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Detection of Cytomegalovirus Infection in Infants with Biliary Atresia: A Meta-analysis

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Abstract

Objectives Biliary atresia (BA) is the most common indication of liver transplantation in children. Several reports attributed BA to both prenatal and perinatal etiologies, including a viral infection-induced autoimmune response that targets the bile ducts. *Cytomegalovirus* (CMV) remains the most common virus being linked to BA. This meta-analysis aimed to estimate to what extent CMV infection is detected in patients with BA.

Methods This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The databases of MEDLINE, Embase, Scopus, WHO-Virtual Health Library (VHL), ScienceDirect, and Google Scholar were used for the systematic search. The risk of bias was assessed using the Newcastle–Ottawa scale. Random effects model was used to estimate the pooled prevalence estimate with the corresponding 95% confidence interval (CI) using Comprehensive Meta-Analysis Software version 3.3.

Results A total of 19 studies that fulfilled the eligibility criteria were included in the meta-analysis. The total number of infants with BA was 630 patients, and the pooled overall prevalence of CMV infection among them was 25.4% (95% CI: 15.9%–38.0%). There was high heterogeneity among studies ($I^2 = 85.1\%$, $p < .001$), and subgroup analyses showed significant regional differences ($X^2 = 48.9$, $p < .001$). Data on the prognosis of CMV-associated BA were scarce and obtainable from few studies that suggested an association between detection of CMV infection and poor prognosis of BA.

Conclusions The limited available data demonstrates that the rate of detection of CMV infection is high in infants with BA. There is still a need for large studies with appropriate controls for obtaining more reliable results about the various aspects of the association between CMV infection and BA.

Keywords

- Cytomegalovirus
- biliary atresia
- prevalence
- meta-analysis

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Background

Biliary atresia (BA) is a common cause of neonatal cholestasis, characterized by extensive fibrosing inflammation of the extrahepatic bile duct, leading to obstruction of bile flow and subsequently resulting in permanent liver damage if not early managed.[1–3] BA is treatable by the Kasai portoenterostomy, which prevents liver injury, caused by cholestasis, if done early.[1,2,4] Despite using Kasai operation, BA is still a leading cause of end-stage liver disease and the most common indication of liver transplantation in children.[1,4–6]

BA is believed to be a disorder of multifactorial etiology, involving both prenatal and perinatal factors.[1,6] Several studies proposed a possible infectious etiology; primarily, a viral infection-induced auto-immune response that targets the bile duct, leading to chronic fibrosclerosing injury.[1,2,4] Patients with BA have been tested for several viruses in an attempt to determine the viruses associated with the disease onset. Among these viruses, *Cytomegalovirus* (CMV) remains the most common virus being linked to BA.[5,7,8] Fischler et al found that immunoglobulin deposits on the hepatocellular canalicular membrane were significantly higher in biopsies from CMV infected patients with BA than their controls.[9] Additionally, the histological findings in the porta hepatis and liver biopsy samples of patients with BA showed that perinatal CMV infection is an initiator of bile duct damage, supporting the link between CMV infection and BA.[10,11]

Worldwide, several studies assessed the prevalence of CMV infection in infants with BA. These studies gave different results of the prevalence of CMV infection in infants with biliary atresia. To the best of our knowledge, there is no meta-analysis assessing the extent of CMV detection in BA patients. Moreover, establishing the role of perinatal viral infection in the pathogenesis of BA could propose and raise the question of a beneficial effect of antiviral as adjuvant therapy to manage and modulate the clinical outcome of BA. A more inclusive consideration of this systematic measurement would help show the magnitude of this finding and aid in a better understanding of the disease etiology and prognosis.

Methods

Search Strategy and Inclusion Criteria

In this study, we followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] We searched the databases of MEDLINE, Embase, Scopus, WHO-Virtual Health Library (VHL), ScienceDirect, and Google Scholar for all studies which assessed the association between CMV infection and BA up to September 2019. The search words used were "*Cytomegalovirus*," "CMV," and "Biliary atresia" to ensure the maximal coverage of possible literature.

The inclusion criteria were all studies published in English that presented sufficient data for estimation of the prevalence of CMV infection in patients with BA. If two or more studies had the same patient population, the study with more complete data or larger sample size was included to avoid duplication. Case reports, case series, editorials, abstracts, reviews, and studies lacking the data of interest were excluded.

Since BA is a congenital malformation, we included only studies that used a reliable method for diagnosing congenital CMV infection (viral deoxyribonucleic acid [DNA] detection by polymerase chain reaction [PCR], viral isolation by culture, and viral antigen detection).[13–15] Studies that relied only on serological testing were not included because the presence of CMV-immunoglobulin G (IgG) does not differentiate between infant infection and transplacental transfer of maternal antibodies, and the presence of CMV-IgM is not sufficiently sensitive and does not differentiate between the congenital infection and acquired infection in the early neonatal period.[13,14]

The titles and abstracts of all papers retrieved from this search were screened for potential inclusion in this review. Then, relevant studies were reviewed (full text) for inclusion, according to the defined eligibility criteria, and any disparity between the reviewers was resolved by discussion and consensus. The risk of bias was assessed using the Newcastle–Ottawa scale (NOS) for studies quality, a tool that determines the quality based on the selection of the study group, comparability of groups, and ascertainment of the exposure and outcomes. Data was extracted using a data extraction form developed to extract data of authors, study region, year of publication, diagnostic methods used for detection of CMV infection, number of patients with BA, and number of patients with confirmed CMV infection.

Statistical Analysis

The pooled prevalence from the random-effects models with the corresponding 95% confidence interval (CI) was calculated using Comprehensive Meta-Analysis Software version 3.3. Heterogeneity among studies was estimated using the I^2 statistics, and publication bias was estimated through visual examination of the funnel plot and Begg's test.[16] To explore the sources of heterogeneity, we conducted subgroup analyses and meta-regression to determine the extent to which variables of interest moderated the overall result. Moreover, a sensitivity analysis was done by recalculating the pooled estimate by omitting studies. This was done to evaluate the effect or weight of each group of studies on the overall result. For the purpose of this review, the sensitivity analyses were performed to test whether the method of CMV detection affected the overall result. For subgroup analysis, the Chi-square (X^2) test was used to assess the differences between the categorical subgroups, and the significance level was set at $p < 0.05$.

Results

The schematic flow of study identification and selection process is presented in (►Fig. 1). The initial search retrieved records for 1584 published articles. We excluded 335 and 1156 articles that were duplicated in the databases or irrelevant articles, respectively. The remaining 84 studies were retrieved for a full-text assessment, and 65 studies were subsequently omitted because of a lack of sufficient

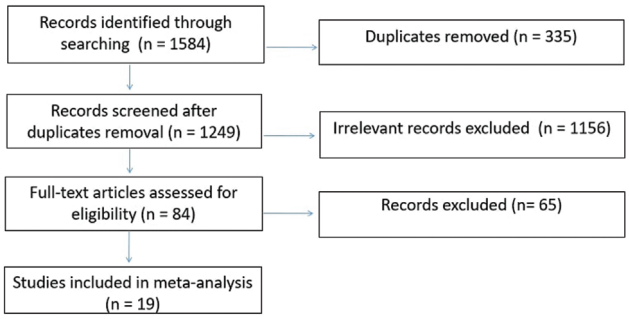

Fig. 1 The flow diagram for the process of study selection and systematic review of literature.

data for estimation of the outcomes of interest. Finally, a total of 19 studies published from 1980 to 2020, which met the eligibility for data extraction and analyses were used for the quantitative synthesis; nine studies from Asia, five studies from Europe, four studies from the Americas, and a study from Africa.[17–35] The main characteristics of these included studies are shown in ►**Table 1**.

Meta-analysis showed that CMV was detected in 25.4% (95% CI 15.9%–38.0%) of the patients with BA (►**Fig. 2**). No publication bias was detected on visual examination of the funnel plot (►**Fig. 3**) and from the results of Begg's test ($p = 0.38$). Duval and Tweedie trim and fill method showed that no potential studies are missing. However, there was high heterogeneity among studies ($I^2 = 85.1\%$, $p < 0.001$). In 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). There was a statistical difference in prevalence between the aforementioned geographical areas ($X^2 = 48.9$, $p < 0.001$). A meta-regression analysis was done to analyze whether the study period affected the heterogeneity among studies in this meta-analysis, and the results showed that the years were not correlated with the outcome (coefficient 0.054: $p = 0.075$). The sensitivity analyses showed some changes in the pooled prevalence estimates (from 22.2% for antigen detection to 35.0% for PCR).

Data on the association between viral infection and the risk of poor prognosis adverse outcome of BA were scarce and obtainable from few studies. Furthermore, the wide variability in defining and measuring the clinical outcome and prognosis of BA among studies made direct analysis and comparisons of the results across studies difficult. Among these clinical findings, Fischler et al found that infants CMV-associated BA had a more pronounced enlargement of the liver and significantly higher levels of serum bilirubin level.[19] Shen et al found that patients with CMV-associated BA had a higher degree of liver fibrosis, higher incidence of cholangitis, and longer time to achieve jaundice clearance.[23] On the other hand, Schukfeh et al showed a nonsignificant association between CMV-associated BA and prognosis after Kasai

Table 1 Descriptive summary of the studies included in the review

Study	Year	Country	Method of detection of CMV infection	Patients with BA	Patients with CMV-associated BA	NOS results
Numazaki et al[17]	1980	Japan	Viral isolation (culture)	18	2	6
Tarr et al[18]	1996	USA	Viral isolation (culture)	23	4	6
Fischler, et al[19]	1998	Sweden	PCR	18	9	6
Domiati-Saad[20]	1998	USA	PCR	12	0	5
Jevon et al[21]	1999	Canada	PCR	12	0	5
Rauschenfels et al[22]	2004	Germany	PCR	74	8	7
Shen et al[23]	2004	China	Antigen detection	27	10	8
Fjær et al[24]	2005	Norway	PCR	10	2	5
De-Thommaso et al[25]	2005	Brazil	PCR	33	9	5
Goedhals et al[26]	2008	South Africa	Antigen detection	42	1	6
Yaghobi et al[27]	2010	Iran	PCR	34	0	5
Xu et al[28]	2011	China	PCR	85	51	7
Soomro et al[29]	2011	Pakistan	PCR	33	14	5
Schukfeh, et al[30]	2012	Germany	PCR	70	8	7
Goel et al[31]	2018	India	PCR	14	11	5
Gou et al[32]	2018	China	Antigen detection	38	6	7
Situmorang et al[33]	2018	Indonesia	PCR	16	7	6
Meshram et al[34]	2020	India	PCR	21	19	6
Smith et al[35]	2020	UK	PCR	50	8	7

Abbreviations: BA; biliary atresia; CMV, Cytomegalovirus; NOS, Newcastle–Ottawa scale; PCR, polymerase chain reaction.

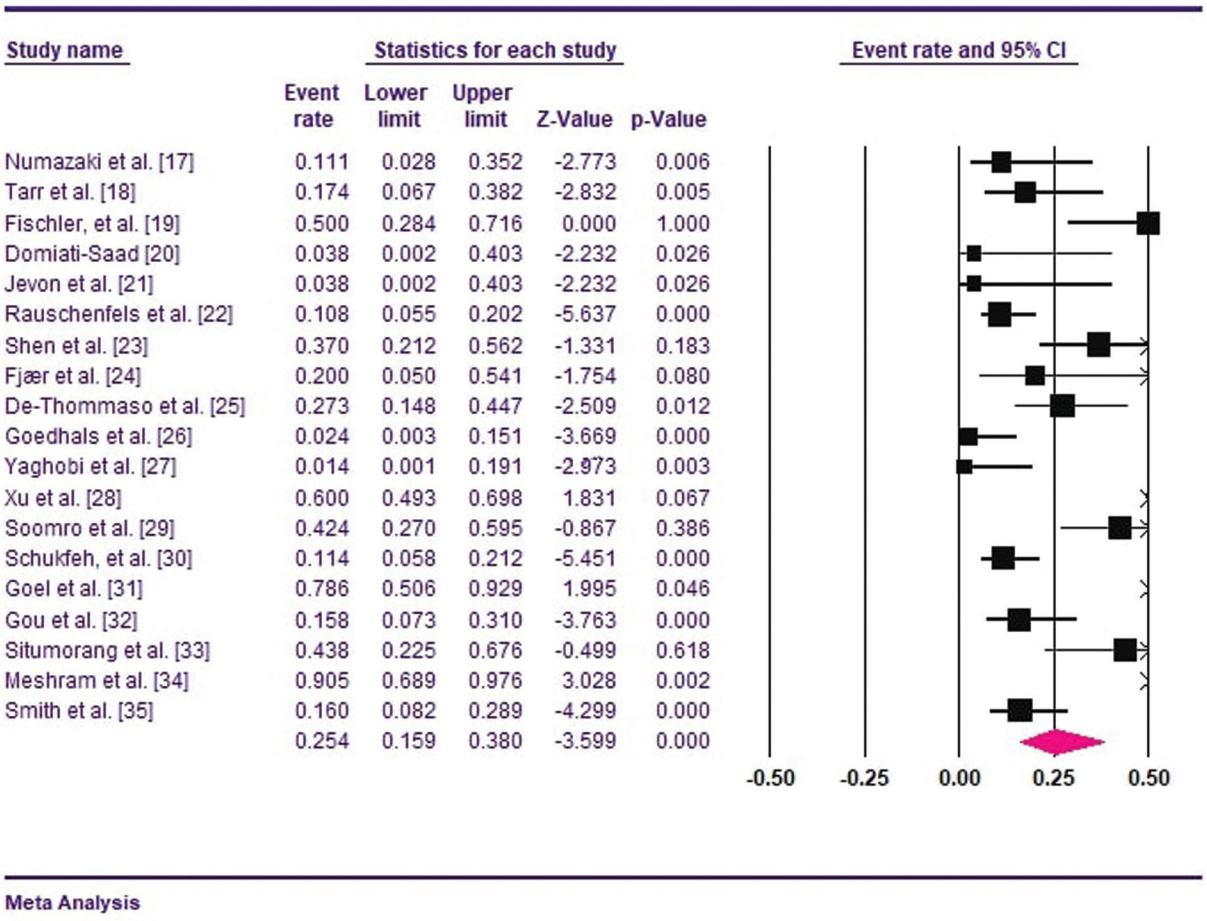

Fig. 2 Pooled prevalence of Cytomegalovirus (CMV) infection among patients with biliary atresia (BA).

portoenterostomy in terms of laboratory parameters and survival with native liver.[30]

Discussion

CMV is a well-known cause of congenital viral infections in humans, and it has been proposed as a possible etiologic agent in the pathogenesis of BA. A previous meta-analysis conducted in 2007 reported that the overall birth prevalence of congenital CMV infection in the general population was only 0.64%, and the majority of the cases were asymptomatic.[36] However, this meta-analysis showed a remarkably higher prevalence of CMV infection in infants with BA (25.4%) than that of congenital CMV infection in the general population.

The studies included in this meta-analysis were mainly from the Americas, Asia, and Europe, while only one study was from Africa. Although there is limited literature published on the association between CMV infection and BA, the available data demonstrate that CMV infection is common in BA as around one-quarter of the infants with BA had evidence of CMV infection, using one of the more reliable methods of CMV detection (viral DNA detection by PCR, viral isolation by culture, and viral antigen detection).

The discrepancy between prevalence rates reported from the reviewed studies might be partially explained by the differences in sensitivity of the detection method used or by the presence of other etiological agents implicated in the pathogenesis of BA. This meta-analysis showed that CMV infection in patients with BA had regional epidemiological differences. While rates of CMV infection have been reported to be considerably lower in most European and American countries, the prevalence rate tends to be higher in Asian countries. This finding is consistent with a socioeconomic link with CMV that has been well-established in several studies, showing that CMV prevalence is higher in individuals of areas of lower socioeconomic groups.[37] Furthermore, some studies demonstrate that BA is more prevalent in Asia than in Europe; it occurs in ⅕ to ⅛,000 live births in Asia and 1/18 to 1/20,000 children in Europe, although no ethnic differences have been demonstrated.[21,38] Also, the regional differences in times of CMV epidemics could aid in the understanding of this variation.[5]

Davenport et al have classified BA into four groups: isolated BA, cystic BA, syndrome BA with associated malformation, and CMV-associated BA.[39] Among these types of BA, several studies showed that the CMV-associated BA yielded the worst prognosis.[23,40] Shen et al reported that the CMV infection group had a lower rate of jaundice disappearance and a higher incidence of postoperative ascending cholangitis, a significant complication of BA.[23] Zani et al findings suggest that CMV-associated BA is a distinct etiological and

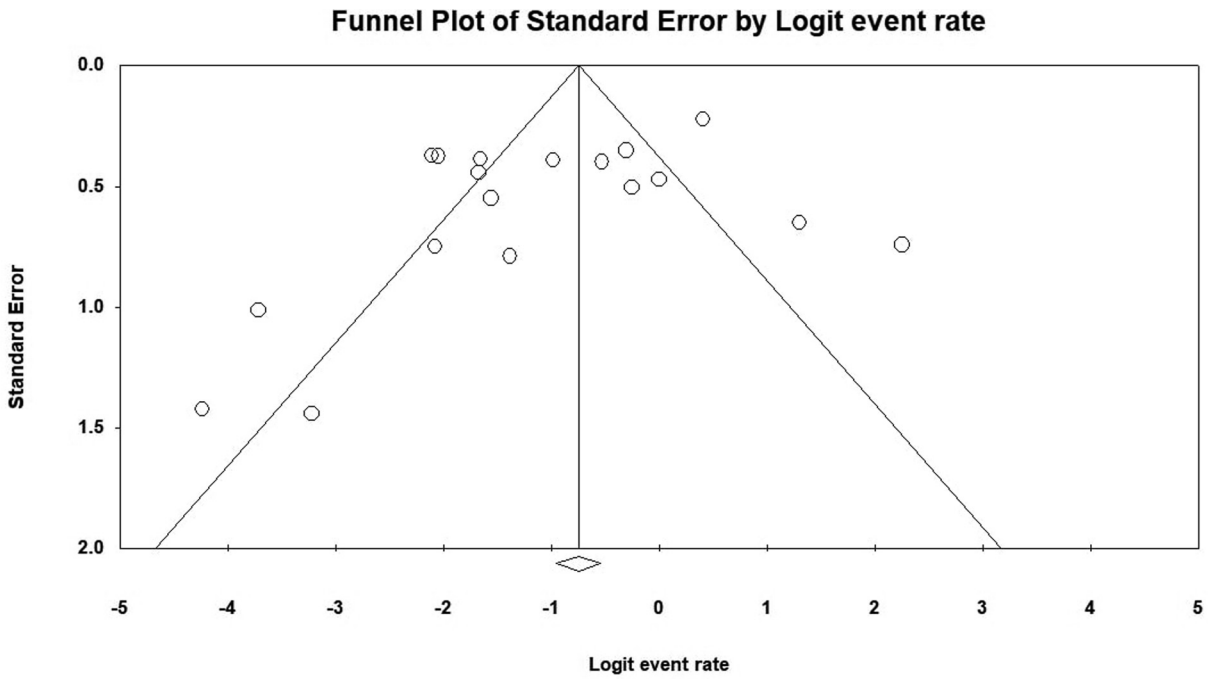

Fig. 3 Funnel plot for assessment of the publication bias.

prognostic subgroup, with reduced clearance of jaundice, native liver survival, diminished response to Kasai portoenterostomy, and increased mortality.[41] Because of the lack of uniformity across the included studies, a systematic assessment of the prognosis of CMV-associated BA could not be done.

Another important concern claimed by several authors regarding the association between CMV infection and BA is that detection of CMV infection might confound the clinical evaluation of neonatal jaundice caused by BA and may lead to misdiagnosis, late referral, and a delay in therapeutic surgery. This usually occurs when the condition is misdiagnosed as neonatal hepatitis secondary to CMV infection.[25,26,40]

There is a suggested role of antiviral therapy in the treatment of BA patients infected with CMV, and it could be a possible intervention that might improve outcomes of BA.[23,25] A recent trial done by Parolini et al showed that antiviral treatment with valganciclovir and ganciclovir appeared to improve outcomes in infants with CMV-associated BA.[42] Shen et al reported a case of a 2-month-old girl with BA who had persistent jaundice after 1 month of Kasai's operation surgery, and she was treated with valganciclovir for 6 weeks.[43] However, there is a need for more trials to confirm the effect of antiviral treatment among those patients.

Limitations

This meta-analysis emphasized the high rate of CMV-associated BA but did not prove causality. The main limitation to be considered in the current review is the paucity of publications on viral infections in BA. Data on the association between viral infection and the risk of poor prognosis adverse outcome of BA was obtainable from few studies. Another limitation is the inclusion of studies published only in English, which could compromise representativeness.

Conclusions

This review provided a comprehensive view of the high rate of detection of CMV infection in infants with BA (25.4%) compared with the previously reported rate of CMV infection among the general population. However, there is still a need for large prospective multicenter studies with appropriate controls to examine various aspects of the association between CMV infection and BA. The findings of this review should be considered in future prognostic models that may be made when exploring the clinical outcomes of BA.

Authors Contribution

S.M. conceptualized the research idea and designed the study; S.M., A.A., M.E. and A.I. undertook articles searching, articles assessment, and review; S.M., M.E., and A.E. undertook data extraction and analysis; All authors interpreted the results and drafted the manuscript. All authors revised and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

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