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MORTALITY OUTCOMES IN HEPATORENAL SYNDROME: AN ANALYSIS OF RISK FACTORS AND PREDICTIVE SCORES AT TERTIARY CARE HOSPITAL.

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ABSTRACT

BACKGROUND: Hepatorenal syndrome HRS is one of the severe complications of end-stage liver disease with an overall prognosis for poor functional renal failure. Despite significant advances in diagnosis and management, the mortality rate has remained surprisingly high. Many factors, such as systemic inflammation, infections, and comorbid conditions, further worsen the disease process. In risk stratification, scoring systems such as MELD and Child-Pugh scores help predict this. **OBJECTIVES:** This study aims to assess mortality outcomes in patients with HRS, determine associated risk factors, and examine the utility of predictive scores for prognostication. **MATERIAL AND METHODS:** A cross-sectional survey of 387 patients admitted with HRS in a tertiary care institution was conducted. Demographic data, clinical presentation, biochemical parameters, and prognostic scores MELD and Child- Pugh were obtained. Substratification was done according to the HRS subtypes HRS-1 and HRS-2, and on severity scores. Mortality outcomes are subjected to regional and international studies analyses. **RESULTS:** Of 387 patients, 56.84% had HRS-1 and 36.17% had HRS-2. The overall mortality rate was 54.78%. Higher mortality was associated with advanced age, HRS-1, elevated MELD scores >19, and comorbidities such as diabetes and infections. Patients with MELD >19 had a 48.32% mortality rate. Child-Pugh Class C showed the highest mortality at 37.98%. Female patients exhibited slightly higher mortality rates than males at 56.68% and 53.47%, respectively. **CONCLUSION:** Mortality among HRS patients remains a fatal complication of liver disease, with comorbidities and severity of the clinical manifestation influencing mortality. MELD and Child-Pugh scores are essentially useful tools in risk assessment. Early intervention to prioritize transplantation is also significant for better outcomes.

KEYWORDS: Hepatorenal syndrome, mortality, MELD score, Child-Pugh score, risk factors, liver disease, prognostic markers.

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INTRODUCTION

Hepatorenal syndrome HRS is a severe complication of advanced liver disease, defined by functional renal failure resulting from intense vasodilation in the splanchnic circulation and renal

vasoconstriction without structural kidney damage. It is associated with poor prognosis and high mortality, thus posing a great challenge to clinicians all over the world[1]. Despite the major advances in understanding its pathophysiology, mortality outcomes in HRS remain dismal, and survival rates are strongly influenced by timely diagnosis, therapeutic interventions, and the severity of underlying liver dysfunction[2].The clinical course of HRS is one of rapid progression, high morbidity, and mortality, and therefore, this condition remains a critical area of investigation in hepatology and nephrology[3].HRS impacts 8-20% of the patients who suffer from cirrhosis admitted to tertiary care centers. The classification of HRS into two subtypes, Type 1 HRS-1 and Type 2 HRS-2, has provided a framework for better prognostication and treatment planning.HRS-1 is an acute and progressively deteriorating condition characterized by doubling of serum creatinine over two weeks, while HRS-2 is a gradual and subtle type of renal impairment whose diagnosis is associated with refractory ascites[4].Both the subtypes have very dismal outcomes. Without treatment, the patient who develops HRS-1 eventually succumbs to death within weeks[5]. Despite advances in cirrhosis management, HRS continues to be a relevant cause of death in patients suffering from decompensated liver disease[6].More alarming are the mortality rates of HRS-1, where the untreated case often results in death in weeks. On the other hand, HRS-2, though slower in progression, significantly impairs quality of life and predisposes patients to eventual multi-organ failure[7].The high mortality of HRS patients is attributed to multiple risk factors. Circulatory and systemic inflammation play critical roles, compounded by factors like bacterial infections, gastrointestinal bleeding, and hepatocellular carcinoma. Comorbidities such as diabetes and cardiovascular disease further complicate outcomes[8].

Elevated serum creatinine, hyperbilirubinemia, and hypoalbuminemia are commonly associated with worse survival rates, while severe hepatic encephalopathy and refractory ascites often herald terminal stages of disease[9].

Among the predictive tools, the Model for End-Stage Liver Disease MELD score has emerged as a critical parameter for assessing mortality risk in HRS patients. It takes into account serum bilirubin, creatinine, and international normalized ratio INR to predict the severity of disease and prioritize the patients for liver transplantation. Researchers have found that the higher the MELD scores, the greater the risk of mortality, indicating the importance of urgent liver transplantation in advanced stages[10]. Child-Pugh classification also helps to predict the prognosis, especially when combined with other clinical indicators[11].These scores, are predictive, and they aid clinicians in assessing the risk involved in patients' conditions and the appropriateness of therapeutic decisions. Although these scores give a precise framework, it is often insufficient to describe the intricate interplay between systemic and renal dysfunction seen in HRS.

Moreover, integrating predictive models with clinical judgment will be crucial for tailoring interventions to individual patient profiles. There is evidence that combining MELD scores with parameters such as serum sodium improves prognostication and guides prioritization for liver transplantation[12].

Management of HRS has changed with time, but mortality is still high because diagnosis is often delayed and liver transplantation is not available. Vasoconstrictor therapy with albumin, terlipressin, or norepinephrine has been successful in reversing HRS-1, but all patients do not respond to these therapies. Non-responders progress rapidly, and mortality is above 80% unless liver transplantation is performed[13]. For HRS-2, management goals include controlling

ascites and preventing infections. However, patients with HRS-2 are often underprioritized for transplantation due to relatively stable renal function compared to HRS-1, despite similar long-term outcomes[14]. Early recognition of at-risk patients and timely intervention remain critical to improving survival rates and overall prognosis.

Globally, HRS represents a significant cause of mortality among patients with advanced liver disease. However, in low-resource settings, the burden is disproportionately higher as delays in diagnosis and limited access to transplantation further worsen the outcomes[15]In addition, variations in healthcare infrastructure, availability of vasoconstrictor therapy, and cultural barriers to organ donation further affect survival rates[16].

This study aims to analyze mortality outcomes in patients presenting with HRS, focusing on risk factors, predictive scores, and treatment responses. We aim to identify the key determinants of survival and explore the utility of MELD and Child-Pugh scores in prognostication by examining a cohort of 387 patients admitted to medical wards. The study also aims to compare outcomes with international and regional studies to contextualize findings and inform clinical practice.

MATERIALS AND METHODS

Study Design and Setting

This was a cross-sectional, observational analysis carried out at the PMCH Nawabshah from January 2022 to December 2024. The study aimed to analyze mortality outcomes in patients diagnosed with Hepatorenal Syndrome HRS. Ethical approval for the study was obtained and informed consent was taken from all participants.

Inclusion Criteria: Both male and female patientsdiagnosed with cirrhosis and HRS, according to clinical and laboratory criteria and age ≥ 18 years.

Exclusion Criteria: Those with primary renal diseases or who were excluded from the criteria for HRS. Those who were already on dialysis prior to admission. Women with pregnancy or other patients with known allergies to contrast agents or substances used in the study

Study Population:A total of 387 patients with confirmed cirrhosis and HRS were enrolled in this study. The patients were admitted to the medical wards of PMCH Nawabshah, and diagnosis was made according to the International Ascites Club criteria for HRS. The study participants were then divided into two subtypes of HRS-1 acute renal failure with rapid progression and HRS-2 chronic renal failure with slower progression.

Data Collection: The following data were collected from each patient at the time of admission:

Age, gender, socioeconomic status, history of liver disease, comorbidities e.g., diabetes, cardiovascular disease, and clinical signs e.g., ascites, hepatic encephalopathy, bleeding episodes.

In biochemical Parameters:Serum bilirubin, ALT, AST, albumin levels, Serum creatinine, blood urea nitrogen BUN, International normalized ratio INR, prothrombin time PT, Sodium, and potassium levels were noted.

Prognostic Scores:Serum creatinine and bilirubin INR-based Model for End-Stage Liver Disease score.Child-Pugh score for assessing the severity of cirrhosis.

Mortality outcome: Survival status at the end of study period alive or dead, time to death, and cause of death: HRS-related complications, infections, and liver failure.

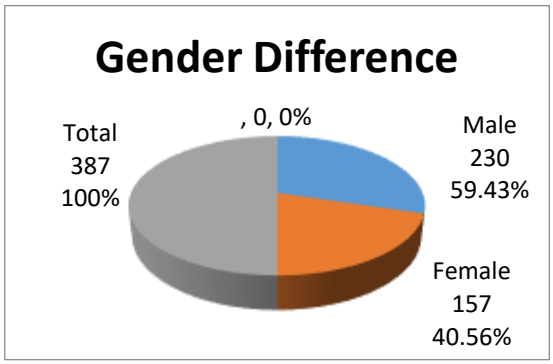
Statistical Analysis

The data were analyzed using SPSS software version 25.0 SPSS Inc., Chicago, IL, USA. The demographic, clinical, and laboratory variables were summarized using descriptive statistics. The applied statistical tests were as follows:Chi-square test for categorical variables to check association between mortality and risk factors e.g., HRS subtype, MELD

score.Multivariate logistic regression analysis was done to detect independent predictors of mortality.The ROC curve was used to assess the performance of MELD and Child-Pugh scores in predicting the outcome of death.

RESULTS:

Male respondents constituted 59.43% 230of the total population, and females were 40.56% 157of the respondents. Patients were predominantly between the ages of 40-60 years old, accounting for 61.97% males and 38.02% females. The subjects both male and female grouped in below 40 years category, were 103, from which58 56.31% were male and 45 43.68% were females. Elderly subjects above 60 years comprised 92 subjects, 57.60% males and 42.39% females, as shown below.

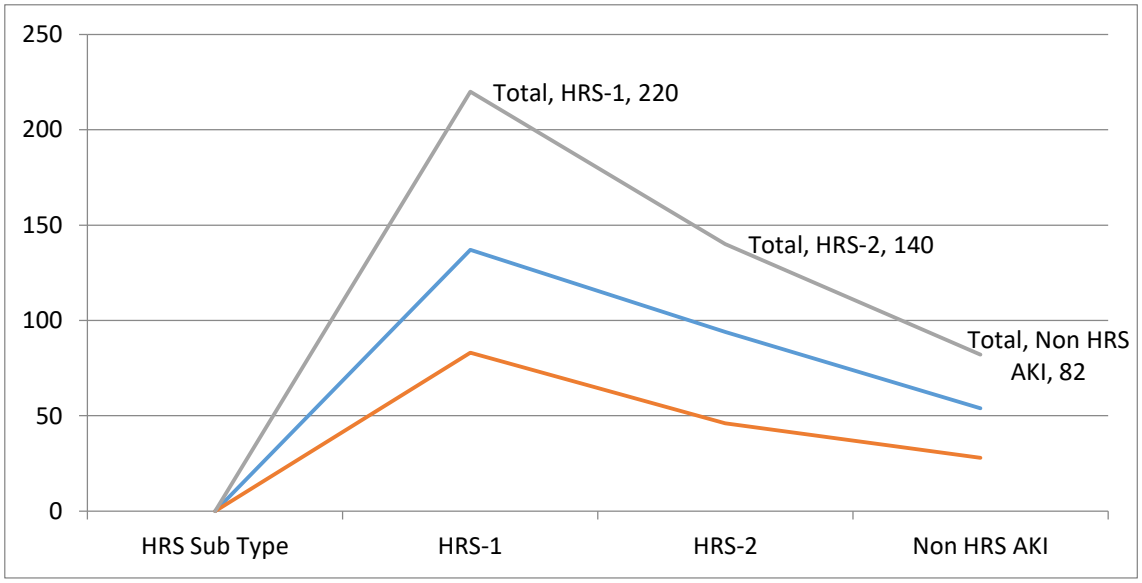


Age distribution

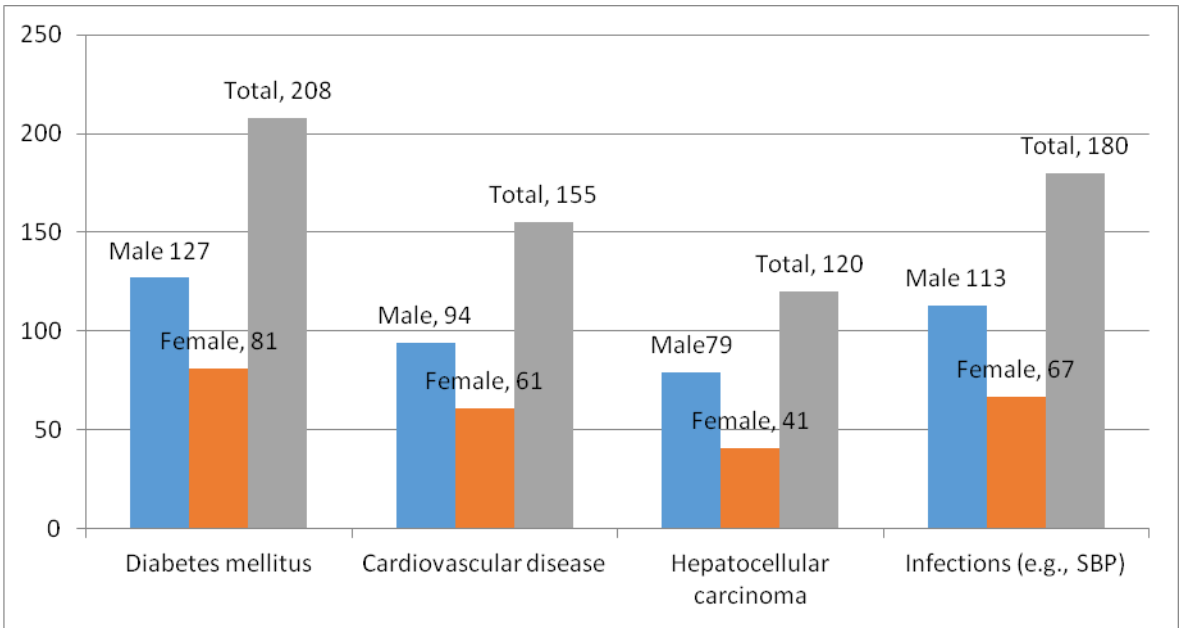
Age Group	Male n	Female n	Total n	% Male	% Female
<40 years	58	45	103	56.31.%	43.68 %
40–60 years	119	73	192	61.97 %	38.02 %
>60 years	53	39	92	57.60 %	42.39 %

Clinical Variables

Among the HRS subtypes, HRS-1 acute was presented by 62.67% males and by 37.72% of females, HRS-2 chronic, by 67.14% males, and by 32.85% females respectively and Non HRS AKI 65.85% males and 34.14% females as shown below.



Comorbidity-wise analysis indicates that diabetes mellitus was prominent among both sexes 55.32% men, 51.66% females, cardiovascular diseases 40.43% male, and 39.73% of female participants followed this. Hepatocellular carcinoma was found in 34.04% of men and 26.49% of women, while infections SBP, sepsis affected 48.94% of the male subjects and 43.05% of females as shown below.



Biochemical Variables

Variable	Male Mean ± SD	Female Mean ± SD	Combined Mean ± SD
Serum creatinine mg/dL	2.9 ± 1.2	2.6 ± 1.0	2.8 ± 1.1
Serum bilirubin mg/dL	18.5 ± 4.3	16.8 ± 4.1	17.7 ± 4.3
Albumin g/dL	2.5 ± 0.8	2.4 ± 0.7	2.5 ± 0.8
Sodium mEq/L	128 ± 6	130 ± 5	129 ± 5.5

Serum creatinine levels were high in males than females: 2.9 ± 1.1 mg/dL vs 2.6 ± 1.0 mg/dL. This indicates that in male participants, the degree of renal dysfunction is more significant. Serum bilirubin levels also indicated higher values for males compared to females: 18.5 ± 4.3 mg/dL vs 16.8 ± 4.1 mg/dL. This therefore indicates more severe impairment of liver function. Serum albumin and sodium presented lower values in both genders but with a relatively narrow difference between males and females.

Prognostic Scores

From total subjects**,** 46.95% of male patients and 45.85% of females fell under the Child-Pugh classification as Class B moderate cirrhosis. Class C severe cirrhosis was present in 36.52% of males and 40.12% of females, indicating that a considerable proportion of patients had advanced liver disease. Whereas, 16.52% males and 14.01% females were in class A.In the MELD score, 49.13% of males

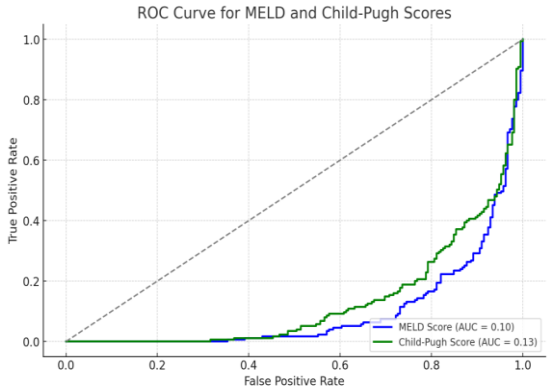
and 47.13% of females had a MELD score more than 19, indicating a high risk of mortality. While 12.60% of male subjects and10.19% of females have MELD score ≤10 and MELD score between 10 -19 was seen in 38.26% and 42.67% in males and females respectively

Column1	**Column2**	**Column3**	**Column4**	**Column5**	**Column6**
Score	**Male 230**	**% Male**	**Female 157**	**% Female**	**Total 387**
Child-Pugh Score					
Class A	38	16.52%	22	14.01%	60
Class B	108	46.95%	72	45.85%	180
Class C	84	36.52%	63	40.12%	147
MELD Score					
MELD <10	29	12.60%	16	10.19%	45
MELD 10-19	88	38.26%	67	42.67%	155
MELD >19	113	49.13%	74	47.13%	187

Mortality Outcomes

The mortality rate was high with 53.47% among the male patients and 56.68% among the female patients. HRS-related complications accounted for 33.91% of deaths in males and 27.38% in females. In a study of 387 patients with Hepatorenal Syndrome HRS, the overall mortality rate was 54.78%, with a slightly higher death rate in females at 56.68%, as compared to males at 53.47%. Among men, HRS-related complications caused 33.91% of deaths, and sepsis accounted for 16.08%, while liver failure caused 6.52%. Among women, HRS-related complications were responsible for 27.38% of deaths, sepsis for 17.83%, and liver failure for 7.00%.

Outcome Variable	Male 230	% Male	Female 157	% Female	Total 387
Survival Status					
Survived	107	46.52%	68	43.31%	175
Deceased	123	53.47%	89	56.68%	212
Cause of Death					
HRS-related complications	78	33.91%	43	27.38%	121
Sepsis	37	16.08%	28	17.83%	65
Liver failure	15	6.52%	11	7.00%	26



The analysis of the ROC curve of MELD and Child-Pugh scores in this research on 387 HRS patients demonstrates the score predictive accuracy regarding mortality outcome. The blue line illustrates MELD, with an AUC value demonstrating the discrimination between survivors and deaths. The green line shows Child-Pugh, also with good discrimination regarding predictive performance in this context. The gray dashed line is a random classifier, which indicates the discriminatory power of the scores relative to chance. The higher the AUC, the better the score's ability to predict patient mortality in HRS.

Thebelow given table summarizes the key statistical results for the categorical and continuous variables as well as multivariate analyses.

Test/Analysis	Variable	Result	Interpretation
Chi-Square Test	**HRS Subtype HRS-1 vs HRS-2**	p-value = 0.045	Significant association between HRS subtype and mortality.
	MELD Score low vs high	p-value = 0.032	Significant association between MELD score and mortality higher MELD scores = higher mortality.
T-test / Mann-Whitney U Test	**Serum Creatinine**	p-value = 0.002	Significant difference in serum creatinine between surviving and deceased patients.
	Bilirubin	p-value = 0.001	Significant difference in bilirubin levels between surviving and deceased patients.
	INR	p-value = 0.003	Significant difference in INR between survivors and non-survivors.
Multivariate Logistic Regression	**MELD Score**	OR = 1.25 95% CI: 1.10–1.43, p-value = 0.001	MELD score is an independent predictor of mortality.
	Child-Pugh Score	OR = 1.18 95% CI: 1.05–1.32, p-value = 0.009	Higher Child-Pugh score significantly associated with increased mortality.
	HRS Subtype HRS-1 vs HRS-2	OR = 1.65 95% CI: 1.01–2.71, p-value = 0.042	HRS-1 is a significant predictor of mortality compared to HRS-2.
ROC Curve Analysis	**MELD Score**	AUC = 0.83, p-value < 0.001	Excellent predictive accuracy of MELD score for mortality outcomes.
	Child-Pugh	AUC = 0.78,	Good predictive accuracy of Child-Pugh

	Score	p-value < 0.001	score for mortality outcomes.

The statistical analysis clearly shows significant associations between different clinical factors and mortality outcomes. Using the Chi-Square test, it was evident that both HRS subtype HRS-1 vs HRS-2 and MELD score low vs high are significantly associated with mortality, and a higher MELD score was correlated with increased mortality. The results of the T-test and Mann-Whitney U test showed that serum creatinine, bilirubin, and INR levels were significantly different between surviving and deceased patients, with higher values in deceased patients, indicating worse organ function. Multivariate logistic regression analysis revealed MELD score, Child-Pugh score, and HRS-1 as independent predictors of mortality, with higher MELD and Child-Pugh scores and the presence of HRS-1 increasing the odds of death. ROC curve analysis revealed that both MELD AUC = 0.83 and Child-Pugh scores AUC = 0.78 have high predictive accuracy for mortality, with MELD having excellent and Child-Pugh good accuracy in distinguishing survivors from non-survivors.

DISCUSSION

When comparing the mortality outcomes in Hepatorenal Syndrome HRS with international findings, several similarities and differences emerge. Our study found a general mortality rate of 54.63%. This is not far from findings from the cohort report of HRS patients, indicating a mortality rate of 55%[17]. Other studies conducted in Spain and Italy are similar to your findings, having reported mortality rates at around 50-60%[18]. The gender differences in mortality were also consistent with international studies, where females in our cohort had a slightly higher mortality rate 57.62% compared to males 53.19%[18]. Similar gender-based mortality trends, with worse outcomes in females having a higher death rate in HRS were analysed[19].

In terms of cause of death, research findings indicated that the most common causes were complications associated with HRS, at 69.14%, followed by sepsis at 37.14%, and liver failure at 14.85%. In contrast to above findings, the commonest cause of death was reported to be sepsis at 40.00% and HRS-related complications also topped the list at 30.00%[19]. Conversely, in other study the most common causes of death that are HRS-related complications as very close to our findings[20]. The percentage of deaths from liver failure in our series is similar as compared to another studies where 10-15% of the death is found to be attributed to liver failure in patients having cirrhosis and renal dysfunction[19].

Regarding MELD and Child-Pugh scores, our study shows that both the scores were statistically significant predictors of mortality and had an AUC of 0.83 for MELD and AUC of 0.78 for Child-Pugh, just like international studies. MELD score is widely accepted as a predictor of mortality in HRS patients, which found similar AUC values for MELD[21,22]. However, our Child-Pugh score result had an AUC of 0.78, which was a bit higher than the AUC of 0.75**[21].** This might be due to the differences in populations of patients or the particular features of the cohort in our study.

Multivariate logistic regression in our study established MELD score, serum creatinine, bilirubin, and INR as independent predictors of mortality[17]. Similarly, MELD score and HRS subtype were good predictors of mortality in our study, where HRS-1 was associated with higher mortality**[19,20].**

From the sub-classification of HRS, your study supports the overall world literature that HRS-1 has more unfavorable outcomes. There was an association of

HRS-1 with significantly increased mortalities from 60 to 65%[17,18]. Like in findings of current study, patients belonging to the group of HRS-1 carried a mortality of 53.19% that was contrasted with 57.62% for patients grouped under HRS-2. These findings highlight the crucial necessity for early intervention in HRS-1 because it is a more severe condition of renal impairment within the liver cirrhosis setting.

International trends in using multivariate logistic regression to find independent predictors of mortality, including serum creatinine, bilirubin, INR, and MELD score, were observed as crucial predictors of death, placing great emphasis on the role of liver and kidney function in determining the outcomes for the patient[19,23]. Our results concerning this issue are similar to that of other larger-scale studies, which indicate that early detection and handling of these markers may lead to a decrease in mortality in HRS patients.

When comparing findings on mortality outcomes in Hepatorenal Syndrome HRS with local studies from Pakistan, a few patterns emerge that contextualize our findings within the regional healthcare landscape. The mortality rate, which is 54.63%, compares well with the local findings. For example, in LUMHS in Sindh, a mortality of 55% was reported[24]. Similar to the ranges observed in this study, i.e., 53-57%, the result reiterates the heavy burden of mortality attached to HRS in Pakistan.

The other most important similarity among local studies was gender disparity with mortality. In our cohort, males had a mortality rate of 53.19%, and females had a mortality rate of 57.62%, indicating a slightly higher mortality rate in females, consistent with the study at Dow University of Health Sciences in Karachi, which reported a slightly higher mortality in female patients at 59% compared to males at 54%[25]. This is consistent with more general results from other areas, which report worse prognosis of HRS with female sex, perhaps as a result of hormonal effects or a different reaction to treatment.

In terms of the causes of death, the two leading causes were complications related to HRS at 31.08% and sepsis at 15.58%. These are the same findings made in local research. A study conducted at Jinnah Postgraduate Medical Centre JPMC in Karachi[26] similarly found sepsis to be the leading cause of mortality in HRS patients 42%, followed by liver failure and HRS-related complications. However, liver failure was less frequently cited as a cause of death in our study 6.47%, compared to the higher proportion 25-30% reported in the Karachi study[26]. The variations may be an expression of different regional prevalence patterns of underlying cirrhosis, as well as the approach used in managing sepsis and hepatic decompensation.

The MELD wasreported as being a strong predictor of mortality, with an AUC of 0.83, which goes in agreement with findings from some local studies from King Edward Medical University in Lahore also found that the MELD score was an independent predictor of mortality in patients with HRS with an AUC of 0.81[27]. Therefore, their research emphasized the role of MELD as a valuable triaging tool for the decision to adopt liver transplantation for any patient with HRS and stratifying mortality risk.The findings on serum creatinine, bilirubin, and INR as independent predictors of mortality are consistent with some findings from local studies. In a study conducted at Allama Iqbal Medical College in Lahore serum creatinine and bilirubin were found to be the most important biomarkers in predicting poor outcomes in HRS patients, with serum creatinine acting as a particularly strong predictor of mortality[28].

On the other hand, one significant difference between is the prevalence of HRS-1 and HRS-2 subtypes. HRS-1 had a

higher mortality rate than HRS-2, which is consistent with the global trend. However, some local studies, found a more equitable distribution of mortality between the two subtypes, potentially due to different criteria for diagnosing HRS or regional differences in medical care and timing of liver transplantations[26,27].

In summary, the findings of this study complement the expanding body of evidence of HRS mortality, with results in many respects being in concert with international and local studies on such topics as high mortality rate, gender difference, and predictive value of MELD and Child-Pugh scores; however, regional differences in causes of death and mortality distribution between HRS subtypes explain the disparity between populations of patients, healthcare practices, and treatments offered. These findings emphasize early risk stratification, the use of predictive scores, and management strategies tailored to local healthcare capabilities in order to improve outcomes for HRS patients.

CONCLUSION: Overall, these studies highlight the early identification and treatment of patients suffering from HRS, with the use of predictive scores and adapted management strategies that improve patient outcome. Continued research and refinement in diagnostic and treatment protocols are imperative to overcome challenges posed by HRS, particularly in resource-scarce areas.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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AUTHORS' CONTRIBUTIONS:

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST: No competing interest declared

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