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Noninvasive prediction of large esophageal varices in liver cirrhosis patients

Abstract

Purpose: Esophageal varices are a dangerous complication of liver cirrhosis. The development of cost effective, noninvasive means for prediction of large esophageal varices could reduce the use of upper gastrointestinal endoscopy in variceal screening and also provide an alternative way to confirm the results of conventional endoscopic diagnosis. Previously proposed predictive models are neither sensitive nor specific.

Methods: A retrospective study based on a group of 104 liver cirrhosis patients was performed. Multiple statistical approaches were used to evaluate the association of large esophageal varices with 20 individual and six compound clinical laboratory variables. A new predictive model was developed.

Results: Univariate analysis suggested that eight out of 26 variables were significantly associated with large esophageal varices. Further stepwise logistic regression eventually identified three variables (hemoglobin level, portal vein diameter and the ratio of platelet count/spleen diameter) that contributed significantly to the final regression model. Receiver operating characteristic (ROC) curve analysis showed that this new regression model achieved 77.8% and 72% of diagnostic sensitivity and specificity, respectively, for the prediction of large esophageal varices. In our study group, its diagnostic accuracy (AUROC=0.814) was found to be significantly higher than six predictive models previously published.

Conclusions: No single variable offers self-sufficient predictive function for large esophageal varices. A comprehensive model using multiple variables significantly improves the predictive accuracy in screening the most at risk patients with potential variceal hemorrhage.

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Esophageal varices are abnormally enlarged submucosal veins in the lower esophagus that may easily rupture, leading to a dangerous esophageal hemorrhage. Esophageal varices most often result from portal hypertension due to liver cirrhosis. Most cirrhotic patients will develop esophageal varices over their life time (5 to 15%/year) and the rate of progression from small to large varices is estimated to be 8% per year and the annual rate of esophageal hemorrhage is 5 to 15% [1]. Despite improved diagnosis and treatment for variceal hemorrhage, the mortality rate still remains high (20%-35%) [1]. Variceal bleeding is intimately associated with the size of esophageal varices. The larger the esophageal varices, the more dangerous they are, since large esophageal varices may cause a higher tension on variceal walls [2, 3]. Gastrointestinal bleeding is attributed only 1-2% to causes other than varices, but 5% to small esophageal varices, and 15-20% to large esophageal varices [4]. Thus, identification of large-sized esophageal varices, before their first bleeding, is essential to prevent or minimize this life-threatening complication of liver cirrhosis.

Current guidelines recommend using upper gastrointestinal endoscopy (UGIE) to screen all cirrhotic patients at diagnosis for identification of varices at a high risk of bleeding [5]. In addition, endoscopic screening should be followed up every 1-2 years for patients with small varices or every 2-3 years for patients with no varices [6]. Even though UGIE is believed to be the gold standard to diagnose esophageal varices, the use of UGIE has its own limitations. First, diagnosis of esophageal varices by UGIE depends on the performance of individual endoscopists [7, 8]. Second, this approach places a heavy burden upon endoscopy units and repeated testing over time may have a detrimental effect on patient compliance [9]. Third, unnecessary UGIE screening also increases the associated health care costs. Forth, the application of UGIE is an unpleasant procedure to patients. Fifth, it may have detrimental effects such as increasing the risk of bleeding and infection. Due to these problems in using UGIE, some noninvasive means have been proposed for prediction of esophageal varices in order to restrict UGIE to the population with high risk of variceal bleeding.

Noninvasive identification of esophageal varices is usually based on regular laboratory parameters and clinical signs relevant to liver fibrosis and function, portal hypertension and hypersplenism. The noninvasive predictive variables include platelet count, splenomegaly, spleen diameter, Child Pugh, size of right liver lobe, albumin level and portal vein diameter. The common features of these noninvasive means that prediction of esophageal varices is reproducible, cost effective, simple and quick with no additional burden to patients. Even though these

variables are clearly preferable to patients, none is comparable to UGIE in terms of sensitivity and specificity in prediction of variceal hemorrhage. To improve the sensitivity and specificity in variceal prediction, several predictive models are proposed using various combinations of the above variables. Apparently, the sensitivity and specificity of the currently proposed predictive models varies with population, the etiologies of liver cirrhosis and the severity of liver disease. In this study, different predictive models, currently reported in literature and based on a Chinese population, were compared. A new model, which is superior for prediction of large esophageal varices, is proposed. The new model has significantly higher sensitivity and specificity for screening the most at risk patients with potential variceal hemorrhage.

Patients and Methods

Study sample

The study has been approved by, and carried out according to the instructions of, the author's Institutional Human Investigations or Ethics Committee. Our study sample was liver cirrhosis patients from Shanghai East Hospital who were recruited between June 2005 and December 2011. Patients with active bleeding, acute hepatic failure, portal vein thrombosis, those treated with nonsteroidal anti-inflammatory drugs or beta-adrenergic receptor antagonists and those who had undergone previous endoscopic sclerosis, band ligation of esophageal varices or splenectomy. The exclusion criteria were established to rule out potential confounding variables for the study outcomes. In total, 104 individuals diagnosed with liver cirrhosis were included in this study. The etiology of liver cirrhosis was pre-determined at diagnosis and mainly included hepatitis B virus (HBV) infection (69 subjects), alcohol intake (18 subjects), combined HBV infection and alcohol intake (13 subjects), and unknown etiology (four subjects, Table 1). The mean age of our study sample was 59 years (ranging from 54-68 years) and 56.7% of the subjects were male.

Diagnosis and grade definition of esophageal varices

The presence and grade of esophageal varices were determined by UGIE for all patients. The grade was classified into small and large based on the criteria proposed at the Baveno I Consensus Conference [10]. Briefly, the small grade was defined as esophageal varices flattening with insufflation or minimally protruding into the esophageal lumen (i.e., Paquet's grades 0-II), while the large grade was defined as esophageal varices obviously protruding into and filling at least 50% of the esophageal lumen (i.e., Paquet's grades III-IV). Our sample included

TABLE 1. The clinical variables of the study sample

Relevant clinical variable	Value
Esophageal varices	
none	1
small	49
large	54
Etiology of liver cirrhosis	
HBV	69
alcohol	18
HBV and alcohol	13
unknown	4
Ascites	
none	39
mild	17
severe	48
Child-Pugh score	9(6-11)
Child-Pugh class (A/B/C)	25/37/42
WBC (10 ⁹ /L)	4.93±3.15
Platelet count (10 ⁹ /L)	76.85±55.60
Hemoglobin level (g/L)	97.54±24.52
Prothrombin time (s)	15.8±4.06
INR	1.66±2.54
ALT (U/L)	41.12±32.99
AST (U/L)	41.32±64.83
Total bilirubin (μmol/L)	38.63±35.20
Total protein (g/L)	62.20±9.36
Albumin (g/L)	29.73±5.92
γ-GT (U/L)	127.78±198.15
Portal vein diameter (mm)	13.32±1.78
Spleen diameter (mm)	141.30±20.42
Spleen width (mm)	49 (45-57)

one subject with no esophageal varices, 49 subjects diagnosed with small esophageal varices and 54 subjects diagnosed with large esophageal varices (Table 1). The one subject with no varices was included in the “small varices” group for the sake of analyses.

Other clinical variables

The following clinical variables were collected: Child-Pugh score, biochemical parameters including hemoglobin level, platelet count, white blood cell count, gamma glutamyl transpeptidase enzyme (γ-GT) activity, glutamine-pyruvic

TABLE 2. The etiological distribution of the study sample

Etiology of liver cirrhosis	Grades of esophageal varices		P value**
	Small*	Large	
HBV	32	37	0.917
alcohol	10	8	
HBV and alcohol	6	7	
unknown	2	2	
Total subjects	50	54	

* Since there is only 1 subject for the grade of “no esophageal varices” (see Table 1) they were included into the grade of small esophageal varices; ** The P value was obtained using chi-square test.

transaminase (ALT) and glutamine-oxaloacetic transaminase (AST) activities, AST/ALT ratio, total bilirubin level, total protein level, albumin level, albumin/globulin ratio, prothrombin time and international normalized ratio (INR). All patients also underwent ultrasonography of the upper abdomen including measurement of spleen diameter, portal vein diameter, right liver lobe diameter and the depth of ascites. Ascites was graded as none (not detected by ultrasonography), mild (depth under ultrasonography less than 3 cm), moderate (depth under ultrasonography between 3-10 cm) and severe (depth under ultrasonography more than 10 cm). The volume of the liver and spleen was measured using plain computerized tomography. These variables are summarized in Table 1.

Statistical analysis

The cross-sectional area of liver and spleen was calculated using ImageJ [11]. The volume of the liver (or spleen) = area of the cross-section × slice thickness. Statistical analyses were performed in SPSS 17.0 and Medcalc 12.1. The normal distribution of continuous variables was determined using the Shapiro-Wilk test. Continuous variables are presented as mean±SD (for normal distributed variables) or median plus interquartile range (for variable deviated from normal distribution). Statistical differences were tested using Student's t-test or non-parametric Mann-Whitney test. Categorical values were compared using chi-square test. The association of the candidate variables with large esophageal varices was assessed using univariate analysis. The significantly associated variables were further included in a stepwise logistic regression model to evaluate their independent contribution to the presence of large esophageal varices. The predictive contribution to large esophageal varices from those candidate variables was further determined by receiver operating characteristic (ROC) curves [12]. The predictive models were then validated by the mean areas under the ROC curves (AUROC). A cut-off value serving as a diag-

TABLE 3. Univariate analysis for screening of variables associated with the grade of esophageal varices

Variables	Grade of esophageal varices		P value
	Small	Large	
Individual Variables			
Age (mean, range)	58 (52-71)	60 (54-68)	0.85
Gender (Male%)	60%	53.70%	0.517
Etiology (%)			0.917
HBV	64%	68.50%	
Alcohol	20%	14.80%	
HBV and alcohol	12%	13%	
Unknown	4%	3.70%	
Ascites (%)			0.785
none	40%	35.19%	
mild	14%	18.52%	
severe	46%	46.30%	
Child-Pugh score	8 (7-10)	9 (6-12)	0.299
Child-Pugh class (A/B/C)	12/21/2017	13/16/25	0.5
WBC (10 ⁹ /L)	5.40±3.40	4.50±2.64	0.23
Platelet count (10 ⁹ /L)	92.14±72.158	62.69±26.70	0.006
Hemoglobin level (g/L)	104.05±26.69	91.52±21.53	0.009
Prothrombin time (s)	15.22±2.70	16.35±4.98	0.272
INR	1.33±0.24	1.96±3.50	0.054
ALT (U/L)	38.19±26.14	44.33±39.21	0.807
AST (U/L)	33.92±29.23	49.53±88.86	0.463
Total bilirubin (μmol/L)	37.65±39.00	39.53±31.62	0.558
Total protein (g/L)	61.78±10.31	62.59±8.46	0.727
Albumin (g/L)	30.48±5.79	29.04±6.00	0.247
γ-GT (U/L)	80.83±105.951	178.48±255.62	0.009
Portal vein diameter (mm)	12.76±1.31	13.84±1.99	0.002
Spleen diameter (mm)	134.46±16.76	147.64±21.58	0.001
Compound Variables			
AST/ALT	1.06±0.92	1.15±1.75	0.85
Platelet count/spleen diameter	0.59±0.23	0.43±0.18	<0.001
Right liver lobe/albumin	4.29±0.41	4.33±0.65	0.003
Albumin/globulin	1.01±0.35	0.93±0.33	0.255
Platelet count/portal vein diameter	6.52±2.53	4.73±2.43	<0.001
Liver volume/spleen volume	4.83±6.37	2.07±1.03	0.245

TABLE 4. The predictive variables remain in the final logistic regression model

Predictive variables	Coefficient	P value
Hemoglobin level	-0.031	0.003
Portal vein diameter	0.32	0.047
Platelet count/spleen diameter	-5.633	0.001

nostic criterion (i.e., presence or absence of large esophageal varices) was optimized for the best predictive function.

Results

Etiology of liver cirrhosis is not associated with the grade of esophageal varices

Liver cirrhosis in our study group resulted from multiple etiological factors including HBV infection, alcohol intake, a combination of the two factors and unknown etiology (Table 1). First, the potential association between the different etiology of liver cirrhosis and the grade of esophageal varices in our study group were examined. A chi-square test was performed to evaluate the significance of the difference in disease etiology between the two groups with small and large esophageal varices. The result showed that there is no significant difference in disease etiology between the two groups (Table 2). This result ruled out the potential confounding effect from disease etiology on our subsequent analyses.

Univariate analysis for initial screening of the relevant variables

To screen the variables that are potentially associated with the grade of esophageal varices, univariate analysis were performed to evaluate age, gender and other 18 individual variables as presented in Table 1. These clinical variables are regularly collected from all patients for the diagnosis of liver cirrhosis. The results showed that five of the 20 individual variables (platelet count, hemoglobin level, γ -GT activity, portal vein diameter and spleen diameter) were significantly associated with the grade of esophageal varices (Table 3). Large esophageal varices appeared to have a lower platelet count and hemoglobin level but higher

γ -GT activity, portal vein and spleen diameters. Since some compound variables (a combination of two different variables) are frequently used in predictive models as previously reported [13-16], here, an additional six compound variables were evaluated (Table 3). The presence of large esophageal varices was significantly associated with lower ratios of platelet count/spleen diameter, right liver lobe/albumin and platelet count/portal vein diameter.

Step-down multivariate logistic regression searches for the predictive variables

The eight significantly-associated individual and compound variables (Table 3 and Table 4) were then combined for multivariate logistic regression analyses to further evaluate their association with the grade of esophageal varices. Multivariate logistic regression was iteratively performed by stepwise exclusion of individual variables with the highest P value until all variables made significant contribution in the regression model. Three variables (hemoglobin level, portal vein diameter and the ratio of platelet count/spleen diameter) with $P < 0.05$ remained in the last regression model (Table 4). A predictive model was proposed for the presence of large esophageal varices based on these three variables. Our predictive model was expressed as:

$$\begin{aligned} \text{Noninvasive Predictive (NIP) value} \\ = 0.32 \times (\text{portal vein diameter}) \\ - 0.031 \times (\text{hemoglobin level}) \\ - 5.633 \times (\text{platelet count} / \text{spleen diameter}) \end{aligned} \quad (\text{Eq.1})$$

The predictive function was derived from the relative contribution of the predictive variables in the final regression equation. The weights for the individual predictive variables were the regression coefficients (Table 4). Here, an example is provided to illustrate the calculation of the NIP based on Eq.1. If a patient had the following parameters: portal vein diameter = 13.32mm, hemoglobin level = 97.54g/L, platelet count = $76.85 \times 10^9/\text{L}$, and spleen diameter = 141.30mm, then his/her NIP would be calculated as $0.32 \times 13.32 - 0.031 \times 97.54 - 5.633 \times (76.85/141.30) = -1.825$.

TABLE 5. Diagnostic evaluation of the predictive variables using ROC analysis

Predictive variable	Cutoff value	AUROC (95%CI)	Sensitivity	Specificity
Hemoglobin level *	-	0.654 (0.548-0.761)	-	-
Portal vein diameter	>12.88	0.771 (0.671-0.972)	0.85	0.72
Platelet count/spleen diameter	<0.575	0.764 (0.663-0.864)	0.833	0.78
NIP **	>-0.196	0.814 (0.732-0.896)	0.778	0.72

* No optimal cutoff value was obtained for the hemoglobin level due to the difficulty to achieve expected diagnostic sensitivity and specificity; ** NIP represents the noninvasive predictive means based on Eq.1.

FIGURE 1. ROC curve of our predictive model for large esophageal varices. The area under the ROC curve (AUROC) is 0.814. The value normally ranges from 0.5-1.0, where 0.5 represents a random prediction (i.e., the diagonal reference line) and 1.00 represents perfect prediction with 100% sensitivity and 100% specificity (i.e., the top left corner). The diagnostic accuracy is generally defined as “Useful” (if AUROC > 0.7) and “Excellent” (if AUROC is between 0.8-0.9).

TABLE 6. Comparison in the diagnostic accuracy of 7 predictive models for large esophageal varices

Model [Ref.]	Predictive variable	AUROC (95%CI)	P value *
NIP	Portal vein diameter, hemoglobin level, platelet count/spleen diameter	0.814 (0.732-0.896)	Ref.
Sharma et al. [15]	Palpable spleen, platelet count	0.694 (0.593-0.796)	0.0283
Alempijevic et al. [14]	Right liver lobe/albumin	0.662 (0.547-0.777)	0.1121
Hong et al. [13]	portal vein diameter, spleen width	0.769 (0.672-0.866)	0.743
Giannini et al. [16]	Platelet count/spleen diameter	0.764 (0.663-0.864)	0.133
Model P	Platelet count	0.656 (0.551-0.761)	0.002
Model S	Spleen diameter	0.688 (0.578-0.798)	0.044

* The P value was obtained by z test.

FIGURE 2. Diagnostic evaluation of predictive models for large esophageal varices. The detailed information including references, predictive variable involved, AUROC and their P values are summarized in Table 6.

Optimization of the diagnostic criteria of the predictive variables

To provide a practical diagnostic criterion for prediction of large esophageal varices using the NIP variable, a diagnostic evaluation was performed using ROC curve analysis [12], during which the optimal criterion value and its associated sensitivity and specificity for each predictive variable were calculated (Table 5). The NIP value calculated from Eq.1 had an increased AUROC compared with other single or compound variables, suggesting that our predictive model based on Eq.1 exhibited the best diagnostic ability. The ROC curve of our predictive model is shown in Fig. 1, where AUROC = 0.814 (95%CI = 0.732-0.896). The diagnostic sensitivity and specificity achieved 77.8% and 72%, respectively, in our study group. The cutoff value of > -1.87 predicted the presence of large esophageal varices at high risk of esophageal hemorrhage; for example, if a patient's predictive value = -1.825, this patient likely has large esophageal varices and should be recommended for further UGIE examination.

The best model for prediction of large esophageal varices

To obtain the predictive model that is best suitable for screening large esophageal varices, an additional six predictive models were selected based on literature reports. ROC curve analysis was performed to compare the six models with our model as described in Eq.1 (Table 6). The ROC curves for these models are presented in Fig. 2. Tested in our study group, the predictive models of Hong *et al.* [13], Giannini *et al.* [16], and our proposed model yielded obviously higher AUROC (>0.7), while the AUROC from other four models was less than 0.7. Even though there was no significant difference from the predictive models of Hong *et al.* [13] and Giannini *et al.* [16], our NIP model achieves the highest AUROC value (Table 6), thus representing the best predictive model for prediction of large sized esophageal varices in our liver cirrhosis patients. Among the tested seven predictive models, as well as other individual and compound variables, our proposed predictive model had the greatest diagnostic ability in predicting large esophageal varices.

Discussion

Large esophageal varices are a dangerous clinical consequence of liver cirrhosis. Since variceal screening causes considerable endoscopic burden and cost, seeking a less expensive, noninvasive means for accurate prediction of large esophageal varices has great clinical importance. The promising predictive marks have been focusing on common laboratory variables such as platelet count [16, 17] and albumin level [14], ultrasound parameters such as spleen and portal vein dimension [13, 17], or data from some minimally invasive approaches such as video capsule endoscopy [18] and computerized tomography [19]. A screening test must be simple and inexpensive, and while some tests are clearly preferable to patients because of ???, none appear to be as accurate as upper GI endoscopy in the diagnosis of esophageal varices. The search for noninvasive tests continues[9].

In this study, 20 individual and six compound parameters were evaluated in 104 liver cirrhosis patients, and their diagnostic ability for large esophageal varices was assessed using multiple statistical approaches. No single parameter was found to offer self-sufficient predictive function for large esophageal varices; however, a combination of multiple parameters (hemoglobin level, platelet count, spleen and portal vein diameters) significantly improves the predictive accuracy. Based on a stepwise multivariate logistic regression analysis, a predictive model was proposed (as expressed in Eq.1) with an optimal cutoff value of -1.87 as the diagnostic criterion. It is worth noting that the cutoff value may vary with different study groups.

The predictive variables included in our final model were also previously reported to be promising in variceal prediction; for example, the diagnostic effectiveness of portal vein diameter in prediction of large esophageal varices has been proven in several studies [13, 20]. Liver cirrhosis-associated portal hypertension causes splenomegaly and hypersplenism and resultant decreases in platelet count and hemoglobin level. Indeed, platelet count/spleen diameter has been shown to be robust in variceal prediction [13, 15-17, 20-22]. Our data are consistent with these reports and further demonstrate a more powerful predictive function for large esophageal varices by pooling these variables together.

The development of esophageal varices and their enlargement are expected to be associated with the severity of liver cirrhosis. Child-Pugh is commonly used for assessment of the progress of liver cirrhosis [23]; thus, Child-Pugh was expected to predict the presence of varices in this study. Surprisingly, in our sample, Child-Pugh was not significantly associated with the presence of large esophageal varices and, thus, was excluded from further diagnostic evaluation. The predominant etiology

of liver cirrhosis in our sample is HBV infection; however, no significant difference in disease etiology was detected between the two groups of small and large esophageal varices. Disease etiology and severity, therefore, have no significant confounding effect on our diagnostic evaluation of the predictive variables. Note that our study sample had only one subject with no esophageal varices in comparison with 49/54 patients with small or large varices. The sample composition, with an insufficient number of patients of normal esophagus, may affect the cutoff predictive value and also other statistical outcomes. Future studies are designed to evaluate our proposed predictive model using additional samples, which should ideally be confirmed in other cohorts.

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