SERUM ASPARATATE TRANSAMINASE PLATELET RATIO INDEX (APRI) IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN BANGLADESH

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ABSTRACT

Objective: *To correlate serum Aspartate transaminase (AST) and Platelet Ratio Index (APRI) with the degree of hepatic fibrosis in patients with non alcoholic fatty liver disease (NAFLD).*

Methodology: *This study was conducted on patients with NAFLD presenting at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2007 to June 2008. In all patients, platelet counts and levels of AST were measured in the sera. Percutaneous liver biopsy was done in these patients to assess the levels of hepatic fibrosis (HF). APRI was calculated by using the formula; AST×UNL×100/platelet count×10^9/L.*

Results: *Out of 30 patients, 28 had HF score of <2, while 2 had HF score of >2. However, high HF score was not associated with high AST. Based on platelet count, patients were divided into 2 groups; patients with platelet counts of <150,000/mm^3 and those with platelet counts of >150,000/mm^3. Sensitivity of APRI (cut off level 1.5) to diagnose significant fibrosis was 0%, specificity 96.4%, positive predictive value .0%, negative predictive value 93.1% and diagnostic accuracy 90.0%. On the other hand, when we considered APRI level of >1.5 as an indicator of significant fibrosis, one person was supposed to have hepatic fibrosis score of >2 from APRI value. But, liver histology of that person did not support hepatic fibrosis of >2.*

Conclusion: *APRI has no correlation with degree of hepatic fibrosis in patients with NAFLD and hence cannot be used as a non-invasive marker of fibrosis in patients with NAFLD in Bangladesh. However large scale studies are required to confirm these findings.*

Key Words: *Aspartate Transaminase Platelet Ratio Index, APRI, Non-Alcoholic Fatty Liver Disease (NAFLD), Hepatic Fibrosis.*

This article may be cited as: Hossain MF, Mahtab MA, Akbar SMF, Rahman S. Serum asparatate transaminase platelet count ratio index (APRI) in patients with non-alcoholic fatty liver disease in Bangladesh. Khyber Med Uinv J 2012;4(2):49-53

INTRODUCTION

Histopathological examination of the liver is an integral part of the diagnosis of patients with chronic liver disease (CLD). In addition, assessment of extent of liver damages and magnitudes of hepatic fibrosis allow proper designing of interventional strategies. Patients with chronic hepatitis with no or minimal fibrosis at presentation usually progress slowly and treatment may be delayed or withheld for the time being[1-3]. On the other hand, patients with significant hepatic fibrosis develop complications like liver cirrhosis, hepatic decompensation and hepatocellular carcinoma[4-6]. These patients should be provided with active therapeutic approaches, the guidelines for which have been provided by most of the professional organizations[7-8].

A well-performed liver biopsy and proper assessment of hepatic histology provides relevant information about extent of hepatic fibrosis in patients with CLD. However, this is not always possible in clinical settings. Also, there may be sampling error in liver biopsy because a small portion of liver tissues is used for evaluation[10,11]. In addition, facilities and trained manpower to accomplish liver biopsy are scanty in developing countries of the world that harbor the major bulk of patients with CLD.

These limitations have exposed the need of alternative and non-invasive methods of assessing hepatic fibrosis that are reliable, accurate, and acceptable to the

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Date Submitted: October 28, 2011
Date Revised: May 22, 2012
Date Accepted: May 25, 2012

patient. Several serum markers such as serum hyaluronic acid, aspartate *transaminase (*aminotransferase)-to-alanine aminotransferase (ALT) ratio (AAR), aspartate *transaminase (*AST)-to-platelet ratio index (APRI), age-platelet count index (API) and many others[12-16]. Among these serum markers, the utility of APRI has been shown in patients with CLD. However, there is lack of consensus about its utility in CLDs due to different etiological agents. Some investigators have shown that APRI may be a good indicator showing various levels of fibrosis, whereas, the others could not confirm that. In general, the utility has been shown in chronic hepatitis C virus (HCV) infection with a moderate degree of accuracy. But, controversy remains about its utility in patients with chronic hepatitis B virus (HBV) infection[17-21]. Furthermore, little has been explored about clinical value of APRI in patients with autoimmune hepatitis as a biomarker of hepatic fibrosis.

Obesity and its associated conditions, including nonalcoholic fatty liver disease (NAFLD), have reached worldwide epidemic proportions. The pathological spectrum of NAFLD extends from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH) to liver cirrhosis. In addition to liver-related complications, patients with NAFLD are more prone to develop insulin resistance, type 2 diabetes mellitus, and coronary heart disease[22-24]. Patients with NAFLD are also prone to develop severe complications. To accomplish a proper management guideline of NAFLD, assessment of extent of hepatic fibrosis is essential. In this context, there is paucity of information about the utility of APRI, a non-invasive marker of hepatic fibrosis, in patients with NAFLD. This study was aimed to correlate serum APRI with the degree of hepatic fibrosis in patients with NAFLD in Bangladesh.

METHODOLOGY

This was an open, non-randomized and consecutive observational type of clinical study. It was conducted at the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh in collaboration with the Department of Pathology of the same University. Thirty patients of NAFLD attending the Department of Hepatology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from July 2007 to June 2008, were enrolled in the study. The diagnosis of NAFL was done from history of illness, body mass index, data of ultrasonography and those of liver function tests. The aims and objectives of the study along with its procedure, alternative diagnostic methods, risks and benefits of this study were explained to all patients in easily understandable local language and then written informed consents were obtained from the patients or their parents.

Patients with ultrasonographic evidence of fatty liver were included in this study. Patients with history of alcohol intake, chronic viral hepatitis (due to HBV and HCV), drug-induced chronic liver disease, patients in whom liver biopsy was contraindicated, and patients who were not willing to undergo liver biopsy were excluded from the study.

For liver biopsy, trucut biopsy needle was used. All aseptic precautions were maintained to avoid any complication. Local anesthetic agent was used. The biopsy needle was introduced through the right 8th or 9th intercostal space along the mid axillary line with the patient holding breath on expiration in quiet breathing. The direction of the needle was kept slightly posterior and cranial to avoid gall bladder injury. After biopsy procedure, the patient was kept lying on right side of the body for at least 2 hours. Pulse rate and blood pressure were recorded every 15 minutes for the first hour and then every 30 minutes for next 2 hours. Routine visits were paid at 4 and 8 hours. Patient was kept in bed rest for 24 hours. The biopsy material was sent for histopathology immersed in 10% formalin solution. Histopathological assessment of liver biopsy specimens was accomplished by two separate histopathologists and they were unaware of the diagnosis and clinical conditions of the patient. The assessment of hepatic fibrosis was done by the criteria of Kleiner et al[25].

Statistical analysis: Data were analyzed with the help of SPSS (Statistical package for social sciences) window's version 13 software. Statistical analysis was done using unpaired t-test and Chi square test. Statistical significance was set at $p<0.05$ and confidence interval was set at 95% level. All probability values quoted were 2-tailed.

RESULTS

The age of study population was 39.37±9.83 years (mean ± standard deviation). Out of all patients 16 (53.3%) were male and 14 (46.7%) were female (Table I). Housewives (40%) represented the commonest group among study population. They were followed by service holders (36.7%), students (16.7%), labourers (3.3%), and businessmen (3.3%).

Out of 30 patients 12 (40%), 16 (53.3%, and 2 (6.7%) patients had fibrosis of stage 1, 2, and 3, respectively (Table I). Taken together, mild to moderate fibrosis (fibrosis levels of 1 and 2) were detected in 28 (93.3%) patients, whereas, severe fibrosis (fibrosis level of 3) were seen in 2 (6.7%) patients. Regarding AST levels, 12 (40%), 9 (30%), and 9 (30%) patients had serum AST levels of <40 IU/ml, 40-50 IU/ml, and >50 IU/ml, respectively. Only 2 (6.7%) patients had fibrosis level 3; one (3.3%) of them

had AST level of <40 IU/ml and the other had AST level of >50 IU/ml.

Patients were divided in 2 groups on the basis of platelet count; platelet counts of <150,000/mm^3 and platelet count of >150,000/mm^3. In patients with mild and moderate fibrosis (fibrosis levels of 1 and 2), 3 of 28 patients had platelet count of <150000/mm^3 and 25 had platelet counts of >150,000/mm^3. In two patients with fibrosis levels of 3, both of the patients had platelet counts of >150,000/mm^3.

To develop more insights about this, we calculated APRI in all patients with NAFLD. The cut-off value of APRI for significant fibrosis was considered 0.5 (Table I). The APRI levels were <0.5 in 15 patients and were >0.5 in 15 patients. However, when these patients with APRI value of >0.5 were evaluated for hepatic fibrosis through assessment of liver biopsy specimens, 14/15 (93.3%) patients had only mild fibrosis. Only, one (6.7%) patient with APRI of >0.5 had significant fibrosis in liver biopsy specimen. In 15 cases, the levels of APRI were less than 0.5 indicating insignificant fibrosis by APRI assessment. One (6.7%) of these patients had significant fibrosis and 12 (80%) had mild fibrosis and 2 (13.3%) had moderate fibrosis by liver biopsy (Table I).

DEMOGRAPHIC PROFILES, HEPATIC FIBROSIS AND APRI IN PATIENTS WITH NAFLD

Number of Patients	30
Mean Age	39.4±9.6 years
Sex (male: female)	16:14
Liver histopathology	
Mild hepatic fibrosis (Fibrosis score 1)	12 (40%)
Moderate hepatic fibrosis (Fibrosis score 2)	16(53.3%)
Severe hepatic fibrosis (Fibrosis score 3)	2 (6.7%)
APRI<0.5	15 (50%)
Mild fibrosis	12
Moderate fibrosis	2
Severe fibrosis	1
APRI>0.5	
Extent of fibrosis by liver histology	15 (50%)
Mild fibrosis	14
Moderate fibrosis	0
Severe fibrosis	1

Table I

On the other hand when we considered APRI level >1.5 as a cut-off value for significant fibrosis, one patient with APRI>1.5 showed significant fibrosis, but that could not be confirmed by assessment of liver histopathology. Chi square test was done to know the association between variables (APRI and histopathological findings). Sensitivity of APRI (cut off level 1.5) to diagnose significant fibrosis was 0%, specificity 96.4%, positive predictive value .0%, negative predictive value 93.1% and histopathology accuracy 90.0%.

DISCUSSION

Proper assessment of liver histopathology, especially understandings about hepatic fibrosis is essential for designing the management of patients with CLDs. Although chronic hepatitis and its complications represented the major bulk of CLDs before one decade, recently NAFLD and their related complications appear to be major concern in clinics[22-24]. In fact, NAFLD and its complications have reached worldwide epidemic level. Thus, proper assessment of hepatic fibrosis represents a major challenge to clinical hepatologists.

To develop insights about utility of non invasive diagnostic approaches for NAFLD patients, we assessed the utility of APRI, a widely-used marker of hepatic fibrosis, for diagnosing patients with chronic liver diseases due to viral etiologies[17-21]. Our study showed that the implication of APRI would be limited, if any, in the diagnosis of hepatic fibrosis in NAFLD patients. The causes underlying this are not still clear. But, the pathogenic process of NAFLD and that of virus-induced chronic hepatitis seems to be different. Few studies have explored the comparative mechanism of fibrosis of chronic hepatitis due to viral etiology and NAFLD. It has been shown that a two-hit theory may be responsible for hepatic fibrosis in NAFLD patients,[23] whereas, alteration of hepatic microenvironment due to virus and their products may induce hepatic fibrosis in chronic viral hepatitis and their complications[26]. The role of hepatic stellate cells may have vital role in the process of fibrogenesis that is activated in different manner due to viral infection and in NAFLD[26].

The findings of this clinical study differs from that what have been reported by Yilmaz et al[27]. They showed that APRI seems to be a potentially good marker of non invasive diagnosis of chronic hepatitis C and NAFLD, but they clearly marked that APRI has limited role in diagnosis of chronic hepatitis B. However, our study supports what that have been reported by Adams et al[28]. They mentioned that any simple serum marker may not be a good predictor of hepatic fibrosis in NAFLD. They also suggested that complex invasive fibrosis model would be required to have an accurate diagnosis of

NAFLD. Thus, emerging evidences have been accumulated to compare the utility of different non invasive markers of diagnosis of chronic liver diseases. Further studies would be required to develop more insights in this regard.

Indeed, there are some limitations of this study that have been compiled in Bangladesh. The sample size is relatively small. We could only enroll 30 patients with NAFLD. The small sample size was mainly attributable to the fact that only those patients who provided consent for liver biopsy were enrolled in this study. In fact, most of the patients in developing countries are reluctant to accept an invasive test like liver biopsy. The next, we enrolled only patients with NAFLD. A comparative analysis of utility of APRI in NAFLD patients and patients with CLDs due to viral etiology would shed more insights about the utility of APRI as a non invasive marker in our population.

Although the outcome of this study is a negative one, but it shows the utility of non invasive marker of hepatic fibrosis should be analyzed cautiously in patients with liver diseases with different etiologies. Also, the study should be conducted in different races and socio-economic groups to validate the real implications of these markers. As this is the first study about utility of APRI in Bangladesh, this study would initiate more studies of this nature with large sample size in future.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

FH: Conception and design, Analysis and interpretation of data.

MAH: Analysis of data, Critical revision of manuscript

SMFA: Drafting the manuscript.

SR: Acquisition of data

CONFLICT OF INTEREST

Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE

NONE DECLARED

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