New index to predict esophageal variceal bleeding in cirrhotic patients

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Abstract

AIM: To develop a safe, simple, noninvasive and affordable system to predict esophageal variceal bleeding (EVB) in decompensated cirrhosis patients.

METHODS: Four hundred and eighty-six patients with decompensated cirrhosis (238 males and 248 females), with a mean age of 63.1 ± 11.2 years, were admitted to Changshu Affiliated Hospital of Suzhou University between May 2008 and March 2011. Patients enrolled in this study underwent ultrasound-Doppler (US-Doppler) to assess left gastric vein (LGV) blood flow velocity (LGVV) and blood flow direction (LGVBFD), and were evaluated by the Model For End-Stage Liver Disease (MELD) scoring system. All patients received follow-up evaluations every three months. The resulting data were entered into a database after each time point collection.

RESULTS: Four hundred and sixteen patients completed follow-up evaluations for an average of 31.6 mo (range: 12 to 47 mo). Fifty-one (12.3%) patients experienced EVB. The change in the MELD score over three months (ΔMELD), LGVV and LGVBFD were independently associated with EVB occurrence. MELD-US-Doppler Index (MUI), a new index, was developed and calculated using the following logistic regression equation: MUI = Logit (P) = 1.667 (ΔMELD) + 2.096 (LGVV) - 3.245 (LGVBFD) - 1.697. The area under the receiver operating characteristic curve for prediction of EVB occurrence was significantly higher for the MUI [0.858 (95%CI: 0.774-0.920)] than for ΔMELD [0.734 (95%CI: 0.636-0.817); P < 0.05], LGVV [0.679 (95%CI: 0.578-0.769); P < 0.05] or LGVBFD [0.726 (95%CI: 0.627-0.810); P < 0.05] alone. When the MUI was set at 46, the index had high diagnostic accuracy (85.8%), with high specificity (80%) and sensitivity (87.27%).

CONCLUSION: The MUI, a noninvasive and affordable index, can predict EVB occurrence in decompensated cirrhotic patients and serve as an alternative when conventional endoscopic screening is declined.

Key words: Portal hypertension; Ultrasound-Doppler; Esophageal variceal bleeding; Decompensated cirrhosis; Endoscopy

Core tip: Bleeding is a common occurrence in cirrhotic patients with portal hypertension and establishing indicators of risk is critical. Although screening by endoscopy is the recommended approach for patients with decompensated cirrhosis, it is an invasive, uncomfortable and costly procedure. In the present study, a new index that combines ultrasound-Doppler and the Model For End-Stage Liver Disease was evaluated as a suitable alternative. This MUI represents a noninvasive, low-cost and convenient method for assessing the risk of esophageal variceal bleeding in decompensated cirrhotic patients.
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**INTRODUCTION**

In patients with cirrhosis, esophageal varices are commonly observed, with an estimated prevalence of 50%.[1] After esophageal varices have formed, the annual risk for bleeding can range from 10% to 30%.[2,3] In patients with decompensated cirrhosis, acute esophageal variceal bleeding (EVB) represents a predominant cause for morbidity and mortality. Due to the increased risk of fatality in cirrhotic patients with EVB, the risk status in patients must be routinely evaluated such that the appropriate prophylactic therapy is administered to prevent variceal bleeding events. Typically, the EVB risk is assessed through endoscopic screening to assign a grade to the varices and determine if red signs are present, which is currently recommended for all patients with diagnosed cirrhosis.[4-6]. Endoscopy, however, is invasive, painful and costly, especially to those in developing countries, which ultimately limits the frequency of examinations.

One way to overcome the obstacle of frequent endoscopies is to develop a safe, noninvasive and affordable system to better predict the risk of variceal hemorrhage in cirrhotic patients. An ultrasound approach that includes duplex ultrasonography and color Doppler is a simple, precise, noninvasive and affordable imaging method that is predominantly used to diagnose and stage cirrhotic portal hypertension. The Model for End-stage Liver Disease (MELD) prognostic scoring system, which has an equal or better predictive ability than the traditional Child-Pugh system, is another method to evaluate portal hypertension for short- or intermediate-term outcome.[7-9]. Monitoring changes in the MELD score over time (ΔMELD) has also been proposed as another way to estimate the risk for complications.[10]. Patients with a rapidly worsening ΔMELD score are at risk for more severe liver disease and complications such as EVB, which ultimately increase the risk of mortality.

The objective, noninvasive and affordable natures of the MELD score and color ultrasound-Doppler (US-Doppler) allow data to be obtained quickly. The capability of a combined approach using the MELD scoring system and US-Doppler to predict EVB has not yet been described. In the present study, the predictive capability of a new index, the MELD-US-Doppler Index (MUI), was evaluated in a cohort of cirrhotic patients.

**MATERIALS AND METHODS**

**Patients**

This study was approved by the ethical committee of Changshu Hospital, a Suzhou University affiliate. All patients provided informed consent prior to study enrollment. The following exclusion criteria were applied: (1) patients who declined the evaluation schedule; (2) patients with hepatocellular carcinoma; (3) patients who frequently took medicines such as proton pump inhibitors, propranolol or antivirals; and (4) patients who underwent a splenectomy, received transjugular intrahepatic porto-systemic shunts (TIPS), sclerotherapy, or band ligation endoscopic treatments before or after enrollment in this study. A total of 486 decompensated cirrhotic patients (238 males and 248 females), with an average age of 63.1 ± 11.2 years, were enrolled in the study between May 2008 and March 2011 at the Changshu Affiliated Hospital of Suzhou. A diagnosis of decompensated cirrhosis was made after analyzing a combination of physical, laboratory and radiological examination results. A diagnosis of EVB was confirmed when esophageal varices with stigmata from recent bleeding (e.g., fibrin plug on the varix, adhered blood clot, etc.) or active bleeding (e.g., ooze or spurting blood) were observed by endoscopy.

**Patient follow-up**

Patients enrolled in this study were subjected to US-Doppler and MELD evaluations every three months. After each patient evaluation, the database was updated with the newly obtained data. The occurrence of EVB served as the end point for patient follow-up. Patients who died for reasons unrelated to cirrhosis or were unable to be reached for follow-up were excluded from the trial.

**MELD score and ΔMELD**

MELD scores were calculated as specified by the United Network of Organ Sharing (UNOS) database using the following equation: MELD = 9.57 [Ln creatinine (mg/dL)] + 3.78 [Ln bilirubin (mg/dL)] + 11.2 (Ln international normalized ratio) + 6.43 (constant for liver disease etiology). For calculations, the minimum values were set to 1. The maximum serum creatinine level applied to the MELD score equation was 4.0 mg/dL. The change in the MELD score over a three month period was represented as ΔMELD.

**Color US-Doppler**

One of two sonographers (WMF and YYG, each with over 20 years of experience), who were blinded to the clinical data for the study duration, performed all examinations using an Aplio color US-Doppler unit (Toshiba, Tokyo, Japan) and a 3.75 MHz phased array curved electronic probe. All patients were imaged while resting (> 15 min) in a supine position the morning following an overnight fast. Quantitative measurements were obtained during a brief inspiratory apnea. To obtain images, the transducer was oriented along the longitudinal axis of the portal vein (PV) and splenic vein (SV), and Doppler traces were obtained at an insonation angle < 60°. The Doppler signal for the PV was obtained at the halfway point between the convergence of the splenic and superior mesenteric veins, and the PV hilar split. For the SV,
the Doppler signal was obtained halfway between the spleen and the PV, prior to the left gastric vein (LGV). The LGV appears as a tubular structure within the gastrohepatic ligament near the esophagogastric junction, emanating from the SV or PV with blood flowing towards the head. The maximum diameter of the LGV was measured from long-axis sonograms taken in the sagittal or transverse oblique plane, depending on the orientation of the vein. The direction of the LGV blood flow was assessed with respect to the portal system (hepatopetal vs hepatofugal). Software associated with the US unit was used to calculate velocity and flow for each vessel.

**Statistical analysis**

All statistical analyses were performed with SPSS 13.0 (IBM, Chicago, IL, United States) and MedCalc 12.7.0.0 (MedCalc Software, Ostend, Belgium). For analysis of categorical data, a $\chi^2$ test or Fisher’s exact test (two-tailed) was used, while an independent samples $t$-test was used to analyze continuous data. A normality test was applied to continuous data to ensure that a t-test was the most appropriate to use. All patient characteristics are expressed as mean ± SD or as percentages when appropriate. A multivariate logistic regression analysis with the Wald test was used to analyze MELD scores. The $\Delta$MELD and US parameters were analyzed to identify independent factors that were predictive of EVB risk. Variables from the univariate analysis with a $P$ value < 0.20 were analyzed by multivariate logistic regression analysis to identify independent predictive factors. Receiver operating characteristic (ROC) curves were constructed for the independent predictive factors, and the area under the curve (AUC) was then determined. To define the best discriminating probability threshold, sensitivity, specificity and predictive values were calculated and compared for diagnostic accuracy. All statistical tests were two-tailed and the threshold for statistical significance was set at $P < 0.05$.

**RESULTS**

Seventy of the original 486 patients were excluded from the trial. Of these, 43 patients declined to undergo US-Doppler or MELD evaluation during the first three-month follow-up, 12 patients had been medicated with proton pump inhibitors, propranolol or antivirals, eight patients underwent a splenectomy and seven patients received other endoscopic procedures after study enrollment. A total of 416 patients were followed until March 2012, with a mean follow-up period of 31.6 months (range: 12-47 months). Fifty-one patients had an EVB episode (EVB+ group), while the remaining 365 patients did not (EVB− group), resulting in an incidence of 12.3%. The characteristics and results for the EVB+ and EVB- groups are displayed in Table 1.

**EVB prediction by univariate and multivariate logistic regression analyses**

Patients in the EVB+ group were significantly older than in the EVB- group (67.5 ± 13.4 years vs 62.3 ± 11.8 years; $P < 0.05$) and had significantly higher MELD (26.5 ± 8.9 vs 18.9 ± 10.3; $P < 0.05$) and $\Delta$MELD (1.89 ± 1.23 vs 0.66 ± 0.47; $P < 0.05$) scores. EVB+ patients also had significantly larger diameters of the SV (29.1 ± 12.9 cm vs 21.0 ± 23 cm; $P < 0.05$) and LGV (0.73 ± 0.33 cm vs 0.61 ± 0.21 cm; $P < 0.05$), and significantly higher SV blood flow (1124 ± 412 mL/min vs 896 ± 331 mL/min; $P < 0.05$). Moreover, the EVB+ group demonstrated a significantly higher proportion of patients with hepatofugal LGV blood flow (49/51 patients vs 73/365 patients; $P < 0.05$) and with a higher velocity (21.1 ± 8.1 cm/s vs 18.6 ± 3.6 cm/s; $P < 0.05$).
Coefficient of 0.781 was found for the MELD system, initially developed to assess mortality risk in patients with cirrhosis. Despite this caveat, the MELD score provides a reliable short-term survival estimate for a broad spectrum of liver diseases[1,2,3]. The MELD scoring system was then adopted by UNOS in February 2002 as a way to prioritize livers for transplantation. A more recent study performed by Merion et al[4] analyzing the utility of MELD in assessing survival of patients awaiting liver transplantation, showed that a change in the MELD over a 30-day period was a better predictor of mortality than a one-time MELD score. The alterations in prothrombin time and serum bilirubin and creatinine levels are factors known to perturb the MELD score. Increased MELD scores are indicative of more severe liver disease and may signify the presence of complications, such as EVB, which ultimately increase the risk for patient mortality.

The results of this prospective study further demonstrate the prognostic value of the MELD score in prediction of EVB risk in cirrhotic patients. The change in MELD score over time provides a more dynamic profile of disease severity that may be indicative of cirrhotic complications. Previously, most studies have calculated a change in the MELD score over a one-month time interval[5,6,7], which is insufficient for an accurate estimate of the dynamically occurring changes. Moreover, the frequency of MELD score evaluations may incite patient resistance to follow-up visits. To overcome this obstacle, the follow-up interval in this study was lengthened to three months. A multivariate logistic regression analysis demonstrated that the ΔMELD score was an independent predictive factor for EVB risk, indicating that patients with a rapid deterioration in liver function, and thus a higher ΔMELD, are at a higher risk for EVB.

Portal hypertension, characterized by an increase in PV pressure, is caused by a blockage in blood flow through the liver. This increase in PV pressure results in the development of varices in the stomach and esophagus in an effort to bypass the blockage. These enlarged vessels are fragile and bleed more easily. Noninvasive, rapid, highly sensitive and specific ultrasound approaches such as duplex ultrasonography or color US-Doppler are the modalities of choice to examine patients for bleeds. Although attention has been predominantly focused on measurement of PV and SV size, dilation of the LGV can also occur as a result of portal hypertension. LGV blood flow direction and velocity within its trunk and branches may affect blood flow to esophageal varices or contribute to their development. To support this idea, previous studies have demonstrated a strong correlation between LGV hepatofugal blood flow velocity and EVB[8,9,10]. To this end, Wachsberg et al[11] showed that portal hypertension patients with preserved hepatopetal LGV flow were at a lower risk for bleeding. In the present study, the EVB+ group had a significantly higher proportion of patients with hepatofugal LGV blood flow and significantly larger LGV diameters. However, a multivariate logistic regression analysis showed that hepatofugal LGV blood flow and an enlarged LGV diameter were not independent predictive factors for EVB.

DISCUSSION
In cirrhotic patients, esophageal varices are a common complication, occurring in 35% to 80% of individuals. Approximately one-third of patients with cirrhosis are at risk for additional bleeding episodes[12]. Prophylactic therapies such as endoscopic variceal ligation, sclerotherapy and surgery should be offered to patients at high risk for EVB. The serious nature of EVB and its complications necessitates the development of a reliable system to predict the risk of bleeding in patients. Although screening by endoscopy is currently recommended for all cirrhotic patients[13,14], can identify esophageal varices and provide information on variceal severity, the procedure is difficult to implement in developing countries due to the high cost, inconvenience and potential complications.

The MELD system, initially developed to assess mortality risk in patients receiving TIPS[15], was based on a highly selective subgroup of cirrhotic patients. The MELD system, initially developed to assess mortality risk in patients receiving TIPS[15], was based on a

### Table 2 Multivariate logistic regression analysis

| Variable   | Coefficient | SE   | Wald  | P value | OR (95%CI)          |
|------------|-------------|------|-------|---------|---------------------|
| ΔMELD      | 1.667       | 0.781| 4.719 | 0.023   | 6.195 (1.193-22.624)|
| LGVV       | 2.096       | 0.658| 13.116| 0.001   | 7.129 (2.725-24.256)|
| LGVBFD     | -3.245      | 1.271| 7.001 | 0.006   | 0.006 (2.376-337.186)|
| Constant   | -1.697      | 0.659| 6.635 | 0.010   | 0.183               |

ΔMELD: Change in the Model for End-stage Liver Disease score over a period of three months; LGVBFD: Left gastric vein blood flow direction; LGVV: Left gastric vein blood flow velocity.

14.1 ± 6.9 cm/s; P < 0.05), while the velocity of the PV was significantly lower (16.9 ± 10.1 cm/s vs 19.9 ± 8.4 cm/s; P < 0.05). Furthermore, multivariate analyses identified ΔMELD, LGVV and LGV blood flow direction (LGVBFD) as being independently associated with EVB occurrence (Table 2). Hepatopetal LGVBFD results in an LGVBFD of 1 and a negative value for the LGVV. Hepatofugal blood flow results in an LGVBFD of -1 and a positive value for the LGVV.
Current management of the complications of EVB.

The MELD-US-Doppler Index (MUI) has a significantly higher AUC compared to the ΔMELD alone (red dotted line) [0.858 (95%CI: 0.774-0.920) vs 0.734 (95%CI: 0.636-0.817); P < 0.05]. Additionally, the AUC for the MUI was significantly higher than those for the LGVBFD alone (orange dotted line) [0.726 (95%CI: 0.627-0.810); P < 0.05] and the LGVV alone (green dotted line) [0.679 (95%CI: 0.578-0.769); P < 0.05].

An ROC analysis demonstrated that the ΔMELD, LGVV, or LGVBFD alone were insufficient in providing diagnostic accuracy for EVB prediction. When the three independent factors were combined to form the MUI, however, a significant diagnostic accuracy was achieved, with a high AUC. Moreover, a MUI of 46 provides high sensitivity, specificity and positive and negative predictive value for the study population. By establishing the above cutoff value, a correct prediction for EVB would have been obtained in 85.8% of patients, without the need for an invasive endoscopy. Thus, the MUI represents a low-cost, convenient and noninvasive index to predict EVB occurrence during a short time-period (three months).

The MUI is a noninvasive, affordable and convenient index to evaluate the risk of esophageal variceal bleeding (EVB). To determine whether a cirrhotic patient is at risk for EVB, they must undergo screening endoscopies to grade the varices and look for the presence of red signs. However, screening endoscopies are invasive, uncomfortable and expensive to those in developing nations, thus the frequency of endoscopic examination is often quite limited.

In conclusion, the newly developed MUI presented here is a noninvasive, affordable and convenient index to assess EVB risk in decompensated cirrhosis patients. It is a suitable alternative for patients who have declined regular screening via endoscopy. It is currently unclear whether the MUI can reduce the requirement for screening endoscopies, and future prospective studies are warranted to further validate the clinical strength of this index.

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