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2-year survival estimation for decompensated cirrhosis patients of prognostic scoring systems

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Abstract. – OBJECTIVE: Prognostic models proposed for cirrhotic patients' survival have not been satisfactorily investigated in the Vietnam population, especially in the medium-term period.

PATIENTS AND METHODS: In this prospective study, we enrolled a total of 904 patients admitted to Hepato-Gastroenterology Center, Bach Mai Hospital from December 2019 to November 2021 and calculated their CP, MELD, MELD-Na score, IMELD, Refit MELD, and Refit MELD-Na after 2-year follow-up to compare their survival prognosis.

RESULTS: The mean age of the patients was 53.8 ±10.8 years, and males constituted 91%. Compared with the surviving group, deceased patients had statistically significant lower albumin, higher INR, serum bilirubin, and creatinine levels with higher means of all prognostic scores. RefitMELD score had the highest AUC (0.768), followed by MELD (0.766), and the lowest belonged to RefitMELDNa (0.669).

CONCLUSIONS: In conclusion, deceased patients had significantly higher values of Child-Pugh score and all MELD-based scores than survival. RefitMELD is the most reliable scoring system to predict 2-year mortality in patients with decompensated liver cirrhosis.

Key Words:
Cirrhosis, MELD, Mortality, Prognostic models.

Abbreviations
CP: Child-Pugh; GI: Gastrointestinal; iMELD: integrated MELD; MELD: Model for End-Stage Liver Disease; MESO index: MELD to sodium index; Refit MELD: Revised Model for End-Stage Liver Disease; SNa: serum sodium.

Introduction

Cirrhosis is usually the prognosable last stage of fibrous proliferation in chronic hepatic diseases[1]. It often begins with an asymptomatic phase, named "compensated cirrhosis", and is followed by "decompensated cirrhosis". The decompensated stage is defined by the presence of ascites, variceal bleeding, encephalopathy, and/or jaundice[2]. Since decompensation was observed in patients, their outcome is predicted to be exaggerated.

Many researchers have attempted to predict the consequences of cirrhosis patients, despite its difficulty due to its dependence on various factors. Traditionally, the prognosis of cirrhosis has been determined by the Child-Turcotte-Pugh (CTP) and currently modified Child-Pugh from the old origin. However, their subjective interpretation of hepatic encephalopathy, ascites level, and experimental variable choice limit their prognostic ability[3]. Therefore, recently, some studies[4,5] have applied the Model for End-Stage Liver Disease (MELD) scoring systems and its modified models to predict short to long-term survival, besides its reliable role in transplantation decisions.

MELD score uses bilirubin, international normalized ratio (INR), and creatinine results. The MELD score-Na (MELD-Na) added serum sodium (SNa) into the equation with SNa between 120 mEq/L and 134 mEq/L. Recent studies[6-8] have shown that the incorporation of SNa into MELD calculations can improve the prediction of short- and intermediate-term mortality in patients with cirrhosis.

Other MELD-based models include iMELD (integrated MELD) and MESO index (MELD to sodium index), and likewise, both scores included the SNa within their equations to improve their prognostic power[9,10]. Additional modifications of the MELD score were proposed for the optimization of the model[11]. These versions, called Refit MELD and Refit MELDNa, incorporate coefficients and restore lower and upper bounds for the variables MELD and MELD-Na, respectively. Refit MELD and Refit MELDNa have

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been shown to be more efficient than the original model as prognostic predictors in patients listed for liver transplantation[11].

Since these prognostic models were proposed for cirrhotic patients' survival, they have not been satisfactorily investigated in the Vietnam population, especially in the medium-term period. This study aimed to evaluate the models MELD, MELD-Na MESO, iMELD, Refit MELD, and Refit MELD-Na as prognostic predictors of 2-year mortality in cirrhotic patients.

Patients and Methods

Study Design

This was a single-centered prospective study including consecutive adult patients with liver cirrhosis admitted to Hepato-Gastroenterology Center, Bach Mai Hospital from December 2019 to November 2021. The study was approved by the Ethics Committee of Bach Mai Hospital, with Ethics Approval acceptance number 624/QĐ-BM.

Patients

Selection criteria

We enrolled a total of 904 patients aged 16 years old and older with a diagnosis of cirrhosis.

Patients with cirrhosis were diagnosed by imaging findings along with evidence of portal hypertension and hepatocellular insufficiency syndrome or APRI index. These tests must be done within 24 hours of admission.

Exclusion criteria

Patients who used diuretics within 5 days before admission, mechanical biliary obstruction (due to common gallstones, pancreatic tumors, cholangiocarcinoma, chronic pancreatitis), and patients with renal failure due to chronic kidney diseases.

Prognostic Models

We followed the methods in the study of Hassan and Abd El-Rehim[12]. Inpatient records were reviewed and information about demographic, clinical and laboratory data was collected and used to calculate CP, MELD and sodium-based MELD variants as follows[10-13]:

– The CP score was calculated based on serum bilirubin and albumin levels, prothrombin time and the presence of, and severity of, ascites and encephalopathy. A total score of 5-6, 7-9 and 10-15 were classified as class A, B and C, respectively.
– MELD score = 0.957 × Loge (creatinine in mg dl^{-1}) + 0.378 - Loge (bilirubin in mg dl^{-1}) + 1.120 × Loge (INR) + 0.643. The score was multiplied by 10.
– MELD-Na score = MELD + 1.59 × (135-Na), with maximum and minimum Na values of 135 and 120 mmol l^{-1}, respectively.
– MESO index = [MELD/Na (mmol l^{-1})] × 10
– iMELD = MELD + [0.3 × age (years)] – [0.7 + Na (mmol l^{-1})] + 100
– Refit MELD = 4.082 × Log_e (bilirubinC) + 8.485 × Log_e (creatinineC) +10.671 × Log_e (INRC) +7.432
– Refit MELD-Na = 4.258 × Log_e (bilirubinC) + 6.792 × Log_e (creatinineC) + 8.290 × Log_e (INRC) + 0.652 × (140 - NaC) - 0.194 × (140 - NaC) × BiliCC + 6.327

Follow-Up

All the patients were followed up for 2 years with an emphasis on their survival status. Predictive factors of morbidity and mortality were analyzed and compared. Morbidity was defined very broadly to include cirrhosis-related complications (variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis) and metabolic complications, whereas 2-year mortality was the outcome 'end' point. We compared the area under the receiver operating characteristic (AUROC) of the 6 models to identify the best scoring system.

Statistical Analysis

Continuous variables were compared using the Student's *t*-test, for normal distributions, or Mann-Whitney, for the remaining cases. Categorical variables were evaluated using a chi-square or Fisher's exact test as needed. The area under receiver operating characteristic curve (AUC) curves were plotted to measure the performance of different prognostic scores in predicting the 2-year mortality of the studied patients. For all analyses, p-value <0.05 was considered statistically significant. The area under receiver operating characteristic curve (AUC) curves were plotted to measure the performance of different prognostic scores in predicting the 2-year mortality of the studied patients. All the remaining tests were two-tailed and were performed by the statistical software STATA, version 14.0 (STATA, Chicago, IL, USA).

Results

The baseline demographic and clinical characteristics of the 904 studied patients with liver cirrhosis are summarised in Table I. The mean age of the patients was 53.8±10.8 years and males constituted 91%. Compared with the surviving group, deceased patients had statistically significant lower albumin, higher INR, serum bilirubin, and creatinine levels with higher means of all prognostic scores consisting of Child-Pugh score, MELD score, MELDNa score, iMELD score, MESO index, RefitMELD and RefitMELDNa ($p < 0.001$ of all) (Table I).

Complications were defined very broadly. Ascites were the most common presentation (65.5%), while SBP was the least frequent complication (8.6%). In addition, mortality was significantly higher among patients with ascites, variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis (Table I). Moreover, patients with multiple cirrhosis-related complications (two or more) had a significantly higher proportion of nonsurvival ($p<0.001$, OR=3.11).

Relations of Cirrhosis-Related Complications and Prognostic Models

The overall 2-year mortality was 13.4% (121 patients). Regarding prognostic models, higher scores were seen in patients with more severe hepatic encephalopathy or with spontaneous bacterial peritonitis than in milder or non-complicated ones ($p < 0.001$) (Table II). In contrast, patients without variceal bleeding had higher prognostic scores than the other group.

Further, we found that patients with ascites grade 2 or 3 had similar scores in almost all models, except for RefitMELD and RefitMELDNa, in which the ascites-grade-2 group had higher scores.

Comparison of AUC at 2 Years Between the Different Prognostic Scores

The comparison of AUC at 2 years between the different prognostic scores was demonstrated in

Table I. Demographic and clinical characteristics of the study population according to the 2-year survival rate.

Variable and category	Total studied patients (No = 904)	Surviving (No = 783)	Death (No = 121)	p
Age (years) ± Mean (SD)	53.8 ± 10.8 (16-91)	53.7 ± 10.9	54.5 ± 10.3	0.67
Gender (M/F) (%)	823/81 (91/9)	717/66 (91.6/8.4)	106/15 (87.6/12.4)	0.155
Smoking (Yes/No) (%)	797/107 (88.2/11.8)	695/88 (88.8/11.2)	102/19 (84.3/15.7)	0.157
Alcohol (Yes/No)	823/81 (91.0/9.0)	717/66 (91.6/8.4)	106/15 (87.6/12.4)	0.155
Alcohol (ml/day)	271.6 ± 218.2 (0-2000)	274.6 ± 218.3	251.8 ± 217.2	0.156
Laboratory values; Mean (SD)/Prevalence (%)				
INR	1.6 ± 0.7 (0.82-13.61)	1.6 ± 0.7	1.9 ± 0.7	**0.0000**
Bilirubin (mg dl^{-1})	83.2 ± 114.7 (3.7-974.5)	72.1 ± 100.7	155.6 ± 163.4	**0.0000**
Albumin (mg dr^{l})	28.5 ± 6.2 (7.4-45.8)	28.8 ± 6.2	26.7 ± 5.9	**0.0003**
Protein	63.5 ± 10.3(32.1-92.4)	63.5 ±10.3	63.4 ± 10.3	0.9499
Platelets	113.7 ± 68.3	115.3 ± 70.6	113.4 ± 67.9	0.9742
Creatinine(mg dl^{-1})	95.2 ± 89 (4.7-988)	92 ± 85.9	115.9 ± 105.5	**0.0000**
Sodium (mmol r^{l})	135.9 ± 5.1 (115.9-151)	135.9 ± 5.1	135.4 ± 5.4	0.3119
Child-Pugh score	8.7 ± 2.3 (5-15)	8.5 ± 2.3	10.1 ± 1.9	**0.0000**
MELD score	13.7 ± 8.3 (-20.3-56.1)	12.8 ± 7.9	20 ± 7.9	**0.0000**
MELDNa score	12.3 ± 13.5 (-29.9-68.1)	11.3 ± 13.2	19.3 ± 13.6	**0.0000**
iMELD score	34.8 ± 10.5 (-2.2-78.5)	33.7 ± 10.1	45.5 ± 10.2	**0.0000**
MESO index	10.2 ± 6.4 (-14.4-44.1)	9.5 ± 6.1	14.9 ± 6.2	**0.0000**
RefitMELD	14.9 ± 8.1 (-16.2-56)	14 ± 7.7	21.1 ± 7.7	**0.0000**
RefitMELDNa	10.1 ± 9.5 (-77.1-75.4)	9.8 ± 8.3	12.1 ± 15.2	**0.0000**
Morbidities; Mean (SD)/Prevalence (%)				
Hyponatraemia[a] (%)	83 (9.2)	15 (12.4)	68 (8.9)	0.188
Ascites (%)	592 (65.5)	496 (63.4)	96 (79.3)	**0.001**
VB (%)	368 (40.7)	340 (43.4)	28 (23.1)	**0.000**
HE (%)	133 (14.7)	93 (11.9)	40 (33.1)	**0.000**
SBP (%)	78 (8.6)	31 (7.8)	17 (14.1)	**0.022**
Complications				
< 2	281 (31.1)	264 (33.7)	17 (14.1)	OR = 3.11
≥ 2	623 (68.9)	519 (66.3)	104 (85.9)	**0.000**

Table I. Comparison of demographics and clinical characteristics between patients with and without cirrhosis-related complications.

		N	MELD $\bar{x}$ ± SD	MELD Na $\bar{x}$ ± SD	MESO $\bar{x}$ ± SD	iMELD $\bar{x}$ ± SD	RefitMELD $\bar{x}$ ± SD	RefitMELDNa $\bar{x}$ ± SD	2-Year (surviving/ dead) %
Ascites (Grade)	0	312	10.3 ± 6.6	7.5 ± 10.7	7.6 ± 4.9	30.3 ± 8.2	11.5 ± 6.4	9.8 ± 5.8	287/25 (92/8)
	1	352	14.6 ± 8.1	13 ± 13.6	10.8 ± 6.2	35.5 ± 10.5	15.8 ± 7.9	9.9 ± 10.6	294/58 (83.5/16.5)
	2	207	17.0 ± 9.0	18.0 ± 14.2	12.8 ± 7.0	39.4 ± 10.9	18.1 ± 8.8	11.1 ± 11.5	173/34 (83.6/16.4)
	3	33	16.3 ± 8.5	18.9 ± 14.9	12.4 ± 6.7	39.7 ± 10.4	17.5 ± 8.4	8.4 ± 11.6	29/4 (87.9/12)
	Total	904	13.7 ± 8.3	12.4 ± 13.5	10. ± 6.4	34.8 ± 10.5	14.9 ± 8.1	10.1 ± 9.5	783/121 (86.6/13.4)
	p		**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.04**
Hepatic encephalopathy (Grade)	0	771	12.5 ± 7.3	10.6 ± 12.1	9.3 ± 5.5	33.3 ± 9.3	13.7 ± 7.1	10.3 ± 75	690/81 (89.5/10.5)
	1	86	19.9 ± 9.9	21.1 ± 16.0	15.0 ± 7.7	42.4 ± 12.1	21.1 ± 9.5	9.8 ± 15.8	60/26 (67.8/30.2)
	2	35	20.9 ± 9.4	23.2 ± 15.8	15.8 ± 7.5	43.8 ± 11.2	22.0 ± 9.1	5.9 ± 20.9	29/6 (82.9/17.1)
	3	11	26.8 ± 14.4	28.6 ± 20.7	20.3 ± 11.3	50.6 ± 16.1	27.6 ± 13.7	11.0 ± 8.1	4/7 (36.4/63.6)
	4	1	25.7 ± 0.00	22.5 ± 0.00	18.8 ± 0.00	43.9 ± 0.00	26.5 ± 0.00	21.6 ± 0.00	0/1 (0/100)
	Total	904	13.7 ± 8.3	11.70 ± 13.51	9.82 ± 6.40	34.8 ± 10.5	14.9 ± 8.1	10.1 ± 9.5	783/121 (86.6/13.4)
	p		**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.2887**	**0.000**
VB	No	536	15.2 ± 8.7	15.2 ± 14.2	11.4 ± 6.8	37.0 ± 10.9	16.4 ± 8.5	9.7 ± 11.3	443/6. (82.7/17.3)
	Yes	368	11.7 ± 7.2	8.1 ± 11.3	8.5 ± 5.4	31.6 ± 8.8	12.8 ± 8.9	10.7 ± 6.0	340/28 (92.4/7.6)
	Total	904	13.7 ± 8.3	12.4 ± 13.5	10.2 ± 6.4	34.8 ± 10.5	14.9 ± 8.1	10.1 ± 9.5	783/121 (86.6/13.4)
	p		**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.516**	**0.000**
SBP	No	826	13.3 ± 8.1	11.5 ± 13.3	9.9 ± 6.2	34.2 ± 10.3	14.5 ± 7.9	10.0 ± 9.3	722/104 (87.4/12.6)
	Yes	78	18.5 ± 9.4	21 ± 12.4	13.9 ± 7.3	41.2 ± 10.3	19.6 ± 9.0	10.7 ± 11.4	61/17 (78.2/21.8)
	Total	904	13.7 ± 8.3	12.4 ± 13.5	10.2 ± 6.4	34.8 ± 10.5	14.9 ± 8.1	10.1 ± 9.5	783/121 (86.6/13.4)
	p		**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0015**	**0.022**

PT: prothrombin time. [a]Serum Na < 130 mmol/r[1]. [b]Serum Na (120-135 mmol r[1]). [c]Serum Na (125-140 mmol r[1]). VB: variceal bleeding; HE: hepatic encephalopathy; SBP: spontaneous bacterial peritonitis; [a]Serum Na< 130 mmol r[1].

Figure 1. All of the prognostic scoring systems, RefitMELD score had the highest AUC (0.768), followed by MELD (0.766), MESO (0.761), iMELD (0.721), MELDNa (0.673), RefitMELDNa (0.669).

Discussion

This prospective study evaluated different prognostic models in Vietnamese cirrhotic patients. Prognosis is not only used for patient information but also as evidence for the treatment decisions of physicians. In hepato-gastrointestinal diseases, it is still a big challenge in clinical practice. The Model for End-Stage Liver disease was used partly to assess death risk. Its modified models, MELD-Na, MESO, iMELD, Refit MELD, and Refit MELD-Na incorporate MELD score coefficients and lower and upper limits of individual variables that have been optimized for the patients for which the MELD score is applied[13]. Often, these models were applied to assess midterm and long-term mortality. Therefore, improving these prognostic evaluations can reduce the mortality and timing of orthotopic liver transplantation on waiting lists, hence affecting long-term survival and quality of life of patients. In 2009, Samuel[14] recognized the importance of improving prognostic scoring systems for cirrhotic patients. He emphasized that it is important to evaluate prognostic scores and their value to patients with cirrhosis and with different etiologies of the disease in the short, medium, and longer terms[14,15]. This study aims to investigate the prognostic ability of different scoring models and their relation to complications to determine the best one to predict 2-year mortality in Vietnamese cirrhotic patients.

In our study, men accounted for a higher proportion than women, the male/female ratio was 10.2. Most studies show a higher proportion of males than females. The sex ratio fluctuates between authors, perhaps because the patient

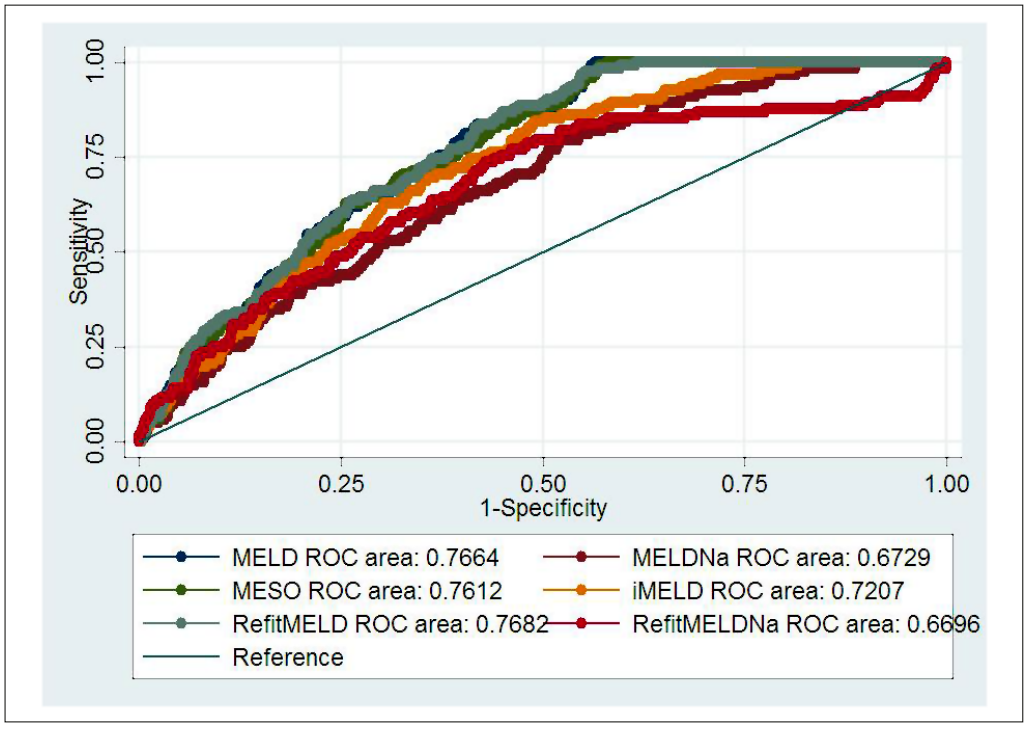

Figure 1. Area under the receiver operating characteristic curve (AUC) to predict 2-year mortality of MELD, MELDNa, MESO, iMELD, RefitMELD, and RefitMELD. RefitMELD was significantly better than other scoring systems ($p < 0.05$) at predicting 2-year mortality.

population selected for each study is different. On the other hand, alcohol is one of the main causes of cirrhosis. Mostly, alcoholic cirrhosis occurs in men because in Vietnam, women rarely drink alcohol. In our study, alcohol use was observed in 91% of patients.

The mean age of patients in this study was 53.8 ±10.8 (range 16-91). The mean age of patients fluctuated in many related studies[16,17] but remained mainly in the middle-age group, since the process of diffuse fibrosis and the formation of proliferative abnormal structures in cirrhosis happens over a long period.

We found that ascites was the most common complication observed in patients with decompensation cirrhosis. This result was consistent with the study of D'Amico et al[18], who analyzed 494 patients with clinical complications of cirrhosis and showed that ascites is the decompensating event with the highest proportion. Refractory ascites is reported to be associated with 1-year mortality of 28-79%[19].

Of all prognostic models, the RefitMELD score, based on bilirubin, creatinine and INR serums, without the presentation of sodium, had the best accuracy and was the only model with higher accuracy than MELD. In our study, hyponatremia happened only in 9.2% of all patients. Even though hyponatremia was used to assess portal hypertension and liver reserve that is often associated with ascites formation, it had a lower prognostic accuracy compared to the MELD scoring systems. We also found that the inclusion of sodium and creatinine into the traditional MELD scores did not result in improving the prognostic ability to predict 2-year mortality. This was consistent with Choi et al[15], who suggested that the MELD-Na score had a weaker power for the prediction of the occurrence of complications such as variceal bleeding and hepatic encephalopathy compared with the MELD score. Kim et al[20] collected the medical records of patients with hepatic cirrhosis and ascites from 2006 to 2011 and found that Refit MELDNa even showed a lower value than Refit MELD as a predictor of 3-month mortality in patients with cirrhosis and ascites. This could be explained by the difference in etiology between studies such as type of viral cirrhosis, alcohol use, or short or long-term mortality evaluation. Another reason is that the measured serum sodium concentration under studied circumstances does not reflect the true status of liver function. This is because blood sodium concentration changes due to the influence of many factors, such as the use of diuretics, or the infusion of hypotonic solutions. The use of diuretics reduces blood sodium levels to an average of about 4 mEq/l, even 10 mEq/l. In contrast, the use of V2 receptor antagonists to manage ascites causes hypernatremia. Therefore, more research on the use of models with Na is needed to avoid misclassification of patients. Another reason is that a change in serum sodium concentration does not reflect the severity of liver disease before the occurrence of severe hyponatremia.

Before the publication of Refit models, studies have compared MELD to its modified models in combination with Sna[21]. Most studies found that new models with the addition of SNa were superior to traditional MELD scores in predicting short-, medium-, and long-term mortality[22,23]. Kim et al[6] reviewed 3,940 patients from the data of U.S. Standard Transplant Analysis and Research, and concluded that MELD score combined with the SNa might improve transplantation allocation and survival rate. However, since the identification of the Refit model for end-stage liver prognosis, several authors[20] realized that Na seems not to be a better predictor of mortality than the Refit model.

We noticed that patients who survived after 2 years had significantly lower INR, bilirubin, creatinine and higher albumin at admission. Also, patients with cirrhosis-related complications had higher scores and mortality risk compared to patients without cirrhosis-related complications, except for variceal bleeding.

According to the results of our study, the prognostic models have no value in predicting variceal bleeding in cirrhotic patients. Acute gastrointestinal (GI) bleeding is a serious complication of cirrhosis. The prognostic factors of mortality for an acute GI disease are blood loss, ongoing bleeding, the possibility of hemostatic interventions, and risk factors. According to Flores-Rendón[24] in a study of 212 cirrhotic patients with GI bleeding due to esophageal varices, MELD and Child-Pugh were not effective scales for predicting failure to control GI bleeding. Another reason may be that in our hospital, endoscopic and vascular interventions in the treatment of gastrointestinal bleeding due to portal hypertension are being performed more and more thoroughly, which helps to reduce the risk of death from gastrointestinal bleeding. At the same time, we have performed better in the outpatient management of cirrhosis to promptly detect esophageal and gastric varices and prevent gastrointestinal bleeding.

Since the prognosis is within 2 years, there can be many other factors that could affect the mortality rate. Also, as our study was a single-center study, MELD and related prognostic scores may not be representative of various populations. Therefore, the study's results needed to be confirmed by further multicenter, well-designed prospective studies while excluding all confounding factors to determine whether these scores would be beneficial for decompensated cirrhotic patients or all cirrhosis.

Conclusions

In conclusion, deceased patients had significantly higher score of Child-Pugh scores and all MELD-based scores than survival. RefitMELD is the most reliable scoring system to predict 2-year mortality in patients with decompensated liver cirrhosis.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Informed Consent
Informed consent was obtained from all individual participants included in the study.

Authors' Contribution
L.C. Nguyen: Design, acquisition, analysis, interpretation of data; drafted and revised the paper. N.M. Nguyen, T.N. Nguyen: analysis, interpretation of data. H.H. Vu, T.T. Khuc: Design, acquisition, analysis. H.D. La, N.T. Nguyen, K.V. Nguyen: Interpretation of data; drafted the paper. O.T. Nguyen, D.T.M. Luu, H.T.N. Doan: analysis, interpretation of data; drafted and revised the paper.

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Ethics Approval
The study protocol was approved by Bach Mai Hospital, with Ethics Approval acceptance number 624/QĐ-BM. The study conforms to the principles outlined in the Declaration of Helsinki.

Availability of Data and Materials
Primary data used in this research article will be available on request.

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