10] and mitochondrial injury with more marked release of AST relative to ALT in CHC[11,12]. It implies that the pathogenesis of liver fibrosis in CHB may be different from that of CHC. Activity of CHB can become quiescent after a period of severe activity. In contrast, CHC is a progressive disease with persistent inflammation that ultimately leads to cirrhosis. Consequently, due to the intermittent necroinflammatory pattern of CHB, the presence of cirrhosis in HBV can occur in the absence of inflammation while this is seldom true for HCV.

With increasing fibrosis and worsening portal hypertension, there is increased sequestration and destruction of platelets in the enlarging spleen[13]. In addition, studies in liver transplant patients showed that progression of liver fibrosis is associated with decreased production of thrombopoietin by hepatocytes, and hence reduced platelet production[14,15].

It can thus be concluded from this study that APRI can be used as a predictor of significant fibrosis and cirrhosis in individuals with chronic hepatitis B. It can be used to monitor the progression of fibrosis in patients with CHB as well as to monitor the response to treatment for those undergoing drug trials. As a result, the need for repeated liver biopsies may be reduced, thereby reducing the cost and complications following biopsy in chronic hepatitis B patients with liver fibrosis.

There are limitations to the study. The study included patients from a university hepatology ward and all the patients were treatment-naïve. All the patients had HBV DNA $>10^5$copies/ml and so these models are not applicable for those with inactive virological disease (HBV DNA $<10^5$copies/ml). Due to fund constraints, other models with higher degrees of accuracy could not be compared with the models in this study. Despite the simplicity and accuracy of the APRI, there was overlap among patients with different stages of fibrosis. Thus the use of APRI in the prediction of advanced fibrosis in individual patients with CHB must be further evaluated in prospective studies.

References:

1. Tse-Ling Fong n.d., Hepatitis B (HBV). Retrieved December 2, 2006, from //http://www.medicinenet.com/
2. Wai CT, Cheng CL, Wee A, Dan YY, Chan E, Chua W, et al. Non-invasive models for predicting histology in patients with chronic hepatitis B. Liver Int 2006; 26: 666-672.
3. Pinzani M. Non-invasive evaluation of hepatic fibrosis: dont count your chickens before they are hatched. Gut 2006; 55: 310-312.
4. Filho RJC, Schiavon LL, Narciso JL, Nishiyama KH, Cara NJ, Lanzoni VP, et al. Simple blood tests can predict advanced liver fibrosis in patients with Hepatitis B virus chronic infection. 41st EASL. Retrieved on January 12, 2007, from //http.www.hivandhepatitis.com/ 2006 icr/easl/docs/diag.html/
5. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991; 13: 372-374.
6. Sherlock S, Dooley J. Chronic hepatitis – General features, and auto immune chronic disease. In: Diseases of the Liver and Biliary Tract, Eleventh edition. Oxford: Blackwell Publishing, 2002. pp-325.
7. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003; 38: 518-526.
8. Bonacini M, Hadi G, Govindarajan S, Lindsay KL. Utility of a discriminate score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection Am J Gastroenterol 1997; 92: 1302–4.
9. Pohl A, Behling C, Oliver D, Kilani M, Monson P, Hassanein T. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. Am J Gastroenterol 2001; 96: 3142-6.
10. Kamimoto Y, Horiuchi S, Tanase S, Morino Y. Plasma clearance of intravenously injected aspartate aminotransferase isozymes: evidence for preferential uptake by sinusoidal liver cells. Hepatology 1985; 5: 367–375.

11. Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology 2002; 122: 366–375.
12. Nalpas B, Vassault A, Le Guillou A, Lesgourgues B, et al. Serum activity of mitochondrial aspartate aminotransferase: a sensitive marker of alcoholism with or without alcoholic hepatitis. Hepatology 1984; 4: 893–896.
13. Aster R. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest 1996; 45: 645–57.
14. Adinolfi LE, Giordano MG, Andreana A, Tripodi MF, Utili R, Cesaro G, Ragone E, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Br J Haematol 2001; 113: 590–595.
15. Kawasaki T, Takeshita A, Souda K, Kobayashi Y, Kikuyama M, Suzuki F, et al. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis. Am J Gastroenterol 1999; 94: 1918-22.