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Predictive ability of Liver-Fatty Acid Binding Protein for all-cause mortality in patients with hepatic encephalopathy: A prospective observational study

Liver-Fatty Acid Binding Proteinin hepatic ensefalopatili hastalarda mortalite öngörme kabiliyeti: Bir prospektif gözlemsel çalışma

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Abstract

Purpose: We investigated the ability of serum and urine Liver-Fatty Acid Binding Protein levels to predict mortality in patients with hepatic encephalopathy and/or compensated cirrhosis.

Materials and methods: We enrolled 48 patients with cirrhosis (19 hepatic encephalopathy, 29 compensated cirrhosis) and 20 control individuals. Serum and urine Liver-Fatty Acid Binding Protein levels were determined. Patients were prospectively followed for three months.

Results: Cox regression analyses showed that urine liver- fatty acid binding protein levels, Model for End-Stage Liver Disease-Sodium scores, and Child-Turcot-Pugh scores were independent predictors of mortality. Receiver operating characteristic curve analyses showed that serum levels of liver- fatty acid binding protein (>8057.5 ng/L), urine liver-fatty acid binding protein (>9892.5 ng/L), and ammonia (>65.5 µg/dL), as well as the Model for End-Stage Liver Disease-Sodium (>21.5) and Child-Turcot-Pugh (>10.5) scores, predict mortality in patients with hepatic encephalopathy. Similarly, the areas under the curve for serum liver-fatty acid binding protein (AUC, 0.701), urine liver- fatty acid binding protein (0.692), and serum ammonia (0.898) levels, as well as Model for End-Stage Liver Disease-Sodium (0.934) and Child-Turcot-Pugh (0.966) scores predicted mortality in patients with hepatic encephalopathy.

Conclusion: Liver-Fatty Acid Binding Protein levels predict mortality in patients with hepatic encephalopathy.

Key words: Liver-Fatty Acid Binding Protein, hepatic encephalopathy, cirrhosis, mortality

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Özet

Amaç: Hepatik ensefalopati ve/veya kompanze sirozu olan hastalarda serum ve idrar Liver- Fatty Acid Binding Protein seviyelerinin mortaliteyi öngörme kabiliyetini araştırdık.

Gereç ve yöntem: Bu çalışmaya 48 siroz hastası (19 hepatik ensefalopati, 29 kompanze siroz) ve kontrol grubuna ise 20 kişi dahil edildi. Serum ve idrar Liver-Fatty Acid Binding Protein seviyeleri ölçüldü. Hastalar prospektif olarak üç ay takip edildi.

Bulgular: Cox regresyon analizi, idrar Liver-Fatty Acid Binding Protein seviyeleri, Model for End-Stage Liver Disease-Sodium skoru, and Child-Turcot-Pugh skoru mortalitenin bağımsız belirleyicileri olduğunu gösterdi. "Receiver operating characteristic curve" analizleri, serum liver-fatty acid binding protein (>8057.5 ng/L), idrar liver- fatty acid binding protein (>9892.5 ng/L), and serum amonyak seviyeleri (>65.5 µg/dL), Model for End-Stage Liver Disease-Sodium (>21.5) ve Child-Turcot-Pugh (>10.5) skorları hepatic ensefalopatii hastalarda mortaliteyi öngördüğü gösterildi. Benzer olarak, eğri altında kalan alana bakıldığında, serum liver-fatty acid binding protein (AUC, 0.701), idrar liver- fatty acid binding protein (0.692), and serum amonyak (0.898) seviyeleri, ek olarak

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Model for End-Stage Liver Disease-Sodium (0.934) ve Child-Turcot-Pugh (0.966) skorları hepatic ensefalopatili hastalarda mortaliteyi öngördüğü gösterildi.
Sonuç: Liver-Fatty Acid Binding Protein seviyeleri hepatic ensefalopatili hastalarda mortaliteyi predikte eder.

Anahtar sözcükler: Liver-Fatty Acid Binding Protein, hepatic ensefalopati, siroz, mortalite

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Introduction

Hepatic encephalopathy (HE) is a serious complication of cirrhosis that also leads to increased socioeconomic burden, morbidity, and mortality [1]. HE shows variable clinical findings that include mental or/and motor dysfunction in patients with decompensated cirrhosis [2]. In patients with cirrhosis, HE is associated with short survival. The expected survival of these patients, after liver transplantation, is lower than that for other liver transplant patients. The development of HE in patients with cirrhosis negatively impacts survival. A previous study showed that HE in patients with cirrhosis is associated with 1- and 3-year survival probabilities of 42% and 23%, respectively [3]. Another study suggested a 30% mortality rate if overt HE occurs in patients with end-stage liver disease [4].

Fatty acid protein binding proteins (FABPs) are a family of 15-kDa cytoplasmic proteins that are involved in the intracellular transport of long-chain fatty acids [5, 6], and have tissue-specific expression profiles. L-FABP occurs mainly in the liver, but is also present, in small quantities, in the kidney and small intestine [7, 8].

Serum and urine L-FABP levels were recently demonstrated to predict acute kidney injury, liver injury, and mortality [9, 10]. Previous studies showed that the prognostic markers associated with HE were age; elevated levels of serum bilirubin, alkaline phosphatase, potassium, blood urea nitrogen, and creatinine; elevated international normalized ratios (INR) and prothrombin activity; high Child-Turcot-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores; and decreased levels of serum albumin and sodium [11, 12]. However, there is no literature suggesting L-FABP as a prognostic marker of mortality in patients with HE.

This study investigated the ability of serum and urine L-FABP levels to predict all-cause mortality in patients with HE with cirrhosis and compensated cirrhosis relative to control individuals without neurologic, psychiatric, or liver disease diagnoses.

Patients and Methods

Study Design

The study was a prospective observational cohort study, approved by our local Ethics Committee. All patients, or a first-degree relative, and control individuals signed informed consent forms. The exclusion criteria included the presence of malignancy, hepatocellular carcinoma (HCC), an active cerebrovascular event, shock, trauma, active infection, inflammatory disease, renal disease, use of nephrotoxic drugs and/or diuretics, intoxication, metabolic disorders, brain disorders, psychiatric diseases, and use of sedatives or psychiatric drugs. Between March 2012 and March 2013, consecutive patients with HE and compensated cirrhosis, admitted to the gastroenterology polyclinic without demonstrating any of the exclusion criteria, were enrolled into this study. We recorded all mortalities and their causes. We also determined the 3-month mortality for all participants; for discharged patients, mortality determinations were determined by telephone calls to family. The endpoint of the study was to investigate the ability of serum and urine L-FABP levels to predict short-term all-cause mortality in patients with HE.

Participants

This study involved three groups of patients. Group 1 comprised the control individuals who were consecutively enrolled upon presentation to the check- up polyclinic. Group 2 comprised patients with compensated cirrhosis. These

patients were diagnosed with cirrhosis resulting from different causes. They did not have serious cirrhosis complications, such as HE, hepatorenal syndrome, bleeding varices, or hepatopulmonary syndrome. Group 3 patients had overt HE as well as being diagnosed with cirrhosis. HE grades were evaluated according to the West Haven Criteria for Semiquantitative Grading of Mental State. Grade 1 HE involves a trivial lack of awareness, euphoria or anxiety, a shortened attention span, and impaired performance of addition. Grade 2 patients demonstrate lethargy or apathy, minimal time or place disorientation, subtle personality changes, inappropriate behavior, and impaired performance of subtraction, Grade 3 HE describes patients in a state of somnolence to semi-stupor, but who are responsive to verbal stimuli, and who demonstrate confusion and gross disorientation, Grade 4 HE patients are comatose (unresponsive to verbal or noxious stimuli) [2].

Each patient underwent an ultrasonographic evaluation to determine ascites severity (mild, moderate, or severe). Mild ascites (grade 1) is only detectable by ultrasound examination, moderate (grade 2) ascites is manifest by moderate symmetrical distension of the abdomen, and severe (grade 3) ascites is characterized by marked abdominal distension [13].

Clinicodemographic data and collection of blood samples

Blood and urine samples were provided for analysis by all of the individuals in the three groups. Each patient determined to be suitable for inclusion in the study underwent a physical examination, and detailed medical histories were recorded. Serum and urine L-FABP levels were analysed from samples collected at baseline.

Serum and urine samples samples were centrifuged (1000×g), at 4°C, for 15 min, and stored at -80°C until analysis. Blood and urine samples were analysed using the Human L-FABP enzyme-linked immunosorbent assay kit (L-FABP, E91566Hu, USCN Life Science, Houston, TX, USA). Samples (100 µL) of serum or urine were added to microtitre plate wells, coated with a monoclonal antibody against human L-FABP, and incubated for 1 h at 37° C. After removing the liquid, each well was incubated with a 100-µL aliquot of biotinylated monoclonal antibody and incubated for 1 h at 37° C. The solution was removed by aspiration and the wells were washed 3 times, followed by the addition of 100 µL of avidin-conjugated horse radish peroxidase and incubation for 1 h at 37° C. After aspirating the liquid and washing the wells 5 times, 100 µL of tetramethylbenzidine substrate was added to the wells to allow for color development, in a dark room. After developing for 10–30 min, the wells were read using a plate reader (Benchmark Plus, BioRad, Hercules, CA, USA) at 450 nm.

Statistical analysis

Data analyses were performed using SPSS for Windows, version SPSS 11.5. The descriptive statistics are shown as means ± standard deviations (SDs) for continuous variables or as numbers and percentages for categorical data. Between-group statistical significance was determined using one-way analysis of variance. The differences in non-normally distributed data (between the compensated cirrhosis and HE groups) were compared using the Mann-Whitney *U*-test; the Kruskal-Wallis test was applied for comparisons among more than two independent groups. When statistically significant p-values were obtained in one-way analysis of variance or Kruskal-Wallis test, post-hoc tests were performed using Tukey's honest significant difference test or Conover's multiple comparison test to determine where the significant difference occurred. Categorical data were analyzed using Pearson's chi-square test. Degrees of association between continuous variables were evaluated using Spearman's rank correlation analysis. Receiver operating characteristic (ROC) curve analyses were performed to determine the sensitivity and specificity of cut-off values for the serum and urinary L-FABP levels, ammonia level, CTP score, and MELD-sodium (MELD-NA) score predicting mortality. Diagnostic performance (i.e., sensitivity, specificity, and positive and negative predictive values) for each clinical measurement were also calculated.

Overall survival time was defined as the time between study entry and death or loss of contact. Based on serum and urine L-FABP categorical variables (above and below 8057.5 for serum L-FABP, above and below 9892.5 for

urine L-FABP), estimated survival times were calculated for each variable using the Kaplan–Meier and log-rank tests. Whether serum or urine L-FABP levels were significantly related to overall survival was evaluated using multiple Cox proportional hazards regression analyses, after adjusting for several potential risk factors. Relative risks, 95% confidence intervals, and Wald statistics were also calculated for each independent variable. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 48 patients with cirrhosis (19 with HE, 29 with compensated cirrhosis) and 20 control individuals were enrolled in this study.

Baseline demographic and clinical features are shown in Table 1. The underlying etiologies for liver disease included hepatitis B (11 patients, 22.9%), hepatitis C (7, 14.5%), primary biliary cirrhosis (2, 4.1%), and cryptogenic cirrhosis (28, 58.3%). The encephalopathy grades were 3 (18 patients with HE) and 4 (1 patient with HE). The ascites severity (grade) was significantly higher in patients with HE than in those with compensated cirrhosis (p=0.010). There was no statistically significant difference between groups in terms of gender (p=0.173).

Patients with HE had significantly higher serum L-FABP levels than control individuals had (p<0.001, Table 1). There was a statistically significant difference between the groups in terms of median serum L-FABP levels (p<0.001). Serum L-FABP levels were higher in patients with HE or compensated cirrhosis than in control individuals (both, p<0.001).

Urine L-FABP levels in patients with HE were higher than in control individuals (p<0.001). Figure 1 shows the levels of serum and urine L-FABP in the three groups.

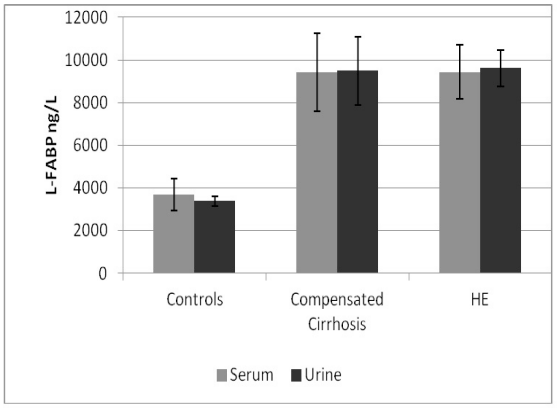


Figure 1. Serum and urine liver fatty acid binding protein levels. The mean level for the control group is compared to the levels for the groups comprised of patients with compensated cirrhosis (p<0.05) and hepatic encephalopathy (HE, p<0.001).

Correlations

Serum and urine L-FABP levels in the three groups showed significant positive correlations with serum ammonia levels. Serum and urine L-FABP levels in the groups showed significant positive correlations with serum creatinine levels. There was a significant positive correlation between both serum and urine L-FABP levels and INR. There was a significant negative correlation between serum and urine L-FABP levels and hemoglobin levels. There was no significant correlation between serum and urine L-FABP levels and the MELD-Na and CTP scores. The results of the correlation analyses are shown in Table 2.

All-cause mortality

In total, 11 patients (22.9%) died during the 3-month follow-up period. Eight patients died during hospitalization, and 3 died after discharge; all 11 were patients with HE. The mortality rate was much higher in patients with HE than in patients with stable cirrhosis (p<0.001).

Among the included patients, there were no statistically significant differences between survivors and nonsurvivors in terms of age or gender, respectively (Table 3).

As shown in Table 3, the mean serum L-FABP level in surviving patients was

Table 1. Demographic features and laboratory parameters. Patients with HE had significantly higher serum L-FABP levels than did control individuals (p<0.001).

	Controls (n=20)	Stable Cirrhosis (n=29)	HE (n=19)	p-value
Age (years)	42.7±16.9[a,b]	63.0±12.9[a]	65.3±14.0[b]	**<0.001**†
Female factor*	12 (60.0%)	10 (34.5%)	7 (36.8%)	0.173‡
HB (g/dL)	14.0±1.1[a,b]	10.2±1.7[a,c]	9.1±1.6[b,c]	**<0.001**†
PLT x10³ (/mm³)	268 ±52[a,b]	92.6± 65[a]	58±32[b]	**<0.001**$
INR	1.0 ±0.1[a,b]	1.5 ±1.2[a,c]	2.1 ±1.5[b,c]	**<0.001**$
AST (U/L)	15±5.5[a,b]	47±28.5[a]	67 ±60[b]	**<0.001**$
ALT (U/L)	14.5 ±9[a,b]	29±19[a]	44±36[b]	**<0.001**$
Total Bilirubin (mg/dL)	0.7±0.2[a,b]	1.7 ±0.5[a,c]	3.9±1.1[b,c]	**<0.001**$
Albumin (g/dL)	3.9±0.2[a,b]	3.1 ±1.3[a,c]	2.6 ±1.4[b,c]	**<0.001**$
Creatinine (mg/dL)	0.6±0.2[a,b]	0.8±0.4[a,c]	1.2±0.5[b,c]	**<0.001**$
Aside grade *				**0.010¶**
0	-	26 (89.7%)	11 (57.9%)	
1	-	2 (6.9%)	4 (21.1%)	
2	-	1 (3.4%)	4 (21.1%)	
MELD-Na score	-	13±8	24±15	**<0.001¶**
CTP score	-	7 ±3	11±3	**<0.001¶**
Serum L-FABP	3672±982.5[a,b]	9715±2462.5[a]	9410±1355[b]	**<0.001**$
Urine L-FABP	3391.5±312.5[a,b]	9350±854[a]	9896 ±1108[b]	**<0.001**$
Follow-up time (days)	90±0[a]	90±0[c]	13±10[a,c]	**<0.001**$

*n (%), †One-Way ANOVA, ‡ Pearson's Chi-square test, ¶ Mann Whitney U test, $ Kruskal Wallis test, a: Control vs Stable Cirrhosis (p<0.05), b: Control vs HE (p<0.001), c: Stable Cirrhosis vs HE (p<0.05).
HB: Haemoglobin, PLT: Platelet, INR: International ratio, AST: Aspartat aminotranspherase, ALT: Alanine aminotranspherase, MELD-Na: Model for end-stage liver disease- sodium, CTP: Child-Turcot-Pugh, L-FABP: Liver fatty acid binding protein

Table 2. The results of correlation analyses. There was no significant correlation between serum and urine L-FABP levels and the MELD-Na and CTP scores.

	Serum L-FABP		Urine L-FABP	
	r	P	r	P
Haemoglobin	-0.571	**<0.001**	-0.548	**<0.001**
INR	0.621	**<0.001**	0.694	**<0.001**
Total Bilirubin	0.372	**0.002**	0.409	**<0.001**
Albumin	-0.608	<0.001	-0.674	**<0.001**
Creatinine	0.429	**<0.001**	0.290	**0.016**
Ammonia	0.471	**<0.001**	0.030	**<0.001**
MELD-Na score	-0.085	0.566	0.036	**0.807**
CTP score	-0.058	0.696	0.078	**0.600**

† Spearaman's rank correlation test.

Table 3. The results of univariate Cox's proportional hazards regression analyses. There was a significant difference in the mean serum ammonia level between patients who did and did not die. Similarly, there were significant differences between these groups with repsect to their CTP and MELD-Na scores (both, p<0.001).

	Survivors (n=37)	Non-survivors (n=11)	p-value †	RR (95% CI)
Age (years)	57.1±17.8	60.8±14.9	0.520	1.012 (0.976-1.048)
Female factor*	12 (32.4)	5 (45.5)	0.824	1.145 (0.349-3.752)
PLT x10^3	141±65	52.8±21	**0.005**	0.999990 (0.999980-0.999999)
INR	1.4±0.7	2.4±1.3	**0.038**	1.920 (1.419-2.599)
Total Bilirubin (mg/dL)	1.0±0.8	4.8 ±3.7	0.283	1.016 (0.987-1.045)
Albumin (g/dL)	3.4±1.2	2.6± 0.5	**0.004**	0.240 (0.091-0.632)
Creatinine (mg/dL)	0.8±0.5	1.5±1.2	**<0.001**	1.872 (1.455-2.409)
Ammonia (µg/dl)	44.5±37	102±42	**<0.001**	1.034 (1.017-1.052)
Ammonia>65.5(µg/dl)*	10 (27%)	11 (100%)	0.067	162.767 (0.706-37509.340)
MELD-Na score	14±8	26±12	**<0.001**	1.165 (1.090-1.245)
MELD-Na>21.5*	3 (8.1%)	10 (90.9%)	**<0.001**	47.650 (6.018-377.263)
CTP score	7±3	12±3	**<0.001**	2.771 (1.731-4.435)
CTP>10.5**	1 (2.7%)	10 (90.9%)	**<0.001**	75.361 (9.377-605.658)
Serum L-FABP	9715±2065	9840±1210	**0.043**	1.0003 (1.00001-1.0005)
Serum L-FABP >8057.5*	18 (48.6%)	10 (90.9)	**0.040**	8.642 (1.106-67.544)
Urine L-FABP	9045±1254	9895±985	**0.044**	1.0002 (1.00001-1.0004)
Urine L-FABP >9892.5*	8 (21.6)	7 (63.6)	**0.007**	5.399 (1.578-18.475)

* n (%), † Univariate Cox's proportional hazards regression analysis, RR: Relative risk, CI: Confidence interval.

9384.6±1723.4 ng/L and was 9554.1±1238.8 ng/L in those who did not survive. There was no statistically significant difference between patients who survived or died in terms of serum L-FABP levels.

Similarly, there was no significant difference in urine L-FABP levels between patients who survived or died during the 3-month follow-up (Table 3).

There was a significant difference in the mean serum ammonia level between patients who did and did not die. Similarly, there were significant differences between these groups with repsect to their CTP and MELD-Na scores (both, *p*<0.001) (Table 3).

Multivariable Cox regression analyses showed that urine L-FABP (*p*=0.034), serum creatinine (*p*=0.050), and MELD-Na scores (*p*=0.002) independently predict mortality. Multivariable Cox regression models determined the best predictors of mortality, based on overall survival (Table 4).

Patients with serum L-FABP levels>8057.5 ng/L survived for a shorter period than those with serum L-FABP levels<8057.5 ng/L (Figure 2, log-rank test).

ROC analysis

The cut-off values for the serum L-FABP level (AUC=0.701), urine L-FABP level (0.692), serum ammonia level (0.898), MELD-Na score (0.934), and CTP score (0.966) that predict the risk of all-cause mortality were determined using an ROC curve analysis (Table 5). The ROC curve plots for serum and urine L-FABP levels are shown in Figure 3.

Discussion

This study showed that serum and urine L-FABP levels are significantly higher in patients

Table 4. Multiple Cox's proportional hazards regression models determining the best predictor(s) affect on overall survival. Multivariable Cox regression analyses showed that urine L-FABP (p=0.034), serum creatinine (p=0.050), and MELD-Na scores (p=0.002) independently predict mortality.

	B	SE	Exp (B)	95% CI	Wald	p-value
Model 1						
Serum L-FABP >8057.5	1.374	1.082	3.950	0.473-32.953	1.611	0.204
Urine L-FABP >9892.5	0.622	0.667	1.863	0.504-6.889	0.870	0.351
CTP>10.5	4.238	1.075	69.264	8.422-569.635	15.540	**<0.001**
Model 2						
Serum L-FABP >8057.5	1.604	1.061	4.974	0.622-39.790	2.286	0.131
Urine L-FABP >9892.5	1.084	0.641	2.957	0.842-10.382	2.862	0.091
MELD-Na>21.5	3.949	1.061	51.887	6.479-415.516	13.841	**<0.001**
Model 3						
CTP>10.5	4.421	1.151	83.158	8.716-793.416	14.756	**<0.001**
PLT	0.000	0.000	1.000	1.000-1.000	2.146	0.143
INR	0.457	0.212	1.580	1.043-2.392	4.669	**0.031**
Serum L-FABP >8057.5	1.566	1.118	4.788	0.536-42.807	1.963	0.161
Model 4						
CTP>10.5	4.414	1.160	82.633	8.507-802.644	14.483	**<0.001**
PLT	0.000	0.000	1.000	1.000-1.000	2.898	0.089
INR	0.351	0.200	1.420	0.960-2.101	3.089	0.079
Urine L-FABP >9892.5	0.243	0.701	1.275	0.322-5.040	0.120	0.729
Model 5						
MELD-Na>21.5	3.696	1.118	40.269	4.505-359.947	10.935	**<0.001**
ALB	-0.531	0.715	0.588	0.145-2.388	0.552	0.458
CRE	0.126	0.158	1.134	0.832-1.546	0.632	0.427
Serum L-FABP >8057.5	1.389	1.163	4.009	0.410-39.197	1.425	0.233
Model 6						
MELD-Na>21.5	3.555	1.138	35.000	3.759-325.898	9.754	**0.002**
ALB	0.327	0.629	1.386	0.404-4.757	0.270	0.604
CRE	0.371	0.189	1.450	1.001-2.100	3.855	**0.050**
Urine L-FABP >9892.5	1.851	0.873	6.363	1.149-35.243	4.490	**0.034**

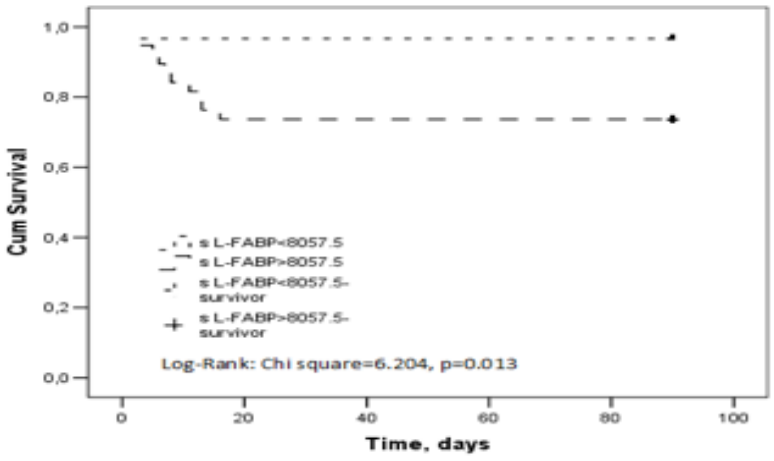
B: Coefficient of regression, SE: Standard error, Exp (B): Relative risk, CI: Confidence interval.

Table 5. Comparison of ROC curves among MELD-Na scores, CTP scores, ammonia, serum L-FABP and urine L-FABP in prediction of mortality. The cut-off values for the serum L-FABP level (AUC = 0.701), urine L-FABP level (0.692), serum ammonia level (0.898), MELD-Na score (0.934), and CTP score (0.966) that predict the risk of all-cause mortality were determined using an ROC curve analysis.

	Cut-off	AUC (95% CI)	p	Sens.%	Spec.%	PPV	NPV
MELD-Na *	>21.5	0.934(0.863-1.000)	**<0.001**	90.9%	91.9%	76.9%	97.1%
CTP *	>10.5	0.966(0.914-1.000)	**<0.001**	90.9%	97.3%	90.9%	97.3%
Ammonia	>65.5	0.898(0.821-0.975)	**<0.001**	100%	73.2%	42.3%	100%
Serum L-FABP	>8057.5	0.701(0.572-0.830)	**0.036**	90.9%	50.9%	26.3%	96.7%
Urine L-FABP	>9892.5	0.692(0.546-0.839)	**0.045**	63.6%	78.9%	36.8%	91.8%

AUC: Area under the curve, CI: Confidence interval, Se: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, * Upper bound of 95% CI is higher than 1.000.

A



B

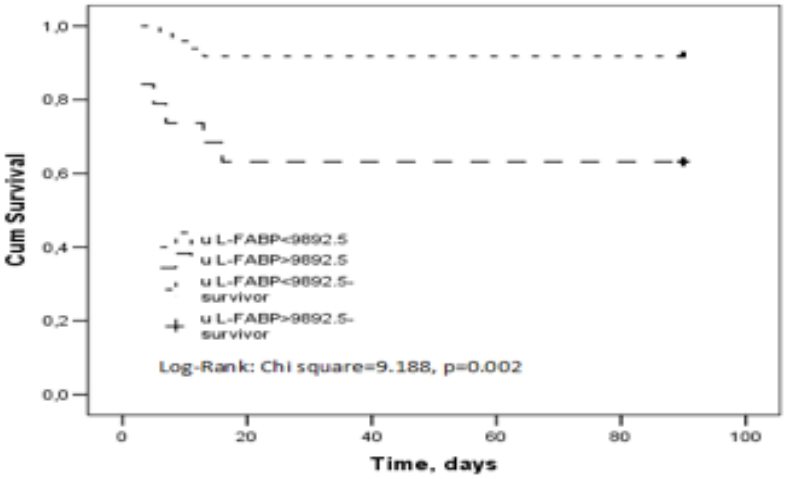


Figure 2. Kaplan-Meier survival curves showing survival times for survivors and nonsurvivors having fatty acid binding protein (L-FABP) levels above and belove the cut-off values for serum (A) and urine (B) L-FABP. Patients with serum L-FABP levels >8057.5 survived for a shorter period than did those with serum L-FABP levels <8057.5.

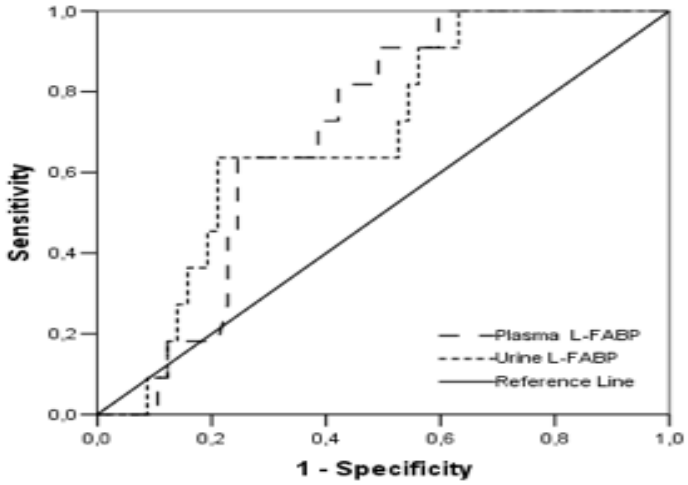


Figure 3. Receiver operating characteristic curves for serum and urine L-FABP in the prediction of survival. ROC curve analysis showed that the cut-off values for the serum L-FABP level (AUC = 0.701), urine L-FABP level (0.692) could predict the risk of all-cause mortality in patients with hepatic encephalopathy.

with HE than in patients with compensated cirrhosis and control individuals.

A previous study showed that MELD scores were correlated with poor prognoses in patients with HE [14]. Another study showed that MELD scores predicted 3-month mortality rates in patients with acute-on-chronic hepatitis B liver failure [15]. The MELD-Na score was a prognostic indicator of 30- and 90-day mortality in patients with end-stage liver disease, following the creation of transjugular intrahepatic portosystemic shunts [16].

Prothrombin time, serum bilirubin levels, use of vasopressors, HE, and systemic inflammatory response syndrome have been suggested to be strongly correlated with the 3-month prognosis for patients with cirrhosis [17]. Bilirubin levels and INRs were significantly associated with transplant-free survival in patients with acute liver failure [18]. Another study showed that the presence of hepatorenal syndrome, MELD scores, CTP scores, and serum creatinine and potassium levels were significant predictors of all-cause mortality in patients with cirrhosis [19].

Previous studies suggested that HE is significantly associated with mortality and post-liver transplantation survival [20-22]. One study showed that acute kidney injury, septic shock, and MELD-Na scores were significantly correlated with 50-day in-hospital mortality rates in patients with decompensated cirrhosis and spontaneous bacterial peritonitis [23].

To date, some studies have been published describing the relationship between L-FABP levels and patient mortality. One showed that urine L-FABP levels predicted mortality in 5-year-old children with sepsis [24]. Another suggested that urine L-FABP levels predicted mortality in patients with acute kidney injuries [25]. A third study showed that urine L-FABP levels were associated with all-cause mortality in women with HIV infections [26]. Serum and intestinal L-FABP levels in patients dying due to sepsis were also shown to be higher than in patients surviving sepsis [27]. Finally, another study suggested that urine L-FABP levels are independent predictors of 90-day mortality in patients in intensive care units [28].

However, no published study has shown a relationship between serum and urine L-FABP levels and mortality in patients with HE. Two studies reported on FABP levels and mortality rates in patients with cirrhosis. One showed that MELD scores, Child-Pugh scores, presence of ascites, serum interleukin-6 levels, and intestinal FABP levels were predictors of infection-free survival in patients with cirrhosis [29]. The other suggested that urine L-FABP levels were markers of acute kidney injury, and predicted mortality in patients with cirrhosis [30].

MELD, MELD-Na, and CTP scores have been shown to predict mortality in patients with cirrhosis and HE. We investigated the ability of serum and urine L-FABP levels to predict the 3-month mortality of patients with HE. Serum L-FABP levels > 8057.5 ng/L, in patients with HE, correlated with all-cause-mortality. A ROC analysis showed that areas under the curve and plots of the levels of serum L-FABP (AUC, 0.701; level, 8057.5 ng/L), urine L-FABP (0.692, 9892.5 ng/L), ammonia (0.898, 65.5 μg/dL), and of the MELD-Na (0.934, 21.5) and CTP (0.966, 10.5) scores predicted 3-month mortality in patients with HE. The serum L- FABP level showed a 90.9% sensitivity and 50.9% specificity for predicting mortality. The positive and negative predictive values for serum L- FABP levels predicting mortality were 26.3% and 96.7%, respectively.

Serum and urine L-FABP levels correlated with the INR, total bilirubin, creatinine, and albumin values, but did not correlate with the MELD-Na and CTP scores. The reason for this interesting issue may be associated with the proportional calculation of the MELD-Na scores. These results may suggest that L-FABP levels should predict mortality in patients demonstrating kidney injury and/or severe inflammation, such as sepsis. In such cases, L-FABP levels may be poor predictors of mortality in the absence of kidney injury and/or inflammation in patients with compensated cirrhosis and/or HE. Previous studies have also suggested that L-FABP levels are predictive of mortality in patients with kidney injury and/or severe inflammation, such as sepsis. Otherwise, the small numbers of patients in our study (a study limitation) may have caused these results.

Neither the serum or urine L-FABP levels were significantly different between surviving and dying patients. This may be because the patients who died were only those in the HE group. L-FABP levels should predict mortality in

patients with cirrhosis, not only in those with HE. Cox multivariate regression analyses showed that urine L-FABP levels, MELD-Na scores, and CTP scores were independent predictors of all-cause mortality in patients with HE. These results suggested that urine L-FABP levels may be more important than serum L-FABP levels for predicting mortality in patients with HE. Urine L-FABP levels should be more predictive than serum L-FABP levels for predicting mortality in patients with HE because urine L-FABP levels should correlate with tubulointerstitial damage and progression.

There were some limitations in our study. First, the number of patients in our study was small and reduced the statistical power of the study. Second, the follow-up period may need to be longer to allow mortality predictions in patients with compensated cirrhosis. The only patients who died, in our study, were in the HE group. Third, there was a broad age range for individuals in the control group and there was a statistical difference between the control group and the other groups relative to age. This was due to the control group including consecutive volunteers during check-ups at the polyclinic. The age difference should be considered to possibly impact L-FABP levels.

There is no study about serum/ urine L-FABP levels and mortality in patients with hepatic encephalopathy. Despite of some limitations, our study showed that urine L-FABP independently predict mortality in patients with hepatic encephalopathy. In addition, larger studies, with longer follow-up times, are needed to clarify the ability of serum and urine L-FABP levels to predict mortality in patients with compensated cirrhosis and/or HE.

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