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Original Article

Bilirubin Levels at 1st and 3rd Postoperative Months are Significant in Determining the Success of the Kasai Portoenterostomy

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ABSTRACT

Aim: The aim of this retrospective study was to determine the indicators of survival with native liver (NLS) of patients operated for biliary atresia (BA).

Materials and Methods: This review included 53 BA patients in a 13-year period. There were two groups: (1) NLS and (2) necessitating transplantation. Age at operation, and bilirubin levels on the 7th day, 1st and 3rd months postoperatively were recorded. Mann-Whitney U and logistic regression analysis were used for statistical analysis for NLS and liver transplantation (LTx).

Results: Kasai portoenterostomy (KPE) was performed on 38 patients, and 15 were directed to LTx due to cirrhotic liver at presentation. Twenty-three of 38 patients with KPE survived with native liver, and 15/38 patients required LTx during follow-up. Mean age at portoenterostomy for NLS and necessitating LTx was 54.43±24.64 and 68.33±24.35 days respectively ($p>0.05$). The 1st and 3rd month bilirubin levels were lower in the NLS group ($p<0.01$). The 1st month and 3rd month bilirubin levels after KP were significant predictors for survival with NLS. A cut-off value of 5.7 mg/dL bilirubin level at the 1st month predicted the necessity of transplantation after KPE with a sensitivity of 83.3% and specificity of 78.9%.

Conclusion: Bilirubin levels of the 1st and 3rd months are reliable predictors for the success of portoenterostomy.

Keywords: Biliary atresia, liver transplantation, biliary cirrhosis, cholestasis

Introduction

Biliary atresia (BA) is a progressive, destructive, and inflammatory disease of the extrahepatic and intrahepatic bile ducts (1,2). The first-line surgical treatment for BA is Kasai portoenterostomy (KPE) introduced by Morio Kasai in 1955 (3). The reported 5-year survival rate with native liver after KPE varies between 35-55% (4,5). Nevertheless, the majority of cases require liver transplantation (LTx) in long-term follow-up. Indications of LTx for BA include biliary cirrhosis, liver failure, portal hypertension, gastrointestinal bleeding, growth retardation, pruritis and hepatopulmonary syndrome.

Several studies have looked into the potential indicators for native liver survival after KPE including age at portoenterostomy, biochemical parameters, histopathological findings and postoperative complications (4-7). Age at portoenterostomy is widely accepted as a prognostic factor. However, there are some counterviews in the literature. For instance, Pakarinen et al. (4) reported that age at KPE is a prognostic factor for clearance of jaundice in

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postoperative follow-up. On the other hand, Ramachandran et al. (8) advocated that age is not a criterion for success of KPE (8). Another popular issue is "prognostic indicator" for success of KPE in the postoperative follow-up period. Ramos Gonzales et al. (6) have shown that total bilirubin >2 mg/dL at 3 months after surgery was an independent predictor for the need for LTx. Similarly, Hukkinen et al. (7) have calculated that conjugated bilirubin levels ≥2.5 µmol/L at postoperative 6th month was a significant predictor, increasing the risk of cirrhosis 35-fold. In this study, we aimed to determine the indicators and predictors of NLS of our patient series operated on for BA in our center.

Materials and Methods

This study was approved by the Institutional Review Board and Research Ethical Committee in accordance with international ethical standards and the World Health Organization Helsinki Declaration (approval no: 20-8T/13). All admissions and surgical procedures were performed after informed consent of the family/parents/caregivers was given.

Study Design and Data Collection

In our clinical protocol, all patients presenting with prolonged jaundice and light-colored stools are initially evaluated with biochemical analysis and detailed hepatobiliary ultrasonography done after starvation of minimum 6 hours. Triangular cord thickness, abnormal gall bladder morphology (starvation and after feeding) as well as findings of subcapsular arterialization, parenchymal heterogeneity, and findings of "BA splenic malformation (BASM)" are considered suggestive for BA. Patients are listed for laparoscopic exploration and intraoperative cholangiogram the day after they are admitted; we generally need to follow this fast-track diagnostic approach since the majority of patients are referred relatively late (Table I), and we usually do not have the liberty of losing another day of valuable time with work-up. In cases where BA is detected during laparoscopy (and cholangiogram), the surgery is completed with KPE if found rational, considering the status of the liver. Extended portal hilar dissection as described in the literature (9) is the preferred method for KPE. Liver biopsy is taken from patients with evident cirrhotic liver (presence of distinctive nodules on the surface with granular appearance, stiffness of the liver) and is sent to frozen section pathological examination during laparoscopy, and those who are reported to display histopathological findings of evident cirrhosis who would not benefit from the KPE are considered for primary LTx, and the procedure is terminated.

Patients are followed in close collaboration with pediatric gastroenterology. Direct/indirect bilirubin levels, gamma-glutamyl transpeptidase (GGT) and liver function tests are checked weekly for the first post-KPE month, and monthly after the first month or as required depending on the clinical progress. Patients who develop liver failure, persistent ascites, portal hypertension, gastrointestinal bleeding, hepatopulmonary syndrome, failure to thrive or pruritis during the follow-up are referred to the LTx program, of which the senior author is also part of the transplant team.

For this study, the hospital records of those patients who were operated for BA between January 2005 and December 2018 were reviewed retrospectively. Demographics, days of admission, age at KPE and surgical findings were detailed. The patients were then divided into two groups; the first group consisted of patients surviving with their native liver (KPE-NLS) after KPE and the second group included those necessitating transplantation (KPE-nLTx) during the follow-up. The two groups were compared according to age at KPE, bilirubin and GGT levels at postoperative 7th day, 1st and 3rd month to determine and compare the success of KPE, as suggested in other studies (10,11).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0.

Table I. Age (days), bilirubin and GGT levels at diagnostic laparoscopy/cholangiography for the two groups

	KPE (38 patients)	Primary LTx (15 patients)	p-value
Age at laparoscopy/cholangiography (days)	53.36±26.49	94.2±26.41	<0.00001
Total bilirubin (mg/dL)	8.60 (7.02-10.05)	8.60 (7.55-12.57)	0.354
Conjugated bilirubin (mg/dL)	6.70 (4.60-8.25)	7.25 (6.17-9.0)	0.424
GGT (U/L)	444.0 (232.5-913.0)	524.5 (212.25-1033.25)	0.990

GGT: Gamma-glutamyl transpeptidase, KPE: Kasai portoenterostomy, LTx: Liver transplantation

Armonk, NY: IBM Corp., USA). The patients' characteristics and clinical parameters were assessed for normality with "Kolmogorov-Smirnov" and "Shapiro-Wilk" tests. Independent "t-test" was used for samples with normal distribution and samples following non-normal distribution were analyzed with "Mann-Whitney U" test. Logistic regression analysis was used to determine predictive factors for NLS. As a result of logistic regression analysis, "receiving operating characteristic" (ROC) curve analysis was used to determine whether the variables had a diagnostic value. Survival curves and tables were constructed for the survival analysis using the "Kaplan-Meier" method. The effect of variables on survival included in the study was examined by "Cox regression" analysis; a "p" value <0.05 was considered significant.

Results

Fifty-three patients operated with for BA were included in this study. Mean age at presentation was 64.9±32.1 (1-176) days. Diagnosis of BA was confirmed with laparoscopy and intraoperative cholangiography for all patients. Fifteen patients with a mean age of 94.2±26.41 (64-176) days at operation who had histopathologically confirmed evident cirrhotic liver during diagnostic laparoscopy did not receive KPE and they were referred to the LTx program for primary LTx. Thirty-eight patients with a mean age of 53.36±26.49 days at operation underwent KPE during the same session. Those patients who were not suitable for KPE had a significantly later presentation when compared to those who received KPE (p<0.00001). Preoperative total/conjugated bilirubin, and GGT levels were statistically similar between the two groups (Table I).

Twenty-three of the 38 patients with portoenterostomy survived with their native livers (KPE-NLS) and the remaining 15 patients required LTx (KPE-nLTx) during their follow-up. Time to LTx following non-functioning KPE was 13.5 (3.9-43.5) months. Three-year NLS was 65.8% and >5-year survival rate was 60.5%. None of the remaining 23 patients with NLS required LTx to date of writing (Figure 1).

In order to determine the effect of native liver survival, portoenterostomy days were assessed for the two groups. Mean age at operation was 54.43±24.64 days for the KPE-NLS patients, and 68.33±24.35 days for the KPE-nLTx patients. Although the mean age at operation was higher

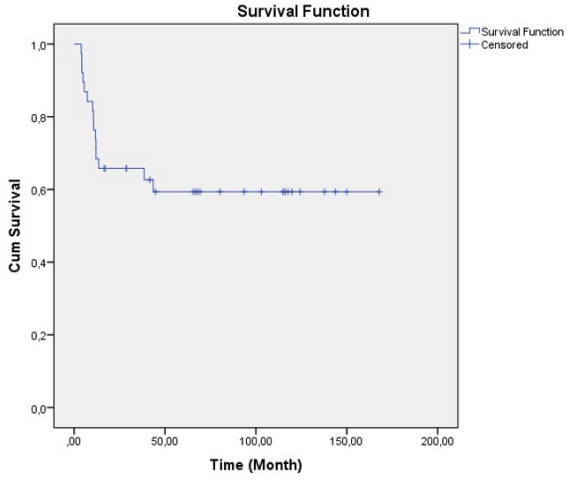

Figure 1. Native liver survival function after Kasai portoenterostomy

Table II. Total bilirubin, conjugated bilirubin and GGT levels of the two groups after Kasai portoenterostomy

	KPE-NL	KPE-nLTx	p-value
7th day			
Total bilirubin (mg/dL)	7.60±2.53	9.28±2.75	0.086
Conjugated bilirubin (mg/dL)	5.90 (4.70-6.90)	7.35 (4.52-9.72)	0.213
GGT (U/L)	635.0 (314.75-1171.5)	1099 (213.75-1695.75)	0.660
1st month			
Total bilirubin (mg/dL)	3.86±3.25	8.39±5.41	0.007
Conjugated bilirubin (mg/dL)	2.0 (0.57-3.62)	5.40 (3.22-9.12)	0.032
GGT (U/L)	530.5 (291.25-1050.5)	1029.0 (380.0-2126.25)	0.182
3rd month			
Total bilirubin (mg/dL)	0.65 (0.40-4.95)	8.35 (2.05-22.85)	0.003
Conjugated bilirubin (mg/dL)	0.55 (0.20-4.05)	6.45 (1.20-16.72)	0.001
GGT (U/L)	288.5 (184.75-492.5)	157.0 (57.0-551.25)	0.305

KPE: Kasai portoenterostomy, NL: Native liver, GGT: Gamma-glutamyl transpeptidase

Table III. Univariate logistic regression analysis to predict the need for liver transplantation after Kasai portoenterostomy		
	Odds ratio (95 CI)	**p-value**
Age at operation	1.025 (0.995-1.056)	0.105
Total bilirubin (preoperative)	0.917 (0.686-1.226)	0.559
Total bilirubin (7th day)	1.305 (0.956-1.782)	0.093
Total bilirubin (1st month)	**1.299 (1.038-1.626)**	**0.022**
Total bilirubin (3rd month)	**1.185 (1.021-1.375)**	**0.026**
Conjugated bilirubin (preoperatively)	0.881 (0.672-1.156)	0.362
Conjugated bilirubin (7th day)	1.343 (0.934-1.932)	0.112
Conjugated bilirubin (1st month)	**1.377(1.024-1.852)**	**0.034**
Conjugated bilirubin (3rd month)	**1.202 (1.031-1.403)**	**0.019**
CI: Confidence interval		

in the KPE-nLTx group, there was no statistically significant difference between the two groups. When the groups were compared according to bilirubin levels in the postoperative period, "total/conjugated bilirubin" levels were similar at postoperative 7th day; however, 1st and 3rd month levels were found to be significantly higher in those patients who required LTx after KPE (Table II). There were no statistically significant differences for postoperative GGT levels in both groups.

Predictive factors for the need for LTx after KPE were evaluated by univariate logistic regression analysis. Total/conjugated bilirubin levels in postoperative 1st and 3rd months were determined to be the most important predictive factors for LTx after KPE (Table III). It was also found that a "1-unit increase" in total bilirubin level at postoperative 1st month increased the risk of LTx by 1.299-fold [odds ratio (OR); 1.299, confidence interval (CI): 1.038-1.626, p<0.05], and also a "1-unit increase" in total bilirubin level in the postoperative 3rd month increased this risk by 1.185-fold (OR: 1.185, CI: 1.021-1.375, p<0.05) (Table III). Age at KPE and bilirubin levels on the 7th postoperative day were not predictive factors for determining the necessity of LTx. As a result of logistic regression analysis, postoperative 1st and 3rd month total and conjugated bilirubin levels were reliable predictive factors for LTx after portoenterostomy.

ROC curve analysis was carried out using these variables to define a cut-off value to determine the requirement for LTx after KPE. ROC curve analysis revealed that "total bilirubin level with a cut-off value of more than 5.70 mg/dL at the 1st postoperative month" was an important indicator (AUC: 0.787, %CI: 0.610-0.965, p<0.01) for future LTx with a sensitivity of 83.3% and specificity of 78.9% respectively (Figure 2). Cox regression analysis has also shown that a one-unit increase in total bilirubin levels at the 1st postoperative month increased the risk of LTx 2.172-fold (95% CI: 1.033-4.566, p<0.05).

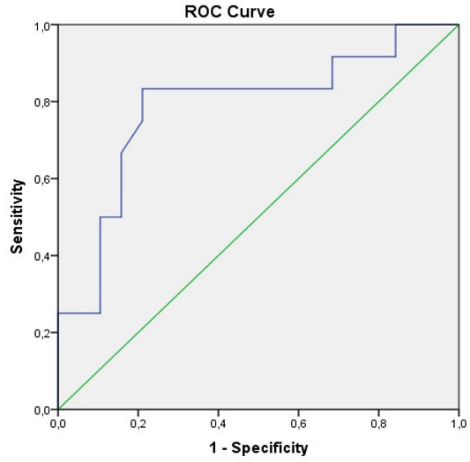

Figure 2. ROC curve analysis to define the cut-off value of 1st month bilirubin for determining the possibility of liver transplantation following Kasai portoenterostomy
ROC: Receiving operating characteristic

Discussion

BA in the 21st century still remains "full-of-unknowns". Although significant progress has been achieved in the effort to elucidate the pathogenesis of this anomaly, KPE is the first surgical option for patients born with BA ever since its introduction in 1955 (3,9,12). On the other hand, BA is the most common indication for LTx in childhood as the success of KPE is limited and depends on many factors. Age at presentation and surgery are considered and have been shown to be two of the most important determinants (4,13). Similarly, the phenotype of the anomaly (i.e., the type of atresia), BASM, an association of Cytomegalovirus infection

and the experience of the surgeon all play an important role in native liver survival after KPE (5,9). Nevertheless, aiming to achieve and prolong native liver survival, KPE remains a bridging operation to LTx for the majority of BA patients. Despite a successful KPE, at least two-thirds of patients, if not all, will require LTx at some point (5,14,15). This has led the researchers try to identify factors that may determine and answer the question of which patient will deteriorate to liver failure and consequently LTx and which will actually achieve native liver survival.

Age at KPE is an important factor thought to determine the success of surgery in the literature (5,13). Schreiber et al. (13) divided their patients into three groups according to KPE age as follows; operated before 30 days, between 31-90 days and after 90 days, and they showed that the 10-year native liver survival rates were 49%, 25% and 15% respectively suggesting that the earlier the KPE, the better the success of surgery (13). In the series by Ferreira et al. (16) analyzing their 117 patients, they have found that the only variable significantly associated with failed biliary drainage was surgery beyond 90 days of age. When they looked at the survival analysis of their patients, absence of biliary flow ($p<0.0001$), age at surgery >90 days ($p=0.035$), and the presence of BASM ($p<0.0001$) alone could predict death or the need for LTx (16).

On the other hand, there are also counterviews in the literature stating that age at KPE is not an indicator for native liver survival (8,17). Quithsi et al. (17) were not able to show any correlation between age at portoenterostomy and survival in their series of 29 BA patients. Ramachandran et al. (8), in their series of 62 infants with BA, operated on 17 patients presenting later than 90 days of age, and showed that one-third of those patients benefitted from KPE concluding that age was not a criterion for the success of the Kasai procedure. Ihn et al. (18), in their large series of 214 patients over 29 years, analyzed their patients in two eras (before and after 2006), and came to the conclusion that the impact of age at the time of KPE on operative outcomes became less significant over time with the increase in the single surgeon's experience and improvement in medical treatment for BA (18).

The findings in our series were also similar to those concluding that age did not matter. However, we believe that the issue of age should be carefully interpreted. The fact that patients presenting relatively late (>90 days) may also benefit from hepatic portoenterostomy does not necessarily mean that all those patients, regardless of the condition of their liver, should receive KPE. The condition of the liver may vary widely; the damage to liver is not the same for the same given age in all patients. Therefore, a patient with a liver that is lobulated, nodular and quite stiff at laparoscopic exploration with confirmed evident cirrhosis on histopathology is hardly likely to benefit from KPE. Nevertheless, a liver that is relatively soft and less nodular in the absence of cirrhosis should definitely be considered for KPE even if the patient is older than 90 days of age. In our series, 38 patients underwent KPE regardless of their ages and 15 patients were directly programmed for primary LTx without portoenterostomy due to evident cirrhosis on histopathological findings during laparoscopic exploration.

The aim of the portoenterostomy is to ensure the biliary drainage and to delay/prevent biliary cirrhosis. Therefore, clearance of jaundice is an important indicator for the success of surgery.

Correspondingly, in our series, those who had a failed KPE and clearance of jaundice required LTx within a period of 13.5 months, and those who had successful clearance of jaundice had a >5-year survival rate of 60.5%. When we further aimed to identify which parameter would be an indicator of NLS or the need for LTx in the future, total and conjugated bilirubin levels in postoperative 1st and 3rd months were determined to be reliable indicators suggesting a clear association between the clearance of jaundice and NLS. Conjugated bilirubin level of 2.0 mg/dL at the 1st month, and normal bilirubin values attained at the 3rd month ensured a 60.5% rate of >5-year NLS. On the other hand, each "1-unit rise" (in mg/dL) in total bilirubin levels increased the risk of LTx by 1.2-fold. A cut-off value of 5.70 mg/dL in total bilirubin at the 1st month of surgery was calculated to be an important indicator for future LTx with a sensitivity of 83.3% and specificity of 78.9% respectively. Huang et al. (11) emphasized that total bilirubin level <4.85 mg/dL at postoperative 1st week was an important predictive factor for NLS. In another study by Khanna et al. (19), the ratio of postoperative 7th day total bilirubin to its preoperative value was found to be reliable predictor for biliary atresia outcome. In our series, 7th day bilirubin levels did not seem to have a predictive effect on outcome. Similarly, Noor et al. (20) also evaluated bilirubin, GGT, and alanine aminotransferase levels at postoperative 7th day of KPE, and no clear association was found between these parameters and survival (20). Rodeck et al. (10) reported that a cut-off bilirubin concentration of 57 µmol/L (3.33 mg/dL) at postoperative 6th week was a predictor for event free survival with a sensitivity of 80% and specificity of 78.6% (10), and this finding was quite similar to ours suggesting that bilirubin levels in postoperative follow-

up, especially at the 1st month, is a consistent parameter to predict native liver survival. Some recent studies have also looked into other biochemical parameters, such as liver function tests and GGT etc., as predictive parameters (20-22). However, in our patient series, we were not able to demonstrate a correlation between serum GGT levels and long-term outcome.

Conclusion

KPE still remains the one and only surgical option in the treatment of patients born with BA. However, controversy still exists as to how patients are best managed and the predictors of its outcome. Although the total number of patients in our series seems to be a limitation, we attained conclusive significant results concerning these debatable issues including age at KPE, postoperative prognostic factors determining the native liver survival after KPE and LTx in the management of BA. Our series has shown that bilirubin levels at postoperative 1st and 3rd months can predict native liver survival after KPE or the need for LTx regardless of age at surgery. We believe these parameters can be used as reliable predictors for the outcomes of patients after KPE.

Ethics

Ethics Committee Approval: It was approved by the Institutional Review Board and Research Ethical Committee in accordance with international ethical standards and the World Health Organization Helsinki Declaration (approval no: 20-8T/13).

Informed Consent: All admissions, surgical procedures were performed after informed consent of the family/parents/caregivers.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: Ü.Ç., G.S., M.K., Analysis or Interpretation: Ü.Ç., Critical Review: M.O.E., Writing: M.O.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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