Aspartate aminotransferase-to-platelet ratio index in children with cholestatic liver diseases to assess liver fibrosis

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To assess the relationship between aspartate aminotransferase-platelet ratio index (APRI) and liver fibrosis in children with chronic hepatocellular and biliary cholestatic liver diseases. A retrospective review of one hundred children's demographic and laboratory findings concurrent with liver biopsy, who were followed-up with prolonged cholestasis. The diagnostic accuracy of the APRI was assessed by receiver operating characteristic (ROC) curves. Advanced fibrosis was more common in the hepatocellular group. The APRI values of the two groups were similar. The patients with advanced fibrosis had significantly higher APRI values than patients with mild fibrosis, in both the hepatocellular and biliary groups. The areas under the ROC were 0.68 and 0.81 in the hepatocellular and biliary groups respectively. The cut-off values of APRI for discriminating advanced fibrosis were 0.93 (65% sensitivity, 69% specificity) in the hepatocellular group and 2.35 (62% sensitivity, 96% specificity) in the biliary group. APRI may be most efficient for discriminating between advanced and mild fibrosis in biliary cholestatic liver disease patients.

Key words: aspartate aminotransferase-platelet ratio index (APRI), liver fibrosis, cholestatic liver diseases.

Histopathologically, liver fibrosis develops by deposition of fibril structures in the extracellular matrix as a response to metabolic, immunologic, toxic and infectious agents. Liver biopsy is the gold standard for evaluation of fibrotic stage and grading of the disease. However, parents often hesitate to accept this invasive procedure because of complications and mortality. Additionally, patchy infiltrates of pathologic tissue may not be seen with biopsy specimens, which are estimated to represent only a 50,000th of the total liver[1]. Sampling errors and inter- and intra-observer variations hamper staging and grading of fibrosis. Affordable, applicable, reliable and simple tests, biomarkers and measurements are required for improved fibrosis assessment. Aspartate aminotransferase (AST) - platelet ratio index (APRI) has been applied for liver fibrosis assessment, especially in adult hepatitis C patients[2,3,4]. Here we study the relationship between APRI and liver fibrosis in children with chronic hepatocellular and biliary cholestatic liver diseases.

Material and Methods

The study was conducted between January 2006 and December 2011 at the Gazi University, Department of Pediatric Gastroenterology and Hepatology. We retrospectively reviewed medical records of patients who were followed-up with prolonged cholestasis. Conjugated or direct bilirubin fraction of >20% of the total serum bilirubin (or conjugated bilirubin level of >2 mg/dl) is defined as cholestasis[5]. Patients with comorbid disease (e.g., sepsis, infections, or muscle disease) which could affect AST and platelet levels were excluded. One hundred patients were included in the study. Demographic

data, platelet count (10^3/ml), prothrombin time–international normalized ratio (PT–INR), biochemical parameters [including total and direct bilirubin, albumin, gama glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were recorded concurrently with liver biopsy. Written informed consent was provided by parents before liver biopsy. APRI was calculated as: serum AST level (U/L)/upper normal×100/platelet count ($10^3/\mu$L). The biopsy specimens were analyzed by an experienced liver pathologist, blinded to the clinical data. Liver fibrosis was evaluated according to the Scheuer scoring system (Table I)[6]. Stages 1 and 2 were defined as mild fibrosis and stages 3 and 4 as advanced fibrosis.

Statistical analysis

Data were represented as median values (25^{th} to 75^{th} percentile). Distribution normality of variables was assessed by the Kolmogorov-Smirnov test. As the continuous data distribution was not normal, comparison between variables were analyzed by the Mann–Whitney U test. Differences in categorical variables were analyzed by the chi-square test. The diagnostic accuracy of the APRI was assessed by receiver operating characteristic (ROC) curves. All of the cut-off values were designated as the probability of a true positive (sensitivity) and a true negative (specificity). SPSS Software (version 17.00, Chicago, IL, USA) was used for all statistical analyses. Values of $p<0.05$ were considered statistically significant. This study was approved by Gazi University institutional ethics committee.

Results

The patients were categorized as either hepatocellular (n=66) or biliary cholestatic liver disease (n=34). Diagnoses of all patients are shown in Table II. Progressive familial intrahepatic cholestasis (PFIC) (n=29), idiopathic cholestasis (n=27), and biliary atresia (n=19) were the most frequent diseases. The clinical characteristics of all patients are shown in Table III.

The median age of the biliary group was younger than the hepatocellular group. The two groups had a similar female to male ratio. Median AST, ALT and ALP values were higher in the biliary group than the hepatocellular group, but without statistical significance. The median GGT and bilirubin levels were significantly higher and the median albumin

Table I. Scheuer Classification for Staging of Liver Fibrosis[6]

Stage	Fibrosis
0	None
1	Enlarged, fibrotic portal tracts
2	Periportal or portal-portal septa, but intact architecture
3	Fibrosis with architectural distortion, but no obvious cirrhosis
4	Probable or definite cirrhosis

Table II. Diagnosis and Classification of Patients (n=100)

		N
Hepatocellular group (n=66)	PFIC	29
	Prematurity, sepsis or total parenteral nutrition related cholestasis	6
	Neonatal hepatitis	2
	Alpha-1 antitrypsin deficiency	2
	Idiopathic cholestasis	27
Biliary group (n=34)	Biliary atresia	19
	Non-syndromic bile duct hypoplasia	2
	Choledochal cyst	4
	Alagille syndrome	9

PFIC; Progressive familial intrahepatic cholestasis

Table III. Demographic and Laboratory Characteristics of Patients

	Hepatocellular group n=66 (66 %)	Biliary group n=34 (34 %)	P
Age, months	10.0 (4.7-36)	2.0 (1.3-6.7)	<0.001
Male, n	38 (57.6 %)	16 (47.1 %)	0.32
Advanced fibrosis, n	40 (60.6 %)	8 (23.5%)	<0.001
AST, IU/L	120.0 (68.5-187.0)	172.0 (111.5-228.5)	0.06
ALT, IU/L	77.5 (44.7-142.0)	96.5 (71.0-135.2)	0.32
GGT, IU/L	89.0 (29.7-179.5)	494.5 (245.5-1128.2)	<0.001
ALP, IU/L	373.0 (278.0-693.7)	569.5 (414.5-705.2)	0.07
Albumin, g/dl	4.1 (3.4-4.4)	3.5 (3.1-3.9)	0.003
T. Bilirubin, mg/dl	4.0 (0.6-9.9)	8.6 (4.6-12.7)	0.02
D. Bilirubin, mg/dl	2.8 (0.2-7.9)	6.51 (2.8-9.1)	0.02
Platelet, x1000/UL	268.0 (144.0-355.7)	358.1 (252.4-520.1)	0.002
PT, sn	13.0 (11.7-15.2)	11.9 (10.9-12.8)	0.02
INR	1.09 (0.99-1.28)	1.015 (0.94-1.09)	0.04
APRI	0.96 (0.67-3.61)	1.045 (0.69-1.98)	0.69

AST: aspartate aminotransferase, ALT: alanine aminotransferase; GGT: gama glutamyl transferase, ALP: alkaline phosphatase, T: total, D: direct, PT: prothrombin time, INR: international normalized ratio, APRI: aspartate aminotransferase - platelet ratio index

Table IV. Characteristics of Patients According to Fibrosis Stage in Hepatocellular Group

	Fibrosis stage F0, F1, F2 n=26 (39.4 %)	Fibrosis stage F3, F4 n=40 (60.6 %)	P
Age, months	6.0 (2.0-36.0)	12.0 (6-40.5)	0.19
Male, n	13 (50 %)	25 (62.5 %)	0.32
AST, IU/L	110.0 (67.2-160.2)	123.5 (65.7-212.5)	0.38
ALT, IU/L	96.0 (49.5-154.2)	71.5 (44.2-136.5)	0.68
GGT, IU/L	103.5 (23.7-246.2)	86.5 (35.2-164.0)	0.85
ALP, IU/L	450.0 (310.2-699.2)	358.0 (244.0-713.0)	0.33
Albumin, g/dl	4.2 (3.6-4.5)	3.9 (3.3-4.3)	0.16
T. Bilirubin, mg/dl	5.3 (0.97-11.3)	2.85 (0.48-9.52)	0.43
D. Bilirubin, mg/dl	4.0 (0.4-8.6)	2.15 (0.22-7.80)	0.43
Platelet, x1000/UL	330.7 (249.5-445.0)	236.45 (126.25-297.75)	0.003
PT, second	12.3 (11.2-14.0)	13.4 (12.2-16.4)	0.047
INR	1.03 (0.93-1.16)	1.12 (1.02-1.38)	0.049
APRI	0.81 (0.45-1.24)	1.20 (0.72-5.25)	0.01

AST: aspartate aminotransferase, ALT: alanine aminotransferase; GGT: gama glutamyl transferase, ALP: alkaline phosphatase, T: total, D: direct, PT: prothrombin time, INR: international normalized ratio, APRI: aspartate aminotransferase - platelet ratio index

level was significantly lower in the biliary group. The median platelet count was lower and the PT-INR values were prolonged in the hepatocellular group compared to the biliary group. Advanced fibrosis was more common in the hepatocellular group than the biliary group. The APRI values of the two groups were similar (Table III).

The patients' characteristics were reevaluated according to the fibrosis stage of the groups. In the hepatocellular group 26 patients had mild fibrosis (39.4%) and 40 patients had

Table V. Characteristics of Patients According to Fibrosis Stage in Biliary Group

	Fibrosis stage F0, F1, F2 n=26 (76.5 %)	Fibrosis stage F3, F4 n=8 (23.5 %)	P
Age, months	2.0 (1.0-4.5)	6.0 (2.1-11.2)	0.11
Male, n	11 (42.3 %)	5 (62.5 %)	0.32
AST, IU/L	157.0 (97.5-195.0)	225.5 (145.0-287.5)	0.04
ALT, IU/L	104.5 (65.0-136.0)	87.5 (74.7-130.2)	0.86
GGT, IU/L	534.5 (288.2-1128.2)	389.0 (219.7-1202.2)	0.70
ALP, IU/L	539.0 (362.5-663.2)	641.5 (502.0-816.0)	0.16
Albumin, g/dl	3.5 (3.2-3.9)	3.15 (2.05-4.2)	0.39
T. Bilirubin, mg/dl	7.0 (2.3-11.4)	12.0 (9.2-14.8)	0.01
D. Bilirubin, mg/dl	4.3 (1.3-8.8)	9.0 (6.8-12.2)	0.01
Platelet, x1000/UL	358.1 (279.5-488.5)	352.5 (126.1-581.2)	0.73
PT, second	11.9 (10.9-12.6)	12.3 (10.7-18.4)	0.37
INR	1.0 (0.94-1.07)	1.03 (0.92-1.56)	0.46
APRI	0.98 (0.69-1.42)	2.4 (1.07-3.16)	0.008

AST: aspartate aminotransferase, ALT: alanine aminotransferase; GGT: gama glutamyl transferase, ALP: alkaline phosphatase, T: total, D: direct, PT: prothrombin time, INR: international normalized ratio, APRI: aspartate aminotransferase - platelet ratio index

advanced fibrosis (60.6%). Neither age nor gender were associated with fibrosis stage. The AST, ALT, GGT, albumin, and bilirubin values were similar in the mild and advanced fibrosis patients. The patients with advanced fibrosis had significantly lower platelet, and higher PT-INR and APRI values, than patients with mild fibrosis (Table IV).

In the biliary group, 26 (76.4%) patients had mild fibrosis and 8 (23.6%) patients had advanced fibrosis. No age or sex differences were observed between these groups. The ALT, GGT, ALP, albumin, platelet and PT-INR

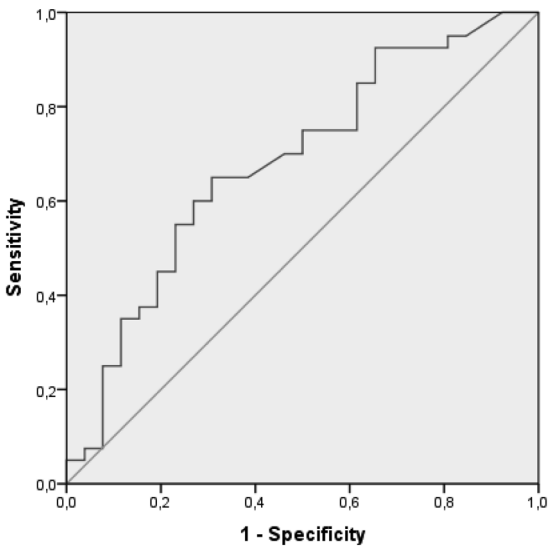

Fig. 1. ROCs for APRI in hepatocellular group; the area under the curve was 0.68 (p=0,013; 95% confidence interval: 0.55–0.82), the cut-off value of APRI for discriminating advanced fibrosis (F=3, F=4) was 0.93 (65% sensitivity, 69% specificity)

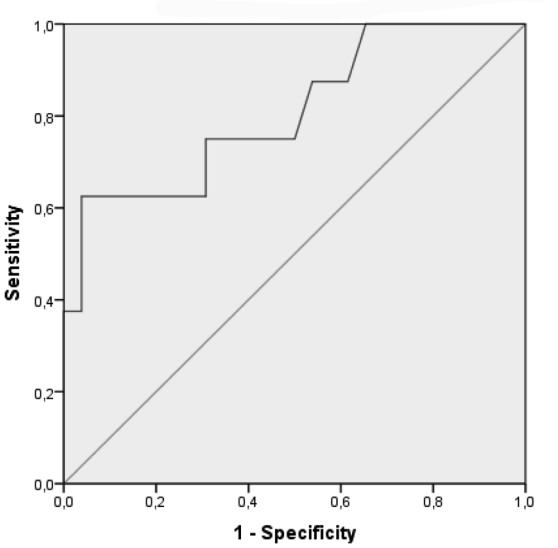

Fig. 2. ROCs for APRI in biliary group; the area under the curve was 0.81 (p=0,009; 95% confidence interval: 0.62–0.99), the cut-off value of APRI for discriminating advanced fibrosis (F=3, F=4) was 2.35 (62% sensitivity, 96% specificity)

values were similar between the two groups. However, the AST, bilirubin and APRI values were significantly higher in the patients with advanced fibrosis ($p<0.05$) (Table V).

ROCs were used to discriminate between mild and advanced fibrosis. The areas under the ROCs (F0–1-2 vs F3–4) were 0.68 and 0.81 in the hepatocellular and biliary groups respectively. The cut-off values of APRI for discriminating advanced fibrosis were; 0.93 (65% sensitivity, 69% specificity) in the hepatocellular group; and 2.35 (62% sensitivity, 96% specificity) in the biliary group (Figs. 1 and 2).

Discussion

Liver biopsy is troublesome during childhood and may lead to complications, especially in advanced liver diseases characterized by portal hypertension, thrombocytopenia, and prolonged PT-INR values. Therefore, recent interest has focused on novel techniques and markers that might replace liver biopsy. Among these tests, APRI show promising results, either used alone or in combination with other tests. Although APRI has been validated for liver fibrosis evaluation in children with biliary atresia[7], to our knowledge, no study has yet evaluated liver fibrosis and APRI in any liver disease other than childhood biliary atresia.

In children with biliary atresia who underwent a Kasai procedure, the post-operative follow-up of liver fibrosis of Metavir classification F4 was related to an APRI cut-off value of 1.42; while a Metavir classification of F≥3 was related to an APRI cut-off value of 1.01[7]. Similarly, in children with biliary atresia who underwent a Kasai procedure, APRI was assessed for predicting the presence of esophageal varices[8]. Colecchia et al.[8] showed that an APRI score of >0.96 had relevance for the presence of esophageal varices, with a sensitivity of 86% and a specificity of 81% (positive predictive value of 87.5%, negative predictive value of 87%).

APRI was especially useful for assessing adult patients' liver fibrosis with chronic hepatitis B, hepatitis C, alcoholic and non-alcoholic fatty liver diseases, autoimmune liver disease, and liver transplant patients[2,9-12]. Most of the studies found that an APRI score of ≤0.5 could be used to exclude advanced fibrosis in hepatitis C patients. In this study, an APRI score of ≤0.5 was found in 42 of 45 advanced cholestatic liver disease patients. A recent meta-analysis demonstrated that the diagnostic accuracy of the 0.7 APRI threshold was 77% sensitive and 72% specific for discriminating advanced fibrosis, and that a threshold of 1.0 was 61% sensitive and 64% specific for discriminating severe fibrosis in chronic hepatitis C patients[2]. Jin's meta-analysis also demonstrated that the diagnostic accuracy of the 0.5 APRI threshold was 84% sensitive and 41% specific, and that the 1.0 threshold was 49% sensitive and 84% specific, for discriminating severe fibrosis with chronic hepatitis B[9]. There is no available APRI value for determining fibrosis in autoimmune liver diseases[10] and the accuracy of APRI in alcoholic fatty liver diseases has been shown to be inconclusive[11].

In this study we evaluated the relationship between APRI and advanced fibrosis in patients with hepatocellular and biliary cholestasis. We also compared hepatocellular and biliary cholestasis groups. The median age was lower in the biliary group than in the hepatocellular group. This finding was probably due to the high number of biliary atresia patients in the biliary group, since biliary cholestatic liver diseases (especially biliary atresia) usually leads to early symptoms and liver fibrosis. Additionally, GGT and bilirubin levels were higher and the albumin level lower in the biliary group than in the hepatocellular group, as would be expected. Advanced liver fibrosis was more common in the hepatocellular group. In line with this finding, prolonged PT-INR and thrombocytopenia were common in the hepatocellular group. These findings might be explained by the older age and higher number of PFIC patients in the hepatocellular group.

Parallel increasing of APRI and fibrosis stage were observed in both groups. According to ROC analysis, APRI was more useful for discriminating between mild and advanced fibrosis in the biliary group than in the hepatocellular group.

The cut-off value of APRI for discriminating advanced fibrosis was 2.35. This value had notable specificity (96%) in the biliary group. In both groups, an increased APRI value was correlated with decreased sensitivity and increased specificity of the test for

discriminating the fibrosis stage.

In conclusion, APRI may be most efficient for discriminating between advanced and mild fibrosis in the biliary group. Prospectively, repeated biopsies and synchronous APRI measurements were not performed; a limitation of this study. APRI could be used as a simple test in children with chronic cholestatic liver diseases to evaluate fibrosis stage. However, correlation of the APRI with fibrosis must be validated in future studies.

REFERENCES

1. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001; 344: 495-500.
2. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 2011; 53: 726-736.
3. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: a systematic review. Hepatology 2007; 46: 912-921.
4. Usluer G, Erben N, Aykin N, et al. Comparison of non-invasive fibrosis markers and classical liver biopsy in chronic hepatitis C. Eur J Clin Microbiol Infect Dis 2012; 31: 1873-1878.
5. Vicky Lee NG, Neonatal Hepatitis. In: Wyllie R, Hyams JS, eds. Pediatric Gastrointestinal and Liver Disease Pathophysiology, Diagnosis, Management. Philadelphia: Saunders Elsevier; 2006: 851.
6. Theise ND. Liver biopsy assessment in chronic viral hepatitis: a personal, practical approach. Mod Pathol 2007; 20 (Suppl 1): S3-S14.
7. Kim SY, Seok JY, Han SJ, Koh H. Assessment of liver fibrosis and cirrhosis by aspartate aminotransferase-to-platelet ratio index in children with biliary atresia. J Pediatr Gastroenterol Nutr 2010; 51: 198-202.
8. Colecchia A, Di Biase AR, Scaioli E, et al. Non-invasive methods can predict oesophageal varices in patients with biliary atresia after a Kasai procedure. Dig Liver Dis 2011; 43: 659-663.
9. Jin W, Lin Z, Xin Y, et al. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis B-related fibrosis: a leading meta-analysis. BMC Gastroenterol 2012; 12: 14.
10. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, et al. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. Ann Hepatol 2008; 7: 350-357.
11. Lieber CS, Weiss DG, Morgan TR, Paronetto F. Aspartate aminotransferase to platelet ratio index in patients with alcoholic liver fibrosis. Am J Gastroenterol 2006; 101:1500-1508.
12. Pissaia A Jr, Borderie D, Bernard D, et al. APRI and FIB-4 Scores Are Useful After Liver Transplantation Independently of Etiology. Transplant Proc 2009; 41: 679-681.