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ORIGINAL ARTICLE

Prospective Study

Can platelet count/spleen diameter ratio be used for cirrhotic children to predict esophageal varices?

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Abstract

AIM

To determine the laboratory and radiologic parameters, including the platelet count (PC)-to-spleen diameter (SD) ratio as a non-invasive marker that may predict the presence of esophageal varices (EV) in children with cirrhosis.

METHODS

Eighty-nine patients with cirrhosis, but without a history of variceal bleeding were prospectively included. The children were grouped into 6-12 and 12-18 years of age groups. These groups were also divided into 2 subgroups (presence and absence of EV). All of the patients underwent a complete biochemical and radiologic evaluation. The PC (n/mm^3)-to-SD (mm) ratio was calculated for each patient.

RESULTS

Sixty-nine of 98 (70.4%) patients had EV. The presence of ascites in all age groups was significantly associated

with the presence of EV. There were no differences in serum albumin levels, PC, SD and the PC-to-SD ratio between the presence and absence of EV groups in both age groups ($P > 0.05$).

CONCLUSION

Laboratory and radiologic parameters, including the PC-to-SD ratio as a non-invasive marker (except for the presence of ascites), was inappropriate for detecting EV in children with cirrhosis.

Key words: Esophageal varices; Variceal bleeding; Platelet count-to-spleen diameter ratio; Children

Core tip: Laboratory and radiologic parameters, including the platelet count (PC)-to-spleen diameter (SD) ratio were investigated in children with cirrhosis as a non-invasive marker that may predict the presence of esophageal varices (EV). This study is the first study to assess the PC-to-SD ratio in children with cirrhosis for detecting EV according to age groups This study demonstrated that the parameters, other than the presence of ascites, were inappropriate for detecting EV in children with cirrhosis.

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INTRODUCTION

Esophageal variceal bleeding is among the most serious consequences of chronic liver disease[1]. Approximately two-thirds of children with cirrhosis have esophageal varices (EV), and the mortality associated with a variceal bleeding episode is 20%-35%[1-4]. Prevention of bleeding from a ruptured EV has become one of the main goals in the follow-up of these patients. Although a consensus has been reached for adults, there is no formal recommendation for endoscopic screening in children with cirrhosis[5].

Esophagogastroduodenoscopy (EGD) is the present reference standard diagnostic test for EV. Nevertheless, only 50%-70% of cirrhotic patients have varices on the first EGD and < 30% have large varices and/or the red wale sign (high-risk EV for bleeding) in adults and children[6-8]. Because of the relatively low prevalence of varices that require primary prophylaxis, the cost, inconvenience, and morbidity associated with endoscopic surveillance may not be justified for all patients with cirrhosis. To reduce the increasing burden on endoscopy units and prevent unnecessary harm to patients, researchers have attempted to identify parameters for non-invasive prediction of EV[9]. Several reports have identified non-invasive variables that may predict the presence of EV in childhood and have shown predictive factors for bleeding risk, such as hypoalbuminemia, the Child-Pugh score, an increased spleen diameter (SD), a low platelet count (PC), the PC-to-SD ratio, the clinical prediction rule, and the aspartate aminotransferase-to-platelet ratio index[6,7,10]. For this purpose, the PC-to-SD ratio was investigated to predict the presence of EV in adult patients with cirrhosis[11-14]. Chawla *et al*[15] concluded that the PC-to-SD ratio is elegant, simple and inexpensive, and it may become a helpful tool to limit the number of endoscopies for primary prophylaxis in adult patients with portal hypertension. Therefore, we conducted this study to investigate laboratory and radiologic parameters, including the PC-to-SD ratio, as predictors of EV in children with cirrhosis.

MATERIALS AND METHODS

All children (6-18 years of age) who had been diagnosed with cirrhosis in the outpatient clinics of the Paediatric Gastroenterology Hepatology and Nutrition at Baskent University, Ankara, Turkey, were included in this prospective study. The diagnosis of cirrhosis was made based on laboratory, radiologic, and physical examination findings or by liver histology in the absence of clear clinical signs of liver cirrhosis. Demographic characteristics (age, gender and underlying disease), blood chemistry evaluations, international normalized ratio, and Child-Pugh scores were recorded for each patient.

Patients with a clinical history of upper digestive hemorrhage, band ligation, sclerosing therapy, transjugular intrahepatic portosystemic stent shunt, surgery for portal hypertension, hepatic encephalopathy, and use of beta-blockers or other vasoactive drugs were excluded from the study.

The children were further grouped into 6-12 and 12-18 year age groups. These groups were divided into two sub-groups (EV-present and -absent) based on the EGD. The EGD was performed by the same paediatric endoscopists in our endoscopy unit using a video endoscope (Olympus GIF-XP 240; Tokyo, Japan or Fujinon EG 590W videoendoscopy; Tokyo, Japan). EV were classified according to the Baveno IV criteria[16,17] and American Association for the Study of Liver Diseases practice guidelines[18] as no, small, and large varices. EV were also classified according to the bleeding risk as high risk and non-high risk using varices diameters and red sign parameters.

The spleen bipolar diameter and presence of ascites were evaluated by ultrasonography (Siemens Sonoline Antares 4.1 MHz or 9.4 MHz probe; Siemens Medical Solutions United States, Inc., Issaquah, WA, United States) by the same radiologist.

The study design was approved by the Ethics Committee of our hospital (Study No. KA11/11252). Before enrollment, written informed consent was obtained from the primary caretaker of each patient.

We used SPSS software (version 16.0; SPSS, Inc.,

Table 1 Laboratory and ultrasonographic data in the age group of 6-12 years

	Patient with varices (n = 29)	Control (n = 13)	P value
Mean age (yr)	9.7 ± 2.0	10.0 ± 1.9	0.595
Gender (% female)	45	38.5	0.384
INR	1.5 ± 0.5	1.4 ± 0.5	0.860
ALT (IU/L)	57.3 ± 50.8	44.3 ± 29.3	0.210
AST (IU/L)	79.1 ± 71.5	53.1 ± 32.9	0.241
Total bilirubin (mg/dL)	3.5 ± 6.0	2.5 ± 4.7	0.618
Albumin (mg/dL)	3.9 ± 0.6	4.2 ± 0.6	0.231
Ultrasonographic ascites (%)	27.5%	0%	0.037
Spleen diameter (mm)	167.3 ± 39.1	151.3 ± 32.4	0.206
Platelet count (thousand/mm^3)	129000 ± 53519	153000 ± 97798	0.312
Platelet count/spleen diameter	976.6 ± 793.5	1062.4 ± 718.0	0.741
Child-Pugh score	6.3 ± 1.5	5.7 ± 1.4	0.193

INR: International normalized ratio; ALT: Alanine transaminase; AST: Aspartate transaminase.

Table 2 Laboratory and ultrasonographic data in the age group of 12-18 years

	Patient with varices (n = 40)	Control (n = 16)	P value
Mean age (yr)	14.2 ± 1.7	13.5 ± 1.2	0.161
Gender (% female)	48	56	0.591
INR	1.3 ± 0.3	1.4 ± 0.6	0.347
ALT (IU/L)	86.5 ± 76.1	60.5 ± 67.2	0.250
AST (IU/L)	115.2 ± 124.2	105.5 ± 231.8	0.842
Total bilirubin (mg/dL)	5.0 ± 10.4	5.3 ± 12.5	0.931
Albumin (mg/dL)	3.8 ± 0.7	3.9 ± 0.7	0.757
Ultrasonographic ascites (%)	35%	6%	0.028
Spleen diameter (mm)	181.4 ± 37.2	150.3 ± 34.2	0.389
Platelet count (thousand/mm^3)	103000 ± 55867	115000 ± 65472	0.499
Platelet count/spleen diameter	733.9 ± 737.4	830.78 ± 553.5	0.637
Child-Pugh score	6.9 ± 1.9	6.2 ± 1.8	0.214

INR: International normalized ratio; ALT: Alanine transaminase; AST: Aspartate transaminase.

Chicago, IL, United States) for statistical analysis. Data are expressed as the mean and standard deviation and proportions. For comparison of categorical variables, Fisher's exact test or a χ^2 test was used. Differences between numeric variables were tested with a Mann-Whitney U-test. Values of $P < 0.05$ were considered to indicate statistically significant differences.

RESULTS

Ninety-eight children with cirrhosis were included in this study. The ages of the children ranged from 6-18 years (median age, 12.16 ± 2.70 years). Forty-six children were females (46.9%) and 52 were males (53.1%).

The etiology of cirrhosis was cryptogenic cirrhosis (n = 40), Wilson's disease (n = 35), progressive familial intrahepatic cholestasis (2), sclerosing cholangitis (n = 4), Budd-Chiari syndrome (n = 4), tyrosinemia (n = 3), glycogen storage disease (n = 3), autoimmune hepatitis (n = 2), hepatitis B infection (n = 2), Allagille syndrome (n = 2), and alfa1-antitrypsin deficiency (n = 1). Sixty-one patients were Child-Pugh class A, 29 were class B, and 8 were class C.

In this study, 69 children (70.4%) were shown to have EV based on the first EGD and 29 children (29.6%) were shown not to have EV.

Fifty-five of the 69 patients had small EV (79.7%) and 14 patients (20.3%) had large EV. There were 11 children (15.9%) with red wale signs (seven children had large EV and four children had small EV). Therefore, 18 of the 69 patients with EV (26.1%) had high-risk EV for bleeding according to the presence of large varices and/or red sign (six patients in the 6-12 year age group, and 12 patients in the 12-18 year age group).

There were no differences in age and gender between the EV-present and -absent sub groups in both age groups ($P > 0.05$). In the two age groups, a higher percentage of ascites was observed among the EV-present group than the EV-absent group (Tables 1 and 2). We did not find a statistically significant difference in the PC-to-SD ratio between patients with large and small varices (636.9 ± 256.5 and 894.1 ± 844.4, respectively; $P = 0.89$).

We did not find a significant difference for serum albumin, PC, SD and the PC-to-SD ratio between the EV-present and -absent varices sub-groups in both age groups ($P > 0.05$; Tables 1 and 2).

DISCUSSION

Despite advances in diagnosis and treatment, bleeding from EV is one of the major causes of morbidity and mortality among patients with cirrhosis. Hence, preventing the first episode of variceal bleeding may reduce mortality and morbidity.

In this prospective study involving children 6-18 years of age with cirrhosis, we found that only the presence of ascites is associated with the presence of EV. There have been several studies identifying non-invasive variables that may predict the presence of EV in children[6,7,10]. The first study, in which the predictive risk factors were evaluated by Fagundes *et al*[6] in a pediatric group [median age at the time of first EGD was 6 years (age range, 0.7-17.6 years)], showed that children with cirrhosis and splenomegaly were nearly 15-fold more likely to have EV compared with children with cirrhosis but without splenomegaly. Fagundes *et al*[6] concluded that hypoalbuminemia, splenomegaly, and a PC < 130000/mm^3 were predictors for the presence of EV, spleen size was not measured by ultrasonography. The second study, conducted by Gana *et al*[7], derived a non-invasive clinical prediction rule capable of identifying children with EV. In this study, 17 of 51 children (< 18 years of age) with liver disease or portal vein thromboses were shown

to have EV, and hypoalbuminemia was shown to be an independent variable for the presence of EV. In the same study[7], a higher percentage of ascites, increased spleen length, and lower PC (cut-off value = 115000/mm^3) were reported among children with EV. Further, the PC-to-spleen length-for age Z score ratio was significantly lower among the EV-present group[7].

Fagundes *et al*[6] and Gana *et al*[7] reported lower albumin levels among children with EV. Our results were not in agreement with the findings of these two studies. A possible explanation may be the difference in etiologic factors in our patients.

A recent study involving 103 patients with a diagnosis of chronic liver disease or extrahepatic portal vein obstruction (mean age, 8.9 ± 4.7 years) showed a significantly higher spleen length and lower PC (cut-off value = 115000/mm^3) among children with EV than children without EV[10]. In the same study, it was reported that a PC-to-spleen size (cm) ratio < 1.0 discriminated between patients with and without EV, despite a lack of statistical significance based on logistic regression. The authors suggested that the lack of statistical significance was explained by the age and gender differences in spleen size.

Based on the findings of these three studies[6,7,10], low PC and increased spleen length are logical parameters by which to determine EV in children with cirrhosis. In addition, Gana *et al*[7] and Adami *et al*[10] reported that PC (cut-off value = 115000/mm^3) was the best predictor of EV.

In the current study, we did not find a significant difference for PC, SD and the PC-to-SD ratio between the EV-present and -absent sub-groups in both age groups. A possible explanation is the heterogeneity of patients studied. Another explanation is the lack of children with portal vein thromboses in the current study. The three studies investigating risk factors for EV included children with cirrhosis and portal vein tromboses[6,7,10]. It is well-known that portal vein thrombosis is a risk factor for splenomegaly and thrombocytopenia. The PC loses discriminatory power because of multi-causality (such as autoimmune events, myelotoxic effects of viruses, or reduced synthesis of thrombopoietin) as a consequence of progressive liver dysfunction; however, in children with portal vein thromboses, thrombocytopenia is directly related to portal hypertension, as well as the development of varices[19].

One of the most important limitations of our study was the small number of patients; however, this study was the first study to assess the PC-to-SD ratio in children in two age groups with cirrhosis as a means to detect EV. We consider the PC, SD and PC-to-SD ratio to lack suitability as non-invasive markers for detecting EV in children with cirrhosis. Further studies on this subject with larger sample sizes are required to assess the importance of the PC, SD and PC-to-SD ratio in cirrhotic children with or without portal vein thrombosis.

COMMENTS

Background

Esophageal variceal (EV) bleeding is among the most serious consequences of chronic liver disease. Approximately two-thirds of children with cirrhosis have EV and the mortality associated with a variceal bleeding episode is 20%-35%. Identification of children with cirrhosis who are at high risk for EV using a non-invasive test is important to reduce the need for endoscopy. The authors' goal was to investigate laboratory and radiologic parameters, including the platelet count (PC)-to-spleen diameter (SD) ratio to predict the presence of EV in children with cirrhosis.

Research frontiers

To reduce the increasing burden on endoscopy units and prevent unnecessary harm to patients with cirrhosis, researchers have attempted to identify parameters for the non-invasive prediction of EV.

Innovations and breakthroughs

A few studies have shown that a low PC and PC-to-SD ratio may predict the presence of EV in patients with cirrhosis. In their study, the authors did not find a significant difference in the PC, SD and PC-to-SD ratio between the EV-present and -absent sub-groups in both age groups of children.

Applications

The PC-to-SD ratio is not an appropriate index with which to predict EV in children with cirrhosis. This may indicate that endoscopy remains the ideal choice for detecting EV in children with cirrhosis.

Terminology

Esophageal varices are abnormal, enlarged veins which generally occur in patients with serious liver diseases. The vessels can leak blood, or even rupture, thus causing life-threatening bleeding.

Peer-review

It is helpful for clinical doctors to perform endoscopic examination promptly.

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