Mac-2 Binding Protein Glycosylation Isomer for Screening High-Risk Esophageal Varices in Liver Cirrhotic Patient

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Abstract: Background: Esophageal varices occur at middle to advanced stages of cirrhosis and are associated with increased mortality due to their potential for rupture and bleeding. The aim of this study is to examine the accuracy of a surrogate marker, Mac-2 binding protein glycosylation isomer (M2BPGi), for screening high-risk esophageal varices in cirrhotic patients. Methods: Ninety-four cirrhotic patients who underwent endoscopy screening at Cipto Mangunkusumo Hospital, Jakarta, Indonesia were included. Patients with a history of ligation, portal vein thrombosis, or hepatocellular carcinoma were excluded. All enrolled patients underwent ultrasonography, transient elastography, and laboratory tests. The HISCL-5000 Sysmex analyzer was used to measure M2BPGi levels. Results: Of these 94 patients, 27 had high-risk esophageal varices and 67 had non-high-risk esophageal varices. M2BPGi levels were higher in patients with high-risk esophageal varices compared with those with non-high-risk esophageal varices (cutoff index (COI) of 11.4 vs. 3.7, \( p < 0.001 \)). The sensitivity, specificity, positive predictive value, and negative predictive value of M2BPGi with a cutoff value of 5 COI was 92.6%, 70.1%, 55.6%, and 95.9%, respectively. Conclusions: M2BPGi could be used as a non-invasive surrogate marker for ruling out high-risk esophageal varices in cirrhotic patients. This method is cheap and non-invasive and could be used as a screening tool in resource-limited settings.

Keywords: cirrhosis; high-risk esophageal varices; M2BPGi; screening; non-invasive

1. Introduction

According to a 2020 Global Burden of Disease study, cirrhosis is ranked 16th in disability-adjusted life-years and has resulted in 1.32 million total deaths, with 0.44 million and 0.88 million deaths in females and males, respectively, in 2017 [1,2]. The mortality rate for cirrhosis is higher in low-income regions such as sub-Saharan Africa, Central Asia, and Southeast Asia [2]. Portal hypertension is a complication of cirrhosis and esophageal variceal bleeding occurs at a portal pressure of >12 mmHg [3]. Variceal bleeding is a dreaded complication of cirrhosis and has a 6-week mortality rate of 26% after an acute episode [4]. Therefore, it is important to detect and treat esophageal varices early to reduce mortality.

Currently, the gold standard for detecting esophageal varices is esophagogastroduodenoscopy. However, this method is invasive and expensive, making it impractical for use in resource-limited settings. Another test method used is transient elastography. However, it has moderate accuracy and has a high rate of failure in obese patients, patients with ascites, and patients with narrow intercostal spaces [5–8]. Computed tomography is widely used in cirrhotic patients but can lead to false-positive and false-negative results due to the difficulty of discriminating between submucosal and subserosal esophageal varices [9]. In addition, computed tomography is cheaper than endoscopy, but more expensive than other
non-invasive methods, which may limit its use in resource-limited settings [10]. Similar to computed tomography, magnetic resonance imaging can detect the presence of varices but is unable to estimate size, and is costly and may not be available in resource-limited settings. Other non-invasive laboratory tests such as aspartate aminotransferase-to-platelet ratio, aspartate aminotransferase-to-alanine aminotransferase ratio, FIB-4, F1, King, Lok, and Forns scores have low to moderate accuracy in predicting esophageal varices [11].

Mac-2 binding protein glycosylation isomer (M2BPGi) is a liver fibrosis biomarker and its serum levels are correlated with fibrosis progression in chronic liver diseases. Previous studies showed that M2BPGi measurement could be used to predict hepatocellular carcinoma (HCC) development, HCC recurrence risk, and the presence of esophagogastric varices [12,13]. The role of M2BPGi as a non-invasive test for detecting esophageal varices with a high risk of bleeding is not fully explored. The aim of this study is to examine the performance of M2BPGi in detecting high-risk esophageal varices in cirrhotic patients.

2. Materials and Methods

2.1. Study Design

This was a cross-sectional study of adult cirrhosis patients who underwent esophagogastroduodenoscopy (EGD) for variceal screening from May 2018 to December 2019 at the Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, a tertiary referral hospital. A total of 94 cirrhotic patients were included in this study. This study was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committees of the Faculty of Medicine, University of Indonesia (approval No. 295/UN2.F1/ETIK/2018). Written informed consent was obtained from each patient.

2.2. Data Collection

All patients underwent physical examination, laboratory tests, ultrasonography (USG), liver stiffness measurement (measured by transient elastography), and EGD. The diagnosis of cirrhosis was based on a combination of typical clinical findings (stigmata of cirrhosis), radiology (morphological changes of the liver, ascites, and splenomegaly), and laboratory tests. Patients were classified based on the Child–Pugh score. Patients with a history of variceal ligation, portal vein thrombosis, or with hepatocellular carcinoma were excluded. The clinical data included age, gender, and etiology of cirrhosis. The laboratory data included hemoglobin, white blood cell count, platelet count, aspartate and alanine aminotransferase (AST and ALT), albumin, total bilirubin, and prothrombin time.

2.3. Endoscopy and USG Evaluation

Endoscopies were performed in one endoscopy unit using a video gastroscope (Pentax EG29-i10) by endoscopists at our Hepatobiliary Division. High-risk esophageal varices were defined as medium or large varices, small varices with red signs or in Child–Pugh C, in accordance with the European Association for the Study of Liver (EASL) guidelines [14]. Patients who did not have those features were considered to be non-high-risk for variceal bleeding. All USG evaluations of the upper abdomen were performed by one experienced operator using a Hitachi HIVISION Avius equipment. The portal vein and spleen bipolar diameter were measured in millimeters during B-mode ultrasound scanning as previously described [15].

2.4. Liver Stiffness Measurement

Liver stiffness was measured using transient elastography (TE) (Fibroscan Touch 502, Echosens, Paris, France) by one experienced operator based on recommendation [16]. The results were expressed in kilopascals (kPa). A success rate of <60% or an interquartile range/median value > 30% were considered to be unreliable.
2.5. Mac-2 Binding Protein Glycosylation Isomer

Venous blood was collected before endoscopy. Three ml of venous blood was centrifuged at 2000 rpm for 15 min at room temperature (25–30 °C) to get serum samples and then stored at −80 °C. Mac-2 binding protein glycosylation isomer was measured on stored serum by employing the lectin-antibody sandwich immunoassay on an automated immunoassay system, HISCL-5000 (Sysmex, Hyogo, Japan), as previously reported [17]. The results were expressed in cutoff index (COI).

2.6. Statistical Analysis

Continuous data were expressed as mean and standard deviation if it was normally distributed, or median and minimum-maximum if was not normally distributed. Categorical data were expressed as numbers and percentages. Continuous data were compared using the Student’s t-test, Mann–Whitney U test, or Chi square test for proportions of categorical data. Stepwise logistic regression analysis was performed to identify independent variables associated with high-risk esophageal varices. The cutoff value of M2BPGi level was determined using receiver operating characteristic (ROC) curve analysis. The diagnostic performance of M2BPGi was compared with the Baveno VI (liver stiffness < 20 kPa and platelet count > 150 × 10^9 cells/L) and Expanded Baveno VI criteria (liver stiffness < 25 kPa and platelet count > 110 × 10^9 cells/L) by calculating sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio. The number of spared EGD was calculated by dividing the number of patients with EGD that could be spared by the total number of patients. Missed high-risk varices was defined by the ratio of high-risk varices to total patients with spared EGD. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered to be statistically significant.

3. Results

3.1. Basic Characteristics of Patients

Table 1 shows the basic characteristics of our patients. The mean age was 56.4 ± 11.1 years old. There were no significant differences in age and sex between the high-risk esophageal varices group and the non-high-risk esophageal varices group. The total proportion of patients with viral hepatitis was higher in the non-high-risk esophageal varices group. Most patients in the high-risk esophageal varices group were Child–Pugh B/C. Compared with the non-high-risk esophageal varices group, the high-risk esophageal varices group had a lower median value of hemoglobin (11.3 vs. 13.5 g/dL, p = 0.002), white blood cell count (4730 vs. 6380/µL, p < 0.001), platelet count (86 × 10^3 vs. 134 × 10^3/µL, mboxemphp < 0.001), and albumin (3.4 vs. 3.9 g/dL, p < 0.001), and a greater spleen bipolar diameter (141.1 vs. 116.5 mm, mboxemphp < 0.001), higher liver stiffness (26 vs. 17 kPa, p = 0.002), and a higher serum M2BPGi level (11.4 vs. 3.7 COI, p < 0.001). Multivariate analysis found that spleen bipolar diameter and M2BPGi levels were independently associated with high-risk esophageal varices (Table 2).

| Variables       | Entire Cohort (n = 94) | Non-High-Risk Varices (n = 67) | High-Risk Varices (n = 27) | p Value |
|-----------------|------------------------|-------------------------------|-----------------------------|---------|
| Age (years), mean ± SD | 56.4 ± 11.1           | 57.7 ± 11.6                   | 53.1 ± 9.4                  | 0.074   |
| Sex, n (%)      |                        |                               |                             |         |
| Male            | 59 (62.8)              | 45 (67.2)                     | 14 (51.9)                   | 0.165   |
| Female          | 35 (37.2)              | 22 (32.8)                     | 13 (48.1)                   |         |
| Etiology, n (%) |                        |                               |                             | 0.038   |
| HBV             | 47 (50.0)              | 33 (49.3)                     | 14 (51.9)                   |         |
| HCV             | 37 (39.4)              | 30 (44.7)                     | 7 (25.9)                    |         |
| Others          | 10 (10.6)              | 4 (6.0)                       | 6 (22.2)                    | 0.016   |
| Child Pugh, n (%)|                       |                               |                             |         |
Table 1. Cont.

| Variables                  | Entire Cohort (n = 94) | Non-High-Risk Varices (n = 67) | High-Risk Varices (n = 27) | p Value   |
|----------------------------|------------------------|--------------------------------|---------------------------|-----------|
| A                          | 60 (63.8)              | 48 (71.6)                      | 12 (44.4)                 |           |
| B                          | 30 (31.9)              | 18 (26.9)                      | 12 (44.4)                 |           |
| C                          | 4 (4.3)                | 1 (1.5)                        | 3 (11.1)                  |           |
| Hemoglobin (g/dL)          | 13 (7.2–17.0)          | 13 (7.2–17.0)                  | 11.3 (7.6–16.3)           | 0.002     |
| White blood cell count (/µL)| 5580 (2300–14,930)     | 6380 (2580–14,930)             | 4730 (2300–5010)          | <0.001    |
| Platelet count (×10³/µL)  | 123 (33–385)           | 134 (33–385)                   | 86 (37–178)               | <0.001    |
| Prothrombin time (s)       | 11.5 (10.1–24.7)       | 11.3 (10.1–16.8)               | 12.4 (10.9–24.7)          | <0.001    |
| Aspartate transaminase (U/L)| 40.5 (10–341)         | 40 (10–341)                    | 41 (22–257)               | 0.330     |
| Alanine transaminase(U/L)  | 3.8 (14–422)           | 3.9 (14–308)                   | 3 (17–422)                | 0.760     |
| Albumin(g/dL)              | (1.9–4.9)              | (2.0–4.9)                      | (1.9–4.3)                 | <0.001    |
| Total bilirubin (mg/dL)    | 1.2 (0.2–5.7)          | 1.1 (0.2–5.4)                  | 1.9 (0.4–5.7)             | 0.014     |
| Portal vein diameter (mm)  | 11 (5.5–23.5)          | 10.9 (5.9–15.7)                | 11.6 (5.5–23.5)           | 0.154     |
| Spleen bipolar diameter (mm)| 120.3 (78.1–219.0)   | 116.5 (78.1–182.4)             | 141.1 (99.3–219.0)        | <0.001    |
| Liver stiffness/TE (kPa)   | 20.8 (7–75)            | 17 (7–75)                      | 26 (10.5–73.5)            | 0.002     |
| M2BPGi level (COI)         | 4.5 (0.6–20)           | 3.7 (0.6–20)                   | 11.4 (1.7–20)             | <0.001    |

Continuous variables are expressed as median (minimum-maximum) unless indicated otherwise. COI: cutoff index; HBV: hepatitis B virus; HCV: hepatitis C virus; M2BPGi: Mac-2 binding protein glycosylation isomer; TE: transient elastography.

Table 2. Multivariate analysis of variables associated with high-risk esophageal varices.

| Variables                  | Odd Ratio (95% CI)   | p Value |
|----------------------------|----------------------|---------|
| Platelet count             | 1.000 (1.000–1.000)  | 0.855   |
| Portal vein diameter       | 0.986 (0.777–1.250)  | 0.905   |
| Transient elastography     | 1.019 (0.982–1.057)  | 0.317   |
| Spleen bipolar diameter    | 1.039 (1.007–1.072)  | 0.017   |
| M2BPGi level (COI)         | 1.160 (1.026–1.312)  | 0.017   |

CI: confidence interval; M2BPGi: Mac-2 Binding Protein Glycosylation Isomer.

3.2. Diagnostic Performance of M2BPGi for Screening High-Risk Esophageal Varices

Based on the ROC curve analysis for M2BPGi, a cutoff value of 5 COI was used with an AUROC of 0.807 (95% CI: 0.716–0.898; p < 0.001) (Figure 1). We compared the diagnostic performance of M2BPGi with the Baveno VI criteria and Expanded Baveno VI criteria, as shown in Table 3. From the table, it can be seen the M2BPGi level had a higher sensitivity (92.6%) than the Expanded Baveno VI criteria (88.9%), and a lower sensitivity than the Baveno VI criteria (100%). However, M2BPGi showed greater specificity, positive predictive value, and positive likelihood ratio than both criteria, while the negative predictive value was higher than the Expanded Baveno VI criteria but slightly lower than the Baveno VI criteria. The value of using M2BPGi is shown by the higher number of spared EGDs (n = 47) compared with the Baveno VI criteria (n = 18) and the Expanded Baveno VI criteria (n = 32) while only missing two cases of high-risk esophageal varices.
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![Figure 1. Receiver operating characteristic (ROC) curve of M2BPGi for screening high-risk esophageal varices in liver cirrhosis. AUC = area under ROC curve.](image)

Table 3. Diagnostic performance of M2BPGi, Baveno VI, and Expanded Baveno VI Criteria.

|                        | M2BPGi (Cutoff 5 COI) (\( n = 49 \)) | Baveno VI Criteria (\( n = 18 \)) | Expanded Baveno VI Criteria (\( n = 35 \)) |
|------------------------|--------------------------------------|-----------------------------------|-------------------------------------------|
| Sensitivity (%)         | 92.6                                 | 100                               | 88.9                                      |
| Specificity (%)         | 70.1                                 | 26.9                              | 47.8                                      |
| Positive predictive value (%) | 55.6                                  | 35.5                              | 40.7                                      |
| Negative predictive value (%) | 95.9                                  | 100                               | 91.4                                      |
| Positive likelihood ratio | 3.1                                  | 1.3                               | 1.7                                       |
| Negative likelihood ratio | 0.1                                  | 0                                 | 0.2                                       |
| Spared EGD, n (%)       | 47 (52.1)                            | 18                                | 32 (34)                                   |
| Missed high-risk varices, n (%) | 2 (4.2)                              | 0                                 | 3 (8.5)                                   |

Note: A cutoff value of 5 was used for M2BPGi based on the ROC curve analysis.

4. Discussion

Non-selective beta-blockers (NSBBs; propranolol, nadolol, or carvedilol) are the mainstay treatment for esophageal varices and endoscopic band ligation is used for large varices [18]. In contrast, etiology-specific treatment and anti-fibrotic drugs are used for the early stages of cirrhosis where there are no varices, or small varices with no red-color signs [19]. Therefore, risk stratification and early diagnosis are important to determine the treatment to be used.

However, endoscopy is invasive and expensive, making it impractical to carry out monitoring every few years for esophageal varices. To circumvent this problem, the Baveno VI criteria was developed in 2015, such that EGD is spared for cirrhotic patients with a platelet count > 150 × 10^9 cells/L and a liver stiffness measurement < 20 kPa [20]. These criteria were modified to platelet count > 110 × 10^9 cells/L and liver stiffness measurement < 25 kPa in the Expanded Baveno VI criteria, which resulted in an increase in the number of EGDs spared [21]. However, these two criteria had a high sensitivity but low specificity. A meta-analysis found that the Baveno VI criteria and Expanded Baveno VI criteria had a sensitivity of 97% and 90%, respectively; and a specificity of 32% and 51%, respectively [22]. This matches the results of our study, that found that the Baveno VI criteria and Expanded
Baveno VI criteria had a sensitivity of 100% and 88.9%, and a specificity of 26.9% and 47.8%, respectively. In contrast, M2BPGi levels had a comparable sensitivity and higher specificity. More endoscopies were spared with the Expanded Baveno VI criteria compared with the Baveno VI criteria, but the number of missed high-risk varices was increased. In contrast, M2BPGi levels resulted in even more endoscopies spared but a comparable number of missed high-risk varices, demonstrating the clinical utility of this marker. M2BPGi levels had excellent negative predictive value, therefore it can be used to rule out the presence of high-risk esophageal varices in liver cirrhosis. This makes it easier to monitor cirrhotic patients regularly as M2BPGi is non-invasive, cheap, and does not require specialized staff and equipment, compared with endoscopy. The cost for M2BPGi screening in our institution is roughly $\frac{1}{4}$ of the cost for EGD. Therefore, it is much cheaper to carry out M2BPGi screening for patients, and especially so for resource-limited settings.

M2BPGi consists of Mac-2 binding protein (M2BP) with alteration in N-glycan residues during liver fibrogenesis that can be specifically recognized by Wisteria floribunda agglutinin (WFA) (WFA$^+$-M2BP). Bekki et al. identified hepatic stellate cells as the source of M2BPGi, which induced Mac-2 expression in Kupffer cells, which in turn increased the expression of $\alpha$-smooth muscle actin in hepatic stellate cells [23]. Hepatic stellate cell activation causes an increase in mechanical intrahepatic resistance and contributes to the development of portal hypertension. Furthermore, a study by Dolgormaa et al. showed that M2BPGi was detected in cirrhotic liver stromal cells and enhanced the growth of HCC through the galectin-3/mTOR signaling pathway [24]. These mechanistic studies provide the pathophysiologic basis that supports the clinical utility of M2BPGi in cirrhosis. Our study is the first study on the clinical utility of M2BPGi in Indonesia and also the first on the value of this biomarker for the screening of high-risk esophageal varices. A recent Japanese study on 102 cirrhotic patients with hepatitis C infection studied M2BPGi levels before and after treatment with direct-acting antivirals. They found that M2BPGi levels were higher in patients with esophageal varices and M2BPGi levels decreased after treatment [13]. This shows that M2BPGi could be a biomarker for esophageal varices, as this study was conducted in another population.

There are a few limitations of our study. Firstly, this is a single center study in Java, Indonesia, and the results cannot be generalized to other regions. Secondly, the sample size is low (<100 patients). However, this is an ongoing study and more subjects are planned for recruitment in the future. In addition, hepatitis B and C are the most common etiologies in our cohort and our results should be validated in patients with other etiologies. However, there is a high prevalence of chronic hepatitis B and C in Asia and sub-Saharan Africa, which are resource-limited settings, and mortality occurs due to cirrhosis [25]. Hence, it is imperative to introduce a cheap and easily available test in these regions to reduce mortality and morbidity due to viral hepatitis-related cirrhosis. An international, multicenter, prospective study could be carried out in the future to validate our results in other populations, such as alcohol-associated liver disease, that is a major cause of liver disease worldwide and results in cirrhosis [26].

5. Conclusions

Our study found that M2BPGi levels can be used as a non-invasive marker for ruling out cirrhotic patients with high-risk esophageal varices. This method is cheap, and does not require trained personnel and specialized equipment, which makes it useful for resource-limited settings.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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