A Clinical Prediction Rule and Platelet Count Predict Esophageal Varices in Children

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BACKGROUND & AIMS: The validation of noninvasive tests to diagnose esophageal varices is a priority in children because repeated endoscopic evaluations are too invasive. We measured the ability of a previously developed noninvasive clinical prediction rule (CPR) to predict the presence of esophageal varices in children. **METHODS:** We analyzed data from 108 children, younger than age 18, who received endoscopies at 8 centers, to assess portal hypertension from chronic liver disease or portal vein obstruction. Blood test and abdominal ultrasound scan results were obtained within 4 months of endoscopy. Grading of varices identified by endoscopy was confirmed by independent blinded review. Spleen size, based on data from the ultrasound scan, was expressed as a standard deviation score relative to normal values for age. **RESULTS:** Of the children studied, 74 had esophageal varices (69%), including 35 with large varices (32%). The best noninvasive predictors of esophageal varices of any size were as follows: platelet:spleen size z-score ratio (area under the receiver operating characteristic curve [AUROC], 0.84; 95% confidence interval [CI] 0.75–0.93), CPR (AUROC, 0.80; 95% CI, 0.70–0.91), and platelet count (AUROC, 0.79; 95% CI, 0.69–0.90). The positive predictive values for the CPR and platelet count were 0.87 and 0.86, the negative predictive values were 0.64 and 0.63, the positive likelihood ratios were 3.06 and 2.76, and the negative likelihood ratios were 0.64 and 0.63, respectively. Based on positive and negative predictive values, the most accurate noninvasive tests were the CPR and platelet counts. **CONCLUSIONS: Noninvasive tests such as CPR and platelet count can assist in triaging children for endoscopy to identify esophageal varices.**

Keywords: Portal Hypertension; Pediatric Chronic Liver Disease; Diagnostic Tests.

Many children with chronic liver disease or portal vein obstruction are at risk of variceal bleeding, which is associated with significant morbidity and mortality.[1–8] Guidelines for adults with portal hypertension recommend performing esophagogastroduodenoscopy (EGD) to identify those with varices who may benefit from prophylactic therapy. Treatment with nonselective β-blockade or endoscopic variceal ligation is effective for the prevention of variceal bleeding in cirrhotic adults.[9–11]

Currently, there are inadequate data to support a similar approach in children. EGD is the reference standard test for the diagnosis of varices, but it is considered especially invasive in children, time consuming, expensive, and associated with risk. There is, therefore, a pressing need for a noninvasive test that is reliable enough to target EGD only to those children with the highest risk of varices. The American Association for the Study of Liver Disease and the American College of Gastroenterology recognize this as one of the most important areas for research in portal hypertension.[12]

In a previous retrospective study, we showed that esophageal varices in children could be predicted accurately by a clinical prediction rule (CPR, calculated from platelet count, spleen size z-score, and albumin concentration) and by the ratio of the platelet count and spleen size z-score (P/SSAZ).[13] A lower CPR score means a higher likelihood for the presence of varices. We now present the results of a multicenter prospective study in which we aimed to validate the ability of the CPR and P/SSAZ ratio to predict the presence of esophageal varices in children with portal hypertension. This study was conducted according to the requirements set by the Quality Assessment of Diagnostic Accuracy Studies checklist.[14,15]

Materials and Methods

Settings and Eligibility

This was a prospective, multicenter study in which 8 centers recruited consecutive children younger than age 18 with chronic liver disease or portal vein thrombosis between 2007 and

Abbreviations used in this paper: CI, confidence interval; CPR, clinical predictor rule; P/SSAZ, ratio of platelet count and spleen size z-score; EGD, esophagogastroduodenoscopy; ROC, receiver operator characteristic; AUROC, area under receiver operator characteristic.

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2010. Inclusion criteria included those undergoing EGD, either to screen for esophageal varices or for investigating gastrointestinal symptoms. Exclusion criteria were previous portal-systemic shunt surgery or transjugular intrahepatic portal-systemic shunt, previous ligation or sclerotherapy of varices, therapy with β-blocker during the previous 6 months, organ transplantation, previous upper gastrointestinal bleeding, and malignancy. The study was approved by the Institutional Review Boards or Research Ethics Committees of all participating centers.

End Points

The primary end point was the presence of esophageal varices of any size. Secondary outcomes included the presence of large varices and changes in the noninvasive test variables in a subset of patients who underwent repeat endoscopy for clinical indications.

Data Collection

Data were recorded on a standardized case report form, including demographic information, primary diagnoses, comorbidities, medications, and details of physical examination. Hepatic encephalopathy was determined using the classification of the Pediatric Acute Liver Failure Study Group for children younger than age 4.[16] For older children, the West Haven classification system was used.[17] Blood test results and abdominal ultrasound scan data were obtained from tests performed within 3 weeks and 4 months of the endoscopy, respectively. Spleen size on ultrasound scan was expressed as a standard deviation score relative to previously established normal values for age.[18] Derivation of the CPR has been described previously.[13] The formula for calculation of the CPR is as follows:

$$\left(\frac{0.75 \times Platelets}{SAZ + 5}\right) + 2.5 \times albumin \qquad (1)$$

The severity of liver disease was measured by the Child–Pugh score and the Model for End-stage Liver Disease (for ages 12 and older) or Pediatric End-stage Liver Disease (for ages less than 12) scores.[19–21]

Physicians who performed the EGD were asked to describe the esophageal varices appearance using two classification schemes: the Paquet[22] and the Cales et al[23,24] classifications. In the Paquet[22] classification, varix size is graded on a 4-point Likert scale: grade 1 varices are small and flattened by insufflation of air; grade 2 varices are slightly larger and do not flatten; grade 3 varices are larger but do not touch in the middle of the lumen; and grade 4 varices are large and touch each other in the middle of the lumen. Physicians were provided with a pictorial description of the 4 grades derived from the original report by Paquet.[22] The Cales et al[23,24] criteria are based on a 3-size graduation: small varices flatten with air insufflation and are not confluent around the esophageal wall, medium varices do not flatten with air insufflation and are not confluent around the esophageal wall, and large varices do not flatten with air insufflation and are confluent around the esophageal wall. This semiquantitative approach was chosen because it is the best validated tool of all variceal sizing systems and it provides good interobserver agreement.[25] Further endoscopic evaluation included the stomach and duodenum. Gastric or duodenal varices were described alongside edema, submucosal petechial areas, and a snake-skin appearance of the stomach was described to be consistent with portal hypertensive gastropathy.

Because EGD was performed as part of routine clinical care, the endoscopists were not blinded to the results of the noninvasive blood tests and ultrasound scans. To minimize this potential bias, EGD findings were recorded by videos and/or pictures, which subsequently were reviewed in random order by two additional experienced pediatric gastroenterologists with at least 5 years of experience, blinded to all clinical data. Each assessor independently graded the variceal size and the presence of red wales or red spots. The final variceal grade was assigned to each patient by majority (2 of 3 assessments). If all 3 assigned a different grade, then agreement was reached by discussion and consensus.

As a post hoc analysis conducted at the time of data analysis, participating children were identified who had undergone a repeat EGD for clinical indications. Data were collected from chart review including the presence and grading of varices, measurement of spleen size on ultrasound scan (performed within 4 months of the repeat EGD), and bloodwork variables including platelet count and albumin (performed within 3 weeks of the EGD). Children with repeat EGD performed after banding ligation (n = 4), liver transplantation (n = 2), surgical shunt (n = 1), or variceal hemorrhage (n = 1) were excluded from this post hoc analysis.

Statistical Analysis

Data are presented using means ± standard deviations, medians (interquartile range), and proportions ± 95% confidence interval (95% CI), as appropriate. Patients were divided into 2 groups: those with varices on EGD and those without. First, data were explored to search for variables that differed between these 2 groups. Continuous variables (such as age, disease duration, laboratory values, and spleen size) were compared using the Student *t* test or the Wilcoxon rank sum test, as appropriate for the data normality. Categoric variables (such as sex, presence of cirrhosis, and comorbidity) were compared using the chi-square test or the Fisher exact test as appropriate. We emphasize that these analyses were exploratory in nature and, thus, no correction was made for multiple comparisons and a *P* value of less than .05 was considered statistically significant for all analyses. Interobserver variability for the grading of varices was calculated using kappa statistics with quadratic weights.

Primary analysis. The primary analysis assessed the ability of CPR and P/SSAZ to predict the presence of any esophageal varices using diagnostic utility methods. A receiver operator characteristic (ROC) curve was constructed and the area under the ROC (AUROC) was calculated with the corresponding 95% CI. An AUROC of greater than 0.7 was considered indicative of a fair test, 0.8 was considered good, and more than 0.9 was considered an excellent test. The optimal cut-off value of the CPR and P/SSAZ score to predict esophageal varices was determined as the point at which the second diagonal crosses the ROC curve (ie, the point where the shoulder of the curve is closest to the left upper corner of the graph). Sensitivity, specificity, predictive values, and likelihood ratios were calculated for this optimal cut-off score and for 2 other cut-off values, one aimed to optimize sensitivity and the other to optimize specificity.

Secondary analyses. Similar diagnostic utility statistics were used for each of the following test variables, as defined in the secondary aims: spleen size, platelet count, and the ratio between aspartate aminotransferase and alanine aminotransferase levels. A logistic regression model then was constructed with the presence of varices as the dependent variables and, governed

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