Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1523936

Anatolian Curr Med J. 2025;7(1):15-21

Evaluation of critical factors predicting the development of hepatorenal syndrome in hospitalized cirrhotic patients

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Cite this article as: Erdoğan Ç, Karpuzcu HC. Evaluation of critical factors predicting the development of hepatorenal syndrome in hospitalized cirrhotic patients. *Anatolian Curr Med J.* 2025;7(1):15-21.

Received: 30.07.2024 • **Accepted**: 02.12.2024 • **Published**: 10.01.2025

ABSTRACT

Aims: This study aimed to determine the factors predicting the development of hepatorenal syndrome (HRS) in cirrhotic patients presenting with acute kidney injury (AKI).

Methods: We retrospectively analyzed 263 cirrhotic patients diagnosed with AKI between September 2022 and March 2024. Demographic characteristics, clinical findings, and laboratory results were analyzed. We diagnosed HRS using the 2019 International Club of Ascites criteria. We used bivariate and multivariate logistic regression models in our statistical analysis.

Results: HRS developed in 31 patients (11.8%). MELD-Na scores were significantly higher in the HRS group (28 vs. 18, p<0.05). In multivariate analysis, independent predictors of HRS development were history of ascites (OR 5.8, 95% CI 2.6-13.0), serum creatinine >2.5 mg/dl (OR 2.5, 95% CI 1.2-5.5), albumin <2 g/dl (OR 3.9, 95% CI 1.1-13.5), bilirubin >2 mg/dl (OR 7.9, 95% CI 3.7-17.0), and presence of spontaneous bacterial peritonitis (OR 5.5, 95% CI 1.4-12.2). Hemodialysis requirement (61.3% vs. 8.6%, p<0.05) and mortality rates (45.2% vs. 6.0%, p<0.05) were significantly higher in the HRS group.

Conclusion: This study revealed important factors predicting the development of HRS in cirrhotic patients presenting with AKI. These findings may help clinicians to identify high-risk patients early and develop appropriate treatment strategies.

Keywords: Hepatorenal syndrome, risk factors, acute kidney injury, hospitalization, liver cirrhosis

INTRODUCTION

Hepatorenal syndrome (HRS) is a serious complication of advanced stages of cirrhosis characterized by both hepatic and renal failure and is a potential cause of acute kidney injury (AKI).[1] This syndrome is usually associated with portal hypertension due to causes such as cirrhosis, severe alcoholic hepatitis or, more rarely, metastatic tumors.[2] HRS represents the end-stage of reductions in renal perfusion as a result of progressive exacerbation of liver injury and is considered a diagnosis of exclusion.[3] The syndrome is usually associated with a poor prognosis.[4]

Systemic inflammation, increased splanchnic blood flow, decreased central volume, hypoperfusion, and excessive renal vasoconstriction, which play a role in the pathophysiology of HRS, result in a hyperdynamic state and a decrease in glomerular filtration rate.[1]

The incidence of AKI in cirrhotic patients hospitalized as a result of acute decompensation has been reported to be between 25-50%.[5] In cirrhotic patients with ascites, the 1-year incidence of HRS development ranged between 8% and 18%, while the 5-year incidence of HRS development was reported to be 39%.[6,7] In patients with cirrhosis and renal failure, the prevalence of HRS was reported to be 45.8%.[8] As can be understood, HRS is an important clinical problem seen frequently in patients with cirrhosis.

Well-known risk factors for the development of HRS include the presence of ascites, serum creatinine levels >2.5 mg/dl, low serum sodium concentration, albumin levels <3 g/dl, infections (especially spontaneous bacterial peritonitis, SBP), serum bilirubin level >2 mg/dl, high plasma renin activity, absence of hepatomegaly, fragility, alcoholic hepatitis, and bleeding[7,9-13]

Depending on the rate of decline in renal function, two types of HRS, HRS-AKI ("type 1" in the old classification) and non-AKI-HRS (NAKI, "type 2" in the old classification), have been defined.[14] HRS-AKI is a more severe form, characterized by a rapid increase in serum creatinine values and oliguria, whereas NAKI is characterized by a slower and less severe renal dysfunction. Currently, the criteria described in a revised consensus report published by the International Club of Ascites in 2019 are used in the diagnosis of HRS.[15] Clinically, HRS is characterized by a progressive increase in serum creatinine, usually normal urine sediment, minimal proteinuria, and a very low sodium excretion rate. The majority of patients are nonoliguric, and urine volume may exceed 400 ml per day in the early stages of the disease.

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HRS represents a significant challenge not only for the affected individuals but also for the healthcare system in general. The management of this condition results in a significant increase in healthcare expenditure due to the need for frequent hospitalization, the use of intensive care services, and the application of advanced treatment modalities. Furthermore, the development of HRS severely reduces the quality of life of patients and places a huge emotional and economic burden on their families. This can lead to psychological and financial distress for family members caring for the patient.

In this study, we aimed to determine the factors that predict the development of HRS, which is an important problem in the management of cirrhotic patients, and thus shed light on the development of strategies to be used in the management of high-risk patients.

METHODS

Study Design and Patient Population

The study was designed as a retrospective study. The study included cirrhotic patients aged 18 years or older who were admitted to the gastroenterology clinic of Ankara Etlik City Hospital between September 2022 and March 2024 with AKI or who developed AKI during their hospitalization. After excluding patients with missing data, the remaining patient files were included in the study. Data were collected from the hospital information management system and patient files, and the demographic characteristics, clinical findings, and laboratory results of the patients were analyzed in detail.

The inclusion criteria were as follows: a diagnosis of cirrhosis, The kidney disease: improving global outcomes (KDIGO) guidelines and being older than 18 years of age. Exclusion criteria were patients with a history of chronic kidney disease not related to cirrhosis, patients receiving renal replacement therapy before the diagnosis of AKI, and patients with incomplete medical records.

This study was approved by the Ethics Committee of Ankara Etlik City Hospital (Date: 24.04.2024, Decision No: AEŞH-BADEK-2024-320). The informed consent form prepared in accordance with the principles of the Declaration of Helsinki was signed by all participants. This process ensured that the study was conducted in accordance with ethical and legal requirements.

Data Collection and Evaluation

Since our study was retrospective in nature, patient data were collected retrospectively from hospital records. Using patient files and data obtained from the electronic medical record system, patients' demographic information, clinical findings, laboratory results and all medical data available from the time of admission were analyzed in detail. The records of 371 patients were analysed in total and 263 patients whose complete data were available were included in the study. Data collected included age, gender, body-mass index (BMI), blood pressure measurements, etiology of liver disease (hepatitis B, hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis and cryptogenic cirrhosis/other), MELD-Na score, presence of ascites, presence of SBP, presence of other infections and other clinical information.

Laboratory data include serum creatinine, albumin, bilirubin, sodium, hemoglobin, platelet and INR values. AKI was diagnosed according to KDIGO criteria. The diagnosis of HRS was made according to the criteria described in a revised consensus report published by the International Club of Ascites in 2019.

In this study, the diagnosis of portal hypertension was based on non-invasive methods and clinical features. The diagnostic criteria were the presence of splenomegaly on ultrasonography, gastroesophageal varices on endoscopic evaluation, visualisation of spontaneous portosystemic shunts and thrombocytopenia (<100 x $10^3/\mu L$) on laboratory tests. Abdominal ultrasonography findings were used in the study, especially to evaluate the presence of ascites, to detect splenomegaly and to support other findings of portal hypertension.

The clinical course and treatment responses of the patients were also obtained from the files and evaluated. These evaluations included important clinical outcomes such as hemodialysis requirement, HRS development and mortality rates.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means with standard deviations (SD), and categorical variables were expressed as frequencies and percentages. Comparisons between patients with HRS and those with other causes of AKI were conducted using independent sample t-tests for continuous variables and chi-square tests for categorical variables. Bivariate analysis was initially performed to identify potential predictors of HRS. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable. Variables found to be significant ($p<0.05$) in the bivariate analysis were subsequently included in a multivariate logistic regression model to determine independent predictors of HRS. The multivariate logistic regression analysis included variables such as history of ascites, serum creatinine >2.5 mg/dl, albumin <2 g/dl, bilirubin >2 mg/dl, and spontaneous bacterial peritonitis. Adjusted odds ratios (AOR) and 95% confidence intervals were reported for each predictor. Additionally, logistic regression analysis was used to further evaluate the OR and confidence intervals for various clinical and laboratory parameters associated with the risk of developing HRS. This analysis allowed us to assess the relative impact of these factors while controlling for potential confounders. Statistical significance was defined as a p-value less than 0.05. The results of the statistical analyses were used to identify and confirm the key factors predicting the development of HRS in cirrhosis patients with acute renal failure.

RESULTS

In this study, we analyzed data from 263 cirrhosis patients admitted with acute renal failure to identify factors predicting the development of HRS. Bivariate and multivariate analyses

were conducted to determine significant predictors. HRS was identified in 31 (11.8%) of the patients. According to the KDIGO criteria, AKI staging in this study was based on both serum creatinine levels and urine output measurements. For stage 1 AKI, which accounted for 55% of patients, urine output was maintained at an average of 0.4–0.5 ml/kg/h over a period of 6-12 hours, resulting in a total output of approximately 189-378 ml. For stage 2 AKI, comprising 23% of patients, the average urine output was around 0.3-0.4 ml/kg/h, sustained for more than 12 hours, yielding an estimated total of 294 ml. In stage 3 AKI, which included 17% of patients, urine output was reduced to approximately 0.1-0.2 ml/kg/h over 24 hours (or anuria for at least 12 hours), with a total urine output around 252 ml. Significant predictors of HRS included a history of ascites, elevated creatinine, low albumin, high bilirubin, and the presence of spontaneous bacterial peritonitis. The cohort had a mean age of 63.2 years (SD 13.1), with 64.3% being male. The primary etiologies of cirrhosis included Hepatitis B (33.6%), Hepatitis C (20.9%), and alcoholic liver disease (16.3%) (**Table 1**).

Table 1. Patient demographics and clinical characteristics

	Patients n=263
Age (years), (SD)	63.2 (±13.1)
Gender, male, n (%)	169 (±64.3)
BMI (kg/m²) (SD)	24.95 (±4.1)
Systolic blood pressure (SD)	119 (±24)
Diastolic blood pressure (SD)	63 (±13)
Etiology	
Hepatitis B, n (%)	88 (33.6)
Hepatitis C, n (%)	55 (20.9)
Alcoholic, n (%)	43 (16.3)
Non-alcoholic steatohepatitis, n (%)	36 (13.7)
Autoimmune hepatitis, n (%)	21 (7.9)
Cryptogenic/other, n (%)	20 (7.6)
KDIGO AKI stage	
Stage 1, n (%)	145 (55)
Stage 2, n (%)	61 (23)
Stage 3, n (%)	45 (17)
Unclassified, other, n (%)	12 (5)
MELD-Na score (SD)	20 (±8)
Ascites	
History of ascites, n (%)	118 (44.9)
Ascites on current admission, n (%)	126 (47.9)
Spontaneous bacterial peritonitis, n (%)	21 (7.9)
Other infection, n (%)	69 (26.2)
Portal hypertension, n (%)	164 (62.4)
Esophageal varices, n (%)	111 (42.2)
Hepatic encephalopathy, n (%)	105 (39.9)
Acute kidney injury etiology	
Pre-renal, n (%)	92 (34.9)
Hepato-renal syndrome, n (%)	31 (11.8)
Cardiac, n (%)	16 (6.1)
Other renal, n (%)	26 (9.9)
Hemoglobin (g/dl)	10.6 (±2.3)
Platelet (x1000)	128 (±94)
Na (meq/L)	132 (±11)
Creatinine (mg/dl)	2.3 (±1.7)
Albumin (g/dl)	3.0 (±0.7)
Bilirubin (mg/dl)	2.1 (±3.8)
INR	1.7 (±0.9)
Hemodialysis	39 (±14.9)
Hospital stays, days (SD)	16 (±9)
Mortality, n (%)	28 (10.6)

SD: Standard deviation, BMI: Body-mass index, MELD-Na: Model for end-stage liver disease-sodium, INR: International normalized ratio

Patients with HRS constituted 11.8% of the study population. These patients exhibited significantly higher MELD-Na scores (28 vs. 18, p<0.05) compared to those with other causes of AKI. HRS patients were more likely to have a history of ascites (74.2% vs. 40.9%, p<0.05) and to present with ascites on current admission (83.9% vs. 43.1%, p<0.05) (**Table 2**).

Key laboratory differences were noted between the HRS group and non-HRS group. HRS patients had lower hemoglobin levels (9.7 g/dl vs. 11.0 g/dl, p<0.05), lower platelet counts (109 x10^3 vs. 161 x10^3, p<0.05), and lower sodium levels (129 meq/L vs. 137 meq/L, p<0.05). Additionally, they exhibited higher serum creatinine (2.9 mg/dl vs. 2.0 mg/dl, p<0.05), higher bilirubin levels (3.8 mg/dl vs. 1.8 mg/dl, p<0.05), and higher INR (2.1 vs. 1.5, p<0.05). The presence of spontaneous bacterial peritonitis was significantly more common in the HRS group (38.7% vs. 3.9%, p<0.05). Hemodialysis was required in 61.3% of HRS patients compared to 8.6% of patients with other AKI causes (p<0.05). Mortality was notably higher in the HRS group (45.2% vs. 6.0%, p<0.05) (**Table 2**).

Bivariate analysis identified several factors associated with HRS, including alcoholic cirrhosis (OR 2.0, 95% CI 1.1–3.6, p<0.05), history of ascites (OR 5.7, 95% CI 2.9-10.9, p<0.05), and spontaneous bacterial peritonitis (OR 4.9, 95% CI 1.9-12.7, p<0.05). Other significant predictors included hemoglobin <11 g/dl (OR 2.6, 95% CI 1.4–5.0, p<0.05), platelets <150 x10^3 (OR 2.4, 95% CI 1.3–4.4, p<0.05), sodium <135 meq/L (OR 3.1, 95% CI 1.7-5.8, p<0.05), creatinine >2.5 mg/dL (OR 3.0, 95% CI 1.7–5.6, p<0.05), albumin <2 g/dL (OR 3.8, 95% CI 1.5–9.5, p<0.05), bilirubin >2 mg/dL (OR 9.5, 95% CI 5.1-17.7, p<0.05), and INR >1.5 (OR 5.6, 95% CI 2.9-11.1, p<0.05) (**Table 3**).

In multivariate analysis, independent predictors of HRS were identified. A history of ascites was a strong predictor (OR 5.8, 95% CI 2.6-13.0, p<0.05), as were serum creatinine >2.5 mg/dl (OR 2.5, 95% CI 1.2-5.5, p<0.05), albumin <2 g/dl (OR 3.9, 95% CI 1.1–13.5, p<0.05), bilirubin >2 mg/dl (OR 7.9, 95% CI 3.7-17.0, p<0.05), and spontaneous bacterial peritonitis (OR 5.5, 95% CI 1.4-12.2, p<0.05) (**Table 3**).

The logistic regression analysis further emphasized the significance of these predictors. Alcoholic liver disease (OR 4.62, 95% CI 2.0-10.68, p<0.05), ascites on current admission (OR 5.0, 95% CI 3.4-8.0, p<0.05), portal hypertension (OR 3.76, 95% CI 2.23-6.33, p<0.05), esophageal varices (OR 3.16, 95% CI 1.71–5.83, p<0.05), and spontaneous bacterial peritonitis (OR 14.77, 95% CI 5.89-37.06, p<0.05) were all strongly associated with an increased risk of developing HRS. The need for hemodialysis (OR 17.72, 95% CI 6.88-45.72, p<0.05) was also significantly higher among HRS patients, highlighting the severity of this condition (**Table 4**).

DISCUSSION

HRS is a common and serious complication in cirrhotic patients. The objective of this study was to identify the critical factors that predict the development of HRS in cirrhotic patients presenting with AKI. The results of our study

Table 2. Comparison of hepatorenal syndrome and other causes of acute kidney injury

	Hepatorenal syndrome n=31	Other causes of AKI n=232	p
Age (years), (SD)	61.7 (±9.7)	64.6 (±12.2)	0.191
Gender (male), n (%)	20 (64.5)	149 (64.2)	0.784
Etiology			
Hepatitis B, n (%)	9 (29.1)	79 (34.0)	0.145
Hepatitis C, n (%)	5 (16.1)	50 (21.5)	0.108
Alcoholic, n (%)	13 (41.9)	30 (11.4)	**<0.05**
Non-alcoholic steatohepatitis, n (%)	3 (9.7)	33 (14.2)	**0.02**
Autoimmune hepatitis, n (%)	1 (3.2)	20 (8.6)	**0.03**
Cryptogenic/other, n (%)	0	20 (8.6)	**<0.05**
MELD-Na score (SD)	28 (±7)	18 (±8)	<0.05
Ascites			
History of ascites, n (%)	23 (74.2)	95 (40.9)	**<0.05**
Ascites on current admission, n (%)	26 (83.9)	100 (43.1)	**<0.05**
Portal hypertension, n (%)	26 (83.9)	138 (59.5)	<0.05
Esophageal varices, n (%)	21 (67.7)	90 (38.8)	<0.05
Hepatic encephalopathy, n (%)	19 (61.3)	86 (37.1)	<0.05
Hemoglobin (g/dl)	9.7 (±1.9)	11.0 (±2.4)	<0.05
Platelet (x1000)	109 (±98)	161 (±101)	<0.05
Na (meq/L)	129 (±7)	137 (±8)	<0.05
Creatinine (mg/dl)	2.9 (±1.0)	2.0 (±0.8)	<0.05
Albumin (g/dl)	2.6 (±0.7)	3.4 (±0.8)	<0.05
Bilirubin (mg/dl)	3.8 (±2.2)	1.8 (±1.6)	<0.05
INR	2.1 (±0.9)	1.5 (±0.7)	<0.05
Spontaneous bacterial peritonitis, n (%)	12 (38.7)	9 (3.9)	<0.05
Other infection, n (%)	8 (25.8)	61 (26.2)	0.742
Hemodialysis	19 (61.3)	20 (8.6)	**<0.05**
Mortality, n (%)	14 (45.2)	14 (6.0)	<0.05

AKI: Acute kidney injury, SD: Standard deviation, MELD-Na: Model for end-stage liver disease-sodium, INR: International normalized ratio

Table 3. Bivariate and multivariate analysis of predictors for hepatorenal syndrome

Variable	Bivariate OR (95% CI)	Bivariate p-value	Multivariate OR (95% CI)	Multivariate p-value
Alcoholic cirrhosis	2.0 (1.1–3.6)	<0.05	1.2 (0.5–2.4)	0.678
History of ascites	5.7 (2.9–10.9)	<0.05	5.8 (2.6–13.0)	<0.05
History of hepatic encephalopathy	3.3 (1.8–6.0)	<0.05	1.5 (0.7–3.1)	0.256
Hb<11 g/dl	2.6 (1.4–5.0)	<0.05	1.7 (0.8–3.7)	0.160
Platelets<150 (x10^3)	2.4 (1.3–4.4)	<0.05	1.5 (0.7–3.2)	0.308
Sodium<135 meq/L	3.1 (1.7–5.8)	<0.05	2.2 (0.9–4.7)	0.053
Cr>2.5 mg/dl	3.0 (1.7–5.6)	<0.05	2.5 (1.2–5.5)	**<0.05**
Albumin<2 g/dl	3.8 (1.5–9.5–8.0)	<0.05	3.9 (1.1–13.5)	**<0.05**
Bilirubin>2 mg/dl	9.5 (5.1–17.7)	<0.05	7.9 (3.7–17.0)	**<0.05**
INR>1.5	5.6 (2.9–11.1)	<0.05	1.4 (0.3–5.8)	0.630
Spontaneous bacterial peritonitis	4.9 (1.9–12.7)	<0.05	5.5 (1.4–12.2)	<0.05

INR: International normalized ratio, OR: Odds ratio

indicate that a history of ascites, elevated creatinine levels, low albumin, elevated bilirubin values, and the presence of SBP are significant predictors of HRS. Furthermore, the MELD-Na scores of patients with HRS were significantly higher than those of patients with other causes of AKI. These findings are of critical importance in determining key clinical and laboratory parameters for the diagnosis and management of HRS.

Our secondary findings revealed notable differences in laboratory parameters between HRS patients and the control group. These included lower hemoglobin levels, lower platelet counts, and lower sodium levels. Moreover, the incidence of hemodialysis and mortality rates were markedly elevated in patients with HRS in comparison to those with other causes of AKI. In the bivariate analysis, several factors were identified as being associated with HRS, including alcoholic cirrhosis, a history of ascites, and SBP. The multivariate analysis confirmed the presence of ascites history, high serum creatinine, low albumin, high bilirubin, and SBP as independent predictors. These findings are critical for the identification and management of patients at risk for the development of HRS.

In the initial comprehensive observational study in the literature to investigate the risk factors associated with HRS, Gines et al.[7] examined 234 non-azotemic cirrhosis patients with ascites. Their findings indicated that a history of ascites and serum sodium concentration ≤133mEq/L were among the factors that increased the risk of developing HRS. The results

Table 4. Odds ratios and confidence intervals for predictors of hepatorenal syndrome

Variable	Odds ratio (OR)	95% CI (lower)	95% CI (upper)	p-value
Age (years)	0.97	0.94	1.01	0.191
Gender (male)	0.99	0.63	1.53	0.784
Alcoholic liver disease	4.62	2.0	10.68	0.0
Non-alcoholic steatohepatitis	0.43	0.12	1.51	0.02
Autoimmune hepatitis	0.35	0.04	2.99	0.03
MELD-Na score	1.17	1.08	1.33	0.0
History of ascites	4.0	2.5	6.5	0.0
Ascites on current admission	5.0	3.4	8.0	0.0
Portal hypertension	3.76	2.23	6.33	0.0
Esophageal varices	3.16	1.71	5.83	0.0
Hepatic encephalopathy	2.74	1.54	4.89	0.0
Hemoglobin (g/dl)	0.78	0.66	0.92	0.005
Platelet count (x1000)	0.67	0.56	0.79	0.0
Sodium (meq/L)	0.59	0.48	0.71	0.0
Creatinine (mg/dl)	2.45	1.22	4.91	0.0
Albumin (g/dl)	0.39	0.3	0.51	0.0
Bilirubin (mg/dl)	2.72	1.41	5.23	0.0
INR	1.67	1.12	2.48	0.005
Spontaneous bacterial peritonitis	14.77	5.89	37.06	0.0
Other infection	0.98	0.58	1.67	0.742
Hemodialysis	17.72	6.88	45.72	0.0

INR: İnternational normalized ratio

of our study yielded comparable findings. In the bivariate analysis, a serum sodium level of less than 135 mEq/L was identified as a significant predictor for the development of HRS, with an odds ratio of 3.1 (95% confidence interval 1.7-5.8, p<0.05). However, this association was found to be borderline significant in multivariate analysis (OR 2.2, 95% CI 0.9-4.7, p=0.053). This discrepancy indicates that serum sodium level ceased to be an independent predictor when we controlled for the effect of other variables. Gines et al.[7] reported that serum sodium level played an important role in the development of HRS. However, our multivariate analysis results demonstrate that serum sodium level alone is not a sufficient predictor of HRS risk and should be evaluated together with other factors.

In a retrospective study conducted by Sasso and colleagues,[9] 529 cirrhotic patients presenting with ascites were examined. The researchers identified that 9.8% of patients had HRS, and that a history of ascites, serum creatinine >2.5 mg/dl, albumin <3 g/dl, bilirubin >2 mg/dl, and SBP were independent factors predicting the development of HRS. Similarly, in our study, significant predictors for the development of HRS included a history of ascites (OR 5.8, 95% CI 2.6-13.0, p<0.05), elevated serum creatinine (OR 2.5, 95% CI 1.2–5.5, p<0.05), low albumin (OR 3.9, 95% CI 1.1-13.5, p<0.05), elevated bilirubin (OR 7.9, 95% CI 3.7-17.0, p<0.05), and the presence of SBP (OR 5.5, 95% CI 1.4-12.2, p<0.05). In both studies, history of ascites and SBP were found to be important predictors for the development of HRS. However, the fact that serum albumin level was found to be <3 g/dl in the study by Sasso et al.[9] and <2 g/dl in our study suggests that different thresholds for determining albumin level should be considered in clinical practice.

Alcoholic cirrhosis was defined as the most common etiology in the study by Sasso et al.[9] In our study, alcoholic cirrhosis was found to be an important factor for the development of HRS in bivariate analysis (OR 2.0, 95% CI 1.1-3.6, p<0.05), but it was not significant in multivariate analysis (OR 1.2, 95% CI 0.5-2.4, p=0.678). Alcohol is the most common cause of cirrhosis in Western societies and it may be misleading to consider it as a risk factor for HRS in a cirrhosis population with a high prevalence of alcoholic cirrhosis in general. In our study, we found that the development of HRS was observed at a significantly higher rate in patients with alcoholic cirrhosis etiology. The lack of a significant association between alcoholic liver disease and the development of HRS in multivariate analysis may be explained by the low rate of alcoholic cirrhosis in our study. In future studies, cohorts with a higher rate of alcoholic cirrhosis should be evaluated. This finding suggests that HRS is more common among patients with alcoholic cirrhosis in our study. Our multivariate analysis results show that the etiology of alcoholic cirrhosis alone is not sufficient to predict the risk of HRS and should be evaluated together with other factors. This finding suggests that further studies in different populations are necessary to further clarify the independent effect of alcoholic cirrhosis on HRS.

Active alcohol consumption can lead to hypovolemia, a major risk factor for AKI in cirrhosis. This is due to the diuretic effect of alcohol, which exacerbates fluid loss and reduces effective intravascular volume, leading to decreased renal perfusion.[16] Alcohol-induced liver injury may accelerate HRS and further compromise renal perfusion by worsening portal hypertension and systemic vasodilation.[17,18] Alcohol increases the production of reactive oxygen species and the systemic inflammatory response resulting from oxidative stress can lead to renal endothelial dysfunction and tubular damage.[19] In conclusion, active alcohol consumption is thought to be both a pathophysiologic and clinical risk factor for HRS in alcohol abusers. However, considering that the alcoholic cirrhosis patients in our study were mostly alcohol abstinent and waiting on the liver transplantation list, we may not have been able to show an independent association between alcohol

etiology and HRS in the multivariate analysis in our study. Therefore, further research by separating alcoholic cirrhosis patients with and without alcohol dependence will provide a better understanding of the effect of alcohol on the risk of HRS.

In an observational study conducted by Montoliu et al.[20] 263 cirrhotic patients were followed for approximately 41 (±3) months after the initial detection of ascites. During the follow-up period, 27.4% of patients developed pre-renal AKI, 14.1% developed infection-related AKI, and approximately 7.6% developed HRS; in total, nearly half of the patients (49%) experienced some form of functional renal failure. While the study by Montoliu et al.[20] focused on general risk factors for AKI, our study specifically examined risk factors for HRS. In both studies, serum creatinine level was identified as a significant predictor. In Montoliu et al.'s study, serum creatinine was found to be an independent predictor of functional renal failure. Similarly, in our study, elevated creatinine levels were found to be a significant predictor of HRS in both bivariate (OR 3.0, 95% CI 1.7-5.6, $p<0.05$) and multivariate analyses (OR 2.5, 95% CI 1.2-5.5, $p<0.05$). This finding indicates that creatinine level is a critical risk factor for the development of both overall AKI and HRS in cirrhotic patients.

In a phase-3 clinical study conducted by Curry et al.[21] it was observed that patients diagnosed with HRS type 1 who were undergoing terlipressin treatment exhibited a diminished response to the medication and experienced more unfavorable outcomes when their serum creatinine levels were elevated. The results of this study demonstrate that patients who receive treatment during the early stages of the disease tend to have more favorable outcomes. Our findings also highlight the role of serum creatinine levels as a key predictor in the development of HRS. These observations underscore the necessity of promptly identifying the risk of HRS and developing effective treatment strategies in clinical practice.

In a retrospective observational cohort study conducted by Janíčko et al. in decompensated cirrhotic patients (n=202), it was reported that serum sodium levels were significantly lower in patients who developed HRS. Additionally, bilirubin and MELD scores were identified as important predictors of HRS.[22] The findings of the Janíčko et al.[22] study bear notable resemblance to those of our own investigation. The results of both studies indicate that serum sodium and creatinine levels, as well as bilirubin and MELD scores, are significant predictors of the development of HRS. Given the sub-parameters included in the MELD-Na score (creatinine, bilirubin, INR, and sodium), it is unsurprising that a high MELD-Na score is associated with an increased risk of HRS. This risk factor has been demonstrated in our study. In our analysis, serum sodium level was a significant risk factor for HRS in the bivariate analysis (OR 3.1, $p<0.05$); however, in the multivariate analysis, it yielded a p-value of 0.053, suggesting it is not an independent predictor when adjusted for other variables. Nonetheless, the lower sodium levels observed in the HRS group may still be clinically relevant and warrant attention in patient management. The use of patient data from disparate populations indicates that caution should be exercised when generalizing the findings.

In a multicenter retrospective cohort study by Oliveira et al.[23] 139 patients with SBP were examined, and it was reported that type 1 HRS developed in 30% of the patients. Furthermore, multivariate analyses demonstrated that the development of HRS increased 30-day mortality in patients with SBP. In a prospective study by El Sharawy et al.[24] that included 121 cirrhosis patients with SBP, HRS was reported to develop in 24.8% of patients. In this study, high MELD-Na scores and high serum bilirubin values were identified as risk factors for the development of HRS in patients with SBP. The observation that HRS was identified with greater frequency in these studies conducted in a specific patient population with SBP in comparison to the general cirrhotic patient population lends support to the conclusion that SBP is an independent risk factor for HRS, as was determined in our study. These findings collectively indicate a robust correlation between SBP and the onset of severe renal dysfunction in patients with cirrhosis and portal hypertension.

A meta-analysis by Salerno et al.[25] encompassing four distinct controlled studies, demonstrated that albumin infusion therapy was associated with a reduced incidence of renal dysfunction in patients with SBP. These observations, derived from treatment approaches, provide indirect support for the identification of SBP and hypoalbuminemia as risk factors for HRS in our study.

In our study, patients with HRS exhibited significantly lower hemoglobin and platelet levels and higher INR levels compared to patients with other causes of AKI. However, bivariate and multivariate analyses demonstrated that these variables were not independent risk factors. Given that the presence of these parameters collectively reflects the findings of advanced portal hypertension, it can be concluded that they are not independent risk factors in and of themselves.

Limitations

The retrospective nature of the study and its single-center design represent the primary limitations of this investigation. In retrospective studies, there may be concerns about the complete collection of patient data. However, the advent of electronic patient files recorded through hospital information management systems has largely mitigated this issue, minimizing the potential for data loss due to human error. Additionally, the reliance on historical data limits our ability to control for certain confounding variables that may influence outcomes, such as treatment responses or socio-economic factors. Furthermore, the single-center design may restrict the generalizability of our findings to cirrhosis patients in other centers. Nevertheless, the inclusion of a substantial number of cirrhosis patients (263 patients) enhances the statistical power and reliability of our findings, providing a solid foundation for identifying predictors of HRS.

In terms of strengths, the study utilized the International Club of Ascites 2019 criteria for diagnosing HRS, ensuring consistency with current global standards. The large sample size and the comprehensive analysis of a wide range of clinical and laboratory parameters also enhance the validity of our

findings. Moreover, both bivariate and multivariate analyses were conducted, allowing for a robust identification of independent predictors. These factors collectively contribute to the scientific rigor and potential applicability of the results, offering valuable insights for the management of cirrhotic patients with AKI.

CONCLUSION

In conclusion, this study revealed important factors predicting the development of HRS in cirrhotic patients presenting with AKI. A history of ascites, high serum creatinine and bilirubin levels, low albumin levels and the presence of spontaneous bacterial peritonitis were found to be independent risk factors for the development of HRS. These findings may help clinicians to identify high-risk patients early and develop appropriate treatment strategies.

The results of this study emphasize the importance of early diagnosis and treatment of HRS. Further research should focus on the development of prognostic models that take these risk factors into account and the creation of new strategies for the prevention and management of HRS. This approach may contribute to reducing the morbidity and mortality associated with HRS in cirrhotic patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Ankara Etlik City Hospital (Date: 24.04.2024, Decision No: AEŞH-BADEK-2024-320).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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