



Creatinine-modified Child-Turcotte-Pugh score is a good predictor of a short-term survival in patients with bleeding from esophageal varices

Child-Turcotte-Pugh skor modifikovan u odnosu na nivo kreatinina dobar je prediktor preživljavanja bolesnika sa krvarenjem iz varikoziteta jednjaka

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Abstract

Background/Aim. Bleeding from esophageal varices is a significant factor in mortality of patients with terminal liver cirrhosis. This complication is a major health problem for recipients on the list for liver transplant. In that regard, studying predictors of variceal bleeding episode is very important. Also, it is important to find the best survival predictor among prognostic scores. The aim of the study was to compare validity of prognostic scores in assessment of survival in hospital-treated patients after bleeding from esophageal varices, and to compare validity of baseline Child-Turcotte-Pugh (CTP) and Modul for End-stage Liver Disease (MELD) scores with CTP creatinine modified (CTP-crea) I and II scores in assessment of survival in patients within a long-term follow-up period after the episode of bleeding from esophageal varices. **Methods.** The study included a total of 126 patients suffering from terminal liver cirrhosis submitted to testing CTP score I and II, MELD score, MELD Na score, integrated MELD score, MELD sodium (MESO) index, United Kingdom Model for End-Stage Liver Disease (UKELD) score and updated MELD score. **Results.** Patients with bleeding from esophageal varices most often had CTP score rank C (46,9%).

Apstrakt

Uvod/Cilj. Krvarenje iz varikoziteta jednjaka je značajan faktor smrtnosti bolesnika sa terminalnom cirozom jetre. Ova komplikacija je i veliki zdravstveni problem za bolesnike na listi za transplantaciju jetre. U tom smislu proučavanje prediktora varicealnog krvarenja je veoma važno. Takođe, važno je pronaći najbolje prediktore preživljavanja među prognostičkim skorovima. **Metode.** Analizom je obuhvaćeno 126 bolesnika koji boluju od terminalne ciroze jetre. Testirani su Child-Turcotte-

CTP score rank B had 37.5% patients, while the smallest percentage of patients had CTP rank A, 15.6% of them. Patients who have values of CTP score higher than 10.50 and bleeding from esophagus, have 3.2 times higher chance for death outcome compared to other patients. Patients who have values of CTP-crea I score higher than 10.50 and bleeding from esophagus, have 3.1 times higher chance for death outcome than other patients. Patients who have values of CTP-crea II score higher than 11.50 and bleeding from esophagus, have 3,7 times higher chance for death outcome compared to other patients. **Conclusion.** Survival of patients with bleeding from esophageal varices in the short-term follow up can be predicted by following CTP score and creatinine modified CTP scores. Patients with bleeding from esophageal varices who have CTP score and CTP-crea I score higher than 10.5 and CTP-crea II score higher than 11.5, have statistically significantly higher risk from mortality within one-month follow-up compared to patients with bleeding from esophageal varices who have lower numerical values of scores of the CTP group

Key words:

liver cirrhosis; esophageal and gastric varices; hemorrhage; prognosis.

Pugh (CTP) skor, CTP kreatinin (CTP-crea) skor I i II, Model for End-Stage Liver Disease (MELD) skor, MELD natrijum (Na) skor, integrisani MELD skor, Meld-Sodium (MESO) indeks United Kingdom Model for End-Stage Liver Disease (UKELD) skor i ažurirani MELD skor. **Rezultati.** Bolesnici sa varicealnim krvarenjem najčešće su imali CTP skor ranga C (46,9%). CTP skor ranga B imalo je 37,5% bolesnika, dok je najmanji procenat bolesnika imao CTP ranga A, njih 15,6%. Bolesnici koji su imali vrednost CTP skora veću od 10,50 i krvarenje iz varikoziteta jednjaka imali su 3,2 puta veći rizik od smrtnog ishoda u odnosu

na ostale bolesnike. Ispitanici koji su imali vrednost CTP-crea I skora veću od 10,50 i krvarenje iz varikoziteta jednjaka imali su 3,1 puta veći rizik od smrtnog ishoda u odnosu na ostale ispitanike. Ispitanici koji su imali vrednost CTP crea II skora veću od 11,50 i krvarenje iz varikoziteta jednjaka imali su 3,7 puta viši rizik od smrtnog ishoda u odnosu na ostale bolesnike. **Zaključak.** Preživljavanje bolesnika sa krvarenjem iz ezofagusnih varikoziteta u periodu kratkoročnog praćenja mogu se predvideti CTP skorom i CTP modifikovanim skorovima. Bolesnici sa

krvarenjem iz ezofagusnih variksa koji imaju CTP skor i CTP-crea I skor veći od 10,50 i CTP-crea II skor veći od 11,50 imaju statistički značajno veći mortalitet tokom jednogodišnjeg praćenja u odnosu na bolesnike sa krvarenjem iz varikoziteta jednjaka i niže numeričke vrednosti skorova CTP grupe.

Ključne reči:
jetra, ciroza; jednjak i želudac, variksi; krvarenje; prognoza.

Introduction

Bleeding from esophageal varices is a significant factor in mortality of patients with terminal liver cirrhosis. This complication is also a major health problem for potential recipients on the list for liver transplant.

Advanced liver disease, in addition to portal hypertension and bleeding from esophageal varices, also brings disorders of platelet number and function, coagulation cascade disorders, so that bleeding is difficult to control and is associated with the increased risk of death as outcome.

Episode of dramatic digestive bleeding is the reason for the occurrence of hemorrhagic shock which becomes the trigger for deterioration of hepatic encephalopathy, deepening on consciousness disorders leading to hepatic coma, as well as for the occurrence of hepatorenal syndrome. A large number of studies clearly show that exactly bleeding from esophageal varices, joined with hepatic encephalopathy, deteriorates survival in patients with terminal liver cirrhosis¹⁻³.

Exactly due to the abovementioned reasons, dealing with variceal bleeding is very important both from the standpoint of clinical medicine, and from the perspective of scientific research. Probably, the most important segment of dealing with this problem is related to the struggle for reduction of mortality rate on the list for liver transplant.

In that regard, studying predictors of variceal bleeding episode is very important. The study of Alempijević et al.⁴ contributed to assessing the presence and size of esophageal varices in cirrhotic patients by using a non-invasive method.

Many recent studies have tried to give an answer to the question which prognostic score has the best features in prediction of episodes of bleeding from esophageal varices. However, there is no clear confirmation that Child Turcotte-Pugh (CTP) or Model for End-Stage Liver Disease (MELD) score have advantages over each other. Also, when it comes to predicting survival of a bleeding episode, opinions are divided. Some studies give more positive opinion on CTP score, while other – on MELD score^{5,6}.

The aim of the study was to compare validity of prognostic scores in assessment of survival in hospital-treated

patients after bleeding from esophageal varices; and to compare validity of baseline CTP and MELD scores with CTP creatinine modified (CTP-crea) I and II scores in assessment of survival in patients within a long-term follow-up period after the episode of bleeding from esophageal varices.

Methods

The study included a total of 126 patients suffering from terminal liver cirrhosis, who underwent hospital treatment at the Clinic for Gastroenterology and Hepatology, Clinical Centre Niš.

The condition of the patients was expressed by numerical values of prognostic scores calculated according to the applicable formulas for calculating. We tested CTP score, CTP creatinine modified (CTP-crea) score I and II, MELD score, MELD New Model (MELD Na) score, integrated MELD (iMELD) score, Meld-Sodium (MESO) index, United Kingdom Model for End-Stage Liver Disease (UKELD) score and updated MELD score. The scores were calculated according to the following formulas:

CTP scores

CTP-A score includes numerical value from 5–6 points. CTP-B score includes numerical value from 7–9 points. CTP-C score includes numerical value from 0–15 points (Table 1).

Creatinine-modified CTP (CTP-crea) scores

a) CTP-crea I score (numerical values 5–19) was calculated by adding the points determined by serum creatinine level. With no added points were patients whose serum creatinine level was less than 1.3 mg/dL, and 4 points were added to numerical value of CTP score in patients whose serum creatinine level was higher than 1.3 mg/dL;

b) CTP-crea II score (numerical values 5–19) includes three categories as follows:

0 points are added to patients whose serum creatinine

Table 1

Child Turcotte Pugh (CTP) Score			
Parameter	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/L}$ (mg/dL)	< 34 (< 2)	34–50 (2–3)	> 50 (> 3)
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
PT/INR	< 1.7	1.71–2.30	> 2.30
Ascites	No ascites	Medium quantity	Medium to large quantity
Hepatic encephalopathy	Stage 0	Stage I–II	Stage III–IV

PT/INR – prothrombin time/international normalised ratio.

level does not exceed 1.3 mg/dL (114.92 μ mol/L); 2 points are added to patients whose serum creatinine level is between 1.3–1.8 mg/dL (114.92–159.12 μ mol/L); 4 points are added to patients whose serum creatinine level exceeds 1.8 mg/dL (159.12 μ mol/L);

MELD

MELD = $\{9.57 \times \ln [\text{creatinine}(\text{mg/dL})] + 3.78 \times \ln [\text{bilirubin}(\text{mg/dL})] + 11.2 \times \ln (\text{INR}) + 6.43\}$;

MELD Na score = $[\text{MELD-Na} (\text{mmol/L}) - (0.025 \times \text{MELD}) \times 140 - \text{Na} (\text{mmol/L}) + 140]$;

MELD Sodium (MESO) index = $[\text{MELD}/\text{Na}(\text{mmol/L}) \times 100]$;

Integrated MELD (iMELD) score = $\{\text{MELD} + \text{age} (\text{in years}) \times 0.3\} - [0.7 \times \text{Na} (\text{mmol/L})] + 100$;

United Kingdom Model for End Stage Liver Disease (UKELD) score = $\{5 \times [1.5 \times \ln (\text{INR}) + 0.3 \times \ln (\text{creatinine} (\mu\text{mol/L})) + 0.6 \times \ln [\text{bilirubin} (\mu\text{mol/L}) - 13 \times \ln (\text{Na} (\text{mmol/L}) + 70)]\}$;

Updated MELD score = $\{[1.27 \times \ln (1 + \text{creatinine} (\text{mg/dL})) + 0.94 \times \ln [1 + \text{bilirubin} (\text{mg/dL})] + 1.66 \times \ln (1 + \text{INR})]\}$.

The abovementioned scores were tested as predictors of the episode of bleeding as well as predictors of mortality in patients with bleeding from esophageal varices.

complications. In addition, the Kaplan-Meier survival curve was established in relation to the variables examined. Log rank test was used to compare the average survival in relation to the parameters examined. Cox's regression analysis was used to determine hazard ratio (HR) for each of the examined biochemical parameters.

Results

From the total number of patients (126), 26 had 32 episodes of bleeding from esophageal varices.

Bleeding from varices occurred in 19 (73.1%) male patients and in 7 (26.9%) female patients. It was found no statistically significant correlation between gender and the occurrence of the complication ($p = 0.702$).

The patients with bleeding from esophageal varices were of similar age as other patients (57.27 ± 12.58 vs 55.79 ± 10.51 , respectively; $p = 0.586$).

Bleedings occurred most often in alcoholic liver cirrhosis (61.5%). No relation between the occurrence of bleeding and etiology of liver cirrhosis ($p = 0.184$) was found as shown in Table 2.

The patients with bleeding from esophageal varices were hospitalised statistically significantly longer ($z = 2.407$; $p = 0.009$) and they spent statistically significantly more time in intensive care unit ($z = 3.242$; $p = 0.001$).

Table 2

Etiology of cirrhosis	Bleeding from esophageal varices		<i>p</i>
	Yes, n (%)	No, n (%)	
Alcoholic	16 (61.5)	71 (71.0)	0.473
B virus	0	9 (9.0)	
C virus	3 (11.5)	7 (7.0)	
Cryptogenic	6 (23.1)	8 (8.0)	
PBC	0	1 (1.0)	
Autoimmune	0	1 (1.0)	
Morbus Wilson	0	1 (1.0)	
Unknown	1 (3.8)	2 (2.0)	
Total	26 (100.0)	100 (100.0)	

PBC – primary biliary cirrhosis.

The obtained data were entered into the database, arranged in tables and presented graphically. Within the scope of descriptive statistics, data were presented in the form of arithmetic mean and standard deviation, median and interquartile range, or in the form of absolute or relative numbers. The normality of data was tested by Kolmogorov-Smirnov test. For comparing two sets of data, in case of normal data distribution we used the *t*-test and if data distribution was not normal, the Mann-Whitney's *U*-tests.

Survival analysis is used for the particular event (e.g. death) during the time, with recording the time when the particular event occurred, while in doing so, the initial time of follow-up was well-defined.

In survival analysis, life tables were applied in order to calculate one-year survival period both in relation to overall mortality as well as in relation to the occurrence of various

It was found that patients with bleeding had statistically significantly higher concentration of urea ($z = 2.752$; $p = 0.006$).

In the patients with bleeding statistically significantly lower values of the following parameters were found: total proteins ($z = 2.928$; $p = 0.003$), the number of erythrocytes ($z = 2.957$; $p = 0.003$), hemoglobin ($z = 3.727$; $p < 0.001$), hematocrit ($z = 3.952$; $p < 0.001$).

The patients with bleeding from esophageal varices most often had CTP score rank C (46.9%). CTP score rank B had 37.5% patients, while the smallest percentage of patients had CTP rank A, 15.6% of them.

We compared the length of survival in patients with bleeding from esophageal varices independently from prognostic scores with that of the followed-up population of patients with terminal cirrhosis of the liver with no

complication. It was shown that the patients with variceal bleeding lived shorter than those who did not have complication. However, among the compared parameters there was no statistically significant difference.

During the first month of follow-up, 6 patients died from bleeding from esophageal varices, in the first three months 7 of them died, and in the first six months 8 of them died.

The survival in the period between 3 and 18 months of the follow-up was on the average 68% (Figure 1).

Between 18-month- and 24-month-period the survival rate decreased, so it was found that two years after bleeding from esophageal varices only 23% of the patients survived (Figure 1).

Tables 3 and 4 show threshold values of prognostic scores of patients in relation to survival up to 30 and 90 days.

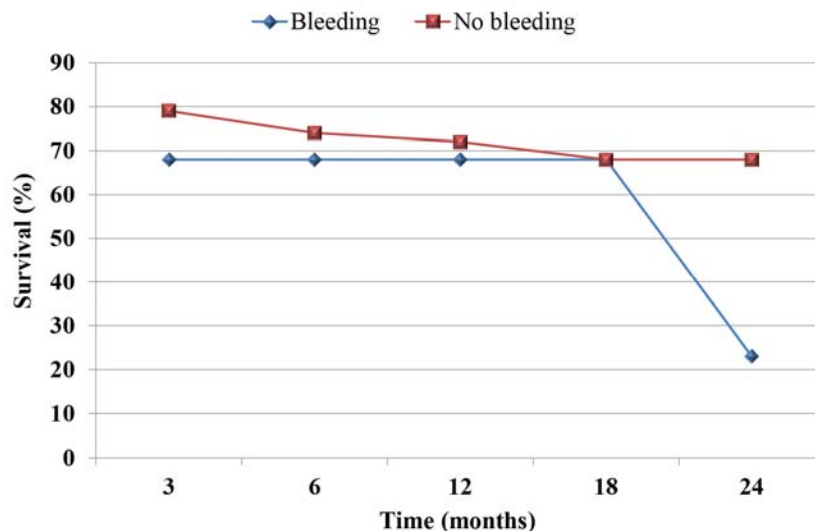


Fig. 1 – Survival in the period between 3 and 18 months of the follow-up

Table 3

Cox regression analysis – survival up to one month

Score	Complication	HR	95% CI	<i>p</i>
CTP > 10.50 +	VB	3.215	1.140–9.063	< 0.001
CTP-Crea I >10.50 +	VB	3.093	1.294–7.393	< 0.001
CTP-Crea II >11.50 +	VB	3.749	1.567–8.971	< 0.001
MELDNa > 27.50 +	VB	3.900	1.383–10.997	0.010
iMELD > 40.50 +	VB	2.838	1.303–6.183	0.009
MELD > 23.50 +	VB	3.063	1.281–7.321	0.012
UKELD > 55.50 +	VB	2.151	0.841–5.503	0.110
Updated MELD > 4.50 +	VB	2.542	0.993–6.507	0.052
MESO > 18.50+	VB	3.863	1.370–10.893	0.011

CTP – Child-Turcotte-Pugh; CTP-crea I – Creatinin modified Child-Turcotte-Pugh I; CTP-crea II – Creatinin modified Child-Turcotte Pugh II; MELDNa – Model for End-Stage Liver Disease New Model; iMELD – Integrated Model for End-Stage Liver Disease; UKELD – United Kingdom Model for End-Stage Liver Disease; MESO – Meld-Sodium; VB – variceal bleeding; HR – hazard ratio; CI – confidence interval.

Table 4

Cox regression analysis – survival up to three months

Score	Complication	HR	95% CI	<i>p</i>
CTP > 10.50 +	VB	3.342	1.182–9.448	0.023
CTP-Crea I >10.50 +	VB	3.254	1.355–7.812	0.008
CTP-Crea II >11.50 +	VB	3.927	1.634–9.436	0.002
MELDNa > 27.50 +	VB	4.085	1.444–11.557	0.008
iMELD > 40.50 +	VB	2.999	1.369–6.568	0.006
MELD > 23.50 +	VB	3.223	1.342–7.737	0.009
UKELD > 55.50 +	VB	2.269	0.883–5.826	0.089
Updated MELD > 4.50 +	VB	2.673	1.041–6.867	0.041
MESO > 18.50+	VB	4.047	1.431–11.449	0.008

CTP – Child-Turcotte-Pugh; CTP-crea I – Creatinin modified Child-Turcotte-Pugh I; CTP-crea II – Creatinin modified Child-Turcotte-Pugh II; MELDNa – Model for End-Stage Liver Disease New Model; iMELD – Integrated Model for End-Stage Liver Disease; UKELD – United Kingdom Model for End-Stage Liver Disease; MESO – Meld-Sodium; VB – variceal bleeding; HR – hazard ratio; CI – confidence interval.

Discussion

Among the compared prognostic scores, we found no prognostic score which, by its features, would have advantage over others in terms of predicting the occurrence of the episode of variceal bleeding.

In addition to factors that may be useful predictors of variceal bleeding in patients with terminal cirrhosis of the liver, it is also important to know predictors of outcome.

In everyday clinical follow-up, rather good predictors of outcome are certain routine parameters which we notice immediately upon the receipt of a bleeding patient. In a 5-day outcome, significant indicators of prognosis are the presence of active bleeding from varices during initial endoscopy, the presence of hemorrhagic shock and the number of units of blood transfusion which are necessary to correct shock and severe anemia in the patient. The platelet count on admission, etiology of cirrhosis and the presence of portal vein thrombosis, did not prove to be significant predictors of the outcome⁷.

The results of our study, on the other hand, indicate that scores from the group of CTP scores are good predictors of a short-term survival in patients with variceal bleeding.

Patients with the values of CTP score higher than 10.50 and bleeding from the esophagus, have 3.2 times higher chance for death outcome compared to other patients. Patients with the values of CTP-crea I score higher than 10.50 and bleeding from the esophagus, have 3.1 times higher chance for death outcome than other patients. Patients with the values of CTP-crea II score higher than 11.50 and bleeding from esophagus, have 3.7 times higher chance for death outcome compared to other patients (Table 3).

The results of our study clearly support CTP scores, in particular creatinine modified CTP scores, in predicting mortality within short-term follow-up of patients with bleeding from esophageal varices. As we can see in Tables 3 and 4, the best results in survival prediction, in both study periods (one and three months) are affirmative for CTP crea scores.

Modified CTP scores emerged from the need to improve comprehensiveness of initial CTP score and was achieved by including creatinine into the score. The first analysis of CTP crea score was performed in 2002 by Angemayr et al.⁸. Several recent studies quite clearly confirm that creatinine modified CTP score contributed to improvement of the initial CTP score in assessment of survival⁹.

If we observe the survival of patients with terminal cirrhosis independently of complications, as very affirming for CTP score and CTP-crea scores stands out the study of Papatheodoridis et al.¹⁰. The study points to the importance of creatinine-modified baseline CTP score and, by comparing predictability in relation to mortality, it gives priority to creatinine modified CTP score in relation to baseline CTP. Comparing CTP-crea I i CTP-crea II, the study shows that CTP-crea II is better than CTP-crea I in predicting a short-term survival¹⁰.

A study of Huo et al.¹¹ compared four modified MELD scores in predicting complications of terminal cirrhosis,

which significantly correlate with the patient survival. The study examined MELD, MELD Na, integrated MELD and MESO index in prediction of hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP) and bleeding from esophageal varices. The study found that all the examined scores were higher in patients with complications.

Quite significant is the paper of Chen et al.¹², which clearly shows the importance of MELD score in prediction of outcome after the bleeding episode and endoscopic ligation of esophageal varices. The authors conclude that MELD score higher than 18 is a significant predictor of rebleeding from esophageal varices within a 5-day period after the current episode, and good predictor of mortality within 6 weeks in patients who developed repeated bleeding from varices despite endoscopic ligation.

In a very nice way, the study of Sempere et al.¹³ presented the results of a research aimed at finding the best predictor of survival in patients with bleeding from esophageal varices. The study points out, as important predictors of mortality, age above 65 years, the presence of hepatocellular carcinoma in cirrhotic liver, CTP score higher than 10 and MELD higher than 18. Those indicators have proved to be essential in all statistical analysis, and in multivariate model of Cox's Regression Analysis, as independent predictors of outcome.

In addition, the study repeats the significance of MELD score in predicting short-term survival but also shows that particularly in the category of patients with variceal bleeding MELD score is more superior to CTP score both in short-term and long-term follow-up (both in 12-month and 36-month periods of follow-up). The highest difference in the compared scores (CTP and MELD) is present in 6-week and 3-month periods of follow-up where MELD score is dominant. Although the difference is still on the side of MELD score, it is lower in 12-month and 36-month periods of follow-up¹³.

The first assessment of survival in the examined population we carried out 30 days after the episode of variceal bleeding. During that time period, we compared the prognostic scores in terms of predicting one-month survival. With Cox's Regression Analysis we obtained relatively similar prognostic validities for scores from the CTP group. However, the strongest predictive value in terms of one-month survival has CTP-crea II score. When in patients with variceal bleeding CTP-crea II score exceeds the threshold value of 11.50, probability of mortality increases by 3.7 times compared to patients who do not have variceal bleeding. The two other scores, CTP crea I and baseline CTP score, also behave in a quite similar way. Those three scores are predictors of one-month mortality with statistical significance ($p < 0.001$). Adding the value of serum creatinine level to the baseline CTP score significantly improved the features of this score, as it can be concluded from the results of our study.

In variceal bleeding the importance of creatinine, first of all, modified baseline CTP score, as an important prognostic factor, also helps to include weakened kidney function. Disorder of kidney function in terminal cirrhosis, in patients with bleeding from esophageal varices, may not be cau-

sed only by hepatorenal syndrome. As with other forms of bleeding in conditions of hemorrhagic shock, there may occur prerenal acute renal failure and acute tubular necrosis. Those are conditions that are associated with high mortality, so it is clear that creatinine-modified CTP score, in prognosis of survival, has a significantly improved baseline CTP score. The risk of lethal outcome initiated by weakened kidney function in patients with variceal bleeding is thus fully covered.

Among scores of the MELD group, as the best predictors of survival stood out MELD Na score and MESO index, which showed almost identical prognostic value. When patients with variceal bleeding have MELD Na score higher than 27.50 and MESO index higher than 18.50, the probability of mortality increases by 3.9 that is by 3.8 times compared to population that does not have variceal bleeding.

Those two prognostic scores are connected by one common feature, which is that both scores were created by modifying MELD score with serum sodium level. As the serum sodium level is an independent indicator of mortality in terminal cirrhosis and retention of free water and dilution hyponatremia correlate well with portal hypertension, it is clear that integration of this biohumoral indicator contri-

buted to improving the quality of MELD score in predicting survival.

Conclusion

Survival of patients with bleeding from esophageal varices in a short-term follow-up can be predicted by following CTP score and creatinine-modified CTP scores.

Patients with bleeding from esophageal varices with CTP score and CTP-crea I score higher than 10.5 and CTP-crea II score higher than 11.5 have statistically significantly higher risk from mortality within 1-month follow-up compared to those with bleeding from esophageal varices with lower numerical values of scores of the CTP group. Among the scores of the MELD group, the best features in predicting survival of patients with bleeding from esophageal varices showed scores created by modifying baseline MELD score with serum sodium, that is, MESO index and MELD Na score.

Among the compared scores there was no any single prognostic score which could be a strong predictor of variceal bleeding episode.

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