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ORIGINAL ARTICLE

APRI is not a Useful Predictor of Fibrosis for Patients with Chronic Hepatitis B

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Background and Aims: **Liver biopsy remains the gold standard to assess hepatic fibrosis, including for those with chronic hepatitis B. The search for a novel, non-invasive alternative to liver biopsy to assess hepatic fibrosis continues. The serum aspartate-aminotransferase-to-platelet ratio index (APRI) has been shown to correlate with the degree of hepatic fibrosis in patients chronically infected with hepatitis C virus (CHC). The aim of this study was to investigate whether the same also applies in cases of chronic hepatitis B (CHB).**

Methods: **One hundred and eleven consecutive patients who tested positive for hepatitis B surface antigen (HBsAg) for more than 6 months in our unit from July 2006 to June 2007 were included in the study. For all of the patients, platelet count, aspartate aminotransferase (AST), hepatitis B e antigen (HBeAg) by enzyme-linked immunosorbent assay (ELISA), hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR), and percutaneous liver biopsy were tested for. APRI was calculated for every patient using the formula, AST x UNL x 100 / platelet count x 109/L. Patient characteristics, including APRI, were compared between those with a fibrosis ? 2 and those having a fibrosis < 2.**

Results: **AST level was found to be higher in those with significant fibrosis (HAI-F > 2) and the proportion of HBeAg-positive patients was higher in those with a fibrosis ≥ 2 (39%) compared to those with a fibrosis < 2. Only 3 patients out of 111 had an APRI > 1.5 and all of them had a fibrosis < 2.**

Conclusions: **Liver biopsy remains the gold standard for assessment of fibrosis in chronic hepatitis and cirrhosis related to Hepatitis B infection. AST level was seen to differ among two groups, but no difference was seen for platelet counts. Although APRI has been shown to have good predictive value for significant fibrosis in patients with chronic hepatitis C infection, it does not appear to be of use in predicting fibrosis in patients with chronic hepatitis B infection.**

Keywords: **Chronic Hepatitis B, Hepatic Fibrosis, APRI**

Introduction

Persistent necro-inflammation in the liver due to chronic hepatitis of any etiology leads to hepatic fibrosis, progressing eventually to cirrhosis. Liver cirrhosis is considered to occur when the hepatic fibrosis score is 4, whereas in a healthy liver the fibrosis score is 0 [(1)]. In Bangladesh the most common cause of chronic hepatitis is hepatitis B virus (HBV), followed by non-alcoholic steatohepatitis (NASH) [(2)]. HBV is also the most common cause of cirrhosis in this country [(3)]. Liver

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biopsy remains the gold standard for assessment of hepatic fibrosis. Although our group has established the safety of per-cutaneous liver biopsy in Bangladesh [4], there are taboos among physicians and patients alike regarding the safety of this procedure in our country as in most other parts of the world.

The quest for a non-invasive alternative to liver biopsy continues. Any method expected to replace liver biopsy to assess hepatic fibrosis must be easy to perform, inexpensive, safe, and free of side effects. It must be acceptable to patients and easy to replicate to permit repeated examinations. In addition, the results have to be specific, sensitive, and reproducible. The test ideally should be independent of metabolic, biliary, and renal changes and should reflect fibrosis regardless of cause. A number of investigations and devices have been employed in an attempt to replace liver biopsy, including FibroScan, Fibrotest, the aspartate-aminotransferase-to-platelet ratio index (APRI), different breath tests, microbubble ultrasonography, wedged hepatic venous pressure, and so forth. Although many of these methods have been shown to be compatible with liver biopsy in advanced liver diseases, liver biopsy still has the edge in chronic hepatitis patients with early fibrosis of the liver.

Materials and Methods

One hundred and eleven consecutive patients who were positive for hepatitis B surface antigen (HBsAg) for more than 6 months in our unit from July 2006 to June 2007 were included in the study. None of them had any complaints or physical symptoms. HBsAg was detected for all study patients at an initial health screening, pre-vaccination screening, or screening before blood donation. All of the study patients tested positive for HBsAg on two occasions 6 months apart. The baseline characteristics of the study population are shown in Tables 1 and 2. The patients who had hepatitis C virus antibodies (anti-HCV), stigmata of cirrhosis of the liver, a history of significant alcohol consumption (*i.e.* > 20 gm/day), or metabolic syndrome were excluded from the study.

In each case, a detailed history was recorded and a clinical examination was done. For all patients, a serum aspartate transaminase (AST) level and platelet count were conducted using an autoanalyzer and prothrombin time by Quick's method. The cutoff value for abnormal AST was 42 U/L. Hepatitis B e antigen (HBeAg) was checked in each case by enzyme-linked immunosorbent assay (ELISA; Abbott Labs, Chicago). Anti-HCV was done using third-generation ELISA. HBV DNA quantification was done by polymerase chain reaction (PCR; Amplicon HBV Monitor Assay, RT-PCR, Roche Molecular Systems, California). The lower limit of the detection was 1000 copies/ml. HBV DNA > 10^8 copies/ml was considered to be a high DNA load. All study patients underwent an ultrasonographic examination of the hepato-biliary system and spleen using a Toshiba ultrasound machine and an endoscopy of the upper gastrointestinal tract using an Olympus video-endoscope.

Percutaneous liver biopsies were conducted for all patients with prior, informed written consent. Biopsies were done under local anaesthesia using tru-cut biopsy needles. Tissue samples ≥ 1.5 cm long and having ≥ 3 portal triads were considered to be adequate. Liver biopsy specimens were sent for histopathological examination, and Knodell scoring (HAI) of the liver tissue were done as well [1]. The

Table 1. Baseline characteristics of the study population.

Male: Female	77: 30
Age in years	18 - 45
Serum AST in U/L	12 - 103
HBV DNA in copies/ml	1.4 x 103- >108
HAI-NI	0 - 11
HAI-F	0 - 4

HBV: hepatitis B virus; AST: aspartate aminotransferase; HAI-NI: HAI necroinflammation; HAI-F: HAI fibrosis;

Table 2. Comparison of baseline characteristics between the two study groups.

Variables	Group II (n = 83) Mean ± SD	Group I (n = 28) Mean ± SD
Age (yrs)	27.02 ± 8.26	26.93 ± 5.93
Sex (Male)	75.9%	67.9%
HBeAg (Positive)	31%	39.3%
AST	39.36 ± 17.69	50.68 ± 17.49
Platelet	243.73 ± 75.81	250.29 ± 69.68
APRI	0.449 ± 0.32	0.523 ± 0.225
DNA(%) < 105/ 105-107/ >107	41.0/43.1/16.9	35.7/35.7/28.6

histopathological examination was done by a single histopathologist who was unaware of the clinical findings or laboratory reports of the patients.

Results

The study subjects were divided into two groups. The first group (Group I) had a fibrosis score > 2 on the liver biopsy and the second group (Group II) had a fibrosis score < 2. Twenty-eight subjects had a fibrosis score > 2 and were included in Group I, and the subjects with a fibrosis < 2 were included in Group II. There was no statistically significant difference in the APRI scores of the two groups. Only 3 of the subjects actually had an APRI score greater than 1.5. Among other variables, platelet count, sex, and age did not differ between the two groups, but the AST level was higher in Group I than in Group II.

The patients were split into two groups based on the histopathological findings. Those with significant fibrosis (HAI-F ≥ 2) were included in Group I, whereas Group II consisted of patients with non-significant fibrosis (HAI-F ≤ 2). 24.3% (26/107) of patients had significant fibrosis and fulfilled the criteria for inclusion in Group I. The remaining 75.7% (81/107) of patients were included in Group II , as they did not show significant hepatic fibrosis. APRI scores were then calculated for each group. As expected, it was seen that in Group I, the APRI score was > 1.5 in 100% (26/26) of patients. Surprisingly though, the APRI score was < 0.5 in 0% (0/81) of patients in Group II.

Discussion

Many studies have attempted to devise non-invasive tools for assessing the degree of liver fibrosis. APRI was discovered rather accidentally. While Dr. Wei was reviewing histology results of a group of patients with chronic hepatitis C (CHC), he happened to see that advanced fibrosis was associated with an opposing trend in AST level and platelet counts [5] . On further investigation, he found that separate studies had found similar results (*i.e.,* a higher stage of fibrosis was associated with higher AST level and lower platelet counts). It was pure coincidence that Dr. Wei put the two in a ratio with very interesting results. APRI has since been validated by various groups, with different levels of certainty and accuracy. ARPI has aroused great interest among various specialties and a web search revealed that the original paper has been cited 198 times since it was first published in 2003.

APRI has several advantages. Firstly, it is readily available, as AST and platelet counts are part of the routine tests in managing patients with chronic hepatitis. No additional blood tests or cost is needed. Secondly, it is easy to compute, without the use of a complicated formula. In fact, clinicians could simply work out the value without even using a calculator. Thirdly, and more importantly, the method is backed by sound pathogenesis. A more advanced state of fibrosis is associated with a lower level of fibrosis through lower production of thrombopoietin and a higher portal hypertension and enhanced pooling and sequestration of platelets at the spleen [6, 7]. APRI has been validated by various groups among patients with CHC. Interestingly, many studies have confirmed the method's accuracy, with an area under the ROC curves (AUROC) of > 0.8 in predicting fibrosis and cirrhosis in most studies. APRI has also been found to be rather accurate in CHC patients with end-stage renal diseases, HIV coinfection, hemophilia, and post-liver transplantation [8-11].

However, we ought to be aware of the limitations of APRI. Firstly, APRI was originally derived in a group of patients with CHC. Its usefulness in other forms of chronic liver diseases remains uncertain. As in our study, two studies of patients with chronic hepatitis B (CHB) showed a poor correlation between liver histology and APRI [12, 13]. Another study also showed poor ARPI correlation with patients with alcoholic liver disease [14]. APRI has not been evaluated for other liver diseases such as non-alcoholic fatty liver disease or primary biliary cirrhosis. Judging from these experiences, APRI is unlikely to be very useful in patients with liver diseases other than CHC. It may be postulated that the pathogenesis of fibrosis in chronic hepatitis C may be different from that of other chronic liver diseases, though this remains to be proven in basic science studies.

One probable reason for the lack of correlation between APRI and fibrosis in chronic hepatitis B is the platelet count. Chronic hepatitis C virus infection is itself known to be associated with low platelet counts. In our study, although AST level was seen to be higher in subjects with significant fibrosis, the platelet counts did not differ between the two groups. Platelet count was shown to have a negative correlation with fibrosis in chronic hepatitis C patients, and consequently, the difference in APRI was significant. Because platelet count is an important denominator in the calculation of APRI, its level has a profound effect on the APRI score.

Thus it appears that the lack of correlation between the platelet count and fibrosis score in chronic hepatitis B infection accounts for the limitation of APRI in predicting fibrosis. In addition, a significant proportion of patients do not fall into the diagnostic categories. As in the original paper, 19% of cirrhotic and 49% of patients with significant fibrosis could not be accurately predicted. Hence, further studies are needed to improve prediction of histology in this group of patients.

Conclusions

To sum up, despite its various shortcomings, APRI remains an important tool in predicting significant fibrosis and cirrhosis in patients infected with HCV. We have shown that although a high APRI correlates with significant fibrosis in CHB, a high APRI does not necessarily mean that there is significant hepatic fibrosis, as all CHB patients with non-significant fibrosis included in our study also had high APRI. We therefore conclude that, unlike CHC, the APRI score may not be a useful tool to predict hepatic fibrosis in patients with CHB. Future studies should focus on how to optimize APRI's predictive value in combination with other non-invasive markers.

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