ORIGINAL ARTICLE

Point-of-care Ultrasonography in Patients with Hepatorenal Syndrome: A Single Center Observational Study

Vedaghosh Amara[1], Anand V Kulkarni[2], Anand Gupta[3], Shantan Venishetty[4], Shanthi R Sripathi[5], L Siva K Reddy[6], Arun Kumar Tirumala[7], Puja Karandikar[8], Manasa Alla[9], Sowmya Iyengar[10], Mithun Sharma[11], Padaki N Rao[12], D Nageshwar Reddy[13]

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Abstract

Aim and Background: A combination of terlipressin and albumin is the standard of care for patients with hepatorenal syndrome-acute kidney injury (HRS-AKI). The study aimed to compare the venous congestion using lung ultrasound score (LUS) and radiographic assessment of lung edema (RALE) scores among terlipressin responders and nonresponders and survivors and non-survivors.

Materials and methods: In this single-center, prospective, observational study, we included adult patients with HRS-AKI who had received terlipressin and albumin from 28th April 2022 to 16th October 2022.

Results: Of the 102 patients included, 74.5% (95%CI: 58.7–93.2) responded to terlipressin. The median dose of terlipressin and albumin was 2 (1–8) mg/day and 100 (40–200) g for a duration of 5 (2–10) days. On Kaplan–Meier analysis, survival was 26.9% of patients in the nonresponder group compared to 61.4% in the responder group ($p = 0.001$). Day 3 LUS score worsened in 76.9% of patients in nonresponders group compared to 52.6% in responder group ($p = 0.03$). There was a significant increase in RALE score in those who died [6 (–6–48) vs alive: 0 (–4– 30); $p < 0.001$]. Lung ultrasound score had improved or been maintained in 63.6% of patients who were alive, compared to 14.9% in those who had died ($p < 0.001$). On multivariable Cox regression analysis, age [HR, 1.02 (1.002–1.05)], terlipressin non-response [HR, 2.8 (1.47–5.34)], APACHE score [HR, 1.07 (1.03–1.12)], duration of terlipressin therapy [HR, 0.37 (0.27–0.5)] and worsening of LUS [HR, 2.9 (1.81–7)] predicted mortality.

Conclusion: Lung ultrasound score and chest X-ray can accurately identify venous congestion in the lungs, which is common in patients with advanced liver disease who receive terlipressin and albumin in the intensive care unit (ICU).

Keywords: Acute kidney injury, Acute-on-chronic liver failure, Cirrhosis, Liver, Point-of-care ultrasonography, Terlipressin.

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Highlights

- Point-of-care ultrasonography is invaluable in the intensive care unit (ICU).
- Use of terlipressin and albumin in the liver ICU is common for Hepatorenal syndrome-acute kidney injury (HRS-AKI).
- Lung ultrasound score (LUS) worsened in terlipressin nonresponders.
- Lung ultrasound score and radiographic assessment of lung edema (RALE) score can identify patients at risk of mortality.
- Acute physiology and chronic health evaluation score >20.5 predicted mortality with a sensitivity of 70.2% and specificity of 74.5%.

[1,3,6–8]Department of Critical Care Medicine, AIG Hospitals, Hyderabad, Telangana, India

[2,4,5,9–13]Department of Hepatology and Liver Transplantation, AIG Hospitals, Hyderabad, Telangana, India

Corresponding Author: Anand V Kulkarni, Department of Hepatology and Liver Transplantation, AIG Hospitals, Hyderabad, Telangana, India

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Introduction

Hepatorenal syndrome-acute kidney injury is a functional renal injury secondary to liver cirrhosis. The definitive treatment for HRS-AKI is liver transplantation. However, it is desired to achieve acute kidney injury (AKI) resolution prior to transplant.[1] Acute kidney injury resolution prior to transplant abates the need for renal replacement therapy and reduces the incidence of chronic kidney disease (CKD) post-transplant.[2,3] To achieve this, a combination of volume expander and vasoconstrictor to counter hypovolemia and splanchnic vasodilation is the approved treatment for HRS-AKI.[4] Human albumin infusions are the drug of choice for volume expansion. Among the three vasoconstrictors (terlipressin, noradrenaline and midodrine), terlipressin is a favored drug due to its superior efficacy and ease of administration.[5] However, recent studies suggest an increased risk of volume overload due to a reduction in cardiac index and an increase in after load with terlipressin.[6,7] Furthermore, the administration of albumin can have additive effects and can precipitate volume overload. Thus, it is important to identify those who develop adverse events early to reduce morbidity and mortality.

Point-of-care ultrasonography (POCUS) has become an indispensable tool for the clinician and has revolutionized the care of critically ill patients.[8–11] Patients with cirrhosis and AKI or septic shock, in the ICU require volume expansion with albumin or crystalloid infusions. Thus meriting frequent monitoring for volume

overload. Currently, few studies have reported the beneficial role of POCUS in patients with HRS-AKI receiving terlipressin.[12] However, no studies have combined POCUS and chest radiography-based RALE scores for assessing outcomes in patients with HRS-AKI being treated with terlipressin plus albumin, which we aimed to assess.

Materials and Methods

In this single-center, prospective, observational cohort study, we included consecutive adult patients with HRS-AKI who had received terlipressin and albumin from 28th April 2022 to 16th October 2022 in the liver ICU. We excluded patients with chest trauma, pleural effusion, pneumothorax, hemothorax, rib fractures, preexisting cardiac failure, chronic kidney disease, pulmonary artery hypertension or cardiac arrhythmias. We also excluded those with a history of allergy to terlipressin or albumin, those who received octreotide/midodrine or noradrenaline, hepatocellular carcinoma and those who refused to participate. The objectives of the study were to assess the terlipressin response rate in advanced liver disease patients admitted to the ICU, compare the venous congestion using LUS and RALE scores in patients receiving terlipressin plus albumin on days 1 and 3 among terlipressin responders and nonresponders and among those who died and were alive, and to assess the predictors of in-hospital mortality using Cox regression analysis. The study was approved by the Institutional Ethical Committee via the letter number AIG/IEC-BH&R21/11.2021-01 and the study was registered at the Clinical Trials Registry of India (CTRI)/2021/12/038610. Informed consent was obtained from the patient or a legally authorized representative before recruitment.

Patients with cirrhosis were included, and the clinical data, including age, gender, etiology, comorbidities, and biochemical data, including hemogram, liver function test and renal function tests, were noted. Severity scores, including sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation-II (APACHE-II) and model for end-stage liver disease (MELD) scores, were calculated. Acute-on-chronic liver failure (ACLF) was defined as per the Asia Pacific Association for Study of Liver (APASL) criteria.[13] Hepatorenal syndrome-acute kidney injury was diagnosed as per previous International Club of Ascites guidelines which identified HRS-AKI as those patients with cirrhosis, ascites and AKI who do not respond to volume expansion and have no other explainable (intrarenal or pre-renal) cause for AKI.[14] The hospital protocol for HRS-AKI includes albumin 20 gm/day with terlipressin 2 mg continuous infusion over 24 hours, and the cumulative dose of albumin and terlipressin was noted.[15] Terlipressin dose was doubled if the serum creatinine did not decrease by 25% every 48 hours.[14,15] A complete terlipressin response was defined as regression in the AKI stage with a final serum creatinine value <0.3 mg/dL of the baseline and partial if >0.3 mg/dL.[14] While those who did not achieve a reduction or had an increase in serum creatinine were labeled as nonresponders. These nonresponders were changed to either noradrenaline octreotide/midodrine. The drug was stopped when the patient developed adverse events, or responded to the therapy, or was a nonresponder despite the maximum recommended duration of therapy (i.e., 14 days). The LUS and RALE scores were assessed on the first and third days of terlipressin therapy. Lung ultrasound score was done using the Philips Ultrasound Solutions machine's curvilinear probe. Twelve regions in both lungs were examined, and the amount of lung aeration loss was calculated.[16,17] The minimum score of LUS was 0, and the maximum was 36 points. Supplementary Table 1 shows the scoring method for LUS.[16] The CXR performed on days 1 and 3 was assessed to calculate the RALE score.[18] The RALE score ranges between 0 (no infiltrates) and 48 (maximum score for dense consolidation). Supplementary Table 2 shows the calculation of RALE score.[18] LUS and RALE scores were assessed by only one of the two senior skilled intensivists (VA or AG) every morning for these patients.

Statistical Analysis

Continuous variables are expressed as mean with standard deviation or median with range for parametric and non-parametric data. Categorical variables are expressed as proportions (*n*, %). Continuous variables are compared using the student *t*-test or Mann–Whitney *U* test, and categorical variables using the Chi-square test or Fisher exact test. Kaplan–Meier survival analysis was performed to compare the survival among terlipressin responders and nonresponders. The predictors of mortality were derived from Cox regression analysis, including variables that were found to be significant ($p < 0.1$) in univariate analysis and presented as hazard ratios (HR). A receiver operator characteristic (ROC) curve analysis was performed for continuous variables that were found to be significant in multivariable analysis. A *p*-value of < 0.05 was considered significant.

Results

A total of 102 patients admitted to the liver ICU during the study period were included after excluding 59 patients due to various reasons (Fig. 1). The mean age was 50.1 ± 12.2 years, and 67.6% of patients were men. The most common etiology of liver disease was alcohol in 60.8% of patients, followed by metabolic dysfunction-associated steatohepatitis (MASH). Approximately 64.7% of patients met the criteria of APASL ACLF, and 35.3% had decompensated cirrhosis. Sixteen percent and 13.7% of patients were diabetic and hypertensive. The mean SOFA, APACHE and MELD Na scores on the day of terlipressin initiation were 11.87 ± 3, 20.8 ± 7, and 25.8 ± 7, respectively. The baseline characteristics of the included patients are described in Table 1.

Response of HRS-AKI

The median serum creatinine levels at diagnosis of HRS-AKI were 2.3 (1.5–9.1) mg/dL in the whole cohort. The median dose of terlipressin was 2 (1–8) mg/day for a duration of 5 (2–10) days. Cumulative dose of albumin received during this period was 102.5 ± 29.7 grams. Approximately 74.5% ($n = 76/102$; 95%CI: 58.7–93.2) responded to terlipressin. Thirty-eight percent (39/102) were complete responders, and 36.3% (37/102) were partial responders. There were no differences between terlipressin responders and nonresponders except APACHE score (responder: 19.9 ± 6.4 vs nonresponder:23.3 ± 8; $p = 0.03$) and terlipressin dose (responder: 2.47 ± 0.9 mg/d vs nonresponders:6.2 ± 1.7 mg/d; $p < 0.001$). Table 2 highlights the differences between terlipressin responders and nonresponders. The proportions of patients responding to terlipressin were similar in ACLF (72.7%) and decompensated cirrhosis (77.8%; $p = 0.57$). There was a significant decline in the serum creatinine in the responders group than nonresponders on day 3 (delta change: −0.95 ± 0.83 vs 0.53 ± 0.86; $p < 0.001$). Radiographic assessment of lung edema scores on days 1 and 3 were similar in both terlipressin responders and nonresponders. The proportion of patients who had worsening RALES scores was similar among responders and nonresponders (50 vs 61.5%; $p = 0.3$).

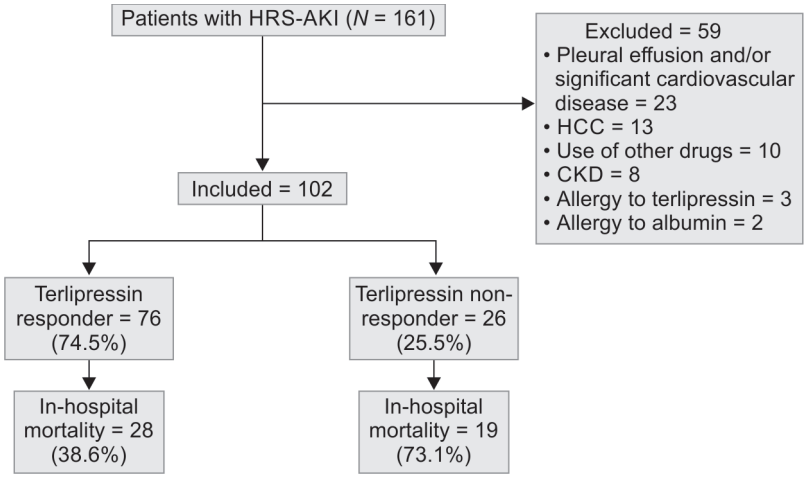

Fig. 1: CONSORT chart

CKD, chronic kidney disease; HCC, hepatocellular carcinoma

Table 1: Clinical and biochemical characteristics of the patients at baseline

Variables	*Total (N = 102)*
Age (years)	50.1 ± 12.2
Men (*n*, %)	69 (67.6%)
Women (*n*, %)	33 (32.4%)
Etiology	
Alcohol	62 (60.8%)
MASH	17 (16.7%)
Viral	10 (9.8%)
Others	13 (12.77%)
Comorbidities	
Diabetes mellitus	16 (15.7%)
Hypertension	14 (13.7%)
ACLF	66 (64.7%)
DC	36 (35.3%)
Hemoglobin (gm/dL)	9.5 ± 2.1
Total leukocyte counts (cells/mm^3)	12,144.1 ± 6,911.6
Platelets (×10^9/L)	117.1 ± 78.1
Total bilirubin (mg/dL)*	11.1 (0.5–45.7)
Direct bilirubin (mg/dL) *	6.3 (0.1–32.6)
Albumin (gm/dL) on day 1	2.6 ± 0.5
Albumin (gm/dL) on day 3	2.9 ± 0.5
INR	2.1 ± 0.8
Blood urea nitrogen (mg/dL)*	55 (13–276)
Serum creatinine (mg/dL) on day 1*	2.3 (1.5–9.1)
Serum creatinine (mg/dL) on day 3*	1.85 (0.62–7.85)
Serum sodium (mEq/dL)	132 ± 8
MELD Na	25.8 ± 7
APACHE score	20.8 ± 7
SOFA score	11.87 ± 3
Terlipressin dose	3.42 ± 2
Duration of terlipressin (days)	5.6 ± 1.4
Albumin dose	102.5 ± 29.7
ET culture positive	10 (9.8%)
Blood culture positive	17 (16.7%)
RALE score day 1	1 (0–27)
RALE score day 3	6 (0–48)
Delta RALE day 3	2 (–6–48)
RALE score	
Improved/Stable	48 (47.1%)
Worsened	54 (52.9%)
LUS	
Improved/Maintained	42 (41.2%)
Worsened	60 (58.8%)
Terlipressin nonresponse	26 (25.2%)

*indicates data are presented in median (minimum-maximum). APACHE, acute physiology and chronic health evaluation; ACLF, acute-on-chronic liver failure; DC, decompensated cirrhosis; ET, endotracheal tube; INR, international normalized ratio; LUS, lung ultrasound score; MASH, metabolic dysfunction associated steatohepatitis; MELD Na, model for end-stage liver disease sodium; RALE, radiographic assessment of lung edema; SOFA, sequential organ failure assessment

However, the LUS score had worsened in 76.9% of patients in the nonresponder group compared to 52.6% in the responder group (p = 0.03). On Kaplan–Meier analysis, 26.9% of patients in the nonresponder group died, compared to 61.4% in the responder group (p = 0.001) (Fig. 2). None of the patients underwent liver transplantation during the hospital stay.

Dead vs Alive

The in-hospital mortality rate was 46% (N = 47/102; 95%CI: 33.8–61.3) after a median hospital stay of 10 (2–41) days. There were few differences between patients who died and those who were alive. Table 3 highlights the differences between those who died and those who were alive. These included age, hemoglobin levels, total leukocyte counts, APACHE score, and proportion of patients with endotracheal (ET) culture positivity. As the proportion of terlipressin nonresponders was higher among patients who died (40.4%;19/47) compared to those who were alive (12.7%; 7/55; p = 0.001), the dose of terlipressin was higher among those who died (3.85 ± 2.3 vs 3 ± 1.67; p = 0.04). The baseline RALE score was higher in those who

Table 2: Characteristics of terlipressin responders and nonresponders

Variables	*Responder (N = 76)*	*Nonresponder (N = 26)*	*p-value*
Age (years)	50.2 ± 11.7	49.4 ± 13.6	0.77
Men (*n*, %)	50 (65.8%)	19 (73.1%)	0.49
Women (*n*, %)	26 (34.2%)	7 (26.9%)	
Etiology			0.62
Alcohol	44 (57.9%)	18 (69.2%)	
MASH	14 (18.4%)	3 (11.5%)	
Viral	7 (9.2%)	3 (11.5%)	
Others	11 (14.5%)	2 (7.7%)	
Comorbidities			
Diabetes mellitus	13 (17.1%)	3 (11.5%)	0.75
Hypertension	12 (15.8%)	2 (7.7%)	0.3
ACLF	48 (63.2%)	18 (69.2%)	0.57
DC	28 (936.8%)	8 (30.8%)	
Hemoglobin (gm/dL)	9.3 ± 2	10 ± 2.4	0.14
Total leukocyte counts (cells/mm^3)	11,821 ± 6,525.7	13,088.4 ± 7,999.5	0.42
Platelets (×10^9/L)	111.9 ± 67	131.9 ± 102.6	0.69
Total bilirubin (mg/dL)*	10.3 (0.5–45.7)	12 (1.1–33.8)	0.83
Direct bilirubin (mg/dL) *	5.8 (0.1–32.6)	7.2 (0.2–15.7)	0.97
Albumin (gm/dL) on day 1	2.6 ± 0.5	2.6 ± 0.4	0.96
Albumin (gm/dL) on day 3	2.9 ± 0.4	2.8 ± 0.4	0.12
INR	2.1 ± 0.8	2.2 ± 0.7	0.65
Blood urea nitrogen (mg/dL)*	57 (17–255)	52.5 (13–276)	0.81
Serum creatinine (mg/dL) on day 1*	2.34 (1.5–8.4)	1.82 (1.53–9.1)	0.75
Serum creatinine (mg/dL) on day 3*	1.4 (0.62–6.89)	2.58 (1.71–7.85)	<0.001
Serum sodium (mEq/dL)	132.1 ± 7.7	131.7 ± 9	0.82
MELD Na	25.9 ± 7.1	25.7 ± 6.7	0.88
APACHE score	19.9 ± 6.41	23.3 ± 8	0.03
SOFA score	12 ± 2.9	11.2 ± 3	0.22
ET culture positive	8 (10.5%)	2 (7.7%)	0.67
Blood culture positive	13 (17.1%)	4 (15.4%)	0.83
RALE score day 1	0 (0–27)	3 (0–18)	0.9
RALE score day 3	6 (0–48)	8 (0–28)	0.94
Delta RALE day 3	1 (–6–48)	4 (–3–24)	0.86
RALE score			
Improved/Stable	38 (50%)	10 (38.5%)	0.3
Worsened	38 (50%)	16 (61.5%)	
LUS			
Improved/Maintained	36 (47.4%)	6 (23.1%)	0.03
Worsened	40 (52.6%)	20 (76.9%)	
Total dose of albumin (g)	102.3 ± 29	103.1 ± 32.3	0.91
Terlipressin dose (mg/d)	2.4 ± 0.9	6.2 ± 1.7	<0.001
Delta creatinine on day 3	–0.95 ± 0.83	0.53 ± 0.86	<0.001
Died	28 (36.8%)	19 (73.1%)	0.001

*indicates data are presented in median (minimum-maximum). APACHE, acute physiology and chronic health evaluation; ACLF, acute-on-chronic liver failure; DC, decompensated cirrhosis; ET, endotracheal tube; INR, international normalized ratio; LUS, lung ultrasound score; MASH, metabolic dysfunction associated steatohepatitis; MELD Na, model for end-stage liver disease sodium; RALE, radiographic assessment of lung edema; SOFA, sequential organ failure assessment;

died [4 (0–27) vs 0 (0–21); $p = 0.01$]. Similarly, the RALE score on day 3 was higher in those who died [12 (0–48) vs 4 (0–48); $p < 0.001$]. There was a significant increase in RALE score in those who died [6 (–6 – 48)] compared to those who were alive on day 3 [0 (–4–30); $p < 0.001$]. LUS score had improved or been maintained in 63.6% of patients who were alive, compared to 14.9% in those who had died ($p < 0.001$).

Predictors of Mortality

The predictors of mortality in the whole cohort are described in Table 4. On univariable Cox regression analysis, age, hemoglobin levels, total leukocyte counts, terlipressin dose, terlipressin non-response, APACHE score, RALE score on day 3, and worsening of LUS predicted mortality. However, on multivariable analysis, only age [HR, 1.02 (1.002–1.05); $p = 0.03$], terlipressin non-response [HR, 2.8

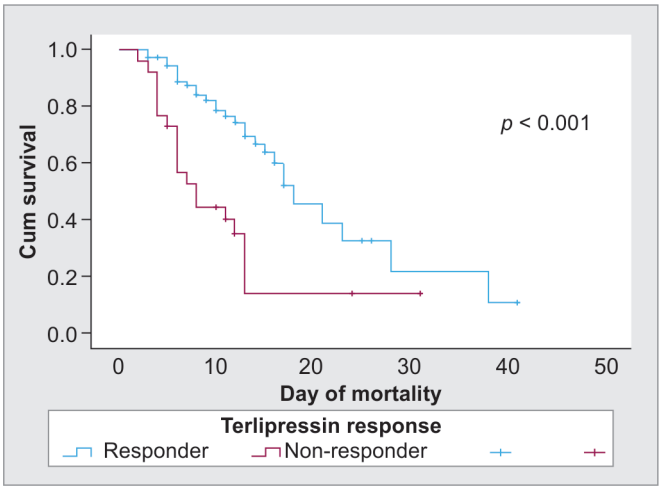

Fig. 2: Kaplan–Meier survival analysis among terlipressin responders and nonresponders

(1.47–5.34); $p = 0.002$], APACHE score [HR, 1.07 (1.03–1.12); $p = 0.001$], duration of terlipressin therapy [HR,0.37 (0.27–0.5); $p < 0.001$] and worsening of LUS [HR, 2.9 (1.81–7); $p = 0.02$] predicted mortality. When we excluded LUS from multivariable analysis, the RALE score on day 3 [HR,1.04 (1.01–1.06); $p = 0.001$], total leukocyte counts, and dose of albumin [HR, 0.97 (0.96–0.98); $p < 0.001$] were a significant predictors of mortality. An APACHE score >20.5 predicted mortality with a sensitivity of 70.2%, and specificity of 74.5%, and AUROC of 0.78 (95%CI: 0.69–0.87; $p < 0.001$). Age and duration of terlipressin were not found to be significant in the ROC analysis.

Adverse Events

A total of 16.7% ($n = 17$) of patients developed adverse events. Most of the adverse events were grade I (47.1%), followed by grade II (29.4%) and III (23.5%). Grade II and III adverse events patients were withdrawn from therapy. The most common adverse event was abdominal pain and diarrhea in varying combinations in 58.8% ($n = 10$) of patients. Seventeen percent ($n = 3$) of patients developed hypertension, and 11.8% ($n = 2$) of each developed arrhythmia and

Table 3: Clinical and biochemical characteristics of the alive and dead patients

Variables	*Alive (N = 55)*	*Dead (N = 47)*	*p-value*
Age (years)	47.7 ± 10.9	52.8 ± 13.1	0.03
Men (*n*, %)	37 (67.3%)	32 (68%)	0.93
Women (*n*, %)	18 (32.7%)	15 (32%)	
Etiology			0.88
Alcohol	33 (60%)	29 (61.7%)	
MASH	10 (18.2%)	7 (14.9%)	
Viral	6 (11%)	4 (8.5%)	
Others	6 (11%)	7 (14.9%)	
Comorbidities			
Diabetes mellitus	12 (21.8%)	4 (8.5%)	0.1
Hypertension	11 (20%)	3 (6.4%)	0.08
ACLF	35 (63.6%)	31 (66%)	0.8
DC	20 (36.4%)	16 (34%)	
Hemoglobin (gm/dL)	9.1 ± 2.1	9.9 ± 2	0.03
Total leukocyte counts (cells/mm^3)	10,849.1 ± 6174.2	13,659.6 ± 7468.9	0.04
Platelets (×10^9/L)	119.8 ± 78	113.7 ± 78.9	0.69
Total bilirubin (mg/dL)*	8.5 (0.6–45.7)	15.5 (0.5–40)	0.59
Direct bilirubin (mg/dL)*	6.5 (0.2–24.6)	8.1 (0.1–32.6)	0.32
Albumin (gm/dL) on day 1	2.6 ± 0.4	2.6 ± 0.6	0.94
Albumin (gm/dL) on day 3	2.9 ± 0.5	2.9 ± 0.4	0.45
INR	2.1 ± 0.8	2.1 ± 0.8	0.1
Blood urea nitrogen (mg/dL)*	51 (17–242)	58 (13–276)	0.45
Serum creatinine (mg/dL) on day 1*	2.34 (1.5–8.4)	2.23 (1.51–9.1)	0.61
Serum creatinine (mg/dL) on day 3*	1.4 (0.62–7.85)	1.99 (0.67–6.91)	0.35
Serum sodium (mEq/dL)	131.8 ± 8.1	132.2 ± 8	0.8
MELD Na	26.3 ± 6.7	25.2 ± 7.3	0.42
APACHE score	17.6 ± 5.2	24.5 ± 6.8	<0.001
SOFA score	12 ± 2.8	11.6 ± 3	0.45
Terlipressin dose	3 ± 1.67	3.85 ± 2.3	0.04
Duration of terlipressin (days)	5.8 ± 1.4	5.3 ± 1.4	0.056
Albumin dose	105.4 ± 31.6	99.1 ± 27.3	0.28
ET culture positive	2 (3.6%)	8 (17%)	0.04
Blood culture positive	10 (18.2%)	7 (14.9%)	0.65

(Contd...)

Table 3: *(Contd...)*

Variables	*Alive (N = 55)*	*Dead (N = 47)*	*p-value*
RALE score day 1	0 (0–21)	4 (0–27)	0.01
RALE score day 3	4 (0–48)	12 (0–48)	<0.001
Delta RALE day 3	0 (–4–30)	6 (–6–48)	<0.001
RALE score			
Improved/Stable	32 (58.2%)	16 (34%)	0.01
Worsened	23 (41.8%)	31 (66%)	
LUS			
Improved/Maintained	35 (63.6%)	7 (14.9%)	<0.001
Worsened	20 (36.4%)	40 (85.1%)	
Terlipressin non-response	7 (12.7%)	19 (40.4%)	0.001

*indicates data are presented in median (minimum-maximum). APACHE, acute physiology and chronic health evaluation; ACLF, acute-on-chronic liver failure; DC, decompensated cirrhosis; ET, endotracheal tube; INR, international normalized ratio; LUS, lung ultrasound score; MASH, metabolic dysfunction associated steatohepatitis; MELD Na, model for end-stage liver disease sodium; RALE, radiographic assessment of lung edema; SOFA, sequential organ failure assessment

Table 4: Predictors of mortality on univariable and multivariable stepwise Cox regression analysis

Variables	*Univariate HR (95%CI)*	*p*	*Multivariate HR (95%CI)*	*p*
Age	1.02 (0.99–1.04)	0.06	1.02 (1.002–1.05)	0.03
Male sex	1.68 (0.85–3.3)	0.12		
Hemoglobin	1.12 (0.98–1.3)	0.09		
TLC	1	0.08	1*	0.03
Platelet count	0.99 (0.99–1.002)	0.34		
Total bilirubin	0.98 (0.96–1.01)	0.31		
INR	1.07 (0.75–1.51)	0.7		
Sodium	1.001 (0.96–1.04)	0.95		
Blood urea	1.002 (0.99–1.007)	0.36		
Creatinine day 1	0.95 (0.77–1.17)	0.95		
Creatinine day 3	1.1 (0.88–1.34)	0.41		
Serum albumin day 1	0.77 (0.44–1.35)	0.37		
Serum albumin day 3	0.85 (0.48–1.5)	0.59		
Terlipressin non responder	2.93 (1.62–5.32)	<0.001	2.8 (1.47–5.34)	0.002
Terlipressin dose	1.16 (1.01–1.34)	0.02		
Duration of terlipressin	0.45 (0.35–0.58)	<0.001	0.37 (0.27–0.5)	<0.001
Albumin dose	0.98 (0.97–0.99)	<0.001	0.97 (0.96–0.98)*	<0.001
MELD Na	0.97 (0.93–1.02)	0.28		
APACHE	1.1 (1.05–1.14)	<0.001	1.07 (1.03–1.12)	0.001
SOFA score	0.96 (0.87–1.07)	0.56		
RALE day 1	1.03 (0.99–1.07)	0.09		
RALE day 3	1.03 (1.01–1.05)	0.002	1.04 (1.01–1.06)*	0.001
LUS (worsened vs improved)	4.05 (1.81–9)	<0.001	2.9 (1.81–7)	0.02
Change in RALE score on day 3	1.03 (1.008–1.05)	0.007		

*When we excluded LUS from multivariable analysis, the variables which were significant were day 3 RALEs score, albumin dose and total leukocyte count, apart from age, APACHE score, and terlipressin non-response. APACHE, acute physiology and chronic health evaluation; LUS, lung ultrasound score; MELD Na, model for end-stage liver disease sodium; RALE, radiographic assessment of lung edema; SOFA, sequential organ failure assessment; TLC, total leukocyte count

volume overload. There was no significant difference in the RALE score on days 1 and 3 in those who developed adverse events [Day 1: 0 (0–12) and Day 3:6 (0–48)] and those who did not [Day 1: 2 (0–27) and Day 3: 6 (0–48)]. Similarly, the LUS score worsened in a similar proportion of patients in both groups (58.8% in each group). Approximately 65% (11/17) died in the hospital in the adverse event group, while 42.4% (36/85) died in the no adverse event group ($p = 0.09$).

Discussion

The salient features noted in the current study include: (a) a quarter of patients admitted to ICU do not respond to terlipressin; (b) survival is significantly poorer in terlipressin nonresponders than responders (26.9 vs 63.2%); (c) LUS had worsened in all patients receiving terlipressin more so in nonresponders and those who died; (d) RALE score worsens in those who die.

Terlipressin, a preferential agonist of V1 (located on the splanchnic vasculature) more than V2 (renal tubules), is the most effective drug for HRS-AKI.[5] In recent studies, the response rate for terlipressin has been reported to be between 40 and 85%.[6,19] The variable response is related to the severity of liver disease (based on MELD score and/or grade of ACLF), severity of kidney dysfunction (higher serum creatinine), and the presence or absence of concomitant sepsis.[5,7,20] In the current study, terlipressin was effective in ICU settings as well, with a cumulative response rate of 75%, and those who did not respond had poor hospital survival similar to the previous studies.[15] The survival noted here was lower primarily due to the inclusion of sick patients from the ICU. Therefore, apart from terlipressin nonresponse, APACHE score also predicted mortality.

The incidence of respiratory failure was significantly higher in the treatment arm (10 vs 3%) than in the placebo in the landmark (CONFIRM) trial, which evaluated terlipressin in HRS-AKI.[6] However, >80% of patients in the said trial had received high volumes of albumin concomitantly, which exponentially increased the risk of pulmonary oedema. In our study, 16.7% of patients developed adverse effects, predominantly abdominal pain and diarrhea and similar to previous studies, volume overload was seen in 11.8% of patients. The depressing effect on cardiac index and concomitant increase in after load and end-diastolic volume with terlipressin have been attributed to pulmonary overload.[7,21] Furthermore, pre-existing low systolic function in patients with undiagnosed cirrhotic cardiomyopathy can further worsen renal dysfunction and precipitate terlipressin-related pulmonary complications.[22,23] These patients, therefore, merit a POCUS and chest X-ray-based regular evaluation. In our study, terlipressin nonresponders had worsening LUS compared to responders (76.9 vs 52.6%). This can also be attributed to the higher terlipressin dose used in nonresponders (6.2 vs 2.47 mg/d). Nevertheless, the worsening of LUS and RALE scores on day 3 predicted mortality.

A recent study reported that early terlipressin initiation (at 12 hours) can lead to a higher response rate and lower mortality for patients with ACLF and AKI. The decision to initiate early was solely based on biochemical criteria, i.e., the lack of creatinine decline with albumin infusions at 12 hours.[24] With the conventional criteria for diagnosis of HRS-AKI, all patients should receive volume expansion for an initial 48 hours, which can be avoided by early initiation of terlipressin. Furthermore, the beneficial role of universal albumin infusions for hospitalized patients with cirrhosis has been contradictory.[25,26] A recent study, therefore, used POCUS to assess volume status and initiate early terlipressin. The authors reported that using POCUS to evaluate inferior vena cava (IVC) diameter and collapsibility can accurately identify volume-depleted patients requiring further volume expansion and those not.[27] Another similar study reported that POCUS performed at admission, and after terlipressin initiation and 24 hours later could identify cirrhotic cardiomyopathy in patients with HRS-AKI, which increased the risk of pulmonary oedema and mortality independent of age, sex and comorbidities.[12] In the absence of ultrasound, chest X-ray can be utilized to identify pulmonary edema, as shown in the current study.

There are a few limitations to this current study. We limited ourselves to lung evaluation and did not perform POCUS for cardiac assessment, which could have added more value. We also did not assess IVC as all the patients had ascites, and IVC assessment in such patients can be fallacious. Further, being a time-bound study with a limited sample size, it is difficult to draw strong conclusions on predictors of mortality, and further research is required. Lastly, a control group from the ICU who did not receive terlipressin could have been included, which would have differentiated the effect of terlipressin from albumin, which we did not.

In conclusion, terlipressin with albumin is effective in patients with HRS-AKI in ICU settings. Lung ultrasound score and RALE scores can identify those at risk of mortality early in these patients. Further randomized studies are required to confirm the role of POCUS and chest X-rays in floor settings and in patients who are less sick.

Clinical Significance

Terlipressin and albumin are commonly used for hepatorenal syndrome-acute kidney injury in the liver intensive care unit. Terlipressin nonresponders have poor survival. Worsening of lung ultrasound scores and radiographic assessment of lung edema scores can predict mortality. Therefore, such patients need to be monitored using lung ultrasound (if available) and chest radiograph.

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Author Contributions

VA and AVK: Conceptualization; VA, AKTM, PK, LSKR and AG: Methodology; AVK: Formal analysis and investigation; AVK and VA: Writing-original draft preparation; AVK, SV, MA and SI: Writing-reviewing and editing; DNR and MS: Resources; PNR: Supervision; SRS: Helped in writing, reviewing and editing.

Supplementary Material

All the supplementary tables 1 and 2 are available on the website www.ijccm.org.

Orcid

Vedaghosh Amara https://orcid.org/0000-0001-5296-2138
Anand V Kulkarni https://orcid.org/0000-0002-1240-1675
Anand Gupta https://orcid.org/0000-0002-7042-0129
Shantan Venishetty https://orcid.org/0000-0002-1346-1311
Shanthi R Sripathi https://orcid.org/0009-0006-9534-0092
L Siva Kumar Reddy https://orcid.org/0000-0003-3316-6579
Arun Kumar Tirumala https://orcid.org/0009-0007-5656-5026
Puja Karandikar https://orcid.org/0009-0006-2388-4381
Manasa Alla https://orcid.org/0000-0001-5318-2897
Sowmya Iyengar https://orcid.org/0000-0002-5098-9246
Mithun Sharma https://orcid.org/0000-0003-4497-9209
Padaki N Rao https://orcid.org/0000-0003-2983-5768
D Nageshwar Reddy https://orcid.org/0000-0001-7540-0496

References

1. Reddy KR, Weinberg EM, Gonzalez SA, Izzy MJ, Simonetto DA, Frederick RT, et al. Safety and efficacy of continuous terlipressin infusion in HRS-AKI in a transplant population. Liver Transpl 2024;30(10):1026–1038. DOI: 10.1097/lvt.0000000000000399.
2. Northup PG, Argo CK, Bakhru MR, Schmitt TM, Berg CL, Rosner MH. Pretransplant predictors of recovery of renal function after liver transplantation. Liver Transpl 2010;16(4):440–446. DOI: 10.1002/lt.22008.
3. Cullaro G, Sharma P, Jo J, Rassiwala J, VanWagner LB, Wong R, et al. Temporal trends and evolving outcomes after simultaneous liver-kidney transplantation: Results from the US SLKT consortium. Liver Transpl 2021;27(11):1613–1622. DOI: 10.1002/lt.26232.
4. Nadim MK, Kellum JA, Forni L, Francoz C, Asrani SK, Ostermann M, et al. Acute kidney injury in patients with cirrhosis: Acute disease

quality initiative (ADQI) and international club of ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol 2024;81(1):163–183. DOI: 10.1016/j.jhep.2024.03.031.
5. Kulkarni AV, Lee J, Reddy KR. Terlipressin in the management of adults with hepatorenal syndrome-acute kidney injury (HRS-AKI). Expert Rev Gastroenterol Hepatol 2023;17(11):1067–1079. DOI: 10.1080/17474124.2023.2273494.
6. Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med 2021;384(9):818–828. DOI: 10.1056/NEJMoa2008290.
7. Kulkarni AV, Arab JP, Premkumar M, Benítez C, Tirumalige Ravikumar S, Kumar P, et al. Terlipressin has stood the test of time: Clinical overview in 2020 and future perspectives. Liver Int 2020;40(12):2888–2905. DOI: 10.1111/liv.14703.
8. Kajal K, Premkumar M, Chaluvashetty SB, Bhujade H, Kulkarni AV. Point-of-care thoracic ultrasonography in patients with cirrhosis and liver failure. Cureus 2021;13(6):e15559. DOI: 10.7759/cureus.15559.
9. Avadhanam M, Kulkarni AV. Intensive care unit care of a patient with cirrhosis. Med Clin North Am 2023;107(3):567–587. DOI: 10.1016/j.mcna.2022.12.006.
10. Premkumar M, Karvellas CJ, Kulkarni AV, Bhujade H, Reddy KR. Role of point-of-care ultrasound (POCUS) in clinical hepatology. Hepatology:10.1097/HEP.0000000000000990. DOI: 10.1097/hep.0000000000000990.
11. Chandy GM, Sathyendra S, Pichamuthu K, Hazra D, Abhilash KP. Differentiating cardiac and pulmonary causes of dyspnea using ultrasonography and dyspnea discrimination index. Indian J Crit Care Med 2022;26(1):33–38. DOI: 10.5005/jp-journals-10071-24089.
12. Premkumar M, Kajal K, Reddy KR, Izzy M, Kulkarni AV, Duseja AK, et al. Evaluation of terlipressin-related patient outcomes in hepatorenal syndrome-acute kidney injury using point-of-care echocardiography. Hepatology 2024;79(5):1048–1064. DOI: 10.1097/hep.0000000000000691.
13. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): An update. Hepatol Int 2019;13(4):353–390. DOI: 10.1007/s12072-019-09946-3.
14. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Gut 2015;64(4):531–537. DOI: 10.1136/gutjnl-2014-308874.
15. Kulkarni AV, Ravikumar ST, Tevethia H, Premkumar M, Kumar K, Sharma M, et al. Safety and efficacy of terlipressin in acute-on-chronic liver failure with hepatorenal syndrome-acute kidney injury (HRS-AKI): A prospective cohort study. Sci Rep 2022;12(1):5503. DOI: 10.1038/s41598-022-09505-1.
16. Bouhemad B, Mongodi S, Via G, Rouquette I. Ultrasound for "lung monitoring" of ventilated patients. Anesthesiology 2015;122(2):437–447. DOI: 10.1097/aln.0000000000000558.
17. Banerjee A, Mehrotra G. Comparison of lung ultrasound-based weaning indices with rapid shallow breathing index: Are they helpful? Indian J Crit Care Med 2018;22(6):435–440. DOI: 10.4103/ijccm.IJCCM_331_17.
18. Warren MA, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. Thorax 2018;73(9):840–846. DOI: 10.1136/thoraxjnl-2017-211280.
19. Kalambokis GN, Christaki M, Tsiakas I, Despotis G, Milionis HJ. Efficacy of treatment with terlipressin plus albumin in hepatorenal syndrome diagnosed with the new acute kidney injury versus the conventional criteria. Eur J Gastroenterol Hepatol 2019;31(10):1292–1294. DOI: 10.1097/MEG.0000000000001460.
20. Kulkarni AV, Kumar P, Rao NP, Reddy N. Terlipressin-induced ischaemic skin necrosis. BMJ Case Rep 2020;13(1):e233089. DOI: 10.1136/bcr-2019-233089.
21. Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. Eur J Gastroenterol Hepatol 2010;22(9):1085–1092. DOI: 10.1097/MEG.0b013e32833a4822.
22. Kaur H, Premkumar M. Diagnosis and management of cirrhotic cardiomyopathy. J Clin Exp Hepatol 2022;12(1):186–199. DOI: 10.1016/j.jceh.2021.08.016.
23. Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut 2010;59(1):105–110. DOI: 10.1136/gut.2009.180570.
24. Jindal A, Singh H, Kumar G, Arora V, Sharma MK, Maiwall R, et al. Early versus standard initiation of terlipressin for acute kidney injury in ACLF: A randomized controlled trial (eTerli Study). Dig Dis Sci 2024;69(6):2204–2214. DOI: 10.1007/s10620-024-08423-8.
25. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med 2021;384(9):808–817. DOI: 10.1056/NEJMoa2022166.
26. Kulkarni AV, Zuberi AA, Chaitanya K, Doolam H, Reddy S, Lakshmi PK, et al. Human albumin infusion is safe and effective even in patients without acute kidney injury and spontaneous bacterial peritonitis. Indian J Gastroenterol 2024;43(2):485–493. DOI: 10.1007/s12664-023-01475-0.
27. Roy A, Premkumar M, Tiwary I, Tiwari S, Ghoshal UC, Goenka MK. Point-of-care ultrasound permits early initiation of terlipressin in suspected hepatorenal syndrome-acute kidney injury: A single arm proof-of-concept report. Indian J Gastroenterol 2024. DOI: 10.1007/s12664-024-01608-z.