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Original Research Article

Development of a clinical risk score for early prediction of hepatorenal syndrome in hospitalized cirrhotic patients with acute kidney injury: a retrospective study from India

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ABSTRACT

Background: Hepatorenal syndrome–acute kidney injury (HRS-AKI) is a severe and potentially reversible complication of advanced cirrhosis associated with high short-term mortality. Early identification of patients at risk remains challenging and currently available prognostic models are not specifically designed to predict the onset of HRS-AKI. Therefore, early risk stratification using simple clinical parameters is essential to facilitate timely therapeutic interventions. This study aimed to develop and internally validate a simple clinical risk score for early prediction of HRS-AKI among hospitalized cirrhotic patients presenting with acute kidney injury (AKI).

Methods: This retrospective cohort study included 260 hospitalized patients with liver cirrhosis and AKI admitted between February 2022 and August 2023. Demographic, clinical and laboratory parameters recorded at admission were analyzed. Independent predictors of HRS-AKI were identified using multivariable logistic regression analysis. A weighted clinical risk score was derived from the regression coefficients and internally validated using bootstrapping techniques. The discriminatory ability of the model was compared with established prognostic scores including MELD, MELD-Na and CLIF-C ACLF.

Results: HRS-AKI developed in 80 patients (30.7%). Independent predictors included mean arterial pressure<80 mmHg, serum sodium <130 mmol/l, serum bilirubin ≥6 mg/dl, serum albumin ≤2.8 g/dl and presence of infection at admission (all p<0.01). The derived clinical risk score (range 0–12) demonstrated good discrimination (AUC 0.83; 95% CI 0.78–0.87) and calibration (Hosmer–Lemeshow p=0.46). The incidence of HRS-AKI increased across low- (0–3), moderate- (4–7) and high-risk (≥8) groups (9%, 29% and 67%, respectively, p<0.001). The model outperformed MELD, MELD-Na and CLIF-C ACLF scores.

Conclusions: A simple bedside clinical risk score using routinely available parameters can accurately predict HRS-AKI in hospitalized cirrhotic patients and may aid early risk stratification and timely management to improve renal and survival outcomes.

Keywords: Acute kidney injury, Cirrhosis, Hepatorenal syndrome, India, Prognostic model, Risk prediction

INTRODUCTION

HRS represents one of the most severe and life-threatening complications of advanced cirrhosis and portal hypertension. It is characterized by functional renal failure resulting from marked splanchnic vasodilatation, reduced effective arterial blood volume and intense renal vasoconstriction in the absence of significant structural kidney damage. Over the last decade, there has been a paradigm shift in the understanding, definition and classification of HRS. The International Club of Ascites (ICA) revised the criteria in 2015, aligning the definition of HRS-AKI with contemporary AKI guidelines based on dynamic serum creatinine changes rather than fixed

cut-offs. This update has allowed earlier recognition and intervention, which are crucial for improving outcomes in cirrhotic patients.[1,2]

AKI is a frequent and serious event among hospitalized patients with cirrhosis, with an estimated incidence ranging from 20% to 50% depending on the population studied and diagnostic criteria used.[3,4] In this setting, AKI may result from multiple etiologies including hypovolemia, infection, nephrotoxic drugs and HRS which often coexist. The prognosis varies dramatically by underlying cause; HRS-AKI carries the worst short-term mortality, reaching up to 50–70% within 90 days, compared with other forms of AKI in cirrhosis.[5] Early identification of patients at risk of developing HRS-AKI is therefore of paramount importance, as timely initiation of vasoconstrictor therapy (e.g., terlipressin with albumin), management of precipitating factors and consideration for liver transplantation can substantially improve renal recovery and survival.[6]

The pathophysiology of HRS is complex and multifactorial. Systemic vasodilatation due to nitric oxide overproduction leads to reduced effective circulating volume, triggering activation of the renin–angiotensin–aldosterone system, sympathetic nervous system and nonosmotic vasopressin release. These adaptive mechanisms, while aimed at maintaining arterial pressure, result in profound renal vasoconstriction and sodium retention.[7,8] In addition, systemic inflammation, bacterial translocation and oxidative stress further amplify circulatory dysfunction and tubular injury, blurring the traditional boundary between "functional" and "structural" renal failure in advanced cirrhosis.[9]

Several prognostic tools have been proposed for assessing severity and outcomes in liver disease, such as the Model for end-stage liver disease (MELD), MELD-Na and the chronic liver failure–consortium (CLIF-C) scores. While these models reliably predict short-term mortality, they are not specifically designed to predict the early onset of HRS-AKI among hospitalized cirrhotic patients with AKI.[10] Moreover, the performance of these scores in predicting renal complications varies across populations and clinical contexts. Existing studies from Western cohorts may not be directly generalizable to the Indian setting, where the etiology of liver disease (predominantly alcohol-related, viral or non-alcoholic steatohepatitis), nutritional status, comorbid burden and infection profiles differ substantially.[11,12]

Indian data indicate that AKI develops in approximately one-third of hospitalized cirrhotic patients, with a considerable proportion progressing to HRS-AKI. These patients have significantly higher MELD scores, serum bilirubin levels and mortality rates compared with those without AKI.[13] Despite this high burden, there is limited evidence on predictive models specifically tailored to identify Indian patients at risk of HRS-AKI early during hospitalization. Given the variability in resource availability and the challenges in early access to vasoconstrictors and transplant evaluation in low- and middle-income settings, a simple, bedside-applicable risk score based on routine clinical and biochemical parameters could be immensely valuable.

Therefore, the objective of the present study was to develop and internally validate a simple clinical risk score for early prediction of HRS-AKI among hospitalized patients with liver cirrhosis and acute kidney injury in an Indian tertiary-care setting. In addition, the study aimed to compare the predictive performance of the derived risk score with established prognostic models such as MELD, MELD-Na and CLIF-C ACLF scores.

METHODS

Study design and setting

This was a retrospective observational cohort study conducted at the Department of General Medicine, JJM Medical College and Hospital, a tertiary care teaching hospital in Karnataka, India. The study was carried out over a period of 18 months from 1st February 2022 to 31st August 2023. Institutional Ethics Committee approval was obtained retrospectively, with a waiver of informed consent due to the observational nature of the study. The study adhered to the principles outlined in the Declaration of Helsinki (2013) and complied with STROBE and TRIPOD guidelines for development and validation of clinical prediction models.

Study population

Consecutive adult patients (aged ≥18 years) with clinically, radiologically or histologically diagnosed liver cirrhosis who were admitted to the inpatient hepatology or medical wards and developed acute kidney injury (AKI) during hospitalization were screened for inclusion.

Inclusion criteria

Adults (≥18 years) with confirmed liver cirrhosis. Presence of AKI as defined by the International Club of Ascites (ICA) 2015 criteria. Increase in serum creatinine ≥0.3 mg/dl within 48 hours or ≥50% increase in serum creatinine from baseline within 7 days. Availability of baseline renal function (within previous 3 months) or first hospital creatinine as baseline if not available.

Exclusion criteria

Hospital records showing presence of chronic kidney disease (CKD) (baseline serum creatinine >1.5 mg/dl for >3 months or ultrasonographic evidence of small kidneys). Structural or obstructive renal disease on ultrasound. Shock or sepsis requiring vasopressors at admission. Ongoing nephrotoxic drug use (e.g., aminoglycosides, NSAIDs, contrast agents) within 7 days

prior to AKI onset. Known hepatocellular carcinoma with macrovascular invasion or extrahepatic malignancy.

Operational definitions

Cirrhosis

Diagnosed based on clinical, biochemical and imaging findings (nodular liver, splenomegaly or portal hypertension) or histological confirmation.

Hepatorenal syndrome–acute kidney injury

Defined according to ICA 2015 criteria as AKI in cirrhotic patients meeting the following:

1No response to diuretic withdrawal and plasma volume expansion with albumin (1 g/kg body weight up to 100 g/day for 2 consecutive days). Absence of shock. No recent use of nephrotoxic drugs. No macroscopic signs of structural kidney disease (proteinuria >500 mg/day, >50 RBC/hpf or abnormal renal ultrasound).

Non- Hepatorenal syndrome–acute kidney injury

AKI due to prerenal causes (e.g., volume depletion, sepsis) or acute tubular injury.

Sample size estimation

Sample size was calculated using the rule of 10 outcome events per predictor variable for logistic regression model development. Based on an anticipated HRS-AKI incidence of 30% among hospitalized cirrhotic patients with AKI (as reported in Indian studies), A minimum of 250 patients was required to ensure stable model estimates using the rule of ≥10 outcome events per predictor variable.[13] A total of 260 patients were included.

Data collection

Data were collected retrospectively using a structured proforma. Demographic, clinical, laboratory and treatment-related data were recorded at baseline and during hospitalization.

Baseline data

Demographics

Age, sex, BMI, socioeconomic status, alcohol or viral etiology.

Clinical variables

Duration and etiology of cirrhosis, presence of ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis (SBP), mean arterial pressure (MAP) and infectious status.

Precipitating events

Gastrointestinal bleeding, infections, paracentesis without albumin, diarrhea, use of diuretics or nephrotoxins.

Comorbidities

Diabetes, hypertension, coronary artery disease.

Laboratory investigations

Liver function tests

Serum bilirubin, ALT, AST, alkaline phosphatase, serum albumin and INR.

Renal parameters

Serum creatinine, urea, sodium, potassium, urine sodium, fractional excretion of sodium (FeNa).

Inflammatory markers

White cell count, C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR).

Scores calculated

MELD, MELD-Na, Child–Turcotte–Pugh (CTP), CLIF-C ACLF score.

Outcomes

The primary outcome was the development of HRS-AKI during admission. Secondary outcomes included renal recovery, length of hospital stay, 30 day and 90-day mortality.

Renal recovery was defined as return of serum creatinine to within 0.3 mg/dl of baseline. Mortality rate was obtained from inpatient records and telephonic communication with family members.

Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY) and R version 4.3.0. Continuous variables were summarized as mean±standard deviation (SD) or median (interquartile range (IQR)) and categorical variables as frequencies and percentages.

Model development

Univariable analysis

Baseline predictors associated with HRS-AKI were assessed using Student's t-test or Mann–Whitney U test for continuous variables and Chi-square/Fisher's exact test for categorical variables.

Multivariable logistic regression

Variables with p<0.10 in univariable analysis and those with biological plausibility (e.g., MAP, bilirubin, sodium, albumin, infection, MELD, NLR) were included. Stepwise backward elimination was used to derive the final model.

Model performance

Discrimination

Assessed using the area under the receiver operating characteristic curve (AUC).

Calibration

Evaluated by calibration plot and Hosmer–Lemeshow goodness-of-fit test.

Sensitivity analysis

Sensitivity analyses were performed after excluding patients with infection-related AKI and those with incomplete follow-up to test robustness of the model.

RESULTS

Baseline characteristics

Hospital record of 280 patients with cirrhosis and AKI were screened during the study period. Twelve patients were excluded (six with chronic kidney disease, four with hepatocellular carcinoma with vascular invasion and two with incomplete records). The final analysis included 260 patients. The mean age of participants was 52.8±10.4 years and 72.6% (n=189) were male. The predominant etiology of cirrhosis was alcohol-related (58.0%), followed by hepatitis B/C (19.5%) and non-alcoholic steatohepatitis (NASH) (14.0%). The mean baseline MELD score was 22.4±6.2 and the median serum creatinine at admission was 1.4 mg/dl (IQR: 1.1–1.8). The most frequent precipitating events for AKI were infection (32%), gastrointestinal bleeding (18%) and large-volume paracentesis without albumin (15%).

Incidence and outcomes

HRS-AKI developed in 80 patients (30.7%). Median time to onset was 5 days (IQR 3–9). Mortality was significantly higher in HRS-AKI patients at both 30 days (61% vs 23%) and 90 days (78% vs 38%; p <0.001). Renal recovery occurred in 17.8% of HRS-AKI patients compared with 41.5% in non-HRS-AKI patients.

Predictors of hepatorenal syndrome–acute kidney injury

Five independent predictors were identified (Table 2). On univariate analysis, the following variables were significantly associated with development of HRS-AKI: presence of infection, low MAP, hyponatremia, high total bilirubin, low albumin, elevated MELD score and increased neutrophil-lymphocyte ratio (NLR). The derived risk score ranged from 0 to 12. Patients were stratified into low (0–3), moderate (4–7) and high (≥8) risk groups.

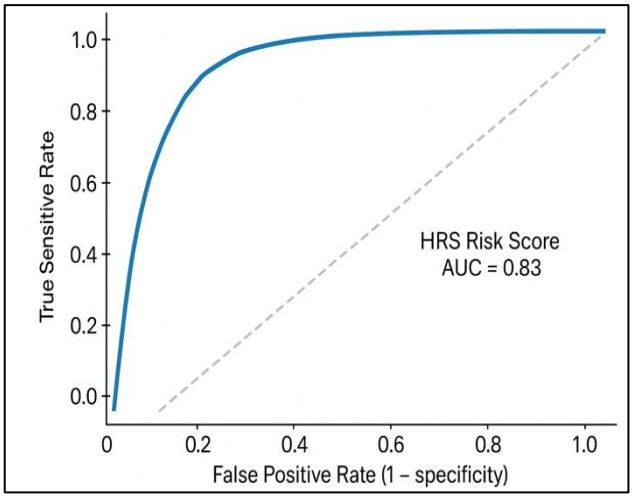

Figure 1: ROC analysis of the HRS risk score showing model discrimination for HRS-AKI prediction.

Model performance

The new HRS Risk Score showed excellent discrimination with an AUC of 0.83 (95% CI: 0.78–0.87) for predicting HRS-AKI (Figure 1). Internal validation using bootstrapping (1000 samples) yielded a bias-corrected AUC of 0.81. The model demonstrated good calibration (Hosmer–Lemeshow p=0.46) and a Brier score of 0.14.

Patients were categorized into three risk groups.

Low risk (score 0–3)

9% developed HRS-AKI.

Moderate risk (score 4–7)

29% developed HRS-AKI.

High risk (score ≥8)

67% developed HRS-AKI (p<0.001 across groups).

Risk scoring was derived from mean arterial pressure (MAP), presence of infection and selected biochemical parameters including serum sodium, total bilirubin and serum albumin. The cumulative score ranged from 0 to 12, offering a comprehensive risk quantification. Compared with conventional models, the new score outperformed. MELD (AUC 0.72), MELD-Na (AUC 0.75), CLIF-C ACLF (AUC 0.77). (DeLong test p<0.05 vs all models).

Secondary outcomes

In-hospital mortality correlated strongly with increasing risk score (8%, 31% and 62% for low-, moderate- and high-risk categories, respectively). Median time to renal recovery was shortest in the low-risk group (6 days) and longest in the high-risk group (12 days).

Table 1: Baseline characteristics of patients who developed HRS-AKI versus those who did not.

Parameter	HRS-AKI (n=80)	Non-HRS-AKI (n=180)	P value
Age (in years)	54.1±9.8	52.2±10.6	0.18
Male (%)	(79.6)	(72.3)	0.11
Alcoholic etiology (%)	63.5	55.3	0.09
Infection at admission (%)	52.5	24.8	<0.001
MAP (mmHg)	76.3±8.1	82.1±7.4	<0.001
Serum bilirubin (mg/dl)	7.8±3.6	5.1±2.8	<0.001
Serum sodium (mmol/l)	128.7±5.9	133.1±4.8	<0.001
Serum albumin (g/dl)	2.6±0.4	3.0±0.5	<0.001
MELD score	26.8±6.3	20.8±5.4	<0.001
NLR (neutrophil/lymphocyte ratio)	8.9±3.2	5.4±2.7	<0.001

Values expressed as mean±SD unless otherwise indicated.

Table 2: Multivariable logistic regression analysis showing five independent predictors.

Predictor	Adjusted odds ratio (95% CI)	P value	Score points
Ref MAP>80 mmHg	2.4 (1.4–4.1)	0.002	2
MAP <80 mmHg			
Ref serum sodium >130 mmol/l	2.7 (1.6–4.5)	<0.001	2
Serum sodium <130 mmol/l			
Ref total bilirubin <6 mg/dl	2.9 (1.7–5.1)	<0.001	3
Total bilirubin ≥6 mg/dl			
Ref serum albumin >2.8 g/dl	2.1 (1.2–3.6)	0.008	2
Serum albumin ≤2.8 g/dl			
Ref no infection	3.5 (2.1–5.8)	<0.001	3
Infection at admission			

Total score range: 0-12.

DISCUSSION

In this retrospective cohort study of hospitalized cirrhotic patients with AKI, we developed and internally validated a simple, bedside-applicable clinical risk score to predict early development of HRS-AKI. The score, derived from five easily available clinical and laboratory parameters mean arterial pressure, serum sodium, total bilirubin, albumin and infection status demonstrated strong discrimination (AUC 0.83) and calibration, outperforming existing liver prognostic models such as MELD, MELD-Na and CLIF-C ACLF in predicting HRS-AKI.

The findings confirm that HRS-AKI remains a major cause of mortality among hospitalized cirrhotic patients, affecting nearly one-third of those with AKI. The observed incidence (30.7%) aligns with previously reported Indian studies (25–35%) and global cohorts (20–40%).[3,5,13] The high mortality in HRS-AKI (78% at 90 days) underscores the critical importance of early detection and intervention. The five predictors identified are pathophysiologically sound. Low MAP reflects impaired effective arterial volume and systemic vasodilatation typical of advanced portal hypertension. Hyponatremia is a marker of circulatory dysfunction and vasopressin activation. Hyperbilirubinemia indicates advanced hepatic failure and poor hepatic clearance of vasodilators. Hypoalbuminemia reflects impaired hepatic synthesis and contributes to decreased oncotic pressure and circulatory collapse. Infection, a common precipitant in cirrhosis, aggravates systemic inflammation and precipitates renal vasoconstriction through cytokine-mediated mechanisms.[7-9]

The derived risk score is clinically intuitive and can be applied at bedside using routine admission parameters, without the need for invasive or costly biomarkers. Stratifying patients into low, moderate- and high-risk groups allows clinicians to individualize management for example, initiating early albumin and vasoconstrictor therapy, avoiding nephrotoxins and considering early referral for liver transplantation in high-risk cases. Previous efforts to predict renal dysfunction in cirrhosis have largely focused on mortality or acute-on-chronic liver failure (ACLF) outcomes. Jalan et al proposed the CLIF-C ACLF score and Angeli et al redefined HRS-AKI to enable earlier recognition.[1,10] However, few studies

have specifically aimed to predict the transition from AKI to HRS-AKI, especially in the Indian population.

The model's AUC of 0.83 compares favorably with Western predictive tools (AUC 0.75–0.80) and uses simpler variables accessible even in resource-limited settings.[5,7] The inclusion of infection as a key variable reflects regional disease patterns, consistent with studies from South and East Asia showing higher infection-triggered HRS incidence.[11,12]

The study has clinical implications -the risk score has immediate clinical utility such as.

Triage

Identify patients needing intensive monitoring and early intervention.

Therapeutic guidance

Prioritize early vasoconstrictor therapy and albumin in high-risk patients.

Resource allocation

Optimize ICU admissions and transplant evaluation in tertiary hospitals.

Research standardization

Provide a uniform tool for risk stratification in future HRS-AKI trials in India.

The study has several important clinical implications. The risk score has immediate clinical utility, single-region design, absence of external validation and potential underestimation of structural kidney injury (due to limited urinary biomarker testing). Future studies integrating biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) or interleukin-18 may further enhance accuracy. The strength of our study is standardized diagnostic criteria (ICA 2015), comprehensive data capture and rigorous internal validation. The score's simplicity enhances its real-world applicability. However, future studies should integration with biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) or interleukin-18 may also enhance accuracy for differentiating functional from structural AKI in cirrhosis.

This study has certain limitations. Its retrospective and single-center design may limit generalizability and introduce potential bias. External validation of the risk score was not performed and advanced renal biomarkers were not routinely available, which may have limited differentiation between functional and structural kidney injury. Future multicenter prospective studies with external validation and incorporation of biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) or interleukin-18 are needed to further improve predictive accuracy.

CONCLUSION

This study successfully developed and internally validated a practical, non-invasive clinical risk score for early prediction of HRS-AKI in hospitalized cirrhotic patients. The score integrates common clinical and biochemical parameters easily measurable in Indian hospital settings, demonstrating superior predictive accuracy compared with traditional liver severity scores. Routine use of this model can assist clinicians in identifying high-risk patients early, guiding prompt albumin therapy, infection control and hemodynamic optimization before irreversible renal injury ensues.

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