Assessment of Liver Fibrosis and Cirrhosis by Aspartate Aminotransferase-to-Platelet Ratio Index in Children With Biliary Atresia

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ABSTRACT

Background: In patients with biliary atresia (BA), liver fibrosis and cirrhosis commonly occur even after Kasai hepatoportoenterostomy. Although liver biopsy is the gold standard to evaluate liver fibrosis, it is invasive and may result in life-threatening complications. The aspartate aminotransferase-to-platelet ratio index (APRI) is a safe and simple method to assess liver fibrosis in patients with chronic liver diseases. To use APRI as a postoperative follow-up tool, we validated the diagnostic power of APRI for the degree of liver fibrosis in postoperative patients with BA.

Patients and Methods: Patients with newly diagnosed BA who underwent the Kasai procedure between March 2006 and May 2009 were analyzed. Several laboratory tests including APRI were performed. Liver wedge biopsy specimens were obtained during the surgical procedure, and histopathologic analyses were performed using the Metavir classification.

Results: Thirty-five patients (12 boys, median age of 1.9 months) were enrolled. Metavir scores were F1 in 0, F2 in 11, F3 in 11, and F4 in 13 patients. The areas under the receiver operating characteristics curves for $F \geq 3$ and $F = 4$ were 0.92 and 0.91, respectively. Distinct optimal cutoff values of APRI for $F \geq 3$ and $F = 4$ were obtained (1.01 and 1.41, respectively). Clinical outcomes of patients were significantly different between 2 groups (noncirrhosis vs cirrhosis) based on APRI before and 3 months after the Kasai procedure.

Conclusion: APRI may be used as a simple and readily available tool for assessing liver fibrosis without additional risks in patients with BA during postoperative follow-up care.

Key Words: aspartate aminotransferase-to-platelet ratio index, biliary atresia, cirrhosis, liver fibrosis, Metavir classification

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Hepatic fibrosis is the end result of various types of liver injury; it is a wound-healing process similar to that observed in other organs (1). One of the most remarkable aspects of the healing process in the liver is enhanced extracellular matrix production, or fibrogenesis. Furthermore, injury-induced fibrogenesis is characterized by a multifold increase in interstitial collagens, such as types I and III, in addition to many other extracellular matrix constituents (2). Liver fibrosis occurs in many patients with chronic liver disease. Early treatment of the underlying etiology can limit the progression, but it cannot always prevent continuation to an advanced stage known as cirrhosis (3). In children, biliary atresia (BA) is the most common cause of liver fibrosis, even after the Kasai hepatoportoenterostomy procedure (KP). All of the patients with advanced liver fibrosis eventually require liver transplantation (4).

Although liver biopsy is the gold standard to evaluate liver fibrosis, such an evaluation can be invasive and may result in life-threatening complications in adults and children (5–7). In addition, an evaluation for liver fibrosis may have many drawbacks, including sampling error, inter- and intraobserver variability in interpretation, and inability to evaluate progression and regression of fibrosis. Liver biopsy can also be associated with complications, such as abdominal pain, hypotension, hemobilia, and intraperitoneal hemorrhage, the last of which has an associated mortality rate of up to 0.5% (8). Furthermore, liver biopsy is not generally accepted by patients, especially when repeated examinations are needed (9). Therefore, there is a need to develop noninvasive methods to accurately assess hepatic fibrosis, cirrhosis, and disease progression in liver diseases (10).

A promising tool with widespread availability, the aspartate aminotransferase-to-platelet ratio index (APRI), is a rapid and noninvasive method to detect liver fibrosis in patients with chronic hepatitis C (3). The APRI is calculated from 2 routine laboratory tests, the serum aspartate aminotransferase (AST) level and the platelet count.

Although previous studies have evaluated the diagnostic performance of the APRI in several liver diseases, no studies have shown the accuracy in assessing liver fibrosis and cirrhosis, especially in patients with BA. The aim of this study was to validate the diagnostic power of the APRI for assessing liver fibrosis in patients with BA at the time of KP to use the APRI as an assessment tool for liver fibrosis during postoperative care.

PATIENTS AND METHODS

Thirty-five patients who were newly diagnosed as having BA and underwent the KP at Severance Children's Hospital in Seoul, Korea, between March 2006 and May 2009 were enrolled. Patients with recent acute febrile illnesses or skin rashes, which could affect AST levels and platelet counts, other than BA, were excluded from this study. This study was approved by our institutional review board, and study protocol was in accordance with the Declaration of Helsinki.

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TABLE 1. Clinical characteristics of all patients and comparison between nonadvanced and advanced fibrosis group according to histological findings (n = 35)

	All children (n = 35)	Metavir (F0-1-2) (n = 11)	Metavir (F3-4) (n = 24)	*P*
Age, mo at Kasai operation	2.36 (1.46)	1.84 (0.77)	2.60 (1.65)	0.002
Boy, %	12 (34.3)	2 (18.2)	10 (41.7)	NS
AST, IU/L	278.4 (172.0)	143.7 (77.6)	340.1 (168.7)	0.001
ALT, IU/L	233.7 (142.7)	142.7 (95.9)	275.4 (142.6)	0.009
Albumin, g/dL	3.8 (0.5)	3.6 (0.5)	3.8 (0.5)	NS
T.bil, mg/dL	8.8 (2.9)	6.9 (2.3)	9.6 (2.7)	0.006
D.bil, mg/dL	6.9 (2.4)	5.4 (2.0)	7.6 (2.3)	0.012
r-GTP, IU/L	498.7 (318.3)	364.9 (178.8)	560.0 (351.3)	NS
ALP, IU/L	642.7 (491.8)	420.0 (215.1)	744.7 (550.3)	NS
Platelet count, $10^3/\mu L$	418.8 (145.4)	438.6 (127.9)	409.7 (154.5)	NS
PT–INR	1.06 (0.16)	0.99 (0.07)	1.09 (0.18)	0.015
APRI	1.66 (1.40)	0.77 (0.55)	2.07 (1.50)	0.008
AAR	1.28 (0.35)	1.21 (0.42)	1.31 (0.32)	NS

All data show mean (SD). AAR = AST/ALT ratio; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APRI = aspartate aminotransferase-to-platelet ratio index; AST = aspartate aminotransferase; D.bil = direct bilirubin; NS = not significant; PT–INR = prothrombin time–international normalized ratio; *r*-GTP = gamma-glutamyl transpeptidase; T.bil = total bilirubin.

Characteristics of Subjects

For all of the subjects, the following parameters were determined at the time of liver biopsy. The demographic information included sex and age in months at the time of the KP. The biochemical parameters included serum AST, alanine aminotransferase, albumin, total bilirubin, direct bilirubin, *r*-glutamyl transpeptidase, alkaline phosphatase, platelet count, and prothrombin time. The APRI was calculated as the serum AST level (U/L)/upper normal × 100/platelet count ($10^3/\mu L$) (3). For the cholangiogram, a needle or catheter was inserted into the gallbladder so that diluted contrast material was injected to document the extent of obstruction and the anatomic variants. These anatomic variants have been proposed by the Japanese Society of Pediatric Surgeons, and consist of 3 main types: type 1, atresia primarily involving the common bile duct; type 2, atresia extending up to the common hepatic duct; and type 3, atresia involving the entire extrahepatic ductular system (11).

Liver Histopathology and Quantification of Liver Fibrosis

Liver wedge biopsy specimens were obtained from all of the patients at the time of KP, fixed in formalin, and embedded in paraffin. Four-micrometer-thick sections were stained with hematoxylin-eosin-safran, Masson trichrome, and Victoria blue. All of the specimens were analyzed twice by an experienced liver pathologist blinded to the clinical data. Liver fibrosis and necroinflammatory activity were evaluated semiquantitatively according to the Metavir scoring system (4,12). The Metavir scoring system consists of 5 stages, based on the architectural features of portal fibrosis: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis and few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis (13).

Statistical Analysis

All of the data management and statistical calculations were performed with SPSS version 13.0 (SPSS Inc, Chicago, IL). Distributed data are presented as the mean (SD); the *t* test and χ^2 test were performed to demonstrate the differences and interobserver reproducibility (Cohen κ). The diagnostic performance of the APRI was assessed using receiver operating characteristics (ROC) curves. All of the cutoff values are associated with the probability of a true positive (sensitivity) and a true negative (specificity). The ROC curve is a plot of sensitivity versus 1-specificity for all of the possible cutoff values. The most commonly used accuracy index is the area under the ROC curve; values near 1.0 indicate high diagnostic accuracy. ROC curves were thus constructed for the detection of subjects with Metavir fibrosis stage 3 or greater and cirrhosis. Optimal cutoff values for APRI were chosen to obtain a 95% sensitivity, to maximize the sum of the sensitivity and specificity, to optimize the diagnostic performance (sum of true positives and true negatives over the total number of subjects), or to obtain a 95% specificity according to the diagnostic question (14).

RESULTS

Thirty-five patients had newly diagnosed BA and underwent the KP in the 39-month period from March 2006 to May 2009 at Severance Children's Hospital. The patients' characteristics at the time of KP are summarized in Table 1. There were 12 boys and 23 girls; the median age at the time of the surgical intervention was 1.9 months. The mean (±SD) size of the wedge biopsy specimen was 44 mm (±17 mm) × 34 mm (±11 mm) × 36 mm (±13 mm). The fibrosis stages were as follows: F1, n = 0; F2, n = 11; F3, n = 11; F4, n = 13. The reproducibility of the Metavir scoring was good (Cohen κ = 0.66). According to the anatomic types of BA, 3 (8.6%) and 2 (5.7%) patients were type 1 and 2, respectively. Type 3 BA comprised 30 (85.7%) patients.

The clinical characteristics of all patients are presented in Table 1. In comparing the nonadvanced and advanced fibrosis groups, the age at the time of KP correlated significantly with the degree of hepatic fibrosis. The parameters of acute hepatic injury (AST, alanine aminotransferase, and prothrombin time–international normalized ratio) had a significant correlation with the degree of hepatic fibrosis at the time of KP ($P < 0.05$ for each). Furthermore, the APRI, as a suggested noninvasive parameter, had a good correlation between the 2 groups ($P < 0.05$).

The APRI was correlated significantly with the degree of hepatic fibrosis, with a high correlation coefficient ($r = 0.77$, $P < 0.001$; Fig. 1). Figure 2 shows the ROC curves for all of the

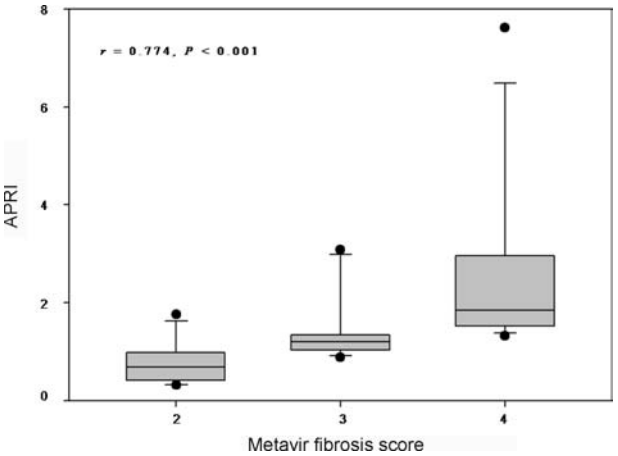

FIGURE 1. Box and whisker diagram of the aspartate aminotransferase-to-platelet ratio index (APRI) in relation to the Metavir fibrosis score. The box represents the interquartile range, the whiskers indicate the highest and lowest values, and the asterisks represent the outliers. The line across the box indicates the median value.

subjects based on 2 different thresholds of the APRI for the stage of fibrosis: F0, F1, and F2 patients versus F3 and F4 patients ($F \geq 3$); and F0, F1, F2, and F3 patients versus F4 patients ($F = 4$). The areas under the ROC curves were 0.92 for $F \geq 3$ and 0.91 for $F = 4$ (asymptotic significance < 0.05).

Table 2 shows the optimal APRI cutoff values obtained for all of the subjects, as well as the corresponding sensitivity, specificity, and likelihood ratio. The cutoff value of the APRI for $F \geq 3$ was 1.01, with a total sensitivity and specificity of 1.78, and the clear cutoff value (1.42) was obtained for $F = 4$ with a total sensitivity and specificity of 1.79. Furthermore, for prediction of significant hepatic fibrosis, the positive predictive value (PPV) and negative predictive value (NPV) for the 1.01 cutoff value of APRI were 96% and 80%, respectively. For the prediction of cirrhosis, the PPV and NPV for the 1.42 cutoff value of the APRI were 86% and 86%, respectively.

Ten (28.6%) patients were in the group with a cutoff value of APRI ≤ 1.01 (nonadvanced fibrosis) before and 3 months after the KP, and 25 (71.4%) patients were in the group with a cutoff value of APRI > 1.01 (advanced fibrosis) before and 3 months after the KP. There were statistically significant differences in the clinical characteristics of acute liver injury between the nonadvanced and advanced fibrosis groups before KP. After 3 months of KP, the clinical characteristics of chronic and acute liver injury in the advanced fibrosis group were aggravated more than the nonadvanced fibrosis group (data not shown). As shown in Table 3, 20 (57.1%) patients were in the group with a cutoff value of APRI ≤ 1.42 (noncirrhosis) and 11 (42.9%) patients were in the group with a cutoff value of APRI > 1.42 (cirrhosis). There were statistically significant differences in the clinical characteristics of acute liver injury between the 2 groups (noncirrhosis vs cirrhosis) based on the APRI value before the KP. Three months after the KP, the clinical characteristics of chronic as well as acute liver injury in the group with a cutoff value of APRI > 1.42 (cirrhosis) were aggravated much more than the group with a cutoff value of APRI ≤ 1.42 (non-cirrhosis).

DISCUSSION

The prognosis of chronic cholestatic diseases depends, in part, on the extent of fibrosis in the liver (15,16). Although liver biopsy is the gold standard method by which to demonstrate liver fibrosis, liver biopsy is invasive and has many serious limitations.

First, liver biopsy is not generally accepted by children because of pain. Saadeh et al (17) and Poynard et al (18) reported that liver biopsy results in pain in 24.6% of patients. A French survey showed that approximately half of patients with hepatitis C refuse to be referred to hepatologists for fear of liver biopsy (19).

Second, the procedure is associated with significant sampling error. Histologic staging is based on a biopsy specimen that represents, at most, 1/50,000th of the total liver mass (8). In addition, the distribution of fibrosis within the liver parenchyma is heterogeneous. Bedossa et al (20) recently reported that by using the Metavir scoring system only 75% of 25-mm biopsy specimens were classified correctly in terms of stage of fibrosis. Using the Batts and Ludwig classification (19), Regev et al (21) showed a difference of at least 1 stage of fibrosis between the right and left lobes in 33% of

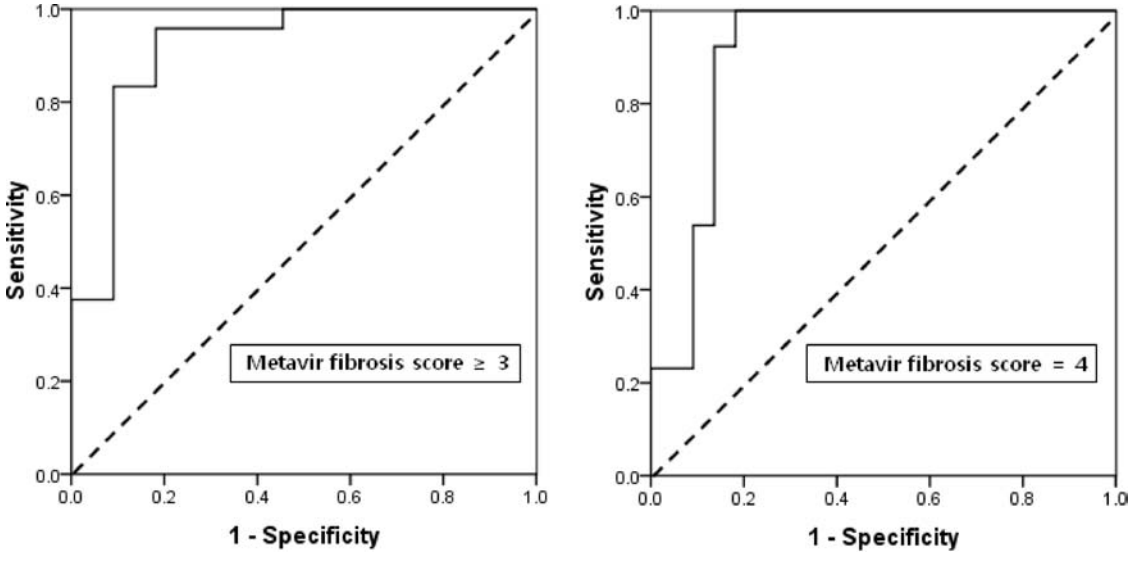

FIGURE 2. Receiver operating characteristics (ROC) curve for aspartate aminotransferase-to-platelet ratio index. The areas under the ROC curves were 0.92 and 0.91 for the determination of Metavir $F \geq 3$ and $F = 4$, respectively.

TABLE 2. Accuracy of APRI cutoff value in predicting significant fibrosis and cirrhosis

APRI	All children (n = 35) n (%)	Metavir F0-1-2 (n = 11) n (%)	Metavir F3-4 (n = 24) n (%)	Sensitivity %	Specificity %	PPV %	NPV %
≤1.01	10 (29)	9 (82)	1 (4)	96	82	96	80
>1.01	25 (71)	2 (18)	23 (96)				
		Metavir F0-1-2-3 (n = 22)	Metavir F4 (n = 13)				
≤1.42	20 (57)	19 (86)	1 (8)	92	86	86	86
>1.42	15 (43)	3 (14)	12 (92)				

APRI = aspartate aminotransferase-to-platelet ratio index; NPV = negative predictive value; PPV = positive predictive value.

124 patients, whereas Siddique et al (22) found that 45% of patients had a difference of at least 1 stage fibrosis between 2 specimens obtained from the same puncture site.

Third, although liver biopsy is the gold standard to evaluate liver fibrosis, it can be invasive and may result in life-threatening complications in children (5–7). Moreover, liver biopsy is associated with complications, including an associated mortality rate of up to 0.5% (8). Saadeh et al (17) and Poynard et al (18) reported that liver biopsy has a risk of severe complications of 3.1/1000.

Because of these limitations, several noninvasive serum markers of the extracellular matrix, such as hyaluronic acid, plasma endothelin-1, matrix metalloproteinase, tissue inhibitor of metalloproteinase, and serum prolyl 4-hydroxylase, have been proposed as indices of liver fibrosis and portal hypertension in chronic liver disease, especially BA (23–27). Recently, Pape et al (28) documented that the mean volume of fibrosis per number of periportal fields is a valid marker in predicting transplant-free survival in children with BA compared with laboratory tests, clinical course, and histology. Indeed, these markers showed a significant correlation with hepatic fibrosis. As another noninvasive index of hepatic fibrosis and cirrhosis, the APRI was developed as an alternative in patients with chronic hepatitis C. Wai et al (3) reported an APRI derived and validated in a cohort of 270 patients with chronic hepatitis C virus; the areas under the ROC curves for significant fibrosis and cirrhosis in the training and validation cohort were 0.80 to 0.88 and 0.89 to 0.94, respectively. Shaheen and Myers (29) demonstrated that based on their recent bivariant meta-analysis of the diagnostic accuracy of the APRI, the 0.5 threshold was 81% sensitive and 50% specific. Assuming a 47% prevalence of significant fibrosis, this translated into an estimated PPV of 59% and a NPV of 75%. Although these predictive values appear suboptimal, the NPV was more acceptable in the lower prevalence settings, such as community-based cohorts (30). The APRI has 1 important advantage: because the data, such as AST and platelet count, are ubiquitously available and the formula is so simple, it can be calculated at the bedside without additional costs (31). For the identification of significant fibrosis, scores <0.5 (on a scale from 0 to 10) had a NPV of 86%, whereas scores >1.5 had a PPV of 88%. On the basis of these high predictive values, APRI could replace the liver biopsy in approximately half of patients. Subsequently, numerous studies have attempted to externally validate these findings, but the results have been controversial (32,33). In 2008, Cales et al (34) documented the overall accuracy of several tests, including the FibroMeter, Fibrotest, Fib-4, APRI, and Hepascore in patients with chronic hepatitis C. The areas under the ROC (F0–1 vs F2–4) were as follows: FibroMeter, 0.853; Fibrotest, 0.811; Fib-4, 0.799; APRI, 0.786; and Hepascore, 0.784. Finally, de Lédinghen et al (4) showed that the APRI was significantly correlated to Metavir fibrosis scores in children with chronic liver diseases, including BA.

TABLE 3. Comparison of outcome between all of the patients according to APRI cutoff value

	Before Kasai operation			3 mo after Kasai operation		
	APRI ≤ 1.42 (n = 20)	APRI > 1.42 (n = 15)	*P*	APRI ≤ 1.42 (n = 20)	APRI > 1.42 (n = 15)	*P*
AST, IU/L	190.8 (93.7)	395.1 (185.4)	<0.001	85.7 (39.7)	170.4 (68.5)	<0.001
ALT, IU/L	166.8 (93.7)	322.9 (150.5)	0.001	89.4 (48.2)	144.6 (70.8)	0.011
Albumin, g/dL	3.9 (0.4)	3.7 (0.6)	0.262	4.4 (0.5)	3.5 (0.5)	<0.001
T.bil, mg/dL	7.3 (2.1)	10.7 (2.5)	<0.001	1.5 (2.4)	5.2 (4.9)	0.007
D.bil, mg/dL	5.7 (1.9)	8.5 (2.0)	<0.001	1.1 (1.7)	4.3 (4.1)	0.004
r-GTP, IU/L	496.7 (276.1)	501.5 (377.6)	0.965	342.3 (273.3)	996.9 (930.3)	0.005
ALP, IU/L	504.1 (254.2)	827.4 (660.0)	0.053	317.5 (149.1)	757.5 (679.2)	0.008
PT–INR	1.00 (0.06)	1.13 (0.22)	0.015	1.01 (0.20)	1.47 (0.70)	0.009
APRI	0.91 (3.40)	2.66 (1.65)	<0.001	0.56 (0.37)	2.64 (1.47)	<0.001
AAR	1.29 (0.41)	1.27 (0.27)	0.896	1.07 (0.37)	1.25 (0.19)	0.123

All data show mean (SD). AAR = AST/ALT ratio; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APRI = aspartate aminotransferase-to-platelet ratio index; AST = aspartate aminotransferase; D.bil = direct bilirubin; NS = not significant; PT–INR = prothrombin time–international normalized ratio; *r*-GTP = gamma-glutamyl transpeptidase; T.bil = total bilirubin.

The BA is a severe, cholestatic disease of infancy of unknown cause characterized by fibro-obliteration of the extrahepatic biliary tree, leading in untreated cases to cirrhosis, end-stage liver disease, and death by 2 years of age (35–37). The only therapy for BA is an early KP, with the hope of establishing bile flow to the gastrointestinal tract; however, BA is the most common indication for liver transplantation in children because the KP fails in one third of cases. Even when bile flow is established, variable liver fibrosis, cirrhosis, portal hypertension, and liver failure may still occur (37).

There are few studies suggesting the APRI as a noninvasive method for the detection of hepatic fibrosis and cirrhosis in BA and comparing the clinical course before and after the KP using the APRI. The classic cutoff values of the APRI are well validated for both ordinary and special patients with chronic hepatitis C, but not for patients with BA. Moreover, hepatic fibrosis and cirrhosis in chronic hepatitis C may differ from fibrosis in BA. Our study determined the accuracy and reliability of the APRI in assessing fibrosis and histopathologic stage in patients with BA at the time of the KP. Although this study had some limitations (the number of patients was small, there were no patients with Metavir F0 and F1 fibrosis among the 5 stages, the follow-up was short term, the APRI has not been validated as a noninvasive method to prospectively assess hepatic fibrosis progression, and repeated biopsies associated with repeated APRI measurements were not performed), our results showed a significant positive correlation between the APRI and fibrosis stages in Metavir F3 fibrosis or greater cirrhosis. Significant areas under the ROC curves for $F \geq 3$ and $F = 4$ were 0.92 and 0.91, respectively. These results, along with high likelihood ratios and distinct optimal cutoff values ($APRI = 1.01$ for $F \geq 3$ and $APRI = 1.42$ for $F = 4$) with high total sensitivity and specificity, suggest that the APRI can be a reliable method to assess extensive hepatic fibrosis ($F \geq 3$) and cirrhosis ($F = 4$) before the KP in patients with BA. Furthermore, the outcome of the patients with an $APRI > 1.42$ had worsened compared with patients with an $APRI \leq 1.42$, even 3 months after the KP.

In conclusion, the APRI may be used as a simple and readily available tool for assessing liver fibrosis in patients with BA without additional risks and costs at the time of KP and during the short-term follow-up care.

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