Research Article

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Assessing hepatorenal syndrome diagnostic criteria

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Comparison of hepatorenal syndrome incidence and outcomes using previous and current diagnostic criteria in cirrhotic patients

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Abstract

Background and Aim: Hepatorenal syndrome (HRS) is a severe complication of liver cirrhosis with evolving diagnostic criteria. This study aimed to examine HRS prevalence, subtypes, and outcomes while comparing previous and current diagnostic criteria.

Materials and Methods: This is a retrospective observational clinical study conducted on hospitalized patients with decompensated cirrhosis. Demographic characteristics, comorbidities, disease duration, disease severity, length of hospitalization, number of rehospitalizations, cirrhosis etiologies, laboratory data, and clinical outcomes were reviewed. The criteria from 2007 by the International Club of Ascites were the previous ones, with the 2015 criteria being the current criteria for diagnosing HRS. The incidence of HRS and its subtypes was determined, and the clinical characteristics of patients with and without HRS were compared using the Mann-Whitney U test.

Results: The study enrolled 212 patients, with a male predominance (57.5%) and a mean age of 63.4±14.5 years. A total of 32.1% of patients developed acute kidney injury (AKI), with prerenal azotemia being the most common type (76.5%), followed by intrinsic renal AKI (23.5%). Under the current criteria, 27 patients (12.7%) received an HRS diagnosis, while under the previous criteria, 16 patients (7.5%) received an HRS diagnosis, and the difference in diagnostic frequencies was statistically significant (p=0.046). In HRS cases, the MELD score (p=0.001), being classified as Child-Pugh C (p=0.043), rehospitalization (p=0.011), requiring intensive care (p=0.001), and creatinine levels (p<0.001) were higher.

Conclusion: AKI is common in hospitalized cirrhotic patients. The current HRS criteria identify more cases that need close monitoring compared to the previous criteria.

Keywords: Acute kidney injury; cirrhosis; creatinine; hepatorenal syndrome; hospitalization; liver disease; MELD score; rehospitalization.

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Introduction

Renal dysfunction represents a severe complication that often occurs in advanced cirrhosis.[1] Traditionally, renal dysfunction in patients with liver disease has been defined by a serum creatinine (sCr) concentration of ≥1.5 mg/dL.[2,3] In addition to the well-recognized types of acute kidney injury (AKI) seen in the general population, cirrhotic patients can develop a specific form of renal dysfunction referred to as hepatorenal syndrome (HRS).[4]

Hepatorenal syndrome is defined as a type of renal dysfunction resulting from reduced renal blood flow due to hemodynamic changes in the arterial circulation and activation of the vasoactive endogenous system.[2,5] Traditionally, HRS has been categorized into two distinct clinical types: Type 1 HRS, characterized by a rapid decline in renal function, defined by either a doubling of the initial sCr to a level exceeding 2.5 mg/dL or a 50% reduction in the initial 24-hour sCr clearance to below 20 mL/min within a span of less than two weeks. Type 2 HRS, on the other hand, is marked by renal dysfunction that progresses less rapidly.

Several factors contribute to lower creatinine levels in cirrhosis, diminishing the effectiveness of sCr in identifying renal dysfunction and leading to an overestimation of renal function. Thus, it's widely recognized that sCr is an unreliable indicator of renal dysfunction in cirrhosis.[6] In recent years, changes have been proposed in the diagnostic criteria for AKI. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, AKI can now be defined by any of the following criteria: 1) an increase in sCr by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; 2) an increase in sCr to ≥1.5 times the baseline, known or presumed to have occurred within the preceding 7 days; or 3) urine volume <0.5 mL/kg/h for 6 hours.[7] In the most recent International Club of Ascites (ICA) consensus, the definition of AKI in cirrhosis was adjusted to align with KDIGO sCr criteria. This modification not only altered the diagnosis of HRS but was also aimed at simplifying nomenclature. Under the current definition based on the KDIGO guidelines, Type 1 HRS is now renamed hepatorenal syndrome-acute kidney injury (HRS-AKI), while Type 2 HRS (HRS-2) is reclassified as hepatorenal syndrome-non-acute kidney injury (HRS-NAKI).[8]

However, there is a lack of studies that assess the implementation of the current HRS criteria in patients with decompensated cirrhosis. This study aimed to investigate the occurrence of AKI in hospitalized cirrhosis patients and compare the frequency and outcomes of HRS based on both the current and previous criteria. Additionally, the study aimed to assess the clinical and laboratory characteristics associated with HRS.

Materials and Methods

In this single-center retrospective observational study, records of 467 patients aged 18 and above who were followed up at a gastroenterology inpatient clinic due to complications of cirrhosis were reviewed. Patients with a history of ascites and a minimum hospital stay of 48 hours were included in the study. The study did not include patients who had undergone liver transplantation, individuals with malignancies, pregnant individuals, or those with incomplete medical records.

Finally, 212 patients with cirrhosis were included in the study, and a total of 430 hospital admission records were examined. Ethical approval for the study was granted by the Istanbul Medeniyet University Clinical Research Ethics Committee on March 29, 2023 (Decision No: 2023/0215). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Clinical Assessment

The demographic characteristics, comorbidities, duration of cirrhosis, etiology of cirrhosis, severity of cirrhosis, number of readmissions, laboratory results, and clinical outcomes (discharge, intensive care requirement, mortality) of patients were reviewed.

For patients with multiple admissions, their records were evaluated based on the development of AKI during any admission; if AKI developed, the records of that admission were assessed, and if it did not develop, the records from the first admission were evaluated. The frequency of HRS was determined according to both previous and current diagnostic criteria. The clinical characteristics of patients diagnosed with HRS according to the current criteria were compared with those of patients who did not meet the criteria for HRS.

Definitions

The diagnosis of liver cirrhosis was established based on clinical evaluation, liver function tests, and imaging, regardless of whether a liver biopsy was performed or not.[9]

The assessment of liver cirrhosis severity was determined using the Child-Pugh and Model for End-Stage Liver Disease (MELD) 3.0 scores.[10,11]

ICA-AKI: An increase in sCr levels of ≥0.3 mg/dL within 48 hours or a 50% increase in sCr levels compared to the baseline.[12]

Exclusion criteria for HRS: The presence of shock, current or recent use of nephrotoxic agents, underlying parenchymal kidney disease, and a response to cessation of diuretics and volume expansion.

HRS Type 1: In a patient diagnosed with cirrhosis and ascites, the diagnosis is made when sCr levels double within a period of less than two weeks, reaching levels greater than 2.5 mg/dL from the baseline, and when exclusion criteria are not present.

HRS Type 2: The diagnosis is made when there is a gradual increase in sCr levels within the range of 1.5-2.5 mg/dL, accompanied by refractory ascites, and when exclusion criteria are not present.

HRS-AKI: (formerly known as HRS Type 1): The diagnosis is made in a patient with cirrhosis and ascites when the ICA-AKI criteria are met, and when exclusion criteria are not present.

HRS-NAKI: (formerly known as HRS Type 2): It has two subtypes:

HRS-Acute Kidney Disease: eGFR <60 mL/min per 1.73m² for <3 months in the absence of other (structural) causes or percent increase in SCr <50% using the last available value of outpatient SCr within three months as the baseline value.

Table 1. Demographic and clinical characteristics of patients

Characteristics	Value*
Age (years) (mean±SD)	63.4±14.5
Gender, Male	122 (57.5%)
Disease duration (years) (mean±SD)	2.4±4.1
Cirrhosis etiology	
Cryptogenic	54 (25.5%)
Hepatitis B	29 (13.7%)
Hepatitis C	24 (11.3%)
Alcohol	32 (15.1%)
Congestive hepatopathy	7 (3.3%)
NASH	49 (23.1%)
Other**	17 (8.0%)
Child-pugh class	
A	8 (3.8%)
B	117 (55.2%)
C	87 (41.0%)
MELD 3.0 Score (mean±SD)	20.2±6.9
Comorbidities	
Diabetes mellitus	76 (35.8%)
Hypertension	61 (28.8%)
Coronary artery disease	24 (11.3%)
Congestive heart failure	12 (5.7%)
Chronic kidney disease	23 (10.8%)
COPD	13 (6.1%)
Hospitalization duration (days) (mean±SD)	10.6±7.4
Number of readmissions (mean±SD)	2.0±1.8
Outcome	
Discharged	182 (85.8%)
Intensive care unit	19 (9.0%)
Exitus	3 (1.4%)
Transferred	8 (3.8%)

*: Values are provided as counts and percentages unless otherwise stated; **: Other includes other etiologies not specified in the table; SD: Standard deviation; NASH: Non-alcoholic steatohepatitis; MELD: Model for end-stage liver disease; COPD: Chronic obstructive pulmonary disease.

HRS-Chronic Kidney Disease: eGFR <60 mL/min per 1.73m² for ≥3 months in the absence of other (structural) causes.

Additionally, in 2019, Angeli et al.[13] established new diagnostic criteria for HRS-AKI, which included the criterion of urine output remaining below 0.5 mL/kg/hour for at least a 6-hour period and fractional sodium excretion being <0.2 (<0.1 highly predictive) as a diagnostic criterion for HRS-AKI.

Statistical Analysis

Descriptive statistical methods (mean, standard deviation, frequency, percentage) were employed to analyze the work data. The normality of the quantitative data was assessed using the Shapiro-Wilk test and graphical examinations. For quantitative variables showing a normal distribution, the t-test for the difference between two dependent proportions and the Student t-test were used for comparisons between two

Table 2. Baseline laboratory values of patients

Variable	Mean±SS
Glucose (mg/dL)	138.5±66.9
INR	1.7±0.5
Albumin (g/dL)	2.9±0.6
AST (U/L)	53.7±42.2
ALT (U/L)	33.3±47.8
Total bilirubin (mg/dL)	3.2±4.8
Direct bilirubin (mg/dL)	1.8±3.6
Na (mmol/L)	133.7±5.4
K (mmol/L)	4.4±0.8
Urea (mg/dL)	66.1±47.5
Creatinine-basal (mg/dL)	1.0±0.8
Creatinine-admission (mg/dL)	1.3±0.9
Creatinine-final (mg/dL)	1.2±0.8
GFR-basal (ml/min/1.73 m^2)	79.8±29.7
GFR-admission (ml/min/1.73 m^2)	70.3±34.9
GFR-final (ml/min/1.73 m^2)	74.2±32.9
WBC (10^3/uL)	7.7±4.7
Hemoglobin (g/dL)	10.0±2.5
Platelet (10^3/uL)	134.9±84.6

INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Na: Sodium; K: Potassium; GFR: Glomerular filtration rate; WBC: White blood cell.

groups, while the Mann-Whitney U test was used for comparisons between two groups for quantitative variables that did not exhibit a normal distribution. In comparing qualitative data, the Pearson Chi-Square test, Fisher's Exact test, and Fisher-Freeman-Halton test were utilized. A statistical significance level of $p<0.05$ was considered. The NCSS (Number Cruncher Statistical System) 2007 program (Kaysville, Utah, USA) was utilized for calculations.

Results

A total of 212 patients were included in the study. Of these, 57.5% (n=122) were male, and the mean age was 63.4±14.5 years. The average duration from diagnosis of cirrhosis to admission was 2.4±4.1 years, with an average hospitalization duration of 10.6±7.4 days. The mean MELD score was 20.2±6.9, mean sCr was 1.3±0.9 mg/dL, mean platelet count was 134.9±84.6 10^3/µL, and the mean INR was 1.7±0.5. According to the Child-Pugh classification, Class B was the most common (55.2%). The clinical and laboratory characteristics of all patients are detailed in Tables 1 and 2.

In 68 patients (32.1%), acute kidney injury (AKI) was observed either at admission (20 patients) or later (48 patients). Among these, 52 (76.5%) were classified as prerenal azotemia, and 16 (23.5%) were considered intrinsic renal AKI; no postrenal AKI was observed. According to the current criteria, 27 patients (12.7%) were diagnosed with HRS, while based on the previous criteria, 16 patients (7.5%) received an HRS diagnosis (p=0.046). It was observed that all 16 patients diagnosed with HRS according to the previous criteria also met the current criteria. The number of patients diagnosed with HRS and the distribution of subtypes were comparatively presented in Figure 1.

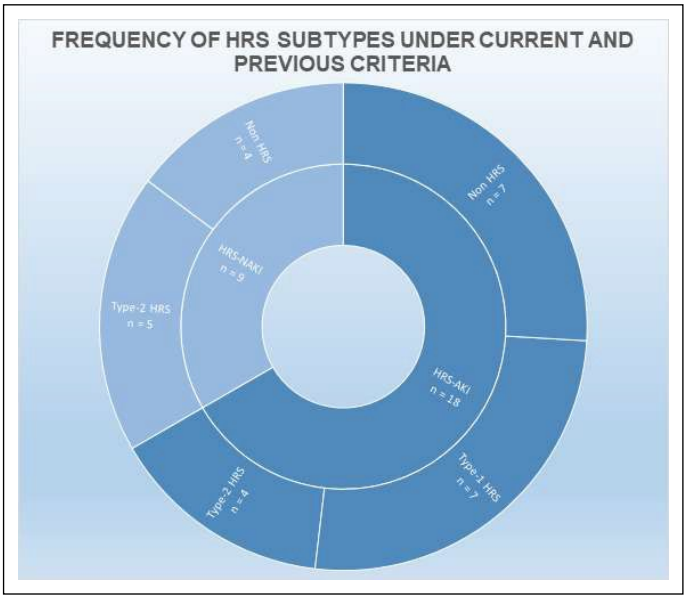

Figure 1. Comparison of the number of patients diagnosed with HRS and the distribution of subtypes based on both current (inner circle) and previous (outer circle) criteria.

HRS: Hepatorenal syndrome; HRS-AKI: Hepatorenal syndrome with acute kidney injury. HRS-NAKI: Hepatorenal syndrome without acute kidney injury; Non HRS: Patients without an HRS diagnosis.

Among the 16 patients diagnosed with HRS based on the previous criteria, the overall mortality rate was 43.8%, with rates of 42.9% for Type-1 HRS and 44.4% for Type-2 HRS. In the 27 patients diagnosed with HRS based on the current criteria, the overall mortality rate was 33.3%, with rates of 44.4% for HRS-AKI and 11.1% for HRS-NAKI. Among the 9 patients who were diagnosed with HRS according to the current criteria and died, 2 (22.2%) were not diagnosed with HRS according to the previous criteria (p=0.231) (Table 3). Patients diagnosed with HRS according to the current criteria had a higher frequency of Child-Pugh Class C (p=0.043), a MELD score of 3.0 (p=0.001), rehospitalization (p=0.011), ICU admission (p=0.001), and higher sCr levels (baseline, admission, and final values) compared to other cases (Table 4).

Discussion

In this study, we examined 430 hospital admissions of 212 cirrhotic patients admitted to a tertiary hospital for decompensated cirrhosis, revealing that approximately one-third of patients developed AKI, and 12.7% developed HRS. When the previous criteria were used, we found that 40.7% of patients with HRS (according to current criteria) were underdiagnosed.

To the best of our knowledge, this study is the first to compare the prevalence of HRS according to previous and current criteria in a specific patient group. Numerous studies in the literature have explored the etiology of AKI in hospitalized cirrhotic patients. In a prospective study conducted by Vaz et al.[14] in Brazil, 154 admissions of 75 patients with decompensated cirrhosis were examined. It was observed that 57.8% of these patients developed AKI. Prerenal azotemia was identified in 69.6% of cases, intrinsic renal AKI in 26.9%, and postrenal AKI in 3.3%. According to a review that included multiple studies conducted by Garcia-Tsao et al.,[15] in hospitalized cirrhotic patients, AKI is frequently observed with a prevalence of 19%. Among these patients, it was determined that 68% of them had prerenal azotemia. In our study,

Table 3. Comparing patient outcomes in hepatorenal syndrome based on previous and current criteria

	HRS (+) (previous criteria)	Type-1 HRS	Type-2 HRS	HRS(+) (current criteria)	HRS-AKI	HRS-NAKI	p
Mortality							0.231*
Alive	9 (56.3)	4 (57.1)	5 (55.6%)	18 (66.7)	10 (55.6)	8 (88.9)	
Exitus**	7 (43.8)	3 (42.9)	4 (44.4)	9(33.3)	8 (44.4%)	1 (11.1)	

HRS: Hepatorenal syndrome; HRS-AKI: Hepatorenal syndrome with acute kidney injury; HRS-NAKI: Hepatorenal syndrome without acute kidney injury; *: Fisher Freeman Halton Test; **: Only one patient died in the internal medicine clinic, while the other patients died in the ICU. Values are provided as counts and percentages.

Table 4. Comparing clinical and laboratory parameters in patients with and without hepatorenal syndrome

	HRS (+) (n=27)	HRS (-) (n=185)	p
Age (years) (mean±SD)	67.0±11.2	62.8±14.8	0.157
Gender (n,%)			0.823
Male	15 (55.6%)	107 (57.8%)	
Female	12 (44.4%)	78 (42.2%)	
Disease duration (years) (mean±SD)	3.2±4.9	2.2±4.0	0.199
Etiology of cirrhosis (n,%)			0.716
Cryptogenic	6 (22.2%)	48 (25.9%)	
Hepatitis B	3 (11.1%)	26 (14.1%)	
Hepatitis C	6 (22.2%)	18 (9.7%)	
Alcohol	4 (14.8%)	28 (15.1%)	
Congestive hepatopathy	0 (0%)	7 (3.8%)	
NASH	6 (22.2%)	43 (23.2%)	
Other*	2 (7.4%)	15 (8.1%)	
Child-pugh class (n,%)			**0.043**
A	0 (0%)	8 (4.3%)	
B	10 (37.0%)	107 (57.8%)	
C	17 (63.0%)	70 (37.8%)	
MELD 3.0 score (mean±SD)	26.5±6.4	19.3±6.5	**0.001**
Length of stay (days) (mean±SD)	12.8±7.9	10.3±7.3	0.075
Number of readmissions (mean±SD)	2.8±2.2	1.9±1.7	**0.011**
Creatinine (baseline) (mg/dL) (mean±SD)	1.2±0.5	1.0±0.8	**0.002**
Creatinine (admission) (mg/dL) (mean±SD)	2.1±0.8	1.2±0.9	**0.001**
AST (U/L) (mean±SD)	49.6±38.7	54.3±42.8	0.389
ALT (U/L) (mean±SD)	28.9±20.3	33.9±50.6	0.962
Albumin (g/dL) (mean±SD)	2.8±0.5	2.9±0.6	0.318
Sodium (mmol/L) (mean±SD)	131.5±6.6	134.0±5.2	0.055

*: Other includes other etiologies not specified in the table; SD: Standard deviation; NASH: Non-alcoholic steatohepatitis; MELD: Model for end-stage liver disease; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

32.1% of patients developed AKI. When the results of our study were evaluated alongside existing literature, it became apparent that the frequency of AKI in hospitalized cirrhotic patients varies depending on the study population. Nevertheless, it is evident that the incidence of AKI is high in these patients, emphasizing the importance of closely monitoring kidney function tests in patients with decompensated cirrhosis.

HRS is a diagnosis of exclusion and represents an advanced manifestation of AKI in cirrhotic patients. It is a functional disorder that corresponds to a noticeable decrease in glomerular filtration rate (GFR) due to severe renal arterial vasoconstriction, systemic inflammation, adrenal dysfunction, intra-abdominal hypertension, and the hepatorenal reflex. In a recent review, the annual incidence of HRS in cirrhotic patients with ascites is reported to be 8%.[16] In our study, a similar pattern was observed with an HRS frequency of 8.5% in cirrhotic patients with ascites. Similarly, in studies evaluating the frequency and etiology of AKI in hospitalized cirrhotic patients, the overall prevalence of HRS appears to be low.[15] The reliance of HRS diagnostic criteria on the exclusion of other causes of kidney injury and the challenges in assessing kidney function in cirrhosis likely contribute to a lower-than-expected frequency of HRS. Nevertheless, the prevalence of HRS can vary depending on the setting where the study is conducted (outpatient clinic, hospitalized patients) and the diagnostic criteria used. In some of the recent studies, current

HRS criteria have been utilized, while in others, the previous HRS diagnostic criteria are still being used.[17–19] In our study, the use of current HRS criteria resulted in 1.69 times more HRS diagnoses compared to the previous criteria, which strengthens the possibility that HRS diagnoses may have been underestimated in previous studies. This information supports the notion that the current criteria based on dynamic changes in sCr enable the earlier detection of kidney dysfunction in cirrhotic patients.

In a study evaluating in-hospital HRS mortality in the United States from 2005 to 2014, it was observed that the mortality rate, which was 44% in 2005, decreased to 24% by 2014.[20] Conversely, a meta-analysis of randomized controlled trials conducted between 2002 and 2018 found that HRS mortality up to 2018 remained similar to that in 2002.[21] In our study, although the mortality rate during clinical admission appeared to be low, when patients who died in intensive care were included, the mortality rate of HRS patients was found to be 33%. It is noteworthy that 2 out of the 9 patients diagnosed with HRS according to current diagnostic criteria and who died during hospitalization did not receive an HRS diagnosis when evaluated using the old diagnostic criteria, representing a significant finding. These findings collectively suggest that the HRS mortality rate is still quite high and underscore the importance of well-understanding clinical characteristics that can predict the development of HRS and the importance of early diagnosis.

In our study, when comparing patients with and without HRS, it was observed that a high MELD score upon admission, being in Child class C, elevated baseline sCr (the last creatinine value before hospital admission), high sCr levels during hospitalization, and a history of repeated hospital admissions were associated with the development of HRS. Similar studies have also demonstrated an association between a high MELD score and elevated sCr levels during hospitalization with the development of hepatorenal syndrome.[22,23] The limitations of our study include its retrospective design, reliance on medical records, and the inability to fully assess the cause of mortality in patients who died during intensive care follow-up.

Conclusion

In this study, the previously recommended criteria and the current criteria by the International Club of Ascites for diagnosing HRS in decompensated cirrhosis patients were compared. When evaluated according to the previous criteria, it was found that there was underdiagnosis of HRS, and some of these patients died without receiving an HRS diagnosis. The results of our study endorse the utilization of current criteria for early diagnosis in these high-mortality patients. However, these findings necessitate further support through more comprehensive prospective studies.

Ethics Committee Approval: The Istanbul Medeniyet University Clinical Research Ethics Committee granted approval for this study (date: 29.03.2023, number: 2023/0215).

Author Contributions: Concept – MMA, MU; Design – MMA, MU, CT; Supervision – MU, OB; Fundings – OB, CT; Materials – MMA, MU, OB; Data Collection and/or Processing – CT, MMA; Analysis and/or Interpretation – CT, MMA, OB; Literature Search – MU, OB, MMA; Writing – MMA, CT, MU; Critical Reviews – MU, OB.

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