ORIGINAL ARTICLE

Cytomegalovirus infection impact on cholangitis in patients with biliary atresia following the Kasai procedure

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ABSTRACT

Introduction: Biliary atresia (BA) is a congenital anomaly often found in neonates, with an incidence reaching 1:5500 per birth. BA is frequently associated with cytomegalovirus (CMV) infection in the patient, which causes a clinical appearance different from other types of BA. BA is usually treated by Kasai procedure, with cholangitis being the most common complication of this procedure. CMV infection is found to affect post-operative survival and bilirubin levels. However, it remains unclear whether the infection may affect the incidence of cholangitis in BA patients post-Kasai procedure.

Materials and Methods: This retrospective study used the medical records of 33 BA patients who underwent the Kasai procedure in Dr. Sardjito Hospital between 2017 and 2021.

Results: Among 33 patients, 17 (51.5%) were infected with CMV, and 12 (36.4%) developed cholangitis. The frequency of cholangitis following the Kasai procedure is not significantly influenced by the CMV infection (p=0.615). Interestingly, the incidence of cholangitis is significantly associated with the pre-operative gamma-glutamyl transferase (GGT) levels (p=0.026). Furthermore, pre-operative ALP appears to have a protective effect against cholangitis, with these associations nearly reaching a significant level (p=0.093).

Conclusion: CMV infection is unlikely to impact the incidence of cholangitis after the Kasai procedure in BA patients. Notably, the pre-operative GGT level might affect the incidence of cholangitis following the Kasai procedure, thereby increasing their risk.

KEYWORDS:
Cytomegalovirus, biliary atresia, Kasai procedure, cholangitis, pre-operative gamma-glutamyl transferase

INTRODUCTION

Biliary atresia (BA) is a disorder in which the obliteration of the biliary duct obstructs bile flow.[1] This condition is the most common cause of neonatal jaundice in the world.[2] In Indonesia, the incidence of BA reached up to 1:7000 births.[3] Symptoms of BA include hyperbilirubinemia, pale stools, dark urine, progressive renal failure, and even death if not promptly treated.[2] The most common treatment for this disorder is the Kasai procedure.[3]

The etiopathogenesis of BA is multifactorial and remains elusive. The two most widely accepted etiologies are embryological malformation of biliary ducts during fetal development and inflammation due to perinatal viral infection that leads to fibrosis and obliteration of the duct.[4-5] Cytomegalovirus (CMV) infection is among the most widely studied. It is known to cause clinically distinct BA symptoms with a greater inflammation and higher mortality, reaching 25% in CMV-associated BA compared to 6.5% in non- CMV-associated BA.[6-7]

There remain conflicting and debatable results on the impact of CMV infections on BA patients post-Kasai procedure. Cholangitis might be found in patients with BA that develop complications after a Kasai procedure, and it serves as a significant predictor for survival and successful outcome of the Kasai procedure. Therefore, this research aimed to compare the incidence of cholangitis between BA patients with and without accompanying CMV infection.

MATERIALS AND METHODS

A descriptive retrospective study was conducted to analyze the association between CMV infection and cholangitis incidence in BA patients post-Kasai procedure. This study was conducted using medical records of BA patients who underwent the Kasai surgery in Dr. Sardjito Hospital in Yogyakarta, Indonesia, between 2017 and 2021. Patients without a complete medical record were excluded.

The diagnosis of BA and cholangitis was based on the patient's clinical medical record. At the same time, CMV infection was defined as the presence of anti-CMV antibodies or a positive result on a PCR CMV test.

Prognostic Factors

In total, 15 variables were collected, including demographic, clinical, and laboratory data. These variables are age at the time of surgery, sex, BA subtype, CMV infection status, pre-operative total and direct bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), INR, albumin, gamma-

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Table I: Baseline characteristics of patients with BA

Characteristics	N (%)	Mean ± SD
Sex		
▪ Male	12 (36.4)	
▪ Female	21 (63.6)	
Age at Kasai surgery (days)		92.18 ± 22.65
BA type		
▪ I	1 (3.0)	
▪ IIA	20 (60.6)	
▪ IIB	2 (6.1)	
▪ III	10 (30.3)	
CMV infection		
▪ Negative	17 (51.5)	
▪ Positive	16 (48.5)	
Pre-operative lab		
▪ Total Bilirubin (mg/dL)		10.24 ± 3.25
▪ Direct Bilirubin (mg/dL)		8.82 ± 2.84
▪ Aspartate Aminotransferase (U/L)		220.76 ± 116.61
▪ Alanine Aminotransferase (U/L)		167.45 ± 129.1
▪ Gamma-glutamyl transferase (U/L)		694.33 ± 506.73
▪ Alkaline Phosphatase (U/L)		472.91 ± 155.8
▪ INR		1.11 ± 0.63
▪ Platelet (103/µL)		361.97 ± 126.25
Post-operative lab		
▪ Total Bilirubin POD7 (mg/dL)		9.79 ± 3.66
▪ Direct Bilirubin POD7 (mg/dL)		8.21 ± 3.25
Cholangitis		
▪ Yes	12 (36.4)	
▪ No	21 (63.6)	

SD, standard deviation; IQR, interquartile range; POD, postoperative day; BA, biliary atresia

Table II: The cut-off points of variables according to the ROC curve

Characteristics	Cut-off	Sn (%)	Sp (%)
Age at surgery (days)	≥99	58.3	76.2
Total Bilirubin (mg/dL)	≥9.215	83.3	47.6
Direct Bilirubin (mg/dL)	<8.825	33.3	47.6
Aspartate Aminotransferase (U/L)	≥152.5	91.7	28.6
Alanine Aminotransferase (U/L)	<220.5	16.7	71.4
Gamma-glutamyl transferase (U/L)	≥979.5	50	90.5
Alkaline phosphatase (U/L)	<368	58.3	9.5
Albumin (g/dL)	≥4.17	41.7	85.7
INR ≥0.975	83.3	52.4	
Platelet (103/µL)	≥315	83.3	47.6
Total bilirubin POD7 (mg/dL)	≥11.78	50	76.2
Direct bilirubin POD7 (mg/dL)	≥9.345	58.3	76.2

Sn: Sensitivity, Specificity; POD, postoperative day

glutamyl transferase (GGT), and alkaline phosphatase (ALP) levels, pre-operative platelet count, and post-operative total and direct bilirubin levels.

Ethics Approval

This study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital (KE/FK/0439/EC/2021). Before participating, the parents or legal guardians of BA patients and controls signed written informed consent forms. The research was performed following the Declaration of Helsinki.

Statistical Analysis

The data were presented as nominal data, and bivariate analysis was performed using Fisher's exact or chi-square tests. Then, further multivariate analysis was performed using binomial logistic regression. For statistical analysis, type I BA was treated as one group alongside type IIA BA, while type IIB BA was categorized with type III BA. All statistical analyses were performed using IBM SPSS Statistics 23.

RESULTS

Forty-six patients were identified, with 13 patients excluded due to incomplete medical records. Of the 33 patients, 17 (51.5%) were infected with CMV, and 12 (36.4%) developed cholangitis (Table I).

Table III: Association between prognostic variables and cholangitis

Characteristic	Cholangitis		p-value	OR (95% CI)
	Yes	No		
Sex				
▪ Male	9	12	0.457	2.25 (0.47-10.78)
▪ Female	3	9		
Age at Kasai surgery (days)				
▪ ≥99	7	5	0.067	4.48 (0.98-20.59)
▪ <99	5	16		
BA type				
▪ IIB/III	5	7	0.716	1.429 (0.33-6.17)
▪ IIA/I	7	14		
Total bilirubin (mg/dL)				
▪ ≥9.22	10	11	0.133	4.55 (0.80-25.98)
▪ <9.22	2	10		
Direct bilirubin (mg/dL)				
▪ ≥8.83	7	12	0.947	1.05 (0.25-4.42)
▪ <8.83	5	9		
Aspartate aminotransferase (U/L)				
▪ ≥152.5	11	15	0.223	4.40 (0.46-41.97)
▪ <152.5	1	6		
Alanine Aminotransferase (U/L)				
▪ ≥220.5	2	6	0.678	0.50 (0.08-2.99)
▪ <220.5	10	15		
Gamma-glutamyl transferase (U/L)				
▪ ≥979.5	6	2	0.015	9.50 (1.5-60.11)*
▪ <979.5	6	19		
Alkaline Phosphatase (U/L)				
▪ ≥368	7	19	0.071	0.15 (0.02-0.94)
▪ <368	5	2		
Albumin (g/dL)				
▪ ≥4.17	5	3	0.106	4.29 (0.8-22.92)
▪ <4.17	7	18		
INR				
≥0.975	10	10	0.067	5.50 (0.96-31.43)
<0.975	2	11		
Platelet (103/µL)				
≥315	10	11	0.133	4.55 (0.80-25.98)
<315	2	10		
Total Bilirubin POD7 (mg/dL)				
≥11.78	6	5	0.149	3.20 (0.71-14.53)
<11.78	6	16		
Direct Bilirubin POD7 (mg/dL)				
≥9.345	7	5	0.067	4.48 (0.98-20.59)
<9.345	5	16		
CMV				
Positive	6	10	0.895	1.10 (0.27-4.55)
Negative	6	11		

POD, post-operative day

Table IV: Multivariate analysis of the association between independent variables and cholangitis

Characteristic	p-value	OR	95% CI
Age at Kasai surgery	0.438	5.11	0.08-313.16
Pre-operative total bilirubin	0.75	1.6	0.09-28.16
Gamma-glutamyl transferase	0.026*	29.37	1.5-576.29
Alkaline phosphatase	0.093	0.04	0.001-1.74
Albumin	0.844	1.45	0.03-65.58
INR	0.44	3.17	0.17-59.09
Post-operative total bilirubin	0.597	2.97	0.05-167.8
Post-operative direct bilirubin	0.987	1.03	0.03-36.04
CMV	0.615	2.94	0.04-197.2

All numerical data were analyzed using the receiver-operating characteristic (ROC) curve to determine their cut-off points (Table II).

Association between prognostic variables and cholangitis
We found no significant association between CMV infection and the incidence of cholangitis (p=0.895). Pre-operative GGT was significantly associated with cholangitis post-surgery, where patients with GGT levels ≥979.5 U/L had a 9.5 times increased risk of developing cholangitis (95% CI=1.50-60.11; p=0.015). Interestingly, we also found that the pre-operative ALP shows a protective effect (OR = 0.15 [95% CI=0.02-0.94]), and these associations almost reached a significant level (p=0.071) (Table III).

Multivariate analysis of the association between independent variables and cholangitis
We found that only pre-operative GGT levels were an independent risk factor for cholangitis incidence post-Kasai surgery (p=0.026) (Table IV).

DISCUSSION

CMV infection is postulated to be involved in the pathogenesis of BA and affects the clinical manifestation and severity of the condition.[7-8] Cholangitis post-Kasai surgery is due to inflammation of the anastomosis site and colonization by intestinal flora, worsened by cholestasis.[9-10] In our study, we were unable to show that the presence of CMV infection has any significant association with the development of cholangitis as a complication of the Kasai procedure in BA patients. This result agrees with previous reports that show no association between CMV infection and cholangitis in BA patients.[8,11] Despite this, other studies have shown an association between cholangitis risk and inflammation in BA patients after a Kasai surgery.[7,12-13] The difference in our results may be due to our small sample size, and further studies with larger sample sizes will help elucidate a better conclusion.

Most of our subjects were female (63.6% vs 36.4%), with a ratio of 7:4 or 1.75:1. These ratios vary among studies.[3,14-19] We did not find any statistically significant association between sex and the incidence of cholangitis. This supports earlier studies that show no significant association between the patient's sex and the success of the Kasai procedure.[3,20]

The association between cytomegalovirus (CMV) infection and biliary atresia appears to vary by geographic region. In Asian populations, several studies have demonstrated regional differences in the prevalence of CMV-positive BA.[21-23] In Asian countries, such as China and Taiwan, CMV DNA has been detected in a significantly higher percentage of BA patients, ranging from 30% to over 50%, compared to Western countries, where reported rates are generally lower, between 10% and 20%.[7,24] The reported incidence of BA varies by geography, with higher incidence found in the Asia and Pacific region. About 1 in 5000 live births in Taiwan, 1 in 10,000 in Japan, 1 in 17,000–19,000 in the UK and France, 1 in 19,000 in the Netherlands, and 1 in 15,000 in the United States have the condition. There are no clear reports regarding the incidence of biliary atresia in Indonesia.[2,25] Extrahepatic biliary atresia, subsequently mentioned as biliary atresia, was reported to occur in 1 in 18,000-20,000 live births, more commonly in Asians (1 in 5.000-8.000).[25-26] Our findings align with this trend, supporting the hypothesis that CMV may play a more prominent role in the pathogenesis of BA in Asian settings.

Our patients' average age at surgery was around 92.8 days, 36.37% of whom were older than 99 days old. It is often reported that earlier age at surgery leads to better outcomes in BA patients, with one study showing that older age at surgery is a risk factor for recurrent cholangitis.[9,20,27] This conclusion, however, has also been often debated, with other reports showing no significant association between earlier surgery and better surgical outcomes.[3,19,28-30] The choice of cut-off point for earlier and later surgery definition might explain the discrepancy, as a report from Song et al. shows no significant difference in survival between >90 days surgery patient and 61-90 days surgery patient but shows a substantial difference between <60 days surgery patient and >90 days surgery patient.[31]

Early surgery for biliary atresia, ideally within 60 to 70 days of life, has been shown to improve outcomes following Kasai portoenterostomy[32-33] significantly. In our cohort, the mean age at surgery was 92 days, which may have negatively influenced postoperative bile flow. This delay was primarily due to late presentation, limited parental awareness, and referral system inefficiencies, common challenges in our healthcare setting. This highlights the urgent need to strengthen early detection programs and streamline referral pathways. A previous study showed that performing the Kasai operation beyond the age of 60 days was not associated with a worse outcome and that a high percentage of patients could still achieve good bile flow with normal bilirubin postoperatively.[34] Thus, it is believed that until the age of 100 days, the age of the patients does not play a significant role in determining the success of the Kasai operation.34 Another study also suggested that when faced with cholestasis, significant clinical attention is typically directed towards diagnosing or excluding BA.[35] Of all cholestatic conditions, BA is the only one that is "time-sensitive" because early diagnosis significantly improves outcomes, and if missed, can have adverse consequences.[35] The benefit of early intervention on survival continues to show a positive correlation with younger age at surgery. Traditionally, the first 60 days of life are critical in establishing bile flow to prevent or ameliorate liver-related morbidity and mortality in BA patients. However, the cutoff of 60 days is somewhat arbitrary because establishing bile flow with Kasai portoenterostomy even beyond that age may still result in favorable outcomes. In the present cohort, almost all cases underwent surgery at or beyond the age of 60 days. Accordingly, the success and survival rates are comparable to previous reports.[35] The optimum treatment for late BA presentation remains controversial, especially considering the difficulty in predicting Kasai procedure prognosis.[35] On the one hand, survival with the native liver for those undergoing the Kasai procedure beyond 60 days appears to be more favorable than previously suggested.

Biliary atresia (BA) is increasingly recognized as a multifactorial disease due to genetic predisposition, immune dysregulation, and environmental or viral triggers. Developmental genes such as Sox17 and Hes1 regulate bile

duct specification, while Lgr4 is essential for gallbladder and cystic duct formation. Polymorphisms in VEGF may contribute to inflammatory angiogenesis, and mutations in CFC1, associated with biliary atresia splenic malformation (BASM) syndrome, further support a genetic role.[36] In Indonesian patients, overexpression of miRNA-21 and downregulation of PTEN correlate with liver fibrosis, while altered expression of collagen genes (COL6A1, COL6A2, COL6A3, COL1A1) suggests a genetic basis for fibrogenesis.[37-38] Cholangiocytes also exhibit innate immune activation via TLR3 in response to viral dsRNA, such as RRV. Stimulation with poly(I:C), a synthetic analogue of viral dsRNA, induces EMT and fibrosis-related pathways, and the failure to develop TLR tolerance sustains biliary injury.[36]

Etiopathogenesis of the perinatal form of BA may be caused by primary viral infection targeting the bile duct epithelium (cholangiotropic infection), which then initiates the destructive cascades.[2,39] It has been proposed that several viruses, not limited to CMV, Reovirus, and Rotavirus, can infect and directly damage bile duct epithelial cells.[39-40] This process may provoke a secondary, damaging immune or autoimmune response, leading to progressive inflammation, fibrosis, and eventual obliteration of the biliary tree, the pathognomonic hallmark of BA.[39] Functional studies further support this hypothesis, as demonstrated by a rotavirus-induced mouse model, which shows that a viral infection in newborns can lead to a phenotype of biliary inflammation and obstruction similar to that seen in human infants.[41] While this evidence suggests a potential mechanism for how CMV initiates inflammation and destruction of the biliary system, its impact on postoperative complications, such as cholangitis, is still unclear. In our study, we were unable to demonstrate a significant association between CMV infection and the development of cholangitis as a complication of the Kasai procedure in BA patients. This result agrees with previous reports of no association between CMV infection and cholangitis in BA patients.[2,8] A 2021 meta-analysis, further supported our inference as although CMV-positive BA patients had significantly lower rates of jaundice clearance after the Kasai procedure, there was no significant difference in the overall incidence of cholangitis.[8] We presume that cholangitis after the Kasai procedure observed in our cases may also be due to inflammation at the anastomosis site and bacterial colonization from the intestine, which is exacerbated by cholestasis.[2,8] The difference in our results compared to studies that do show an association may be due to our small sample size, and further studies with larger cohorts are needed to draw a more definitive conclusion.

Recurrent cholangitis is a well-known complication after Kasai portoenterostomy and is associated with progressive liver damage and poorer prognosis due to progressive liver injury and fibrosis.[42-44] One preventive strategy is ensuring an adequate length of the Roux-en-Y limb. A length of at least 40–50 cm has been recommended to minimize the risk of ascending bacterial infection from the intestine.[42-43,45] A randomized controlled trial comparing standard (30–40 cm) versus shorter (13–20 cm) Roux limbs showed comparable rates of cholangitis and bile flow, indicating shorter loops may be equally effective in selected populations.[42] Furthermore, in cases of recurrent cholangitis without mechanical obstruction, extending the Roux limb, including lengths up to 90 cm, has been reported to resolve symptoms completely by reducing bile reflux and bacterial stasis.[43] These findings emphasize that while limb length is essential, optimal outcomes likely depend on individualized surgical planning and vigilant postoperative management.[42-45]

Gamma-glutamyl transferase is one of the ductal enzymes that serves as an indicator of ductal and canaliculi damage.[46] A higher level of GGT would indicate more significant ductal damage and inflammation. Our study shows that pre-operative GGT level ≥979.5 U/L is associated with up to a 9.5-fold increase in the risk of cholangitis. We also show that pre-operative GGT is an independent predictor for cholangitis in patients that undergo the Kasai procedure. This agrees with another report showing that patients with cholangitis have greater GGT levels.[9] Other studies also support our result by showing the association between higher GGT levels and failure in jaundice clearance and lower native liver survival.[27,47]

Alkaline phosphatase is another ductal enzyme that indicates damage to the canaliculi and bile system, and its elevation is one indicator of cholestasis and cholangitis.[48] However, our result did not show the association between pre-operative ALP level and the incidence of cholangitis. Plenty of previous studies reported similar results, showing no association with other outcomes of Kasai surgery.[14,18,20,27,49]

One of the common indicators of a successful Kasai surgery is jaundice clearance, often defined as a serum level of total bilirubin under 20 µmol/L.[9,35] Another standard definition is serum bilirubin level under 2 mg/dL or 1.2 mg/dL.27-28 Our patients show an average total bilirubin level of 9.79 mg/dL 7 days after Kasai surgery and an average of 8.21 mg/dL for direct bilirubin level 7 days after the surgery. We fail to show any significant association between pre-operative and post-operative total and direct bilirubin levels and cholangitis incidence post-surgery. These findings vary among reports. Another study agrees that earlier jaundice clearance is not associated with cholangitis post-Kasai surgery, and another reported that direct bilirubin level shows no association with a patient's prognosis two weeks after the surgery.[9,50] One study even reported that early jaundice clearance is a risk factor for cholangitis after Kasai surgery.[10] Meanwhile, other studies report a better prognosis in patients with lower bilirubin levels post-surgery.[27,49,51-52] The discrepancies between these results might be explained by the varying definitions of the "post-surgery" period, ranging from one week to several months.

LIMITATIONS

Our study is constrained by its small sample size and the single-center source of our samples. Research involving a larger sample size from multiple centers could further validate our results.

CONCLUSIONS

CMV infections might not be linked to the risk of cholangitis in BA patients who undergo the Kasai procedure. Pre-operative GGT levels might serve as a valuable predictor for the incidence of cholangitis in BA patients after Kasai surgery.

Abbreviations

BA, biliary atresia; IQR, interquartile range

CONFLICT OF INTEREST

All the authors declare that there are no conflicts of interest.

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