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Prognostic Factors for Survival of Patients with Biliary Atresia Following Kasai Surgery

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Biliary atresia (BA) is a progressive obstruction and fibro-obliteration of the extrahepatic and intrahepatic biliary tract that causes cholestatic jaundice in infants, resulting in biliary cirrhosis and even death in the first year of life if the Kasai procedure is not performed at an earlier age. There are many prognostic factors that could affect the survival of patients with BA after Kasai surgery, however results still show some conflicting findings. A retrospective study was conducted using medical records of patients with BA who underwent Kasai surgery at Dr. Sardjito Hospital, Yogyakarta, Indonesia from June 2012 to April 2018. Twenty-nine BA patients were involved in our study, with 16 males and 13 females. Log-rank analysis showed a significant association between survival rate of BA patients with albumin level 1 month and 3 months after Kasai surgery, with *p*-values of 0.043 and 0.016, respectively. Interestingly, multivariate analysis revealed that cholangitis tended to have an association with BA patients' survival (*p*=0.09). In conclusion, the BA patients' survival might be affected by the presence of cholangitis after Kasai surgery. Further multicenter studies with a larger sample size are important to verify our results.

INTRODUCTION

Biliary atresia (BA) is a progressive obstruction and fibro-obliteration of the extrahepatic and intrahepatic biliary tract that causes cholestatic jaundice in infants, resulting in biliary cirrhosis and even death in the first year if the Kasai surgery is not performed at an earlier age (1, 2). The incidence of BA is reported to occur in 1: 8,000 to 1: 18,000 live births (2, 3), while its incidence in Yogyakarta, Indonesia is 1:7,000 live births (4).

BA needs to be treated promptly early in life to prevent biliary cirrhosis and liver failure (5). The Kasai surgery is the main surgical action in dealing with BA (6). However, the life expectancy of BA patients after Kasai procedure in 5 years is only 65% (7). There are many prognostic factors that could affect the survival of patients with BA after Kasai surgery, however results still show some conflicting findings (7-10). Therefore, we investigated the association of prognostic factors and the survival rate of patients with BA after Kasai surgery in an Indonesian population.

MATERIALS AND METHODS

Patient samples

A retrospective study was conducted using medical records of infants with BA who underwent Kasai surgery at Dr. Sardjito Hospital in Yogyakarta, Indonesia from June 2012 to April 2018. Our study was approved by the Institutional Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital (KE/FK/1088/EC/2017).

We analyzed 29 BA patients during our designated study period with 16 male and 13 female patients, with the median of age at Kasai surgery of 103 (Interquartile range - IQR, 86-131) days.

Prognostic factors

We evaluated and correlated the following prognostic factors and the survival rate of patients with BA after Kasai surgery: gender, age at Kasai surgery, presence of cholangitis, portal hypertension, and esophageal varices, total bilirubin and albumin levels 1 month and 3 months after Kasai procedure. We defined the survived patient as 5-year survival rate.

We divided total serum bilirubin (TB) levels at 1-month and 3-months post-Kasai samples into normal (<2 mg/dL) and abnormal (≥2 mg/dL) according to a previously published study (11). We divided serum albumin levels at 1-month and 3-months post-Kasai samples into normal (≥3.5 g/dL) and abnormal (<3.5 g/dL).

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Moreover, we also defined postoperative jaundice-free ratio as TB postoperative day 30 and preoperative (TB30/TB0) ratio. Its cutoff value was determined by receiver operating characteristics (ROC) curve.

Statistical Analysis

The data were presented as frequencies. Univariate analysis using Fisher exact test was performed to identify the association between prognostic factors and BA patients' survival rate, followed by multivariate analysis using logistic regression. Survival analysis using Kaplan Meier test method and log-rank test were utilized to analyze patients' cumulative survival.

RESULTS

Baseline characteristics

We ascertained 29 BA patients with the overall survival after Kasai operation of 51.7% (Table I).

Association between prognostic factors and BA patients' survival

First, we analyzed the association of BA patients' characteristics with their survival rate. We found that only albumin level at 3 months after surgery was significantly associated with 5-year survival rate (OR=28.33 [95% CI=1.30-617.96]; p=0.013) (Table I).

Table I. Association between prognostic factors and BA patients' survival after Kasai surgery.

Prognostic Factor	Dead (n, %)	Survived (n, %)	OR (95% CI)	*p*
Gender				
▪ Male	6 (20.7)	10 (34.5)	0.38 (0.08-1.69)	0.27
▪ Female	8 (27.6)	5 (17.2)	Reference	
Age at Kasai surgery				
▪ <60 days	1 (3.4)	1 (3.4)	1.08 (0.06-19.05)	1.0
▪ ≥ 60 days	13 (44.8)	14 (48.3)	Reference	
Albumin level 1 month after surgery				
▪ <3.5 g/dL	8 (29.6)	4 (14.8)	4 (0.80- 20.02)	0.13
▪ ≥3.5 g/dL	5 (18.5)	10 (37)	Reference	
Albumin level 3 months after surgery				
▪ <3.5 g/dL	8 (42.1)	4 (21.1)	28.33 (1.30-617.96)	0.013*
▪ ≥3.5 g/dL	0	7 (36.8)	Reference	
Total bilirubin level 1 month after surgery				
▪ ≥2 mg/dL	12 (41.4)	11 (37.9)	2.18 (0.33-14.36)	0.65
▪ <2 mg/dL	2 (6.9)	4 (13.8)	Reference	
Total bilirubin level 3 months after surgery				
▪ ≥2 mg/dL	7 (35)	7 (35)	5 (0.46-54.52)	0.32
▪ <2 mg/dL	1 (5)	5 (25)	Reference	
Cholangitis				
▪ Present	10 (34.5)	6 (20.7)	3.75 (0.80-17.72)	0.14
▪ Absent	4 (13.8)	9 (31)	Reference	
Portal hypertension				
▪ Present	7 (24.1)	4 (13.8)	2.75 (0.58-12.98)	0.26
▪ Absent	7 (24.1)	11 (37.9)	Reference	
Esophageal varices				
▪ Present	0	1 (3.4)	0.50 (0.02-8.38)	1.0
▪ Absent	14 (48.3)	14 (48.3)	Reference	

*, significant (p<0.05); BA, biliary atresia; CI, confidence interval; OR, odds ratio.

Multivariate analysis of prognostic factors for BA patients' survival

Interestingly, multivariate analysis revealed that cholangitis tended to have an association with the BA patients' survival (p=0.09) (Table II).

Table II. Multivariate analysis of prognostic factors for BA patients' survival.

Prognostic Factor	OR (95% CI)	*p*
Gender	1.30 (0.45-36.86)	0.88
Albumin level 1 month after surgery	0.83 (0.01-41.95)	0.63
Total bilirubin level 1 month after surgery	-	1.0
Total bilirubin level 3 months after surgery	1.56 (0.13-18.92)	0.62
Cholangitis	0.74 (0.21-2.69)	0.09
Portal hypertension	0.52 (0.17-1.63)	0.20

BA, biliary atresia; CI, confidence interval; OR, odds ratio.

Kaplan-Meier (log rank) test

We compared the survival curves between groups using the Kaplan-Meier method (Fig. 1). Interestingly, log-rank test showed a significant association between 5-year survival rate of BA patients with albumin levels 1 month and 3 months after Kasai surgery, with *p*-value of 0.043 and 0.016, respectively (Fig. 1).

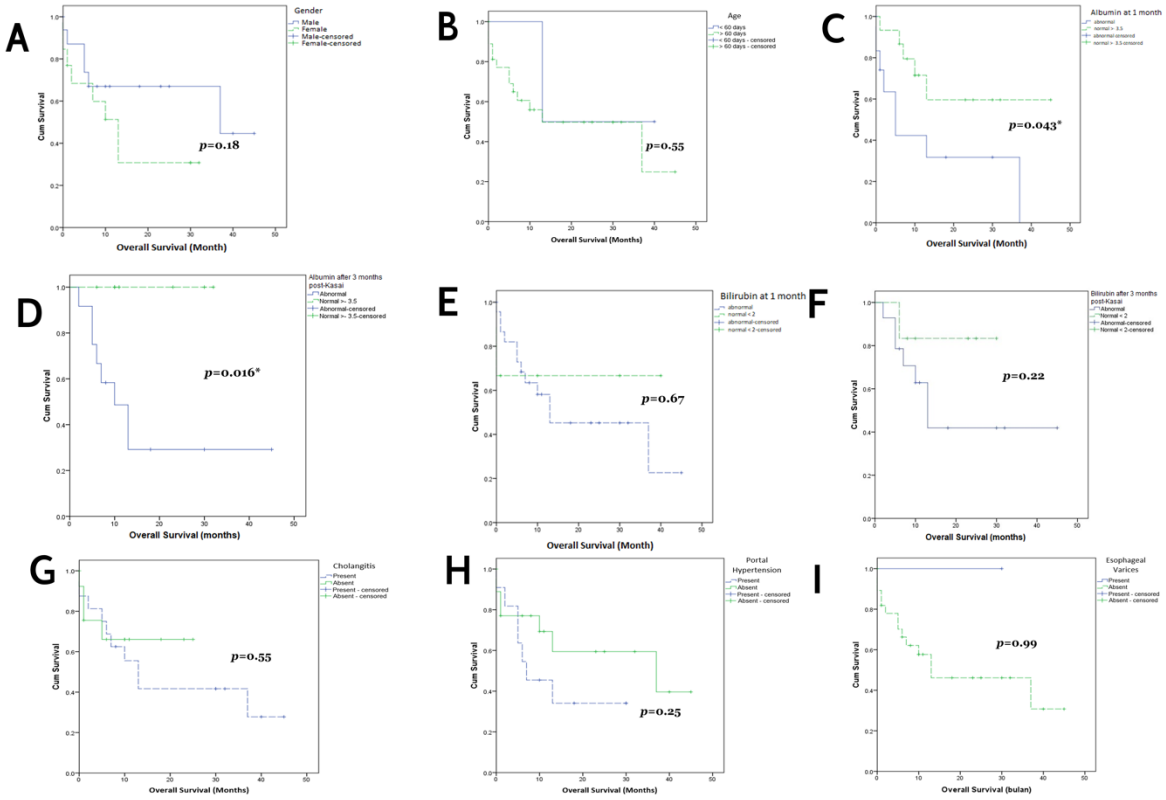

Fig. 1. Kaplan-Meier analysis for association between prognostic factors: A) Gender; B) Age at Kasai surgery; C) Albumin level at 1 month after surgery; D) Albumin level at 3 months after surgery; E) Total bilirubin level at 1 month after surgery; F) Total bilirubin level at 3 months after surgery; G) Cholangitis; H) Portal hypertension; I) Esophageal varices; and BA patients' survival. Log rank test showed that albumin levels 1 month and 3 months after surgery had a significant association with the survival of BA patients after Kasai surgery, with *p*-value of 0.043 and 0.016, respectively.

Furthermore, the cutoff value of TB30/TB0 for this study was 0.92 (sensitivity 76.9%, specificity 61.5%, and area under curve 0.72 [95% CI=0.52-0.92]). Log-rank test did not reveal a significant association between 5-year survival rate of BA patients after Kasai surgery with TB30/TB0 (*p*=0.07).

DISCUSSION

We were able to show that the albumin levels 1 month and 3 months after operation can predict the BA patients' survival rate following Kasai surgery. Patients with albumin level of <3.5 g/dL at 1 month and 3 months after surgery had a higher risk (~4 and ~28-fold, respectively) for poor prognosis compared with those with albumin level of ≥3.5 g/dL (Table 1). These findings were consistent with previous reports that serum albumin levels of BA patients <3.5 mg/dL at 3 months after Kasai surgery was a poor prognostic indicator for native liver survival (12, 13). Low albumin causes ascites, resulting in increased mortality of infants with chronic liver disease. The

presence of ascites implies liver decompensation and has a higher risk for bacterial peritonitis and hepatorenal syndrome adding to the risk for mortality due to liver failure (14).

Cholangitis is one of the most common complications after Kasai surgery occurring in 40-93% of cases (15, 16). The incidence of cholangitis in our study was similar to these reports with approximately 55%. Interestingly, our study revealed that cholangitis is an indicator of poor prognosis for patients after Kasai procedure. This finding was compatible with previous studies (15, 17). The incidence of cholangitis has been strongly associated with preoperative nutritional status of BA patients after Kasai procedure (18). Therefore, it might be necessary to perform additional studies to clarify the effect of preoperative nutritional status on BA patients' survival after surgery.

Total bilirubin level after Kasai surgery has been shown to be a significant prognostic factor for native liver survival in BA patients (7, 11-13, 19). However, our study failed to show their association, which might be due to the small sample size, becoming a limitation of our report. Further study with a larger sample size is necessary to support the hypothesis.

Most of our patients underwent Kasai surgery at more than 60 days of age. Although not significantly correlated with the age when the Kasai surgery was performed, the survival rate of BA patients in our report was only 51.7%. It has been proved that earlier age of operation has a good prognosis for BA patients' survival (3, 20, 21). However, this hypothesis is not always confirmed (13, 22, 23). Ramos-Gonzales *et al.* (13) presented that only total bilirubin > 2mg/dL and albumin < 3.5g/dL at 3 months after Kasai operation were significant predictors for transplantation need in future, but not age at Kasai nor gender. Thus, the best time for the Kasai surgery to be performed to gain a better outcome for BA patients is still controversial (3, 13, 20-23).

The frequency of BA was slightly higher in male patients than females (55.2 *vs.* 44.8%, respectively) in this study. In contrast, other reports described that BA is more commonly found in female patients (60.3%) than males (39.7%) (24). In addition, we found that the association between gender and BA patients' survival was not statistically significant. This result was supported by previous reports (25, 26).

Our study also did not find any impact of portal hypertension and esophageal varices on BA patients' survival. The results of this study are similar to a previous study which concluded that the presence of portal hypertension within 1 year postoperatively was not a significant risk factor in predicting initial surgery failure (25). However, our study's results differed from previous studies (27-29). Most BA children will develop progressive liver fibrosis resulting in portal hypertension (27). Esophageal varices are one of the portal hypertension manifestations, including splenomegaly, hypersplenism and ascites. These complications will cause significant morbidity and mortality of BA patients (27).

There are several weaknesses of our study. First, the small sample size in our study might affect the results of non-significant association between some prognostic factors and BA patients' survival after Kasai surgery. Second, this was a single center study that might not reflect the other pediatric surgical centers in Indonesia.

In conclusion, the BA patients' survival might be affected by the presence of cholangitis after Kasai procedure. Further multicenter studies with a larger sample size are important to verify our results.

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