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Original Article

Gastrointestinal tract bleeding in children with chronic cholestasis: Prevalence and risk factors in a tertiary referral hospital in Indonesia

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Abstract

Background Cholestasis can lead to several complications, including portal hypertension and risk of gastrointestinal bleeding. However, there is a paucity of studies on the risk factors and prevalence of gastrointestinal tract bleeding in children with chronic cholestasis, particularly in Indonesia.

Objective To determine the prevalence and risk factors for gastrointestinal bleeding in children with chronic cholestasis in Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Methods This was a retrospective cohort study in a national referral hospital in Indonesia. Medical records of children with chronic cholestasis who visited the gastroenterohepatology outpatient clinic were collected for five years. Data on clinical symptoms, etiologies, and complications were obtained.

Results A total of 97 participants were recruited on this study. The median age of the group was 0.31 years old. The most common causes of chornic cholestasis were biliary atresia, toxoplasma, other infections, rubella, cytomegalovirus, and herpes simplex virus (TORCH) infection, and urinary tract infection. Gastrointestinal bleeding occurred in 27.8% of patients, with hematemesis-melena being the most prevalent symptom. We found that liver cirrhosis, splenomegaly, thrombocytopenia, portal hypertension, and esophageal varices were all highly related with gastrointestinal bleeding. Splenomegaly, thrombocytopenia, and esophageal varices were associated with an increased risk of gastrointestinal bleeding in children with chronic cholestasis (P=0.018, P=0.008, and P=0.039, respectively).

Conclusions The prevalence of gastrointestinal tract bleeding in children with chronic cholestasis is 27.8%, with splenomegaly, thrombocytopenia, and esophageal varices as significant risk factors. **[Paediatr Indones. 2023;63:370-5; DOI: https://doi.org/10.14238/pi63.5.2023.370-5**].

Keywords: *prevalence; risk factors; cholestasis; hemorrhage; child; tertiary care centers*

Cholestasis is defined as an impairment of bile flow, resulting in the accumulation of bile components. In children, the impairment can be acute or chronic and can lead to significant complications. This condition arises due to impaired formation and/or biliary flow leading to symptoms such as fatigue, pruritus, and icterus.[1,2] An increased fraction of conjugated bilirubin in the serum, exceeding 20% of total blood serum bilirubin levels, signifies a state of cholestasis in infancy.[3]

Biliary atresia is the leading cause of cholestatic liver disease in children.[1,2,4] Other etiologies include progressive familial intrahepatic cholestasis (PFIC), preterm birth, Alagille syndrome, neonatal hepatitis, and high-risk antenatal history. Left untreated, cholestasis may lead to severe complications including liver cirrhosis, hypersplenism, thrombocytopenia, and portal hypertension, all of which can place children at risk for gastrointestinal bleeding.[3] In the United States, nearly half of the pediatric patients

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listed for liver transplant have cholestasis as the indication for the procedure.[2] Portal hypertension and gastrointestinal bleeding are common complications in patients scheduled for liver transplant, including pediatric patients with cholestasis.[2,5]

Despite the significance of this problem, there is a noticeable study gap on the risk factors and prevalence of gastrointestinal tract bleeding in children with chronic cholestasis, particularly in developing regions such as Indonesia. This information gap may impede the timely identification of children with chronic cholestasis who are at high risk of bleeding, thus hindering the timely employment of management strategies to reduce related morbidity and mortality. The purpose of this study was to assess the prevalence and risk factors for gastrointestinal bleeding in children with chronic cholestasis.

Methods

This retrospective cohort study was conducted at the Cipto Mangunkusumo Hospital, a national referral, tertiary care, and teaching hospital in Jakarta, Indonesia. The study population consisted of children aged 0-1 years old who visited the gastroenterohepatology outpatient clinic. Data from medical records of participants were collected throughout a five-year period. A total of 97 children were included in this study. Participants whose parents refused to provide consent were excluded from participating in this study. Data regarding clinical symptoms, etiologies, and complications were collected to evaluate the risk factors of gastrointestinal tract bleeding in children with chronic cholestasis.

Cholestasis was defined as a direct bilirubin level of >1 mg/dL if the total bilirubin level was <5 mg/dL or a direct bilirubin level of >20% of total bilirubin level if the total bilirubin level was >5 mg/dL. Liver cirrhosis and splenomegaly were confirmed based on physical examination and ultrasound performed by a certified pediatric gastroenterologist. Portal hypertension was diagnosed based on a hepatic venous pressure gradient (HVPG) value of ≥6 mmHg. Esophageal varices was diagnosed based on endoscopic findings performed by a pediatric gastroenterologist. Thrombocytopenia was defined a peripheral blood platelet count of <150 x 10^9/L. Coagulopathy was defined as an increased prothrombin time (PT) over the normal limit and an international normalized ratio (INR) value of ≥2.

The *IBM® SPSS version 26.0* (*IBM,* Armonk, New York) was used in data analysis. The normality of numerical data was assessed using the Kolmogorov-Smirnov test. Data was presented as mean and standard deviation (SD) if normally distributed and as median and interquartile range (IQR) if abnormally distributed. Numerical data were analyzed using the unpaired t-test for normally distributed data and the Mann-Whitney test otherwise. Categorical data were analyzed using the chi-square test or the Fisher's exact test whenever appropriate. Multivariate analysis was performed using binomial logistic regression. We presented comparison data using odds ratio (OR) with 95% confidence interval (95%CI). P values of <0.05 were considered statistically significant.

Written informed consent was obtained from the parents/guardians prior to data collection. The study was approved by the Ethics Committee, Faculty of Medicine, Universitas Indonesia.

Results

A total of 97 participants were recruited in this study. Median age of subjects was 0.31 years (IQR: 0,14-0,87 years old). Gender distribution was found to be fairly equal, with male participants comprising 55.7% of subjects. The majority of the children were diagnosed with intrahepatic cholestasis (60.8%), while the remaining 39.2% had extrahepatic cholestasis (**Table 1**).

The most frequent causes of chronic cholestasis were biliary atresia (38.1%), toxoplasma, others (syphilis, varicella zoster, parvovirus B19), rubella, cytomegalovirus, and herpes simplex virus (TORCH) infection (14.4%), and urinary tract infection (UTI) (13.4%). Less common causes included Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC), and common bile duct cysts, each accounting for approximately 3.1% of cases. Sepsis and inspissated bile syndrome were identified in 2.1% of cases each. The remaining conditions, including neonatal hepatitis, infiltration, common bile duct calcification, and bile duct paucity, were responsible for 1% of cases each. The cause was unknown in 10.3% of subjects

(**Table 1**).

Gastrointestinal bleeding was found in 27/97 (27.8%) of subjects. Bleeding manifestations varied among patients, with hematemesis-melena being the most common (14/97; 14.4%). Hematochezia was reported by 9/97 (9.3%) of subjects, while 4/97 (4.1%) had a combination of hematemesis and hematochezia. We also evaluated the associations between various conditions that can be found in patients with chronic cholestasis and the occurrence of gastrointestinal bleeding. Gastrointestinal bleeding was slightly more common in patients with liver cirrhosis than those without (51.7% *vs.* 17.6%, P=0.001). Participants with splenomegaly were more likely to experience gastrointestinal bleeding compared to those without (45.8% *vs.* 10.2%, P<0.001). Thrombocytopenia was strongly associated with gastrointestinal bleeding, with bleeding occurring in 88.9% of children with this condition compared to 21.6% in those without (P<0.001). In contrast, coagulopathy was not significantly relationship with gastrointestinal bleeding (P=1.000). Portal hypertension was associated with a higher occurrence of gastrointestinal bleeding compared to no portal hypertension (56.2% *vs.* 22.2%, P=0.006). Finally, patients with esophageal varices had a significantly higher prevalence of gastrointestinal bleeding than those without (80% *vs.* 21.8%, P<0.001). These results underscore the potential relationships between these conditions and gastrointestinal bleeding in pediatric patients with chronic cholestasis (**Table 2**).

Table 1. Subject characteristics

Variables	(N=97)
Median age (IQR), years	0.31 (0.14-0.87)
Gender, n (%)	
Female	43 (44.3)
Male	54 (55.7)
Type of cholestasis, n (%)	
Intrahepatic	59 (60.8)
Extrahepatic	38 (39.2)
Etiology of chronic cholestasis, n (%)	
Biliary atresia	37 (38.1)
TORCH infection	14 (14.4)
UTI	13 (13.4)
Alagille syndrome	9 (9.3)
PFIC	3 (3.1)
Common bile duct cyst	3 (3.1)
Sepsis	2 (2.1)
Inspissated bile syndrome	2 (2.1)
Neonatal hepatitis	1 (1)
Infiltration	1 (1)
Common bile duct calcification	1 (1)
Bile duct paucity	1 (1)
Unknown	10 (10.3)

TORCH = toxoplasma, others (syphilis, varicella zoster, parvovirus B19), rubella, cytomegalovirus, and herpes simplex virus; UTI=urinary tract infections; PFIC=progressive familial intrahepatic cholestasis

Table 2. Association between risk factors and gastrointestinal tract bleeding in children with chronic cholestasis

Variables	Gastrointestinal bleeding		P value
	No	Yes	
Liver cirrhosis, n(%)			0.001
No	56 (82.4)	12 (17.6)	
Yes	14 (48.3)	15 (51.7)	
Splenomegaly, n(%)			<0.001
No	44 (89.8)	5 (10.2)	
Yes	26 (54.2)	22 (45.8)	
Thrombocytopenia, n(%)			<0.001
No	69 (78.4)	19 (21.6)	
Yes	1 (11.1)	8 (88.9)	
Coagulopathy, n(%)			1.000
No	68 (72.3)	26 (27.7)	
Yes	2 (66.7)	1 (33.3)	
Portal hypertension, n(%)			0.006
No	63 (77.8)	18 (22.2)	
Yes	7 (43.8)	9 (56.2)	
Esophageal varices, n(%)			<0.001
No	68 (78.2)	19 (21.8)	
Yes	2 (20)	8 (80)	

On multivariate analysis, splenomegaly, thrombocytopenia, and esophageal varices were found to have be significant risk factors of gastrointestinal bleeding. Meanwhile, liver cirrhosis and portal hypertension did not show a statistically significant association with gastrointestinal bleeding after taking into account other risk factors (**Table 3**).

Table 3. Multivariate analysis of risk factors of gastrointestinal bleeding in children with chronic cholestasis

Variables	OR (95% CI)	P value
Cirrhosis of the liver	2.090 (0.590 to 7.329)	0.254
Splenomegaly	4.811 (1.314 to 17.618)	0.018*
Thrombocytopenia	23.563 (2.274 to 244.119)	0.008*
Portal hypertension	0.795 (0.154 to 4.114)	0.784
Esophageal varices	7.779 (1.107 to 54.642)	0.039*

*significant results

Discussion

In our sample of 97 patients, the median age was 0.31 years (3.72 months), indicating that our study mostly involved infants or young children. This is in line with a study conducted in India that reported a proportion of neonatal cholestasis of 1.2 per 1000 patients.[6] Our study also revealed that boys constituted the majority of the study group (55.7%), which is in line with findings from other studies conducted in South Korea and India.[6,7]

Intrahepatic cholestasis was found to be more prevalent (60.8%) among our study participants. Biliary atresia, a major cause of cholestasis in children, was also common in our study group.[6] This agrees with a report from South Korea which identified biliary atresia in 1.06 per 10,000 of a total of 240 pediatric patients with the condition.[8] Similarly, a German study found biliary atresia to be the most common cause of cholestasis (41%), followed by idiopathic (13%), PFIC (10%), and cholestasis secondary to total parenteral nutrition in preterm infants (10%).[9]

The prevalence of gastrointestinal bleeding in children with chronic cholestasis in this study was notably high at 27.8%. It exceeded the reported prevalence in a previous study in Asia, which obtained a gastrointestinal bleeding prevalence of 4.4% among children with biliary atresia (4.4%).[8] Our prevalence also surpassed gastrointestinal bleeding rates among biliary atresia patients in Italy (19.5% to 22%).[5,10] This discrepancy in prevalence could be attributed to variations in sample size, differences is study population, or potential differences in local medical practices and patient care.

Our study found that hematemesis-melena was the most common manifestation of gastrointestinal bleeding (14.4%) followed by hematochezia (9.3%) as well as combined hematemesis and hematochezia (4.1%). This aligns with previous studies which reported upper gastrointestinal tract bleeding to be more common than lower gastrointestinal tract bleeding and a combination of both (63.6%, 20.7%, and 15.6%, respectively).[11] Similar findings were also reported in Iran and Turkey.[12,13]

Interestingly, our univariate analysis identified several factors as statistically significant risk factors for gastrointestinal bleeding in children with biliary atresia, such as liver cirrhosis, splenomegaly, thrombocytopenia, portal hypertension, and esophageal varices. This is consistent with some previous studies, including a report which also recognized thrombocytopenia as a significant risk factor in children with upper gastrointestinal bleeding (P=0.008).[14] However, this result contradicts with an earlier study in Italy, which found neither platelet count or splenomegaly as a significant factor associated with gastrointestinal bleeding.[10]

Our findings regarding the incidence of esophageal varices stand in partial agreement with the Italian study. This previous study reported that esophageal varices were detected during endoscopy in 93.8% of patients with biliary atresia who presented with a gastrointestinal bleeding episode.[10] On the other hand, a different study reported a notably lower incidence of esophageal varices (11.1%) among children with upper gastrointestinal bleeding.[11] The disparity in these findings could be attributed to differences in diagnostic procedures, patient selection, and variations in disease severity across the studied populations.

Our multivariate analysis showed that splenomegaly, thrombocytopenia, and esophageal varices were statistically significant risk factors of gastrointestinal bleeding in children with chronic cholestasis. This is in contrast to findings from some previous studies in which none of these factors

were significant risk factors of gastrointestinal bleeding.[10,14] This may be due to a different definition of thrombocytopenia used. A previous study reported that the degree of thrombocytopenia was associated with the severity of liver disease rather than with spontaneous bleeding, unless platelet counts fall below 50,000-60,000/≥μL.[15] When platelet counts are still above 50,000-60,000/≥μL, primary hemostasis is maintained by increasing Von Willebrand factor and decreasing ADAMTS13 levels, hence, sustaining normal thrombin generation.[16] Once platelet counts fall below that threshold, the risk of spontaneous bleeding increases significantly as those compensation mechanisms begin to fail. However, even though in our study we used different cut-off to define thrombocytopenia (<150 x 10^3/≥μL), most of our patients likely had platelet counts below 50,000-60,000/≥μL, thereby increasing their risk of gastrointestinal bleeding. A recent study suggests that clotting time, PT, and INR are unable to predict the risk of bleeding in liver cirrhosis.[16] Rather, measuring platelet count and fibrinogen levels before high-risk procedures is recommended, as these laboratory parameters have been proposed as more reliable indicators of bleeding risk in patients with cirrhosis, which is in accordance with the results of our study.[16] The pathomechanism of thrombocytopenia in chronic liver disease (CLD) such as biliary atresia is multifactorial. It is attributed to both a decrease in platelet production, due to factors such as reduced thrombopoietin production in the liver and the limited capacity of the bone marrow to produce platelets, and an increase in platelet destruction, due to splenic sequestration and immune-mediated destruction.[17]

Liver cirrhosis is frequently associated with complications such as splenomegaly and hypersplenism. Cirrhosis-associated splenomegaly involves the promotion of hepatic fibrinogenesis, alteration in hepatic immune microenvironment, and inhibition of liver regeneration. Splenomegaly often occurs in parallel with hypersplenism, which is thought to be related with cytopenia and thrombocytopenia in patients with liver cirrhosis. Splenomegaly in liver cirrhosis is thought to be attributed to portal congestion and increasing pooling of platelets.[17,18] However, the precise mechanism underlying liver cirrhosis-associated splenomegaly and hypersplenism remains unclear.[18]

The significantly higher proportion of gastrointestinal bleeding among patients with esophageal varices supports the notion that esophageal varices may play a critical role in gastrointestinal bleeding in children with chronic cholestasis in our study. Our observation is in line with the broader understanding of the chronic liver disease, where esophageal varices most commonly occur due to portal hypertension as a complication of cirrhosis. The enlarged varices will rupture and bleeding will occur. In this context, it is expected that the presence of esophageal varices would be significantly associated with gastrointestinal bleeding. The severity of liver disease is correlated with the presence of varices and risk of bleeding. Variceal bleeding comprises the third most prevalent cause of upper gastrointestinal bleeding.[19]

Our study on pediatric patients with chronic cholestasis and found a relatively high prevalence of gastrointestinal bleeding (27.8%). Splenomegaly, thrombocytopenia, and esophageal varices were identified as significant risk factors for gastrointestinal bleeding in these children. These findings highlight the necessity of early detection and therapy of gastrointestinal bleeding in pediatric patients with cholestasis, as well as the importance of close monitoring of platelet counts, splenomegaly, and symptoms of portal hypertension. Further study is needed in this area to improve patient outcomes and provide focused therapies for this population.

Conflict of interest

None declared.

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