Noninvasive Methods of Predicting Large Esophageal Varices in Children With Intrahepatic Portal Hypertension

*Marina Rossato Adami, *Carlos Oscar Kieling, †Fernando Pereira Schwengber, ‡Vania N. Hirakata, and §Sandra Maria Gonçalves Vieira

ABSTRACT

Objective: Esophageal variceal bleeding is a severe complication of portal hypertension. The standard diagnostic screening test and therapeutic procedure for esophageal varices (EV) is endoscopy, which is invasive in pediatric patients. This study aimed to evaluate the role of noninvasive parameters as predictors of large varices in children with intrahepatic portal hypertension.
Methods: Participants included in this cross-sectional study underwent a screening endoscopy. Variceal size, red marks, and portal gastropathy were assessed and rated. Patients were classified into two groups: Group 1 (G1) with small or no varices and Group 2 (G2) with large varices. The population consisted of 98 children with no history of gastrointestinal (GI) bleeding, with a mean age of 8.9 ± 4.7 years. The main outcome evaluated was the presence of large varices.
Results: The first endoscopy session revealed the presence of large varices in 32 children. The best noninvasive predictors for large varices were platelets (Area under the ROC Curve [AUROC] 0.67; 95% CI 0.57–0.78), the Clinical Prediction Rule (CPR; AUROC 0.65; 95% CI 0.54–0.76), and risk score (AUROC 0.66; 95% CI 0.56–0.76). The logistic regression model showed that children with a CPR value under 114 were 8.59 times more likely to have large varices. Risk scores higher than −1.2 also increased the likelihood of large varices (OR 6.09; $P = 0.014$), as did a platelet count/spleen size z score lower than 25 (OR 3.99; $P = 0.043$). The combination of these three tests showed a high negative predictive value.
Conclusions: The CPR, the risk score, and the platelet count/spleen size z score could be helpful in identifying cirrhotic children who may be eligible for endoscopy.

Key Words: esophageal and gastric varices, gastrointestinal endoscopy, liver cirrhosis, pediatrics, portal hypertension

(*JPGN* 2018;66: 442–446)

What Is Known

- Platelet count, the Clinical Prediction Rule described by Gana et al, and the risk score could be used in children with portal hypertension to reduce the number of unnecessary endoscopies.

What Is New

- A combined analysis of the Clinical Prediction Rule, risk score, and platelet count/spleen size z score could be helpful as a pre-endoscopy risk assessment to select children with intrahepatic portal hypertension who may benefit from a surveillance endoscopy.

Approximately 50% of pediatric patients with chronic liver disease are estimated to present with gastrointestinal (GI) bleeding at some point. Such symptoms may require blood transfusions and intensive care hospitalization, and may potentially lead to the development of sepsis, ascites, and occasionally, death (1,2).

Duché et al estimated that the prevalence of endoscopic esophageal varices (EV) in children with cirrhosis because of biliary atresia is 70.4%. The first episode of GI bleeding observed in these children generally occurred before the 2nd year of age and was found to be associated with large EV, gastric varices and/or the presence of red marks on endoscopic examination (3). A study by Miga et al (4) also reported that patients with biliary atresia have a 50% risk of death or need for liver transplantation at the 6-year mark after their first episode of EV bleeding.

Hepatology guidelines recommend that all cirrhotic adult patients undergo endoscopic screening for EV (5). However, due to a lack of evidence for use of primary prophylaxis in pediatric patients, the benefit of endoscopic screening remains controversial (6).

Upper endoscopy is the gold standard for diagnosing varices, and therapy can be provided as the diagnostic assessment is performed. However, this procedure is expensive and associated with risks, especially in children. Preliminary data suggest that noninvasive methods may predict the presence of EV in adult (7–20) and pediatric patients (21–23). Noninvasive pediatric markers such as the Clinical Prediction Rule (CPR) presented good diagnostic accuracy in identifying children with EV, but they were not superior to upper endoscopy for patients who may have varices (22,23). Recently, we also observed that platelet count, the CPR as described by Gana et al (22,23), and the risk score (20) could be used in children with portal hypertension to reduce the number of unnecessary endoscopies (24).

Received May 29, 2015; accepted September 13, 2017.
From the *Pediatric Gastroenterology Unit and Pediatric Liver Transplantation Program, Hospital de Clínicas de Porto Alegre, the †Medical School, Universidade Federal do Rio Grande do Sul, the ‡Research and Post Graduation Unit, Hospital de Clínicas de Porto Alegre, and the §Pediatric Department, Hospital de Clínicas de Porto Alegre, Pediatric Gastroenterology Unit and Pediatric Liver Transplantation Program, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.
Address correspondence and reprint requests to Marina Rossato Adami, MD, MSc, Rua Jari 671/812, 91350-170 Porto Alegre, Rio Grande do Sul, Brazil (e-mail: marinaadami2008@gmail.com).
This article has been developed as a Journal CME Activity by NASPGHAN. Visit *http://www.naspghan.org/content/59/en/Continuing-Medical-Education-CME* to view instructions, documentation, and the complete necessary steps to receive CME credit for reading this article.
Source of Support: Fundação de Incentivo a Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre: FIPE-HCPA.
No other financial disclosures are reported.
The other authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000001841

It is well known that the risk of EV bleeding is related to variceal size, the presence of red signs on varices as assessed by endoscopy, and to the degree of liver dysfunction determined by the Child-Pugh classification (5). Although the Child-Pugh classification is not validated in children, a higher Child-Pugh score has been previously associated with a higher rate of complications and mortality in children waiting for liver transplantation (25). Methods such as CT scans, transient elastography and endoscopic capsule imaging seem to be promising tools for detecting large EV, but their cost-effectiveness is questionable (26). To the best of the authors' knowledge, few studies have investigated the use of noninvasive methods to predict large EV in pediatric populations.

The aim of the present study was to assess the role of noninvasive methods in predicting large EV in pediatric patients with intrahepatic portal hypertension.

MATERIALS AND METHODS

The study was conducted on patients younger than 18 years with a diagnosis of chronic liver disease who had undergone esophagogastroduodenoscopy (EGD) between 2000 and 2011 at the Hospital de Clínicas de Porto Alegre, a tertiary care medical center in southern Brazil. All patients were retrospectively evaluated, and those who met the following criteria were excluded from the analysis: active or previous variceal bleeding; any kind of variceal treatment or variceal bleeding prophylaxis (such as nonselective β-blocker use, endoscopic variceal ligation/sclerotherapy, surgical portosystemic shunt, or transjugular intrahepatic portosystemic shunt insertion); or previous liver transplants or malignancies. The primary variable assessed was the presence of EV in the endoscopy. Clinical and demographic patient data, as well as information regarding diagnosis, medication use, and previous physical examinations, were collected. The results of any laboratorial tests and ultrasound scans performed within 3 months of the EGD were also included in the analysis.

The endoscopy procedures were carried out as part of a clinical care routine by 4 different endoscopists. Endoscopic features such as variceal size (F1, F2, and F3), red marks, and portal gastropathy were classified according to the Japan Society for Portal Hypertension system (27), and gastric varices were categorized according to the Sarin classification (28). Patients were classified into two groups: small or no varices (F1, Group 1: G1) or large varices (F2 and F3, Group 2: G2).

We assessed the role of the following noninvasive markers in predicting large EV: platelet count ($10^3/\mu L$); spleen z score, expressed as standard deviation from the expected values for the patient's age (29); platelet count ($10^3/\mu L$)/spleen z score ratio; platelet count ($10^3/\mu L$)/spleen size (cm) ratio; the CPR, calculated according to the following formula proposed by Gana et al (22): $([0.75 \times \text{platelets}]/[\text{spleen } z \text{ score} + 5]) + (2.5 \times \text{albumin})$; Aspartate aminotransferase (AST)-to-Platelet Ratio Index (APRI) test; risk score: $(14.2 - 7.1 \times \log_{10} \text{platelets } [10^9/L]) + (4.2 \times \log_{10} \text{bilirubin [mg/dL]})$ (20); and the Child-Pugh classification and score.

Follow-up data regarding upper GI bleeding in both groups and progression to large EV in Group 1 were also reported.

STATISTICAL ANALYSIS

Data are presented as mean and standard deviation, median and interquartile range, proportions and 95% confidence interval (95% CI), as appropriate. A P value of less than 0.05 was considered statistically significant in all analyses. Continuous variables (such as laboratory data, spleen z score, CPR, risk score) were compared using Student t-test or the Mann-Whitney test. Categorical variables (such as the presence of ascites, encephalopathy, splenomegaly) were compared by the chi-squared test or Fisher exact test.

TABLE 1. Demographic characteristics of the sample

Variables	G1 (F1 or no varices) (n = 66)	G2 (F2 or F3) (n = 32)
Age	8.8 (±4.8)	9.1 (±4.7)
Sex		
Man	29 (44%)	17 (53%)
Woman	37 (56%)	15 (47%)
Diagnosis		
Biliary aresia	18 (27%)	8 (25%)
Autoimmune hepatitis	12 (18%)	9 (28%)
Idiopathic biliary cirrhosis	10 (15%)	2 (6%)
Sclerosing cholangitis	5 (7%)	1 (3%)
Cystic fibrosis	6 (9%)	0
Other causes	15 (23%)	12 (37%)

G1 = Group 1; G2 = Group 2.

To assess the performance of the variables evaluated for EV prediction, a receiver operator characteristic (ROC) curve was constructed, and the area under the curve (AUROC) was calculated. This analysis determined the following cut-off values for each variable assessed: platelet count, 115 ($10^3/\mu L$); platelets/spleen size z score, 25; CPR, 114; risk score, −1.2; platelets/spleen size, 1; and APRI test, 1.4 (24).

Independent predictors for large EV were assessed by including variables that reached statistical significance in the univariate analyses ($P < 0.05$) into subsequent multivariate analyses. In order to enhance the prediction of large EV, a combined analysis of these variables was performed. We categorized them into three classes: all variables positive, at least one variable positive, and none positive.

Statistical analysis was performed using the SPSS software, version 18.0.

This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre, accredited by the National Research Council of the Brazilian Ministry of Health, and registered at the Office for Human Research Protection—OHRP-USDHHS (Institutional Review Board-IRB00000921) under the code 110635.

RESULTS

Three thousand EGDs were reviewed, and 122 patients with chronic liver disease were identified. Twenty-four patients were excluded: 11 due to previous variceal bleeding, 4 due to nonselective β-blocker therapy, 4 due to liver transplants, 2 whose laboratory tests were performed over 3 months following the EGD, 1 due to surgical shunting, 1 due to a lack of etiologic confirmation of the diagnosis and 1 due to band ligation. Ninety-eight (95%) patients were selected for participation. Sixty-eight (69.4%) patients presented EV. Demographic data are described in Table 1. Thirty-two patients were classified as G2 (F2 and F3), and red spots were identified in 10 patients. Fifteen patients presented both esophageal and gastric varices, and 1 had gastric varices only. Eighteen patients had portal hypertensive gastropathy.

Univariate analyses showed that platelets, CPR, the Child-Pugh scores, platelets-spleen size ratio, platelets-spleen size z score ratio, and risk score discriminated between patients in G1 and G2 (Table 2).

According to the ROC curve analysis, the best predictors for large EV were: platelet count; the ratio of platelet count/spleen z

TABLE 2. Univariate analysis of large esophageal varices (LEV)

Variables	No varices or F1 (n = 66)	Varices F2 or F3 (n = 32)	*P* value
Platelets ($10^3/\mu L$)	147.5 (±83.35)	98.08 (±47.06)	0.000
Bilirubin (mg/dL)	0.9 (0.5–2.2)	1.5 (0.9–2.2)	0.060
Albumin (g/dL)	3.98 (±0.70)	3.79 (±0.59)	0.149
Splenomegaly	84.6% (55)	96.9% (31)	0.073
Spleen size (cm)	13.4 (±3.2)	14.8 (±3.3)	0.081
Spleen size *z* score	5.16 (±3.11)	6.31 (±3.35)	0.110
Platelets/spleen size *z* score ratio	27.42 (13.15–58.19)	15.25 (7.9–31.7)	0.020
Platelets/spleen size ratio	0.93 (0.57–1.44)	0.52 (0.4–1.21)	0.016
CPR	112.38 (±21.98)	102.42 (±14.96)	0.013
Risk score	−0.23 (±3.16)	1.37 (±2.42)	0.005
Child-Pugh classification A/B/C	41/20/5	12/17/3	0.079
Child-Pugh score	6.77 (±1.4)	7.14 (±1.3)	0.043
MELD	5.75 (±6.03) (n = 23)	6.28 (±2.69) (n = 8)	0.740
PELD	−2.09 (±10.25) (n = 43)	−0.82 (±7.14) (n = 24)	0.538
APRI	1.6 (0.7–3.92)	2.3 (0.9–3.1)	0.495

APRI = AST-to-Platelet Ratio Index; CPR = Clinical Prediction Rule; MELD = Model for End-stage Liver Disease; PELD = Pediatric End-stage Liver Disease.

score; the CPR; the risk score; platelet count/spleen size and the spleen size *z* score.

A logistic regression model was applied, with G2 group membership as the dependent variable, correcting for albumin, bilirubin, spleen size *z* score, and the Child-Pugh score (Table 3). Children with CPR values under 114 were 8.59 times more likely to have large EV. A risk score value over −1.2 increased the likelihood of having large EV (OR = 6.09), as did having a platelet/spleen size *z* score ratio <25 (OR = 3.99). The results regarding the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of each variable studied are presented in Table 4. Combined analysis showed that sensitivity and negative predictive value were 100% for CPR values >114, risk scores < −1.2, and platelet count/spleen size *z* score >25 (Table 5).

During Group 1 follow-up, 1 (1.5%) patient presented upper digestive bleeding, and 40 (60.6%) patients underwent at least 1 additional EGD. Of those, 19 (47.5%) presented with large varices on follow-up EGD, during a period of time ranging from 0.15 to 7.98 years (mean 3.41, SD 2.30). Each of these patients was submitted to between 2 and 9 EGDs (mean 4.26, SD 1.98).

During Group 2 follow-up, 22 (68.7%) patients were submitted to variceal band ligation, of which 3 (13.6%) presented upper digestive bleeding later on. From those who did not undergo variceal band ligation, 3 (30.0%) presented upper digestive bleeding later on.

TABLE 3. Logistic regression for large esophageal varices with platelets, spleen size *z* score, albumin, bilirubin and Child-Pugh score as independent variables

Variables	OR	95% CI	P value
Platelets	0.99	0.98–1.00	0.055
Platelets <115 $10^3/\mu L$	1.74	0.63–4.82	0.287
Platelets/spleen size *z* score <25	3.99	1.04–15.32	0.043
Platelets/spleen size <1	1.76	0.55–5.68	0.342
CPR <115	4.87	1.10–21.55	0.037
CPR <114	8.59	1.78–41.38	0.007
Risk score >−1.2	6.09	1.43–25.90	0.014
APRI >1.4	0.48	0.14–1.57	0.226

APRI = AST-to-Platelet Ratio Index; CPR = Clinical Prediction Rule.

DISCUSSION

We and other authors have demonstrated that some noninvasive EV tests allow for the identification of pediatric patients who may benefit from EGD while taking into account the known risks of the procedure (21,23,24). However, the question of whether these methods are able to identify patients at risk for variceal bleeding remains unanswered. This issue is without a doubt relevant, as the first episode of variceal hemorrhage can be catastrophic, particularly in children (30). This risk seems to be higher in patients with EV grades II and III (F2 and F3), endoscopic red marks and gastric varices as observed in adult cirrhotic patients (5).

To address this research question, we assessed the sensibility, specificity, positive predictive value, and negative predictive value of 7 noninvasive methods in predicting large EV, which are at risk of bleeding and should always receive immediate treatment. The predictive power of these tests was tested in a pediatric population.

In the present study, of the 5 tests that reached statistical significance in a univariate analysis, 3 were identified as good predictors of large EV: the CPR (OR: 8.59), the risk score (OR: 6.09), and the platelet/spleen size *z* score <25 (OR: 3.99).

In a prospective, multicenter clinical trial, Gana et al validated CPR as a means to predict the presence of EV in children with chronic liver disease, 79% of them classified as Child-Pugh A. The secondary outcome pursued was the diagnosis of large EV. They demonstrated that CPR scores under 115 were able to predict the presence of EV of any size, but not large EV (AUROC = 0.68 [95% CI 0.58–0.79]) (23).

We demonstrated that patients with a CPR score under 114 were about 8 times more likely to have large EV. Our patients had a more severe disease than those studied by Gana et al (46% Child-Pugh B or C), and the estimated cut-off value for diagnosis was slightly below the one previously identified. After applying the 115 cut-off point, we observed that both scores presented reasonable diagnostic performance and low accuracy. CPR values are calculated based on results of unspecific tests, which could explain the low accuracy results observed in this and other studies. We hypothesized that, with a 114 cut-off point, the model proposed by Gana

TABLE 4. Predictive power of Clinical Prediction Rule, platelet count, platelet/spleen *z* score, platelet/spleen size, risk score and AST-to-Platelet Ratio Index as large esophageal varice predictors

Variables	Sensibility (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Platelets <115 $10^3/\mu L$	65.7 (47.7–80.3)	54.4 (41.9–66.3)	75.5 (60.8–86.2)	42.5 (29.5–56.7)	1.44 (1.01–2.05)	0.63 (0.38–1.05)
Platelets/spleen size *z* score <25	71.4 (53.4–84.7)	54.7 (40.5–68.2)	74.3 (57.6–86.4)	51.0 (36.5–65.3)	1.58 (1.10–2.27)	0.52 (0.29–0.93)
Platelets/spleen size <1	71.4 (53.5–84.7)	44.4 (31.1–58.5)	70.6 (52.3–84.2)	45.4 (32.2–59.3)	1.29 (0.94–1.77)	0.64 (0.35–1.17)
CPR <115	80.0 (62.5–90.9)	47.2 (33.5–61.2)	78.1 (59.5–90.0)	50.0 (36.5–63.5)	1.51 (1.12–2.05)	0.42 (0.21–0.87)
CPR<114	80.0 (62.5–90.9)	52.8 (38.7–66.4)	80.0 (62.5–90.9)	52.8 (38.7–66.4)	1.70 (1.22–2.36)	0.38 (0.19–0.77)
Risk score >−1.2	85.7 (68.9–94.6)	46.3 (34.2–58.8)	86.1 (69.7–94.7)	45.4 (33.3–58.1)	1.60 (1.23–2.07)	0.31 (0.13–0.72)
APRI >1.4	57.1 (39.5–73.2)	47.0 (34.9–59.5)	68.0 (52.7–80.5)	35.7 (23.7–49.7)	1.08 (0.75–1.55)	0.91 (0.58–1.44)

APRI = AST-to-Platelet Ratio Index; 95% CI = 95% confidence interval; CPR = Clinical Prediction Rule; PLR = positive likelihood ratio; PPV = positive predictive value; NLR = negative likelihood ratio; NPV = negative predictive value.

et al may be useful as a screening tool for predicting large EV in patients with a more severe disease.

Park et al (20), with a study design that differs from our own, determined the diagnostic accuracy of a laboratory protocol in predicting the presence of EV in adult patients with advanced fibrosis. The variables assessed (platelets and bilirubin) were combined to produce a risk score. With a cut-off point of −1.0, this score showed good sensibility and specificity. The authors did not test the accuracy of the score in discerning between patients with different EV sizes. Our study is a pioneer effort in assessing the sensibility and specificity of a risk score in pediatric patients with intrahepatic portal hypertension and large EV. Using a similar cut-off point, the score was successful in predicting large EV. Children with risk scores >−1.2 had a 6-fold probability of having large EV, which is not surprising. According to the study by Park et al (20), a similar model allowed for the identification of patients with advanced fibrosis and a significant degree of portal hypertension as measured by hepatic venous pressure gradient.

Although the tests involved in the study by Park et al (20) are all routine laboratory procedures, the model developed may have some disadvantages: its scores are laborious to calculate, and the present results have not yet been validated in any prospective studies. The predictive validity of this model in children is also unknown.

Another noninvasive parameter worth mentioning is the platelet count/spleen size *z* score ratio. In a previous study, Giannini et al (7) demonstrated that a platelet count to spleen diameter ratio under 909 may be independently associated with the presence of EV, even in patients with compensated disease. These results, however, have not been consistently obtained in the literature (17,31,32), and a recent meta-analysis has raised some questions about the cut-off point used by Giannini et al (19). In the present study, this variable was not able to accurately detect patients with large EV. As the spleen size in children varies linearly with age, we replaced the ''spleen size'' variable with a *z* score of the expected spleen size, using this value to calculate the ratio. The resulting numbers reached statistical significance in a logistic regression (OR = 3.99; 95% CI 1.04–15.32; $P = 0.043$). The spleen size *z* score was 1 of 3 variables studied by Gana et al (23) in an investigation of a model to predict EV in children with portal hypertension.

Despite the enthusiastic OR values obtained, none of the parameters evaluated alone outperformed upper endoscopy in detecting the presence of varices at risk of bleeding. Thus, we conducted an analysis combining these variables. With an isolated null accuracy to identify patients with large EV and a moderated accuracy to identify patients without large EV, the combination of these 3 tests showed a high negative predictive value. This suggests that the probability of patients with CPR values >114, risk scores <−1.2, and platelet count/spleen size *z* score >25 having large EV was null. However, we should stress that the overall sample size studied does not allow us to generalize findings.

The present study has limitations. An important limitation of retrospective studies is that they generate a great deal of missed data. Missing data have the effect of reducing the size and power of a study. The wide confidence interval reflects a small sample size. In order to discriminate the true state of patients, we constructed a ROC curve, calculated the AUROC, and determined the cut-off values for each variable. With this approach, the reducing effect should be minimized. The strength of this study lies in its originality.

In conclusion, despite upper endoscopy being the gold standard for detecting varices at risk for bleeding, our results suggest that the CPR, the risk score, and the platelet count/spleen size *z* score ratio could be used to screen children with portal hypertension and to identify individuals who should be considered for endoscopic treatment.

We should emphasize that our conclusions need to be replicated with a larger sample size before these noninvasive markers replace the routine screenings already performed based on an experienced hepatologist's clinical assessment.

TABLE 5. Predictive power of combined and isolated analysis of Clinical Prediction Rule, platelet count and platelet/spleen *z* score as large esophageal varice predictors

Criteria	Sensibility (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All negatives	100 (86.7–100)	32.7 (20.7–47.2)	47.8 (35.6–60.2)	100 (77.1–100)
At least, 1 positive	84.4 (66.5–94.1)	50 (36–64)	50.9 (37–64.7)	83.9 (65.5–93.9)
All positives	65.6 (46.8–80.8)	67.3 (52.8–79.3)	55.3 (38.5–71)	76.1 (60.9–86.9)

95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value.

Acknowledgment: We thank FIPE-HCPA (Research and Events Support Fund at Hospital de Clínicas de Porto Alegre) for the financial support.

REFERENCES

1. Ling SC, Walters T, McKiernan PJ, et al. Primary prophylaxis of variceal hemorrhage in children with portal hypertension: a framework for future research. *J Pediatr Gastroenterol Nutr* 2011;52:254–61.
2. El-Tawil AM. Trends on gastrointestinal bleeding and mortality: where are we standing? *World J Gastroenterol* 2012;18:1154–8.
3. Duché M, Ducot B, Tournay E, et al. Prognostic value of endoscopy in children with biliary atresia at risk for early development of varices and bleeding. *Gastroenterology* 2010;139:1952–60.
4. Miga D, Sokol RJ, Mackenzie T, et al. Survival of first esophageal variceal hemorrhage in patients with biliary atresia. *J Pediatr* 2001; 139:291–6.
5. de Franchis R. Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010;53:762–8.
6. Shneider BL, Bosch J, de Franchis R, et al., Expert Panel of the Children's Hospital of Pittsburgh of UPMC. Portal hypertension in children: expert pediatric opinion on the report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Pediatr Transplant* 2012;16:426–37.
7. Giannini E, Botta F, Borro P, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut* 2003;52:1200–5.
8. Zein CO, Lindor KD, Angulo P. Prevalence and predictors of esophageal varices in patients with primary sclerosing cholangitis. *Hepatology* 2004;39:204–10.
9. Giannini EG, Botta F, Borro P, et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with cirrhosis: a validation study based on follow-up. *Dig Liver Dis* 2005;37:779–85.
10. Giannini EG, Zaman A, Kreil A, et al. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: results of a multicenter, prospective, validation study. *Am J Gastroenterol* 2006; 101:2511–9.
11. Sharma SK, Aggarwal R. Prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. *J Gastroenterol Hepatol* 2007;22:1909–15.
12. Qamar AA, Grace ND, Groszmann RJ, et al., Portal Hypertension Collaborative Group. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. *Hepatology* 2008;47:153–9.
13. Qamar AA, Grace ND, Groszmann RJ, et al., Portal Hypertension Collaborative Group. Incidence, Prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clin Gastroenterol Hepatol* 2009;7:689–95.
14. Barrera F, Riquelme A, Soza A, et al. Platelet count/spleen diameter ratio for non-invasive prediction of high risk esophageal varices in cirrhotic patients. *Ann Hepatol* 2009;8:325–30.
15. Treeprasertsuk S, Kowdley KV, Luketic VA, et al. The predictors of the presence of varices in patients with Primary Sclerosing Cholangitis. *Hepatology* 2010;51:1302–10.
16. Schwarzenberger E, Meyer T, Golla V, et al. Utilization of platelet count spleen diameter ratio in predicting the presence of esophageal varices in patients with cirrhosis. *J Clin Gastroenterol* 2010;44:146–50.
17. Sarangapani A, Shanmugam C, Kalyanasundaram M, et al. Noninvasive prediction of large esophageal varices in chronic liver disease patients. *Saudi J Gastroenterol* 2010;16:38–42.
18. Tafarel JR, Tolentino LHL, Correa LM, et al. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. *Eur J Gastroenterol Hepatol* 2011;23:754–8.
19. Chawla S, Katz A, Attar B, et al. Platelet count/spleen diameter ratio to predict the presence of esophageal varices in patients with cirrhosis: a systematic review. *Eur J Gastroenterol Hepatol* 2012;24:431–6.
20. Park SH, Park TE, Kim YM, et al. Non-invasive model predicting clinically-significant portal hypertension in patients with advanced fibrosis. *J Gastroenterol Hepatol* 2009;24:1289–93.
21. Fagundes ED, Ferreira AR, Roquete ML, et al. Clinical and laboratory predictors of esophageal varices in children and adolescents with portal hypertension syndrome. *J Pediatr Gastroenterol Nutr* 2008; 46:178–83.
22. Gana JC, Turner D, Roberts EA, et al. Derivation of a clinical prediction rule for the noninvasive diagnosis of varices in children. *J Pediatr Gastroenterol Nutr* 2010;50:188–93.
23. Gana JC, Turner D, Mieli-Vergani G, et al. A clinical prediction rule and platelet count predict esophageal varices in children. *Gastroenterology* 2011;141:2009–16.
24. Adami MR, Ferreira CT, Kieling CO, et al. Noninvasive methods for prediction of esophageal varices in pediatric patients with portal hypertension. *World J Gastoenterol* 2013;19:2053–9.
25. Dehghani SM1, Gholami S, Bahador A, et al. Comparison of Child-Turcotte-Pugh and pediatric end-stage liver disease scoring systems to predict morbidity and mortality of children awaiting liver transplantation. *Transplant Proc* 2007;39:3175–7.
26. de Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. *J Hepatol* 2008;49:520–7.
27. Tajiri T, Yoshida H, Obara K, et al. General rules for recordings endoscopic findings of esophagogastric varices. *Dig Endosc* 2010; 22:1–9.
28. Sarin S, Sundaran K, Ahuja R. Predictors of variceal bleeding: an analysis of clinical, endoscopic, and haemodynamic variables, with special reference to intravariceal pressure. *Gut* 1989;30:1757–64.
29. Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. *Radiology* 2004;231:129–34.
30. D'Antiga L. Medical management of esophageal varices and portal hypertension in children. *Semin Pediatr Surg* 2012;21:211–8.
31. de Mattos AZ, de Mattos AA. Platelet count/spleen diameter ratio: can it replace endoscopy for the screening of esophageal varices in cirrhotic patients? *Eur J Gastroenterol Hepatol* 2012;2:1113.
32. Mangone M, Moretti A, Alivernini F, et al. Platelet count/spleen diameter ratio for non-invasive diagnosis of oesophageal varices: is it useful in compensated cirrhosis? *Dig Liver Dis* 2012;44:504–7.