Prognostic factors for five-year survival in children with biliary atresia after the Kasai procedure

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ABSTRACT

Introduction: Biliary atresia (BA) is an idiopathic disease characterized by progressive fibro-obliteration of extra- and intrahepatic biliary ducts manifesting jaundice >2 weeks. The primary treatment for BA is the Kasai procedure. However, patient survival in BA is influenced by several prognostic factors. We aimed to identify the prognostic factors for 5-year survival of BA patients following the Kasai procedure at Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Materials and Methods: This observational analytic study employed a retrospective cohort design, included BA patients who underwent Kasai procedures at our hospital between January 2012 and December 2018.

Results: There was no association between age at surgery (p=0.408), TB7 (p=0.973), operator experience (p=0.649), AST0 (p=0.973), AST7 (p=1), the AST7/AST0 ratio (p=0.682), ALT0 (p=0.682), ALT7 (p=0.697), and the ALT7/ALT0 ratio (p=1) with 5-year survival in BA patients after Kasai procedure. A log-rank analysis showed no significant results: age at surgery (p=0.264), TB7 (p=0.961), operator experience (p=0.479), AST0 (p=0.993), AST7 (p=0.931), AST7/AST0 ratio (p=0.562), ALT0 (p=0.708), ALT7 (p=0.640), and ALT7/ALT0 ratio (p=0.963).

Conclusion: The timing of surgery, total bilirubin levels at 7 days post-surgery, surgeon experience, and both pre-and post-operative AST and ALT may not predict 5-year survival outcomes in BA patients following Kasai surgery. Further extensive cohort studies are necessary to confirm these preliminary findings.

KEYWORDS:
Biliary atresia, 5-year survival, Kasai procedure, prognostic factors

INTRODUCTION

Biliary atresia (BA) is an idiopathic condition in infants marked by the obliteration or discontinuity of the extrahepatic and intrahepatic bile ducts, resulting in bile flow obstruction.[1] Progressive fibro-obliteration of the biliary tract leads to jaundice lasting more than two weeks. The clinical features of BA include pathological jaundice, pale or clay-colored stools, dark urine, and hepatomegaly. BA is classified into two forms: syndromic BA (embryonic type) and non-syndromic BA (perinatal type).[2] Its incidence ranges from 1 in 12,000 in the US and the UK to 1 in 9,600 in Japan and 1 in 5,000-8,000 in China.[3] In Indonesia, the incidence of BA is also high, affecting 1 in 7,000 live births.[4]

Kasai portoenterostomy, which involves resecting the obstructed bile duct and forming an anastomosis between the hepatic portal and the jejunum using a Roux loop to enhance bile drainage from the intrahepatic ducts to the small intestine, remains the treatment of choice for BA.[5] When the Kasai procedure fails, liver transplantation becomes the secondary treatment, guided by post-Kasai liver transplantation scoring systems.[4] BA is the leading cause of end-stage liver disease in children and a primary indication for liver transplantation.[6] Due to the limited availability of liver transplants in Indonesia, the Kasai procedure serves as the first-line treatment for BA, enhancing survival with the native liver without the need for transplantation.[4]

The outcomes of the post-Kasai procedure are not consistently favorable.[5] Several prognostic factors that influence the success of the Kasai procedure include the age at the time of operation, total serum bilirubin levels seven days after surgery, and the experience of the surgeon.[7-10] However, studies on prognostic factors for 5-year survival of patients with BA post-Kasai surgery are still limited. Therefore, we aimed to identify the prognostic factors, including age at the Kasai operation, bilirubin levels 7 days post-Kasai (TB7), surgeon experience, preoperative AST levels (AST0), AST levels 7 days post-Kasai (AST7), AST7/AST0 ratio, preoperative ALT levels (ALT0), ALT levels seven days post-Kasai (ALT7), and ALT7/ALT0 ratio, for the 5-year survival of BA patients following the Kasai surgery.

MATERIALS AND METHODS

This observational analytic study employed a retrospective cohort design. The study population included BA patients treated at Dr. Sardjito Hospital, Yogyakarta, Indonesia. Inclusion criteria comprised BA patients who underwent Kasai procedures at our hospital between January 2012 and December 2018—exclusion criteria involved excluding patients with incomplete medical records. The Kasai portoenterostomy procedures performed at our institution

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adhered to the institutional guidelines for the surgical management of biliary atresia. These guidelines maintained a standardized approach of the Kasai procedure.[11-12] Following the Kasai procedure, patients also received standardized post-operative care at our institution. This included routine antibiotic prophylaxis, nutritional support, and a standardized high-dose corticosteroid regimen based on the principles of high-dose intravenous methylprednisolone, followed by a gradually tapered oral steroid regimen to improve bilirubin clearance.[13-14] Data collection involved reviewing the medical records of BA patients who underwent Kasai procedures during the specified period.

Prognostic variables included age at surgery, bilirubin levels 7 days post-surgery (TB7), surgeon experience, preoperative AST levels (AST0), AST levels 7 days post-surgery (AST7), AST7/AST0 ratio, preoperative ALT levels (ALT0), ALT levels 7 days post-surgery (ALT7), and ALT7/ALT0 ratio.

This research received ethical approval from the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing at Universitas Gadjah Mada/Dr. Sardjito Hospital (Ref. #KE/FK/1252/EC/2018). Before participating in the study, all patients' parents or guardians provided informed consent.

Data Analysis

The chi-square or Fisher's exact test was used to examine the association between independent and dependent variables. The receiver operating characteristic (ROC) analysis was employed to determine cut-off values for laboratory parameters, and the Kaplan-Meier test was utilized to assess 5-year survival rates. Data was analyzed using IBM's Statistical Package for the Social Sciences (SPSS), version 23.

RESULTS

This study included 24 patients, the majority of whom were male (70.83%). Table I presents the subjects' baseline characteristics.

Next, we determined the cut-off values for the prognostic factors using ROC (Figure 1). For the age of the Kasai procedure, we defined the groups as <90 and ≥90 days. None of the prognostic factors were associated with the 5-year survival rate of BA patients following the Kasai procedure (Table II).

Subsequently, we performed the Kaplan-Meier analysis. None of the prognostic factors showed any significant association with the 5-year survival rate in BA patients following Kasai surgery (Figure 2).

DISCUSSION

Subject Characteristics

There was a male preponderance among the participants in our study, with 17 (70.83%) patients being male, while 7 (29.16%) were female. However, sex distribution in BA varies across different studies. Gunadi et al. (2018) reported a higher prevalence of BA among male patients[4], while Andrade et al. (2018) found a higher prevalence of female patients (60.31%) compared to males (39.69%).[15] Nonetheless, multiple reports demonstrated that sex does not significantly affect the prognosis of BA patients following the Kasai procedure, thus sex was not included in the further analysis.[16-17]

BA is often associated with syndromic conditions and is recognized as a factor influencing disease progression and surgical outcomes, including the success of the Kasai procedure, making the assessment of these factors valuable for understanding long-term survival.[18] Based on medical records, three patients died due to sepsis, one died from cholangitis, and others died from Disseminated Intravascular Coagulation (DIC), internal bleeding, and multiple organ failure. Additionally, one patient was identified as having Down syndrome.

Age of Surgery

Early age at the time of Kasai procedure has often been associated with better outcomes in BA patients. In our analysis, patients underwent surgery before 90 days of life showed a slightly higher survival rate than those operated on at or after 90 days (OR: 2.7, 95% CI: 0.51-14.37, $p=0.408$) indicating better survival with earlier surgery (Table II). However, this association was not statistically significant. Similarly, Gunadi et al. (2018) reported that patients younger than 60 days at the time of surgery had better outcomes compared to those aged ≥ 60 days, although not statistically significant.[4] Furthermore, Saragih (2019) also reported no statistically significant correlation between age at surgery and patient survival.[19] Hoshino et al. (2023) also found that patients who had Kasai procedure at a later timing (>30 days) have an earlier need for liver transplantation compared with patients with earlier KP (<=30 days).[20]

Based on our Kaplan-Meier analysis (Figure 1A), patients who underwent surgery at <90 days had better 5-year survival outcomes. However, according to the log-rank test, age at surgery was not associated with the 5-year survival of biliary atresia patients post-Kasai procedure ($p = 0.264$). This suggests that while early intervention may be beneficial, the age of surgery alone may not influence survival outcomes in BA patients who underwent Kasai surgery.

Total Bilirubin Seven Days Post-Surgery (TB7)

The cut-off value for TB7 was 9.635, with a sensitivity of 46.2% and a specificity of 54.5% (Figure 2A). Our findings found no significant correlation between total bilirubin (TB) levels seven days post-Kasai and five-year survival, although patients with TB7 < 9.635 demonstrated a slightly higher survival rate (Table II). Similarly, Chusilp et al. (2016) suggest that >20% decrease in serum TB7 is a reliable indicator of a favorable outcome as patients with TB7/TB0 ratios less than 0.8 have a significantly higher 5-year survival rate compared to those with ratios greater than 0.8.[21] Furthermore, previous report demonstrated that higher long-term (3 months) (more than 2.0 mg/dL) in the first 3 month following Kasai procedure had a higher risk of disease progression, leading to an earlier need of liver transplant.[22]

The Kaplan-Meier survival curve (Figure 1B) and the log-rank test indicated that the bilirubin levels 7 days post-surgery were not statistically significant in affecting the 5-year

Table I: Baseline characteristics of BA patients.

Characteristics	N (%)	Mean ± SD
Sex		
▪ Male	17 (70.83)	
▪ Female	7 (29.16)	
Age at Surgery		
▪ <90 days	10 (41.66)	
▪ ≥90 days	14 (58.33)	
TB7 (mg/dL)		9.42 ± 3.33
Surgeon		
▪ Consultant	18 (75)	
▪ Not-consultant	6 (25)	
AST (IU/L)		
▪ Pre-operative (AST0)		384.29 ± 495.37
▪ 7 days after surgery (AST7)		151.17 ± 101.37
ALT (IU/L)		
▪ Pre-operative (ALT0)		191.67 ± 165.08
▪ 7 days after surgery (ALT7)		186.58 ± 142.26
Survival		
▪ Alive	11 (45.83)	
▪ Deceased	13 (54.17)	

Table II: Association of prognostic factors with the 5-year survival rate in BA patients following Kasai surgery.

Prognostic Factor	Survived (N, %)	Deceased (N, %)	OR (95% CI)	p
Age at Surgery				
▪ < 90 days	6 (25)	4 (16.7)	2.7 (0.51-14.37)	0.408
▪ ≥ 90 days	5 (20.8)	9 (37.5)	Reference	
TB7				
▪ < 9.635	6 (25)	7 (29.2)	1.03 (0.21-5.15)	0.973
▪ ≥ 9.635	5 (20.8)	6 (25)	Reference	
Surgeon experience				
▪ Consultant	9 (37.5)	9 (37.5)	2 (0.29-13.81)	0.64
▪ Non-consultant	2 (8.3)	4 (16.7)	Reference	
AST0				
▪ < 265.5	6 (25)	7 (29.2)	1.03 (0.21-5.15)	0.973
▪ ≥ 265.5	5 (20.8)	6 (25)	Reference	
AST7				
▪ < 92.5	4 (16.7)	4 (16.7)	1.29 (0.23-7.05)	1.000
▪ ≥ 92.5	7 (29.2)	9 (37.5)	Reference	
AST7/AST0				
▪ < 0.473	5 (20.8)	7 (29.2)	0.71 (0.14-3.58)	0.682
▪ ≥ 0.473	6 (25)	6 (25)	Reference	
ALT0				
▪ < 162	5 (20.8)	7 (29.2)	0.71 (0.14-3.58)	0.682
▪ ≥ 162	6 (25)	6 (25)	Reference	
ALT7				
▪ < 135	4 (16.7)	6 (25)	0.67 (0.13-3.45)	0.697
▪ ≥ 135	7 (29.2)	7 (29.2)	Reference	
ALT7/ALT0				
▪ < 0.667	4 (16.7)	4 (16.7)	1.29 (0.23-7.05)	1.000
▪ ≥ 0.667	7 (29.2)	9 (37.5)	Reference	

OR, odds ratio; CI, confidence interval

survival of biliary atresia patients post-Kasai surgery (p=0.961). These suggest that although persistently elevated TB7 levels post-Kasai have been linked to poor bile drainage and increased risk of liver fibrosis or failure in previous research[21-23], our findings suggest that TB7 alone did not demonstrate the prognostic association for the survival of BA patients who underwent Kasai surgery.

Surgeon Experience

In this study, consultant surgeons resulted in a higher survival rate (37.5%) than non-consultants (8.3%). However, the odds ratio (2.0, 95% CI: 0.29-13.81, p=0.649) was not statistically significant, possibly due to the small sample size. Based on the Kaplan-Meier analysis (Figure 1C), senior surgeons demonstrated a better 5-year survival rate. However, according to the log-rank analysis, surgeon experience was not statistically significant (p=0.479) (Figure 2).

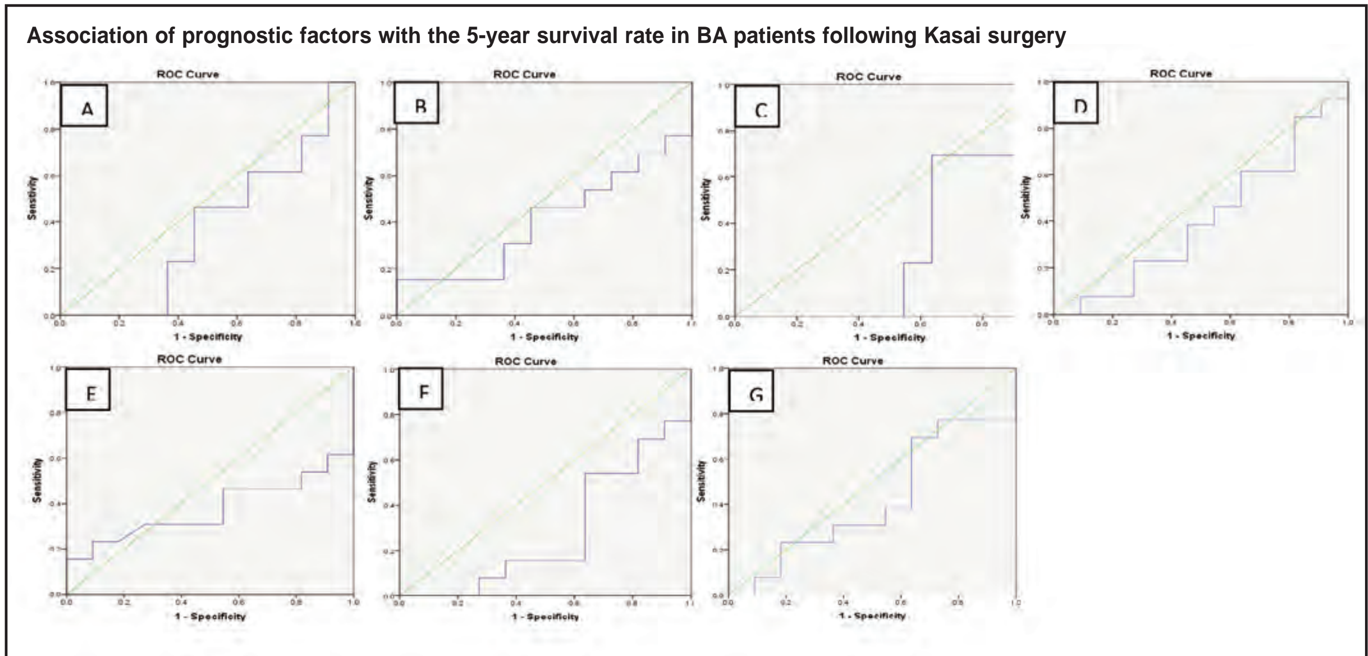

Fig. 1: ROC curve for: A) total bilirubin on postoperative day 7 (TB7); B) pre-operative AST; C) AST on postoperative day 7 (AST7); D) AST7/AST0 ratio; E) pre-operative ALT (ALT0); F) ALT on postoperative day 7 (ALT7); and G) ALT7/ALT0 ratio, with the AUC of 0.378 (95% CI=0.141-0.614), 0.406 (95% CI=0.174-0.637), 0.301 (95% CI=0.066-0.535), 0.406 (95% CI=0.172–0.639), 0.374 (95% CI=0.140-0.608), 0.280 (95% CI=0.069-0.49), and 0.413 (95% CI=0.178-0.647), respectively.

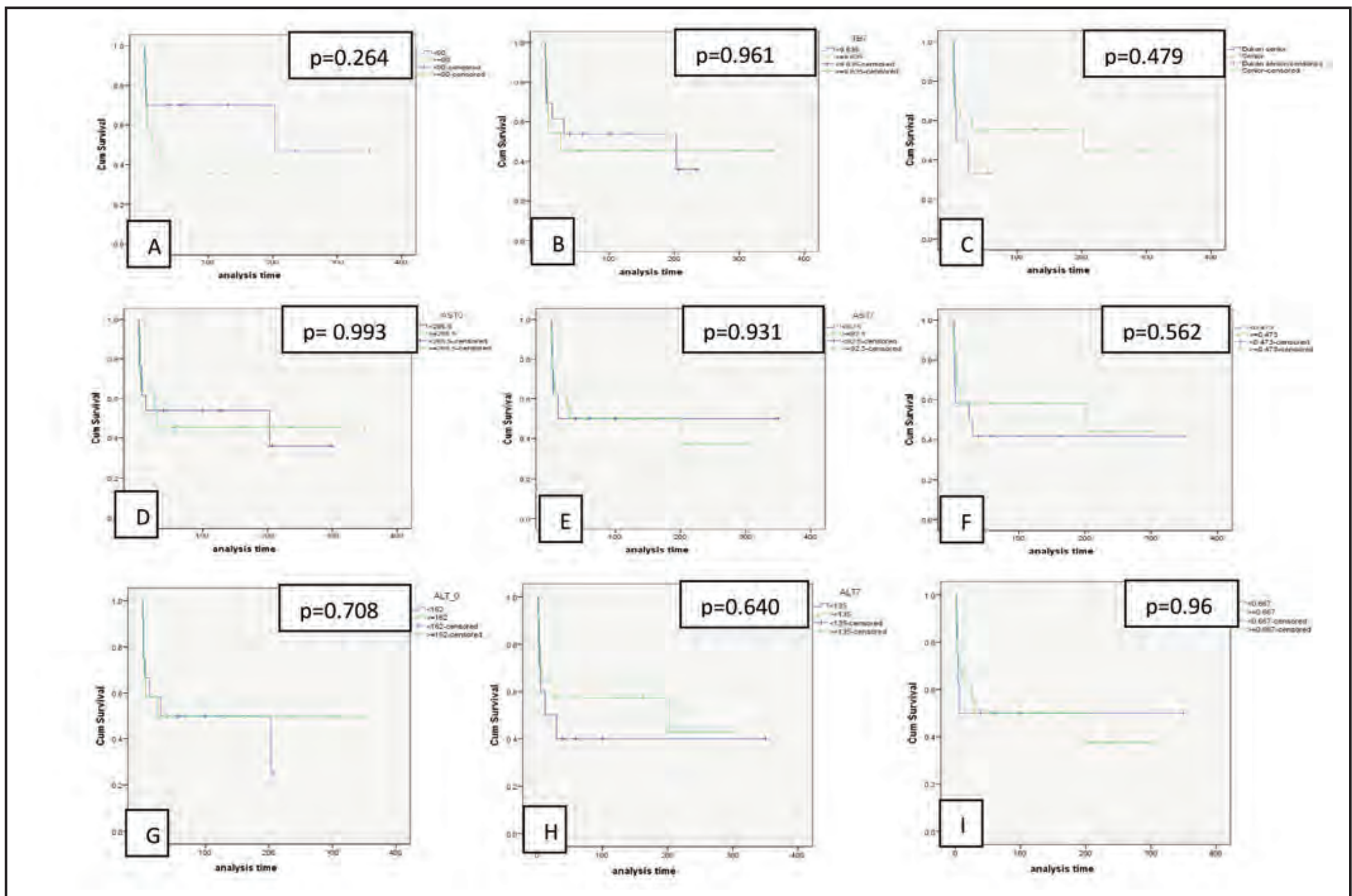

Fig. 2: Kaplan-Meier analysis of prognostic factors for the 5-year survival rate of BA patients after the Kasai procedure: A) age at the time of Kasai surgery; B) total bilirubin on post-operative day 7 (TB7); C) surgeon experience; D) pre-operative AST (AST0); E) AST on post-operative day 7 (AST7); F) AST7/AST0 ratio; G) pre-operative ALT (ALT0); H) ALT on post-operative day 7 (ALT7); I) ALT7/ALT0 ratio.

Nevertheless, studies have shown that surgeons with extensive experience in performing KPE achieve better outcomes, including higher rates of jaundice resolution and lower rates of complications such as cholangitis.24-25 Furthermore, a large multi-centre study from Germany highlighted that the outcomes of BA surgeries were significantly better in specialized centres, with a 2-year survival rate with the native liver of ~20% in less experienced settings.[26]

Pre-operative AST (AST0) and Post-operative AST Day 7 (AST7)
In our study, patients with AST0 levels below 265.5 had a survival rate of 25%, with an odds ratio of 1.03 (95% CI: 0.21-5.15, p=0.973). Likewise, patients with AST7 levels below 92.5 had a survival rate of 16.7%, with an odds ratio of 1.29 (95% CI: 0.23-7.05, p=1.000), indicating no profound prognostic association (Table II).

The pre-operative AST cut-off value was determined using ROC analysis (Figure 2B, 2C), with a cut-off of AST0 and AST7 were 265.5 and 92.5, respectively. Based on the Kaplan-Meier analysis (Figure 1D), AST0 ≥ 265.5 showed a better 5-year survival rate, but the log-rank test indicated that pre-operative AST levels were not statistically significant in affecting the 5-year survival of biliary atresia patients post-Kasai surgery (p =0.993). Similarly, while the Kaplan-Meier graph above shows that the AST7 < 92.5 group had better 5-year survival (Figure 1E). The log-rank test showed that AST levels 7 days post-operation were not statistically significant in influencing the 5-year survival of BA patients post-Kasai (p=0.931).

These findings suggest that pre- and post-operative AST levels alone may not be a strong predictor of survival. However, AST levels combined with serum direct bilirubin (DB) at 2 months after Kasai surgery were reported to be reliable for predicting long-term BA outcomes.[27] Moreover, Degtyareva et al. (2024) suggest that lower levels of postoperative AST were significantly associated with successful outcomes of Kasai surgery.[28] Additionally, Wang et al. (2019) revealed that AST, along with alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) levels tended to be increased during the first month before returning to normal levels within one year after Kasai surgery, which may explain a higher percentage of patients in AST7 ≥ 92.5 group.[29]

AST7/AST0 Ratio
The cut-off value for the AST7/AST0 ratio is 0.473, with a sensitivity of 46.2% and specificity of 45.5% (Figure 2D). A low ratio of AST7/AST0 (<0.473) was associated with slightly lower odds of survival (95% CI: 0.14-3.58, p=0.682), meaning that an AST7/AST0 ratio of ≥ 0.473 may act as a protective factor for patient survival. However, there was no statistically significant association between AST7/AST0 ratio and survival rates. Interestingly, Kaplan-Meier analysis shows that the group with an AST7/AST0 ratio cut-off ≥0.473 experienced a considerably increased mortality, with a mortality rate of 57.3% in week 203 (Figure 1F).

Altogether, our findings highlight that AST0, AST7 and AST7/AST0 ratio lacks significant prognostic value for AST levels alone in predicting long-term 5-years survival of BA patients who underwent Kasai surgery.

Pre-Operative ALT (ALT0) and Post-Operative ALT Day 7 (ALT7)
Patients with ALT0 levels below 162 had a survival rate of 20.8%, with an odds ratio of 0.71 (95% CI: 0.14-3.58, p=0.682). Similarly, ALT7 levels below 135 had a survival rate of 16.7%, with an odds ratio of 0.67 (95% CI: 0.13-3.45, p=0.697).

The preoperative ALT (ALT0) cut-off value was determined using ROC analysis (Figure 2E), with a result of 162. Based on the Kaplan-Meier analysis (Figure 1G), ALT0 ≥ 162 has a better 5-year survival rate, but the log-rank test revealed that preoperative ALT levels were not statistically significant in affecting the 5-year survival of BA patients after Kasai surgery (p=0.708). Furthermore, based on ROC analysis (Figure 2F). The cut-off value for post-operative ALT (ALT7) was determined to be 135. Based on the Kaplan-Meier analysis (Figure 1H), ALT7 ≥ 135 group had better 5-year survival but not statistically significant (log-rank test p=0.640)

Previous findings also revealed that pre-operative ALT levels were similar between the good outcome group (serum TB < 2 mg% or jaundice-free) and the poor outcome group (serum TB > 2 mg% or persistent jaundice), with a median of 162 IU/L.21 Another study also revealed no significant association, although patients with jaundice clearance had overall lower post-operative ALT levels (588.9 ± 288.7) compared to patients with impaired jaundice clearance (635.9 ± 273.2, p>0.05).[30]

ALT7/ALT0 Ratio
The cutoff value for the ALT7/ALT0 ratio is 0.667, determined through receiver operating characteristic (ROC) curve analysis, as it provided the best balance between sensitivity (69.2%) and specificity (36.4%) among the tested values. The corresponding AUC was 0.413 (95% CI: 0.178–0.647), indicating poor diagnostic performance; however, 0.667 remained the most appropriate cutoff based on the available data. (Figure 2G). Our study found no association between the ALT7/ALT0 ratio in predicting survival in BA patients following Kasai surgery. ALT7/ALT0 ratio of <0.667 had an odds ratio of 1.29 (95% CI: 0.23-7.05, p=1.000), showing no significant association between ALT ratio and survival. Previous findings also reported that BA patients post-Kasai surgery with an ALT7/ALT0 ratio ≥ 0.95 had a higher mortality rate, with mortality reaching 80% by day 43. However, no statistically significant findings were demonstrated.[31] These findings suggest that neither preoperative nor postoperative AST and ALT levels, nor their ratios, have significant prognostic value for AST levels alone in predicting long-term 5-years survival of BA patients who underwent Kasai surgery.

LIMITATIONS

The limited findings in our study may be attributed to several factors. Firstly, the sample size of this study is relatively small, and consequently, the variables examined were limited. To produce more robust outcomes regarding the 5-year survival rate and further elucidate prognostic factors, future research would significantly benefit from a larger sample size, ideally through a multi-center study design. The retrospective nature of the study may also introduce selection bias, and each patient's biochemical profiles were not measured at identical follow-up time points. Furthermore, reliance on biochemical markers measured only at Day 0 and Day 7 post-surgery may not fully capture the dynamic and longer-term post-operative changes critical for predicting native liver survival. Thus, further inclusion of relevant factors such as the types or regimens of post-operative medication (e.g., steroids, antibiotics) received, the presence and management of complications like cholangitis, and longer-term (e.g., 3-6 months) post-operative liver function biomarkers would strengthen future investigations.[32] Moreover, previous studies have shown that histologic factors such as scoring systems, fibrosis, and other common factors significantly affect the survivability of BA patients.[33] However, no data about histological factors were available at the time, and due to the nature of the retrospective cohort study design, the histological factors could not be analyzed. Future studies with a prospective design that provide more complete data (including histology data) need to be conducted to add perspective regarding the results. Further studies are also needed to analyze the potential relationship between these specific syndromes and the survival rate of BA patients after the Kasai procedure. This study also did not include an analysis of post-operative complications, such as cholangitis, which have been widely recognized as significant factors influencing outcomes in patients with biliary atresia following the Kasai procedure. Additionally, CMV serological status, which has been suggested as a potential prognostic factor in biliary atresia[34], was not included in our analysis due to the retrospective nature of the study and the lack of consistent CMV testing data in patient records. This study was primarily designed to evaluate clinical and biochemical parameters that are routinely available, with the objective of identifying early and accessible prognostic markers.

CONCLUSIONS

Our analysis indicates that several prognostic factors, including age at which Kasai surgery is performed, surgeon experience, total bilirubin on postoperative day 7, and AST and ALT levels on both preoperative and postoperative day 7, as well as the AST and ALT postoperative/preoperative ratios, lack association with 5-year survival outcomes in BA patients following Kasai surgery. Further extensive cohort studies are required to validate these preliminary findings due to the limited sample size.

List of abbreviations

BA: biliary atresia; AST: aspartate transaminase; ALT: alanine transaminase; AST7/AST0: AST postoperative day 7/preoperative ratio; ALT7/ALT0: ALT postoperative day 7/preoperative ratio; TB: total bilirubin; TB7: total bilirubin postoperative day 7; AUC: area under the curve; CI: confidence interval; OR: odds ratio; ROC: receiver operating characteristic curve; SD: standard deviation; IU/L: international units per liter.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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