

# The impact of serum total bilirubin, alanine transaminase and gamma-glutamyl transferase on survival of biliary atresia patients following Kasai procedure

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## ABSTRACT

**Background:** Many prognostic factors have been reported for the outcomes of biliary atresia (BA) patients after Kasai procedure, however, it still shows a conflicting result. Our study was to determine the impact of total bilirubin post-operative day-7 and pre-operative ratio (TB7/TB0), gamma-glutamyl transferase post-operative day-7 and pre-operative ratio (GGT7/GGT0), and alanine transaminase post-operative day-7 and pre-operative ratio (ALT7/ALT0) on the survival of BA patients following Kasai surgery.

**Methods:** We reviewed the medical records of BA patients who underwent Kasai procedure at the Dr. Sardjito Hospital, Indonesia from August 2012 to December 2018. The cut-off values of TB7/TB0, GGT7/GGT0, and ALT7/ALT0 for prediction of patients' survival were determined by receiver operating characteristics (ROC) curves. Log-rank tests were utilised to test the association between cut-off values and overall survival.

**Results:** In all 46 BA patients (23 males and 23 females) after Kasai procedure were included, consisting of one type 1, 17 type 2A, seven type 2B, and 21 type 3. The cut-off values of TB7/TB0, ALT7/ALT0 and GGT7/GGT0 for overall survival was 0.455 (sensitivity 87.5%, specificity 22.7%, area under curve (AUC) 0.59; 95% Confidence Interval (95%CI): 0.42, 0.75), 0.481 (sensitivity 87.5%, specificity 18.2%, AUC 0.49; 95%CI: 0.31, 0.65), and 0.31 (sensitivity 79.2%, specificity 9.1%, AUC 0.34; 95%CI: 0.18, 0.50), respectively. However, these cut-off values were not significantly associated with overall survival, with *p*-values of 0.18, 0.49, and 0.56, respectively.

**Conclusion:** The TB7/TB0, ALT7/ALT0, and GGT7/GGT0 might not predict the overall survival of BA patients after Kasai procedure. Further multicentre studies with a larger sample size is needed to clarify our findings.

## KEY WORDS:

*Alanine transaminase; biliary atresia; bilirubin; gamma-glutamyl transferase; Kasai surgery; overall survival*

## INTRODUCTION

Biliary atresia (BA) is an inflammatory sclerosing cholangiopathy, affecting both the extrahepatic and

intrahepatic bile ducts to a variable extent.<sup>1</sup> Although the Kasai repair may significantly improve the overall survival, but the prognosis of patients with BA is still uncertain while most patients still need liver transplantation.<sup>1,2</sup>

Many prognostic factors, including serum total bilirubin (TB), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) level, have been reported to influence the outcomes of BA patients after Kasai surgery, however, it still shows a conflicting result.<sup>3-7</sup> Our study was conducted to determine the impact of TB postoperative day-7 and preoperative (TB7/TB0) ratio, ALT postoperative day-7 and preoperative (ALT7/ALT0), and GGT postoperative day-7 and preoperative (GGT7/GGT0) ratio on the survival of BA patients following Kasai repair.

## MATERIALS AND METHODS

### Patients

We reviewed the medical records of BA patients who underwent Kasai procedure at the Dr. Sardjito Hospital, Indonesia from August 2012 to December 2018. Data included age at Kasai surgery performed, gender, and serum TB, ALT and GGT levels preoperative- and postoperative seven days after surgery (POD7).

The Medical and Health Research Ethics Committee of Faculty of Medicine, Universitas Gadjah Mada/Dr. Sardjito Hospital approved this study: (KE/FK/0311/EC/2019).

### Statistical Analysis

The cut-off values of TB7/TB0, GGT7/GGT0, and ALT7/ALT0 for prediction of the survival of patients were determined by receiver operating characteristics (ROC) curves. Kaplan Meier curve and log-rank tests were used to determine any association between cut-off values and overall survival of BA patients after Kasai repair.

## RESULTS

In all 67 medical records of BA patients were reviewed of which 21 were excluded due to incomplete data. Finally, 46 BA patients (23 males and 23 females) were included for further analysis, consisting of one type 1, 17 type 2A, seven type 2B, and 21 type 3 (Table 1).

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**Table I: Characteristics of biliary atresia patients who underwent Kasai procedure**

Characteristics	N (%); mean ± SD
Gender	
• Male	23 (50)
• Female	23 (50)
Age at Kasai procedure (days)	
• <60	4 (8.7)
• ≥60	42 (91.3)
Biliary atresia type	
• 1	1 (2.2)
• 2A	17 (37)
• 2B	7 (15.2)
• 3	21 (45.6)
Laboratory findings	
• Total bilirubin (mg/dL)	
a. Preoperative	10.48 ± 4.04
b. POD 7	9.22 ± 4.61
• Alanine aminotransferase (U/L)	
a. Preoperative	132.78 ± 72.75
b. POD 7	149.39 ± 147.09
• Gamma glutamyl transferase (U/L)	
a. Preoperative	724.46 ± 542.51
b. POD 7	663.65 ± 487.45
Outcome	
• Survived	22 (47.8)
• Died	24 (52.2)

POD, postoperative day; SD, standard deviation

**Table II: Cutoff value of TB7/TB0, GGT7/GGT0, and ALT7/ALT0 for prediction of BA patients' survival determined by ROC curves**

Prognostic Factor	Cutoff value	Sensitivity	Specificity	AUC (95% CI)
TB7/TB0	0.46	87.5	22.7	0.59 (0.42-0.75)
ALT7/ALT0	0.48	87.5	18.2	0.49 (0.31-0.65)
GGT7/GGT0	0.31	79.2	9.1	0.34 (0.18-0.50)

ALT, alanine aminotransferase; AUC, area under curve; BA, biliary atresia; CI, confidence interval; GGT, gamma glutamyl transferase; ROC, receiving operator characteristic; TB, total bilirubin

**Table III: Association between TB7/TB0, ALT7/ALT0, GGT7/GGT0 and BA patients' survival after Kasai repair**

Prognostic Factor	Died	Survived	p	OR (95% CI)
TB7/TB0				
• ≥0.455	21	17	0.45	2.06 (0.43-9.87)
• <0.455	3	5		
ALT7/ALT0				
• ≥0.481	21	18	0.69	1.56 (0.31-7.89)
• <0.481	3	4		
GGT7/GGT0				
• ≥0.31	19	20	0.42	0.38 (0.07-2.20)
• <0.31	5	2		

ALT, alanine aminotransferase; BA, biliary atresia; CI, confidence interval; GGT, GGT, gamma glutamyl transferase; OR, odds ratio; TB, total bilirubin

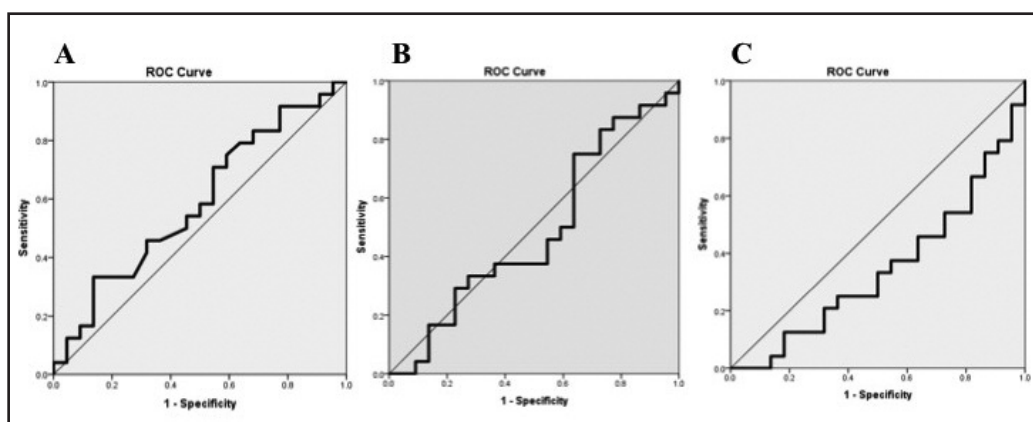
The cut-off values of TB7/TB0, ALT7/ALT0 and GGT7/GGT0 for overall survival were 0.46 (sensitivity 87.5%, specificity 22.7%, area under curve (AUC) 0.59; 95% Confidence Intervals (95%CI): 0.42, 0.75), 0.48 (sensitivity 87.5%, specificity 18.2%, AUC 0.49; 95%CI: 0.31, 0.65), and 0.31 (sensitivity 79.2%, specificity 9.1%, AUC 0.34; 95%CI: 0.18, 0.50), respectively (Fig. 1; Table II).

Next, we determined the association between prognostic factors and BA patients' survival following Kasai procedure. TB7/TB0, ALT7/ALT0 and GGT7/GGT0 did not reveal any

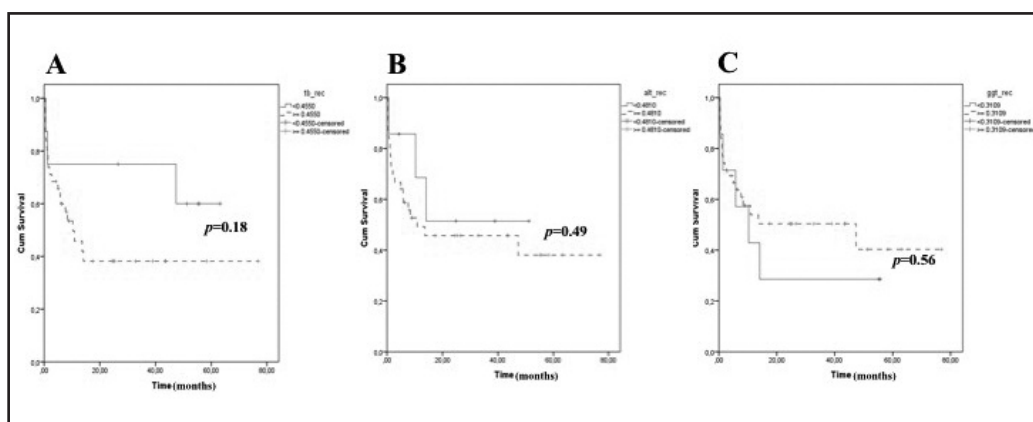
association with the BA patients' survival (p-values=0.18, 0.49, and 0.56, respectively) (Fig. 2; Table III).

**DISCUSSION**

We were unable to show the association between TB7/TB0 and overall survival of BA patients after the Kasai repair. A previous study showed that TB7/TB0 was a good predictor for of BA patients' outcome after Kasai surgery.<sup>2</sup> This difference may be due to a different cut-off for the TB7/TB0 (our study: 0.46 vs. 0.8).<sup>2</sup> In addition, most studies reported the timing of



**Fig. 1:** Receiver Operating Characteristics (ROC) curves for: A) TB7/TB0; B) ALT7/ALT0; and C) GGT7/GGT0 for prediction of BA patients' survival. The AUC for TB7/TB0, ALT7/ALT0, and GGT7/GGT0 were 0.59 (95% CI=0.42-0.75), 0.49 (95% CI=0.31-0.65), and 0.34 (95% CI=0.18-0.5), respectively.



**Fig. 2:** Kaplan-Meier analysis for association between prognostic factors: A) TB7/TB0; B) ALT7/ALT0; C) GGT7/GGT0; and BA patients' survival. Log rank test showed that none of the prognostic factors showed a strong correlation with the BA patients' survival following Kasai surgery ( $p=0.18, 0.49, \text{ and } 0.56$ , respectively).

TB analysis were at 6 weeks, 3 and 6 months.<sup>4,7-9</sup> It is also still controversial whether TB or direct bilirubin are good predictors for outcome of BA patients.<sup>9,10</sup>

Serum ALT level is the most sensitive test for hepatocyte cell necrosis. The abnormal ALT level in BA patients is due to backflow or bile stasis in hepatocyte cells. ALT is more specific for detecting liver disease because it is found only in low concentrations in other tissues, such as muscles.<sup>11</sup> However, we failed to show the association between ALT level and outcome of BA patients. It was similar with previous study that only GGT and aspartate aminotransferase (AST)-to-platelet ratio index were significantly associated with the jaundice free patient after the Kasai procedure, but not ALT level.<sup>2</sup> Goda et al., also reported that only direct bilirubin and AST are good predictors of outcome of BA patients.<sup>9</sup>

The role of serum GGT as a predictor for BA outcome reveals a conflicting result.<sup>5,2</sup> We did not find any correlation between GGT7/GGT0 ratio and BA outcome. The increased level of GGT is believed to be due to postoperative biliary obstruction and ongoing liver fibrosis.<sup>2</sup> Furthermore, serum GGT level has been shown as a good biomarker to differentiate between BA and other causes of neonatal cholestasis.<sup>12,13</sup>

Most of our patients were type 3 BA, which is comparable with previous study.<sup>14</sup> In addition, ~90% of our patients underwent a Kasai surgery at age of  $\geq 60$  days. Delayed diagnosis and management of BA are the common problems among developing countries.<sup>15</sup> Interestingly, the appropriate time on when to perform Kasai surgery to achieve a good outcome is still controversial.<sup>3,16-19</sup>

This study had some limitations, such as being a retrospective study, therefore, approximately 30% of medical records of BA patients were excluded due to incomplete data. Moreover, our study did not involve other biochemical markers in the analysis, including serum AST, direct bilirubin, and alkaline phosphatase level, that might have had an impact on the survival of BA patients after Kasai repair. Notably, the prognosis of BA patients after Kasai procedure are influenced not only by biochemical parameters, but also by other variables, such as liver biopsy results, fibrosis score, and recurrent cholangitis.<sup>20-24</sup> Unfortunately, this study relied on the extracted data from medical records of patients. Therefore, some data were missing, thus a weakness in the study. These facts should be considered during the interpretation of our findings.

In addition, our study was designed to focus on the role of biochemical parameters as prognostic factors of BA patients after Kasai surgery. Therefore, further multicentred and prospective cohort studies with other prognostic factors (e.g., liver biopsy results, fibrosis score, and recurrent cholangitis)<sup>20-24</sup> and a larger number of patients are needed to confirm and clarify our findings. According to a previous study, the possible required numbers for getting a significant result is approximately 180 patients.<sup>23</sup>

### CONCLUSION

The TB7/TB0, ALT7/ALTO, and GGT7/GGT0 may not predict the overall survival of BA patients after Kasai procedure. Further multicentred studies with larger sample size is needed to clarify our findings.

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