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Performance of the AST to Platelet Ratio Index (APRI) as a Noninvasive Marker of Fibrosis in Pediatric Patients with Chronic Viral Hepatitis

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Abstract

We investigated the performance of AST to platelet ratio index (APRI) as a non-invasive marker of fibrosis and cirrhosis in children with chronic viral hepatitis. All patients 0–20 years old with chronic hepatitis B or C seen at a tertiary medical center from 1992–2008 were identified. 36 patients were evaluated with 48 biopsy results. The areas under the ROC curve were 0.71 for fibrosis and 0.52 for cirrhosis. When examining subgroups, the APRI performed better in older patients and in those with vertically transmitted HCV. Further research into APRI and other non-invasive markers of fibrosis in children with chronic viral hepatitis is warranted.

Keywords

hepatitis B; hepatitis C; APRI; non-invasive markers; fibrosis

Introduction

Chronic viral hepatitis remains a relatively rare, but significant problem among pediatric patients. Current prevalence estimates of hepatitis C among pediatric patients are 0.2 – 0.4% with an estimated cost of $160–400 million for the 2010–19 decade[1, 2]. The incidence of acute hepatitis B has declined rapidly in the United States due to vaccination, but neonates

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and young children are much more likely to progress to chronic hepatitis B infection than adults[3–6]. The optimal management of children with chronic viral hepatitis is still being investigated[7].

For patients with chronic viral hepatitis, liver biopsy is the standard for evaluation of disease severity and progression. Unlike adults who undergo liver biopsy as outpatients with only local anesthesia, pediatric patients routinely require general anesthesia and at least an overnight hospital stay post-procedure to observe for potential complications. Although the overall complication rate of percutaneous liver biopsy is low, significant hemorrhage leading to death can occur[8, 9]. Noninvasive markers of fibrosis in adults with chronic hepatitis B or hepatitis C have been evaluated with some success, but these markers would potentially have an even greater value in children[10–15].

The use of the Aspartate Aminotransferase (AST) to Platelet ratio index (APRI) as a correlate of disease progression is founded in the liver pathobiology. AST levels rise with the progression of liver disease as a likely result of direct hepatocellular damage and membrane leak although they may normalize in patients with compensated cirrhosis[16, 17]. Platelet counts decrease with progression of liver disease and the resultant changes in splenic blood flow[17–19]. These tests are collected as part of the standard of care for children with liver disease and thus would not result in added cost or effort.

Our goal was to investigate the performance of APRI as a potential non-invasive marker of fibrosis in children chronically infected with hepatitis B or C.

Materials and Methods

This study was reviewed and approved by the Duke University Institutional Review Board. All patients ages 0 – 20 years old with a diagnosis of chronic hepatitis B or hepatitis C seen at a tertiary medical center from January 1992 until January 2008 were evaluated. Patients were identified using several methods: 1) a search of inpatient/outpatient hospital databases for ICD-9 diagnosis codes related to hepatitis B or C (070.2, 070.3, 070.4, 070.5, 070.7, 070.9, V02.61, V02.62), 2) records obtained from the clinical laboratories for all pediatric patients with a positive result for a) HCV RNA, b) HCV antibody test, c) Hepatitis B surface antigen, or d) HBV DNA. Using the compiled roster of patients, the diagnosis of chronic HBV or HCV infection was confirmed by chart review. Dictated pathology reports of liver biopsies performed on any of these patients were then evaluated to determine the fibrosis score using the METAVIR system (fibrosis stage I – IV). Laboratory data within 4 months of liver biopsy was used for the calculations. AST was measured using the Vitros system enzymatic rate reaction and platelets were measured using electronic impedance (resistance) or fluorescent flow cytometry. An AST value of 40 was used as the upper limit of normal (ULN). APRI was calculated with the following formula:

$$\text{APRI} = \frac{\text{AST level (/ULN)}}{\text{Platelet count } (10^9/\text{L})} \text{ X } 100$$

Patients were excluded for incomplete data, or if they were recent liver transplant recipients. Fibrosis was defined as a METAVIR score of II or III and cirrhosis was defined as a score of IV on biopsy. 6 patients had a dictated pathology report that did not assign a METAVIR score. In those cases, one investigator (SC) blinded to the patient's historical data used the elements of the report to assign a METAVIR score range. In our analysis, we conducted separate analyses using the higher and lower scores and they did not influence the performance of the test. We utilized the lower scores and proceeded as described below.

We evaluated the value of the APRI in predicting liver fibrosis or cirrhosis by using nonparametric methods to produce receiver operator characteristic (ROC) curves. The main analysis was limited to the first reported biopsy results for the patient. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) were calculated for APRI of 0.5 and 1.5. We conducted the analysis with STATA 10 (College Station, Texas).

Results

We identified 36 patients with complete data who had a total of 48 biopsies performed. The average age of the patients was 11.6 years (range, 1–20 years), 50% (18/36) of the patients were male, and HCV infected patients made up 69% (25/36) of the cohort. The vast majority of the patients were treatment naive at the time of biopsy. Among the HCV infected children, 7 had vertical transmission, 9 had transfusion transmission and 9 had an unknown route. On average, children with vertical transmission were younger than those with transfusion transmission (8.0 yrs vs. 14.9 yrs) and had lower fibrosis scores (1.1 vs. 1.6 respectively).

The median APRI was 0.44 [IQR, 0.24, 0.97] and 0.33 [0.20, 0.44] among the patients with Hepatitis B and C, respectively (P=0.33). The median fibrosis score was 2 [1, 2] and 1 [1, 2] among the patients with Hepatitis B and C, respectively (P=0.22).

ROC curves were generated for the entire cohort, as well as the following subgroups: Hepatitis B vs. Hepatitis C infected; age <13 years and ≥ 13 years. The area under the ROC (AUC) was 0.71 for identifying patients with fibrosis and 0.52 for identifying patients with cirrhosis on liver biopsy. Table 1 summarizes the performance and 95% confidence intervals of each subgroup. APRI performed reasonably well when predicting fibrosis in patients with HBV and HCV (0.64 and 0.75, respectively) and in children > 13 (0.65). Within the HCV infected patients, the performance was better in predicting fibrosis among those patients with vertically transmitted infection compared to transfusion transmitted infection (1.00 vs. 0.53). When all biopsy results were included in a separate analysis (n=48), ROC values were 0.63 and 0.47 for fibrosis and cirrhosis, respectively.

The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratios for APRI cutoff values of 0.5 and 1.5 for predicting fibrosis or cirrhosis are given in Table 2.

Discussion

The APRI was designed to be a convenient marker of fibrosis since it incorporates laboratory data that are routinely obtained as standard of care. Initial studies showed that it performed well in predicting fibrosis and cirrhosis in both a training and validation set of adults with chronic HCV infection[11, 13, 15].

There have been few studies in children. Our study found that the APRI was moderately useful in predicting significant fibrosis where it could be a substitute for liver biopsy with AUC of 0.71. This is in line with the findings of Lebensztejn et al in their study of children with hepatitis B which found an AUC of 0.74 in predicting advanced liver fibrosis[12]. de Ledinghen et al studied APRI in comparison to Fibrosure and Fibroscan and found an AUC of 0.73 for predicting cirrhosis in children with various chronic liver diseases[10]. This study did not generate ROC values for APRI and fibrosis and they only had 2 children with Hepatitis B or C so direct comparisons between our study and their study would be difficult.

The finding that APRI predicted fibrosis slightly better in patients older than 13 is worth further discussion. When examining this closely, this may reflect some bias in the analysis. Since we had several patients with multiple biopsies, we used one data point per patient and chose the most recent value. Since some of these patients had disease progression, this may reflect some sampling bias. The fact that APRI performed comparatively well in the subset of HCV patients with vertically transmitted disease is also interesting, but this also may reflect sampling bias in a small subpopulation.

The APRI is inherently limited by the use of a standard upper limit of normal value. Past studies have shown that many pediatric patients have normal AST values of 15–20, but an AST of 40 would likely generate a low APRI value despite the fact that this value would be twice that patient's normal value[20]. Unfortunately, we, as clinicians taking care of these patients, are rarely provided with an AST value that precedes their viral hepatitis.

Another limitation of the APRI that has been fairly consistent is the lack of sensitivity for mild to moderate fibrosis. This is logically based on the pathobiology involved. AST levels rise and platelet counts fall relatively late in disease progression, and the data in children with HBV and HCV reinforce this point[17, 21–28]. In patients with compensated cirrhosis with normal AST values, the test would also be a poor predictor of significant fibrosis.

This study is limited by its small sample size, retrospective nature, and analysis of patients from a single center. Although some of the laboratory data was obtained as far as 4 months from the biopsy date, Wai et al have validated the APRI using lab data up to 4 months from the biopsy date[15]. Given the duration of 16 years of patient records, the study is also limited by intra- and interobserver variability of pathologists examining biopsy samples. We did not have the resources to re-examine all biopsies to limit this variability. There was also no consideration of inflammatory activity. We chose to focus on the ability of APRI to predict fibrosis and cirrhosis alone, but we recognize that in certain scenarios (HBV infection), inflammatory activity is an important factor to consider. The method of AST measurement changed at our institution in April 2008. Despite a listed ULN value of 60 for adults, we used a value of 40 for this pediatric study given the historical values[20]. This change in methodology may alter the value of the APRI index going forward.

A validated noninvasive marker of fibrosis would be very useful in pediatric patients. Such a marker could help guide clinicians in whom to treat, and serve as a longitudinal marker of treatment efficacy without the need for repeated liver biopsies. The results of this study indicate that APRI is not such a marker except perhaps in a defined group of patients. Further research is needed in this area to identify noninvasive markers that are reliable and feasible for use in pediatric patients.

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Table 1

Summary of Demographics

Mean age of patients at biopsy	12.4 years (range 1 – 20 years)
Hepatitis B	14 (29%)
Hepatitis C	34 (71%)
Mean fibrosis score	1.6 (range 0–4)
Sex	50% male, 50% female

Table 2

APRI for prediction of fibrosis and cirrhosis

	Sensitivity	Specificity	PPV	NPV	+ LR	− LR
Fibrosis						
APRI >0.5	47	90	80	65	4.5	0.6
APRI >1.5	18	100	100	58	n/a	0.8
Cirrhosis						
APRI >0.5	33	73	10	92	1.2	0.9
APRI >1.5	0	91	0	91	0	1.1

Key: positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR)