Non-invasive Predictors of Esophageal Varices With a High Risk of Bleeding in Pediatric Cirrhotic Patients

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ABSTRACT

Objectives: To evaluate non-invasive predictive factors of varices with a high risk of bleeding in pediatric cirrhotic patients.

Methods: This retrospective, cross-sectional study included data from 158 children with cirrhosis, median age of 5.38 years (interquartile [IQ] 2.08−11.52 years), and no history of upper gastrointestinal bleeding. Patients underwent an endoscopy to screen for esophageal varices. Varices with a high risk of bleeding were defined as those with a medium to large caliber, presence of red spots, or the presence of gastric varices and identified as high-risk varices (HRV). Laboratory and clinical factors were evaluated as possible predictors of HRV.

Results: HRV were detected in 30 children (19%) after the first endoscopy. In the multivariate analysis, only the risk score (RS), as described by Park et al, and the aspartate aminotransferase-to-platelet ratio index (APRi) were predictive of HRV. The best non-invasive predictor of HRV was the RS with an area under the receiver operating characteristic curve of 0.764. When used a cut-off point of −1.2, the sensitivity of the RS was 90% and specificity was 53%. The use of RS or APRi correctly identified 96% of children with HRV.

Conclusions: The described predictors allow the correct identification of patients with HRV. The association of RS >-1.2 or APRi >1.4 has a good sensitivity to identify HRV and to prevent unnecessary endoscopy in about one-third of children with no HRV.

Key Words: children, esophageal varices, liver cirrhosis

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What Is Known

- Variceal bleeding can cause significant morbidity in children with cirrhosis.
- There are no non-invasive tests that permit evaluation of varices with a high risk of bleeding in children with cirrhosis

What Is New

- The risk score (RS) was the best predictor of varices with a high risk of bleeding in children with cirrhosis.
- The association of RS >-1.2 or aspartate aminotransferase-to-platelet ratio index (APRi) >1.4 has a good sensitivity to identify high-risk varices (HRV) and to prevent unnecessary endoscopy in about one-third of children with no HRV.

Portal hypertension (PH) is a complication of liver cirrhosis with systemic repercussions such as ascites, hepatorenal syndrome, hepatic encephalopathy, and the formation of esophageal varices (EV) or gastric varices (GV) (1). Upper gastrointestinal

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bleeding (UGIB) secondary to the rupture of EV is the most significant complication impacting morbidity and mortality (2).

Until 2015 when the recommendations for adults with cirrhosis changed (2), endoscopy was recommended for every cirrhotic adult patient to search for varices (3). However, endoscopy is an invasive, expensive examination and current recommendations have changed to avoid unnecessary procedures in patients who did not have a high risk of bleeding. Adult patients with a liver stiffness <20 kPa and with a platelet count >150,000/mm^3 have a extremely low risk of having varices requiring treatment, and can avoid screening endoscopy (2). Using these parameters, more than 95% of the high-risk esophageal varices (HRV) cases can be correctly identified and 20% of cirrhotic adults avoid undergoing unnecessary endoscopy (4).

The concern regarding unnecessary examinations is even more acute in children (5). Since the first publication about noninvasive predictors of EV in children in 2008 (6), there remains little guidance on the effectiveness of predictive factors to exclude pediatric patients without HRV (5,7–9). Because there is limited data in the literature regarding cirrhotic children and adolescents, the present study aims to evaluate the strength of predictive factors to identify HRV in pediatric cirrhotic patients.

METHODS

This retrospective, cross-sectional study was conducted through the Pediatric Hepatology Ambulatory outpatient services of the Hospital das Clínicas of Universidade Federal de Minas Gerais (HC-UFMG) from January 2004 to September 2018. The study was approved by the Ethics Committee of HC-UFMG number 60087316.2.00005149.

Patients under 18 years of age with liver cirrhosis who submitted to a first endoscopy for the screening of EV with no history of previous UGIB were included in the study. Diagnosis of cirrhosis was confirmed by biopsy after clinical, laboratory, and radiological investigation.

Were excluded from the study patients 18 years or older, patients with a history of previous UGIB, use of beta-blockers, previous endoscopic intervention, previous surgical portosystemic shunt or liver transplant, or malignant neoplasms of the liver.

After the diagnosis of liver cirrhosis, the patients were submitted to endoscopy. Examinations were carried in the presence of at least two experienced pediatric endoscopists to validate endoscopic findings. Gastric varices were classified according to Sarin et al (10). PH gastropathy was classified as mild when a light mosaic pattern was found with no presence of red spots and severe when the mosaic pattern was covered by red spots, or if any other red spot was present (11).

EV were classified according to the Japanese Research Society for Portal Hypertension (12) system in three grades: Grade I (thin caliber): small, not tortuous; Grade II (medium caliber): moderately increased, tortuous; and Grade III (large caliber): greatly increased, nodular, occupying more than one-third of the esophageal lumen. The presence of red wale markings, cherry-red spots, hematocystic spots, and other evidence of bleeding in EV was classified as red spots.

Several laboratory and clinical factors were evaluated in addition to predictive scores of fibrosis and PH, in particular, platelet count, presence of palpable spleen on physical examination, Child-Pugh classification, aspartate aminotransferase-to-platelet ratio index (APRi) (13), fibrosis index (FI) (14), risk score (RS) (15), and variceal prediction rule (VPR) (7). These scores were calculated as follows:

- APRi: $\frac{\frac{AST}{ULN}}{platelets\frac{10^9}{L}} \times 100$ (ULN = upper limit of normality)
- Variceal prediction rule: $Albumin\frac{g}{dL} \times platelets\frac{10^9}{L}/100$
- Risk score: $14.2-\left(7.1\times\log\ \ platelets\frac{10^9}{L}\right)+\left(4.2\times\log\ \ bilirrubin\frac{mg}{dL}\right)$
- Fibrosis index: $8.8-\left(Albumin\frac{g}{dL}\times 1.08\right)-\left(0.01\times\frac{platelets\frac{units}{mm^3}}{1000}\right)$

Laboratory tests were carried out within a maximum of 3 months from the endoscopy procedure. Splenomegaly in children older than 1 year was determined by the presence of a palpable spleen regardless of the size. In children younger than 1 year, splenomegaly was diagnosed when the spleen was present more than 2 cm of the left costal margin.

Statistical Analysis

For the statistical analysis, patients were divided into those with and without HRV. Esophageal varices with medium and/or large caliber, the presence of red spots, or the presence of GV were considered as HRV (16–19).

Calculations of means, medians, standard deviation, interquartile interval ([IQI] 25−75%), and interquartile range (IQR Q3−Q1) were used to summarize group characteristics. Categorical variables were assessed by Fisher exact test and chi-square test for comparison. For continuous variables, the normality test was performed and for normal variables, the Student *t*-test was performed. For non-normal variables, a non-parametric test to compare medians was used. A receiver operating characteristic curve (ROC) was built to analyze the sensitivity and the specificity of continuous variables and then the positive predictive value (PPV) and the negative predictive value (NPV) were assessed for each variable studied according to the point of best sensitivity and specificity.

The univariate logistic regression model was adjusted for the multivariate analysis. Continuous variables were dichotomized according to the point of best sensitivity and specificity on the ROC curve. All variables that were significant at the level of 0.20 were considered for the multivariate model. The multivariate logistic model was adjusted and variables with higher values of *P* were removed step-by-step until the final model contained variables significant at a level of 0.05 and a 95% confidence interval (CI). The adjustment quality of the logistic regression model was verified by the Hosmer & Lemeshow test. The level of significance was 0.05. The software used was SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 158 patients with a median age of 5.38 years (IQI: 2.08–11.52 years) were included in the present study. The most prevalent etiologies were biliary atresia (BA) and autoimmune hepatitis (AIH). Patient demographic data are summarized in Table 1.

EV of any grade were identified in 71 patients (44.9%) and HRV were identified in 30 patients (19%). Gastric varices were seen in 9 patients (5.7%) and all cases were associated with medium to large caliber EV. PH gastropathy was present in 29 patients (18.4%) with 24 mild and 5 severe cases.

Table 2 shows the main variables studied for the presence of HRV. Statistically significant variables in the univariate analysis were: Child-Pugh classification, splenomegaly, platelet count, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TB), and all of the clinically evaluated scores.

In the multivariate model, RS and APRi were the only factors associated with HRV. RS >−1.2 increased the likelihood of having HRV in almost 10 times (odds ratio [OR] 9.89, 95% CI 2.16–45.26;

TABLE 1. Demographic characteristics of the sample

Variable	HRV (n = 30)	Absence of HRV (n = 128)	*P* value
Sex (male/female)	10/20	60/68	0.136
Age, years (IQR)	4.25 (11.16)	5.41 (9.42)	0.922
Etiology, n (%)			0.094
Biliary atresia	13 (23.2)	43 (76.8)	
Autoimmune hepatitis	5 (11.4)	39 (88.6)	
Autoimmune cholangitis	4 (33.3)	8 (66.7)	
Sclerosing cholangitis	2 (18.2)	9 (81.8)	
Alpha 1-antitrypsin deficiency	1 (7.7)	12 (92.3)	
Cryptogenic cirrhosis	4 (40)	6 (60)	
Others	1 (8.8)	11 (91.7)	

HRV = high-risk varices; IQR = interquartile range.

TABLE 2. Univariate analysis of the presence of HRV

Variable	HRV (n = 30)	Absence of HRV (n = 128)	*P* value
Child-Pugh, A/B/C	17/11/2	106/19/3	**0.009**
Splenomegaly	29	91	**0.019**
Platelets/mm^3 (IQR)	114,500 (112,000)	177,000 (148,000)	**0.009**
Albumin g/dL (IQR)	3.65 (1.18)	4.00 (0.70)	0.070
AST U/L (IQR)	160 (260)	99.5 (137)	0.690
ALT U/L (IQR)	126 (187)	113 (141)	0.670
ALP U/L (IQR)	588 (616)	327 (339)	**0.010**
GGT U/L (IQR)	339 (307)	138 (262)	**0.003**
INR (IQR)	1.19 (0.50)	1.09 (0.25)	0.062
TB mg/mL (IQR)	2.1 (2.62)	1.0 (2.00)	**0.002**
APRi (IQR)	3.24 (7.43)	1.49 (2.65)	**0.002**
FI (SD)	3.8 (1.17)	2.5 (1.4)	**<0.001**
VPR (IQR)	3.5 (1.49)	6.9 (1.88)	**<0.001**
RS (SD)	1.56 (2.22)	−1.29 (2.74)	**<0.001**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APRi = aspartate aminotransferase-to-platelet ratio index; AST = aspartate aminotransferase; FI = fibrosis Index; GGT = gamma-glutamyl transferase; HRV = high-risk varices; INR = international normalized ratio; IQR = interquartile range; RS = risk score; SD = standard deviation; TB = total bilirubin; VPR = variceal prediction rule.

$P = 0.003$) and APRi >1.4 in almost four times (OR 3.92, 95% CI 1.05–14.59; $P = 0.042$). Splenomegaly, which is associated with the presence of EV, did not remain as a risk factor for HRV in the multivariate analysis.

In ROC curve analyses, the RS showed the best result for detecting HRV. However, the area under the ROC curve (AUC) for each test showed no significant differences (Table 3).

Indices of sensitivity, specificity, PPV, and NPV were calculated and can be seen in Table 3. The platelets showed the best results for specificity (83.5%), with a sensitivity of 43.3%, which was lower than most predictors alone. Although splenomegaly was not significant in the multivariate analysis, when used alone it had the best index of sensitivity (96.7%) to detect HRV but with low specificity (28.3%).

The predictors were analyzed according to the etiologies of cirrhosis and divided into three groups with significant sample size, and the result is given in Table 4. There were no statistical differences between the groups in the performance of the scores, but all of them exhibited the best AUC in the AIH group.

The association of two factors improved the sensitivity to detect HRV (Table 3). The presence of RS >−1.2 or APRi >1.4 successfully identified 95% of the children with HRV and would avoid endoscopy in approximately 34% of patients without HRV.

DISCUSSION

The present study aimed to evaluate the strength of predictive factors to identify HRV in pediatric cirrhotic patients and found that the association of tests may be the best strategy. The association of RS >−1.2 or APRi >1.4 successfully identified 96% of the children with HRV and would avoid endoscopy in approximately one-third of patients without HRV if used as an indicator to screen high-risk patients. Upper digestive hemorrhage is one of the main complications of cirrhosis and approximately 90% of cirrhotic children who had UGIB have medium to large caliber EV (19). Because endoscopy is an invasive procedure, the best strategy is to focus on identifying patients with HRV that can benefit from primary prophylaxis of bleeding. Good clinical triage methods should be easy to use, slightly or noninvasive, have good reproducibility and low cost. Conversely, imaging tests require experienced technicians and the results are not easily reproduced.

The present study is the second to assess the RS, elaborated by Park et al (15) to detect a significant PH and EV in adult patients with advanced liver fibrosis, for its potential to detect HRV in children and it was the score with the best performance. Adami et al (20) conducted the first study using the score in children, they

TABLE 3. Evaluation of factors for predicting HRV

Variable (cut-off point)	AUC	95% CI	*P* value	Sens	Spe	PPV	NPV
Platelets (<100,000/mm^3)	0.709	0.612–0.807	<0.001	0.433	0.835	0.617	0.860
(<150,000/mm^3)				0.633	0.601	0.271	0.874
APRi (>1.4)	0.744	0.654–0.834	<0.001	0.867	0.507	0.292	0.913
VPR (<7.2)	0.752	0.662–0.842	<0.001	0.833	0.484	0.274	0.925
FI (>3.12)	0.762	0.676–0.849	<0.001	0.800	0.632	0.338	0.930
RS (>−1.2)	0.764	0.691–0.847	<0.001	0.900	0.530	0.310	0.957
Splenomegaly				0.967	0.283	0.242	0.973
Splenomegaly or RS (>−1.2)				1.000	0.197	0.227	1.000
Splenomegaly or APRi (>1.4)				1.000	0.181	0.224	1.000
RS (>−1.2) or APRi (>1.4)				0.966	0.341	0.252	0.977

APRi = aspartate aminotransferase-to-platelet ratio index; AUC = area under the ROC curve; CI = confidence interval; FI = fibrosis index; HRV = high-risk varices; NPV = negative predictive value; PPV = positive predictive value; RS = risk score; Sens = sensitivity; Spe = specificity; VPR = variceal prediction rule.

TABLE 4. AUC for factors predicting HRV according to etiology of cirrhosis

Variable	AUC		
	BA (n = 56)	AIH (n = 44)	Others (n = 58)
Platelets	0.639 (95% CI 0.488–0.789)	0.826 (95% CI 0.667–0.985)	0.809 (95% CI 0.669–0.949)
VPR	0.696 (95% CI 0.546–0.846)	0.856 (95% CI 0.735–0.978)	0.832 (95% CI 0.714–0.951)
FI	0.715 (95% CI 0.566–0.863)	0.859 (95% CI 0.721–0.997)	0.853 (95% CI 0.751–0.955)
RS	0.782 (95% CI 0.664–0.901)	0.923 (95% CI 0.837–1.000)	0.870 (95% CI 0.771–0.969)
APRi	0.662 (95% CI 0.512–0.813)	0.846 (95% CI 0.680–1.000)	0.814 (95% CI 0.685–0.943)

AIH = autoimmune hepatitis; APRi = aspartate aminotransferase-to-platelet ratio index; AUC = area under the ROC curve; BA = biliary atresia; CI = confidence interval; FI = fibrosis index; RS = risk score; VPR = variceal prediction rule.

analyzed 98 cirrhotic children for HRV and found an AUC of 0.66, a sensitivity of 85.7% and specificity of 46.3% using the same cut-off point, similar to our results (20).

APRi has been elaborated as a predictor of fibrosis and cirrhosis in adults with chronic hepatitis C virus (13) and as a predictor of EV. In children, it was studied with conflicting results with sensibility varying between 60% and 70% and specificity 55% and 63% (7,8,21). Adami et al (20) using a cut-off point of 1.4 found a lower sensitivity and specificity, 57.1% and 47%, respectively. In the present study, with the same cut-off point, APRi had a higher sensitivity (86.7%), but a similar specificity (50.7%). Differences between the results from these studies may be partly due to different cut-off points used and the etiology of cirrhosis, which affect the performance of the predictive factors of HRV. We did not found any statistical difference between BA and AIH, but it is necessary more studies with a larger sample size. Only multicenter studies, with an adequate number of patients, may delineate these differences.

In adults, only the association of both platelets and liver elastography enabled safe screening for the presence of HRV (2). Elastography is still a test that is not easily accessible to all centers, depends on an operator, and in children still lacks evidence of its superiority to other methods (21–24). Consequently, it is still desirable to make the decision of triage based on laboratory and clinical tests that are easily accessible and used in routine patient assessment. In the present study, an association of RS and APRi correctly identified 96% of patients with HRV while preventing unnecessary tests. This is a good result, but it still needs validation in other studies with children and adolescents. The idea of associating tests was also explored by Adami et al but in their work, they used scores that rely on ultrasound findings, what we aimed to avoid, and found encouraging results, with the sensibility of 100% when clinical prediction rule, platelet count, and platelet/spleen z score were used (20).

Although the present study relied on a large number of patients for the pediatric age range, it has some limitations. It is a retrospective study, based in cost records, single-center, with high heterogeneity of cirrhosis etiology, which may have confounded the variables and there are no established cut-off points for the variables studied so the values used may not be suitable for other populations. Further studies are required to optimize scores or algorithms, which include the etiology of cirrhosis, to stratify patients according to UGIB risk.

In conclusion, the predictors described in the present study allow for the correct identification of patients at risk of HRV; however, they are still limited for detecting patients with a low risk of upper digestive hemorrhage. The association of RS and APRi has a good sensitivity to identify HRV and to prevent unnecessary endoscopy in about one-third of children with no HRV.

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