Predictors of demand for liver transplantation in children undergoing Kasai portoenterostomy for biliary atresia

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Context
Biliary atresia (BA) remains the most common indication for pediatric liver transplantation worldwide. Ultimately, 50–80% of BA patients will require a liver transplant Thus, much of the research in the field has focused on identifying predictors for transplant and optimizing the efficacy of Kasai portoenterostomy (KPE), in order to decrease the need for transplantation and avoid the risks of lifelong immunosuppression.
Aim
The aim of this study was to identify perioperative risk factors for the need of liver transplantation following KPE operation for BA.
Patients and methods
A retrospective analysis of 150 patients undergoing KPE for BA at Hepatobiliary and Pancreatic Surgery Department, National Liver Institute, Menoufia University, from May 2013 to May 2018, was carried out. Patients were divided into two groups: group one included 73 (48.7%) patients who survived without the need for liver transplantation and group two included 77 (51.3%) patients with mortality, listed for liver transplantation or transplanted; thereafter, logistic regression analysis was used to identify the independent predictors of cases needing liver transplantation.
Statistical analysis used
Continuous variables were expressed as mean±SD and categorical variables as proportions. Univariate analysis for the two groups were carried out using the independent samples *t* test for continuous variables and χ^2 test for categorical variables. Logistic regression analysis was used to identify the independent predictors of cases needing liver transplantation. Receiver operating characteristic analysis was used for the cut-off determination of predictive parameters using MedCalc application, version 18.2.1.
Results
The mean age at the time of operation was 74.9±14.6 days after birth (range, 31–111 days); there were 70 (46.7%) male babies and 80 (53.3%) female babies. The mean preoperative weight was 4.6±0.6 kg, while the mean preoperative height was 57.3±3.58 cm.
Total bilirubin and albumin levels at 1 and 3 months following KPE were associated with death or the need for liver transplantation; however, only a total bilirubin level of more than 6 mg/dl at 3 months is an independent predictor of the need for liver transplantation. Age at the time of KPE and postoperative steroid use were not associated with improved transplant-free survival.
Conclusion
Total bilirubin level of more than 7.3 mg/dl at 1 month and a level of more than 6 mg/dl at 3 months after KPE are predictive of the need for liver transplantation ($P< 0.001$). Albumin level of less than or equal to 2.5 g/dl at 1 month and a level of less than or equal to 3 g/dl at 3 months after KPE are predictive of the need for liver transplantation ($P< 0.001$); however, only total bilirubin level of more than 6 mg/dl at 3 months is an independent predictor of the need for transplantation ($P< 0.001$). Age at the time of KPE and postoperative steroid use were not associated with improved transplant-free survival.

Keywords:
biliary atresia, Kasai portoenterostomy, transplant-free survival

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Introduction

Biliary atresia (BA) is the most frequent surgical cause of cholestatic jaundice in neonates. The common histopathological picture is one of inflammatory

damage to the intrahepatic and extrahepatic bile ducts, with sclerosis and narrowing or even obliteration of the biliary tree [1]. Untreated, this condition leads to cirrhosis and death within the first years of life. Surgical treatment usually involves an initial attempt to restore bile flow using Kasai portoenterostomy (KPE), which is performed as soon as possible after diagnosis [2]. Later, liver transplantation may be needed if the Kasai operation fails to restore the biliary flow or if cirrhosis complications occur [3]. BA remains the most common indication for pediatric liver transplantation worldwide. Ultimately, 50–80% of BA patients will require a liver transplant. Thus, much of the research in the field has focused on identifying predictors for transplant and optimizing the efficacy of KPE, in order to decrease the need for transplantation and avoid the risks of lifelong immunosuppression [4]. The purpose of this study was to determine the perioperative risk factors associated with progression to liver transplantation following KPE.

Patients and methods

A retrospective analysis was performed on the data of all patients who underwent the traditional technique of KPE for BA type III at the National Liver Institute, Menoufia University, from May 2013 to May 2018. This study followed our institutional guidelines and was approved by the Ethical Committee. Patients whose procedure was performed elsewhere and had reintervention or continued postoperative care at our institution were excluded. About 54 patients who underwent KPE in the same period of the study were excluded from the study, as they were missed from the follow-up.

Cases were divided into two groups: group 1 included 73 (48.7%) patients who survived without the need for liver transplantation and group two included 77 (51.3%) patients with mortality, listed for liver transplantation or who were transplanted, or who were patients needing liver transplantation but had no suitable donor, and even included those who refused liver transplantation. The criteria for the need for liver transplantation were as follows:

(1) Failure to thrive requiring aggressive nutritional support.
(2) Recurrent cholangitis despite appropriate antibiotic therapy.
(3) Recurrent hospitalizations impairing quality of life.
(4) Complications of portal hypertension (PHT), such as refractory variceal bleeding, significant ascites and episodes of spontaneous bacterial peritonitis (SBP) and symptomatic thrombocytopenia.
(5) Severe pruritus.

The date of last follow-up was determined by the last surgery or Hepatology Clinic visit. Patients were identified as premature if they were born at less than 37 weeks of gestational age. Steroid use was defined as receiving steroids at any point during the postoperative course, regardless of the length of steroid use. Successful clinical outcome was defined by jaundice clearance, with a blood level of total bilirubin less than 2.0 mg/dl.

Statistical analysis

Continuous variables were expressed as mean±SD and categorical variables as proportions. Univariate analysis for the two groups was carried out using independent samples t test for continuous variables and χ^2 test for categorical variables. Logistic regression analysis was used to identify the independent predictors of cases needing liver transplantation. Receiver operating characteristic analysis was used for the cut-off determination of predictive parameters using MedCalc application version 18.2.1 (MedCalc Software's, Republic of Korea). The cumulative survival rates were analyzed using Kaplan–Meier survival curves, and the statistical difference was assessed using the log-rank test. A P value of less than 0.05 was considered statistically significant. All analyses were performed with SPSS version 23.0 (SPSS, Chicago, Illinois, USA).

Table 1 Ultrasound finding and intraoperative associated anomalies

Variables	*n* (%)
Gall bladder	
Contractile	37 (24.7)
Noncontractile	57 (38)
Atretic	56 (37.3)
TC sign	
Positive	86 (57.3)
Negative	64 (42.7)
Hepatomegaly	
Yes	115 (76.7)
No	35 (23.3)
Splenomegaly	
Yes	73 (48.7)
No	77 (51.3)
Associated anomalies	
Preduodenal PV	5 (3.3)
Polysplenia	11 (7.3)
Intestinal malrotation	16 (10.7)
Cardiac anomaly	7 (4.7)
No	111 (74)

PV, portal vein; TC, triangular cord.

Table 2 Univariate analysis of risk factors among the 2 groups

	Group 1 (*N*=73) [*n* (%)]	Group 2 (*N*=77) [*n* (%)]	χ^2 or Fisher exact (value)	*P* value
Sex				
Male	31 (42.5)	39 (50.6)	1.008	>0.05
Female	42 (57.5)	38 (49.4)		
Onset of jaundice				
Since birth	11 (15.1)	30 (39)	14.491	0.001
After birth	12 (16.4)	3 (3.9)		
Insidious onset	50 (68.5)	44 (57.1)		
Portal fibrosis pre				
Grade I	7 (9.6)	14 (18.2)	2.944	>0.05
Grade II	6 (8.2)	7 (9.1)		
Grade III	54 (74)	48 (62.3)		
Grade IV	6 (8.2)	8 (10.4)		
Gall bladder contractility				
Contractile	20 (27.4)	17 (22.1)	3.149	>0.05
Noncontractile	31 (42.5)	26 (33.8)		
Atretic	22 (30.1)	34 (44.1)		
TC sign				
Positive	40 (54.8)	46 (59.7)	0.375	>0.05
Negative	33 (45.2)	31 (40.3)		
Hepatomegaly				
Positive	52 (71.2)	63 (81.8)	2.347	>0.05
Negative	21 (28.8)	14 (18.2)		
Splenomegaly				
Positive	38 (52.1)	31 (40.3)	0.653	>0.05
Negative	35 (47.9)	46 (59.7)		
Steroid use				
Positive	25 (34.2)	88 (64.2)	0.579	>0.05
Negative	48 (65.8)	49 (35.8)		
Congenital anomalies				
Positive	16 (21.9)	23 (29.9)	1.232	>0.05
Negative	57 (78.1)	54 (70.1)		
	Group 1 (*N*=73)	Group 2 (*N*=77)	Mann–Whitney value or *t* test	*P* value
Age at surgery (days)				
Mean rank	69.15	82.2	–1.840	0.066
Sum ranks	5324.5	6000.5		
Preoperative total bilirubin (mg/dl)	10.91±2.7	11.05±2.8	0.304	>0.05
Preoperative albumin (g/dl)	3.51±0.68	3.62±0.56	1.056	>0.05
Total bilirubin at 1 month (mg/dl)				
Mean rank	59.51	90.66	–4.389	<0.001
Sum ranks	4344.5	6980.5		
Total bilirubin at 3 months (mg/dl)				
Mean rank	39.26	109.86	–4.389	<0.001
Sum ranks	2866.00	8459.00		
Albumin at 1 month (mg/dl)				
Mean rank	91.38	60.44	–4.394	<0.001
Sum ranks	6671.00	4654.00		
Albumin 3 months (mg/dl)				
Mean rank	103.91	48.56	–7.819	< 0.001
Sum ranks	7585.50	3739.50		

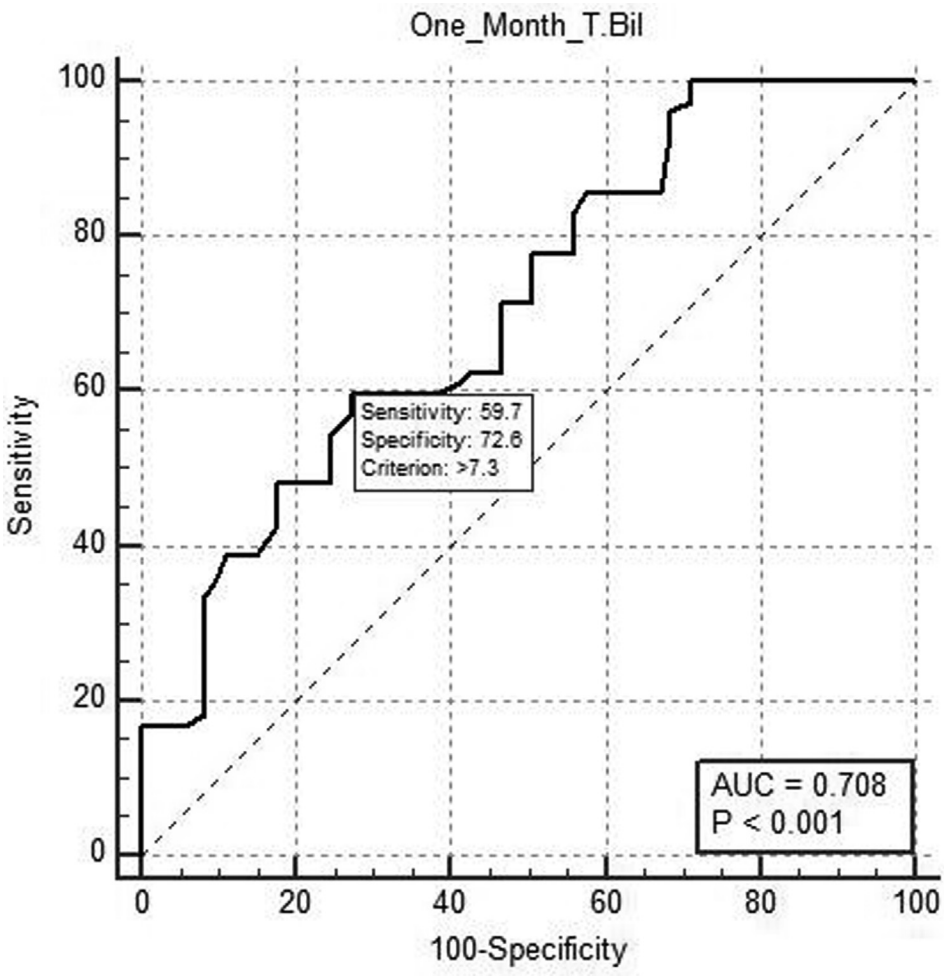
TC, triangular cord. No significance of underline value except for highlight that it is statistically significant.

Results

A retrospective analysis was performed on the data of 150 patients who underwent KPE for BA type III at the National Liver Institute, Menoufia University, from May 2013 to May 2018.

The mean age at the time of operation was 74.9 ±14.6 days after birth (range, 31–111 days); there were 70 (46.7%) male babies and 80 (53.3%) female babies. The mean preoperative weight was 4.6 ±0.6 kg, while the mean preoperative height was 57.3±3.58 cm.

Figure 1



ROC curve analysis for total bilirubin level 1 month postoperatively defining cutoff value. ROC, receiver operating characteristic.

The mean follow-up time was 36.99±13.54 months, ranging from 5 to 60 months.

The mean preoperative serum total bilirubin was 10.98 ±2.76 mg/dl, while the mean direct bilirubin level was 8.01±2.8 mg/dl.

As regards the clinical data, the onset of jaundice was since birth in 41 (27.3%) cases, developed after birth in 15 (10%) cases and with insidious onset in 94 (62.7%) cases, while clay stool was reported in all 150 cases.

As regards US finding and intraoperative associated anomalies, please refer Table 1.

As regards liver biopsy according to Biliary Atresia Research Consortium, portal fibrosis grading was as follows:

21 (14%) cases with absent or fibrous expansion of some portal tract.

13 (8.7%) cases with fibrous expansion of most portal tracts.

102 (68%) cases with focal portal-portal bridging.

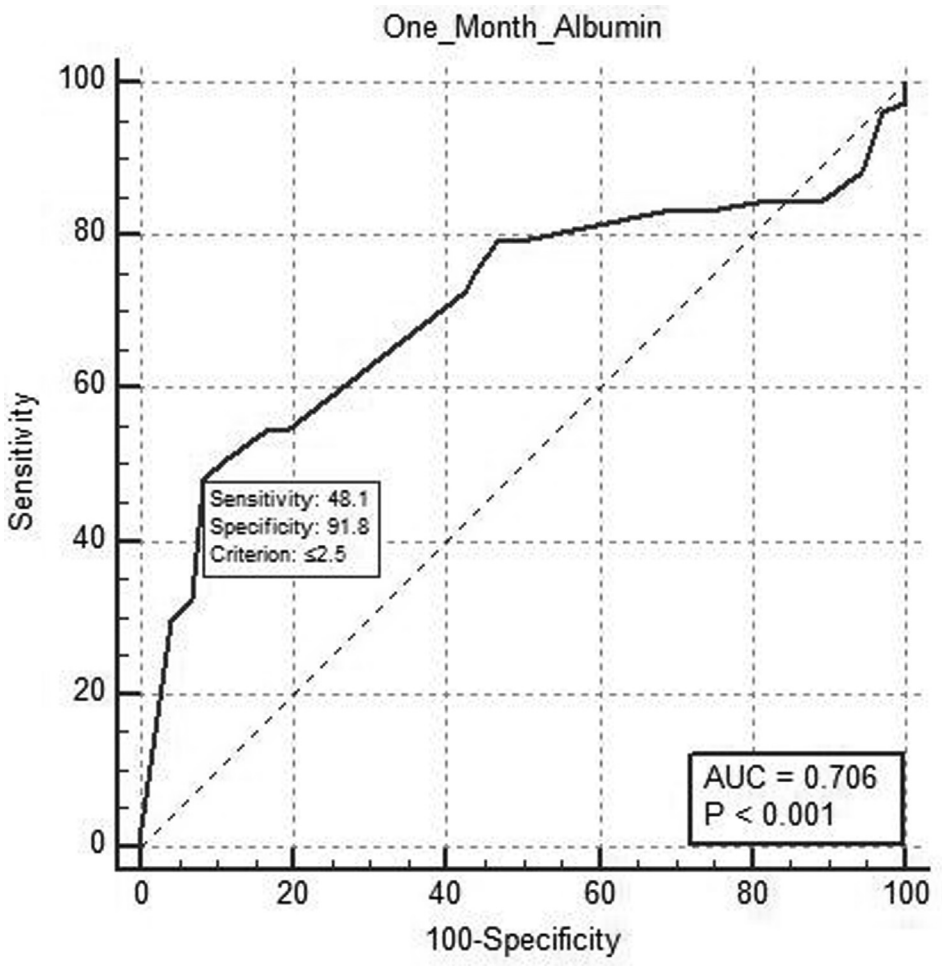
14 (9.3%) cases with marked bridging.

As regards the use of postoperative steroids, 56 (37.3%) cases were given steroids as a regimen of intravenous methylprednisolone (4 mg/kg/day) for 2 weeks tapered down to oral prednisolone (2 mg/kg/day) for a further 9 weeks.

As regards the postoperative complications, 27 (18%) cases were complicated by signs of portal hypertension in the form of ascites and gastrointestinal tract bleeding, two (1.3%) cases suffered synthetic liver failure, 20 (13.3%) cases had infection (including chest, wound, and peritonitis), and seven (4.7%) cases had a burst abdomen.

As regards mortality, 33 (22%) cases died postoperatively from various causes:

Figure 2



ROC curve analysis for albumin level one month postoperatively defining cutoff value. ROC, receiver operating characteristic.

17 (11.3%) cases died from liver failure.
12 (8%) cases due to pneumonia.
Two (1.3%) cases due to septicemia.
Two (1.3%) cases due to a sudden event.

According to predictor analysis between the two groups, it was observed that onset of jaundice (since birth), the level of total bilirubin one month after Kasai operation, total bilirubin three months postoperatively, and level of albumin 1 month and 3 months postoperatively were all statistically significant (Table 2).

By those statistically significant predictors, a cutoff value could be determined for both total bilirubin and albumin levels at 1 and 3 months postoperatively as follows (Figs 1–4 and Table 3).

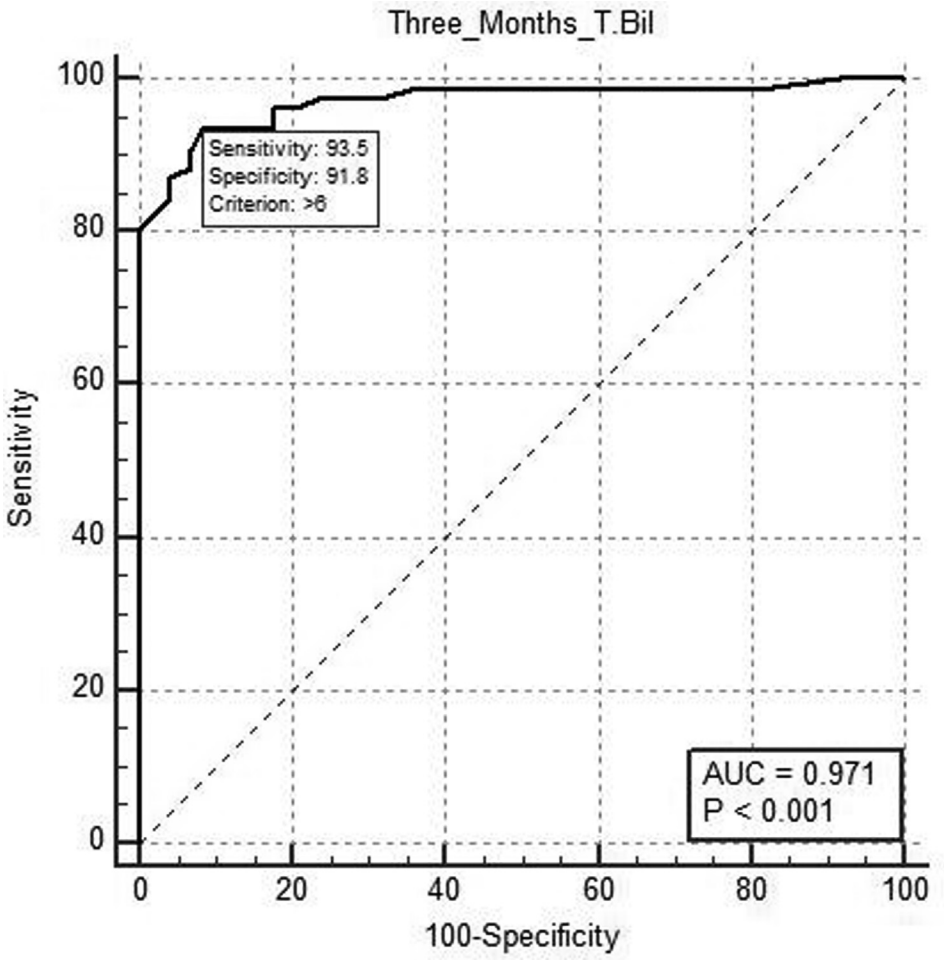
Univariate analysis showed that, at 1 and 3 months after the Kasai operation, mean total bilirubin and albumin, along with onset of jaundice and patient age at the time of kasai porto-enterostomy (KPE), were predictors of death or the need for liver transplant following Kasai operation (Table 2). Patient sex, portal fibrosis degree before Kasai, concomitant congenital syndromes, and the use of steroids were not significantly associated with death or the need for transplantation. After adjusting for sex, prematurity, and steroid use, further multivariable logistic regression analysis showed that total bilirubin more than 6 mg/dl (odds ratio, 0.381; $P< 0.001$) at 3 months after surgery was an independent predictor of the need for transplantation (Table 4).

Discussion

Although BA is an uncommon pediatric disease, its incidence has nearly increased two-fold from the end of the 1990s to the early 2010s, and it is still the most common cause for liver transplantation in children [5].

The experience at our institution shows an increase in the average rate of kasai porto-enterostomy (KPE) performed per year in this study period to about two folds the last 5 years before this study. This nearly two-

Figure 3



ROC curve analysis for total bilirubin 3 months postoperatively defining cutoff value. ROC, receiver operating characteristic.

fold increase might reflect an increase in the incidence of BA, but is most likely attributable to an increase in our referrals due to the strengthening of our liver transplant program that occurred during this same time period.

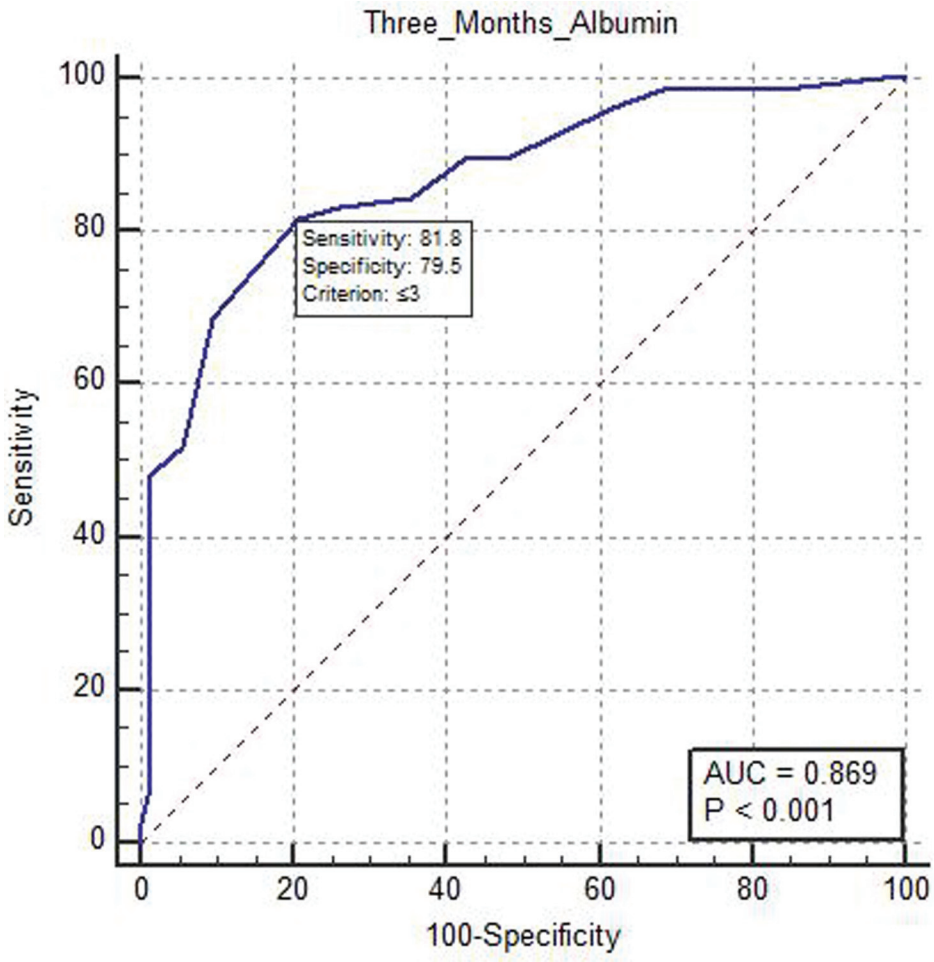
The composition of the cohort in this study does not resemble what has been described in many other published series with a 3 : 2 female to male ratio; in our study, the male percent is 46.7%, and 13% of patients had a concomitant congenital syndrome (i.e. biliary atresia splenic malformation syndrome (BASM), congenital cardiac defect, heterotaxy, and interrupted inferior vena cava); however, in our study, 26% of patients had congenital anomalies in the form of preduodenal portal vein, polysplenia, intestinal malrotation, and cardiac anomalies [6].

The ideal age for KPE has been under much debate in the BA literature for many years. The majority of series present the median age at HPE to be between 60 and 65 days, with over half of the children with BA in the United States undergoing KPE after 60 days of life [7]. Initially, Kasai *et al.* [8] suggested that the ideal age for HPE was before 60 days of life, as outcomes seemed to worsen after this time due to progressive liver fibrosis.

In our study, the age at surgery had marginal statistical significance (P=0.066), and mean age (days) in group 2 (78.04±11.5) was higher than in group 1 (71.97±16.6). Since then, there have been multiple reports demonstrating that younger age at HPE is associated with improved outcomes [4,6]. Although a consensus on the specific age at which outcomes seem to deteriorate is still lacking, similar outcomes have been demonstrated among groups of patients undergoing HPE at different ages up to 90 days [6]. In a large multicenter study in the United States, Shneider *et al.* [9] observed that a trend of younger age patients having better outcomes, but with no statistically significant association, could be drawn.

KPE is the initial surgical treatment of choice for BA; for most patients, it is only a temporizing solution and

Figure 4



ROC curve analysis for albumin level 3 months postoperatively defining cutoff value. ROC, receiver operating characteristic.

Table 3 Cutoff value for total bilirubin and albumin at 1 and 3 months postoperatively

Predictor	Criterion (cutoff value)	Sensitivity	Specificity	Significance level *P* (area=0.5)	Area under the ROC curve
Total bilirubin at 1 month	>7.3	59.74	72.60	<0.0001	0.708
Albumin at 1 month	≤2.5	48.05	91.78	<0.0001	0.706
Total bilirubin at 3 months	>6	93.51	91.78	<0.0001	0.971
Albumin at 3 months	≤3	81.82	79.45	<0.0001	0.869

ROC, receiver operating characteristic.

a bridge to liver transplant. Nonetheless, transplant-free or native liver survival BA patients have an excellent long-term overall survival; as seen in our cohort, the 2-year survival was 80%, and 5-year survival was 65%. Moreover, in other cohort studies, the transplant-free or native liver survival is an element of much more variability in the literature with 2- and 10-year survival reported in the range of 50–60 and 30–35%, respectively [9]. Such diverse results are expected, as clinicians and centers might differ in their threshold to proceed to transplantation, for which much research has been dedicated to determining predictive factors of the need for transplantation.

Table 4 Multivariable logistic regression analysis of risk factors for mortality or transplant

	Odds ratio	95% CI	*P* value
Onset of jaundice	1.520	0.03–78.1	0.835
Patient age	1.008	0.95–1.06	0.741
Total bilirubin at 1 month	1.234	0.9–1.6	0182
Albumin at 1 month	0.992	0.18–5.4	0.993
Total bilirubin at 3 months	0.381	0.25–0.58	**<0.001**
Albumin at 3 months	1.074	0.11–10.1	0.951

No significance of bold values except for highlight that it is statistically significant.

In this cohort study, the total bilirubin level of more than 7.3 mg/dl at 1 month and a level of more than 6 mg/dl at 3 months after KPE are predictive of the

need for liver transplantation ($P< 0.001$). We also have demonstrated that an albumin level of less than or equal to 2.5 g/dl at 1 month and a level of less than or equal to 3 g/dl at 3 months after KPE are predictive of the need for liver transplantation ($P< 0.001$) but, after multivariate regression analysis, only a total bilirubin level of more than 6 mg/dl at 3 months is an independent predictor of the need for transplant ($P< 0.001$).

Ramos-Gonzalez *et al*. [10] reported that a total bilirubin level of < 2 mg/dl at 3 months after KPE is an independent predictor of the need for transplant ($P<0.001$). Furthermore, He demonstrated that an albumin level of < 3.5 g/dl at 3 months after HPE is an independent predictor of the need for transplant ($P=0.037$).

We found no association between the use of steroids in the postsurgical management of KPE and risk for death or transplant.

Conclusion

Overall survival for children with BA is excellent. However, the majority of patients who underwent KPE will ultimately require liver transplantation. A total bilirubin level of more than 7.3 mg/dl at 1 month and a level of more than 6 mg/dl at 3 months after KPE are predictive of the need for liver transplantation ($P< 0.001$). Albumin level of less than or equal to 2.5 g/dl at one month and a level of less than or equal to 3 g/dl at three months after KPE are predictive of the need for liver transplantation ($P< 0.001$), but only a total bilirubin level of more than 6 mg/dl at 3 months is an independent predictor of the need for transplant ($P< 0.001$). Age at the time of KPE and postoperative steroid use were not associated with improved transplant-free survival.

Declaration of patient consent

Nil.

Conflicts of interest

There are no conflicts of interest.

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