

Re-Bleeding in Patients With Cirrhosis: Evaluation of Esophageal and Gastric Variceal Bleeding and Their Relationship With a Model for the End-Stage Liver Disease (MELD) Score and Child-Pugh Score

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Background: Variceal bleeding is one of the leading causes of mortality in patients with cirrhosis. Child-pugh (CP) score and model for the end-stage liver disease (MELD) score systems are the two main methods for predicting the complications and mortality of cirrhosis; however, none of these methods has been definitively superior to the other.

Objectives: In this study we compare and determine these scores in both groups of patients with esophageal and gastric variceal bleeding. Furthermore, re-bleeding rate in these two groups will be studied and compared.

Patients and Methods: In this cohort study all patients with upper gastrointestinal bleeding chief complaint referred to the emergency ward of Imam Reza Hospital, Mashhad, Iran from April 2012 to April 2013 were enrolled. Then patients distributed in to two groups of esophageal and gastric variceal bleeding based on the endoscopic results. Finally the relationship between different clinical and paraclinical variables and bleeding rate in these two groups compared by means of Child-Pugh and MELD scores. T-test, χ^2 test, and the Kruskal-Wallis test were used for analysis by means of SPSS 17.0 for Windows. Data were expressed as mean \pm standard deviation and $P < 0.05$ was considered to be significant.

Results: Among 34 understudied patients, 12 patients (8 males) had gastric varices and 22 patients (15 males) had esophageal varices. No significant difference between these two groups was observed. Two patients (5.8%) including 1 patient with gastric varices and 1 patient with esophageal varices had re-bleeding before six weeks; also 8 patients (23.5%) including 3 patients were also reports with gastric varices and 5 patients with esophageal varices had re-bleeding after six weeks. Fisher's exact test showed that there is no statistically significant relationship between the re-bleeding and the disease groups (P value = 0.098). The results showed that there is no difference between the variable levels in both groups.

Conclusions: The level of two CP and MELD scores and their individual variables in two groups of patients with esophageal and gastric varices bleeding were not significantly different. On the other hand, re-bleeding rate was not different between these two groups.

Keywords: Liver Diseases; Esophageal and Gastric Varice; Bleeding

1. Background

Variceal bleeding is one of the leading causes of mortality in patients with cirrhosis (1). Approximately forty percent of cirrhotic patients are affected by variceal bleeding in the process of their disease in which death occurs in 13-30% of the cases (2-6). Despite the available treatments, one out of four cirrhotic patients has difficulty either in bleeding control or they are affected by the recurrence of bleeding in the first 6 weeks after the initial bleeding (7). Although varices can form in any part of the gastrointestinal tract, the risk of bleeding from varices in cirrhotic patients varies depending on the varices location, size, and appearance (8). Esophagus and stomach are the most

common parts which form varices (9). The gastric fundus varices and distal esophageal varices are more superficial and less supported than the other varices locations; therefore, there are more prone to rupture and bleeding (10). So far, many noninvasive factors have been used to estimate the varices progress situation in cirrhotic patients. Studies have shown that low levels of albumin, high levels of urea nitrogen, infection, and the presence of varices in stomach are the predicting factors of variceal re-bleeding (11-14). On the other hand, different scoring systems have been used in order to predict morbidity and mortality in cirrhotic patients. Two samples of the

Implication for health policy/practice/research/medical education:

As far as we know, no study has reviewed and compared these two CP and MELD scores in both groups of patients with esophageal and gastric varices bleeding. In this study, we compare and determine the CP Score and MELD Score in both groups of patients with esophageal and gastric varices bleeding. Furthermore, rebleeding rates in these two groups will be studied and compared.

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most commonly used systems are Child-Pugh (CP) score and MELD (Models for the End-Stage Liver Disease) scores (15). However, none of these methods are definitively superior to the other. Each of the scores has some usage limitations, CP score is restricted considering the two criteria of encephalopathy and ascites which are diagnosed individually and may vary depending on each practitioner; and also the complicated formula to calculate the final MELD score, using three biochemical parameters, is the limitation of this new scoring system (16-19). Several studies have shown that a higher score of CP or MELD is associated with a higher risk of bleeding (20). Also the history of variceal bleeding shows the increased risk of re-bleeding (21-23).

2. Objectives

As far as we know, no study has investigated and compared the two CP and MELD scores in both groups of patients with esophageal and gastric varices bleeding. In this study, we compare and determine the CP Score and MELD Score in both groups of patients with esophageal and gastric variceal bleeding. Furthermore, re-bleeding rate in these two groups will be studied and compared.

3. Patients and Methods

In this cohort study, all the patients complaining about their upper gastrointestinal bleeding (UGIB) referred to the Emergency Ward of Imam Reza (AS) Hospital from April 2012 to April 2013 were enrolled. Inclusion criteria were liver cirrhosis of any etiology; presence of esophageal or gastric varices based on the endoscopic results, and the first incidence of variceal related UGIB. Also, patients with congestive gastropathy, ectopic varice, hepatocellular carcinoma, and non-cirrhotic UGIB were excluded. This study has been approved by the Ethics Committee of Mashhad University of Medical Sciences and all patients were informed about the content of the study. Patients' data were entered in the analysis program by code and data of the patients were published as a general result. The diagnostic basis for liver cirrhosis was the histological, clinical, and biochemical tests and the used diagnostic tools for the varices were ultrasound and endoscopy. Bleeding type was determined according to the endoscopic reports; then the patients were divided into two groups of esophageal or gastric variceal bleeding groups.

For each patient, variables such as age, sex, creatinine, bilirubin, albumin, INR (International Normalized Ratio), ascites, liver hepatic encephalopathy, ALT (alanine aminotransferase), AST (aspartate aminotransferase) and PT (prothrombin time) were obtained. Through the evaluation of the mentioned variables, CP and MELD scores were calculated for each patient. CP score was formed from the 5 total factors of bilirubin, albumin, INR, ascites, and hepatic encephalopathy (8). Also, MELD score was calculated using the following formula pro-

posed by the Mayo Clinic (24): MELD SCORE: $10 (0.957 \text{ Ln} [\text{creatinine (mg/dL)}] + 0.378 \text{ Ln} [\text{bilirubin (mg/dL)}] + 1.12 \text{ Ln} \text{ INR} + 0.643)$. The readers of the MELD and CP scores were different and were blinded to the results of the other tests. Finally, patients were followed up for 6 months for recurrent bleeding. Early re-bleeding was considered if the recurrent bleeding was within less than six weeks of the first incidence, and it was a late re-bleeding if the recurrent bleeding was within more than six weeks. Results and information about demographic, clinical and paraclinical observations were entered into the computer and the statistical analysis was performed using SPSS 17.0 for Windows. Data are expressed as mean \pm standard deviation and $P < 0.05$ was considered to be significant. In order to compare the quantitative variables, unpaired t-test or its nonparametric equivalent, the Mann-Whitney was used. In order to compare the qualitative variables, χ^2 test was used and, if necessary, the Fisher's exact test was applied. In order to evaluate the difference between the values of a variable among multiple independent variables, one-way ANOVA or its nonparametric equivalent, the Kruskal-Wallis test was used. In order to have a simultaneous evaluation of the understudied variants in predicting the disease, method of multiple logistic regressions was used.

4. Results

Among 52 patients who referred to the emergency ward, forty-seven patients who had the inclusion criteria entered the study; then 13 patients were excluded due to the unrelated UGIB (9 patients) and ectopic varices (4 patients).

4.1. Basic Information

Among 34 understudied patients (mean age of 58.06 ± 15.9 years), 12 patients (8 males) had gastric varices and 22 patients (15 males) had esophageal varices. The average level of ALT and AST were 63.25 ± 58.56 (mg/dL) and 76.64 ± 76 (mg/dL), respectively. Prothrombin time of patients was as 5.77 ± 17.98 seconds and the albumin level of patients was 0.37 ± 2.86 . The average of three parameters of bilirubin, creatinine and INR was obtained as 2.36 ± 2.55 mg/dL, 1.01 ± 1.37 (mg/dL) and 0.96 ± 1.8 , respectively. The results obtained from the ultrasound and clinical examinations also revealed that 15 subjects were in the medically controlled ascites and 14 patients were in the poorly controlled ascites. Hepatic encephalopathy in 5 patients was reported as medically controlled and in 9 patients as poorly controlled. MELD score and CP score were 8.75 ± 16.67 and 2.54 ± 9.73 , respectively. However, there was no significant difference between two groups of esophageal varice and gastric varice in the first episode of UGIB (Table 1).

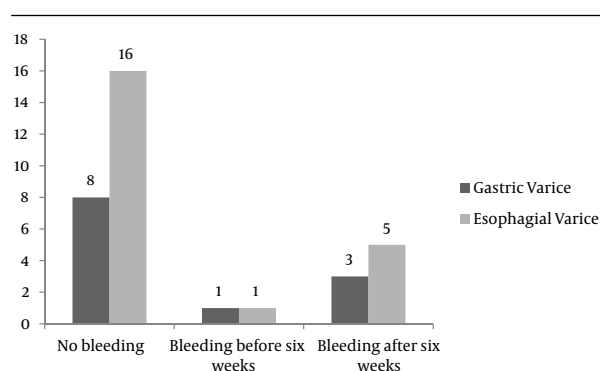
4.2. Re-Bleeding Follow-up

A total of 10 (29.4%) patients (gastric versus esophageal

Table 1. Clinical and Biochemical Characteristics, MELD and Child-Pugh Between Two Groups of Study (Gastric Varice vs. Esophageal Varice)^a

Parameters	Gastric Varice (n = 12)	Esophageal Varice (n = 22)	P Value
Sex			0.29
Male	8	15	
Female	4	7	
Age, y	60.75 ± 19.03	56.59 ± 14.18	0.47
ALT, mg/dL	80 ± 91.58	46.86 ± 38.56	0.34
AST, mg/dL	91.42 ± 88.48	67.69 ± 70.14	0.42
Serum albumin, mg/dL	2.76 ± 0.37	2.92 ± 0.36	0.23
Serum bilirubin, mg/dL	2.81 ± 2.96	2.4 ± 2.02	0.69
Serum creatinine, mg/dL	1.39 ± 0.86	1.35 ± 1.09	0.74
Prothrombin time, s	16.28 ± 4.31	18.91 ± 6.33	0.16
INR	1.6 ± 0.77	1.91 ± 1.05	0.24
Ascites			0.14
Number	0	5	
Moderate	5	10	
Severe	7	7	
Hepatic encephalopathy			0.31
Number	5	15	
Moderate	3	2	
Severe	4	5	
MELD score	15.83 ± 9.26	17.14 ± 8.65	0.6
CHILD score	10.33 ± 2.39	9.41 ± 2.61	0.32

^a Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for the end-stage liver disease.

**Figure 1.** Frequency of Re-Bleeding According to the Patient Groups During a Six Months Follow-up

varice group: 4 versus 6 patients) had recurrent bleeding during a six-month follow-up. Fisher's exact test showed that there is no statistically significant relationship between the re-bleeding and the disease groups (P value = 0.098) (Figure 1).

4.3. Re-Bleeding Risk Factors

In order to investigate the relationship between the understudied variables and re-bleeding occurrence, patients were divided in to three groups of without re-bleeding, with less than six weeks re-bleeding and more than six weeks re-bleeding. Results showed that there was no significant difference between the studied variables in these three groups (Table 2). Considering the fact that no significant difference was found between the two groups of with and without re-bleeding in MELD and CP scores, it can be concluded that sensitivity and specificity of these two scores for predicting re-bleeding could not be determined.

5. Discussion

Bleeding from gastroesophageal varices is one of the major causes of mortality in patients with liver cirrhosis (13, 25). So far, no study is conducted to compare the re-bleeding risk factors between two groups of patients with esophageal and gastric varices bleeding, and most studies have also tried to determine the re-bleeding

Table 2. Results of Kruskal-Wallis Test Concerning the Study Variables in the Re Bleeding

	Re-bleeding After Six Weeks (n = 8)		Re-Bleeding Before Six Weeks (n = 2)		No Re-Bleeding (n = 24)		P Value	χ^2
	Mean \pm SD	Middle	Mean \pm SD	Middle	Mean \pm SD	Middle		
Age, y	60.0 \pm 16.7	65.0	57.0 \pm 0.0	57.0	57.3 \pm 16.5	57.5	0.72	0.632
Child-Pugh score	9.3 \pm 1.6	10.0	13.5 \pm 0.7	13.5	9.5 \pm 2.6	9.0	0.13	3.97
MELD score	13.2 \pm 4.4	13.1	29.0 \pm 1.4	29.0	16.8 \pm 9.2	14.0	0.14	3.87
AST, mg/dL	88.8 \pm 110.0	42.5	113.0 \pm 15.5	11.3	68.6 \pm 71.5	53.5	0.25	2.74
ALT, mg/dL	75.7 \pm 11.4	34.0	90.5 \pm 7.7	90.5	50.1 \pm 4.1	36.0	0.25	2.21
INR	1.25 \pm 0.07	1.25	2.7 \pm 1.14	2.8	1.53 \pm 0.72	1.4	0.10	9.16
Serum creatinine, mg/dL	2.4 \pm 0.71	1.25	1.56 \pm 0.75	2.8	1.22 \pm 1.06	1.4	0.00	11.08
Prothrombin time, s	14.6 \pm 0.42	14.6	22.71 \pm 6.14	22.5	16.69 \pm 5.08	15.3	0.02	7.51
Serum bilirubin, mg/dL	1.05 \pm 0.35	1.05	4.7 \pm 2.89	4.7	1.95 \pm 1.81	1.3	0.06	5.5
Serum albumin, mg/dL	2.45 \pm 0.21	2.45	2.85 \pm 0.13	2.95	2.9 \pm 0.37	2.8	0.22	3.01

risk factors, regardless of the type of varices. Previous studies have shown that the factors such as high urea, low albumin in patients with gastric varices and high hepatic venous pressure gradient, are good predictors for re-bleeding in patients with variceal bleeding (11-14). However, it is believed that the two scores of MELD and CP in patients with liver cirrhosis are highly important in determination of patients' prognosis. The result of this study showed that CP score and MELD score were not significantly different in patients with re-bleeding before and after 6 weeks and without bleeding, it means that in this study, these two scoring systems could not be effective in the predicting of re-bleeding; whereas other studies have shown that these two scores have been extremely efficient in predicting the mortality of patients (26). In a study by Hunter et al. the patients with a higher level of MELD scores (above 18) had significantly more re-bleeding in comparison with the group of lower than 18 scores (7). In another study, it is shown that MELD score has a significant relationship with the occurrence of variceal re-bleeding during hospitalization (27). It seems that the underlying variables such as simultaneous underlying disease or concomitant factors such as varices size, number and location have not been addressed by any of the studies so far. In the present study; although, the frequency of re-bleeding was more in the esophageal varices group than the gastric varices group, no statistically significant relationships were found between the re-bleeding and disease group. In our study, early bleeding was observed in 5.8% of the patients. In another study, 9.6% of patients experienced re-bleeding

during their hospitalization and 50% after their discharge from the hospital (28); also in another study conducted by Bambha et al. the re-bleeding rate was reported as 16% within 5 days after the first bleeding (27). On the other hand, the late re-bleeding rate in our study was 23.5%, while in other studies, the incidence of re-bleeding in cirrhotic patients has been reported approximately 9 to 19% (29). However, regardless of the bleeding before or after six weeks, a total of approximately 30% of patients in this study have experienced re-bleeding which was pretty much close to the reported frequency in the studies by Fallatah et al. and Bambha et al. This difference could be resulted from differences in treatment protocols and used interventions or differences in the method of patients' selection and the sample size (27, 28). However, some factors such as varices location, size, appearance, and pressure may be considered as the other causes of these differences. Also, another difference which is obvious in other studies comparing with the conducted study is the relationship between variables such as ascites, varices size, the number of bands used for legating the wound and prothrombin time with the occurrence of re-bleeding. These four variables are among the factors that have had a significant relationship with the occurrence of re-bleeding in other studies; however, besides the varices size and number of bands used for legating the wound which have not been examined in the present study, 2 variables of prothrombin time and ascites did not have a significant relationship with the risk of re-bleeding. In the previous studies, ascites has been mentioned as an important factor in predicting the severity of variceal

acute bleeding. The reason that the previous studies focused on this topic was the impact of increased intra-abdominal pressure on portal vein hypertension (30), whereas in this study we did not examine the relationship between the severity of bleeding and the studied variables, but the results showed that there was no association between the incidence of variceal re-bleeding and ascites in cirrhotic patients. Another important finding of our study which has been confirmed in other similar studies is the insignificant aminotransferase levels (AST and ALT) roles in prediction of re-bleeding (27, 31). Among the biomarkers that can be used to determine the liver dysfunction status, we can mention the blood bilirubin, albumin and prothrombin time or INR; but the results of this study showed that there was no significant correlation between any of the liver function biomarkers and re-bleeding, either in the cases of less than six weeks or more than six weeks. This insignificant relation was found for age and creatinine as well. One of the main limitations of our study is the lack of evaluation of the understudied treatment protocols which could have a significant relation to the re-bleeding outcome. On the other hand, socio-economic differences of patients and their varying attend towards the treatment of diseases were probably other effective factors in re-bleeding which was not noticed in this study. Also, the effects of some of other variables such as bacterial peritonitis, infection, and hyponatremia were not remarked in predicting factors for re-bleeding; although, none of these variables can directly influence on CP and MELD scores. Other effective issues in this study are probably the frequency and position of varices and the relationship between these two variables which have not been assessed in this study. Since the results of this study showed that in there is no difference between patients with esophageal and gastric varices in relation to the clinical and paraclinical factors, it is recommended to compare patients with different varices position, size and other factors which mentioned in the study limitations section in further studies. It is also proposed to design a study with a higher number of samples to find a sensitive and specific score based on ROC curve for predicting re-bleeding based on MELD and CP scores. The level of two CP and MELD scores were not significantly different between two groups of patients with esophageal and gastric variceal bleeding. In addition, individual variables of CP and MELD scores were not effective as a predictive factor of re-bleeding. On the other hand, re-bleeding rate in these two understudied groups showed no significant differences.

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Authors' Contribution

The contribution of the authors as mentioned below

with their responsibility in the research. Mohsen Ebrahimi: writing the manuscript, conception and designing. Ehsan Bolvardi: writing the manuscript, final approval of the manuscript, literatures search. Hamidreza Reihani: critical revision of the manuscript, provision materials, patients, or resources. Masumeh Pashayi: writing the manuscript, administrative support, analysis and interpretation. Elham Pishbin: critical revision of the article, provision materials, patients, or resources.

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This manuscript has been read and approved by all of the Authors and there is not potential conflict of interest for them.

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