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AST to Platelet Index Correlates with Hepatic Cirrhosis But Not with Fibrosis in Pediatric Patients with Intestinal Failure

Juan J Díaz, MD, PhD^{1,*}, Kathleen M. Gura, Pharm.D^{2,3}, Julianna Roda, MD⁴, Antonio R. Perez-Atayde, MD⁵, Christopher Duggan, MD, MPH³, Tom Jaksic, MD, PhD⁶, and Clifford W. Lo, MD, PhD³

¹Pediatric Gastroenterology and Nutrition, Hospital Universitario Central de Asturias

²Department of Pharmacy, Boston Children's Hospital, Boston, MA

³Center for Advanced Intestinal Rehabilitation, Center for Nutrition, Division of GI/Nutrition, Boston Children's Hospital, Boston, MA

⁴Hospital Pediátrico de Coimbra-CHC, Coimbra, Portugal

⁵Department of Pathology, Boston Children's Hospital, Boston, MA

⁶Center for Advanced Intestinal Rehabilitation, Division of Pediatric General Surgery, Boston Children's Hospital, Boston, MA

Abstract

Patients with Intestinal failure (IF) require parenteral nutrition (PN) support to obtain enough nutrients to sustain growth. long-term PN use is associated with significant liver damage.

Objective—To analyze the utility of a non-invasive test, the aspartate aminotransferase (AST) to platelet ratio index (APRI), in the diagnosis of liver disease in pediatric patients with IF.

Methods—Medical records of all Boston Children's Hospital patients who received PN and underwent a liver biopsy from January 2006 until November 2010 were reviewed. Patients with a clinical diagnosis with IF were selected. APRI was calculated as follows (AST (U/L)/ upper normal limit) × 100/ platelets (10⁹/L). Presence of fibrosis and cirrhosis was estimated using the METAVIR score in liver biopsies.

Results—62 liver biopsies from 48 patients (22 female) were studied. Mean APRI values in the different METAVIR categories (0-1; 2-3; 4) were: 1.80, 1.17, and 4.24 respectively (ANOVA; P=0.053; Bonferroni test for cirrhosis versus fibrosis P=0.048). APRI could significantly predict cirrhosis (OR 1.2.; 95% CI 1.001-1.43) but not significant fibrosis (METAVIR 2-3, OR 1.00; 95% CI =0.86-1.18). Area under the receiver operating characteristic curve for cirrhosis was 0.67 (95% CI= 0.45-0.89; p=0.13).

Conclusion—APRI, a non invasive, easy to obtain bedside test significantly predicts cirrhosis but not fibrosis in pediatric patients with IFALD. As the clinicians need a non invasive test to differentiate among different stages of liver fibrosis rather than differentiating cirrhosis from

*Corresponding Author's Address: Juan J Díaz . Unidad de Gestión Clínica de Pediatría. Sección de Gastroenterología y Nutrición Pediátrica. Hospital Universitario Central de Asturias, Oviedo. SPAIN. Phone number: 0034-985108000 (ext 38242), juanjo.diazmartin@gmail.com.

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normal, we cannot recommend the use of this test in pediatric patients with IFALD for this purpose.

Keywords

Intestinal failure; Liver disease; Parenteral nutrition; Diagnostic test

INTRODUCTION

Intestinal failure (IF) is defined as the inability of the gut to acquire the appropriate amount of nutrients necessary to sustain growth. Children with IF are typically dependent on parenteral nutrition (PN) support for prolonged periods of time. Long term PN is a life saving therapy for these children and home PN programs are a part of the standard care of many IF patients (1,2).

Long term PN use, however, has numerous complications, including catheter related sepsis, metabolic imbalance and organ dysfunction. Intestinal failure associated liver disease (IFALD) is a potentially life-threatening complication in this population. (3).

IFALD progresses from a mild periportal inflammation and cholestasis, to bile duct proliferation, fibrosis and cirrhosis (4). A diagnosis of IFALD is typically determined by laboratory values, whereas the development of fibrosis and cirrhosis can only be demonstrated by a liver biopsy. Although liver biopsy is the gold standard to evaluate the presence and degree of fibrosis, it is invasive procedure and may result in life-threatening complications (5). Other drawbacks associated with the use of liver biopsies for diagnosis of fibrosis include: sampling error, inter- and intra-observer variability and an inability to assess progression/regression of fibrosis (6-8).

The need to identify a non invasive test to assess disease progression in children with IFALD is imperative. Noninvasive measurements of hepatic fibrosis have been developed in adults with chronic hepatitis C (9,10). Previous studies have shown promising results with an easy, non invasive tool, the aspartate aminotransferase (AST) to platelet ratio index (APRI) (11).

Over the past several years, a number of pediatric studies have been published, mainly in children with biliary atresia and chronic hepatitis B and C, describing the utility of APRI (12-14). Little is known, however, about the performance of non-invasive liver function tests in children with IF. The aim of our study was to evaluate the utility of the APRI in assessing liver fibrosis and cirrhosis in children and young adults with intestinal failure.

PATIENTS AND METHODS

The medical records of all Boston Children's Hospital patients who received PN a minimum of three months and had a liver biopsy from January 2006 until November 2010 were retrospectively reviewed. Only those patients with a clinical diagnosis consistent with IF were included. These included those patients followed by either the Home Parenteral Nutrition Program or the Center for Advanced Intestinal Rehabilitation (CAIR) Program. Patients were considered to have IF if they were unable to maintain adequate protein-energy, fluid, electrolyte, or micronutrient intake without PN support for more than 3 months. Only patients with complete laboratory and clinical data at the time of the liver biopsy were included in the study. The study protocol was approved by the Boston Childre's Hospital Institutional Review Board.

Biochemical Parameters

For all children, the following laboratory determinations were obtained within 1 week from the liver biopsy sampling: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total and direct bilirubin, and the International Normalized Ratio for prothrombin time (INR). When several laboratory data were available within 1 week of the biopsy, the one chosen for the calculation of the APRI score was the value closest to the date of the biopsy.

An AST value of 40 IU/L was used as the upper normal limit. APRI was calculated according to the formula developed by Wai et al (11): $\text{AST (U/L) / upper normal limit} \times 100 / \text{platelets (10}^9\text{/L)}$.

Liver Histology

Liver biopsies were reviewed by an experienced liver pathologist who was blinded for the laboratory and APRI score values of the patients. Fibrosis status was estimated using the METAVIR score (15). This score consists of 5 stages based on the degree and type of fibrosis: F0 (no fibrosis), F1 (periportal fibrosis without septa), F2 (portal fibrosis with few septa), F3 (numerous septa, bridging fibrosis) and F4 (cirrhosis). For analysis purposes, METAVIR scores 2 and 3 were considered indicative of significant fibrosis.

Statistical Analysis

Data were collected in a database created ad hoc for the study with logic and range filters in order to avoid wrong data input. Analysis was performed using the Statistical Package for the Social Sciences (SPSS; SPSS Inc, Chicago, Ill) version 15.0 for Windows. Data are shown as mean (SD). Statistical analysis included: t test, one way ANOVA, Bonferroni post-hoc test, Pearson and Spearman correlation coefficients, logistic regression analysis and receiver operating characteristic (ROC) curve. P values < 0.05 were considered statistically significant.

RESULTS

Sixty-two liver biopsy samples from 48 patients (22 female), with ages ranging from 0.2 to 19 years (mean 2.03, SD 3.2 years), were included in the study. IF was secondary to necrotizing enterocolitis in 14 patients (29.2%), gastroschisis in 11 (22.9%), intestinal atresia in 10 (20.8%) and chronic intestinal pseudoobstruction in 4 (8.3%). Other causes including Hirschsprung's disease, midgut volvulus, arterial portal fistulae, cloacal extrophy, post prandial antral hypomotility, and apple peel intestinal atresia, were also observed.

Only one biopsy was a surgical wedge biopsy, 60 were needle biopsies and one sample came from an explant. The median length of the needle biopsy core was 1.6 cm. Thirty-two percent of the biopsy cores were greater than 1.9 cm.

Clinical characteristics of the patients are summarized in Table I. Significant fibrosis (METAVIR 2-3) was present in 45.2% and cirrhosis (METAVIR 4) in 12.9% of the biopsies. Mean APRI values in the different METAVIR categories (0-1; 2-3; 4) were: 1.80, 1.17, and 4.24 respectively (ANOVA; $P=0.053$). Bonferroni post hoc test for cirrhosis vs. fibrosis $P=0.048$. (Fig 1) The APRI score correlated significantly with all the other hepatic function parameters included in the study (Table II). Fibrosis score showed a significant positive correlation with INR (Spearman correlation coefficient= 0.28; $p = 0.03$) and with total (Spearman correlation coefficient= 0.26; $p = 0.04$) and direct bilirubin (Spearman correlation coefficient= 0.29; $p = 0.03$), but not with APRI score, or albumin values (data

not shown). No significant correlation was observed between age and APRI scores ($r = 0.13$; $p = 0.33$).

APRI could not significantly predict significant fibrosis (OR 1.006; 95% CI = 0.86-1.18). On the other hand, APRI values were able to predict cirrhosis (OR 1.2.; 95% CI = 1.001-1.43). Figure 2 shows the ROC for the prediction of cirrhosis (METAVIR 4) versus the rest of the patients (METAVIR 0-3). The area under the ROC was 0.67 (95% CI = 0.45-0.89; asymptotic $p = 0.13$).

Using an APRI value of 2 as cut off point for the diagnosis of cirrhosis, we obtained a Specificity of 83.3%, a 37.5% Sensitivity and a positive Likelihood ratio of 2.2. Table 3 shows the performance of the test using different cut off values.

DISCUSSION

The prognosis of IFALD depends greatly upon the extent of hepatic fibrosis. Liver biopsy remains the gold standard to determine disease progression and response to therapy, but has numerous limitations and is not without risk (16). Complications such as hemobilia, hypotension, and intraperitoneal hemorrhage can occur, some of which are fatal (17,18). It is also a particularly painful procedure in children, further limiting its usefulness in assessing disease progression on a routine basis. In recent years, several non-invasive tests have been developed. Transient elastography (FibroScan®) measures the elasticity or stiffness of the liver; the stiffer the liver, the more severe the hepatic fibrosis. It has shown promising results in adults (19), but its use in children is still limited. The 1-13C-methionine breath test (MBT) is another noninvasive method of assessing hepatic function. This test uses 1-13C-methionine, a non radioactive isotope that is metabolized exclusively by hepatic mitochondria. When metabolized, 1-13C-methionine results in an increased concentration of 13-CO₂ in the expired breath. It is thought that the quantity of 13-CO₂ measured in the breath correlates to the severity of liver disease. Duro et al (20), demonstrated the utility of MBT in assessing IFALD, although, like transient elastography, the technology involved is complex and expensive limiting its usefulness in routine clinical practice.

The APRI has been used to detect fibrosis and cirrhosis in adult patients with hepatitis B and C, alcoholic liver disease and nonalcoholic fatty liver disease with promising results. In a recent meta-analysis, Lin and colleagues (21) included 40 studies comprising a total of 8739 adult patients with chronic hepatitis C, with a prevalence of severe fibrosis and cirrhosis of 28 and 19% respectively. APRI showed a diagnostic accuracy of 0.80 for severe fibrosis and 0.83 for cirrhosis.

Studies in children are scarce, and have been developed mainly in children with chronic hepatitis and biliary atresia. McCoogan (13) studied a series of 36 pediatric patients with chronic hepatitis (B or C) and observed an area under the ROC curve of 0.71 for fibrosis and 0.52 for cirrhosis. Moreover, Lebensztejn (14) observed similar results for 71 hepatitis B children with a ROC of 0.748 to differentiate between mild and advanced liver fibrosis. In a group of 77 obese children with NAFLD (22), APRI was significantly higher in those with significant fibrosis compared with those with mild fibrosis. The area under the ROC curve was 0.7 for this type of disease. Unfortunately, fibrosis was not assessed using the METAVIR scores, making difficult any kind of comparison. De Lédighen (23) studied 115 children with different chronic liver diseases and 33 of them were biopsied including patients with biliary atresia, autoimmune hepatitis, Wilson's disease and congenital fibrosis. They observed that APRI scores correlated significantly with fibrosis stages and a significant area under the ROC curve for the diagnosis of cirrhosis of 0.73 (0.49-0.87). Kim (12) observed, in a series of 35 pediatric patients with biliary atresia, a significant

relationship between APRI and liver fibrosis. In this group of children there were no patients with low fibrosis scores (METAVIR 0-1), and a significant correlation between APRI and the degree of hepatic fibrosis was observed ($r=0.77$). Moreover, they could demonstrate an area under the curve of 0.92 and 0.91 for the determination of METAVIR 3 and 4 respectively. Conversely, Lind et al. (24) could not demonstrate a similar relationship in 31 biliary atresia patients, in which APRI values were not different between METAVIR categories.

To our knowledge, there is only one study performed in pediatric IF patients. Magnus and colleagues studied a group of 15 infants with IF who underwent intestinal transplantation alone or in combination with liver transplant (25). They demonstrated an area under the ROC curve of 0.88 and 0.94 for predicting significant fibrosis and cirrhosis respectively. They also demonstrated that APRI is associated with liver fibrosis progression (25,26). Our results are quite similar to these. We could also demonstrate a significant association between APRI scores and degree of fibrosis, and a positive correlation between APRI and bilirubin values. On the other hand, the APRI values observed in our study were lower, especially when considering the cirrhosis group (APRI 14.16 vs. 4.24), and we were not able to demonstrate a significant diagnostic accuracy for the APRI index in the diagnosis of significant fibrosis or cirrhosis.

There are several differences between the Magnus study and ours that may explain the differences observed. Patients in the aforementioned study are all infants below 3 years of age while our population includes infants, children and young adults. None of our patients had undergone intestinal transplantation before the calculation of the APRI. Moreover, our APRI values were calculated with laboratory data obtained within 1 week of the liver biopsy sampling, while in that study, all laboratory values were selected for each patient during each 2-week period for which laboratory values were available. The maximum values for each period were then selected and pooled, and the median value of all the peak values for each of the periods.

APRI consistently demonstrated a good diagnostic accuracy in children and adults with chronic hepatitis C, a condition for which it was initially developed. Hepatitis C is a disease typically with hepatocellular damage. On the other hand, IFALD is classically a cholestatic disorder, with a different pattern of fibrosis progression. APRI scores in children with other cholestatic diseases, such as biliary atresia, appear less predictive (24). Moreover, METAVIR scores were also validated for hepatitis C infection, so their applicability to IFALD, where there is a variant fibrosis pattern, is questionable. Hence the differences observed in our study could be due to multiple factors.

Unlike many previously published studies which included laboratory data obtained within 4 months of liver biopsy, our data were obtained within 1 week of the biopsy sample, which we believe may strengthen our findings. Moreover, in order to limit the inter-observer variability associated to the interpretation of liver biopsies, a single liver pathologist, who was blinded regarding the APRI score and laboratory values of the patients read all samples. In addition, all the histological slides were retrieved and re-read by the pathologist in a 12-week period of time in order to diminish intra-observer variability. Regardless, we consider that this study has several limitations. First of all, it is a retrospective study including patients from a single center. Secondly, sample size although not small, could be insufficient to detect significant differences in some of the analysis performed. And thirdly, although all children had IFALD, other causes of primary liver disease, genetic or metabolic, were not entirely excluded.

In conclusion, APRI, a non invasive, easy to obtain bedside test significantly predicts cirrhosis but not fibrosis in pediatric patients with IFALD. As the clinicians need a non invasive test to differentiate among different stages of liver fibrosis rather than differentiating cirrhosis from normal, we cannot recommend the use of this test in pediatric patients with IFALD for this purpose.

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Figure 1.

Aspartate aminotransferase to platelet ratio index by degree of liver damage.

Round dots represent those values larger than the upper quartile plus 1.5 times the interquartile range. Asterisks represent those values larger than the upper quartile plus 3 times the interquartile range.

APRI: Aspartate aminotransferase to platelet ratio index

† Bonferroni *post-hoc* test.

Figure 2.
Receiver operating characteristics (ROC) curve for aspartate aminotransferase to platelet ratio index in the detection of cirrhosis

TABLE I
Clinical characteristics of the sample and comparison between METAVIR score group

Variables Mean (SD)	All group (n=62)	No/mild fibrosis METAVIR 0-1 (n= 26)	Fibrosis (METAVIR 2-3) (n= 28)	Cirrhosis (METAVIR 4) (n=8)	p
Age (years)	2.0 (3.2)	1.8 (2.4)	2.5 (4.1)	1.1 (0.88)	0.5
PN time (months) *	12.5 (2-84)	9.4 (2-84)	14.9 (2-75)	12 (5-32)	0.4
AST (IU/L)	105.5 (88.9)	98.5 (72.4)	104.5 (99.3)	131.3 (111.8)	0.66
ALT (IU/L)	91.8 (87.7)	97.5 (80.4)	82.1 (92.2)	108.0 (100.6)	0.71
Total Bilirubin (mg/dL)	4.3 (6.7)	3.1 (5.1)	4.2 (5.6)	8.5 (12.1)	0.14
Direct Bilirubin (mg/dL)	2.8 (4.3)	2.1 (3.6)	2.7 (3.6)	5.3 (7.3)	0.19
Platelet count (10 ³ /μL)	287.2(170.8)	319.1 (221.1)	288.6 (114.9)	178.9 (106.6)	0.13
INR	1.20 (0.25)	1.14 (0.18)	1.19 (0.15)	1.39 (0.54)	0.04
Albumin (g/dl)	3.1 (0.65)	3.2 (0.7)	3.0 (0.7)	3.1 (0.5)	0.44
APRI	1.83 (3.2)	1.80 (3.1)	1.17 (1.5)	4.24 (6.1)	0.053

* median (range). AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; APRI: AST to platelet ratio index; PN: parenteral nutrition.

Table 2

Correlations between APRI index and other variables of liver function

	Pearson Correlation coefficient	P value
Albumin (g/dL)	−0.30	0.027
Total Bilirubin (mg/dL)	0.75	<0.0001
Direct Bilirubin (mg/dL)	0.73	<0.0001
INR	0.67	<0.0001

INR: international normalized ratio

Table 3

Performance of the APRI in the diagnosis of cirrhosis

<i>Cut off value</i>	Sensitivity	Specificity	LR+
APRI = 1	62.5	68.5	1.98
APRI = 2	37.5	83.3	2.2
APRI = 3	25	89	2.25

LR+: Positive Likelihood ratio