

Serum Biochemical Markers and Newer's Ratios in Predicting the Short Term Outcomes in Children Undergoing Kasai's Portoenterostomy

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ABSTRACT

BACKGROUND

Biliary Atresia (BA) is described as an obliterative cholangiopathy of progressive type resulting in fibrosis and cirrhosis of liver. The proxy marker utilized to detect fibrosis of liver is the aspartate aminotransferase to platelet ratio index (APRI) in liver disorder cases and in biliary atresia affecting old children. The study therefore was done to evaluate the role of simple composite indices like Alanine aminotransferase (ALT) to Platelet index (ALPRI), INR / Platelet ratio in predicting the short-term outcomes in terms of 6-month bilirubin clearance < 2 mg / dL.

METHODS

This was a longitudinal cohort study conducted over a period of 22 months, in the Department of Paediatric Surgery at Amrita Institute of Medical Sciences, Kochi. The study group comprised of 40 consecutive biliary atresia children who underwent Kasai's portoenterostomy (KPE) between 2016 and 2018 in whom various routine serum biochemical markers were studied and APRI, ALPRI, INR / Platelet ratio were studied. Demographic information including gender, age in months at the time of Kasai operation, date of surgery, biochemical parameters included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, direct bilirubin, r- glutamyl - transpeptidase (GGT), alkaline phosphatase, platelet count, prothrombin time / INR (International Normalised Ratio), TORCH (Toxoplasmosis, Rubella, Cytomegalovirus and HSV) panel. Each variable was reviewed once prior to surgery and then after 2 weeks, third month and after 6 months of KPE. Early cholangitis was defined as hyperpyrexia (38.0 °C) along with serum total bilirubin, leukocytosis with left shift, and normal to acholic stools within 6 months after KPE. SPSS 22.0 version (IBM) was employed for statistical assessment. ROC analysis, Chi square tests were employed.

RESULTS

Using a cut-off value of APRI > 0.45 [AUC 0.731 (95 % CI 0.542 – 0.931)] a sensitivity of 78 % and a specificity of 69.2 % for clearance of jaundice at 6 months was seen. APRI at 3 months > 0.505 [(AUC 0.82 (95 %CI)] a sensitivity of 77.8 % and specificity of 76.9 % was seen. Above mentioned cut-off APRI at 2 weeks and 3 months correlated with persistence of jaundice (p<0.05). Median ALPRI was 0.53 (0.04-3.52); using cut-off value of ALPRI > 0.610 (AUC 0.78) showed 79.4 % sensitivity and 76.2 % specificity) at 2 weeks post-operatively and it correlated with persistence of jaundice (p<0.05). APRI at 3 months postoperatively with cut-off < /= 0.98 showed better survival prediction (p<0.05).

CONCLUSIONS

APRI and ALPRI have shown their usefulness as a noninvasive tool, which has provided with means to predict clearance of jaundice and mortality as short term outcome much earlier than in comparison to conventional biochemical parameters.

KEYWORDS

Biochemical Markers, Mortality, Bilirubin, Biliary Atresia

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BACKGROUND

Biliary Atresia (BA) is a rare, life threatening liver disorder with limited prognosis affecting infants. Biliary atresia is seen in 1 in 10,000 and 1 in 16,700 live births, with occurrence being higher in Asians.^{1,2} It is characteristic of progressive obstructive cholangiopathy which affects both intra - and extrahepatic biliary ducts.³ The precise cause of biliary atresia remains blurred and poses a multifactorial origin. Models proposing genetic, inflammatory, and infectious aetiologies are presented,⁴ but remains non - conclusive.⁵

Hepatic portoenterostomy or Kasai operation is regarded as conventional therapy for decades.^{6,7} In Kasai's portoenterostomy (KP) the atretic extra hepatic mass was removed, and a Roux - en - Y jejunal loop was anastomosed to the hepatic hilum. Among good prognostic Portoenterostomy, the flow of bile could be brought back to normal with clearance of jaundice. Yet, BA cases undergoing Kasai intervention present an uncertain prognosis. Though the surgery enhances prognostic rates, greater number of cases might still need transplantation in their latter part of lives.⁸ Factors determining prognosis are intervention employed and outcomes of operation. In case of not performing portoenterostomy, fibrosis gets progressed inevitably into final stage cirrhosis and eventually death in first year in about 50 - 80 % of child population and about 90 - 100 % cases in third year.⁹

In regards to lab values, aspartate aminotransferase - to - platelet ratio index (APRI) is employed to analyse fibrosis of liver in cases affected by BA and is suggestive of predictive parameter of native liver survival (NLS).¹⁰ Aspartate Platelet ratio index (APRI) stands as illustration of a non-invasive biochemical marker based on restricted cost and universal available option, presumed to reflect the degree of intrahepatic fibrosis.¹¹

We hypothesize that simple composite indices like INR/platelet ratio, APRI, ALPRI, AST / ALT ratio (AAR) can prognosticate effectively the short term outcome in terms of jaundice clearance and help in becoming a better tool in counselling the parents of infants with Biliary atresia. The aim of this study is to illuminate on current data in the literature regarding current understanding of biliary atresia and role of biochemical markers and the APRI, ALPRI, AST / Platelet index, AST / ALT ratio, INR / Platelet index in predicting the short term outcomes in terms of bilirubin clearance by 6 months post-surgery.

METHODS

The present prospective observational study was conducted among forty successive patients of biliary atresia who underwent Kasai portoenterostomy from paediatric surgical unit of Amrita Institute of Medical Sciences Hospital, Kochi, between Jan 2015 and June 2018 who came for regular follow-up for at least 6 months. Cases with biliary atresia who had undergone KPE, who were lost for follow-up, and infants with co-infection with hepatitis B, hepatitis C, hepatitis D or HIV were excluded from the study. Ethical

consent was taken from The Institute Ethical Review Board. Patients were asked to sign an informed written consent after explaining the need for the procedure, their possible outcomes and the significance of the results.

Since no other study with required information to study various ratios namely INR / Platelet ratio index, Aspartate Platelet ratio index (APRI), Alanine aminotransferase Platelet ratio index (ALPRI), ALT / AST ratio in measuring the short term outcomes could be located in existing literature. My study will be a pilot study with sample size of 40.

Demographic information which includes gender, age in months at the time of Kasai operation, date of surgery, Biochemical parameters included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, direct bilirubin, Gama-Glutamyl-Transpeptidase (GGT), alkaline phosphatase, platelet count, prothrombin time/INR (International Normalised Ratio), TORCH (Toxoplasmosis, Rubella, Cytomegalovirus and HSV) panel. Data recorded also included if early cholangitis started post KPE, duration to become JF (Jaundice Free), even if LT was done, time of LT, time of last follow-up, and final outcome. Each variable was reviewed as prior to surgery and then after 2 weeks, third month and after 6 months of KPE. INR-Platelet ratio was calculated as PT INR divided by the Platelet count (10 x 6 mcl) Aspartate aminotransferase Platelet Ratio index (APRI) was calculated as serum AST level. (U / L) / upper normal (85) x 100 / platelet count (10 / L). ALT / AST ratio was calculated as Serum ALT divided by Serum AST levels.

Alanine aminotransferase Platelet ratio Index (ALPRI) was calculated as serum ALT (U / L) /Upper normal (45u / l) x 100 / platelet count (10 / L). Early cholangitis was defined as hyperpyrexia (38.0 °C) along with enhanced serum total bilirubin, leukocytosis with left shift, and normal to acholic stools within 6 months after KPE. All data was collected from online database of Amrita hospital information system and all the candidates was explained regarding the study and the department protocol. All KPE procedures were performed using standard Kasai's portoenterostomy technique. Postoperative care encompassed the usage of prophylactic antimicrobials for 3 months, ursodeoxycholic acid, and nutritional and vitamin supplementation for all patients undergoing KPE. The study population was segmented into the JF (Jaundice free) group (serum total bilirubin < 2.0 mg within 6 months after KPE) and the persistent jaundice (PJ)/Bilirubin Non Clearance (NC) group (serum total bilirubin ≥ 2.0 mg within 6 months after KPE). The changing trends in INR / Platelet ratios, APRI, ALPRI in each group were analysed. All ratios will be calculated and tabulated into the proforma for each patient. Follow up of cases were to December 20, 2018.

Statistical Analysis

Statistical analysis was run utilising IBM SPSS version 20.0 software. (Chicago SPSS Inc., Chicago, IL, USA)) Categorical variables are expressed using frequency and percentage. Numerical variables are presented using mean and standard deviation. ROC curve was used to find ideal cut-off for APRI at 2 weeks, 3 months, 6 months and ALPRI for predicting at

2 weeks to predict bilirubin clearance. ROC curve was also used for finding the ideal cut-off for the variables- bilirubin, and APRI at 3 months and ALPRI for predicting mortality. Chi-Square test with continuity correction was done to find the association of APRI and ALPRI with bilirubin clearance and mortality. p value <0.05 is considered to be statistically significant.

RESULTS

There were 17 females and 23 males; their median age at the time of Kasai operation was 63.5 days (37 - 150) days. Preoperative laboratory parameters assessed just prior to surgery of the cohort showed S total bilirubin with median of 18.1 mg / dL (with a range of 5.9 - 21) mg / dL and Gamma glutamyl transpeptidase with mean of 660 IU / L with median of 644. Preoperative INR was with median of 1.1 (range 0.8 - 3.4), Platelet count median of 481.5 x 10³ / mcl. INR platelet ratio with mean of 1.30 and APRI with median of 0.58 and ALPRI 0.53.

Table 1 shows the association of APRI at different intervals and ALPRI at 2 wks. post operatively with Clearance of Bilirubin. Post - operatively 3 months, 21 patients (87.5 %) have non clearance of bilirubin with APRI at >=0.505 three months postoperatively, and 3 patients (12.5 %) have clearance / Jaundice free, which shows statistical significance with p value 0.003. After 6 months, out of 37 patients, 6 patients (75 %) have bilirubin clearance / jaundice free with APRI at <0.27 six months postoperatively, and 2 patients (25 %) have non clearance / Persistent Jaundice which shows statistical significance with p value 0.024.

The Area under curve is 0.760 with 95 % confidence interval, the cut-off of APRI at 6 months post operatively 0.270 has sensitivity of 91.7 % and specificity of 46.2 % and cut off more than 0.9950 has a sensitivity of 50 % with specificity of 100 % in non - clearance of jaundice (Figure 1). Receiver operator characteristics (ROC) curve for ALPRI at 2 weeks for the determination of Bilirubin clearance by 6 months (Figure 2). The area under ROC curve is 0.782 with 95 % confidence interval, the cut-off of ALPRI at 2 wks. post operatively 0.610 has sensitivity of 79.4 % and specificity of 76.2 % bilirubin clearance at 6 months of age (Table 2).

Out of 40 patients, 19 patients (100 %) were alive by 6 months with S bilirubin at 2 wks. < 8.13 mg / dL and none were dead when S bilirubin was < 8.13 mg / dL which shows statistical significance with p value 0.009. Survival prediction for patients with APRI < .98 which shows statistical significance with p value 0.003 (Table 3).

13 of the patients who were jaundice free showed change in mean APRI of 0.0815 ± 0.51 from preoperative values and assessment at 6 months, whereas bilirubin non clearance group (n = 24) patients showed change in APRI at mean of 0.1850 ± 1.09 which was not statistically significant, p value 0.408 (Graph 2).

APRI Values	Clearance of Bilirubin		P Value
	Non Clearance	Jaundice Free	
2 wks. post operatively			
≥0.45 (N=27)	21 (77.8 %)	6 (22.2 %)	0.045
<0.45 (N=13)	6 (46.2 %)	7 (53.8 %)	
3 Months post operatively			
<0.505 (N=16)	10 (62.5 %)	6 (37.5 %)	0.003
≥0.505 (N=24)	3 (12.5 %)	21 (87.5 %)	
6 Months post operatively			
<0.27 (N=8)	6 (75 %)	2 (25 %)	0.024
≥0.27 (N=29)	7 (24.1 %)	22 (75.9 %)	
ALPRI; 2 wks. post operatively			
≥0.610 (N=22)	19 (86.3 %)	3 (13.6 %)	0.003
<0.610 (N=18)	8 (44.4 %)	7 (55.55 %)	

Table 1. Association of APRI at Different Intervals and ALPRI at 2 Wks. Post Operatively with Clearance of Bilirubin

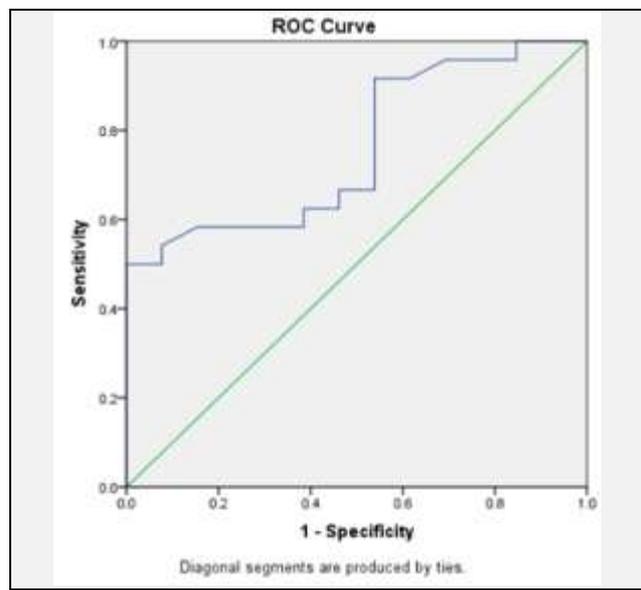


Figure 1. ROC Curve; APRI at 6 Months for BC

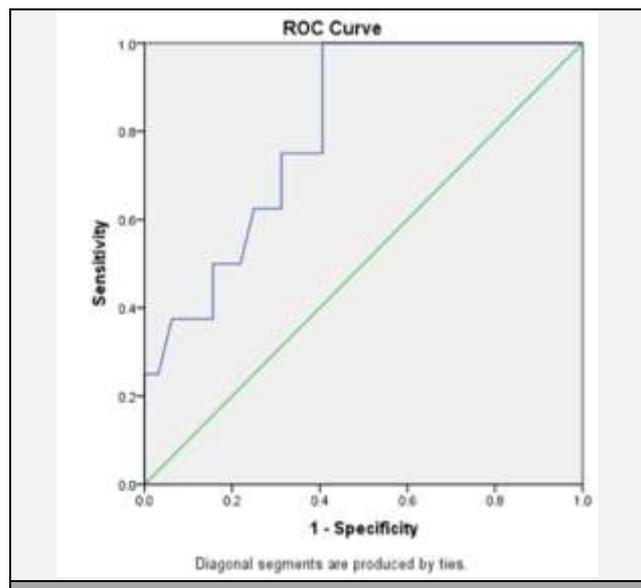


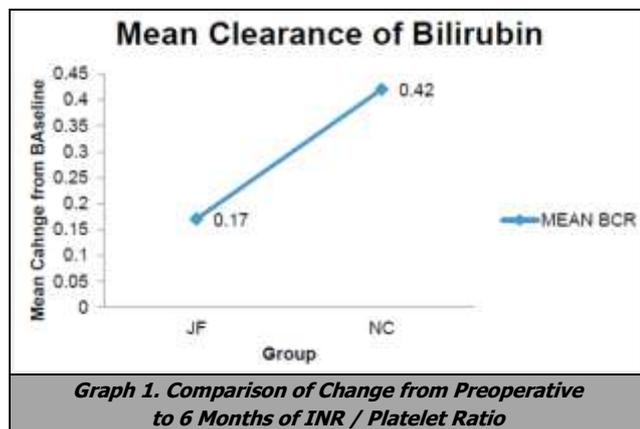
Figure 2. ROC Curve - ALPRI at 2 Wks. for BC

Time Intervals	Sensitivity %	Specificity %	Accuracy %
APRI			
2 wks. post operatively	77.78 (57.74, 91.38)	53.85 (25.13,80.78)	70 (53.47,83.45)
3 Months post operatively	77.78 (57.74, 91.38)	76.92% (46.19, 94.96)	77.5 (61.55,89.16)
6 Months post operatively	91.67 (73, 98.9)	46.15 (19.2, 74.87)	77.68 (58.58, 88.23)
ALPRI			
2 wks. post operatively	70.37 % (49.82, 86.25)	76.92 (46.82, 94.96)	72.50 (56.11, 85.40)

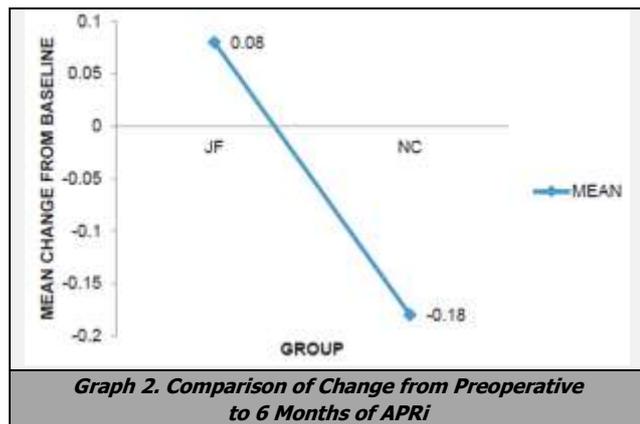
Table 2. Diagnostic Measures of APRI and ALPRI at Different Intervals Post Operatively with Clearance of Bilirubin

Values	Mortality (6 months)		p value
	Dead	Alive	
Serum Bilirubin (mg/dL)			
≥8.13 (N = 21)	8 (38.1 %)	13 (61.9 %)	0.009
<8.13 (N = 19)	0 (0 %)	19 (100 %)	
APRI at 3 months			
≥0.98 (N = 21)	6 (54.5 %)	5 (45.45 %)	0.003
<0.98 (N = 19)	0 (6.89 %)	27 (93.11 %)	
ALPRI at 2 Weeks			
≥1.745 (N=5)	3 (54.5 %)	2 (45.45 %)	0.043
<1.745 (N=35)	5 (14.29 %)	30 (85.71 %)	

Table 3. Association of S Bilirubin, APRI and ALPRI with Mortality by 6 Months of Age



Graph 1. Comparison of Change from Preoperative to 6 Months of INR / Platelet Ratio



Graph 2. Comparison of Change from Preoperative to 6 Months of APRI

DISCUSSION

The prognostic outcome of chronic cholestatic diseases is dependent partially on the extent of fibrosis in liver.¹² Although liver biopsy is the gold standard method for the determination of liver fibrosis, it is invasive and also, the distribution of fibrosis in liver parenchyma is heterogeneous. Due to these limitations, APRI was developed as an alternative. APRI is an indirect biochemical marker of hepatic fibrosis²³ on the basis of widespread availability and

routinely done laboratory parameters reflecting the change in hepatic fibrosis.

Our study is the first, to validate the composite indices of ALPRI, APRI, INR / Platelet ratio in assessing the bilirubin clearance (BC) and short term outcomes with a cohort of BA infants from Kerala (South India). In our study S bilirubin at two weeks postoperatively is a simple and logical predictor for outcome in BA. The cut - point of 8.13 mg / dL was determined by area under curve of 0.805 with 95 % CI with sensitivity of 100 % and specificity of 60%. Patients with S bilirubin < 8.13 mg % at 2 weeks showed 100% survival for 6 months duration (p<0.05). It is found in our study that S bilirubin 2 weeks postoperatively after KP makes a reasonable grade depicting moderate flow of bile. Of the greater benefits employing these markers is that clinician might educate the cases attendants about the outcome probability in 2 weeks post surgically and the 1st post-operative visit, as in case of our department protocol. It helps in early counselling of patients who will require liver transplantation.

It was noted in our study that those patients with an APRI > 0.45 at 2 weeks postoperatively and APRI at 3 months with >0.505 have high chance of persistence of jaundice by 6 months of age (p<0.05). This was independently established in these patients. Similarly the other composite index, ALPRI at 2 weeks with patients having ALPRI >0.610 have a higher chance of persistence/non clearance of bilirubin (p<0.05).

In our study, patients with S bilirubin <8.1 mg / dL at 2 weeks have 100% survival at six months of age (p<0.05), which corresponds to good bile drainage. APRI calculated at 3 months postoperatively, patients with value<0.98 have better survival at 6 months (p<0.05). It was observed in our study group that 93 % of patients who were alive had APRI <0.98. It was also observed in our study group that BA children with ALPRI >2.1 at 3 months had mortality at six months with sensitivity of 100 %. Out of the 5 patients who lost the native liver (mortality / liver transplant) by six months post KP (2 transplant patients), 3 were found to have high APRI and ALPRI by 2 weeks and 3 months. This gives impetus to the hypothesis that APRI and ALPRI are fairly reliable indicator of progression of the disease and can be used as early as 2 weeks post operatively.

Yang LY et al¹² revealed that greater counts of platelets and lesser AST grades on clinical presentation was correlated with a greater effect among infants suffering from BA. It was also noted that by multiple regression analysis both variables were independent of each other. Following which, the composite index APRI was formed presumably independently utilising both variables but validated greatly in chronic liver disease in adults. Dos Santos de Oliveira et al¹³ and Chusilp S et al¹⁴ showed that APRI was significantly correlated to METAVIR fibrosis scores in children with hepatitis C. APRI, ALPRI, AST / ALT, INR / Platelet ratio has the advantage of requiring only three routine laboratory tests (LFT, CBC, INR). Davenport et al⁵ have also demonstrated the usefulness of APRI in children with biliary atresia and have shown that APRI at the time of KP is a useful indicator in assessing grading of liver disease. There is scanty literature available on simple composite indices like

ALP_{Ri}, INR / Platelet ratio and ALT / AST ratio in predicting the outcomes in biliary atresia.

The present assessment has demonstrated that clearance of jaundice wasn't obtained in any child with an initial AP_{Ri} of >3.0, and additionally all would have needed liver transplant to survive. This lends weight to our impression that this indeed is a better indicator of the status of the liver at the time of presentation. This study hence validates AP_{Ri} and ALP_{Ri} as an useful adjunct tool in evaluating the severity of disease in BA at presentation and immediate post-operative period and on early follow up, hence helps in counselling the parents on the prognosis of the disease.

Limitations

1. Follow up period was short.
2. Sample size was limited as it was a pilot study
3. A prospective study with longer follow-up would have enabled us to substantiate the findings of our study with respect to the native liver survival and 5-year mortality.

CONCLUSIONS

In our study, AP_{Ri} and ALP_{Ri} have shown their usefulness as noninvasive tools, which have provided with means to predict clearance of bilirubin and mortality at 6 months, much earlier, in comparison to conventional biochemical parameters.

Financial or Other Competing Interests: None.

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