# Prognostic Utility of Hypokalemia in Cirrhotic Patients

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## Abstract

***Background and Aim :*** **We researched the relationships between serum potassium level and prognostic scores and complications of cirrhosis, and mortality.**

***Methods :*** **This study was performed retrospectively in Turkish High Specialty Training and Research Hospital between 2009 and 2015. Patients who had missing patient files and electrolyte disorder for another reason, showed complications at the time of application and were using diuretics were excluded from the study.**

***Results :*** **218 patients were included in the study. During the follow-up period, 23.4% (n: 51) of the entire population passed away. Compared to the patients who survived, the patients who passed away had higher HCC and HES development rate, mean Child-Pugh and MELD score and lower mean blood potassium level. The stepwise multivariable Cox regression model which included significant independent predictors showed that Child-Pugh score (HR: 1.29; p< 0.001), MELD score (HR:1.13; p= 0.006), and potassium level (HR: 0.18; p< 0.001) were independent predictors of mortality. The cut off value for potassium level in predicting mortality was found to be ≤ 3.4 mmol/L with 80.4% sensitivity and 100% specificity. Compared to the patients with a potassium level > 3.4 mmol/L, the patients with a potassium level ≤ 3.4 mmol/L had higher mortality rate, HCC and HES development rate, mean Child-Pugh and mean MELD scores.**

***Conclusion :*** **Hypokalemia is an important prognostic factor in cirrhotic patients.** (Acta gastroenterol. belg., **2018**, 81, **398-403**).

**Key words :** Child-Pugh, MELD, hyponatremia

## Introduction

Cirrhosis is a chronic disease characterized by progressive hepatic fibrosis resulting from hepatic structure and formation of regeneration nodules. Although it usually develops on the basis of chronic ethyl intake and hepatitis, many factors are blamed in its etiology (1). It causes high morbidity and mortality due to progressive hepatic failure and complications. It is the 14th most common cause of death in the world and kills more than one million people annually (2). Therefore, identifying its prognosis is significant for early liver transplant and aggressive treatment. Child-Pugh and modified end stage liver disease (MELD) scorings are frequently used to this end (3).

Some studies suggest that blood electrolyte levels may be used as mortality and prognosis markers in cirrhotic patients. Low blood sodium level in particular was found to be an independent risk factor for poor prognosis in cirrhotic patients (4). The MELD-Na score was developed in addition to the MELD score in the light of this finding and accepted as the gold standard for evaluation of the need for liver transplant (5-8). After the use of hyponatremia as an important marker of mortality and need for liver transplant in cirrhotic cases, researchers began focusing on correlations of other electrolytes with prognosis, need for liver transplant, and cirrhosis complications. Although the number of studies on this subject is limited, one study showed that hypokalemia considerably prolonged hospitalization time in patients with hepatic encephalopathy (9). However, to the best of our knowledge, there is no study in the literature on relationships between serum potassium level and prognostic scores of cirrhosis, complications associated with cirrhosis, and mortality.

For this reason, the aim of this study was to research the relationship of hypokalemia with prognostic scores (Child-Pugh, MELD), complications associated with cirrhosis (hepatic encephalopathy, hepatocellular carcinoma), and mortality in 218 cirrhotic patients.

## Material and Methods

This study was performed retrospectively by examining the files of patients who had applied to the Liver Transplant Polyclinics of Turkish High Specialty Training and Research Hospital. Patients who had applied to the polyclinics between 1 January 2009 and 31 December 2015 were incorporated into the study.

Patients who were under the age of 18, had missing patient files, showed complications such as hepatic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma, or spontaneous bacterial peritonitis and patients who were using diuretics at the time of application, had severe cardiac insufficiency, electrolyte disorder for another reason, and nephrotic syndrome were excluded from the study.

Newly diagnosed cirrhotic patients were included and cirrhosis diagnosis was made through a combination of clinical findings, laboratory examinations, imaging

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Submission date : 06/09/2017
Acceptance date : 23/02/2018

methods, and histological examinations. Hemoglobin, white bloodcell count (WBC), blood platelet, international normalized ratio (INR), albumin, creatinine, sodium, and potassium values of the patients at the time of application were obtained from patient files. Child-Pugh and MELD scores at the time of application were calculated. Follow up scores, potassium levels and kalium supplementation during folow up were not included in our study. Only complication reviews were performed for the patients included in the study through 6-month follow-up examinations. Patients underwent abdominal ultrasonography, routine blood values including alpha-fetoprotein were studied and detailed history was taken. Those who were subject to follow-up for less than six months were excluded from the study. The maximum follow-up period was limited to 84 months.

Patients who had onset of disorientation or asterixis according to HESA score suggested by 'The International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus' and thus hospitalized were noted (10). Magnetic resonance imaging was performed on patients who were suspected to have hepatocellular carcinoma (HCC) during the follow-up and those who had typical arterial hypervascularity and venous wash out and were diagnosed with HCC were noted (11). Any mortality among the patients during the follow-up period was recorded using the national databases.

The present study was designed in accordance with 2013 Brazil version of the Helsinki Declaration and approved by the Ethics Board and Research Committee of our hospital.

**Statistical analysis**

Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, USA) was used for statistical assessments. The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Values with normal distribution were presented as mean ± standard deviation and values without normal distribution were presented as median (min-max). Categorical variables were presented as numbers and percentages. Independent samples t-test (for numeric variables with normal distribution) and Mann Whitney U test (for numeric variables without normal distribution) were used to determine differential risk factors between two groups. Chi-square test and Fisher's exact Chi-square test were used to compare categorical data. The relation between potassium level and laboratory findings was examined with Pearson and Spearman's correlation analysis. Stepwise multivariable cox regression analysis was used to determine independent predictors of mortality. Receiver operating characteristic (ROC) curve was used to examine diagnostic odds of potassium levels. Predictive values were calculated with the Youden index. In statistical analysis, $p< 0.05$ was considered to be statistically significant.

**Results**

*Study population*

A total of 218 patients, 147 males (67.4%) and 71 females (32.6%), were included in the study. The mean age of the population was 50.0 ± 11.7 years. The most common etiological cause was viral hepatitis (58%). The mean Child-Pugh score of the patients was 6.5 ± 1.6 (range: 5-12) and the mean MELD score was 11.8 ± 3.3 (range: 6-21). The follow-up time varied from 6 months to 84 months and the median follow-up time was 60 months. During the follow-up period, HCC developed in 6.4% (*n*: 14) and HES developed in 15.1% (*n*: 33) of the patients and 23.4% (*n*: 51) of the entire population passed away.

Considering laboratory findings, the mean hemoglobin value was 12.5 ± 2.4 g/dL, the median white bloodcell count was 4300 x10^3/uL (range : 300-12300), the median platelet value was 86.5 x10^3/uL (range : 12-570), the mean INR was 1.3 (range : 0.9-4.4), the mean blood sodium level was 139.6 ± 3.6 mmol/L, the mean creatinine was 0.8 ± 0.2 mg/dl, and the mean albumin level was 3.8 ± 0.7 g/dL.

*Possible Prognostic Factors Associated with Mortality*

Compared to the patients who survived, the patients who passed away had higher mean age, HCC and HES development rate, mean Child-Pugh score, mean MELD score and lower mean hemoglobin, mean blood sodium, and mean blood potassium level ($p< 0.05$) (Table 1).

As shown in Table 1, the stepwise multivariable Cox regression model which included significant independent predictors showed that Child-Pugh score (*HR*: 1.29; $p< 0.001$), MELD score (*HR*:1.13; $p= 0.006$), and potassium level (*HR*: 0.18; $p< 0.001$) were independent predictors of mortality. According to this finding, increased Child-Pugh and MELD scores and decreased potassium level indicate higher risk of mortality. A decrease of 1 unit (mmol/L) in potassium level increases the mortality risk by 5.56 (1/0.18) times (Table 2). The cut off value for potassium level in predicting mortality was found to be ≤ 3.4 mmol/L with 80.4% sensitivity and 100% specificity (Figure 1).

Potassium level was found to be negatively correlated with age ($r= -0.340$; $p< 0.001$), Child-Pugh score ($r= -0.391$; $p= 0.005$), and MELD score ($r= -0.393$; $p= 0.004$) and positively correlated with follow-up time ($r= 0.278$; $p< 0.001$) and albumin level ($r= 0.348$; $p< 0.001$). Compared to the patients with a potassium level > 3.4 mmol/L, the patients with a potassium level ≤ 3.4 mmol/L had higher mean age (55.3 ± 10.5 vs 48.2 ± 11.6; $p< 0.001$), mortality rate (100% vs 5.6%; $p< 0.00$), HCC and HES development rate (17.1% vs 4.01%; $p= 0.004$; 31.7% vs 11.3%; $p= 0.003$, respectively), mean Child-Pugh and mean MELD scores (7.2 ± 2.1 vs 6.3 ± 1.5; p= 0.001; 13.2 ± 3.7 vs 11.5 ± 3.4; $p= 0.006$, respectively),

Table 1. — **Possible prognostic factors associated with mortality**

| Variables | Mortality | | Univariable Cox Regression | | |
|---|---|---|---|---|---|
| | No n=112 | Yes n=36 | HR | 95% CI Lower-Upper | p |
| Age | 47,9±11,7 | 55,0±10,0 | 1,06 | 1,03-1,10 | 0,010* |
| Sex | | | | | |
| Female | 1(0,6) | - | ref | | |
| Male | 111(66,5) | 36(70,6) | 1,11 | 0,61-2,03 | 0,727 |
| HCC | | | | | |
| No | 162(97,0) | 42(82,4) | ref | | |
| Yes | 5(3,0) | 9(17,6) | 4,62 | 2,23-9,54 | <0,001* |
| HES | | | | | |
| No | 152(91,0) | 33(64,7) | ref | | |
| Yes | 15(9,0) | 18(35,3) | 3,35 | 1,88-5,95 | <0,001* |
| Child-Pugh Score | 6,2±1,4 | 7,4±2,1 | 1,30 | 1,14-1,48 | <0,001* |
| MELD Score | 11,4±3,5 | 13,2±3,5 | 1,11 | 1,03-1,20 | <0,001* |
| Hemoglobin | 12,7±2,4 | 12,0±2,2 | 0,89 | 0,79-0,99 | 0,045* |
| WBC | 4300(300-12300) | 4300(600-8300) | 1,00 | 0,98-1,02 | 0,863 |
| Platelets | 93(12-570) | 81(18-205) | 0,99 | 0,99-1,01 | 0,057 |
| INR | 1,3(0,9-4,4) | 1,5(1,1-2,3) | 0,99 | 0,63-1,59 | 0,997 |
| Sodium | 139,8±2,8 | 136,9±5,5 | 0,94 | 0,89-0,98 | 0,030* |
| Creatinine | 0,8±0,3 | 0,8±0,3 | 1,74 | 0,72-4,19 | 0,217 |
| Albumin | 3,9±0,6 | 3,4±0,7 | 0,46 | 0,34-0,64 | 0,463 |
| Potassium | 4,1±0,4 | 2,8±0,6 | 0,17 | 0,12-0,24 | <0,001* |

Categorical variables were presented as number (%).Values are presented in mean ±SD, median (min-max) or percentage. *p< 0.05 shows statistical significance. HR: Hazard ratio. CI: Confidence interval.
Abbreviations : HCC-Hepatocellular carcinoma, HES-Hepatic encephalopathy, MELD-Model for end-stage liver disease, WBC-White blood count, INR-International normalized ratio

Table 2. — **Independent predictors of mortality**

| Variables | HR | 95% CI Lower-Upper | p |
|---|---|---|---|
| Child-Pugh score | 1,29 | 1,14-1,48 | <0,001* |
| MELD score | 1,13 | 1,05-1,22 | 0,006* |
| Potassium | 0,18 | 0,13-0,28 | <0,001* |

*p< 0.05 shows statistical significance. HR : Hazard ratio; CI : Confidence interval
Abbreviations : MELD-Model for end-stage liver disease,

median INR level (1.4 vs 1.3; $p$= 0.044) and lower mean albumin level (3.4 ± 0.7 vs 3.8 ± 0.7; $p$< 0.001). No significant difference was found in terms of other demographic and laboratory findings ($p$> 0.05) (Table 4).

## *Discussion*

According to our literature review, this study is the first on hypokalemia's relationship with prognostic scores, HCC-HES development, and mortality in cirrhotic patients. The study showed that hypokalemia was an independent risk factor for mortality similar to Child-Pugh and MELD scores and a blood potassium level

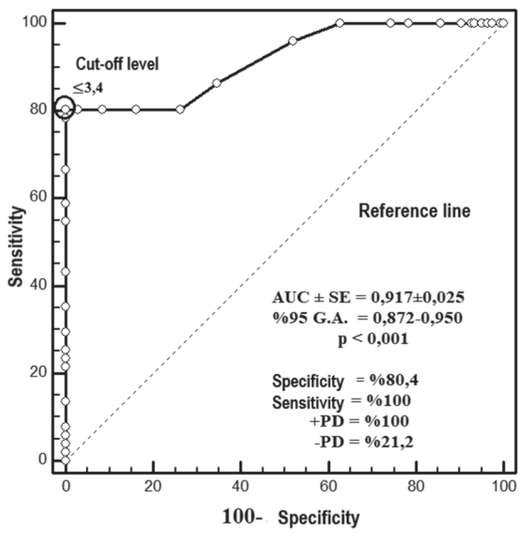


Figure 1. — Cut off value for potassium level in predicting mortality.

below 3.4 mmol/L was related with mortality, HES and HCC development rate, increased INR and creatinine levels, and decreased blood sodium and albumin levels.

Table 3. — **Potassium-related variables**

| Variables | POTASSIUM | |
|---|---|---|
| | r | p |
| Age | -0,340 | <0,001* |
| Child-Pugh score | -0,391 | 0,005* |
| MELD score | -0,393 | 0,004* |
| Follow-up time | 0,278 | <0,001* |
| Hemoglobin | 0,081 | 0,233 |
| WBC | 0,070 | 0,302 |
| Platelets | 0,213 | 0,102 |
| INR | -0,028 | 0,680 |
| Sodium | 0,120 | 0,078 |
| Creatinine | -0,083 | 0,224 |
| Albumin | 0,278 | <0,001* |

*p< 0.05 shows statistical significance.
Abbreviations: MELD- Model for end-stage liver disease, WBC-White blood count, INR-International normalized ratio

Table 4. — **Demographic and clinical findings associated with predicted cut-off potassium levels**

| Variables | Potassium | | p |
|---|---|---|---|
| | ≤3,4 n=41 | >3,4 n=177 | |
| Age | 55,3±10,5 | 48,2±11,6 | <0,001* |
| Sex | | | |
| Female | 10(24,4) | 61(34,5) | 0,268 |
| Male | 31(75,6) | 116(65,5) | |
| Mortality | | | |
| No | - | 167(94,4) | <0,001* |
| Yes | 41(100,0) | 10(5,6) | |
| HCC | | | |
| No | 34(82,9) | 170(96,0) | 0,006* |
| Yes | 7(17,1) | 7(4,0) | |
| HES | | | |
| No | 28(68,3) | 157(88,7) | 0,003* |
| Yes | 13(31,7) | 20(11,3) | |
| Child-Pugh score | 7,2±2,1 | 6,3±1,5 | 0,001* |
| MELD score | 13,2±3,7 | 11,5±3,4 | 0,006* |
| Hemoglobin | 12,1±2,1 | 12,6±2,4 | 0,215 |
| WBC | 4300(600-8300) | 4300(300-12300) | 0,992 |
| Platelets | 83(18-184) | 87(12-570) | 0,150 |
| INR | 1,4(1,1-2,3) | 1,3(0,9-4,4) | 0,044* |
| Sodium | 136,5±6 | 139,8±2,8 | 0,179 |
| Creatinine | 0,9±0,3 | 0,8±0,3 | 0,040* |
| Albumin | 3,4±0,7 | 3,8±0,7 | <0,001* |

Categorical variables were presented as number (%). Values are presented in mean ±SD, median (min-max) or percentage. *p< 0.05 shows statistical significance. HR : Hazard ratio; CI: Confidence interval
Abbreviations : HCC-Hepatocellular carcinoma, HES-Hepatic encephalopathy, MELD-Model for end-stage liver disease, WBC-White blood count, INR-International normalized ratio

It was found in this study that the patients who passed away had higher mean age, mean Child-Pugh and MELD scores, and HCC and HES development rates. Findings in the literature support our findings. Indeed, Peng *et al.* found Child-Pugh and MELD scores, widely used for determining cirrhosis stage and transplant need, to be significant markers of mortality (12). HCC, which is the second most common cancer-associated cause of death in the world and usually develops on the basis of cirrhosis, influences the mortality directly. Also, HES is one of the most common reasons of application to hospital among cirrhotic patients and elevates septic complications such as pneumonia, thereby increasing mortality (13).

Electrolyte disorders are frequently observed in cirrhotic patients due to increased diuretic use, impaired renal function, and splanchnic/systemic vasodilatation. Researchers focus on hyponatremia in particular. Ennaifer *et al.* found that serum sodium level below 130 mmol/L is correlated with mortality and prognostic scores (14). In this study which we conducted inspired by the prognostic significance of hyponatremia, we found a relationship between low blood sodium and potassium levels and mortality. The fact that the patients who passed away had considerably lower blood potassium levels, all of the patients with a potassium value below 3.4 mmol/L passed away, and the stepwise multivariable Cox regression model pointed to hypokalemia as an independent risk factor for mortality leads to the idea that hypokalemia may have clinical uses, similar to hyponatremia. The increase in mortality in hypokalemic patients may be a result of electrolyte disorder's aggravating conditions such as renal failure (15) or increased arrhythmia frequency due to hypokalemia. Gundling *et al.* reported that cardiac arrhythmia was commonly seen in cirrhotic patients and hypokalemia was one of the most significant precipitants causing cardiac arrhythmia (16). Another speculation which indicates a correlation between hypokalemia and mortality is that hypokalemia accelerates non-alcoholic steatohepatitis formation and liver fibrosis, thereby contributing to disease progression (17). Uslan *et al.* studied mortality markers in cirrhotic patients and, contrary to our findings, found that patients with higher serum potassium levels had higher mortality rates (18). This might be due to the fact that the sample of the study included patients with renal failure and hepatorenal syndrome only or potassium value over a certain threshold might have triggered cardiac depression, thereby increasing mortality.

Today, hypertonic solutions or drugs such as Tolvaptan are commonly used to prevent complications and mortality in cirrhotic patients with hyponatremia. We believe that using a more aggressive treatment for patients with hypokalemia at the time of application, adjusting diuretic use according to potassium level, and treating hypokalemia by replacement when necessary may be effective on prognosis. Based onthe results of our study, similar to hyponatremia, hypokalemia may be associatedwith mortality.

After the prognostic importance of hyponatremia in cirrhosis cases was demonstrated in numerous studies, the MELD-sodium score has become the gold standard in determination of liver transplant need. Similarly, we believe that a scoring such as MELD-potassium may be used for determination of cirrhosis prognosis and early transplant need. Because, a significant correlation was found between hypokalemia and MELD score in our study. Furthermore, blood potassium level was found to be correlated with INR, creatinine, and blood

sodium levels, which are used to calculated the MELD-sodium score. This supports the idea that hypokalemia and MELD-sodium score are correlated. Randomized controlled studies are necessary to support the thesis that the MELD-potassium score can be used for prognostic purposes in cirrhotic cases.

Albumin level, which shows liver synthesis functions, was found to be correlated with hypokalemia in our study. Also, albumin level was lower and INR level was higher in patients with a serum potassium level lower than 3.4 mmol/L. Considering that low albumin level aggravates spontaneous bacterial peritonitis and high INR aggravates complications such as variceal hemorrhage, hypokalemia's relationship with these parameters has prognostic significance. It is known that low albumin and platelet levels in laboratory examinations support cirrhosis diagnosis. The fact that hypokalemia is related with these laboratory parameters commonly used for cirrhosis diagnosis leads to the idea that hypokalemia may be used for diagnostic purposes. However, diuretic intake and other possible hypokalemia causes must be excluded for hypokalemia to have diagnostic value. For this reason, studies with larger samples are necessary.

A serum potassium level below 3.4 mmol/L was found to be correlated with HES development in our study. In one study conducted by Gaduputi *et al.*, hypokalemia was shown to prolong hospitalization time in patients with HES[9]. Devrejani *et al.* listed hypokalemia among factors that precipitate HES (19). Also, Rattanasupar *et al.* listed decreased hemoglobin, Child-Pugh score, and serum potassium level below 3.5 mmol/L among significant risk factors predicting HES risk in patients who applied to the hospital with variceal hemorrhage (20). All these studies show that hypokalemia may be important in prognosis of HES. Hypokalemia cut-off value was accepted to be 3.5-4 mmol/L in these studies. In our study, on the other hand, the cut off value for potassium level was found to be $\leq$ 3.4 mmol/L with 80.4% sensitivity and 100% specificity.

A serum potassium value below 3.4 mmol/L was found to be correlated with HCC development in our study. There is no evidence in the literature regarding hypokalemia's precipitating HCC development, but based on our data, we believe that more frequent follow-ups for patients with hypokalemia at the time of application due to HCC development risk and performing ultrasonography and AFP every three months instead of every six months would be more beneficial.

The most significant limitation of our study is its retrospective design. Also, the hypokalemia's relationship with spontaneous bacterial peritonitis and variceal hemorrhage, which are other major complications and important mortality causes in cirrhotic cases, was not explored in our study. The main reason behind this is the missing patient records and retrospective design of the study.

In conclusion, the present study showed that hypokalemia was an independent risk factor for mortality in cirrhotic patients similar to Child-Pugh and MELD scores and a blood potassium level below 3.4 mmol/L was related with mortality, HES and HCC development rate, increased INR and creatinine levels, and decreased blood sodium and albumin levels. Due to prognostic significance of hypokalemia, it is important to use an early and aggressive treatment for patients with hypokalemia at the time of application.

## Conflict of Interest

The authors declare there are no conflicts of interest.

## Funding

None

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