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Research article

Prospective Evaluation of Predictive Indexes for Esophageal Varices in Children and Adolescents with Portal Hypertension

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Abstract

Introduction: Esophageal varices (EV) are a consequence of portal hypertension (PH) that could lead to death if a rupture occurs. The EV survey is performed with the use of esophagogastroduodenoscopy (EGD), aiming at diagnosis and early treatment. It is important to establish noninvasive predictive indexes of EV that could help avoid unnecessary UE. Objectives: to evaluate the accuracy of noninvasive predictive indexes, when compared to UE, to diagnose EV in children and adolescents with PH; follow-up the patients with initial diagnosis of EV that is considered treatable (grades 2 and 3) in three consecutive moments; to correlate the increasing of the portal gastropathy (PG) with the eradication of the EV. Methods: Prospective, single-center study, in pediatric patients diagnosed with PH from 2014 to 2017. The variables platelet count, albumin, Z score of the spleen, APRI (AST to platelet radio index), P/SSAZ (platelet to spleen Z score radio) and CPR (clinical prediction rule) were evaluated. Values <0.05 were considered significant different. Sensitivity was calculated based on the cutoff points for the different predictive variables. ROC curve area was calculated with the corresponding 95% Mean Confidence Interval. Results: 69 patients were included, 46 with and 23 without EV at the first UGD. Prematurity, splenomegaly and umbilical catheterization were risk factors associated with EV. Platelet count < 117,000 mm³, albumin < 3.9 mg/dL, z score of the spleen >3.67, APRI > 0.64, P/SSAZ< 24.86 and CPR< 108.2 were the cutoff values for EV graded as treatable (grades 2 and 3). During the follow-up of 14 patients that received EBL in 3 consecutive UEs, the accuracy of the evaluated variables was maintained. The eradication of varices was positively correlated with the increase of the HG. Conclusion: Platelet count, albumin, z score of the spleen, APRI, P/SSAZ and CPR were good predictive indexes of EV, and should be used to select the patients for UE, avoiding unnecessary exams.

Introduction

Portal hypertension (PH) may be defined in children and in adults, as pressure in the portal venous bed higher than 10mmHg [1]. When the pressure in the portal circulation exceeds 12 mmHg, complications as splenomegaly, hypersplenism, hypertensive gastropathy (HG), esophageal varices (EV), gastric varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, pulmonary hypertension and hepatorenal syndrome may occur [2]. The main PH causes in childhood are biliary atresia (BA), extra hepatic portal vein obstruction (EHPVO) and congenital hepatic fibrosis.

The gastrointestinal hemorrhage caused by the EV rupture is the main cause of morbidity and mortality in the pediatric PH patients [3]. The age of the first bleeding episode varies with the PH etiology. It is 3 years old in BA, 5 years old in the EHPVO [3]and 8.6 years old in the congenital hepatic fibrosis [4]. Data from Pediatric Hepatic Centers show that more than 50% of cirrhotic children have EV [5,6]. Duché et al. [7] suggested primary prophylaxis for EV with a high risk of bleeding, after the prospective evaluation of 139 children operated on BA. They observed that

90% presented with signs of PH, 70% developed EV and 20% had EV rupture and gastrointestinal bleeding before 17 months old. However, there are few reports of the EV prevalence in children with PH, and therefore it is difficult to predict who would benefit from the routinely endoscopic screening. Besides this fact, the uncertainty of the impact of any type of prophylaxis makes the endoscopic screening questionable [8].

There are no consensus about the periodicity that the endoscopic exams should be performed in EV screening programs. Besides the diagnosis of EV, its stage and the rupture risk, the esophagogastroduodenoscopy (EGD) may also treat prophylactically the EV [3]. Otherwise, it is an invasive exam, with risks related to the anesthesia, to the procedure itself and has a high financial cost. The American Association for the Study of Liver Diseases and the American College of Gastroenterology recognized the study of predictive tests of EV as one of the most important areas of PH research [9]. In the last years, several studies related the presence of EV with clinical, laboratory and/or ultrasonographic parameters aiming the prediction of their existence, without the EGD. Two retrospective studies in pediatric population analyzed predictive parameters of EV, trying to avoid EGDs. Fagundes et al. [10] reported splenomegaly and hypoalbuminemia as indicators of the occurrence of EV in 85 patients with chronic PH (EHPVO and CHF). Gana et al. [11], in a multicentric study with 108 children with PH, evaluated the size of the spleen using ultrasonography (US) and related the results with the platelets count and albumin concentration at CPR index (Clinical Prediction Rule) and concluded that this index was an indicator of EV.

Considering the paucity and controversies of the studies about the routine use of EGD in children with PH, the aim of this study was to evaluate prospectively the accuracy of the noninvasive predictive tests, when compared to EGD to diagnose and follow-up the EV in children and adolescents with PH.

Methods

We conducted a prospective, single-center study in children aged <15 years old, with diagnosis of PH, from 2014 to 2017 at Botucatu Medical School Hospital, a referral center for pediatric hepatic diseases. Children that had previously used β-blockers, presented active variceal bleeding, had been submitted to surgical portosystemic shunt or transjugular intrahepatic portosystemic shunt insertion or liver transplantation were excluded from the study.

Demographic and clinical data (gender, age, prematurity, umbilical catheterization, hepatomegaly, splenomegaly), laboratory tests (hemoglobin, platelets count, aspartate aminotransferase - AST, alanine aminotransferase - ALT, gamma-glutamyl transpeptidase – GGT, alkaline phosphatase – AP, bilirubin, albumin, prothrombin activity time – PAT, partial thromboplastin time – PTT) and ultrasound were performed in the previous 2 months of EGD.

The EGD was carried out as part of routine clinical care of children with PH. The same endoscopist recorded variceal size (F1, F2 and F3), red color signs and hypertensive gastropathy, according to Japanese Research Society for Portal Hypertension Classification. These data were used to separate the patients in groups considered non treatable (F1 varices) and treatable (F2 and F3 varices). The mean time between EGDs was determined according to the findings of the first exam. If there were no varices, the next EGD was performed in 2 years. If there were varices grade 1, the next EGD was performed in one year. After EV eradication, the next EGD would be in 6 months, and if it was normal, the next exam would be every 1- 2 years. Patients that had their EV treated with EBL (esophageal band ligation), were followed during 3 consecutive EGDs, repeating laboratory tests and ultrasound to analyze the performance of the non-invasive predictive tests also in a time line.

The predictive indexes calculated were:

- APRI (Aspartate aminotransferase-to-platelet ratio index): AST/platelet count ratio [12,13].

- P/SSAZ: Platelets count/ spleen size Z score on US [14]

- CPR: (0,75 x platelets count/ spleen size Z score+5) +2,5 x albumin [13]

The spleen size z score was expressed as a standard deviation score relative to normal values for age and gender [15].

Statistical analysis: p values <0,05 were considered significant different. Sensitivity was calculated based on the cutoff points for the different predictive variables. ROC curve area was calculated with the corresponding 95% Mean Confidence Interval. GraphPad Prism Version 5.0, 2005 (GraphPad Software Inc. San Diego, CA, USA) was used.

Result

The PH etiologies were autoimune hepatitis (n=15), biliary atresia (n=12), EHPVO (n=9), glycogenosis (n=5), autoimune sclerosing cholangitis (n=5), idiopatic (n=5), Deficiência de alpha1 antitrypsine deficiency (n=4), progressive intrahepatic familial cholestasis type 1 – PFIC (n=2), PFIC type 2 (n=2), PFIC type 3 (n=1) , Budd-Chiari syndrome (n=1), pileflebite (n=1), congenital hepatic fibrosis (n=1) , doença veno-oclusiva (n=1), Caroli syndrome (n=1), Wilson's disease (n=1), coledochal cyst (n=1), Alagillle syndrome (n=1), cystic fibrosis (n=1).

The comparison between children with and without EV in demographics, clinical and laboratory variables showed that there were higher values in prematurity, splenomegaly, previous umbilical catheterization, PAT, PTT, platelets count, albumin, SSAZ, APRI, P/SSAZ and CPR in the EV group (Table 1).

Table 2 compares the demographics, clinical and laboratory data of the 23 children with EV divided according to their EV grades (F1 or F2 e F3) in their first EGD. There were difference between groups to prematurity, splenomegaly and previous umbilical catheterization.

The cutoff values, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under ROC curve (AUROC) to the presence of EV are presented in table 3. The highest AUROC were noticed for platelets count, P/SSAZ and CPR and were considered excellent.

In the patients with varices F2 and F3, the highest values to AUROC were found for platelets, P/SSAZ and CPR that were considered excellent (Table 4).

In the follow-up of patients with EV that required EBL, in

Table 1. Demographics, clinical and laboratory characteristics in PH children, divided according to the presence or absence o

	Varices n=23	No varices n=46	p<
Gender M/F(%M)*	11/23 (47%)	28/46 (60%)	0,3
Age (months)**	60 (19-96)	48 (24-97)	0,9
Prematurity*	10/23 (43%)	4/46 (8,5%)	0,01
Hepatomegaly*	09/23 (39%)	26/46 (56%)	0,2
Splenomegaly*	23/23 (100%)	38/46 (82%)	0,04
Umbilical catheterization*	09/23 (39%)	01/46 (2%)	0,001
Hemoglobin (g/dL)**	11,3 (9,8-12,9)	11,9 (11,4-12,7)	0,19
AST u/L**	54 (35-84)	49 (36-104)	0,8
ALT u/L**	88 (48-125)	53 (33-150)	0,2
Gama GT u/L**	52 (22-360)	49 (24-97)	0,59
Alkaline phosphatase u/L**	26 (204-451)	257 (224-329)	0,51
Bilirrubin mg/dL**	0,8 (0,5-1,6)	0,85 (0,5-1,1)	0,9
TAP**	1,2(1,1-1,4)	1,1(1,02-1,2)	0,02
TTPA**	1,23(1,2-1,5)	1,1(1,03-1,2)	0,001
Platelets x10³µ	93 (78-115)	259 (188-319)	0,0001
Albumin g/dL	3,5 (3,1-4,0)	4,1 (4,0-4,5)	0,001
Spleensize Z score (SSAZ)	4,8 (3,7-5,5)	1,0 (0,2-3)	0,0001
APRI	0,97 (0,63-1,4)	0,23 (0,1-0,5)	0,0001
P/SSAZ	21,3 (16,2-24,6)	258 (80-1194)	0,0001
CPR	95 (83-107)	130,5 (121-150)	0,0001

*n(%); **median (IQR)

Table 2. Demographics, clinical and laboratory data and predictive indexes divided in groups with F1 and F2/F3 EV.

	Varices F1 (07)	Varices F2 e F3 (16)	p<
Gender (M/F)*	4/7 (57%)	7/16 (43%)	0,3
Age (months)**	60 (19-96)	48 (24-97)	0,9
Prematurity*	2/7 (28%)	7/16 (43,5%)	0,01
Hepatomegaly*	03/7 (42%)	6/16 (37,5%)	0,2
Splenomegaly*	7/7 (100%)	16/16 (100%)	0,04
Umbilical catheterization *	01/7 (14%)	8/16 (50%)	0,001
Hemoglobin (g/dL)**	4,79 (4,4-4,9)	4,16 (3,7-4,7)	0,09
AST u/L**	118 (44-298)	50 (29-67)	0,2
ALT u/L**	109 (54-221)	66 (44-108)	0,3
GamaGT u/L**	253 (30-455)	33 (19-301)	0,2
Alkaline phosphatase u/L**	266 (190-568)	215 (204-426)	0,7
TAP**	1,17 (1,01-1,3)	1,24 (1,16-1,5)	0,2
TTPA**	1,25 (1,18-1,41)	1,24 (1,16-1,5)	1,0
Plateletsx10³µ	100(87-113)	88(51-110)	0,3
Albumin g/dL	4,0(3,4-4)	3,2(3-3,9)	0,08
Spleen size Z score (SSAZ)	4,5(3,6-4,9)	5,2(3,6-5,8)	0,2
APRI	1,2(0,57-2)	1,0(0,6-1,3)	0,5
P/SSAZ	24(21-29,5)	19,6(9-24)	0,2
CPR	107(94-109)	86(81-105)	0,058

three consecutive endoscopies, only the platelets count presented significant variation (Table 5).

Discussion

In the last decade, studies tried to stablish predictive tests trying to avoid repeated and unnecessary EGDs (16-18).

43% of our patients that presented with EV were born prematurely. Nowadays, 10% of labors worldwide are premature with high survival rates [19]. There are no previous studies relating the prevalence of prematurity and PH. The umbilical catheterization occured in 39% of the patients with EV, and in 50% of the treatable varices (grades 2 and 3). A prospective study with 100 premature newborns that received umbilical catheterization showed that 43% of these patients presented with asymptomatic portal vein thrombosis on US Doppler from 2 to 7 days after the procedure. However, 56% of the patients spontaneously resolved the thrombus a few days later [20].

The occurrence of splenomegaly and the increase of the spleen size Z score were positively related to the presence of EV. However, these two markers were not adequate to distinguish between variceal grades. It was also possible to notice in the follow-up period that the spleen size z score did not increase at the end of the three moments. Fagundes et al. [10] in their retrospective study with 111 PH children showed that splenomegaly occurred in 65% of the children with EV. Thus, in this study they concluded that using splenomegaly as a predictive index, EGD could had been avoided in 26.8% of cases. Ferreira et al. [3] in their retrospective study with 127 PH children, concluded that 83.5% presented with splenomegaly and it was a discriminative variant to the presence of EV.

We found a strong positive relation between the presence of EV and the reduction of platelets count, with the cutoff point of 117,000.mm³. Alcântara et al. [21] in their retrospective study with Brazilian children and adolescents with PH found the platelets cutoffs points of 92,000/mm³ for patients with EV and of 118,000/mm³ for those without EV.

The albumin values found in our study were not useful to discriminate EV treatable and non-treatable. Gana et al. [13] studying predictive indexes for EV, found values of albumin of 4 g/dL in the patients with EV and 3.9 g/dL in those without EV. Adami et al. [22] in a similar retrospective study found the values 3.8 g/dL and 4.1g/dL for the albumin values in ptients with and without EV respectively. Therefore, albumin alone is not enough as a predictor of EV, but it is an important exam to calculate the CPR.

The cutoff APRI value for EV grades 2 and 3 was >0.64. Castera et al. [23], in their retrospective study with 297 adults with hepatitis C proposed a cutoff point of 1.r for APRI as a predictive value for EV.

The ratio P/SSAZ found a cutoff point of 24.86 for treatable varices, what was similar to the previous study performed by Gana et al. [13]. In their prospective multicentric study with 111 children, Gana et al. showed association between values of the ratio ratio P/SSAZ lesser than 24 and the occurence of EV. The association between LV and platelet count on spleen Z score (p <0.001) was statistically significant, however, it did not discriminate the degree of the same Gianini et al. [14] in their retrospective study with 266 adult patients showed statistical significance

Table 3. Cutoff, sensitivity, specificity, PPV, NPV and AUROC values to the predictive indexes for EV

	Cutoff	Sensitivity	Specificity	PPV	NPV	AUROC (IC 95%)
Plateletsx10^3µL	139	1,0	0,93	0,88	1,0	0,96(0,91-1,0)
Albumin g/dL	3,95	0,65	0,78	0,6	0,81	0,71(0,58-0,85)
Spleen size Z score	3,5	0,82	0,78	0,73	0,9	0,81(0,68-0,92)
APRI	0,6	0,78	0,8	0,66	0,88	0,8(0,67-0,91)
P/SSAZ	36,2	1,0	0,98	0,958	1,0	0,99(0,95-1,0)
CPR	113,8	1,0	0,98	0,958	1,0	0,99(0,95-1,0)

Table 4. Cutoff values, sensitivity, specificity, AUROC and OR for the predictive indexes in varices F2 and F3

	Cut off	Sensitivity	Specificity	AUROC (IC 95%)	OR
Platelets(x10^3) µL	<117	0,87	0,87	0,95(0,9-0,99)	0,97
Albumin g/dL	<3,9	0,75	0,75	0,83(0,72-0,95)	0,84
Spleen size Z score	>3,67	0,75	0,25	0,87(0,79-0,96)	1,14
APRI	>0,64	0,68	0,7	0,79(0-68-0,9)	0,72
P/SSAZ	<24,86	0,87	0,89	0,95(0,9-0,99)	0,91

Table 5. Predictive indexes values in three endoscopic moments in patients with EV that required EBL.

	Endoscopy 1	Endoscopy 2	Endoscopy 3	
Platelets (x10^3) µL	93 (50,0-115,0)	115,0 (60-140)	79,0 (52-113)	*0,03*
Albumin g/dL	3,2 (2,9-4,0)	3,6 (3,0-4,0)	3,4 (2,7-3,9)	*0,1*
Spleen size Z score	5,4 (4,5-6,6)	5,4 (4,5-6,6)	5,6 (4-6,6)	*0,07*
APRI	0,8 (0,6-2)	0,6 (0,4-1,2)	1,1 (0,8-2,1)	*0,4*
P/SSAZ	18,9 (7,1-24,6)	24,6 (9,6-26,9)	14,1 (8-23,8)	*0,08*
CPR	83,1 (77,0-107,5)	98,6 (77-110)	96,0 (75,4-104,9)	*0,1*

median and (IQR)

when comparing patients with and without EV (p=0,0001). Gana et al. [13] proposed the CPR index and obtained value <116 for LV diagnosis. In our study, cut-off values of CPR for patients diagnosed with VE F2 and 3 <108. In a study with 103 children with PH, Adami et al. [22] found a cutoff value of <114 for the variance. Therefore, the CPR index was close to the values already reported in the literature for children.

Conclusion

We conclude that the parameters platelets count, the spleen size Z score, APRI, P/SSAZ and CPR were predictors of EV and should be used with the cutoff values found in the present study to avoid unnecessary UDE. As far as we know, this is the first prospective study with endoscopic follow-up in children with PH. Other multicentric prospective studies should be conducted to confirm the results showed herein.

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