Original Article

Risk Prediction Scoring System to Predict the Postsurgical Outcomes of Biliary Atresia

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Aim: To find out association between liver function, liver histopathology and outcomes of biliary atresia (BA) following Kasai Portoenterostomy (KPE).

Materials and Methods: This is a retrospective study of children who underwent KPE at a single institute by single surgeon. The patient records analyzed and data of complete blood counts, liver function tests, coagulation profile and histopathology reports collected. The outcomes recorded as alive and jaundice free, alive but jaundiced, and deceased. Statistical analysis done using SPSS 23.

Observations: Total of 148 children operated during January 2000 to December 2018. Of these, 26 matched inclusion criteria. The parameters assessed were percentage of direct bilirubin, ratios of Aspartate transaminase (AST) to Alanine transaminase (ALT); Gamma glutamyl transferase (GGT) to AST; GGT to ALT and Aspartate transaminase to platelet ratio index (APRi). Among histopathology reports, fibrosis grade and bile ductular size noted. Among 26, 16 alive and ten are deceased. Among 16 alive, all are jaundice free. Of the parameters, ratio of AST to ALT, APRi and grade of fibrosis found statistically significant and further analysis showed if AST to ALT ratio < 2.1, APRi < 1.8 and grade of fibrosis < four, irrespective of age at surgery, had 96.2% probability of successful KPE. Based on these observations, a scoring system and risk prediction model constructed based on Receiver operating characteristic (ROC) curves which are first in BA management.

Results and Conclusion: Although numbers are sufficient for statistical analysis, we further intend to validate the scoring system in a prospective trial. BA children can be subjected to risk prediction model and KPE performed in those who have a score less than seven and offered to those with score between eight and 16 out of 20.

Key Message: The scoring system and risk prediction model can guide in the management and post-operative follow up of children with biliary atresia.

Keywords: Aspartate platelet ratio index, biliary atresia, kasai portoenterostomy, outcomes, risk prediction model

INTRODUCTION

Biliary atresia if left untreated is almost surely fatal by 3 years of age due to liver failure.[1] There are no current guidelines for surgical management, and the available options are performing a kasai portoenterostomy (KPE) or liver transplantation.[2] Liver transplantation can be performed as a primary procedure or a rescue procedure following failed KPE.[3] The success of KPE is variable, and the reported success rates are over and above 50%.[4] There are multiple factors which are considered to play an important role in the outcome of these children, and the most important one was the age at surgery. The age at surgery was considered as a golden window of opportunity in these cases.
children, and when operated within this time frame, the likelihood of a successful outcome was higher. The outcome of these children can be represented by a spectrum, where on the one end, there are children who are jaundice free following KPE, and on the other end, there are children who have persistent symptoms.[1]

We have shown that the outcomes of these children who are operated between 30–60 days and 61–90 days were compared with those who were operated between 91 and 120 days.[3] Anticipating that there is more than just age at work which predicts the outcomes of these children, this is an attempt to identify these probable factors at work.

**Materials and Methods**

This is a retrospective observational study. After getting the institutional ethics committee clearance, the records of the operated children of biliary atresia by a single surgeon at the same institute were studied. Data of complete blood counts, liver function tests including coagulation profile, and TORCH titer reports done during the admission before the procedure were collected. After confirmation of diagnosis with an intraoperative cholangiogram, KPE was performed with a 40 cm Roux-en-Y limb. A liver biopsy was done at the same time. The children were followed up initially every month up to 3 months and 3 monthly up to 1 year followed by yearly visits up to at least 10 years of age. All the children who did not fulfill the above criterion were excluded from the study. All the children with syndromic biliary atresia were excluded from the study. Further, the data were analyzed, and percentage of direct bilirubin was calculated, aspartate transaminase (AST)-to-alanine transaminase (ALT) ratio was calculated, aspartate platelet ratio index (APRI) was calculated, and gamma-glutamyltransferase (GGT)-to-AST and GGT-to-ALT ratios were calculated. The histopathology report was analyzed, and data regarding the grade of fibrosis according to Ishak grading,[8] the bile ductular size, and the presence of cytomegalovirus (CMV) inclusion bodies studied by H and E staining and presence of CMV antigens by immunohistochemistry (IHC) (Biocare Medical DT 10+ BC 90 CMV clone) staining were collected. All the data collected were tabulated and analyzed using SPSS version 23.0 software (IBM, NY, USA).

**Observation and Results**

Out of the 149 cases, there were 26 cases which fulfilled the above criteria and included in the study. There were 10 female and 16 male children. The youngest of the infants operated was of 40 days and the oldest infant was 169 days. All the children underwent KPE and liver biopsy at the same time. Among 26 children, 10 are deceased and 16 are alive, and all the alive children are jaundice free with the minimum follow-up period of 1 year. The eldest child alive and jaundice free among these is 9 years old. The calculated percentage of direct bilirubin ranged from 61% to 99%. The AST-to-ALT ratio ranged from 0.62 to 3.64, whereas the APRI ranged from 0.36 to 5.15. The calculated ratios between GGT to AST and GGT to ALT ranged between 0.24–7.32 and 0.33–13.38, respectively. The grade of fibrosis as per Ishak staging ranged from 1 to 6 [Table 1] and bile duct size from 20 to 200 µm on the liver biopsy.

All the 26 liver biopsy tissues were negative for CMV antigens through IHC staining. Only one biopsy showed CMV antigen positive in lymph node. Among the parameters studied, the AST-to-ALT ratio, APRI index, and grade of fibrosis were found to be statistically significant in predicting the outcome of these children post KPE.

It was found that the ratio of AST to ALT, APRI index, and grade of fibrosis had an impact on outcome of these children post KPE [Table 2]. When these factors were found to be statistically significant, it was then tried to find the corroborative impact of these factors when added together. This led to finding that if the ratio of AST to ALT is <1.8, APRI <2.2, and grade of fibrosis is <4, then the rate of survival increases to 96.2% irrespective of age at surgery following KPE.

| Microscopic appearance | Grade of Fibrosis |
|------------------------|-------------------|
| No fibrosis            | 0                 |
| Fibrous expansion of some portal areas, with or without fibrous septa | 1                 |
| Fibrous expansion of most portal areas, with or without short fibrous septa | 2                 |
| Fibrous expansion of most portal areas with occasional portal to portal bridging | 3                 |
| Fibrous expansion of portal areas with marked bridging | 4                 |
| Marked bridging with occasional nodule (incomplete cirrhosis) | 5                 |
| Cirrhosis, probable or definite | 6                 |

**Table 2: Statistical analysis**

| Variables | Score | df | Significance | AUROC |
|-----------|-------|----|--------------|-------|
| Grade of fibrosis | 6.754 | 1   | 0.009 | 0.816 |
| AST/ALT ratio | 7.490 | 1   | 0.006 | 0.866 |
| APRI | 6.949 | 1   | 0.008 | 0.863 |
| Bile duct size | 2.340 | 1   | 0.126 | 0.659 |
| Overall statistics | 18.604 | 4   | 0.001 |   |

**AUROC**: Area under receiver operating characteristic curve, AST: Aspartate transaminase, ALT: Alanine transaminase, APRI: Aspartate platelet ratio index
These parameters were statistically analyzed further to find the diagnostic power of these tests. For this, the adequacy of number of cases was calculated using the Kaiser-Meyer-Olkin measure of sample adequacy and factor analysis, and the numbers were found to be adequate. Further, receiver operating characteristic curve (ROC) for each of the parameters was plotted [Figure 1] and found that they can be used as tests for diagnosis when clubbed together. When all these three tests were found to have diagnostic strengths, a scoring system was developed [Table 3] incorporating these factors which would help predict a successful outcome following KPE in children with biliary atresia. Such a scoring system and risk prediction model is the first of its kind to the best of our knowledge.

To construct the scoring system, the grade of fibrosis, the ratio of AST to ALT, and APRI were graded according to clinical significance. The histological grade of fibrosis was given a higher value, and both the other parameters were given the same value. Using the scores given, the outcomes of our analysis were then plotted to draw ROC [Figure 2] which helped us to decide the cumulative cutoff for the risk prediction model. They are summarized in Table 2.

By applying this risk prediction score on our cases in the study, a 100% match for mild and severe risk group was seen [Figure 3]. Based on this risk prediction model, which was developed using the ROC, a cumulative score between 3 and 7 had a 100% survival rate, a score between 8 and 16 had a 45% survival rate, and a score of more than 17 had a 100% mortality rate irrespective of the age at operation.

We intend to further validate this scoring system by applying this to our prospective cases and analyze their results.

**DISCUSSION**

Biliary atresia is a progressive disorder causing liver failure. The extent of liver failure can be variable depending on the time of onslaught of etiological process which can either be antenatal or postnatal. Hence, the child presents at different ages with different clinical profiles and different degrees of liver damage. The exact cause of biliary atresia is unknown but speculated to occur in three forms: the syndromic form also known as biliary atresia splenic malformation or BASM, the acquired form found sporadically, and the ones associated with CMV. Biliary atresia associated with CMV has bagged a name of its own due to its propensity to have worse prognosis than the rest.

With the etiology being unclear and the age at surgery which was considered as a window of opportunity
for success being challenged, an attempt was made to find the other probable factors at play which lead to progressive liver damage and failure. It was also found that age is just a number and does not individually influence the outcomes of these children,\(^\text{[3]}\) and this is an attempt to find other probable factors at play.

Looking at the literature, there are several factors which have been studied at the time of surgery to predict the outcomes of these cases post KPE. These can be grouped into the effect of age at surgery,\(^\text{[8]}\) effect of immune mediators at the time of surgery,\(^\text{[9]}\) effect of type of biliary atresia, and effect of portal plate histology\(^\text{[10]}\) including the level of fibrosis and cirrhosis of the liver.\(^\text{[11]}\)

For finding the other probable factors at play, we focused on immune mediators, the histopathology of liver biopsy and liver function tests. To keep a similar playing field, we excluded the cases of syndromic biliary atresia that are known to have poor prognosis.

Various markers have been studied to identify the extent of liver damage in these children. Of these, the AST-to-ALT ratio is one of the most common factors studied and more so in the adult population,\(^\text{[12]}\) and it was attempted to extrapolate the same in these children. Whenever there is a reversal of AST-to-ALT ratio, the liver seems to have undergone a certain degree of damage. As ALT is more specific for liver and AST has more than one source, low ALT indicates a failing liver. This ratio is found to be associated with chronic liver disease. This ratio of more than two is suggestive of cirrhosis and has been used as a surrogate marker in adults.\(^\text{[13]}\) In our study, the ratio of <1.8 had a good outcome post KPE.

Aspartate to platelet ratio index is another such study to predict the prognosis of biliary atresia and this was developed by Wai et al. for patients suffering from hepatitis C in order to prevent performing repeated liver biopsies.\(^\text{[14]}\) In this article, they went on to conclude that this noninvasive test can be utilized for monitoring these patients with chronic hepatitis C, and this could replace performing repeated liver biopsies. Many other studies have been later conducted and found this test to be useful in monitoring the grade of fibrosis in liver.\(^\text{[15]}\)

While in children with biliary atresia, this has been used as a surrogate marker to predict their outcomes. In a study by Yang et al., APRI effectiveness in diagnosing significant liver fibrosis, especially cirrhosis, in biliary atresia infants was studied and they concluded that is it effective way to screen the children with biliary atresia.\(^\text{[16]}\) APRI was calculated using the formula:

\[
\text{APRI} = \frac{\text{AST/Upper limit of AST}}{\text{Platelet counts in } 10^5} \times 100
\]

In another study by Davenport et al., APRI value of 1.22 had the sensitivity and specificity of 75% and 84% for identifying cirrhosis in biliary atresia children.\(^\text{[17]}\)

While in our study, we had a cut off value of 2.19 for predicting significant cirrhosis and poor outcome post KPE.

While in yet another study, APRI value of more than 3 was considered to have failure of jaundice clearance and need for liver transplantation.\(^\text{[18]}\)

Further, in biochemical tests, we studied a percentage of direct bilirubin, and this was calculated using the formula:

\[
\text{Percentage of direct bilirubin} = \frac{\text{Direct bilirubin}}{\text{Total bilirubin}} \times 100
\]

This is probably more indicative of obstructive liver damage and probably removes the age of these children as a confounding factor. For analysis, they were divided into four groups, starting from 61%–70% to 91%–100%. The outcome when compared to percentage of direct bilirubin was not found to be statistically significant.

The GGT-to-AST and ALT ratios were also studied.\(^\text{[13]}\) These ratios are studied previously in biliary atresia cases, but nothing conclusive has been proved so far. The present study also did not find this factor to be of any significance.

Liver biopsy is the next parameter requiring mention in the study. The biopsies were done at the time of KPE and all were reported by the same institutional histopathologist. The grading of fibrosis was done according to the Ishak staging.\(^\text{[6]}\)

Among histological parameters, the level of α-SMA is known to affect the degree of fibrosis. Higher the α-SMA, higher was the grade of fibrosis and cirrhosis.
This could help predict the outcomes of native liver survival in the children post KPE.\[^{19}\] The other parameters studied are cytokeratin-7-positive percentage which is also a marker for fibrosis and cirrhosis. In our study, we had children who had Grade 1 fibrosis and had fibrosis all the way up to Grade 6. It was noted that higher the grade of fibrosis, higher was the failure rate of KPE which was statistically significant. Anything higher than Grade 4 had a significantly higher risk of a failed KPE. It was noted that greater age at surgery was not uniformly associated with higher grades of fibrosis or cirrhosis. This also shows that the time of onslaught of the disease process is not uniform in these children.

The bile ductular size in the portal plate was also assessed in our study. The sizes ranged from 20 to 2000 µ. It was noted that all children with larger bile ductules did not have uniformly successful KPE, but we did note that children with larger bile ductules faring better than those which smaller bile ductules. Although the bile duct size of >250 µ has been reported in the literature to have a better outcome,\[^{20}\] the size of bile duct was not found to be statistically significant in our study probably as a result of a very large range of values.

The role of CMV has been widely studied in relation to both etiology and prognosis of biliary atresia. In one of the studies, it was found that CMV-positive biliary atresia had a significantly higher degree of inflammation in the liver biopsy, poorer outcome, poorer jaundice clearance, poorer native liver survival, and increased mortality.\[^{21}\] In the current study, analysis of TORCH had found CMV DNA from liver tissue in any of the 12 children that they were investigating.\[^{22}\] In other studies, Fischler et al. had found CMV DNA from liver tissue in 9 of the 18 children that they were investigating\[^{23}\] and the studies done by Domiati-Saad et al. had similar results.

In a similar study by Jevon and Dimmick, they did not report CMV DNA in liver biopsy tissue in any of the 12 cases they were investigating.\[^{24}\] The exact mechanism by which CMV causes obliteration of the bile duct is not known, but their affection is definitely proved when more intense stains were obtained from children who did poorly following surgery than those who did well after KPE.\[^{25}\]

The results of this study indicate that whatever the etiology of biliary atresia is, does not affect all the children at the same time. The pathogenesis is a continuous process which manifests in varying degrees at different ages of the child. Hence, the time of affection of the liver is more important than age at surgery. With the three parameters stated above, we can identify those children with biliary atresia whose liver is salvageable with KPE as their disease process is not advanced to irreversible cirrhotic stage.

**Conclusion**

Since biliary atresia is a progressive disorder and liver damage is ongoing, the exact extent of liver failure cannot be predicted based on the age of the patient. Using this scoring system and risk prediction model, one can predict the extent of liver damage irrespective of age and either perform a KPE, suggest KPE, or suggest liver transplantation. With the results of this study, it is possible to carefully select children who will benefit from KPE and help to monitor these children post KPE. Since the numbers are only significant statistically, we intend to further validate the scoring system in a prospective trial.

**Recommendations**

Based on the above findings of the study, the authors would like to recommend the following.

The risk prediction scoring system will be applied to all the children presenting with biliary atresia and based on the scores, and the following can be undertaken:

a. If the score is between 3 and 7—should perform a KPE
b. If the score is between 8 and 16—should perform a KPE if the child is not fit for a liver transplant
c. If the score is between 17 and 20—should recommend a liver transplantation.

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**Conflicts of interest**

There are no conflicts of interest.
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