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The Relationship between MELD Score, Bilirubin, Albumin, and INR Levels and Prognosis in Patients with Hepatic Encephalopathy in the Emergency Department

Acil Serviste Hepatik Ensefalopatili Hastalarda MELD Skoru, Bilirubin, Albümin ve INR Düzeylerinin Prognozla İlişkisi

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ABSTRACT

Aim: This study aimed to evaluate the relationship between prognosis and model for end-stage liver disease (MELD) score, albumin, bilirubin, and international normalized ratio (INR) levels in patients diagnosed with hepatic encephalopathy (HE) based on Child-Pugh staging.
Material and Methods: This prospective observational study included a total of 49 patients diagnosed with cirrhosis of the liver who presented to the emergency department due to HE. Clinical findings and laboratory values of the patients were prospectively recorded. Each patient's Child-Pugh score, MELD score, INR, albumin, total and direct bilirubin levels were determined and compared according to the Child-Pugh stage.
Results: Of the 49 patients included in the study, 32 (65.3%) were male and 17 (34.7%) were female, and the median age was 57 (range, 46-85) years. Of the patients, 28 (57.1%) were in Child-Pugh stage B, and 21 (42.9%) were in Child-Pugh stage C. The most commonly observed encephalopathy symptoms were ataxia (93.9%, n=46) and amnesia (81.6%, n=40). MELD score, INR, and bilirubin levels were found significantly higher in the Child-Pugh C group compared to the Child-Pugh B group ($p<0.001$ for all). Albumin levels were found significantly lower in the Child-Pugh C group ($p=0.001$).
Conclusion: In patients diagnosed with HE, higher MELD score, INR, and bilirubin levels, along with lower albumin levels, are significantly associated with a poor prognosis. These biochemical parameters and scoring systems could serve as important prognostic indicators for early risk stratification and management of patients in the emergency department.
Keywords: Hepatic encephalopathy; Child-Pugh score; MELD score; emergency department.

ÖZ

Amaç: Bu çalışmanın amacı, hepatik ensefalopati (HE) tanısı alan hastalarda, prognoz ile son dönem karaciğer hastalığı modeli (model for end-stage liver disease, MELD) skoru, albümin, bilirubin ve uluslararası normalleştirilmiş oran (international normalized ratio, INR) düzeyleri arasındaki ilişkinin Child-Pugh evrelemesine göre değerlendirilmesidir.
Gereç ve Yöntemler: Bu prospektif gözlemsel çalışmaya, HE nedeniyle acil servise başvuran ve karaciğer sirozu tanısı alan toplam 49 hasta dahil edildi. Hastaların klinik bulguları ve laboratuvar değerleri prospektif olarak kaydedildi. Her hastanın Child-Pugh skoru, MELD skoru, INR, albümin, toplam ve direkt bilirubin düzeyleri belirlendi ve Child-Pugh evresine göre karşılaştırıldı.
Bulgular: Çalışmaya dahil edilen 49 hastanın 32'si (%65,3) erkek ve 17'si (%34,7) kadın olup ve hastaların ortanca yaşı 57 (aralık, 46-85) yıl idi. Hastalardan 28'i (%57,1) Child-Pugh B evresinde ve 21'i (%42,9) ise Child-Pugh C evresindeydi. En sık gözlenen ensefalopati semptomları ataksi (%93,9; n=46) ve amnezi (%81,6; n=40) idi. MELD skoru, INR ve bilirubin düzeyleri Child-Pugh C grubunda Child-Pugh B grubuna göre anlamlı derecede daha yüksek bulundu (hepsi için $p<0,001$). Albümin düzeyleri ise Child-Pugh C grubunda anlamlı derecede daha düşük bulundu ($p=0,001$).
Sonuç: HE tanısı alan hastalarda yüksek MELD skoru, INR ve bilirubin düzeyleri ile düşük albümin düzeyleri kötü prognoz ile anlamlı şekilde ilişkilidir. Bu biyokimyasal parametreler ve skorlama sistemleri, acil serviste hastaların erken risk sınıflandırması ve yönetimi açısından önemli prognostik göstergeler olabilir.
Anahtar kelimeler: Hepatik ensefalopati; Child-Pugh score; MELD skoru; acil servis.

INTRODUCTION

Hepatic encephalopathy (HE) is a complex and heterogeneous neuropsychiatric syndrome that results from the accumulation of neurotoxic substances in the systemic circulation due to liver failure. The clinical presentation varies widely, ranging from subtle cognitive impairments to deep coma (1). HE is a frequent and clinically significant complication in patients with cirrhosis, affecting approximately 30-45% of this population (2). Patients diagnosed with liver cirrhosis are at a high risk of developing HE, particularly within a five-year follow-up. In a large-scale study conducted in the United States involving over 9,000 liver cirrhosis patients, one-third were reported to have decompensated cirrhosis, and 51% of these patients developed varying degrees of HE (3). Although several classification systems for HE have been proposed, a unified system based on the degree of neurological dysfunction was established at the 11th World Congress of Gastroenterology held in Vienna in 1998 (4,5). Among these, the West Haven Criteria are the most widely used in clinical practice (2). According to these criteria, HE is classified into four grades (6): *Grade I:* attention deficits, restlessness, depression, and subtle personality changes; *Grade II:* lethargy, behavioral changes, memory and calculation disturbances, sleep disturbances; *Grade III:* confusion, disorientation, stupor, and amnesia; and *Grade IV:* coma.

One of the most critical objective parameters for assessing prognosis in cirrhotic patients is the Child-Pugh classification, which evaluates the severity of liver dysfunction (Table 1). This scoring system incorporates the presence of HE, ascites, total bilirubin, albumin, and the international normalized ratio (INR), resulting in a composite score. Scores of 5-6 correspond to Child-Pugh class A, 7-9 to class B, and 10-15 to class C (7). Another widely accepted prognostic tool is the model for end-stage liver disease (MELD) score, which is calculated using serum bilirubin, serum creatinine, and INR levels as follows: MELD = 11.2 × log(INR) + 3.78 × log(serum bilirubin [mg/dL]) + 9.57 × log(serum creatinine [mg/dL]) + 6.43 (8). The MELD score reliably predicts mortality risk in patients with end-stage liver disease; higher scores indicate greater severity and increased mortality risk (8,9). However, it is also known that the MELD score does not strongly correlate with HE severity (10). Liver fatty acid-binding protein (L-FABP), a member of the fatty acid-binding protein family identified in the early 1970s, is a 15 kDa cytoplasmic protein. It is primarily synthesized by hepatocytes but is also present in jejunal and ileal enterocytes, colonocytes, and proximal tubular cells. To detect L-FABP in human tissue and plasma, a sandwich enzyme-linked immunosorbent assay (ELISA) method using recombinant L-FABP has been developed. L-FABP is secreted in a gradient from the portal to the central vein within hepatic lobules and has emerged as a promising biochemical marker for the early detection of hepatocellular injury. Over time, the need for biomarkers more sensitive and earlier than alanine aminotransferase (ALT) in detecting hepatocellular damage has become increasingly apparent (11).

The primary objective of this study was to investigate the relationship between MELD scores, albumin, bilirubin, and coagulation parameters and the prognosis of patients diagnosed with HE in the emergency department, classified according to the Child-Pugh system.

MATERIAL AND METHODS

This prospective observational study included 49 patients who presented to the Emergency Department of Ondokuz Mayıs University Faculty of Medicine, diagnosed with liver cirrhosis (confirmed by liver biopsy and/or clinical and laboratory findings) and HE. The study was conducted after obtaining approval from the Ondokuz Mayıs University Ethics Committee (approval date: 28.09.2012, decision number: 2012/98), and informed consent was obtained from all patients and/or their relatives. The diagnosis of HE was established based on a detailed medical history, physical examination, and laboratory findings. The recorded laboratory parameters included white blood cell count (WBC), hemoglobin (Hgb), hematocrit (Hct), platelet count (Plt), sodium (Na), potassium (K), chloride (Cl), blood urea nitrogen (BUN), creatinine (Cre), glucose, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), ALT, total protein, albumin, coagulation panel (aPTT, PT, INR), HBsAg, anti-HBs, and anti-HCV. Patients under 18 years old, those with neurological and/or psychiatric diseases, those with a history of drug or substance use that could cause altered consciousness, and those who chose to withdraw from the study were excluded. Additionally, venous blood samples were collected to determine serum L-FABP levels, which were analyzed using an ELISA method (Cusabio Biotech kit) in accordance with the manufacturer's instructions. Patients were classified according to the West Haven Criteria for HE and the Child-Pugh classification for cirrhosis, where scores of 7-9 indicated class B, and scores of 10-15 indicated class C. MELD scores were calculated using the specified formula, and MELD scores, Glasgow coma scale (GCS) scores, as well as AST, ALT, INR, albumin, and total/direct bilirubin levels were compared between Child-Pugh class B and C groups.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY). The distribution of variables was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics were presented as frequency, percentage, mean±standard deviation, or median (minimum-maximum). Continuous variables were compared between two groups using the Mann-Whitney U test and among three or more groups using the Kruskal-Wallis test. Categorical variables were analyzed using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 49 patients diagnosed with HE were included in this study. Demographic characteristics, vital signs, etiological factors, Child-Pugh scores, and HE grades were summarized in Table 2. Among the participants, 32 (65.3%) were male and 17 (34.7%) were female, with a median age of 57 (range, 46-85) years. The median systolic blood pressure was 120 mmHg, the diastolic blood pressure was 70 mmHg, the body temperature was 36.3 °C, and the heart rate was 80 beats per minute. Regarding etiology, 46.9% (n=23) of the patients had hepatitis C virus (HCV) infection, 8.2% (n=4) had hepatitis B virus (HBV) infection, 32.7% (n=16) had cryptogenic cirrhosis, and 12.2% (n=6) had alcohol-related cirrhosis. None of the patients were classified as Child-Pugh class A; 28 (57.1%)

patients were in class B, and 21 (42.9%) patients were in class C. Based on the West Haven Criteria, 21 (42.9%) patients were categorized as grade I, 13 (26.5%) patients as grade II, 8 (16.3%) patients as grade III, and 7 (14.3%) patients as grade IV (Table 2).

When serum L-FABP levels of the patients were compared, they were significantly lower in the patient group compared to the control group (84.5 (range, 21.8-298) pg/ml vs. 276.2 (range, 99.2-567.9) pg/ml, p<0.001).

All patients presented with clinical symptoms, including attention deficits, restlessness, asterixis, sleep disturbances, behavioral abnormalities, tremors, and impaired coordination. The following most commonly reported symptoms were ataxia (93.9%, n=46) and amnesia (81.6%, n=40). The distribution of HE-related symptoms is detailed in Table 3.

Descriptive statistics and comparative analyses of GCS scores, MELD scores, and laboratory parameters according to the Child-Pugh stages were presented in Table 4. AST levels were significantly higher in Child-Pugh class C patients compared to class B patients (p=0.021). Similarly, INR values were also found significantly higher in class C patients (p<0.001), while albumin levels were found significantly lower (p=0.001). Moreover, both total and direct bilirubin levels were significantly higher in class C patients than in class B patients (both p<0.001). While MELD scores were also significantly higher in class C patients (p<0.001), no statistically significant differences were observed in the GCS (p=0.151).

DISCUSSION

Male predominance among cirrhotic patients has been widely reported in the literature, and the gender distribution in our study group is consistent with these findings. While chronic alcohol consumption remains the leading cause of cirrhosis in developed countries, viral hepatitis is more prevalent in developing countries, including Türkiye (1). In our study group, the majority of the cases were attributed to HBV and HCV, whereas alcohol-related cirrhosis accounted for only 12.2%, highlighting the regional etiological differences. The most commonly observed symptoms of HE include attention deficits, psychomotor slowing, ataxia, and amnesia (12). In our study, nearly all patients presented with ataxia, amnesia, and attention deficits. Additionally, restlessness, asterixis, sleep disturbances, behavioral changes, tremor, and coordination disorders were frequently reported. The high prevalence and severity of these clinical manifestations likely reflect the advanced stage of liver dysfunction in this study. Our results showed significantly higher MELD scores, INR, and bilirubin levels, and significantly lower albumin

Table 1. Child-Pugh scoring

Variables	A	B	C
HE (stage)	None	1-2	3-4
Ascites	No	No-Mild	Medium-Advanced
T.Bil (mg/dl)	<2	2-3	>3
Albumin (mg/dl)	>3.5	2.8-3.5	<2.8
INR or PT	<1.7	1.7-2.3	>2.3
	<14	14-17	>17

HE: hepatic encephalopathy, T.Bil: total bilirubin, INR: international normalized ratio, PT: prothrombin time, stage A: 5-6, stage B:7-9, and stage C:10-15 points

Table 2. Age, gender, vital signs, etiology, Child-Pugh score, and HE staging of the patients (n=49)

Age (year), median (min-max)	57 (46-85)
Gender, n (%)	
Male	32 (65.3)
Female	17 (34.7)
SBP (mmHg), median (min-max)	120 (70-175)
DBP (mmHg), median (min-max)	70 (40-95)
Body Temp (°C), median (min-max)	36.3 (35-38)
Heart Rate (bpm), median (min-max)	80 (56-114)
Etiology, n (%)	
HCV	23 (46.9)
HBV	4 (8.2)
Cryptogenic	16 (32.7)
Alcohol	6 (12.2)
Child-Pugh Stage, n (%)	
A	0 (0.0)
B	28 (57.1)
C	21 (42.9)
HE Stage, n (%)	
I	21 (42.9)
II	13 (26.5)
III	8 (16.3)
IV	7 (14.3)

HE: hepatic encephalopathy, SBP: systolic blood pressure, DBP: diastolic blood pressure, HCV: hepatitis C virus, HBV: hepatitis B virus

Table 3. Frequency of encephalopathy symptoms (n=49)

Symptom	n (%)
Attention deficit	49 (100)
Sleep disturbance	49 (100)
Conduct disorder	49 (100)
Coordination disorder	49 (100)
Asterixis	49 (100)
Tremor	49 (100)
Restlessness	49 (100)
Ataxia	46 (93.9)
Amnesia	40 (81.6)
Confusion	39 (79.6)
Apraxia	20 (40.8)
Lethargy	15 (30.6)
Nystagmus	15 (30.6)
Clonus	12 (24.5)
Rigidity	8 (16.3)
Stupor	8 (16.3)
Coma	7 (14.3)

Table 4. Comparison of laboratory values, MELD score, and GCS of the patients according to the Child-Pugh stages

	Stage B (n=28)	Stage C (n=21)	p
AST (U/L)	41.5 (11-227)	81.7 (26-372)	**0.021**
ALT (U/L)	20.5 (8.4-123)	42 (9.2-279)	0.060
INR	1.43 (1.20-1.87)	2 (1.24-3.71)	**<0.001**
Albumin (mg/dL)	2.94 (1.82-3.54)	2.29 (1.40-3.52)	**0.001**
T.Bil (mg/dL)	1.85 (0.47-4.98)	4.6 (1.44-27)	**<0.001**
D.Bil (mg/dL)	0.75 (0.16-1.92)	2.28 (0.65-26)	**<0.001**
GCS	15 (10-15)	14 (5-15)	0.151
MELD score	14 (9-26)	22 (13-36)	**<0.001**

MELD: models for end-stage liver disease, GCS: Glasgow coma scale, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, T.Bil: total bilirubin, D.Bil: direct bilirubin

levels in Child-Pugh class C patients compared to class B patients. These findings are consistent with previous studies demonstrating that prolonged prothrombin time, elevated bilirubin, and reduced albumin levels are associated with poor prognosis in cirrhotic patients (13-15). A study conducted in India involving 183 patients with end-stage liver disease identified high bilirubin, low albumin, elevated creatinine, and INR as independent predictors of 90-day mortality; moreover, MELD and Child-Pugh scores were emphasized as reliable prognostic indicators (16). Similarly, Rahimi et al. (17), in a study involving 1,218 cirrhotic patients, reported that bilirubin and INR levels were significantly higher and albumin levels significantly lower in patients with altered mental status. Our study corroborates these observations, as Child-Pugh class C patients demonstrated higher bilirubin and INR levels and lower albumin levels compared to class B patients, despite being limited to HE patients with advanced liver failure. The reported prevalence of HE in cirrhotic patients ranges from 12% to 60%, depending on the inclusion of minimal or overt HE (18). Pun et al. (18) described the distribution as 25% grade 0, 22% grade I, 19% grade II, 23% grade III, and 11% grade IV. In a study of 160 pediatric patients with chronic liver disease, HE grades were reported as 26.2% grade I, 37.7% grade II, 18% grade III, and 18% grade IV (19). Another study involving 389 cirrhotic patients reported an overt HE prevalence of 57.5%, with grade II being the most frequent (20). Although our study only included overt HE cases, the distribution of HE grades aligns with these prior reports. The MELD score remains a widely accepted and objective tool for predicting mortality risk in patients with end-stage liver disease; higher scores indicate worse prognosis (21-23). In parallel, serum albumin level, which reflects hepatic synthetic capacity, is also a critical prognostic marker (8). Reduced albumin levels not only indicate poor hepatic function but also have been associated with unfavorable outcomes and have driven studies on albumin replacement therapies in cirrhosis (23-25). Bustamante et al. (26) reported that elevated bilirubin, low albumin, advanced HE (grade III-IV), and Child-Pugh class C were all significantly associated with poor prognosis. Similarly, Zipprich et al. (27), in a large cohort of 729 cirrhotic patients, demonstrated strong correlations between albumin and bilirubin levels and Child-Pugh and MELD scores.

Our findings are in agreement with these studies and underscore the importance of comprehensive assessment using MELD and Child-Pugh scores, in conjunction with key laboratory parameters such as INR, bilirubin, and albumin levels. This integrated evaluation is critical for accurately predicting outcomes and guiding clinical management in HE patients with advanced liver disease.

CONCLUSION

This study demonstrated that as the Child-Pugh classification worsens, HE patients exhibit significant increases in INR and bilirubin levels and a notable decrease in albumin levels. Correspondingly, MELD scores were also significantly higher in Child-Pugh class C patients. The combination of elevated INR, bilirubin, and MELD scores and reduced albumin levels was strongly associated with poor prognosis in HE patients.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (28.09.2012, 2012/98).

Conflict of Interest: This manuscript was derived from the specialty thesis of the first author, Yahya Şahin, and all authors declare that there is no conflict of interest.

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