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MELD SCORE AND HEPATIC ENCEPHALOPATHY AS PREDICTORS OF MORTALITY IN PATIENTS WITH DECOMPENSATED ALCOHOLIC LIVER CIRRHOSIS

Andrija Rančić[1], Mirjana Radisavljević[1], Marko Milanović[1], Stefan Todorović[2], Lazar Bajić[3]

Cirrhosis is the final stage of numerous chronic liver diseases. The disease most often occurs as a result of chronic alcohol consumption and infection with hepatitis C and B viruses. Over 3 million people die globally as a result of alcohol consumption. Prognostic scores have been developed to estimate survival rates. The MELD score (model for end-stage liver disease) is used today in the prognosis of short-term survival of patients with decompensated liver cirrhosis.

This prospective/retrospective study was conducted on a sample of 56 patients (52 male and 4 female) with an average age of 55.23 ± 10.82. MELD score values were calculated at the end of hospitalization and correlated with defined treatment outcomes. Based on the conducted receiver operating characteristic (ROC) analysis, cut-off values of MELD score over 23.5 were statistically significant in the prognosis of mortality. Of the total examined population, 72% of patients with a score higher than the obtained cut-off value died. The total number of patients with hepatic encephalopathy was 34 (61%), of which 23 died. ROC analysis in the group of patients with hepatic encephalopathy revealed a cut-off value of the MELD score of 30.5, which is statistically not significantly different from the cut-off value of the MELD score for survival. The male-to-female ratio in the subsamples of deceased and survived patients in this study was approximately equal.

The cut-off value of the MELD score proved to be statistically significant in predicting short-term survival. The increase in the cut-off value of the MELD score in patients with hepatic encephalopathy was not statistically significant. In the group of patients with hepatic encephalopathy, 92% of patients died, although no statistically significant increase in the cut-off value of the MELD score was found.

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Key words: *alcoholic liver cirrhosis, model for end stage liver disease score, hepatic encephalopathy*

[1]University Clinical Center Niš, Clinic of Gastroenterology and Hepatology
[2]University Clinical Center Niš, Clinic of Neurology
[3]University of Niš, Faculty of Medicine

Contact: Rančić Andrija
44 Vase Pelagića St., 18000 Niš, Serbia
E-mail: andrija.m.rancic@gmail.com
Phone: +381 69 2007994, +381 18 200288

Introduction

Cirrhosis (from the Greek word kirrhos—yellow) represents the most common final stage of numerous chronic liver diseases (1, 2). This condition is characterized by irreversible damage to the liver parenchyma and permanent loss of its normal architecture. The end result of this process is the development of fibrosis and numerous regenerative nodes (2).

Cirrhosis of the liver can be developed due to chronic infection with hepatitis C and B viruses. Consumption of large amounts of alcohol is also closely associated with the development of hepatitis, cirrhosis and fibrosis (3). Non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) are both predispositions for the development of liver cirrhosis (4). A much rarer cause of liver cirrhosis can be an autoimmune or the presence of chronic cholestasis syndrome, Wilson's disease, hemochromatosis and primary sclerosing cholangitis (5, 6). The precise incidence of liver cirrhosis is difficult to determine due to its multifactorial etiology. Liver cirr

hosis is estimated to be the fourth most common cause of death in Europe and fourteenth worldwide (7). Hepatitis B virus is the main cause of disease development in Asia, and hepatitis C virus, NAFLD and chronic alcohol consumption are the primary causes in Western countries (8, 9). Frequent alcohol intake is associated with 48% to

50% of deaths from liver cirrhosis in America (10). In addition to the primary effect on liver damage, alcohol intake accelerates the progression of chronic hepatitis C to liver cirrhosis (11).

MELD score

The effect of ethanol on the liver parenchyma is complex. The main enzyme systems affected by alcohol are alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1) and catalase. These enzymes are responsible for the oxidation of ethanol into acetaldehyde and the production of hydroxyethyl, superoxide and hydroxyl radicals that directly damage hepatocytes (12). In the early stages, the disease is compensated, liver function is partially preserved, and patients are often without major symptoms. With the progression of liver damage, the disease becomes decompensated and patients contact a doctor because of complications of the disease (13). Due to the decompensation of liver cirrhosis, the risk of mortality increases about 9.7 times, and the average survival of these patients is from 2 to 3 years (14, 15). Numerous scores have been developed with the aim of estimating the survival of patients with terminal disease. The MELD score (model for end-stage liver disease) was first developed in 1999 at the Mayo Clinic to estimate the survival of patients with transjugular intrahepatic portosystemic shunt (TIPS) (16, 17). This score was adopted on February 27, 2002 by the UNOS organization (The United Network for Organ Sharing) for patients on the liver transplant list. Higher score values mean higher priority for liver transplantation (18). MELD score values above 15, which are maintained during follow-up, indicate that the patient is a candidate for liver transplantation (19). The use of this score has been shown as a precise survival predictor over the next 3 months in patients with chronic, decompensated liver disease (20). This short-term patient survival is calculated using three parameters: total bilirubin value, serum creatinine value, and international normalized ratio for prothrombin time (INR) (18). An online calculator (available at the web address: http://www.unos.org/resources) allows calculating the numerical value of the MELD score using the complex formula: 9.57 × logecreatinine (mg/dL) + 3.78 × logebilirubin (mg/dL) + 11.20 × logeINR + 6.43 (19). The higher the score values, the shorter the three-month survival, so patients with a score less than 9 have the best prognosis (1.9–3.7% chance of death in the next 3 months), and patients with a score over 40 (71%–100% chance of death in the next 3 months). Alternative forms of the MELD score are often used today. Those forms are corrected with values of serum sodium and serum creatinine (sodium MELD, corrected creatinine MELD) (21). The Δ-MELD (delta-MELD) score, which represents the difference between the MELD scores at the beginning and end of treatment, can also be calculated in order to evaluate the short-term survival of patients with decompensated liver cirrhosis (22).

Objective

The aim of this research was to determine the prognostic validity of the MELD score in relation to survival only in the population of patients with decompensated alcoholic liver cirrhosis and developed hepatic encephalopathy examined in the period from admission to hospital treatment to defined treatment outcomes.

Material and Methods

The prospective/retrospective study was conducted at the Clinic of Gastroenterology and Hepatology of the University Clinical Center in Niš. The research included 56 patients with a diagnosis of decompensated alcoholic liver cirrhosis treated between January and December 2022. For each admitted patient, the MELD score was calculated as standard at the end of hospital treatment using an online calculator. In order to calculate the MELD score, a blood sample was taken from the patients for analysis of the blood count and biochemical parameters. Patients were also examined for the presence of hepatic encephalopathy and asked about the accompanying diseases and alcohol consumption. After the insight into the obtained anamnestic data, the statistical processing of the data was performed.

The state of decompensation of alcoholic cirrhosis of the liver meant aggravation of the terminal phase of the disease due to the development of one or more complications (hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, bleeding from esophageal varices, hepato-renal syndrome). Hepatic encephalopathy was diagnosed based on the clinical condition of the patient, lack of orientation, specific shaking movement of the limbs (asterixis) and exclusion of other potential etiologies of encephalopathy such as intracranial lesions, stroke of hemorrhage, seizure activity etc.

The defined treatment outcomes in this study were:

1. survival of the patient in the episode of the decompensated phase of the disease, and
2. fatal outcome of the patient in the episode of the decompensated phase of the disease.

Differences in gender structure between patients who died and those who survived were tested with the chi-square test. The difference in mean age between patients who died and those who survived was tested by t-test for two independent samples. The normality of the data was confirmed by the Kolmogorov–Smirnov test. Finally, the z/proportion test was used to test the difference in the number of patients who died and patients who survived.

Results

Based on the obtained results, it can be concluded that the ratio of males and females in the subsamples of deceased and survived patients was approximately equal. The average age of survived and deceased patients did not show a statistically significant difference. There was also no significant difference between the number of deceased and the number of survived patients in this sample.

The difference in the number of patients with and without hepatic encephalopathy was tested using the *z*/proportion test.

No significant difference between the number of patients with and without hepatic encephalopathy was found in this sample.

The cut-off value of the MELD score was calculated using ROC analysis.

Based on the ROC analysis, it was found that the value of the MELT score at discharge from hospital treatment could be used as a diagnostic predictor for survival. Based on the ratio of sensitivity and specificity, a cut-off value of 23.5 was determined. Patients with a measured value of less than 23.5 were more likely to survive. The predictive power was statistically significant.

The chi-square test confirmed the good diagnostic power of the MELD score.

The chi-square test was used to check whether there was a relationship between survival rate and the presence of hepatic encephalopathy in patients.

Table 1. Demographic characteristics of the studied population

Population characteristics		Survived/Deceased		Total	Chi2/t/z	sig
		survived	deceased			
gender	Male	28 (90.32%)	24 (96%)	52 (92.86%)	.673	0.412
	Female	3 (9.68%)	1 (4%)	4 (7.14%)		
age		54.03 ± 11	56.72 ± 10.62	55.23 ± 10.82	-0.923	0.360
	Total	31 (55%)	25 (45%)	56 (100%)	0.668	0.504

Table 2. Demographic characteristics in relation to hepatic encephalopathy

	Hepatic encephalopathy		Total	z	sig
	no	yes			
Total	22 (39%)	34 (61%)	56 (100%)	-1.472	0.141

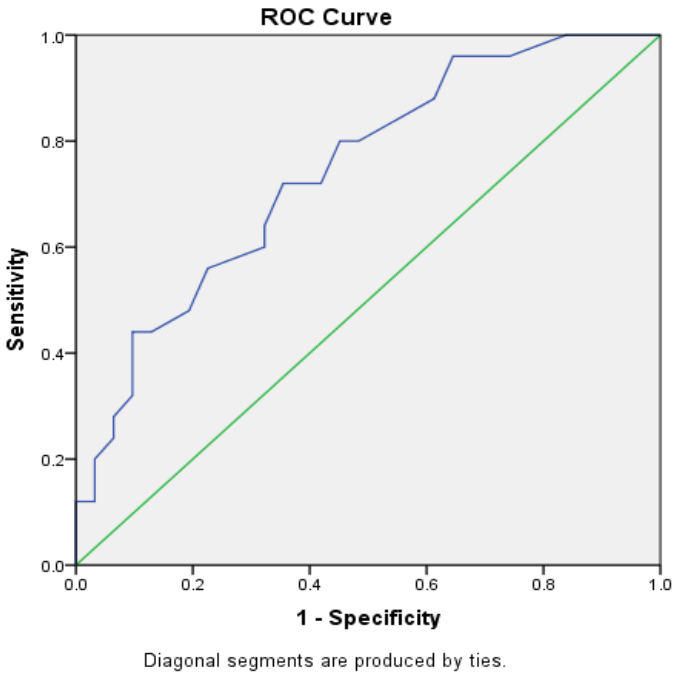

Figure 1. ROC analysis of the cut-off value of the MELD score

Table 3. Cut-off value of the MELD score of survival

Area Under the Curve					Cut off value
Test Result Variable(s): MELD					
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval		
			Lower Bound	Upper Bound	
.743	.065	**.002**	.615	.871	**23.5**

Based on the results of the chi-square test, it can be concluded that there was a statistically significant connection between these two characteristics. The percentage of deceased patients was significantly higher in the subsample of patients with hepatic encephalopathy.

The cut-off value of the MELD score in patients with hepatic encephalopathy was calculated using ROC analysis.

ROC analysis only determined the cut-off value of the MELD score at discharge from hospital treatment in patients with hepatic encephalopathy. The obtained result was not statistically significant, although the obtained value was close to the threshold of significance. This would mean that the MELD score should not be used as a prognostic survival score in patients with hepatic encephalopathy. In addition, based on the ratio of sensitivity and specificity, the established cut-off value was 30.5. This obtained cut-off value of the MELD score in the group of patients with hepatic encephalopathy who died was higher than the initial value of 23.5, previously shown to be statistically significant for survival. In the group of patients with hepatic encephalopathy, 92% of patients died, although no statistically significant increase in the cut-off value of the MELD score was found.

Table 4. Survival rate in relation to the cut-off value of the MELD score

		Survived/Deceased		Total	Chi2	sig
		survived	deceased			
MELD score positive (>23.5)	no	20 (64.52%)	7 (28%)	27 (48.21%)	7.391	.007
	yes	11 (35.48%)	18 (72%)	29 (51.79%)		

Table 5. Survival rate in relation to the presence of hepatic encephalopathy

		Survived/Deceased		Total	Chi2	sig
		survived	deceased			
Hepatic encephalopathy	no	20 (64.52%)	2 (8%)	22 (39.29%)	18.532	**0.000**
	yes	11 (35.48%)	23 (92%)	34 (60.71%)		

Table 6. Cut-off value of the MELD score in patients with hepatic encephalopathy

Area Under the Curve					
Test Result Variable(s): MELD					
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval		Cut off value
			Lower Bound	Upper Bound	
.680	.094	.094	.495	.864	30.5

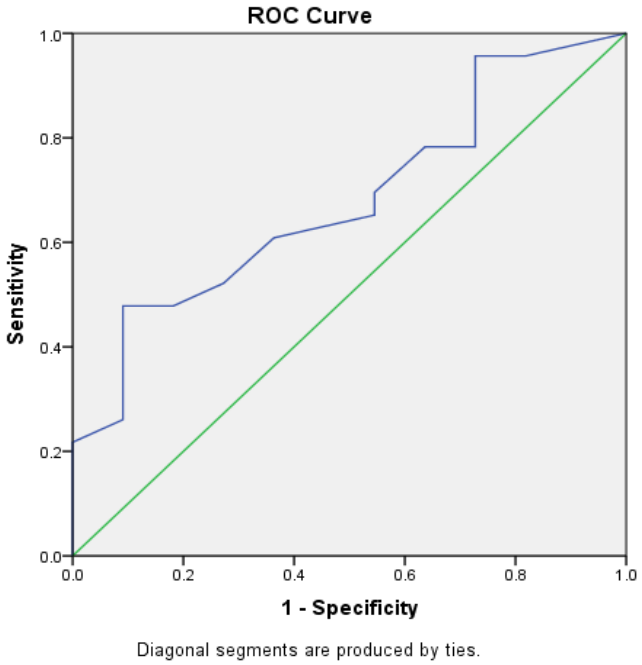

Figure 2. ROC analysis of the cut-off value of the MELD score only in patients with hepatic encephalopathy

Discussion

In this research, we examined the significance of the MELD score as a prognostic parameter of survival in a selected population of patients with decompensated alcoholic cirrhosis of the liver observed in the period from admission to hospital treatment to defined treatment outcomes.

According to the report of the World Health Organization (WHO), about 3.3 million people around the world die as a result of long-term alcohol consumption (23). The WHO records that the average alcohol consumption is 13.5 g of alcohol per day, or about 6.2 liters of alcohol per year. (24). It is estimated that 1 in 12 adults consumes alcohol daily, men more than 3 and women more than 2 drinks per day. The National Institute for Alcoholism also defines alcohol abuse in the form of acute intake of over 5 drinks in men and over 4 drinks in women in a period of 2 hours (25). The largest number of alcoholic cirrhosis of the liver is recorded in individuals between 45 and 54 years of age, but this limit has been moving for a whole decade towards a younger age (26). Men are more likely to develop liver cirrhosis than women, due to more frequent and higher intake of alcohol. However, women are sensitive to the direct toxic effects of alcohol, so the risk of developing alcoholic cirrhosis in women who drink alcohol is up to 2 times higher than in the male population (27, 28). Patients with alcoholic cirrhosis of the liver usually contact a doctor due to the development of jaundice, elevated body temperature and weight loss. In the decompensated phase of the disease, there are ascites, hepatic encephalopathy, bleeding from esophageal varices and kidney failure (29). In patients who are already treated for alcoholic cirrhosis of the liver, further intake of alcohol increases mortality in the next 5 years, so it is estimated that the 5-year survival rate in this case is about 35% (30). In addition to well-known diagnostic methods, the MELD score is often used as a predictor of three-month survival in patients with decompensated alcoholic cirrhosis of the liver (18).

The MELD score was implemented to assess the risk of mortality in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) (18). The score has also been used in patients who are candidates for liver transplantation, and it is widely used as a simple score to predict the survival of patients with decompensated liver cirrhosis (31, 32). Numerous studies have addressed the importance of the MELD score. A large meta-analysis including 16 studies and a sample of 2, 337 patients was conducted by Wu Shi-Lan et al. This analysis established the reliability of the MELD score in clinical application, and above all in predicting mortality in the next 6 to 12 months (33). Wu Shi-Lan points to the importance of the MELD score because of the reliable values of the laboratory parameters used to calculate the score. The results obtained in this way are more objective and most often correlate with the clinical condition of the patients (34). Our conducted research shows similar results. Measured MELD score values that were higher than the obtained cut-off value (23.5) are associated with a shorter survival rate. In practice, the clinical condition of the patient includes other parameters such as the

presence of hepatic encephalopathy, ascites, spontaneous bacterial peritonitis and acute variceal bleeding. These independent mortality factors are not included in the MELD score, although they are very important in the treatment outcome of patients (35). Stewart CA et al. conducted a study on a sample of 271 patients with decompensated liver cirrhosis and developed hepatic encephalopathy. The study determined the statistical significance of the MELD score in surviving patients, however, hepatic encephalopathy was shown to be an independent predictor of mortality (36). Patients who were treated in our hospital due to decompensated liver cirrhosis with hepatic encephalopathy had a shorter survival rate than patients without this complication. This difference was statistically significant. The established cut-off value of the MELD score for the patient with hepatic encephalopathy (30.5) was slightly higher compared to the cut-off value for survival (24.5). Although this increase in the cut-off value was not statistically significant, the largest number of deceased patients had hepatic encephalopathy. This complication develops relatively late in the decompensated phase of the disease as a consequence of the appearance of portosystemic shunts. Toxic substances bypass the liver via shunts, their detoxification is absent and they reach the cerebral circulation directly. Because of this, the presence of hepatic encephalopathy could directly affect the biochemical parameters, and therefore the values of the MELD score (36). The research conducted by Kamath concluded that the MELD score is highly reliable in the assessment of the three-month mortality rate in patients with decompensated liver cirrhosis, regardless of its etiology. The results of this study were that albumin values, the presence of hepatic encephalopathy, ascites and spontaneous bacterial peritonitis did not significantly increase the accuracy of the MELD score (18). The results of our research have shown similarities to this research. Hepatic encephalopathy was an independent predictor of mortality. Although this complication had a partial effect on the change in the cut-off value of the MELD score in patients who died, this effect was not statistically significant. This topic of association between MELD score and hepatic encephalopathy was addressed by Yoo Iwan and Edwin David. By examining a smaller population of 66 patients, they found that the subclinical and clinical presence of hepatic encephalopathy correlates weakly with the change in the MELD score. Therefore, they point out that the MELD score may not be the most reliable score for assessing the survival of patients with advanced encephalopathy (37). The group of subjects in the present study counted only 10 patients less, but the results we obtained were similar to theirs. The presence of this complication primarily influenced the increase in patient mortality, but not a significant change in the MELD score. The impact of hepatic encephalopathy on the survival of patients with decompensated cirrhosis was also studied by Bjerring Peter and Gluud Lise. In their 2017 study, hepatic encephalopathy again stood out as an independent prognostic factor from the MELD score. The conclusion of this study suggests that the accuracy of the MELD score increases if it is combined with hepatic encephalopathy (38). Similar results on a sample of 1,560 patients with cirrhosis were obtained by Bajaj who claims that hepatic encephalopathy must be considered when calculating the MELD score (39). The evaluation of the effectiveness of the MELD score was also done by Elzouki Aiello et al. On a sample of 109 patients diagnosed with decompensated liver cirrhosis with hepatic encephalopathy, the MELD score was a reliable predictor of mortality in patients over the age of 60 (40). The average age of deceased patients in our present study was 56.72 ± 10.62. The largest number of these patients had MELD score values higher than the calculated cut-off value for survival. These obtained results are very similar to the results of the previous research. Florencia et al. point out the imperfection of the MELD score, which is why it is not the most reliable prognostic marker of mortality. The reason for this is the lack of precision of the creatinine value as one of the parameters of the MELD score. These values may vary individually in relation to age, sex, protein intake and liver and kidney function (41). Due to the difference in standardized creatinine values between the sexes, the score values are often higher in women. This would indicate worse survival in women, which is not always the case when dealing with decompensated liver cirrhosis (42). Numerous substances such as pyruvate and various drugs can also affect serum creatinine values, so such measured creatinine values can be unreliable (43). In our country, the level of serum creatinine is expressed in millimoles per liter (mmol/L). The exact creatinine values used to calculate the MELD score were obtained by dividing the value in mmol/L by the coefficient 88.4, which gives the value in milligrams per deciliter (mg/dL). Different to the study by Florencia et al., the cut-off value of the MELD score in our study was statistically significant for survival, and therefore the value of serum creatinine as part of this score. A large cohort study of 830 subjects by Peeraphatdit Thoetchai points to certain shortcomings of the MELD score. In the decompensated phase of the disease, bilirubin values are often unchanged on a daily basis, considering the chronic state of the disease. Also, INR values may vary due to the administration of anticoagulant therapy, fresh frozen plasma or vitamin K. These are the reasons why the MELD score at the end of treatment does not have to be precise, and often does not correlate with the more severe clinical condition of the patient. According to this study, the MELD score at discharge from treatment does not precisely correlate with the patient survival rate (22). Porte RJ et al. dealt with similar challenges. Their study indicates a large variability of INR values because of the laboratories where this analysis was performed. The MELD score calculated in this way could differ by 3 to 5 MELD

points, which significantly reduces the accuracy of this prognostic marker. For this reason, it is considered that INR is not a reliable parameter for any prognosis in patients with decompensated liver cirrhosis (44). Our MELD score calculations used the INR obtained at the end of hospitalization, but we cannot say with certainty how reliable this parameter was. Given that a higher MELD score meant shorter survival, INR values would probably be reliable. Although Kamath et al. have previously spoken about the reliability of the MELD score, they are also pointing out its flaws. Similar to previous studies, they claim that the measurement of renal function by determining the clearance of some other substances, besides creatinine, could increase the reliability of this prognostic marker if they are combined with the MELD score (18). Since the score is based on parameters that are likely to change, there was a need to increase the accuracy of this score. Shortly after the creation of the MELD score, in 2003, Ruf et al. suggested adding the value of serum sodium as an additional parameter of the MELD score. It has been noted that patients with hyponatremia have ascites, which is one of the independent prognostic parameters of mortality (45). Accordingly, the modified MELD-Natrium (MELD-Na) score more accurately predicts the mortality of these patients (45, 46). A meta-analysis by Wu Shi-Lan shows a higher prognostic accuracy of the MELD-Na score compared to the MELD score. According to this meta-analysis, the MELD-Na score is superior in estimating mortality in the next 12 months (33). Chen Si-Hai in his examination of markers for the prognosis of liver cirrhosis, suggests the combination of the MELD score with other parameters of inflammation, such as C-reactive protein (CRP) and procalcitonin (PCT). The MELD-CRP and MELD-PCT scores improve the prediction of mortality in the next 30 days. These results are in agreement with results on the same topic of research conducted at the Mayo Clinic (47). The previously mentioned problem of accuracy of the MELD score due to the variability of INR as one of the score parameters could be overcome by simply eliminating INR from this score. The MELD score calculated without the INR value (the so-called MELD-XI) would be a suitable prognostic marker of mortality only in patients whose renal function is significantly impaired due to the primary disease. Although a large number of decompensated liver cirrhosis is followed by hepatorenal syndrome with renal failure, this may not always be the case. MELD-XI could be prognostically quite accurate in decompensated alcoholic liver cirrhosis, but not in liver cirrhosis of other etiologies (48). It is also suggested to replace the INR with coagulation factor V or coagulation factor VII. MELD scores modified in this way have not yet found wider application in clinical practice (49). Our experience with modified MELD scores is very poor. Further research on this topic, adding the sodium value to the score and correlating it with other complications of decompensated liver disease could increase the accuracy of the MELD score. Possible combination of this score with the values of serum CRP and procalcitonin, or some other laboratory parameter, would probably give a better short-term prognosis of mortality in patients suffering from decompensated alcoholic liver cirrhosis.

Conclusion

This study of a selected patient population aimed to determine the prognostic validity of the MELD score in relation to the survival rate of patients with decompensated alcoholic cirrhosis of the liver with developed hepatic encephalopathy. The MELD score is proved to be a statistically significant predictor of mortality, but hepatic encephalopathy did not significantly affect changes in this score. Statistically, there was a significant difference in the group of deceased patients who developed hepatic encephalopathy compared to the group without this complication. The cut-off value of the MELD score in the group of deceased patients who developed hepatic encephalopathy was not statistically significantly different from the cut-off value of the MELD score of survival. To determine if hepatic encephalopathy is an independent mortality predictor, it is necessary to perform a study on a larger patient population.

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MELD SKOR KAO PREDIKTOR MORTALITETA KOD BOLESNIKA SA DEKOMPENZOVANOM ALKOHOLNOM CIROZOM JETRE I RAZVIJENOM HEPATIČNOM ENCEFALOPATIJOM

Andrija Rančić[1], Mirjana Radisavljević[1], Marko Milanović[1], Stefan Todorović[2], Lazar Bajić[3]

[1]Univerzitetski klinički centar Niš, Klinika za gastroenterologiju i hepatologiju, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija
[3]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija

Kontakt: Andrija Rančić
Vase Pelagića 44, 18000 Niš, Srbija
E-mail: andrija.m.rancic@gmail.com
Telefon: 069/20-07-994; 018/200-288

Ciroza je završni stadijum brojnih hroničnih bolesti jetre. Bolest najčešće nastaje usled hroničnog konzumiranja alkohola i infekcije virusima hepatitisa C i B. U svetu od posledica unosa alkohola godišnje umre više od tri miliona ljudi. Prognostički skorovi razvijeni su sa ciljem procene preživljavanja. Prilikom prognoze kratkoročnog preživljavanja bolesnika sa dekompenzovanom cirozom jetre danas se koristi MELD (engl. *Model for End-stage Liver Disease*) skor.

Ova prospektivno/retrospektivna studija sprovedena je na uzorku od 56 bolesnika (52 muškarca i četiri žene), čija je prosečna starost bila 55,23 ± 10,82 godine. Vrednosti MELD skora računate su na kraju hospitalizacije i bile su u korelaciji sa definisanim ishodima lečenja. Sprovedena ROC (engl. *Receiver operating characteristic*) analiza pokazala je da su *cut-off* vrednosti MELD skora preko 23,5 bile statistički značajne u prognozi mortaliteta. U ukupno ispitivanoj populaciji, preminulo je 72% bolesnika sa skorom većim od dobijene *cut-off* vrednosti. Ukupan broj bolesnika sa razvijenom hepatičnom encefalopatijom bio je 34 (61%); od toga, preminulo je njih 23. ROC analizom u grupi bolesnika sa hepatičnom encefalopatijom utvrđena je *cut-off* vrednost MELD skora 30,5, što se statistički signifikantno ne razlikuje od *cut-off* vrednosti MELD skora za preživljavanje. Odnos muškog i ženskog pola u poduzorcima preminulih i preživelih bolesnika u ovom istraživanju bio je skoro ujednačen.

Cut-off vrednost MELD skora pokazala se kao statistički značajna u prognozi kratkoročnog preživljavanja. Zabeležen porast *cut-off* vrednosti MELD skora kod bolesnika sa hepatičnom encefalopatijom nije bio statistički značajan. U grupi bolesnika sa hepatičnom encefalopatijom zabeležen je smrtni ishod kod 92% bolesnika, premda nije utvrđeno statistički signifikantno povećanje *cut-off* vrednosti MELD skora.

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***Ključne reči**: alkoholna ciroza jetre, model for end stage liver disease skor, hepatična encefalopatija*

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