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Original Article

Predictor of Liver Biochemistry Improvement in Patients with Cytomegalovirus Cholestasis after Ganciclovir Treatment

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Cholestasis resulting from cytomegalovirus (CMV)-induced hepatitis manifests in 40% of patients with a CMV infection. Ganciclovir treatment in children with CMV infections has proven to be highly effective. Until now, there are very few studies have identified predictive factors for liver biochemistry improvement after ganciclovir therapy. This study aimed to identify the predictors of liver biochemistry improvement in patients with CMV cholestasis after ganciclovir treatment.
Methods: A retrospective cohort study was conducted using medical records from Dr. Sardjito General Hospital Yogyakarta, Indonesia from 2013 to 2018. CMV cholestasis was confirmed based on serum CMV IgG and IgM positivity and/or blood and urine CMV antigenemia positivity. Incomplete medical records and other etiologies for cholestasis, such as biliary atresia, choledochal cyst, metabolic diseases, and Alagille syndrome, were excluded. Patient age at cholestasis diagnosis and ganciclovir treatment, duration of CMV cholestasis, history of prematurity, central nervous system involvement, and nutritional status were analyzed and presented as an odds ratio (OR) with a 95% confidence interval (95% CI).
Results: CMV cholestasis with ganciclovir therapy was found in 41 of 54 patients. Multivariate analysis showed that a shorter duration of CMV cholestasis (OR: 4.6, 95% CI: 1.00-21.07, p=0.04) was statistically significant for liver biochemistry improvement after 1 month of ganciclovir treatment. The remaining factors that were analyzed were not significant predictors of liver biochemistry improvement in patients with CMV cholestasis after ganciclovir treatment.
Conclusion: A shorter duration of CMV cholestasis is the predictor of liver biochemistry improvement after 1 month gancyclovir treatment.

Keywords: Cytomegalovirus cholestasis; Liver biochemistry; Ganciclovir

INTRODUCTION

Cytomegalovirus (CMV) is a type of herpesvirus that can cause congenital infections, resulting in multiorgan disorders in infected children [1]. Previous studies have shown that the involvement of CMV infection in hepatobiliary disease is very high (at approximately

40%), where the virus replicates in both hepatocytes and cholangiocytes [2,3]. The clinical impact of CMV cholestasis in children is progressive liver failure and death [4]. In the United States, approximately 20,000 to 40,000 babies are born with congenital CMV infection per years [5]. Several studies have reported that the incidence of CMV infection with hepatobiliary organ involvement is approximately four cases per 100,000 each year [5,6]. Based on medical record data from Dr. Sardjito General Hospital in Yogyakarta, Indonesia, there were 207 cases of children infected with CMV between 2013 and 2018, with 54 cases recorded as CMV cholestasis. Forty-one of these cases were children with complete medical records who received ganciclovir therapy. Proper treatment of CMV cholestasis generally results in good outcomes. Ganciclovir is an effective treatment option for CMV infection because it reduces viremia by inhibiting viral DNA synthesis [7]. Tezer et al. [4], reported that 75% of children with CMV cholestasis had improved liver biochemistry following ganciclovir treatment. Cholestatic patients had more severe nutritional deficits, especially in nutrients related to age-appropriate height and weight [8]. To the best of our knowledge, research on the factors predicting liver biochemistry improvement in children with CMV cholestasis after ganciclovir therapy in Indonesia has not been conducted before; therefore, it was important that this research be taken up in order to obtain information on the possible prognostic factors of liver biochemistry improvement to enhance the quality of life in these patients.

MATERIALS AND METHODS

This study was a retrospective cohort study that examined medical record data from Dr. Sardjito General Hospital from January 2013 to December 2018. The inclusion criteria were as follows: patients aged 0 days to 3 years who had clinical symptoms with cholestasis and CMV infection (confirmed by serum CMV IgM and IgG antibody positivity and/or blood and urine CMV antigenemia positivity), and patients who received ganciclovir therapy at Dr. Sardjito General Hospital in the study period. Exclusion criteria were cholestasis with other comorbidities, such as biliary atresia, choledochal cyst, metabolic anomaly, and Alagille syndrome; patients who refused ganciclovir therapy; and/or patients who had incomplete medical record data.

The dependent variable was the improvement of liver biochemistry. The independent variables were age at cholestasis onset, duration of CMV cholestasis, age at ganciclovir therapy initiation, history of preterm birth, central nervous system involvement, and nutritional status. Abnormal liver biochemistry was defined by a value exceeding the upper reference limit for one or more liver biochemistry markers, such as bilirubin, aminotransferase, prothrombin time (PT), and activated partial thromboplastin time, except for serum albumin. Cholestasis was defined by tea-colored urine and pale stools during the icteric stage of disease and an increase in direct bilirubin to more than 50% of the total bilirubin. Ganciclovir therapy was administered to children with cholestasis and simultaneous central nervous system involvement, serum CMV IgM and IgG antibody positivity, and/or blood and urine CMV antigenemia positivity. The ganciclovir dosage was 6 mg/kg body weight, administered intravenously every 12 hours. Improvement of liver biochemistry was defined by a decrease of 50% in at least one liver biochemistry parameter with no deterioration of other parameters within 30 (±15) days after comparing liver biochemistry results pre- and post-ganciclovir administration. Age at cholestasis onset was defined as the age at the first development of icteric stage symptoms. Duration of CMV cholestasis was defined as the length of time from when the patient was diagnosed

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with CMV cholestasis up to the administration of ganciclovir therapy. Age at ganciclovir therapy was defined as the age the patient first received ganciclovir therapy. Nutritional status was defined as anthropometry measurements, classified according to the World Health Organization-2006 standard, taken before ganciclovir administration, which is an ideal method for monitoring patients with cholestasis. The involvement of the central nervous system was defined as patients with microcephaly, hearing loss, calcification, and chorioretinitis. Microcephaly was defined by a head circumference of >2 standard deviations below the mean compared to age and sex. Hearing loss was defined as a result of "refer" on an otoacoustic emissions screening exam and/or whether the brainstem evoked response audiometry test showed mild to severe hearing loss. Calcification was diagnosed by head ultrasonography. Chorioretinitis was diagnosed by fundoscopy and defined as active chorioretinal inflammation and/or by detection of leukocytes in the vitreous humor on ophthalmic examination. A history of preterm birth was defined as a gestational age <37 weeks calculated from the first day of the last menstrual period.

Data were analyzed using SPSS version 20.0 (IBM Co., Armonk, NY, USA). The relationship between the independent variables and the dependent variable was analyzed by bivariate statistical analysis (chi-square test). Variables with *p*-values <0.25 from the bivariate analysis were further analyzed with multivariate logistic regression methods. Multivariate analysis results are reported as an odds ratio (OR) with a 95% confidence interval (95% CI). This study was approved by the Medical and Health Research Ethics Committee on August 31, 2018, with licensing number KE/FK/0917/EC at Universitas Gadjah Mada, Yogyakarta, Indonesia. As a teaching hospital, all patients or guardians are required to sign an informed consent form related to data usage for education and research purpose at patients' admission time.

RESULTS

There were 41 eligible cases of CMV cholestasis in Dr. Sardjito General Hospital during January 2013 to December 2018. The basic characteristics of the patients are shown in **Table 1**. The occurrence of improved liver biochemistry after ganciclovir therapy was 68.3% (28/41). The mean age at cholestasis presentation was 3.32±2.76 months.

Clinical characteristics of CMV cholestasis

All children (100%) had clinical manifestations of jaundice. The most common additional clinical manifestations were tea-like urine (97.6%) and hepatomegaly (90.2%). No maternal CMV infection result was noted in the medical records. Most patients were of normal birth weight (61.0%), and twelve patients (29.3%) were born preterm at <37 weeks. The presence of fat malabsorption in CMV cholestasis resulted in some undernourished children (41.5%). Almost all children with CMV cholestasis had central nervous system involvement, with the most common clinical manifestation being microcephaly (87.8%). The main side effect post-ganciclovir therapy was hematological disorder, with anemia (39.0%) being the most common. There were no neutropenic conditions reported during ganciclovir therapy in this research.

Liver biochemistry characteristics of CMV cholestasis

Hepatic abnormalities in the form of cholestasis were found in all patients (100%) and were identified by impaired bilirubin secretion of the biliary tract, which manifested as elevated serum total and direct bilirubin levels and aspartate amino transferase (AST) serum levels. Hypoalbuminemia (serum albumin <3.5 g/dL) was noted in 43.9% of patients, elevated serum

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Table 1. Basic characteristics of patients (n=41)

Characteristic	Value
Age (mo)	3.32±2.76
Outcome	
Improvement	28 (68.3)
Persisted	13 (31.7)
Sex	
Female	15 (36.6)
Male	26 (63.4)
Clinical manifestation	
Jaundice	41 (100)
Tea-like colored urine	40 (97.6)
Acholic feces	36 (87.8)
Hepatomegaly	37 (90.2)
Splenomegaly	27 (65.9)
Others	5 (12.2)
Birth history	
Premature	12 (29.3)
Asphyxia	4 (9.8)
Low birth weight	14 (34.1)
Normal birth weight	25 (61.0)
Nutritional status	
Good	19 (46.3)
Undernourished	17 (41.5)
Malnutrition	5 (12.2)
Central nervous system involvement	
Microcephaly	36 (87.8)
Calcification	26 (63.4)
Hearing loss	31 (75.6)
Chorioretinitis	2 (4.9)
Side effect ganciclovir	
Anemia	16 (39.0)
Thrombocytopenia	6 (14.6)

Values are presented as mean±standard deviation or number (%).

Table 2. Liver biochemistry analysis of cytomegalovirus cholestasis

Liver function	Pre-ganciclovir	Post-ganciclovir	*p*-value
Total bilirubin (mg/dL)	10.7 (4.21–55.83)	0.77 (0.17–5.65)	<0.001
Direct bilirubin (mg/dL)	9.4 (3.8–39.81)	0.48 (0.09–5.06)	<0.001
Albumin (g/L)	3.5 (2.1–4.5)	3.7 (2.1–4.77)	0.066
PT (sec)	15.1 (12.5–23.7)	13.8 (11.9–19.3)	0.025
aPTT (sec)	39.7 (31–59)	37.3 (27–49.6)	0.219
AST (U/L)	220 (72–978)	103 (36–778)	0.001
ALT (U/L)	114 (20–659)	83 (18–423)	0.103

Values are presented as median (interquartile range).
PT: prothrombin time, aPTT: activated prothrombin time, AST: aspartate amino transferase, ALT: alanine aminotransferase.

alanine aminotransferase (ALT) was noted in 87.8% of patients, coagulopathy with prolonged PT was noted in 12% of patients, and activated prothrombin time (aPTT) was noted in 17% of patients. We analyzed the results using the Wilcoxon statistical test, which showed a significant decrease in liver biochemistry, such as total and direct bilirubin, AST, and PT (p<0.005). Liver biochemistry analysis results of CMV cholestasis are shown in **Table 2**.

Clinical course of CMV cholestasis after ganciclovir treatment

Twenty-eight out of 41 patients showed improved liver biochemistry post-ganciclovir therapy. Twenty-two (78.6%) of these 28 patients showed improved liver biochemistry at 30 (±15) days post-ganciclovir administration, while three (10.7%) patients showed improved

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liver biochemistry at 90 (±15) days. In addition, three (10.7%) of the 28 patients showed an improvement in liver biochemistry at 180 (±15) days post-ganciclovir administration.

Predicting factors for improved liver biochemistry of CMV cholestasis patients after ganciclovir therapy

Bivariate analysis revealed that CMV cholestasis duration (relative risk [RR], 2.32; 95% CI, 0.85 to 6.33; p=0.075) showed no statistically significant association with liver biochemistry improvement. Nevertheless, the result was clinically significant because the chance of liver biochemistry improvement when CMV cholestasis duration was less than 3 months was 2.3 times higher than when CMV cholestasis lasted beyond 3 months. The bivariate analysis results are presented in **Table 3**.

To analyze the relationships between independent variables (predictors) and liver biochemistry outcome, we performed a multivariate analysis. All variables with a p-value <0.25 from the bivariate analysis were included in the multivariate backward logistic regression analysis. The variable that was significantly associated with liver biochemistry improvement was a shorter CMV cholestasis duration (OR, 4.6; 95% CI, 1.00 to 21.07; p=0.04). The multivariate analysis results are presented in **Table 4**.

Table 3. Bivariate analysis of predictive factors of liver biochemistry improvement in patients with CMV cholestasis after one month of ganciclovir therapy

Predictor	Improvement (n=22)	No improvement (n=19)	Bivariate		
			RR	95% CI	p-value
Age at cholestasis diagnosis					
Age <1 mo	11	6	1.41	0.81 to 2.47	0.23*
Age ≥1 mo	11	13			
Duration of CMV cholestasis					
Age ≤3 mo	19	11	2.3	0.85 to 6.33	0.07†
Age >3 mo	3	8			
Involvement of CNS					
No	3	1	1.46	0.76 to 2.78	0.61†
Yes	19	18			
Prematurity					
No	14	15	0.72	0.41 to 1.25	0.28*
Yes	8	4			
Nutritional status					
Good	11	8	0.96	0.43 to 2.17	>0.99†
Undernourished	8	9	0.78	0.33 to 4.29	>0.99†
Malnutrition	3	2			
Age at ganciclovir therapy					
≤3 mo	16	10	1.54	0.77 to 3.07	0.18*
>3 mo	6	9			

Chi-square/fisher exact test is statistically significant if p-value <0.05.
CMV: cytomegalovirus, RR: relative risk, CI: confidence interval; CNS: central nervous system.
*Chi-square. †Fisher exact test.

Table 4. Multivariate analysis of predictive factor of liver biochemistry improvement in patients with CMV cholestasis after one month of ganciclovir therapy

Predictor	OR	95% CI	p-value
Age at cholestasis diagnosis	1.58	0.40 to 6.17	0.50
Duration of CMV cholestasis	4.6	1.00 to 21.07	0.04
Age at ganciclovir therapy	0.79	0.11 to 5.33	0.81

CMV: cytomegalovirus, OR: odds ratio, CI: confidence interval.

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DISCUSSION

CMV as a non-hepatotropic virus plays an important role in CMV cholestasis. The most common CMV cholestasis occurrences are during the early ages of life and are asymptomatic. However, the long-term effects of CMV cholestasis may present as hepatomegaly and portal hypertension development [9]. In our study, there were 54 patients (48.2%) with CMV cholestasis, which was similar to previous studies in other countries. However, 41 of the 54 patients were treated with ganciclovir and had complete medical records. Previous studies showed that the involvement of CMV infection in hepatobiliary disease is very high (at approximately 40%) where the virus replicates in both the hepatocytes and cholangiocytes [2,3]. The higher incidence of CMV cholestasis in this study may be due to the children being treated in a tertiary hospital where many patients had recently been diagnosed with CMV cholestasis.

The mean age of the patients in this study was 3.32±2.76 months, with the cohort being mostly male (63.4%). This is similar to the study by Min et al. [10] who reported that CMV cholestasis was diagnosed in mostly males (56%), though the study also showed that the condition was detected at a different age from that in the current study, occurring mostly in children under 3 months (55.3%) of age. Clinical jaundice persists from 2 to 3 weeks of age and the difficulty in establishing a CMV cholestasis diagnosis in a primary health care setting causes some children to be referred to a tertiary hospital when they are more than 3 months old.

In this study, 12 patients had a history of prematurity (29.3%), which was a higher percentage than Tezer et al. [11] found in Turkey, where 14.2% of patients had the same history. The high percentage of patients with a history of prematurity in Dr. Sardjito General Hospital was probably because the different socioeconomic conditions of the children may have influenced the number of incidences of prematurity in both the studies.

In our study, we found that 17 patients were undernourished (41.5%), and five patients were malnourished (12.2%). The findings in this study are consistent with previous studies that showed the prevalence of malnutrition in children with liver diseases to be approximately 9.1 to 71.1%, depending on the severity of the liver disease. Malabsorption of macronutrients, such as fats, carbohydrates, proteins, and vitamins, affect nutritional status [8].

The main clinical manifestations of CMV cholestasis in this study were jaundice (100%), tea-like colored urine (97.6%), and hepatomegaly (90.2%). Furthermore, we found that all patients had elevated serum total and direct bilirubin levels, elevated serum AST (100%), hypoalbuminemia (43.9%), elevated ALT (87.8%), and abnormalities in coagulopathy factors, including PT (12%) and aPTT (17%). This finding is similar with the study of Hasosah et al. [2], who reported that the most common clinical manifestations of CMV cholestasis were jaundice (100%), tea-like colored urine (44%), and hepatosplenomegaly (44%). Cholestasis identified by elevated serum total and direct bilirubin levels were found in all patients (100%), and coagulopathy dysfunction was noted in three patients (33%) [2].

CMV infection is attributed to viral replication in epithelial and endothelial cells, which can ultimately result in multi end-organ damage. Sequelae resulting from congenital CMV infections can cause particularly severe neurodevelopmental disorders [12]. Ross and Boppana [13] showed that a clinical manifestation of congenital CMV infections is the involvement of the central nervous system, including microcephaly (53%), while some

asymptomatic children develop sensorineural hearing loss (10%). In this study, we found that involvement of the central nervous system caused microcephaly (87.8%), hearing loss (75.6%), calcification (63.4%), and chorioretinitis (4.9%). The high percentage of these disease features in our study may have been caused by the patients' older ages when diagnosed with CMV infections. Tezer et al. [11] reported findings similar as our study, with only a low percentage of patients presenting with chorioretinitis (2.04%).

The gold standard for diagnosing CMV cholestasis is with a liver biopsy. The major biopsy findings are multinucleated giant cells, a cytomegalic inclusion resembling an "owl's eye," granuloma formation, mild hepatocellular necrosis, or sinusoidal infiltration of mononuclear cells [1,14,15]. A biopsy was not performed in this study because of the invasiveness and difficulty obtaining family approval. CMV infection diagnosis in this study was confirmed by positive CMV IgG and IgM serology and/or positive blood and urine CMV antigenemia. The sensitivity of IgM in detecting CMV infection varies but can be as high as 72.97%, with a specificity of 62.06%. The CMV antigenemia assay detects pp65 antigen expression in cells during viral replication. The sensitivity of the CMV antigenemia assay to detect CMV in solid organ tissue is 64%, with a specificity of 81%, a positive predictive value of 76%, and a negative predictive value of 71% [16,17].

Improved liver function occurred in 28 (68.3%) patients after ganciclovir therapy. An assessment of liver function improvement in this study found that at least one liver function parameter decreased by 50% with no deterioration in other liver function parameters after ganciclovir therapy. Results showing significant reductions (those with a p-value <0.05) were obtained with direct bilirubin, total bilirubin, AST, and PT. Similar studies also reported results showing that three out of four (75%) patients with CMV cholestasis who received ganciclovir therapy had improved liver biochemical factors, including AST, ALT, bilirubin, and gamma-glutamyl transferase levels. These results indicate that ganciclovir is effective in the acute phase of CMV cholestasis. The duration required to improve liver biochemistry was after 30 (±15) days of ganciclovir therapy in as many as 16 (39%) patients. This is similar to the study by Tezer et al. [11], which reported 7 to 180 days (mean 53.92±40.8) as the period of time after ganciclovir therapy initiation where an improvement in liver function tests was seen.

We found that the duration of CMV cholestasis was the significant predictive factor for the improvement of liver biochemistry in patients with CMV cholestasis after receiving ganciclovir therapy. In our study, patients with a shorter duration of CMV cholestasis had a 4.6 times higher chance of achieving improved liver biochemistry than patients with longer CMV cholestasis durations. In line with other studies, the mean age at CMV cholestasis diagnosis was 2.9±0.9 months (a range of 2 to 4 months, and a median of 3 months). After receiving ganciclovir therapy, three out of four cases (75%) improved. These results provide evidence that ganciclovir is effective in the acute phase of CMV cholestasis [4].

The limitations of this study included the retrospective design and use of secondary data from medical records, which caused the researchers difficulty in collecting complete data when compared with prospective studies. Moreover, we did not use gold standard examinations like a liver biopsy for supporting laboratory tests. To the best of our knowledge, a study examining prognostic factors of liver biochemistry improvement in children with CMV cholestasis after ganciclovir therapy has not been perfomed in Indonesia. By knowing the predictors of liver function improvement in children with CMV cholestasis, clinicians can optimize ganciclovir management in children with CMV cholestasis to prevent severe liver damage.

In conclusion, a short duration of CMV cholestasis is a statistically and clinically significant predictor of liver biochemistry improvement in patients with CMV cholestasis after receiving ganciclovir therapy. We believe that this study should be conducted in a prospective cohort so that other predictive factors can be determined that otherwise cannot be assessed through medical records alone. We also recommend that researchers make observations over a longer period with a sufficient number of samples so that more information about the prognosis of CMV cholestatic patients and more accurate results can be obtained.

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