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Original Article

# Demographic Characteristics of Children with Biliary Atresia in dr. Kariadi General Hospital, Semarang

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**Abstract:**

***Background***: Biliary atresia (BA) is a progressive fibrosing obstructive cholangiopathy involving both the intrahepatic and extrahepatic biliary system; resulting in obstruction of bile flow and neonatal jaundice. Early diagnosis of biliary atresia and Kasai procedure improves patients outcome. Data form several studies revealed that BA is the most common cause of neonatal cholestasis (25%) and the leading cause of end-stage liver disease in pediatric population. The aim of this study is to determine the outcome and characteristics of children with biliary atresia in dr. Kariadi General Hospital, Semarang.

***Methods***: In this study, a retrospective database analysis of 80 infants diagnosed with biliary atresia was conducted. Patient's demographic data including age, sex, age at disease onset, were collected from year 2018 to 2022; including all comorbidities and complications. Data regarding procedure performed for each patient and their outcome were included in this study.

***Results***: Eighty children were included in this study. The mean age of children referred with biliary atresia was 1.89 month, while the mean age at diagnosis was 2.5 month. Most of the patients were girls. The incidence of cytomegalovirus infection comorbidity in patients with biliary atresia is quite high, which were reported at 82%. Children diagnosed with biliary atresia and cytomegalovirus infection resulted in worse prognosis than those without.

***Conclusion***: Our study support the theories that biliary atresia may be caused by the exposure of external environment during perinatal period such as viral infection. The prognosis of patients with cytomegalovirus comorbidity is worse than that without.

**Keywords:** biliary atresia, characteristics, pediatric patients**,** demographic, cytomegalovirus

## Introduction

Biliary atresia (BA) is a progressive fibrosing obstructive cholangiopathy involving both the intrahepatic and extrahepatic biliary system; resulting in obstruction of bile flow and neonatal jaundice.[1] Several studies have reported that biliary atresia is the

most common cause of neonatal cholestasis (25%) and the leading cause of end-stage liver disease in pediatric population.[2] Hence, early diagnosis of biliary atresia and Kasai procedure are exceedingly important to improve patients outcome. If left untreated, the survival rate is less than 10% at 3 years of age.

Clinical manifestations of biliary atresia often emerged during neonatal period with persistent jaundice, clay-coloured stools, and hepatomegaly. Theories suggest that genetic and environmental factors are the main contributing factors, since approximately 3-20% of children with biliary atresia had been associated with other syndromes or other congenital abnormalities. Evidence of CMV infection has been reported in 10-38% of infants with biliary atresia.[2] Biliary atresia is more common in certain geographic areas, suggesting that several genetic components may play an important role in pathogenesis of the disease.

Currently, there is limited data regarding biliary atresia patients in Indonesia, especially in Semarang. Thus, this study is conducted to demonstrate the current data of biliary atresia which includes epidemiology, clinical characteristic and outcome in Indonesian population.

## Methods

Retrospective database analysis of 80 infants diagnosed with biliary atresia was conducted in dr. Kariadi General Hospital, Semarang, Indonesia from 2018-2022. Cases of cholestasis with clinical, biochemical data and surgical findings that consistent with biliary atresia, were included in this study. Patient's demographic including age, sex, age at disease onset, and any co-infections were recorded; including complications and outcome.

## Result

Eighty medical record of children that consistent with biliary atresia were included in this study. The mean age of children referred with biliary atresia was 1.89 months, while the mean age at diagnosis was 2.5 months and at death was 20.1 months. Children diagnosed with biliary atresia had high average bilirubin levels (total bilirubin 18.32, direct bilirubin 11.82, indirect bilirubin 2.96) as well as levels of liver damage parameters (SGOT, SGPT, alkaline phosphatase, gamma GT) as shown on **Table 1**.

**Table 1.** Data of age and laboratory parameters of children with biliary atresia

| Parameter | Mean (SD) |
|---|---|
| **Age** | |
| Age at referral (month) | 1.89 (4.711) |
| Age at diagnosis (month) | 2.5 (2.677) |
| Age at death (month) | 20.1 (15.39) |
| **Laboratory Parameters** | |

| | |
|---|---|
| Total bilirubin | 18.32 (56.25) |
| Direct bilirubin | 11.82 (22.89) |
| Indirect bilirubin | 2.96 (10.45) |
| SGOT | 249.58 (2256.4) |
| SGPT | 142.23 (540.6) |
| Alkaline phosphatase | 532.06 (1525.3) |
| Gamma GT | 596.168 (3514.9) |

Most of the subjects in this study were girls (53.75%). Most children with biliary atresia was born with low birth weight, and had poor nutritional status, ranging from moderate to severe malnutrition. Abdominal ultrasonography was performed on children with suspicion of biliary atresia and only 56.25% of the results show a triangular cord sign. Children with biliary atresia have a high survival rate with 51.25% of patients underwent IOC. About 82% of patients also recorded to have comorbidities of congenital CMV infection (**Table 2**).

**Table 2.** Demographic characteristics of children with biliary atresia

| **Characteristics** | **n (%)** |
|---|---|
| **Gender** | |
| Male | 37 (46.25) |
| Female | 43 (53.75) |
| **Birthweight** | |
| Normal birth weight | 18 (22.5) |
| Low birth weight | 38 (47.5) |
| Very low birth weight | 18 (22.5) |
| Extremely low birth weight | 6 (7.50) |
| **Nutrition Status** | |
| Normal | 16 (20) |
| Moderate malnutrition | 40 (50) |
| Severe malnutrition | 24 (30) |
| **Abdominal Ultrasonographic (Presence of Triangular Cord Sign)** | |
| Yes | 45 (56.25) |
| No | 35 (43.75) |
| **IOC** | |
| Yes | 41 (51.25) |
| No | 39 (48.75) |
| **Death** | |
| Yes | 15 (18.75) |

| | |
|---|---|
| No | 65 (81.25) |
| **CMV Infection** | |
| Yes | 66 (82.5) |
| No | 14 (17.5) |

Notes: IOC: intraoperative cholangiography; CMV: Cytomegalovirus

Only half of children (53.33%) who died of biliary atresia had CMV. Even so, most of these children had high levels of bilirubin profile and liver damage parameters, as well as poor nutritional conditions. IOC may provide higher life expectancy in children with biliary atresia (**Table 3**).

**Table 3.** Characteristics and laboratory parameters of children who died of biliary atresia

| Parameter | n (%) |
|---|---|
| **Total Bilirubin (mg/dL)** | |
| >5 | 11 (73.33) |
| 1-5 | 4 (26.67) |
| **Indirect Bilirubin (mg/dL)** | |
| >5 | 9 (60) |
| 1-5 | 6 (40) |
| **Direct Bilirubin** | |
| >5 | 10 (66.67) |
| 1-5 | 5 (33.33) |
| **Nutritional Status** | |
| Normal | 1 (6.67) |
| Moderate Malnutrition | 8 (53.3) |
| Severe Malnutrition | 6 (40) |
| **IOC** | |
| Yes | 4 (26.67) |
| No | 11 (73.3) |
| **CMV Infection** | |
| Yes | 8 (53.33) |
| No | 7 (46.67) |

## Discussion

Biliary atresia is a progressive, inflammatory liver disease characterized by obstructive cholangiopathy and disrupted bile flow in early infancy. The incidence of biliary atresia ranges from 4.2 to 32 per 100,000 live births, with the highest incidence reported in French Polynesian and East Asian countries. Although the exact pathogenesis of

biliary atresia remains unknown, recent research suggests that multifactorial immunologic responses, triggered by various factors (e.g. ethnicity, infections, genetic and environmental factors), play important roles.[1]

The etiology of biliary atresia is unknown. Theories suggest a multitude of etiological and causative factors that are both genetic and acquired. Since about 3% to 20% of children with biliary atresia are associated with other syndrome or congenital abnormality, and as biliary atresia is more common in certain geographic regions, it is likely that some genetic component is present in the pathogenesis of the disease, although no single etiology has been found so far. Only a few familial cases are described and no increase in the incidence has been noted in the case of twins.[2,3]

The extrahepatic bile ducts first become visible as an out-pouching of the foregut at 20 days of gestation, and the intrahepatic bile ducts become visible at 45 days, which was formed from the primitive hepatocytes. The porta-hepatis is the place of the interface between the extra and intrahepatic bile ducts, and the successful union is crucial for the development of the patent biliary system. The non-syndromic isolated type of biliary atresia might result from faulty remodelling in fetal life at the hepatic hilum. This is supported by the fact that there are similarities in the cytokeratin staining of the bile ducts in patients with biliary atresia and first-trimester fetal bile ducts strengthening the possibility that biliary atresia could occur due to the failure of the bile duct remodelling at the hepatic hilum with the persistence of fetal bile ducts.[4]

Other theories favor a possible acquired, inflammatory, and infectious cause for the pathogenesis of the disease. Rotavirus and reovirus type 3 are specifically mentioned, as perinatal animal models infected by those viruses produced biliary atresia; however, these results have not been consistently seen in humans.[5,6] There have also been studies that show immune-related damage to the ductules of patients with biliary atresia due to an increase in the expression of intercellular adhesion molecule (ICAM)-1 in the bile ductules.[7]

In this study, cases of biliary atresia were more common in female infants than male infants. The study by Bellomo-Brandao et al. found that from 165 infants, intrahepatic cholestasis was found in 62.64% male infants, while extrahepatic cholestasis was found in 55.25% female infants with p-value = 0.026. This finding was similar to this study; despite no significant differences were found, this study showed that BA or extrahepatic cholestasis was commonly found in female infants.[8,9]
The data in this study were children who were enrolled at an average age of 1.89 month where they were only diagnosed as BA when they were 2.5 month old. these findings indicate an early detection of cases. Data also showed that the patient was referred

before the age of 8 weeks. The diagnosis can be made before the end of 12 weeks or 100 days.

The diagnosis of BA was based on clinical manifestations (yellowing of the eyes and whole body, a cholic stool) and anatomical pathology examination (histopathological features such as bile plug, ductular proliferation, and portal edema with and/or fibrosis of liver biopsy tissue). Biopsy samples were taken and extracted from liver tissue.[10] Cytomegalovirus infection is initially more common in intrahepatic cholestasis (without BA); however, several studies have shown that CMV infection can be found in extrahepatic cholestasis (BA). The study found that viruses including CMV can be a trigger leading to dysregulation of immune mechanisms with genetic influences and eventually causes BA. Cytomegalovirus infection has the ability to replicate both in hepatocytes and cholangiocytes. This virus can directly induce damage to the liver and biliary duct system and induce damage to the immune system in infected cells, leading to the formation of inclusion of bodies in hepatocyte and vascular cells of epithelial cells, especially along with 21 biliary duct epithelial cells.[10]

In the past, most patients with biliary atresia died before the age of 3 years; however, the 5-year survival rate has increased sharply, from 30% to 75%, since the introduction of Kasai portoenterostomy in 1968. Although timely Kasai procedure is a primary surgical option for early survival, liver transplantation is also required as a curative option because the 4-year survival rate after Kasai is as low as 42%. This research show that children with biliary atresia were less likely to die and death often resulted from sepsis. Twenty three-percent underwent IOC with Kasai and other procedures. Ascending cholangitis is the most common complication after Kasai, and is a causative factor of liver damage. Bacterial cholangitis occurs at a rate of 70%-90% and recurs in most cases. [11,12] In this study, 51.25% of infants underwent IOC, continued with Kasai procedure. While the infant mortality rate is 81.25% in infants with biliary atresia, while infants who survive are 18.75%.

## Conclusion

Biliary atresia is a congenital disorder in the form of progressive fibrosing obstructive cholangiopathy involving both the intrahepatic and extrahepatic biliary system; resulting in obstruction of bile flow and neonatal jaundice. Data obtained from biliary atresia in children at dr. Kariadi Hospital Semarang found that the mean age of children who came with biliary atresia was 1.89 months, while the age at diagnosis was 2.5 months. Children with biliary atresia are more likely to die from postoperative sepsis. Almost half of the patients underwent IOC with the Kasai Procedure and other procedures. Our study is in accordance to the theories that biliary atresia may cause by exposure form the external environmental factors during the perinatal period such

as viral infection. The prognosis of patients with cytomegalovirus co-infection is worse than that in the absence of the co-infection.

## Conflict of Interest

None declared.

## Funding

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