Risk factors for portal hypertension in children with biliary atresia

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Abstract

Introduction: Biliary atresia is a hepatobiliary disease which frequently results in portal hypertension.

Objectives: To analyse the risk factors for portal hypertension in children with biliary atresia.

Method: A case-controlled study was performed on 96 children with biliary atresia. Subjects were enrolled based on the inclusion and exclusion criteria. Medical history, physical examination results, imaging data, and laboratory examination results were collected prospectively. Patients were divided into two groups based on the signs of portal hypertension clinically during the follow-up period. Risk factors for portal hypertension were analysed using SPSS. Univariate analysis was used first to identify possible risk factors. A multivariate analysis was performed using logistic regression with *p* significant <0.05.

Results: The median age was 18.21 (3.14-128.86) weeks in the portal hypertension group and 9.07 (1.00-50.57) weeks in the non-portal hypertension group. Age, duration of illness, birth weight, gestational age, and laboratory examination [Haemoglobin (Hb), white blood cell (WBC) count, albumin, direct bilirubin, total bilirubin, prothrombin time (PT), gamma-glutamyl transferase (GGT), aspartate transaminase (AST), and AST: alanine transaminase (ALT) ratio] were significantly different in the 2 groups (p<0.05). For every one-week increase in the subject's age, the risk of portal hypertension increased by 1.127. For every one unit increase in Hb, PT, GGT, and the AST:ALT ratio, the risk of having portal hypertension was 0.746, 1.125, 1.00, and 2.862 in children with biliary atresia (p<0,05).

Conclusions: The risk factors for portal hypertension in children with biliary atresia were age, Hb, PT, GGT levels, and the AST:ALT ratio.

(Key words: Biliary atresia, Portal hypertension, Children)

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Introduction

Clinical manifestations of biliary atresia include prolonged jaundice, cholestasis, clay-coloured stools, and hepatomegaly[1]. It is thought that a genetic component is present in the pathogenesis of biliary atresia in approximately 3-20% followed by other congenital abnormalities[1,2]. Portal hypertension is a frequent occurrence in biliary atresia and causes significant morbidity and mortality[3,4]**.** Portal hypertension is a major complication of liver cirrhosis that occurs due to high resistance to portal blood flow to the liver. Liver fibrosis is a massive structural change that causes an increase in intrahepatic vascular resistance and an increase in vascular tone in the hepatic microcirculation[5]. Portal hypertension is diagnosed in children with liver disease in the presence of splenomegaly, evidence of portal-systemic collaterals, or both, on either physical examination or ultrasonography. In later stages, symptoms may be followed by signs of hypersplenism (thrombocytopenia and leucopenia), variceal bleeding (melaena and haematemesis) and hepatopulmonary syndrome[6]. In portal hypertension, the lining of the extrahepatic vessels in the splanchnic and systemic circulation changes, leading to arterial vasodilatation and formation of collateral vessels. This causes impaired blood flow to the portal vein and hyperdynamic circulation syndrome[7,8]. In biliary atresia, risk of variceal bleeding was 17% over a period of 5 to 10 years[9].

In contrast to portal hypertension in adults, portal pressure in children is usually not measured[10]. Measurement of the hepatic venous pressure gradient in children does not always reflect portal pressure[11]. Until now, there has been no recommendation for regular screening of oesophageal varices with endoscopy in those with biliary atresia because there was no effective prevention of first variceal bleeding in children[6]. Recent studies suggest that endoscopic examination is recommended in cases of biliary atresia with thrombocytopenia, high aspartate aminotransferase-to-platelet ratio index (APRI) scores, and splenomegaly to prevent variceal bleeding[12].

Objectives

To analyse the risk factors for portal hypertension in children with biliary atresia.

Method

A case-control study was conducted for 96 children with biliary atresia. Subjects were enrolled between January 2022 and May 2023 based on the inclusion and exclusion criteria using consecutive sampling. Inclusion criterion was biliary atresia. Subjects with congenital anomalies and sepsis were excluded. Subjects were excluded from analysis if portal hypertension status could not be determined due to the absence of clinical data. Medical history, physical examination results, imaging data, and laboratory examination results were collected prospectively. Patients were divided into two groups

based on the signs of portal hypertension clinically during follow-up period, based on whether they had portal hypertension. Portal hypertension was clinically defined as 'definite' if there was 1) a history of complications of portal hypertension or 2) clinical findings consistent with portal hypertension [met 2 criteria of: splenomegaly (spleen palpable >2 cm below the costal margin), ascites or thrombocytopenia (platelet count <150,000/cu mm)]. However, if these criteria are not found, then 'no portal hypertension'[4]. Clinical evaluation of splenomegaly was carried out by a consultant paediatric gastro-hepatologist. Splenomegaly and ascites were confirmed by abdominal ultrasonography examination by a radiologist.

Ethical issues: This study was approved by the ethical committee of Dr Soetomo General Academic Hospital, Surabaya, Indonesia (No. 0500/KEPK/X/2022) on 10. 10. 2022. Written informed consent was obtained from the parents of the participants before conducting the study.

Statistical analysis: Descriptive statistics (sums and percentages for categorical variables; mean and standard deviation for continuous variables) were used. Bivariate analysis was performed to determine differences between the portal hypertension vs non-portal hypertension groups. Risk factors for portal hypertension were analysed using SPSS. Univariate analysis was used first to identify possible risk factors. A multivariate analysis was performed using logistic regression with *p* significant <0.05.

Results

At baseline, definite portal hypertension was present in 50% and absent in 50% of subjects. Table 1 shows the basic characteristics of the subjects. Table 2 shows the laboratory examination of the subjects.

Table 1: ***Basic characteristic of the subjects***

Variable	Cases *(n=48)* (Portal hypertension)	Controls *(n=48)* (Non-portal hypertension)	p
Sex: n (%)			
Male	23 (47.9)	32 (66.7)	0.99[a]
Female	25 (52.1)	16 (33.3)	
Birth: n (%)			
Preterm	04 (08.3)	13 (27.1)	**0.03**[a]
Term	44 (91.7)	35 (37.9)	
Kasai operation: n (%)			
Yes	08 (16.7)	01 (02.1)	**0.03**[a]
No	40 (83.3)	48 (97.9)	
Liver biopsy: n (%)			
Fibrosis	24 (77.4)	08 (33.3)	**0.00**[a]
No Fibrosis	07 (22.6)	16 (66.7)	
Age (weeks): Median (Min–Max)	18.21 (3.14-128.86)	9.07 (1.00-50.57)	**0.00**[b]
Onset of jaundice (weeks): Median (Min–Max)	4.00 (1.00-20.00)	2.00 (1.00-8.00)	0.09[b]
Duration of illness (weeks): Median (Min–Max)	12.57 (1.71-117.43)	5,86 (0.00-49.57)	**0.00**[b]
Birth weight (g): Median (Min–Max)	3050 (1800-4.200)	2900 (900-3.900)	**0.03**[b]
Gestational age (weeks): Median (Min–Max)	38.50 (36.00-41.00)	38.00 (32.00-41.00)	**0.00**[b]

[a] *Chi square test;* [b] *Mann-Whitney test; p significant <0.05*

Table 2: ***Laboratory examination of the subjects***

Variable	Cases *(n=48)* (Portal hypertension)	Controls *(n=48)* (Non-portal hypertension)	p
Haemoglobin (g/dL)	9.80 (5.20-15.8)	11.45 (5.90-21.50)	**0.00**[a]
White blood cell count (/cu mm)	13,565 (4.450 – 27.900)	11,120 (5,730-28,430)	**0.01**[a]
Platelet count (/cu mm)	305,271 ± 20,448	351,437 ± 22,608	0.29[b]
Albumin (g/dL)	3.29 (1.80-4.40)	3.80 (2.33-4.32)	**0.03**[a]
Direct bilirubin (mg/dL)	9.36 (1.16-22.05)	6.10 (1.10 -23.29)	**0.00**[a]
Total bilirubin (mg/dL)	12.57 (5.80-34.06)	8.55 (1.90-33.25)	**0.00**[a]
Activated partial thromboplastin test (seconds)	33.3 (11.40-73.20)	34.10 (16.70-48.30)	0.28[a]
Prothrombin time (seconds)	13.30 (0.00 -121.40)	11.45 (0.00-23.80)	**0.00**[a]
Gamma glutamyl transferase (GGT) (U/L)	360 (37-2,386)	148.5 (23.9-1261)	**0.00**[a]
Aspartate transaminase (AST) (U/L)	237 (100-1.642)	177.5 (29.9-5,775)	**0.02**[a]
Alanine transaminase (ALT) (U/L)	140 (35-505)	140.1 (22.3-3,284)	0.65[a]
AST:ALT ratio	1.70 (0.54-4.51)	1.31 (0.38-4.52)	**0.02**[a]
GGT:AST ratio	1.58 (0.08-15.1)	0.76 (0.04-9.92)	0.99[a]
GGT:ALT ratio	3.44 (0.7-15.2)	1.35 (0.08-12.4)	**0.02**[a]

[a] *Mann-Whitney test;* [b] *Independent Sample t-test; p significant <0.05*

Table 3 is a multivariate analysis of the risk factors for portal hypertension. For every one-week increase in the subject's age, the risk of portal hypertension increased by 1.127. For every one unit increase in Hb, PT, GGT, and the AST:ALT ratio, the risk of becoming portal hypertension was 0.746, 1.125, 1.00, and 2.862 in children with biliary atresia (p<0,05).

Table 3: Multivariate analysis of risk factors for portal hypertension

Variable	p	OR (95% confidence interval)
Age (weeks)	0.006[a]	1.127 (1.035-1.227)
Haemoglobin (g/dL)	0.015[a]	0.746 (0.590- 0.944)
Prothrombin time (seconds)	0.027[a]	1.125 (1.013-1.249)
Gamma glutamyl transferase (U/L)	0.006[a]	1.000 (1.001-1.005)
Aspartate transaminase: alanine transaminase ratio	0.028[a]	2.862 (1.124-7.289)

[a] *logistic regression; p significant <0,05*

Discussion

Portal hypertension is a complication of biliary atresia and one of the indications for liver transplantation in children[13]. Studies on biliary atresia show a high percentage of portal hypertension[14,15]. As many as 70% of children with biliary atresia have oesophageal varices, and 59% of cases are younger than 2 years[16]. In biliary atresia, collateral vessels are often found between the hepatic veins. A previous study found hepatic venous shunt in 7 of 9 patients with biliary atresia[10]. Although portal hypertension is often determined by the development of complications or endoscopic findings, it can present at an advanced stage. Endoscopic screening examination is not practical in all children with biliary atresia[13]. Platelet count, spleen size, and platelet count/spleen size ratio can be used to predict the presence of portal hypertension. Splenomegaly predicts portal hypertension with a sensitivity of 97.7% and a specificity of 26.8% in children[6].

Defining portal hypertension based on the presence of bleeding oesophageal varices clinically can reduce its prevalence. Oesophageal variceal bleeding is rarely found in biliary atresia. Portal hypertension in biliary atresia occurs due to increased portal pressure that occurs earlier than the appearance of oesophageal varices and ascites. In addition, endoscopy has not been routinely recommended in biliary atresia[4,13,18]. Studies show that high serum total bilirubin levels, young age, and high number/grade of oesophageal varices correlate with the development of high-risk varices in biliary atresia[19]. Previous studies showed that the aspartate aminotransferase-to-platelet ratio index (APRI) could predict 96% of children with high risk varices[20].

In this study, comparing definite to absent portal hypertension, significant differences were found in AST, ALT, AST/ALT ratio, GGT, direct and total bilirubin, albumin, prothrombin time, white blood cell count, and haemoglobin. Previous studies showed that the ratio of platelet Z-score/spleen length, platelet count, international normalized ratio, AST/ALT ratio, and albumin levels were markers for children with oesophageal varices. Variables such as platelet count, spleen length Z-score, and albumin have a sensitivity of 94% and a specificity of 81% in predicting oesophageal varices in children[21]. Other studies suggest that splenomegaly and hypoalbuminaemia remain significant indicators of oesophageal varices in children. Splenomegaly has a sensitivity and negative predictive value of up to 97.7% and 91.7% in predicting oesophageal varices in children, higher than transient elastography[22,23].

In this study, for every one unit increase in haemoglobin, the risk of portal hypertension was 0.746 ($p<0.05$). Studies in adults suggest that the prevalence of iron deficiency anaemia is significantly higher in patients with severe portal hypertensive gastropathy which often occurs in liver cirrhosis[24]. The prevalence of anaemia with haemoglobin <10 g/dL increases with the severity of portal hypertension in adults with chronic liver disease[25]. The more severe the degree of liver disease, the more the haemoglobin can decrease[26]. There are several mechanisms that explain the relationship between anaemia and portal hypertension. Oesophageal varices can cause gastrointestinal bleeding leading to anaemia. Other conditions that can be found, such as portal hypertensive gastropathy and gastric antral vascular ectasia, can worsen anaemia in conditions of severe liver disease. The presence of defects in the erythrocyte lipid membrane can lead to the formation of acanthocytes which have a short lifespan due to the range of degradation in the spleen[27]. In portal hypertension, hypersplenism caused by splenomegaly can occur, causing pancytopenia and therefore can contribute to anaemia.

The risk of mortality and liver transplantation in biliary atresia with bleeding oesophageal varices increased with elevated total serum bilirubin levels, being 12-fold when total serum bilirubin level was >10 mg/dL; if the total serum bilirubin level was 4-10 mg/dL, the risk was reduced to 7.2-fold and 0.6-fold if the total serum bilirubin level was ≤4 mg/dL compared to biliary atresia without oesophageal variceal bleeding[9]. By knowing the non-invasive risk factors for portal hypertension, prospective treatment of children with biliary atresia can be carried out[4].

The approach to managing portal hypertension is well defined for adults, but is still limited in children with biliary atresia. The clinical diagnosis of portal hypertension is necessary in paediatric hepatology because direct measurement of portal pressure in children was highly invasive, especially in biliary atresia[4]. In addition to the basic physical examination, routine haematological and biochemical examinations are required periodically in biliary atresia to predict portal hypertension in children. Data on the characteristics of portal hypertension and laboratory markers in biliary atresia are limited. The main strength of this study is that it is prospective in biliary atresia. Further studies on risk factors for portal hypertension in biliary atresia are needed so that early detection can be made without invasive endoscopy.

Conclusions

In this study the risk factors for portal hypertension in children with biliary atresia included age, haemoglobin, prothrombin time, GGT levels, and the AST:ALT ratio.

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