Original Article

Serum Adiponectin and Fibroscan as Non-invasive Post-operative Prognostic Markers for Biliary Atresia

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Abstract

Background: Majority of patients with biliary atresia (BA), including those who undergo Kasai hepatico-portoenterostomy, develop cirrhosis, hepatic fibrosis and eventually progress to end-stage liver disease. Therefore, early assessment of hepatic status and fibrosis is essential. The study objective was to estimate serum adiponectin, liver function tests and to associate them with liver stiffness scores in post-operative BA patients. **Materials and Methods:** A total of 30children (20 post-Kasai BA cases and 10 healthy controls) were enrolled in this prospective case–control study. Serum adiponectin was measured by enzyme-linked immunosorbent assay, and hepatic fibrosis by transient elastography (TE) (FibroScan). The BA patients were further divided into two groups: a jaundiced group (total bilirubin [TB] ≥2 mg/dl) and a non-jaundiced group (TB <2 mg/dl). Comparison of biomarkers was also done in these subgroups and controls by Kruskal–Wallis test. **Results:** Adiponectin levels were significantly higher in BA cases than controls (median and interquartile range: 27.4 and 14.7 vs. 3.65 and 3.45 μg/ml, $P = 0.001$). Liver stiffness values in BA patients were also markedly more than controls (9.95 and 5.45 vs. 4.60 and 4.48 kPa, $P = 0.002$). Furthermore, serum adiponectin and liver stiffness scores were considerably higher in cases with jaundice in comparison to non-jaundiced cases ($P = 0.013$ and 0.001, respectively). Serum adiponectin revealed a positive correlation with TB ($r = 0.81$, $P < 0.00001$) and FibroScan status ($r = 0.96$, $P < 0.00001$). **Conclusion:** The estimation of adiponectin levels and TE can be considered to be novel non-invasive methods to monitor post-Kasai hepatic status in BA patients.

Keywords: Kasai hepatico-portoenterostomy, liver fibrosis, transient elastography

Introduction

While most cases of neonatal jaundice are physiological and self-limiting, serious pathological causes, such as Biliary atresia (BA), choledochal cyst and Alagille syndrome, are not uncommon.[1] BA is a unique anomaly that causes progressive cholangiopathy, leading to cholestasis and fibrotic obstruction of the biliary tract.[2-4] However, even after undergoing Kasai operation, the majority of children develop biliary cirrhosis and hepatic fibrosis and eventually require liver transplantation.[5-7] Therefore, an early diagnosis of liver fibrosis is essential.

Serum adiponectin and FibroScan as novel parameters are studied in chronic liver diseases. However, studies relating these non-invasive parameters in post-operative BAs are rare.

Aim

The objective of this study was to estimate serum adiponectin and liver stiffness scores by FibroScan and to compare them with healthy controls so as to determine the ideal prognostic marker in this anomaly.

Materials and Methods

This was case–control study carried out in the Department of Pediatric Surgery from October 2019 to March 2022. The Helsinki Declaration of Ethical Principles of Medical Research (1975) was followed, and approval from the Institutional Ethics Committee (IEC/SCBMC/40/2021/471)

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was obtained. The participants' parents were informed about the purpose and procedure of the research, and written consent was obtained from them.

Study population

The study comprised a total of 30 children: 20 BA patients who had undergone Kasai hepatico-portoenterostomy (HPE) and 10 children who had attended the paediatric outpatient department (OPD) for vaccination and had normal physical characteristics without any underlying morbidity (controls). Both the cases and controls were subjected to estimation of adiponectin levels in serum and liver fibrosis by FibroScan. In BA cases, the estimations were done during post-operative follow-up, when the patients were asymptomatic and without any features of cholangitis. Comparison of serum adiponectin levels and FibroScan scores was done between cases and controls. Liver function tests were also done in BA patients to correlate the degree of hepatic dysfunction with serum adiponectin and the status of fibrosis of liver. After surgery some patients were having persistent jaundice, and some were jaundice free. Hence, they were divided into two categories: a jaundiced group (total bilirubin [TB] ≥2 mg/dl) and a non-jaundiced group (TB < 2 mg/dl). This was done to find out any association of the jaundice status of patients with the biomarker adiponectin. Patients of BA were further divided into two groups based on liver fibrosis status: significant fibrosis (stiffness ≥ 7 kPa) and non-significant fibrosis (stiffness < 7 kPa). This cut-off score (7 kPa) between significant and non-significant liver stiffness was in accordance with a report by Castera *et al*.[8] who detected 89% specificity and 67% sensitivity. This was done in order to find out, whether there is any association of serum parameters with the degree of hepatic fibrosis.

Laboratory methods

Peripheral blood was collected and centrifuged at 1000×g for 15 min to separate out the serum. It was then stored at − 80°C to estimate adiponectin using a two-step sandwich enzyme-linked immunosorbent assay (R and D Systems, Inc., Minneapolis, MN, USA). The intra-assay and inter-assay precision was 2.5%–4.7% and 5.8%–6.9%, respectively. Sensitivity of the assay was 0.246 ng/ml. Test for hepatic function, such as TB, direct bilirubin (DB), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were performed using an automated clinical chemistry analyser.

Liver fibrosis measurement

Hepatic stiffness was measured using transient elastography (TE) or FibroScan (Echosens, France), which emits a 50 MHz ultrasound wave from the probe.[6] The patients were asked to lie in the dorsal decubitus position with abduction of the right arm. The transducer probe was placed in the right intercostal space to target a portion of the liver with a 6 cm thickness and no major vascular structures. FibroScan measures liver thickness between 25 and 65 mm from the surface of the skin (i.e. almost equivalent to a cylinder volume of 1 cm in diameter and 4 cm long). It was measured till 10 validated results were received, at a minimum success rate of 80%. The median of these 10 validated scores was taken as the elastic modulus and reported in kilopascals (kPa).

Statistical analysis

Data analysis was conducted by Jamovi software version 2.3.26, 2024. The Jamovi Project (https://www.jamovi.org Sydney, Australia) (GNU Affero General Public License and GNU General Public License) software and presented as median (interquartile range [IQR]). Shapiro–Wilk tests for normality were performed, and wherever applicable, Student's *t*-test, Fischer's exact test and Mann–Whitney *U*-test were applied for comparison of parameters between the groups. Kruskal–Wallis (non-parametric) analysis followed by Dwass-Steel-Critchlow-Fligner pairwise comparison was done to compare the controls, BA with jaundice, and BA without jaundice. Pearson's correlation coefficient (*r*) was used for measuring the correlation between adiponectin, other biochemical parameters, and liver stiffness score. $P < 0.05$ was considered significant. Binomial logistic regression was used to assess the ability of adiponectin as a predictor variable for fibrosis. The receptor operator characteristic (ROC) curve was used to assess the accuracy of adiponectin in identifying clinical outcome after Kasai's operation.

RESULTS

Twenty patients of BA were operated in our hospital during the abovementioned study period of 2½ years. Kasai HPE was performed in all these patients. There were 7 males and 13 females with a gender ratio of 1:1.85. The children who attended our OPD for vaccination were enrolled as controls. There were five males and five females with a gender ratio of 1:1. The age range of cases was 8–36 months, and controls were 9–36 months. The median age and IQR of the BA patients were 12.0 and 15 months, while that of the controls were 25.5 and 11.5 months.

Comparison of biliary atresia cases and healthy controls

The demographic features, biochemicals and FibroScan findings of both groups are shown in Table 1. No statistical difference was found in age ($P = 0.069$) and sex ($P = 0.461$) between BA cases and controls; however, serum adiponectin levels were elevated in patients of BA when compared to those of the controls (median and IQR: 27.4 and 14.7 vs. 3.65 and 3.45 μg/ml, $P = 0.001$). Similarly, liver stiffness, a marker for liver fibrosis, was markedly higher in BA patients than controls (median and IQR: 9.95 and 5.45 vs. 4.60 and 4.48 kPa, $P = 0.002$).

Comparison of biliary atresia cases with and without jaundice

Jaundice is one of the manifestations of any liver disorder, and therefore the difference in various clinicodemographic features was measured in BA cases with and without jaundice. In the present study, the median (IQR) serum bilirubin was 3.90 (1.92) mg/dl in patients. The BA cases were further classified into a jaundice group and a non-jaundice group. Persistence of jaundice (TB ≥2 mg/dl) was detected in 16 patients, and four patients were jaundice free (TB <2 mg/dl) [Table 2].

The median age and sex ratios of these two groups were not statistically different, indicating similar demographic features between these groups. However, the median (IQR) serum adiponectin levels of the BA with jaundice group were significantly higher than those of the BA without jaundice group (32.79 [20.2] vs. 15.50 [20.6]) µg/ml, P = 0.013; [Figure 1].

The enzymes associated with liver parenchymal damage and liver obstruction, serum AST and ALP, respectively, were statistically higher in jaundiced BA patients than in non-jaundiced BA patients (P = 0.037 and 0.017, respectively). Further, there was a statistically significant difference in the liver stiffness scores between the groups, with the jaundice group expressing more degree of fibrosis (11.25 and 5.48 vs. 6.50 and 0.325 kPa, P = 0.001).

Comparison of biliary atresia cases with and without significant fibrosis

BA patients were also categorised on the degree of fibrosis into groups of non-significant and significant fibrosis. BA patients with significant fibrosis (n = 16) had raised serum adiponectin levels than those without significant fibrosis [n = 4; 32.79 and 14.13 vs. 15.50 and 2.71 µg/ml, P = 0.002; Table 3].

Serum TB, DB, AST and ALP values were also markedly elevated in patients with significant fibrosis (P = 0.001, 0.004, 0.037 and 0.017, respectively). However, the liver-specific enzyme of ALT showed no significant difference between the two groups.

Pearson's correlations were conducted to express the degree of correlation between the various biomarkers of liver function; these are summarised in the heatmap in Figure 2. Serum adiponectin revealed a significant positive correlation with TB (r = 0.81, P < 0.00001), DB (r = 0.63, P < 0.000191), AST (r = 0.9, P < 0.00001), ALT (r = 0.43, P = 0.017), ALP (r = 0.73, P < 0.00001), jaundice status (r = 0.64, P = 0.00014) and FibroScan (r = 0.96, P < 0.00001).

The model fit from binomial logistic regression measures (Nagelkerke's R^2 = 0.704) using adiponectin as a predictor and all other predictors constant was used to identify fibrosis and is depicted in Table 4.

Keeping all predictors constant, the odds of developing fibrosis increased by 0.672 times by one unit change in adiponectin. The ROC curve analysis showed that adiponectin > 15 µg/ml was predictive of hepatic dysfunction in BA and predicting prognosis after HPE (specificity = 90%, sensitivity = 95% and area under curve of 98%) is represented in Figure 3.

Therefore, serum adiponectin, enzymes and liver stiffness scores are positively correlated with clinical manifestations of hepatic dysfunction and degree of liver fibrosis. These noninvasive markers will indicate post-operative prognosis

Table 1: Demographic variables, biochemical characteristics, and liver stiffness values of controls and biliary atresia cases

Variables	Control (n=10)	BA patients (n=20)	P
Age (months)	25.5 (11.50)	12.0 (15.0)	0.069*
Gender (male:Female)	5:5	7:13	0.461†
Total bilirubin (mg/dL)	-	3.90 (1.92)	NA
Direct bilirubin (mg/dL)	-	2.45 (0.87)	NA
AST (IU/L)	-	56.0 (23.50)	NA
ALT (IU/L)	-	38.0 (9.50)	NA
ALP (IU/L)	-	285 (135.0)	NA
Adiponectin (µg/mL)	3.65 (3.45)	27.4 (14.70)	<0.001‡
Liver stiffness (kPa)	4.60 (4.48)	9.95 (5.45)	0.002‡

*Mann–Whitney, †Fisher's exact test, ‡Student's t-test. Data represented as median (IQR). IQR: Interquartile range, BA: Biliary atresia, AST: Aspartate transaminase, ALP: Alkaline phosphatase, NA: Not applicable, ALT: Alanine aminotransferase

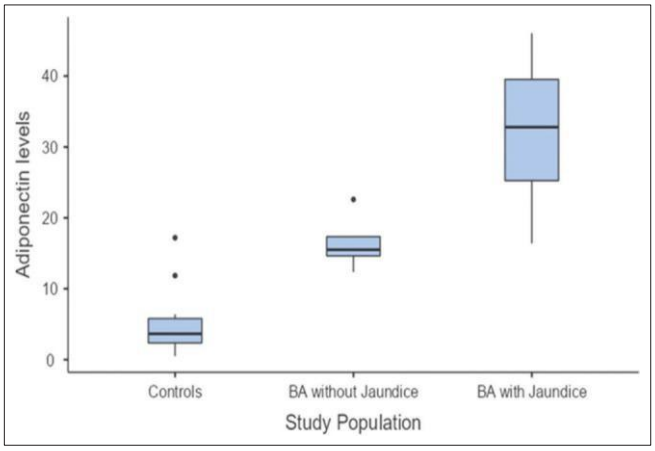


Figure 1: Comparison of serum adiponectin levels in controls, biliary atresia (BA) cases without jaundice, and BA cases with jaundice

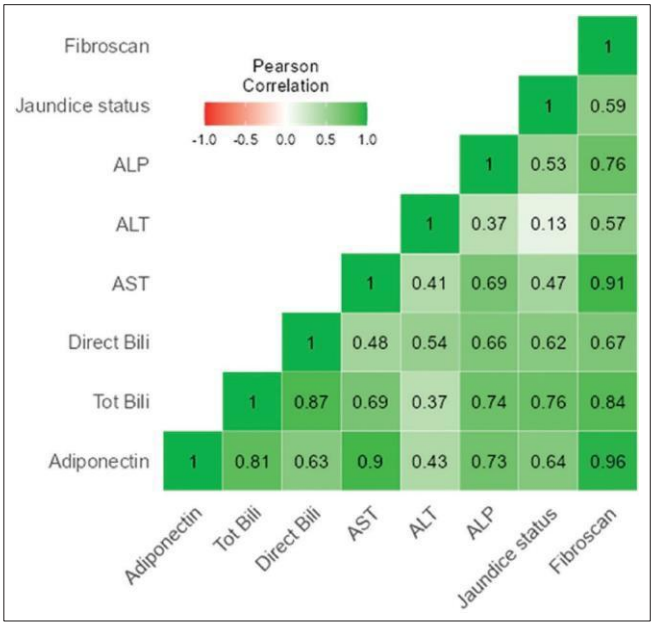


Figure 2: Pearson's correlation heat map of different biomarkers in biliary atresia

following Kasai HPE. They will predict the progression towards liver cirrhosis, end-stage liver disease and subsequent need for liver transplantation in BA patients.

Discussion

BA occurs with a higher frequency in East Asian countries than in Western countries.[1,3] For example, in Europe, the incidence of BA is 1:18,000 live births, while in Japan, it is 1:9,640.[5] The introduction of HPE by Professor Kasai in 1959 had a major impact on the disease; today, 90% of infants undergo Kasai HPE after being diagnosed as BA, while hepatic transplantation is performed on some patients with progressed liver disease.[2,4] However, progressive deterioration of hepatic function is common, even after successful HPE.[5]

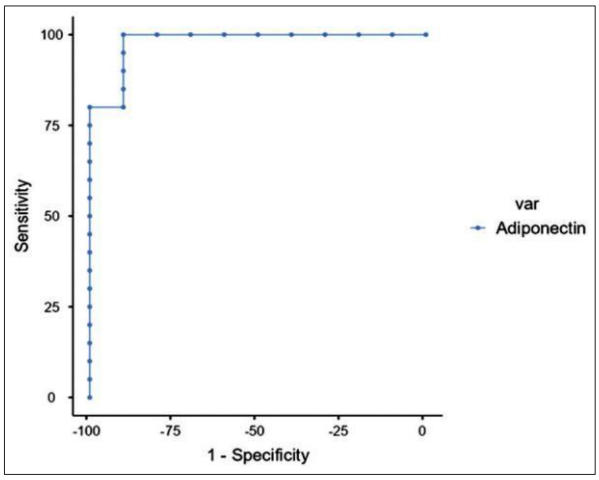


Figure 3: Receptor operator characteristics curve for adiponectin

Table 2: Comparison between biliary atresia cases with and without jaundice

Variables	BA without jaundice (*n*=4)	BA with jaundice (*n*=16)	*P*
Age (months)	11.0 (5.5)	13.0 (18.0)	0.478
Gender (male:Female)	2:2	5:11	0.587*
Total bilirubin (mg/dL)	1.7 (0.325)	4.01 (1.2)	<0.001
Direct bilirubin (mg/dL)	1.1 (0.450)	2.5 (0.650)	<0.001
AST (IU/L)	42.0 (4.50)	58.0 (23.0)	0.037
ALT (IU/L)	38.0 (1.5)	40.0 (15.0)	0.597
ALP (IU/L)	170.0 (55.0)	305.0 (118.0)	0.017
Adiponectin (µg/mL)	15.50 (20.6)	32.79 (20.2)	0.013
Liver stiffness (kPa)	6.50 (0.325)	11.25 (5.48)	<0.001†

*Fisher's exact test, †Mann–Whitney test. Data represented as median (IQR). IQR: Interquartile range, BA: Biliary atresia, AST: Aspartate transaminase, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase

A liver biopsy is standard method for assessing fibrosis. However, it is invasive and can include bleeding, excessive pain and, rarely, life-threatening complications.[6,7,9] These complications, together with other limitations of liver biopsy, such as the potential for sampling error and observer variability, have led to a search for alternative non-invasive methods.[2,6] Recently, the hepatic fibrosis scan (FibroScan) has emerged as one of the most validated non-invasive investigations for monitoring hepatic fibrosis.[2,6,8,9] It is rapid, painless and based on TE.[8,10] In this study, the hypothesis was that adiponectin and the liver stiffness scores would be higher in postoperative BA cases as comparison to controls and in those patients having persistent jaundice than non-jaundiced. To prove the above hypothesis, we have estimated the adiponectin levels and stiffness of the liver in postoperative BA cases and controls.

Bile duct inflammation and cytokines cause hepatic parenchymal damage and fibrosis in BA.[11] The fibrogenic role of adipokines in chronic hepatic diseases is well known.[7,12] Adiponectin is a unique adipokine produced by adipocytes and secreted into systemic circulation.[13,14] An increased level of adiponectin in circulation is associated with liver fibrosis.[15] Multiple causes further lead to fibrosis, biliary cirrhosi and hepatic failure.[2,7] Hepatic stellate cells (HSCs) are the primary fibrogenic cells. Adiponectin has an antifibrotic effect in the liver, as it inhibits the activation of HSC, which leads to fibrogenesis due to the production and accretion of collagen and extracellular matrix inside the hepatic parenchyma, causing fibrosis.[15-17] Adiponectin regulates HSC proliferation via its action through transmembrane receptors.[15]

Increased circulating adiponectin reflects liver cell damage and dysfunction and is considered an acceptable biochemical marker for detecting fibrosis in various chronic hepatic diseases.[7,15] This study focused on the relationship between serum adiponectin and postoperative outcomes and liver stiffness in post-Kasai BA patients. Elevated levels of serum adiponectin and higher liver stiffness scores are regarded as adverse indicators and advanced warning about hepatic deterioration. These patients will get benefit from liver

Table 3: Comparison of biochemical parameters between biliary atresia cases with non-significant and significant fibrosis

Variables	BA with non-significant fibrosis (*n*=4)	BA with significant fibrosis (*n*=16)	CI, *P*
Adiponectin (µg/mL)	15.50 (2.71)	32.79 (14.13)	6.36 to 25.09, 0.002
Total bilirubin (mg/dL)	1.70 (0.32)	4.01 (1.20)	1.51 to 3.78, <0.001
Direct bilirubin (mg/dL)	1.10 (0.45)	2.50 (0.65)	0.52 to 3.78, 0.004
AST (IU/L)	42.0 (30.0)	58.0 (36.0)	1.2 to 33.78, 0.037
ALT (IU/L)	38.0 (1.5)	40.0 (15.0)	−10.54 to 17.79, 0.597
ALP (IU/L)	170.0 (55.0)	305.0 (118.0)	20.09 to 176.40, 0.017

Data represented as median (IQR). IQR: Interquartile range, CI: Confidence interval, BA: Biliary atresia, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase

Table 4: Logistic regression showing adiponectin as a predictor of fibrosis

Predictor	Estimate	SE	Z	P	OR	CI (95%)
Intercept	7.519	4.020	1.87	0.061	1838.450	4.85e+6
Adiponectin	−0.397	0.197	−2.02	0.043	0.672	0.457 to 0.988

CI: Confidence interval, OR: Odds ratio, SE: Standard error

transplantation. In the present study, controls were enrolled considering the age group of cases. Although there was no statistical difference in age or gender ratios between BA cases and controls, serum adiponectin was significantly higher in BA cases ($P = 0.001$). Similar results have been reported in previous studies.[7,18]

TE (FibroScan) was recently introduced as a non-invasive procedure to determine the extent of hepatic fibrosis.[5,8,9] It emits an ultrasonic wave from its probe, which measures shear wave velocity when passing through the hepatic parenchyma.[5] TE is a validated technique for investigating the severity of liver fibrosis in children with BA.[6,8] This technique has been found to have significant reproducibility and minimal variability, and it is used in various chronic liver diseases.[10,19] The results obtained from FibroScan are adequately correlated with the histological status of fibrosis.[8] Hepatic volume evaluated by TE is more than 100 times larger than a liver biopsy sample. Therefore, the outcome is more representative of the total liver parenchyma.[20] The stiffness values measured by FibroScan in the current study were higher in BA patients than in the healthy controls ($P = 0.002$). Similar results have been reported in previous studies.[3,7] Further analysis was done to correlate serological markers and FibroScan scores with postoperative jaundice status. Jaundice is the principal clinical manifestation of BA like any other liver disorder, and persistence of jaundice after HPE is associated with poor prognosis. In a comparison of BA patients with and without jaundice, the serum levels of adiponectin, AST and ALP were considerably higher in jaundiced patients ($P = 0.002$, 0.037 and 0.017, respectively), as were liver stiffness scores ($P = 0.001$). Higher levels of these enzymes are considered to be associated with hepatic parenchymal damage and dysfunction. The study by Honsawek *et al*.[7] detected similar findings.

In the present study, adiponectin levels were higher in BA cases with significant hepatic fibrosis compared to those with non-significant fibrosis ($P = 0.002$). Although serum ALT showed no significant difference between these two groups, serum AST, ALP and bilirubin were markedly elevated in significant fibrosis group. Statistically, serum adiponectin revealed a positive correlation with TB ($r = 0.81$, P 15 µg/ml was predictive of hepatic dysfunction in postoperative BA patients.

The pathogenesis of the pathways leading to progressive hepatic fibrosis in BA is still unknown.[2] Although an association between adiponectin and liver fibrogenesis has been reported, the exact mechanism remains uncertain. Adiponectin interacts with its receptors in the liver through specific signalling pathways.[15] It attenuates the action of HSC and suppresses the expression of pro-fibrogenic genes. Due to its multifaceted role, it can be speculated that adiponectin will emerge as a new therapeutic option for the management of hepatic fibrosis. Elevated adiponectin levels might occur due to an imbalance between production and clearance. With regard to advanced BA with hepatocyte damage, there may be decreased clearance of adiponectin, which reflects an increased circulating level.[7] Therefore, it is reasonable to consider serum adiponectin a non-invasive biomarker for detecting hepatic fibrosis. Additional features of adiponectin, such as its abundance in the human body, high stability in circulation and little diurnal variation, make it a novel biomarker for accessing hepatic status in postoperative BA patients.[15]

There are a few limitations of this study. This was a single-centre study, and BA being less common in our state than in East Asian countries; thus, the sample size was relatively small. However, this was a prospective study with a case–control design highlighting the scenario in our region. Second, instead of histological findings, which are considered the gold standard, the clinical and biochemical categories were focused on due to the non-invasiveness of the parameters and the limitations associated with liver biopsy. Third, the follow-up duration after HPE was relatively short. However, the results provided significant information. A multicentre study with having larger sample size and follow-up would provide more information regarding the ideal prognostic parameters of postoperative Kasai HPE. The preliminary results of this study will be correlated with future research regarding this aspect.

Conclusion

The present study estimated serum biomarkers and liver fibrosis status using FibroScan to evaluate the post-Kasai prognosis of BA. Elevated levels are indicators of deteriorating hepatic status. Adiponectin levels and liver stiffness scores were significantly higher in BA patients than in healthy controls. They were also considerably higher among postoperative BA patients with jaundice than those without jaundice. These non-invasive prognostic markers should be included aspost-Kasai follow-up protocol, thereby providing BA patients with an advanced warning regarding hepatic complications and progression to end-stage liver disease.

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Conflicts of interest

There are no conflicts of interest.

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