

Non-Invasive Predictors of Moderate–Large Esophageal Varices in Compensated Cirrhotic Patients

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ABSTRACT

AIM: to identify a non-invasive and low-cost tool that could predict the presence of moderate-to-large EV in compensated cirrhotic patients to lower the number of unnecessary endoscopies.

MATERIALS AND METHODS: A cross-sectional study was conducted in newly diagnosed patients with non-Child-Pugh C liver cirrhosis, without a history of variceal bleeding. The presence and degree of esophageal varices were determined during endoscopy. Univariate and multivariate logistic regression were used to identify independent predictors for the presence of esophageal varices.

RESULTS: Of the 180 patients enrolled in this study, EV was found in 99 patients (55%). Moderate-large varices were detected in 23.3%

and 51.7% of patients with CP-A and CP-B class, respectively. In univariate analysis, CP class B, low platelet count ($\leq 100\ 000/\mu\text{L}$), increased bipolar diameter ($\geq 135\ \text{mm}$), and ratio of platelet count to bipolar spleen diameter (≤ 847) were associated with the presence of moderate-to-large EV. In multivariate analysis, CP class and ratio of platelet count to bipolar spleen diameter were associated with the presence of moderate-to-large EV. The AUC, sensitivity, and specificity of combined predictors were 0.76, 88% and 55.4%, respectively.

CONCLUSION: Platelet count/bipolar spleen diameter ratio value of ≤ 847 could be used as a non-invasive predictor of the presence of moderate-to-large EV in compensated cirrhotic patients. Future validation in a larger cohort is needed before applying this parameter in clinical practice.

Key words: Non-invasive predictors; Compensated cirrhosis; Esophageal varices

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INTRODUCTION

Esophageal varices (EV) is a severe complication of portal hypertension in liver cirrhotic patients. In newly diagnosed liver cirrhotic patients, more than 50% of patients had EV during screening procedure. The incidence rate of varices in this population is 4.5% per year^[1,2]. The presence of EV has been associated with the degree of severity in liver cirrhosis. The prevalence of EV in cirrhotic patients with compensated and decompensated cirrhosis were 30% and 60%, respectively^[3]. The progression rate from small to moderate large size varices was 12% and 31% at 1 and 3 years, respectively. The increase of variceal diameter was associated with elevated pressure on the varices wall, which was at a critical point resulting in rupture and life-threatening bleeding^[4].

Approximately 20% of patients with EV had a minimum of one episode of variceal hemorrhage (VH) in one year after the diagnosis

of EV. The North Italian Endoscopic Club (NIEC) index has been developed to predict the risk of first variceal hemorrhage episode in cirrhotic patients. It includes three variables, i.e. CP class, size of varices, and severity of red wale marks^[5]. The mortality rate due to the bleeding episode varies from less than 10% in CP-A class to more than 33% in CP-C liver cirrhotic patients^[6].

Due to the high mortality rate of VH, prevention of variceal bleeding is one of the primary goals of the management of liver cirrhotic patients. Screening of EV and gastric varices (GV) through esophagogastroduodenoscopy (EGD) is currently recommended for all newly diagnosed liver cirrhotic patients, as stated in Practice Guidance by the American Association for the Study of Liver Diseases (AASLD) and World Gastroenterology Organisation (WGO) Global Guidelines^[7,8]. However, in daily clinical practice, only 40% of patients with compensated cirrhosis are found to have EV^[9]. Furthermore, EGD screening is also an invasive and costly procedure. Due to the high risk of bleeding in moderate-to-large EV, a non-invasive and cost-effective examination is needed to predict the presence of moderate-to-large EV in non-CP-C liver cirrhotic patients.

MATERIALS AND METHODS

Study Design and Sample Size

A cross-sectional study was conducted to determine the predictors of EV in cirrhotic patients classified as CP-A and CP-B. Data was collected in the Hepatology Clinic and Integrated Procedure Room of the Hepatobiliary Division of our hospital between June 2017 and June 2018. The minimal sample size was calculated using rule of thumbs method (10 samples for each variable)^[10]. As many as seven potential parameters were used in this study, therefore a minimum of 70 subjects were recruited to perform a multivariate analysis.

Patients

All liver cirrhotic patients classified as CP-A or CP-B classes, aged 18 years or older, and who would undergo EGD procedure for EV screening, were included. The exclusion criteria in this study were: (1) patients who had a history of upper gastrointestinal bleeding, propranolol or other beta-blocker consumption, and previous EGD procedure; (2) patients who were administered blood transfusion within four weeks before blood sampling was performed; and (3) patients with hepatocellular carcinoma (HCC), aplastic anemia, idiopathic thrombocytopenia purpura (ITP), and other hematologic disorders causing thrombocytopenia. Informed consent letters were obtained from each patient who participated in this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation by local ethic committee of the Faculty of Medicine Universitas Indonesia and with the Helsinki Declaration of 1975, as revised in 2000.

Diagnosis and Classification of Cirrhosis

Diagnosis of cirrhosis was established based on: (1) stigmata of cirrhosis (spider naevi, palmar erythema, gynecomastia, ascites, splenomegaly) on physical examination; (2) characteristic findings of liver cirrhosis (heterogenous liver echostructure, nodular liver surface, widening of portal and splenic vein, narrowing of hepatic vein) on ultrasound (US); and (3) fibrosis stage F4 on transient elastography (FibroScan®) examination. The CP scoring system was used to assess the degree of severity and survival rate of cirrhotic patients. Child-Pugh class was determined by five parameters (serum bilirubin, serum albumin, international normalized ratio (INR) value,

presence of ascites, and presence of encephalopathy) and classified into three classes according to the CP total score, including (1) CP class A (5-6); (2) CP class B (7-9) and (3) CP class C (10-15).

Grading of Esophageal Varices

According to EGD findings, EV was classified into three categories: (1) small varices, which appear as slight protrusion above the esophageal mucosal surface; (2) moderate-sized varices, which occupy < 1/3 of the esophageal lumen, and (3) large-sized varices, which occupy >1/3 lumen of the esophagus. In this study, we categorized the EV findings into two groups. The first group is no-to-small varices group and the other is moderate-to-large varices group.

Spleen bipolar diameter and portal vein diameter: Spleen bipolar diameter and portal vein diameter were determined by ultrasound and expressed in millimeters (mm). Platelet count was obtained from venous blood sample mixed with EDTA anticoagulant. The ratio of platelet count/spleen bipolar diameter was calculated by dividing platelet count (n/ μ L) with spleen bipolar diameter (mm).

Data Analysis

All normally distributed numerical data was presented in mean and standard deviation or in median and range if not normally distributed. Categorical data was presented in absolute and relative frequencies. Univariate analysis was performed with Chi-Square test or Fisher's exact test. All predictors with p-value less than 0.2 in univariate analysis were included in multivariate analysis with logistic regression method. All predictors with p-value less than 0.5 in multivariate analysis were considered statistically significant. All data was analyzed with SPSS 20.0 statistical package.

RESULTS

Clinical characteristics of the patients

As many as 180 cirrhotic patients with CP class A and B were enrolled between June 2017 and February 2020. Of these patients, 120 patients were classified into CP class A and 60 patients were classified as CP class B. Baseline characteristics are shown in Table 1. The majority of patients were male and the most common etiologies of cirrhosis were hepatitis B and hepatitis C.

Esophageal varices events in cirrhotic patients

Esophageal varices were detected in 46.7% and 71.7% of patients with CP class A and B, respectively. Large varices were found in 25 of 120 patients (20.8%) with CP class A and 27 of 60 patients (45%) with CP class B. The prevalence of EV and their grading are shown in Table 2. As moderate-large varices were treated equally in clinical practice, patients with moderate and large varices were classified as one group for the analysis.

Factors Associated with Moderate – Large EV in Cirrhotic Patients

In univariate analysis, the presence of moderate-to-large grade of EV in cirrhotic patients was associated with Child-Pugh class B, low platelet count ($\leq 100,000/\mu$ L), increased bipolar spleen diameter (≥ 135 mm), and ratio of platelet count to bipolar spleen diameter ≤ 847 , as shown in Table 3. In multivariate analysis, CP class and platelet count/bipolar spleen diameter ratio were associated with the presence of moderate-large EV in cirrhosis (Table 4). The area under the curve (AUC) of CP class and ratio of platelet count/bipolar spleen diameter was 0.76 ($p = 0.001$; 95% CI 0.70-0.84), with sensitivity and specificity of 88% and 55.4%, respectively (Figure 1).

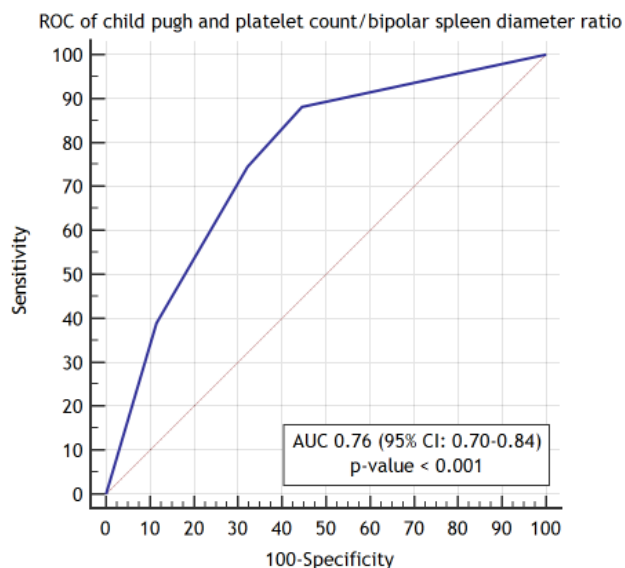


Figure 1 Receiver-operating curves (ROC) of platelet count/bipolar spleen diameter ratio for prediction of moderate-large esophageal varices (estimated AUC = 0.76; 95% CI 0.70-0.84).

Table 1 Baseline characteristics of the study participants.

Variables	Esophageal varices (moderate-large) (n=59)	Esophageal varices (no or mild)(n=121)
Sex: n (%)		
Male	38 (64.4)	81 (66.9)
Age (years), median (range)	50 (34-74 years)	57 (22-88 years)
Etiology: n (%)		
Hepatitis B	28 (47.5)	50 (41.3)
Hepatitis C	21 (35.6)	61 (50.4)
Hepatitis B and C	2 (3.4)	1 (0.8)
NASH	1 (1.7)	1 (0.8)
Autoimmune Hepatitis	1 (1.7)	1 (0.8)
Non B and Non C	5 (8.5)	7 (5.2)
Unknown	1 (1.7)	0 (0)
Child Pugh Classification: n (%)		
A	28 (47.5)	92 (76)
B	31 (52.5)	29 (24)
Hemoglobin: median (range) (g/dL)	11.30 (7.50-16.50)	13.40 (7.20-17.0)
Leucocyte: mean (SD)(10 ³ /μL)	4.69 (2.20-9.70)	6.29 (2.28)
Platelet: median (range) (10 ³ /μL)	81 (20-280)	134 (33-640)
INR: median (range)	1.02 (0.96-1.55)	1.0 (0.87-10.90)
Albumin: median (range) (g/dL)	3.34 (1.94-4.60)	4.0 (2.13-6.20)
Bilirubin: median (range) (mg/dL)	1.53 (0.40-8.65)	1.01 (0.21-6.12)
Portal vein diameter: mean (SD) (mm)	11.90 (3.26)	11.13 (2.55)
Spleen bipolar diameter: mean (SD) (mm)	138.88 (25.84)	117.55 (25.03)

Table 2 Esophageal Varices and Grading in CP-A and CP-B Patients.

Variables	Child-Pugh A(n=120)	Child-Pugh B(n=60)
Esophageal Varices, n (%)		
No	64 (53.3)	17 (28.3)
Yes	56 (46.7)	43 (71.7)
Esophageal Varices Grading, n (%)		
Normal	64 (53.3)	17 (28.3)
Small	28 (23.3)	12 (20)
Moderate	3 (2.5)	4 (6.7)
Large	25 (20.8)	27 (45)

Table 3 Univariate analysis of factors associated with moderate-large esophageal varices.

Variables	OR (95% CI)	p-value
Sex		
Female	1	-
Male	0.89 (0.47-1.72)	0.865
Age		
< 50 years	1	-
≥ 50 years	0.51 (0.27-0.97)	0.055
Child Pugh Class		
A	1	-
B	3.51 (1.82-6.79)	<0.001
Platelet count		
> 100.000 /μL	1	-
≤ 100.000 /μL	3.97 (2.06-7.65)	<0.001
Portal Vein Diameter		
< 13 mm	1	-
≥ 13 mm	1.94 (0.99-3.77)	0.074
Bipolar Spleen Diameter		
< 135 mm	1	-
≥ 135 mm	5.50 (2.78-10.88)	<0.001
Platelet count / bipolar spleen diameter ratio		
< 847 mm	1	-
≥ 847 mm	6.17 (3.07-12.41)	<0.001

Table 4 Predictors of the presence of moderate-large EV in cirrhosis.

Predictors	OR (95% CI)	p-value
Child-Pugh class B	2.80 (1.37-5.70)	0.005
Ratio of platelet to bipolar spleen diameter	5.39 (2.63-11.02)	<0.001

DISCUSSIONS

Liver cirrhosis is an irreversible fibrosis or scarring process in the liver due to chronic inflammation, which represents the late stage of chronic liver disease. The cirrhotic process is initiated by asymptomatic compensated condition, which is followed by decompensated cirrhosis as the disease progresses. In compensated cirrhosis, the portal pressure is relatively normal or slightly elevated. Ascites, encephalopathy, jaundice, and EV were developed in decompensated cirrhosis due to elevated portal pressure (portal hypertension) and reduced liver function^[11].

Of the 75 patients with EV, moderate-large varices were found in 23 patients with CP-A and 23 patients with CP-B class. Child-Pugh classification has been developed to predict the survival rate of liver cirrhotic patients and categorize the degree of severity in liver function^[12]. In multivariate analysis, there is a statistical significant difference of CP class and patients with CP class B had 3.34 higher risk of developing EV. These results coincide with the results of studies by Sumon *et al*^[13], Thapa *et al*^[14], and Ashraf *et al*^[15].

Several non-invasive parameters have been extensively studied to predict the presence of EV, including platelet count, spleen diameter size, platelet count/spleen diameter ratio, portal vein diameter and degree of ascites. However, none of the above provide consistent results in predicting the presence of EV. In multivariate analysis, the ratio of platelet count / bipolar spleen diameter was associated with moderate-large sized of EV during EGD screening.

AASLD recommends the combination of liver stiffness measurement with transient elastography (TE) and platelet count as non-invasive test in the diagnosis of gastroesophageal varices, in order to exclude patients with low risk of having moderate-

large varices^[7]. However, the availability of TE tools is limited in developing countries, including Indonesia. Sharma SK *et al* found low platelet count as an independent predictor of the presence of large varices, besides palpable spleen. Patients with platelet count >105 000/ μ L had 80% probability for the absence of large EV, with an AUC of 0.76^[16]. Different results were shown by Qamar *et al*^[17] who found that platelet count of less than 100 000/ μ L could not be used as a non-invasive predictor of EV. In this study, platelet count of less than 100 000/ μ L was found associated with the presence of moderate-large EV.

Thrombocytopenia is one of the most common complications in patients with chronic liver disease. There are three basic mechanisms for low platelet count in cirrhosis patients, including reduced production, increased destruction, and sequestration. The sequestration process is initiated with portal hypertension which resulted in enlarged spleen and splenic sequestration of platelets. The most common mechanism of reduced platelet production is the reduction of thrombopoietin (TPO), a hemopoietic growth factor produced primarily in the liver. Other etiologies are bone marrow suppression by viral infection, particularly HCV and the adverse effect of antiviral treatment, especially interferon-based therapy. The increased destruction of platelet is caused by shear stress, bacterial translocation, sepsis, and hyperfibrinolysis^[18,19].

Enlarged spleen was often observed in liver cirrhotic patients and was associated with a higher risk of complications related to portal hypertension. The spleen diameter was significantly increased in decompensated cirrhosis, as compared to compensated cirrhosis^[20]. A systematic review reported bipolar spleen diameter >150 mm in ultrasonography examination might be used as an alternative tool for VE diagnosis in liver cirrhosis^[21]. Several mechanisms of splenomegaly have been known, such as portal congestion, fibrosis, and tissue hyperplasia^[22].

The use of the ratio of low platelet count/spleen bipolar diameter to predict the presence of EV in cirrhotic patients was first proposed by Giannini *et al*^[23], in 2003. They found that application of platelet count alone could be misleading and that platelet count/spleen bipolar diameter ratio was the only predictor independently associated with the presence of EV. The negative predictive value (NPV) of the value of platelet count/spleen bipolar diameter ratio of 909 was 100%, in order to predict the presence of EV. A recent meta-analysis reported the use of platelet count to spleen diameter ratio with a cutoff value of 909 showed the AUC value for any varices was 0.88. Cirrhotic patients with ratio < 909 are recommended to be evaluated with EGD procedure^[24].

Abu El Makarem *et al*^[25], used a different cut-off value of platelet count/spleen diameter ratio. With a cut-off value of 939.7, the AUC, sensitivity, and specificity were 0.84, 100%, 86.3%, respectively. Another study from Baig *et al*^[26] applied the cut-off value of 1014, with AUC value, sensitivity, and specificity as high as 0.94, 98.1%, and 86%, respectively. In our study, a lower cut-off value of 847 was established. It is probable that the difference is due to the different characteristic of the study population. The patient selection in our study was limited to cirrhotic patients with CP class A and B, instead of any CP class. A lower cut-off is needed to select those patients with CP class A or B, who do not need endoscopy screening at diagnosis of cirrhosis.

In summary, our results indicate that ratio of platelet count to bipolar spleen diameter of ≤ 847 could be used as a non-invasive predictor of the presence of moderate-large EV in compensated cirrhotic patients. However, our findings need to be validated in other cohort with a larger number of samples before any application in clinical practice.

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