APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Literature Review

CMV-Positive Biliary Atresia in Infants: A Review of Prognosis and Therapeutic Impact

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e-ISSN: 2830-5442

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Published:
31st May 2025

DOI:
https://doi.org/10.58427/apghn.4.2.2025.83-96

Citation:
Rahmadiena Q, Rahmah N, Karyanti MR, Rahman HA. CMV-positive biliary atresia in infants: a review of prognosis and therapeutic impact *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(2): 83-96

Abstract:

Background: Biliary atresia (BA) is a progressive cholangiopathy of infancy that can lead to end-stage liver disease and is the leading indication for pediatric liver transplantation. Among various proposed etiologies, cytomegalovirus (CMV) infection has emerged as a significant factor, giving rise to a distinct clinical subset known as CMV-positive BA.

Discussion: CMV-positive BA is frequently associated with delayed diagnosis, increased incidence of postoperative cholangitis, and advanced liver fibrosis at initial presentation. These features contribute to lower rates of jaundice clearance and native liver survival. Mortality is also higher in CMV-positive patients than in their CMV-negative. Diagnostic methods include performing polymerase chain reaction (PCR) tests on saliva, urine, or dried blood spot samples, as well as conducting abdominal ultrasound examinations that focus on identifying specific indicators, such as the triangular cord sign, which is commonly observed in patients with BA. Antiviral therapy, particularly with ganciclovir or valganciclovir, shows promise in improving native liver outcomes in CMV-positive BA patients. Early surgical intervention remains critical, yet CMV-positive BA often presents later, worsening prognosis. Preventive strategies are under investigation, including maternal CMV screening and neonatal testing.

Conclusion: Early identification and tailored antiviral intervention may play a critical role in altering the disease trajectory. Increased awareness of CMV-positive BA is essential for timely diagnosis and optimal management. This review emphasizes the need to recognize CMV-positive BA as a clinically important biliary atresia subset with distinct pathophysiology and worse prognosis, underscoring the importance of early CMV screening and targeted antiviral therapy.

Keywords: biliary atresia, cytomegalovirus infection, prognosis

Introduction

Biliary atresia (BA) is a cholangiopathy affecting the intra- and extrahepatic bile ducts, leading to liver fibrosis, portal hypertension, and eventual liver failure.[1] Viral infections have long been hypothesized to contribute to the development of biliary atresia (BA), with several viruses, including Reovirus 3, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and human papillomavirus (HPV), detected in the livers of BA patients. Notably, CMV has been identified in 60% of BA cases in China.[2]

The role of viruses in initiating or causing biliary atresia (BA) has been debated for at least 30 years but without a definitive consensus. Of all the possible viruses proposed, CMV appears to have the strongest evidence. Some reports indicate that infections with reovirus 3, rotavirus C, or cytomegalovirus (CMV) could be important. The hypothesis of a viral etiology is further supported by suggestions of an uneven distribution of the birth months in patients with BA.[3]

Cytomegalovirus (CMV) has emerged as one of the most clinically significant potential contributors to biliary atresia (BA). Its involvement was first noted in a Swedish study that detected CMV DNA in around half of BA cases, along with an IgM immune response localized to the canalicular membranes of liver cells. Building on this, Brindley et al. found a CMV-specific T cell response in liver tissue in just over 50% of BA infants in a U.S. study, which was linked to higher plasma CMV IgM levels.[4] This immune response was also associated with a decrease in circulating regulatory T cells (Tregs).[5]

Interestingly, the rate of CMV exposure observed in these studies is significantly higher than in some European populations, such as the 10% reported by the authors and 11% in a German cohort.[6, 7] These higher rates are more aligned with data from China—for instance, Xu et al. detected the CMV-pp65 antigen in 60% (51 out of 85) of liver samples from BA patients, a figure much greater than for other viruses like Reovirus 1.[8]

A meta-analysis study by Mohamed et al, showed that CMV was detected in 25.4% (95% CI 15.9%–38.0%) of the patients with BA. But, in their subgroup analysis, the detection of CMV infection in patients with BA was higher in the Asian studies (37.9%) than in European and American studies (25.5% and 15.3%, respectively).[9]

Congenital cytomegalovirus (CMV) infection occurs in approximately 0.2% to 2.2% of all live births, while perinatal transmission is even more frequent, ranging from 10% to 60% within the first six months of life. Perinatal CMV infection typically occurs through exposure to maternal genital secretions or breastmilk. Although most

perinatal CMV infections are asymptomatic, they can sometimes lead to cholestasis, which may mimic the symptoms of biliary atresia.[10]

Davenport further classified CMV-positive BA as a distinct subgroup of the disease, characterized by the presence of immunoglobulin M (IgM) antibodies against CMV in liver biopsy specimens and onset during the perinatal period.[11] CMV-positive BA is also defined by a positive polymerase chain reaction (PCR) test for CMV in saliva, urine, or dried blood spot (DBS) samples collected within the first three weeks of life.[12] Hereafter, this condition will be referred to as CMV-positive BA throughout this manuscript.

Evidence suggests that active CMV infection is associated with a poorer prognosis in patients with biliary atresia. CMV-positive infants tend to experience delayed jaundice clearance and slower recovery following Kasai portoenterostomy. Additionally, they have a higher incidence of cholangitis, reduced native liver survival, and increased mortality rates compared to CMV-negative patients.[6]

This literature review aims to introduce the entity of biliary atresia associated with CMV infection, explain its impact on infant health, and encourage healthcare professionals—especially doctors—to be more aware of this condition in order to ensure proper management and prevent poor outcome in the future.

Methodolgy

This literature review was conducted using a structured literature search based on the PICO framework, where **P** (Population) refers to perinatal patients with biliary atresia, **I** (Intervention) indicates no specific intervention, **C** (Comparison) involves CMV-positive versus CMV-negative infection status, and **O** (Outcome) focuses on prognosis and therapeutic outcomes in CMV-positive and CMV-negative biliary atresia patients. The search was performed using the PubMed database with several keywords, including *"biliary atresia," "CMV-positive BA," "prognosis,"* and *"antiviral therapy"*.

CMV-positive Biliary Atresia

What is CMV-positive biliary atresia, and how does it differ from other types of biliary atresia?

Diagnosis of CMV infection is confirmed when PCR of CMV is positive within three weeks after birth. Various methods have been explored for diagnosing congenital CMV infection using samples such as saliva, urine, and dried blood spots (DBS) collected from newborns. The heels of neonates were punctured and capillary blood was blotted onto filter paper and dried. Traditionally, culture-based testing of urine

and saliva has been the gold standard for identifying infants with congenital CMV infection. However, these methods are not easily automated, making them unsuitable for large-scale newborn screening. Laboratory tests using easily obtainable clinical samples from infants are essential for timely diagnosis. While viral isolation remains the most reliable method for confirming infection, it is labor-intensive, time-consuming, and impractical for large-scale use. Additionally, collecting urine samples using sterile bags is technically challenging, further limiting its feasibility for widespread screening. Early detection of congenital CMV infection is crucial for effective monitoring and reducing long-term complications. BA diagnosis can also relies on imaging, liver function tests, and liver biopsy.[12]

Patients with biliary atresia who present with cholestasis (reduced bile flow) and persistent jaundice beyond 14 days of age typically show elevated total bilirubin levels in laboratory findings. This is characterized by direct bilirubin exceeding 1 mg/dL (17.1 μmol/L; when total bilirubin is <5 mg/dL [85.5 μmol/L]) or greater than 20% of total bilirubin (when total bilirubin is >5 mg/dL [85.5 μmol/L]).[13]

These results strongly indicate cholestasis. Additionally, elevated liver function tests (AST and ALT) suggest hepatocellular injury.[14] Additionally, a study by Hasohah et al., obtained that jaundice is the most common clinical feature of CMV infection in infancy. Hyperbilirubinemia or cholestasis (100%) and increased level of aminotranferases serum (77%).[15] Similar findings were reported in a study conducted by Reddy et al., most (71.7%) infants with CMV had raised SGPT level. But in their study, gamma-glutamyl transferase (GGT) was higher in only 30% of infants while Hasosah et al. found higher GGT in 77% of cases.[15, 16]

Abdominal ultrasound findings using 2 phase ultrasonography (USG) is also required to diagnose BA, such as parenchymal abnormalities, hepatic vascular system irregularities, spleen abnormalities, or the presence of cysts, further aid in the diagnostic evaluation.[14] Abdominal ultrasonography, as a non-invasive diagnostic tool, plays a pivotal role in confirming biliary atresia, especially as an initial screening method in infants presenting with elevated conjugated bilirubin levels.[17] It allows for early, prompt, and accurate diagnosis, thereby enabling timely surgical intervention when indicated.[17, 18] A recent study by Anindita et al. reported that abdominal ultrasound demonstrated an overall diagnostic accuracy of 73.7%.[17] One of the key ultrasonographic markers is the triangular cord (TC) sign, defined objectively as an echogenic anterior wall of the right portal vein (EARPV) measuring more than 4 mm on longitudinal imaging.[19] Additional sonographic findings include abnormal gallbladder morphology ($p = 0.01$) and the presence of hepatic subcapsular flow ($p = 0.04$).[17] Furthermore, the use of color Doppler ultrasonography has shown sensitivity and specificity of 100% and 86%, respectively, in detecting hepatic subcapsular flow.[20]

Another study by Lee et al. identified abnormal gallbladder morphology and increased triangular cord thickness (greater than 3.4 mm) as the most reliable predictors for diagnosing biliary atresia.[21] In a study involving 188 children with cholestasis who underwent two-phase ultrasonography, the diagnostic accuracy was found to be 86.3% following a 4-hour fasting period and 93.5% in the non-fasting state. The overall diagnostic accuracy for biliary atresia was 88.7% (157 out of 177 patients).[18]

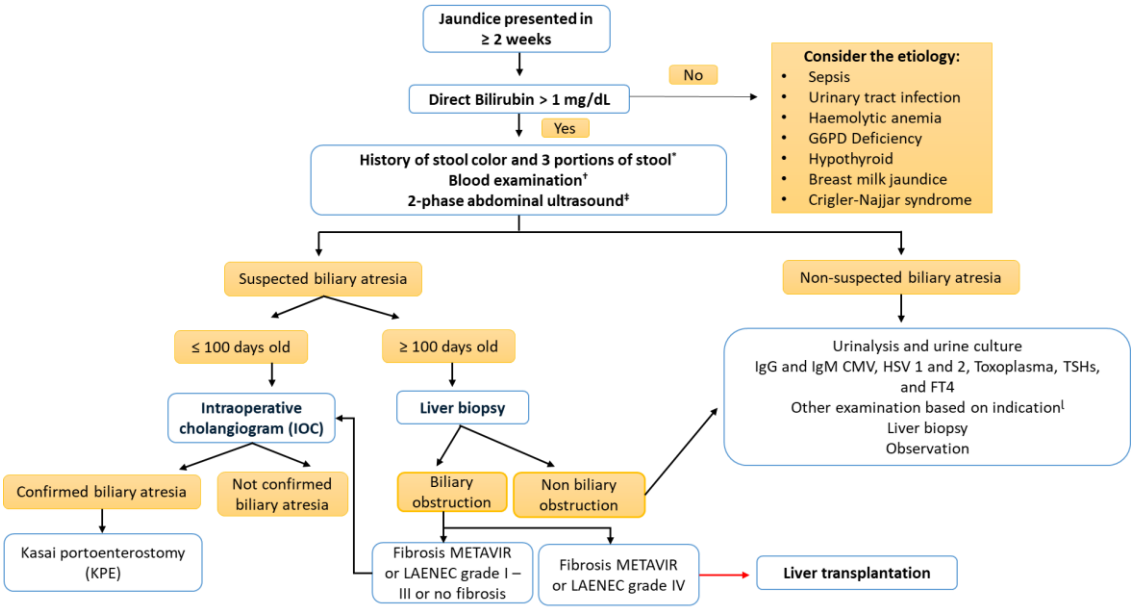
In cases of fetal CMV infection, the presence of specific IgM antibodies to cytomegalovirus (CMV) detected after the fourth week of life may suggest either congenital or perinatal infection. Studies conducted in Brazil have found that positive IgM to CMV prevalence between the second and fourth months of life ranges from 8.1% to 14.7%. When combined with the detection of CMV in urine through viral isolation in cultured cells, the prevalence of infection increases to approximately 30.9% to 38%. Importantly, the majority of these cases are asymptomatic.[22]

Dried blood spots, routinely collected from all newborns, have been investigated as a potential sample for polymerase chain reaction (PCR)-based CMV testing. However, a large-scale newborn screening study by Boppana et al. found that real-time PCR testing of dried blood spots had low sensitivity, failing to detect the majority of CMV-infected infants when compared to the standard saliva rapid culture method. This highlights the ongoing challenges in achieving sufficient sensitivity with dried blood spot testing for effective newborn CMV screening.[23]

CMV-positive BA is one of the theories underlying the pathogenesis of biliary atresia. [5] However, it is important for clinicians to be aware of other potential causes. Approximately 3% to 20% of children with biliary atresia present with an associated syndrome or other congenital abnormalities.[5, 24] Another proposed pathogenesis, aside from CMV-positive biliary atresia, is the Biliary Atresia Splenic Malformation (BASM) syndrome. Infants with BASM often present with unusual anomalies such as polysplenia (or occasionally asplenia), vascular abnormalities (including a preduodenal portal vein or absence of the inferior vena cava), situs inversus, and congenital heart defects. A case report by Allotey et al. described additional congenital anomalies such as esophageal atresia, jejunal atresia, and cat eye syndrome.[5, 25]

[26]Cystic biliary atresia (CBA) is the third form, which can be detected prenatally through fetal sonography.[5] Caponcelli et al. found that out of 270 infants with biliary atresia, 29 (9 males) were diagnosed with the cystic form. Antenatal ultrasonography detected abnormalities in 12 (41%) of these infants at a median gestational age of 22 weeks (ranging from 17 to 34 weeks). All infants exhibited conjugated jaundice, with a median total serum bilirubin concentration of 159 μmol/L (range: 50–337 μmol/L) at the time of surgery.[26]

The last but not least, the largest group is isolated biliary atresia (accounting for 70–80% of cases), formerly known as perinatal or acquired BA. Harpavat et al. reported that the exact onset of this type of biliary atresia remains unknown.[27] In contrast to CMV-positive BA—where patients are typically older at the time of diagnosis and undergo Kasai surgery later—isolated biliary atresia is believed to be acquired sometime after birth in otherwise healthy infants.[5, 27] However, the elevated direct/conjugated bilirubin (DB/CB) levels detected shortly after birth in their study suggest that biliary obstruction may already be present at birth. Based on these findings, the authors recommend screening all newborns for elevated DB/CB levels regardless of clinical appearance and total bilirubin (TB) levels. Hopefully these recommendations have the potential to transform the management of biliary atresia by enabling earlier identification of affected infants, even before clinically significant liver injury occurs.[27] **Figure 1.** presents the diagnostic algorithm for jaundice during the perinatal period.



* Stool color cards No. 1, 2, and 3 are used as early screening tools.

† Laboratory findings may show elevated levels of complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, albumin, prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), and blood glucose. A GGT level >250 U/L is highly suggestive of biliary atresia.

‡ The procedure should be preceded by a minimum fasting period of four hours to ensure optimal examination conditions.

Clinical suspicion of biliary atresia is based on the following features: normal birth weight, persistent pale or acholic stools, GGT >250 U/L, and characteristic ultrasound (USG) findings, including a non-contractile gallbladder, a small or absent gallbladder, presence of a triangular cord sign, a hepatic artery to portal vein ratio >0.45, hepatic artery diameter >1.5 mm, and detectable arterial flow in the subcapsular region of the liver.

Figure 1. Diagnostic algorithm for biliary atresia in the perinatal period.[28, 29]

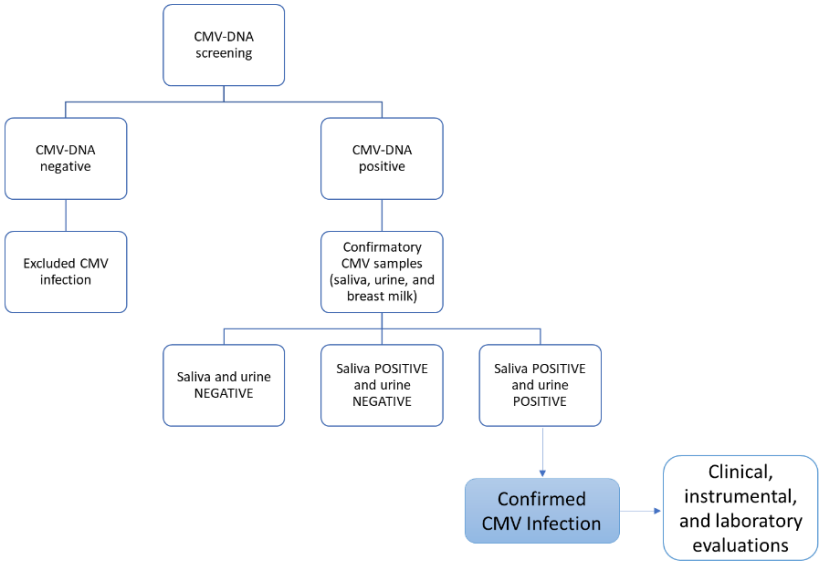


Figure 2. Diagnostic flowchart for Congenital or Perinatal CMV infection.[28, 30]

If CMV-positive biliary atresia is identified, what treatment should be administered?

For acquired CMV-positive BA, antiviral therapy should be administered. There are two treatment options:

1. Valganciclovir with a dose of 7xBody Surface Area (BSA)x Glomerular Filtration Rate (GFR) for 6 weeks and continue for 2 weeks, or
2. Ganciclovir for 2 weeks and continue with Valganciclovir for 4 weeks.

   The therapy can be stopped if the CMV PCR is negative.

While CMV congenital should be treated with Valganciclovir for 16 weeks and continue with 7 days of Valganciclovir. The antiviral therapy (AVT) included:

1. Oral valganciclovir at a dosage of 10–40 (up to 58) mg/kg per day or
2. Intravenous ganciclovir at a dosage of 5.3–11 mg/kg per day.

Antiviral treatment for patients with acquired CMV-positive BA requires regular monitoring.[28]

A prospective study by Parolini et al. investigated the use of adjuvant antiviral therapy in patients with CMV-positive BA following Kasai portoenterostomy (KPE). Treatment involved starting intravenous ganciclovir (5 mg/kg twice daily) within the first week after surgery, and in some cases, switching to oral valganciclovir (520 mg/m^2 twice daily) until CMV DNA levels became undetectable. The results suggest that this antiviral approach, particularly with oral valganciclovir, may counteract the

harmful effects of CMV. Although overall survival rates did not differ significantly between the Antiviral Therapy (AVT) group (100%) and the Control group (82%) (χ^2 = 1.3, P = 0.24), the AVT group showed a statistically significant improvement in native liver survival compared to the Control group (χ^2 = 4.1, P = 0.04).[31]

Retrospective studies examining outcomes in infants with congenital CMV infection, whose mothers received CMV hyperimmunoglobulin (HIG) during pregnancy, have indicated potential benefits. However, inconsistencies in confirming primary maternal CMV infection, variations in CMV HIG preparation and administration, and selection bias complicate the ability to draw definitive conclusions. On the other hand, maternal treatment with valacyclovir during pregnancy has shown a positive impact on fetal CMV infection outcomes. Researchers suggest that a randomized trial comparing valacyclovir treatment to standard care could help confirm these findings.[32]

Current treatment options are limited to a surgical procedure known as Kasai portoenterostomy (KPE). This surgical intervention is required for BA patients to restore bile flow and prevent liver failure. It is most effective when performed early, ideally within the first 60 days of life. However, KPE fails to improve the condition in approximately 50% of patients and does not resolve intrahepatic cholangiopathy. Additionally, BA often leads to complications such as fibrosis, portal hypertension, and liver failure. In many cases, liver transplantation becomes necessary, requiring lifelong immunosuppression, which significantly impacts the quality of life for BA patients. The Kasai procedure fails in approximately 50% of cases, often leading to the need for liver transplantation.[33]

Liver transplantation: When is it necessary?

Early diagnosis of BA is critical as a surgical Kasai portoenterostomy (KPE) may restore bile flow if performed prior to age 3 months and help prevent rapid progression of liver injury and development of cirrhosis. Unfortunately, the vast majority of affected children will eventually develop end-stage liver disease, with BA being the leading indication for pediatric liver transplantation.[34] Biliary atresia (BA) occurs exclusively in childhood and is the most common cause of chronic cholestasis and liver transplantation in children.[35] Kemme et al, summarize several indications and timing of liver transplantation, such as early failed KPE, late diagnosis (defined as age >90, 100 or 120 days), failure to thrive, recurrent bacterial cholangitis, jaundice-associated pruritus, portal hypertension, hepatopulmonary syndrome (HPS), hepatorenal syndrome, and hepatic malignancy.[36]

Other systematic reviews by Utterson et al. shows from 755 patients who will perform liver transplantation, more than 70% were under 1 years old, and 60% were female. Most (82%) were not hospitalized at the time of listing. Most had pediatric end-stage liver disease (PELD) scores between 10 and 20 (mean, 11.7; median, 12.1). More than

40% of patients had growth failure, although only 16% received nasogastric supplements. The mean height z-score at listing was 21.3 ± 1.8, and the mean weight z-score at listing was 21.4 ± 1.8 SD.[37]

Furthermore, what is the prognosis?

CMV-positive BA is associated with a poorer prognosis than CMV-negative BA. We assessed the outcome of CMV-positive BA based on several parameters reported in the literature, including jaundice clearance, incidence of cholangitis, native liver survival, and mortality.

Jaundice Clearance

A meta-analysis conducted by Zhao et al. demonstrated that patients with CMV-positive BA had a significantly lower rate of jaundice resolution. Eight studies with a total of 666 patients (283 CMV-positive BA, 383 CMV-negative BA) described jaundice clearance. The pooled OR was 0.47 (95% CI: 0.32–0.69, $p < 0.001$). Three studies reported jaundice clearance within 6 months. The pooled OR was 0.31 (95% CI: 0.18–0.53, $p < 0.001$).[38]Additionally, Shen et al. demonstrated in their research that CMV infection negatively impacts the prognosis of biliary atresia. In the group with cytomegalovirus infection, the rate of jaundice resolution post-surgery was notably lower ($P<0.05$) than those in the control group, while the occurrence of reflux cholangitis was higher ($P<0.05$). The histopathological analysis further indicated that liver fibrosis and inflammation were more advanced in the CMV infection group rather than the non-CMV infection group ($P<0.05$).[38]

A study conducted by Vig et al. shows a significant difference of mean total bilirubin between CMV-positive BA and CMV-negative BA. Six months post-surgery, the CMV-negative group demonstrated significantly lower mean total bilirubin levels (0.96 mg/dL ± 0.66) compared to the CMV-positive group (5.76 mg/dL ± 4.32). In addition, a marked difference was observed in direct bilirubin levels between the two groups, with the CMV-negative group averaging 0.47 mg/dL, while the CMV-positive group had a considerably higher mean of 3.42 mg/dL. Their study found that, according to the criteria for a successful Kasai portoenterostomy—defined as a serum bilirubin level below 2 mg/dL at six months—all patients the CMV-negative group met this benchmark. In contrast, four infants in the CMV-positive group had total serum bilirubin levels exceeding 2 mg/dL at the six-month follow-up. Additionally, one patient in the CMV-positive group succumbed to liver failure during the postoperative period.[39]

Jaundice clearance following Kasai portoenterostomy (KPE) also showed a significant association with CMV status. a study by Zani et al. showed that only 3 out of 20 (15%) infants with CMV-positive BA achieved jaundice clearance, compared to 57 out of 109 (52.2%) in the CMV-negative (control) group, a difference that was statistically

significant [P = 0.002; OR 5.9, 95% CI: 1.6–21]. Regression analysis further confirmed that CMV positivity was significantly linked to reduced likelihood of jaundice clearance (P = 0.011; 95% CI: 0.188–0.686), with CMV-positive status reducing the log odds of jaundice clearance by 1.671. In contrast, the age at the time of KPE was not significantly associated with jaundice clearance (P = 0.09; 95% CI: 0.98–1.00). During the study period, two infants from the control group required primary liver transplantation.[6]

Interestingly, infants with CMV-positive BA who underwent surgery between 51 and 60 days of age had the highest rate of jaundice clearance (76.2%), compared to those who had surgery before 40 days of age (25%) or between 41 and 50 days of age (50%) (P = 0.036). A similar pattern was observed in syndromic BA with associated malformations, where infants who underwent surgery between 51 and 60 days also had the highest rate of jaundice clearance (77.8%), in contrast to those who had surgery before 40 days of age (25%) or between 41 and 50 days of age (50%) (P = 0.017).[40]

Another study reported notable differences among biliary atresia patients who underwent the Kasai procedure, depending on their CMV status. The 21 CMV-positive patients had significantly higher total bilirubin levels, lower platelet counts, a longer time to jaundice resolution following surgery, and a worse aspartate aminotransferase to platelet ratio index (APRI), suggesting more advanced liver fibrosis. Liver ultrasounds in these patients also revealed larger spleens and more severe inflammation and fibrosis compared to CMV- patients. In contrast, the CMV-negative group showed more pronounced lobular cholestasis, though there was no significant difference between the two groups in terms of ductular cholestasis.[40]

Incidence of Cholangitis

Cholangitis is a common and serious complication of biliary atresia, often linked to poor outcomes following Kasai portoenterostomy (KPE). Repeated cholangitis can promote fibrosis, obstruct bile flow, and exacerbate jaundice and cirrhosis. Patients with active CMV infection (defined as PCR or pp65-positive with or without IgM positivity) had significantly higher rates of cholangitis after the Kasai procedure, along with more extensive bile canaliculi hyperplasia and broader areas of inflammation compared to those who were CMV-negative or had past infection (IgM and/or IgG positive but pp65-negative).[2] A meta-analysis by Zhao et al. also showed that from two studies including 74 patients reported cholangitis data. The pooled OR was 2.76 (95% CI: 0.57–13.45, p = 0.21) and heterogeneity was not significant (I2 = 0.0%, p = 0.534). There was no significant difference in cholangitis incidence between CMV-positive BA and CMV-negative BA patients.[38]

A retrospective study conducted by Shen et al. compared between CMV-positive BA group and CMV-negative BA group based on their prognosis after Kasai procedure

showed that one patient (20%) in the CMV- group was re-hospitalized for treatment of reflux cholangitis 6 months after operation. Two patients (18%) in the CMV-positive group were hospitalized 2 to 3 times for increased levels of serum bilirubin with rectal temperature higher than 38.5ºC with unknown reasons. Four patients (36%) in the CMV-negative group had reflux cholangitis in 6 months post-operation. There was no significant difference between the CMV-negative group and the CMV-positive group, but the incidence of reflux cholangitis in the CMV infection group was obviously higher than those in the other two groups ($P<0.05$).[33] Interestingly, another study conducted by Song et al. showed infants with CMV-positive BA who underwent surgery between 51 and 60 days of age exhibited the lowest incidence of cholangitis (33.3%), as compared with infants who underwent surgery at less than 40 days of age (50% incidence) or between 41 and 50 days of age (40% incidence) ($P=.045$).[40]

Native Liver Survival (NLS)

A single-center study from the UK involving 121 infants with biliary atresia found that those who were CMV IgM-positive at diagnosis were older at presentation, had more severe liver inflammation and fibrosis on biopsy, and experienced significantly worse outcomes after hepatic portoenterostomy (HPE), including lower native liver survival and higher mortality, compared to CMV-negative infants.[6]

Two-year survival rates of autologous liver in CMV-positive BA were significantly lower than in cystic BA, however, there was no significant difference when compared with syndromic BA and associated malformations. Thus, the impact of etiologic heterogeneity on 2-year survival rates of autologous liver may differ between infants who undergo surgery at less than 60 days of age as compared with those who undergo surgery at greater than 60 days of age.[40]

Histopathological findings

In a study by Vig et al., all patients in the CMV-positive group and three in the CMV-negative group had fibrosis greater than Grade 2. Additionally, four CMV-positive patients had progressed to nodular cirrhosis. These findings suggest that CMV-positive BA patients tend to present with more advanced liver fibrosis. However, when the degree of fibrosis was statistically correlated with CMV status, the association was not significant ($P = 0.50$). [39]

Mortality

For patients who ultimately need liver transplantation, CMV-positive BA also comes with a poorer prognosis. Kemme et al. reported that cytomegalovirus infection in biliary atresia is linked to an increased risk of pretransplant mortality. The probability of death prior to transplantation was significantly higher in the CMV-positive group compared to the CMV-negative group ($p = 0.013$). Specifically, 4 out of 29 (14%)

CMV-positive participants died before receiving a liver transplant, compared to 8 out of 220 (4%) CMV− participants. Furthermore, CMV-positive infants with BA had a higher probability of pretransplant death within 40 months after hepatoportoenterostomy (HPE) compared to their CMV-negative counterparts.[36] Zani et al. also reported that there was a significantly higher mortality rate in the CMV BA group (n=5, 25%) in comparison with controls (n=7, 6.3%; P=0.02).[6]

Several studies have indicated that patients with CMV-positive BA tend to develop symptoms later and undergo surgery at a later stage. Furthermore, CMV-positive BA was associated with more severe fibrosis and inflammation during surgery compared to CMV-negative BA. Notably, CMV IgM-positive patients following the Kasai procedure exhibited a worse prognosis, which improved with antiviral treatment (AVT).[38] **Table 1.** summarizes the comparison of prognosis and therapeutic outcomes of antiviral treatment between CMV-positive BA and CMV-negative BA groups.

Table 1. Comparative table of prognosis and therapeutic outcomes of antiviral use between CMV-positive BA and CMV-negative BA groups

	CMV-positive BA	CMV-negative BA
Jaundice Clearance	Earlier	Later (6 months)
Incidence of Cholangitis	Higher	Lower
Fibrosis Grade and Inflammation	Higher	Lower
Native Liver Survival	Lower	Higher
Mortality	Higher	Lower
Antiviral treatment impact	Beneficial	Not Applicable

Prevention

Although the direct role of cytomegalovirus (CMV) infection in the development of biliary atresia remains a subject of ongoing debate, several findings have demonstrated a correlation between neonatal cholestasis and CMV infection. In a study conducted by Setyoboedi et al. among 113 infants with cholestasis, 94.7% (n = 107) were found to be CMV IgG-positive. Based on these findings, the researchers recommended that screening for TORCH infections should be considered in all infants presenting with cholestasis.[41] However, in contrast, a study conducted by Zhao et al. revealed that the incidence of cholestasis was similar between the biliary atresia groups with CMV IgM-positive and CMV IgM-negative status. Thus, the presence of CMV infection did not influence the conventional predictive parameters used to distinguish biliary atresia from intrahepatic cholestasis.[42]

Conclusion

In conclusion, biliary atresia remains a critical condition that requires close attention, characterized by elevated levels of total bilirubin, and is still a leading cause of chronic cholestasis and liver transplantation in children. Given the broad spectrum of potential etiologies, cytomegalovirus (CMV) infection should be prioritized in the diagnostic workup due to its association with poorer outcomes. In addition to abdominal ultrasonography as non-invasive diagnostic tool for biliary atresia, CMV detection via polymerase chain reaction (PCR) serves as a valuable diagnostic tool for the etiology. CMV-positive BA represents a distinct and clinically significant subset of biliary atresia with a demonstrably poorer prognosis compared to CMV-negative cases. CMV-positive BA is associated with delayed diagnosis, more severe liver inflammation and fibrosis at presentation, reduced jaundice clearance after Kasai portoenterostomy (KPE), increased incidence of postoperative cholangitis, and lower native liver survival, often leading to earlier liver transplantation or pretransplant mortality. Therefore, we hope that future studies will explore various strategies for early detection of infection, with the aim of reducing the prevalence of CMV infection in biliary atresia and mitigating its associated poor prognosis.

Acknowledgement

The author would like to express sincere gratitude to all those who contributed to this work.

Conflict of Interest

None declared.

Funding Statement

This study was not supported by any external funding.

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