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Prevalence and Short-term Outcomes of Hepatorenal Syndrome in Patients with Chronic liver Disease: Single Center Experience

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Abstract

Introduction: Hepatorenal syndrome [HRS] is a severe form of functional kidney failure that occurs in advanced liver cirrhosis and is associated with poor prognosis. Early recognition and management are crucial for improving outcomes. This study aimed to evaluate the prevalence, clinical characteristics, and short-term outcomes of HRS in patients with chronic liver disease.

Methods: This retrospective study included 270 patients with acute kidney injury and advanced liver cirrhosis who were hospitalized between January 2018 and December 2019. Patients meeting the diagnostic criteria for HRS were classified into HRS type 1 or HRS type 2. Treatment outcomes with terlipressin and albumin, as well as survival up to 90 days after treatment initiation, were analyzed.

Results: HRS was diagnosed in 32.6% of the studied cohort, with 40.9% having HRS type 1 and 59.1% having HRS type 2. The most common precipitating factor for HRS was large-volume paracentesis within the preceding four weeks [80.6% in HRS type 1 vs. 53.8% in HRS type 2; $p = 0.010$]. MELD scores were significantly higher in HRS type 1 [mean 32.0 ± 2.95] compared to HRS type 2 [mean 21.0 ± 2.45; $p < 0.001$]. A complete response to treatment was achieved in 31.8% of patients [13.9% in HRS type 1 vs. 44.2% in HRS type 2; $p = 0.008$]. The overall 90-day mortality rate was 72.7%, with significantly higher mortality in the HRS type 1 group [91.7%] compared to the HRS type 2 group [59.6%; $p = 0.001$].

Conclusion: HRS is a prevalent and severe complication of advanced liver disease. HRS type 1 is associated with worse clinical outcomes, emphasizing the need for prompt and aggressive management strategies.

Keywords: Acute Kidney Injury; Advanced Liver Disease; Ascites; Hepatorenal Syndrome; Mortality; Outcomes.

INTRODUCTION

The definition of hepatorenal syndrome has evolved, as it is primarily a diagnosis of exclusion and is founded on various criteria. A decrease in kidney function is referred to as hepatorenal syndrome in individuals with severe end-stage cirrhosis. Among cases with advanced cirrhosis, it is 1 of the most severe complications [1].

The prevalence of hepatorenal syndrome among cases with ascites and hepatic cirrhosis is eighteen percent following one year rising to thirty-nine percent at five years [2].

The diagnostic criteria for hepatorenal syndrome were initially defined by the International Club of Ascites [ICA] in 1996 [3], and then Revised in 2007 [4]. In 2015, The updated diagnostic criteria for HRS were devised by the International Club of Ascites-Acute Kidney Injury [ICA-AKI] criteria [5].

The ICA categorizes hepatorenal syndrome into 2 types Type-1 hepatorenal syndrome [HRS1] is distinguished by a quick deterioration of kidney function, which results in a doubling of serum creatinine [sCr] to values exceeding 2.5 milligrams per deciliter within two weeks. In contrast, type-2 hepatorenal syndrome [HRS2] is characterized by a less rapid rise in serum creatinine to values exceeding 1.5 milligrams per deciliter. While type 1 hepatorenal syndrome is characterized by an acute decline in circulatory, renal, and hepatic function, type 2 hepatorenal syndrome is characterized by a more incremental development of these abnormalities. Type 2 hepatorenal syndrome typically develops de novo in cases with refractory ascites, whereas type-1 hepatorenal syndrome is frequently related to a precipitating factor. Type-2 hepatorenal syndrome may occasionally progress to Type-1 hepatorenal syndrome due to a precipitating event. The prognosis is poor, with results ranging from weeks in Type-1 hepatorenal syndrome to months in type-2 hepatorenal syndrome [4].

The first step in managing hepatorenal syndrome is to address the cause of hepatic decompensation. This might involve therapy of the primary disease process, such as alcohol cessation in severe alcoholic hepatitis or antiviral treatment in infection with hepatitis B, with careful utilization of antibiotics. Medical treatment is the initial phase in reversing the AKI related to hepatorenal syndrome when immediate enhancement in the function of the liver is not possible [1]. The medical treatment of hepatorenal syndrome was demonstrated to enhance short-term results; however, prolonged results are poor without liver transplantation. The medical treatment involves early management of AKI and utilization of vasoconstrictor [6].

The primary objective was to determine and manage reversible factors, including gastrointestinal [GI] hemorrhage, infection and sepsis, nephrotoxic medications, and dehydration [7].

Suppose large-volume paracentesis is required, especially over three to five litters, intravenous albumin replacement must be utilized with six to eight grams of albumin for each litter of ascitic fluid removed. In addition to antibiotics, cases with spontaneous bacterial peritonitis must receive intravenous albumin [1.5 grams per kilogram on day one, followed by one gram per kilogram on day three] to enhance the result of cases [8]. Vasoconstrictors induce constriction of splanchnic vessels, which results in a rise in the efficient circulating blood volume. This, in turn, enhances the perfusion of the kidneys and glomerular filtration [9].

Vasoconstrictors are more effective when administered with intravenous albumin [10]. Terlipressin is the most frequently utilized vasopressor and acts on the V1 receptors in vascular smooth muscle cells [11]. Terlipressin has been correlated to a fifteen percent and nine percent decrease in all-cause and HRS-related death, respectively, in a meta-analysis and systematic review of eight randomized trials [12].

This study aimed to evaluate the prevalence and short-term outcomes [90-day survival] of HRS in patients with chronic liver disease treated at the National Liver Institute, Egypt.

PATIENTS AND METHODS

The patients under investigation:

The design of this research was a retrospective study on consecutive cases suffering from decompensated liver cirrhosis hospitalized with acute kidney injury, and met the criteria of hepatorenal syndrome at National Liver Institute, between January 2018 to December 2019. The investigation has been approved by the Ethical Committee of the National Liver Institute and carried out in line with the 1975 Declaration of Helsinki.

Included cases aged from 18-75 years who met the diagnosis of hepatorenal syndrome concerning ICA-AKI 2015 diagnostic criteria: [1] Diagnosis of ascites and cirrhosis; [2] Diagnosis of AKI [an elevated serum creatinine ≥ fifty percent of baseline and >1.5 milligrams per deciliter [133 micromoles per litters]]; [3] No response following 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin [one gram per kilogram per litters of body weight]; [4] Absence of shock; [5] No current or recent utilization of nephrotoxic medications; and [6] No macroscopic signs of structural kidney injury, described as the absence of proteinuria [> 500 milligrams per deciliters], absence of microhematuria [greater than fifty red blood cells per high power field], and normal results on kidney ultrasound. The following cases had been excluded: cases with obstructive uropathy, cases undergoing renal replacement therapy [hemodialysis/renal transplantation], following transplantation of liver cases, cases with a history of coronary artery disease, peripheral vascular illness, ventricular arrhythmia, or ischemic cardiomyopathy, and those with multinodular hepatocellular carcinoma [more than three nodules].

Cases have been categorized into **HRS1:** cases with twice the initial creatinine [more than 2.5 milligrams per deciliters] in less than two weeks; and **HRS2:** creatinine at least 1.5 milligrams per deciliters and with slow course of progressive.

Study procedures:

All included participants in the investigation were subjected to full history taking including [Age, sex, and demographic data: history of DM or HTN and the etiology of cirrhosis], full clinical examination was done, Laboratory data were collected including [serum Albumin and bilirubin, AST, ALT, prothrombin time, blood urea, serum creatinine, complete blood count, eGFR [estimated by CKD-EPI Creatinine 2009 equation], random blood sugar and urine analysis. Child-Pugh and MELD scores were calculated at the time of diagnosing kidney injury and at the end of management.

During the 6th month of the investigation, hospitalized cases with cirrhosis who developed kidney injury and were diagnosed as

HRS were enrolled. Treatment was initiated as soon as the diagnosis was confirmed as follows: Terlipressin was typically administered intravenously in boluses at a commencing dose of 0.5-1 milligrams every four to six hours. The dose has been subsequently increased to a maximum of two milligrams every four hours in cases of non-response, which has been defined as a serum creatinine concentration reduction of less than twenty-five percent following three days, and no adverse effects occurred. In general, human albumin twenty percent was administered in conjunction with vasoconstrictors. The initial dose was one gram per kilogram per day for 2 days, followed by twenty to forty grams IV once daily for fourteen days. The dosages were sustained for a maximum of fourteen days, contingent upon the responses to the treatment. The Terlipressin and albumin doses were maintained until the serum creatinine level reached a final value of less than 1.5 milligrams per deciliters or until the baseline creatinine level was reached. In cases that exhibited no response or a partial response, the medication was discontinued within fourteen days.

Follow-up of clinical [vital signs, urine output, signs of more decompensation, and signs of hepatic encephalopathy] and laboratory parameters [RFTs were assessed 48 hours, after treatment initiation to assess the response and then every 72 hours and for 2 weeks in patients with partial or complete response]. After 90 days of treatment initiation, any complications were recorded, as well as transplant-free and overall survival.

Study outcome measures:

Primary Outcome Measures:

1. Evaluation of the function of the kidney at the beginning and the end of treatment [Time Frame: 2 weeks]. 2. Response to therapy in each intervention group [Time Frame: two weeks] was classified into: Complete response [regression of acute kidney injury stage with a reduction in serum creatinine to within 0.3 milligrams per deciliters of baseline], Partial response [regression of acute kidney injury stage with a reduction in serum creatinine to not less than 0.3 milligrams per deciliters above baseline], and No response [no regression of acute kidney injury].

Secondary Outcome Measures:

1] Circulatory function [Time Frame: two weeks]; 2] Complications and the predictors of response to treatment [Time Frame: 28 days]; 3] Survival [Time Frame: twenty-eight days]; 4] Medication-associated Side effects/ complications [Time Frame: twenty-eight days].

Statistical Analysis:

Data have been fed to the computer and analyzed utilizing IBM SPSS software package version 20.0. [IBM Corp., Armonk, NY] Numbers and percentages were utilized to characterize qualitative data. The normality of the distribution has been confirmed utilizing the Kolmogorov-Smirnov test. Range [maximum and minimum], mean, standard deviation, median, and interquartile range [IQR] have been utilized to describe quantitative data. The outcomes were assessed at the five percent level of significance. The following tests have been utilized: the Chi-square test [for categorical variables, to compare among various groups], Fisher's Exact [Correction for chi-square when over twenty percent of the cells have expected count less than five], Student t-test [for normally distributed quantitative variables, to compare among the groups under investigation], Mann Whitney test [for abnormally distributed quantitative variables, to compare among both groups under investigation], and Kruskal Wallis test [for abnormally distributed quantitative variables, to compare between more than 2 groups under investigation]. The following assumptions were used to determine the sample size of 270 subjects: α=0.05 and power=eighty percent, as calculated by the Epicalc2000 software.

RESULTS

Baseline demographics and disease characteristics:

Out of the 270 patients, 32.6% [n=88] were diagnosed with HRS, while 67.4% [n=182] were classified as non-HRS cases. Of the HRS patients, 40.9% [n=36] had HRS1 and 59.1% [n=52] had HRS2. In the HRS type 1 group, 83.3% were men. The mean age was 54.64 ± 11.36. While, in the HRS type 2 group, 76.9% were men and the mean age was 60.50 ± 11.50, with statistically insignificant variance among both groups [p-value =equal 0.464 and 0.932 respectively]. As regards the etiology of chronic liver disease, in the HRS type 1 group, 80.6% had viral hepatitis, 11.11% had cryptogenic cirrhosis and 8.33% had immune-related liver disease. While, in the HRS type 2 group, 82.7 % had viral hepatitis, 9.61 % had cryptogenic cirrhosis and 7.69% had immune-related liver disease [p-value = 0.798]. 80.6% of HRS type 1 had a history of hepatic encephalopathy. While only 67.3% had a history of hepatic encephalopathy in group 2 [p-value = 0.170]. The majority of subjects in both groups were child C [86.1 %in group 1 and 80.8% in group 2 respectively, p-value = 0.512] **[Table 1]**.

Precipitating factors of HRS:

The main trigger of hepatorenal syndrome in both types was large-volume paracentesis [80.6% in HRS1 vs 53.8% in HRS2, p=0.010]. Also, GI bleeding within the last 4 weeks was a trigger factor in both types but without significant difference [30.6% vs. 21.2%, p=0.317]. Regarding the infection in the last 2 weeks, it was 38.5% in HRS1 compared to 0% in HRS2 with p=<0.001 **[Table 1]**

Baseline laboratory parameters of the two groups under investigation:

Considering the laboratory data of both groups, statistically insignificant variance has been detected among both groups with regard to the mean ± SD of TLC [5.25 ± 1.55 in HRS1vs. 5.44 ± 1.36 X103/mm3 in HRS2 respectively, p-value= <0.430]. While other parameters showed statistically significant variance among both groups as follows:

The mean±SD of PLT was considerably lower in HRS1 [65.67 ± 20.82x103 vs. 94.02 ± 21.53x103 in HRS2, p-value= <0.001]. The mean ± standard deviation of Hb was 9.60 ± 0.81 in HRS1 vs. 10.41 ± 0.80 gm/dl in HRS2, p-value= <0.001]. The mean ± SD of total bilirubin was 18.06 ± 4.68 in HRS1 vs. 4.68 ± 1.13 mg/dl in HRS2, p-value= <0.001. The mean ± SD of INR was greater in HRS 1 [1.70 ± 0.13 vs 1.30 ± 0.13 in HRS2, p-value= <0.001]. The mean ± SD of serum Na lower in HRS1 [127.0 ± 4.11 vs. 129.0 ± 3.15 mEq/L ± 0.50 in HRS2, p-value= <0.001]. Serum potassium was lower in HRS1 [3.72 ± 0.48 mEq/L vs. 5.41 ± 0.50 mEq/L in HRS2, p-value= <0.001] **[Table 2].**

Regarding the serum albumin, the mean ± SD was lower in HRS1 [2.40± 0.27 gm/dl vs. 2.82 ± 0.38 gm/dl in HRS2]. MELD score

varied in both groups; its mean value was higher in HRS1 [32.0 ± 2.95 vs. 21.0 ± 2.45 in HRS2] **[Table 2]**.

Response to treatment of HRS:

Our outcomes demonstrated that the complete response rate was greater in the HRS2 group than in the HRS1 group [44.2% vs. 13.9% in HRS1], and partial response [11.1 % in HRS1 vs 11.5% in HRS2]. No response to treatment was found in 75.0% of the HRS1 group vs. 44.2% in the HRS2 group with p= 0.008 **[Table 3]**.

Regarding the 90-day mortality rates in the two groups, 91.7% [33 subjects] in the HRS1 group died vs. 59.6% [31 subjects] of the HRS2 group [p-value equal to 0.001] **[Table 3]**.

Factors affecting the response to treatment:

HRS1 group:

Studying univariate logistic regression analysis for the parameters impacting response in the HRS1 group, it has been found that the baseline serum level of bilirubin and INR were the only significant predictors of response [p-value equal to 0.007 and 0.025 respectively]. The multivariate analysis showed that the baseline serum concertation of bilirubin was the only significant predictor of response [p-value equal to 0.046] **[Table 4]**.

HRS2 group: Studying univariate logistic regression analysis for the parameters impacting response in HRS Type 2, it has been found that the baseline serum concentration of creatinine was the only significant predictor of response [p-value equal to 0.011]. While the multivariate analysis demonstrated statistically insignificant variance among both groups **[Table 5]**.

Factors affecting the mortality:

HRS1 group:

Studying univariate logistic regression analysis for the parameters impacting the mortality in HRS Type 1, it has been found that the baseline serum bilirubin was the only significant predictor of mortality [p-value equal to 0.039]. While the multivariate analysis demonstrated statistically insignificant variance among both groups **[Table 6].**

HRS2 group: Studying univariate logistic regression analysis for the parameters impacting response in HRS Type 2, it has been found that the baseline serum concentration of bilirubin and creatinine in addition to Child score were significant predictors of mortality [p-value equal 0.009, 0.001, and 0.044 respectively]. The multivariate analysis demonstrated that only baseline serum concentrations of bilirubin and creatinine were significant predictors of mortality [p=0.012 and 0.001 respectively] **[Table 7]**.

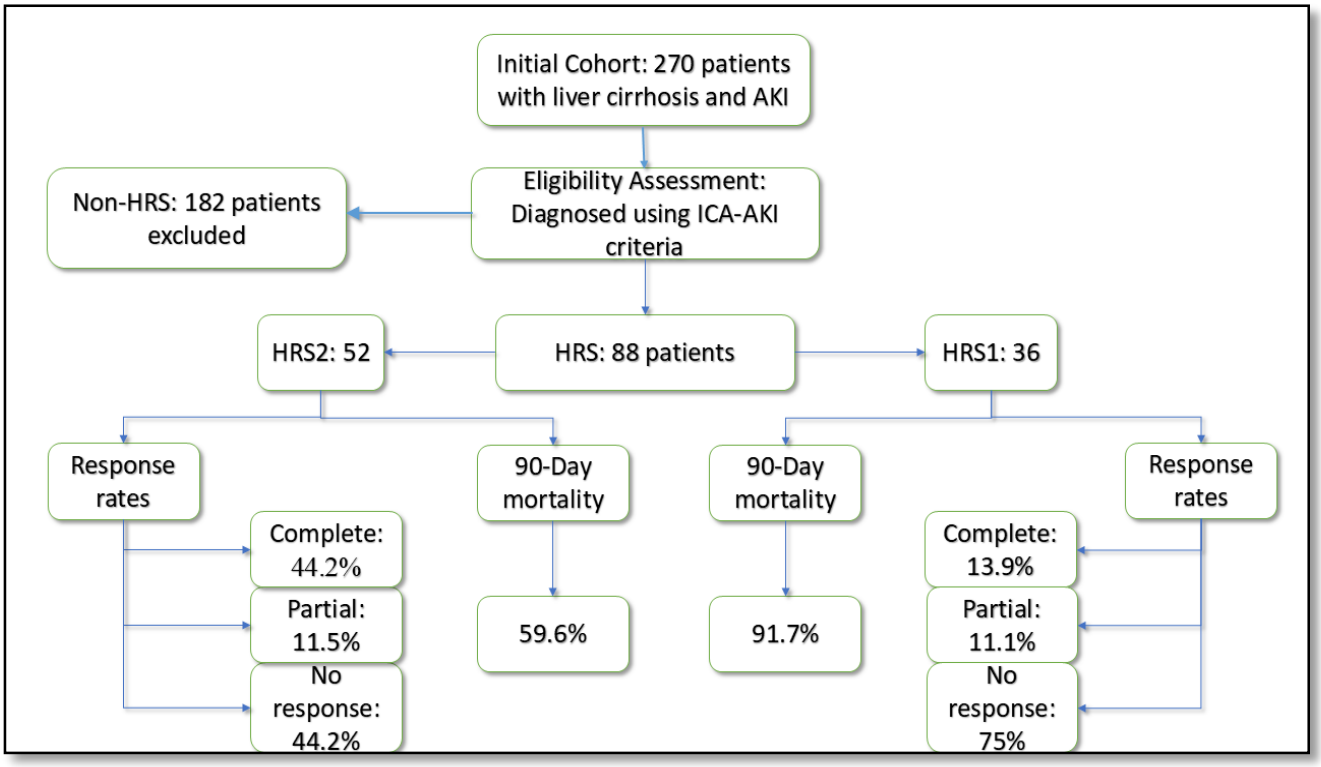

Figure [1]: Flowchart for all patients**. Description**: A total of 270 patients hospitalized with liver cirrhosis and acute kidney injury were initially screened for eligibility. Based on ICA-AKI diagnostic criteria, 182 patients were classified as non-HRS cases and excluded from further analysis. Among the 88 patients diagnosed with HRS, 36 were categorized as type 1 HRS [HRS1], and 52 as type 2 HRS [HRS2]. Treatment outcomes, including response to therapy and 90-day survival, were analyzed for both groups.

Table [1]: Comparison among both groups under investigation according to general characteristics and triggers for HRS

	Variable	Type 1 [number = 36]	Type 2 [number = 52]	Test of Sig.	P
Gender [n, %]	Men Women	30 [83.3%] 6 [16.7%]	4 [76.9%] 12 [23.1%]	$\chi^2 = 0.537$	0.464
Age [years] [n, %]	Min. – Max. Mean ± SD.	43.28 –66.0 54.64 ± 11.36	49.0 – 72.0 60.50 ± 11.50	t=0.086	0.932
Cause of CLD [n, %]	Viral Immune Cryptogenic	29 [80.6%] 3 [8.33%] 4 [11.11%]	43 [82.7%] 4 [7.69%] 5 [9.61%]	t=0.065	0.798
History of Hepatic encephalopathy [n, %]	No Yes	7 [19.4%] 29 [80.6%]	17 [32.7%] 35 [67.3%]	t=1.882	0.170
Child Score [n, %]	B C	5 [13.9%] 31 [86.1%]	10 [19.2%] 42 [80.8%]	t=0.429	0.512
Triggers for HRS [n, %]	Large volume paracentesis Infection last 2 weeks Intestinal bleeding last 4 weeks	29 [80.6%] 0 [0.0%] 11 [30.6%]	28 [53.8%] 20 [38.5%] 11 [21.2%]	$\chi2$=6.651* 17.919* 1.003	0.010* <0.001* 0.317

χ^2: Chi-square test t: Student t-test p: p-value for comparing among both groups under investigation. *: Statistically significant at a p-value not more than 0.05. **Abbreviations**: HRS; Hepatorenal Syndrome, CLD; Chronic Liver Disease, SD; Standard Deviation.

Table [2]: Comparison among both groups under investigation regarding the baseline laboratory data

	Variable	Type 1 [n = 36]	Type 2 [n = 52]	Test	P
TLC [X10^3/mm3]	Min. – Max. Mean ± SD	3.0 – 9.0 5.25 ± 1.55	3.0 – 7.84 5.44 ± 1.36	43.0	0.430
Platelet [/mm3]	Min. – Max. Mean ± SD.	25.0 – 104.0 65.67 ± 20.82	59.0 – 129.0 94.02 ± 21.53	354.0	<0.001*
Hb [milligram per decilitres]	Min. – Max. Mean ± SD.	8.10 – 11.10 9.60 ± 0.81	9.10 – 11.70 10.41 ± 0.80	4.631	<0.001*
Total Bilirubin[mg/dl]	Min. – Max. Mean ± SD.	9.0 – 27.0 18.06 ± 4.68	2.50 – 6.80 4.68 ± 1.13	16.799	<0.001*
INR	Min. – Max. Mean ± SD.	1.50 – 1.90 1.70 ± 0.13	1.10 – 1.50 1.30 ± 0.13	14.390	<0.001*
Na [mEq/L]	Min. – Max. Mean ± SD.	120.0 – 135.0 127.0 ± 4.11	123.0 – 132.0 129.0 ± 3.15	0.263	0.793
K [mEq/L]	Min. – Max. Mean ± SD.	3.10 – 5.50 3.72 ± 0.48	4.70 – 6.10 5.41 ± 0.50	15.890	<0.001*
Serum albumin [gm/dl]	Min. – Max. Mean ± SD.	1.80 – 3.0 2.40 ± 0.27	2.30 – 3.30 2.82 ± 0.38	80.50	<0.001*
MELD score	Min. – Max. Mean ± SD.	28.0 – 38.0 32.0 ± 2.95	17.0 – 26.0 21.0 ± 2.45	19.050*	<0.001*

SD: Standard deviation. HR; Heart Rate, TLC; Total Leucocytic Count, Na; sodium, K; potassium, MELD; model of end-stage liver disease, Hb; Hemoglobin, INR; International Normalized Ratio.

Table [3]: Comparison among both groups under investigation regarding the response to treatment and mortality rate

	Variable	Type 1 [number = 36]		Type 2 [number= fifty-two]		χ^2	p
Response to treatment	No Response Partial Complete	27 4 5	75.0 11.1 13.9	23 6 23	44.2 11.5 44.2	9.703	0.008*
Mortality after 90 days	No Yes	3 33	8.3 91.7	21 31	40.4 59.6	11.018	0.001*

$\chi2$: Chi-square test

Table [4]: Univariate and multivariate Logistic regression analysis for the parameters impacting response in HRS Type 1

	Univariate		#Multivariate	
	P	OR [LL – UL ninety-five percent C.I]	P	OR [LL – UL ninety-five percent C.I]
Age [years]	0.637	0.984[0.920 – 1.052]	**0.688**	1.02 [0.98 – 1.06]
Gender [female]	0.608	1.643[0.247 – 10.946]	**0.611**	0.95 [0.75 – 1.32]
Cause of CLD [Viral]	0.808	1.257[1.198 – 7.793]	**0.765**	1.10 [0.67 – 1.92]
Child Score [C]	0.413	0.438[0.061 – 3.160]	**0.452**	1.18 [0.72 – 1.45]
MELD score	0.298	0.857[0.640 – 1.146]	**0.385**	1.06 [0.95 – 1.21]
Baseline S.creatinine [mg-dl]	0.054	8.331[0.964 – 71.986]	**0.092**	1.20 [0.92 – 1.34]
INR	0.025*	0.0[0.0 – 0.287]	**0.062**	1.18 [0.99 – 1.45]
Serum albumin [g-dl]	0.588	2.221[0.124 – 39.734]	**0.619**	1.14 [0.82 – 1.32]
T.Bilirubin [milligram per deciliter]	0.007*	0.695[0.534 – 0.905]	**0.046***	1.42 [1.07 – 1.82]

OR: Odd`s ratio C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with p-values; less than 0.05 were included in the multivariate.
Abbreviations: INR, international normalized ratio, CLD; Chronic Liver Disease, MELD; Model of End Stage Liver Disease.

Table [5]: Univariate and multivariate Logistic regression analysis for the parameters affecting response in HRS Type 2

	Univariate		#Multivariate	
	P	OR [LL – UL ninety-five percent C.I]	P	OR [LL – UL ninety-five percent C.I]
Age [years]	**0.677**	0.988[0.935 – 1.044]	**0.693**	1.01 [0.97 – 1.06]
Gender	**0.838**	1.145[0.310 – 4.227]	**0.812**	0.90 [0.68 – 1.23]
Cause of CLD [Viral]	**0.989**	0.990[0.233 – 4.202]	**0.967**	1.12 [0.79 – 1.34]
Child Score [C]	**0.320**	0.471[0.107 – 2.075]	**0.355**	1.08 [0.87 – 1.32]
MELD score	**0.908**	0.987[0.788 – 1.236]	**0.921**	1.03 [0.92 – 1.18]
Baseline S.creatinine [mg-dl]	**0.011***	4.330[1.390 – 13.484]	**0.011***	1.32 [1.08 – 1.61]
INR	**0.439**	0.181[0.002 – 13.720]	**0.472**	1.10 [0.89 – 1.22]
Serum albumin [gram per deciliters]	**0.602**	0.678[0.158 – 2.917]	**0.611**	1.11 [0.93 – 1.45]
T.Bilirubin [milligram per deciliter]	**0.202**	0.720[0.434 – 1.193]	**0.243**	1.14 [0.95 – 1.35]

Table [6]: Univariate and multivariate Logistic regression analysis for the parameters affecting mortality in HRS Type 1

	Univariate		#Multivariate	
	P	OR [LL – UL ninety-five percent C.I]	P	OR [LL – UL ninety-five percent C.I]
Age [years]	**0.996**	1.0[0.900 – 1.111]	**0.992**	1.01 [0.97 – 1.04]
Gender [female]	**0.434**	0.357[0.027 – 4.724]	**0.459**	0.95 [0.79 – 1.31]
Cause of CLD [Viral]	**0.534**	0.444[0.034 – 5.739]	**0.562**	1.06 [0.89 – 1.38]
Child Score [C]	**0.335**	3.625[0.264 – 49.703]	**0.351**	1.12 [0.85 – 1.37]
MELD score	**0.680**	1.097[0.705 – 1.708]	**0.718**	1.03 [0.92 – 1.21]
Baseline S.creatinine [mg-dl]	**0.573**	0.438[0.025 – 7.690]	**0.611**	1.15 [0.92 – 1.35]
INR	**0.338**	237.304 [0.003– 16971765.9]	**0.364**	1.13 [0.94 – 1.35]
Serum albumin [g-dl]	**0.488**	5.070[0.052 – 498.64]	**0.509**	1.10 [0.88 – 1.38]
T.Bilirubin [mg/dl]]	**0.039***	1.661[1.025 – 2.689]	**0.041**	1.25 [1.03 – 1.65]

Table [7]: Univariate and multivariate Logistic regression analysis for the parameters impacting mortality in HRS Type 2

	Univariate		#Multivariate	
	P	OR [LL – UL ninety-five percent C.I]	P	OR [LL – UL ninety-five percent C.I]
Age [years]	**0.664**	1.012[0.957 – 1.071]	**0.689**	1.02 [0.97 – 1.07]
Gender	**0.918**	0.933[0.252 – 3.461]	**0.930**	0.88 [0.67 – 1.19]
Cause of CLD [Viral]	**0.314**	0.474[0.111 – 2.027]	**0.329**	1.05 [0.81 – 1.48]
Child Score [C]	**0.044***	4.667[1.044 – 20.851]	**0.115**	1.15 [0.91 – 1.49]
MELD score	**0.907**	1.014[0.806 – 1.274]	**0.722**	1.05 [0.91 – 1.26]
Baseline S.creatinine [mg/dl]	**0.001***	0.130[0.037 – 0.457]	**0.001***	1.45 [1.22 – 1.88]
INR	**0.162**	24.930[0.274 – 2270.4]	**0.198**	1.09 [0.92 – 1.32]
Serum albumin[g-dl]	**0.284**	2.261[0.508 – 10.053]	**0.296**	1.12 [0.90 – 1.44]
T.Bilirubin [mg-dl]	**0.009***	2.222[1.224 – 4.034]	**0.012**	1.32 [1.10 – 1.68]

DISCUSSION

Hepatorenal syndrome is a type of kidney dysfunction that is typically observed in cases with liver cirrhosis. It is distinguished by a

marked reduction in renal function as a result of circulatory and hemodynamic changes that happen in the advanced stages of liver cirrhosis, which are further exacerbated by bacterial translocation and systemic inflammation [13]. The prognosis for cases with hepatorenal syndrome remains poor, especially for those with type 1 HRS. Various treatment modalities, including vasoconstrictors like Terlipressin and albumin, have been employed to manage HRS, but outcomes vary significantly.

In our study, 32.6% of hospitalized cirrhotic cases with acute kidney injury had confirmed diagnosis of HRS, with a higher prevalence of hepatorenal syndrome type 2 [59.1%] compared to hepatorenal syndrome type 1 [40.9%]. This aligns with findings from **Rey *et al***., who stated a prevalence rate of 35% in a high-complexity hospital in Colombia [13]. In addition, **Razafindrazoto *et al***. detected that the occurrence of HRS in cirrhotic cases in Madagascar was 22.5% [14]. **Patidar *et al***. documented an HRS prevalence of 30.1% and AKI occurrence in 45% of hospitalized cirrhotic patients in the US, further underscoring the burden of HRS in this patient population[15].

Accurate diagnosis and prognostic indicators are crucial for managing HRS effectively. In our study, patients with hepatorenal syndrome type 1 exhibited significantly lower platelet counts [median 70,000/µL], higher INR [median 2.3], and elevated bilirubin levels [median 5.8 mg/dL] compared to those with HRS type 2. Our findings highlight that the severity of liver involvement, as indicated by elevated MELD scores and high bilirubin levels, strongly influences outcomes in HRS patients. This is consistent with prior studies, such as **Patidar *et al***. and **Razafindrazoto *et al***., who identified similar trends in HRS-related mortality and poor treatment responses. **Fida et al.** [16-18] detected that 40% of cirrhotic cases suffering from HRS had elevated serum creatinine levels, indicating severe renal impairment. **Musunuri *et al.*** [19] identified predictors of short-term death in cirrhosis cases presenting with AKI, finding that 62% of these cases had a high MELD score [>30] and that 58% of them had severe ascites, which is consistent with our findings that patients with higher bilirubin levels and severe liver dysfunction are at greater risk [20].

Understanding the triggers of HRS is essential for prevention and management. In our study, large-volume paracentesis and infections were identified as significant triggers for HRS. Specifically, 80.6% of HRS type 1 cases were triggered by large-volume paracentesis, while infections within the last two weeks were predominant triggers for HRS type 2 [38.5%]. These findings are corroborated by prior research that also highlights the role of infections [35%] and procedural complications [25%] in precipitating HRS. **Avazovna** found that 45% of HRS cases in cirrhotic patients with viral etiology were triggered by bacterial infections, reinforcing the importance of infection control in this population [21]. **Kiani and Zori** highlighted that 60% of HRS cases were related to bacterial infections, with spontaneous bacterial peritonitis being the most frequent cause [22]. Recent advances in the understanding of the diagnosis, treatment, and pathophysiology of hepatorenal syndrome have been pivotal in improving patient outcomes. The response to treatment with terlipressin and albumin differed significantly among both groups. HRS type 2 cases had a greater complete response rate [44.2%] compared to HRS type 1 patients [13.9%]. The current management strategies for HRS, particularly in the United States, have seen significant advancements with the use of terlipressin. **Flamm *et al***. discussed the potential of terlipressin in managing HRS-AKI, reporting that 35% of patients achieved complete response with terlipressin treatment, highlighting its efficacy and the challenges in its implementation [23]. Previous studies, including those by **Buccheri and Da** reported a response rate of 30-50% with terlipressin therapy, supporting our findings about the need for aggressive treatment for HRS type 1 [24]. **Loftus *et al.*** emphasized the potential of updated guidance and a new management paradigm in improving the management of HRS-AKI, with terlipressin showing promise in achieving a higher complete response rate [40%] when used in combination with albumin [25]. Tariq and Singal [2020] reviewed various management strategies for HRS and underscored the importance of early intervention with albumin and terlipressin, highlighting a success rate of 50-70% in reversing kidney dysfunction when administered promptly [26]. **Hasan *et al***. provided an extensive update on the pathophysiology and evidence-based management of HRS, noting that terlipressin combined with albumin enhanced the function of the kidney in sixty percent of cases, reinforcing its role in current treatment protocols [27]. Our study revealed a 90-day death rate of 91.7% in hepatorenal syndrome type 1 and 59.6% in HRS type 2. **Patidar *et al***. reported a 90-day death rate of 85% in hepatorenal syndrome type 1 and 60% in HRS type 2, providing a comparative mortality perspective that supports our findings on higher mortality in HRS type 1 [91.7% vs 59.6% in HRS2] [15]. **Patel *et al***. highlighted that the overall in-hospital mortality for HRS patients was 62%, with significant cost burdens associated with prolonged hospital stays and intensive treatments [28]. **Sheng *et al***. developed a prognostic model for HRS and found that patients with higher MELD-Na scores had a significantly worse prognosis, which aligns with our observations of higher mortality in more severe cases [29]. While our study focused on short-term outcomes, it is essential to consider the long-term prognosis of HRS cases. **Morató Catafal** highlighted the importance of modeling survival data from HRS-related acute kidney injury, showing that the median survival time for HRS cases was 3 months, with a 1-year survival rate of 20% [30].

In conclusion, HRS is a prevalent complication of advanced liver disease, with distinct differences in clinical characteristics, triggers, and outcomes between HRS1 and HRS2. HRS1 is a more severe form of the syndrome, requiring prompt and aggressive management. Future research should focus on identifying early predictors of treatment response to improve outcomes for these high-risk patients. To further validate our findings and make them more reliable we recommend repeating the study in multiple Egyptian governorates with a larger size of sample and longer duration of follow-up while keeping in consideration the new criteria of HRS.

Ethical approval and consent to participate: This study was approved by the Ethical Committee of the National Liver Institute, Menoufia University, on December 2023, under protocol number 00529/2023 and IRB number NLI IRB 00014014. Written informed consent was obtained from all patients for their participation in the study and the publication of anonymized data.

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