Safety And Efficacy of Terlipressin In Acute-On-Chronic Liver Failure With Acute Kidney Injury – A Prospective Cohort Study

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Abstract

Background: Terlipressin with albumin, the recommended treatment for hepatorenal syndrome-acute kidney injury (HRS-AKI), is associated with adverse events. Furthermore, the course of AKI in patients with acute-on-chronic liver failure (ACLF) is unknown. We aimed to analyze the safety and efficacy of terlipressin infusion and AKI course in patients with ACLF.

Methods: We prospectively enrolled consecutive adult patients with ACLF with HRS-AKI (satisfying either EASL or APASL criteria) treated with terlipressin infusion between 14 October 2019 and 24 July 2020. The objectives were to assess the incidence of adverse events, response to terlipressin, and differential treatment response in EASL and APASL subgroups.

Results: Of the 116 patients, 51 satisfied EASL criteria, and 65 satisfied APASL criteria. Twenty-one percent of patients developed adverse effects. Only 1/3rd of patients who developed adverse events were alive at day 90. Sixty-five percent of the patients responded to terlipressin. Nearly 22% developed recurrence of HRS, and 5.2% progressed to HRS-chronic kidney disease. Response to terlipressin was higher in EASL (78.43%) than APASL subgroup (53.84%; $P=0.006$). Terlipressin non-response predicted mortality in EASL (aHR, 6.35[1.15-35.13]; $P=0.03$) and APASL subgroups (aHR, 3.07[1.47-6.4]; $P=0.003$).

Conclusion: ACLF patients who develop terlipressin adverse events have dismal prognoses. Terlipressin non-response predicts mortality in patients with ACLF and HRS-AKI.

Introduction

Acute kidney injury (AKI) is common in acute-on-chronic liver failure (ACLF). Organ failures, especially AKI, form the diagnostic criteria for ACLF according to the European Association for the Study of the Liver (EASL) definition [1]. There is some disagreement on the definition/precipitants of ACLF across the continents. However, it is acknowledged that the presence of AKI does determine the outcome of patients with ACLF [2-4]. The cause of AKI in ACLF is multi-factorial [3, 5]. Apart from the pre-existing profound systemic inflammation in ACLF, diuretics, sepsis, and cholestasis may impair the renal function by exacerbating hypovolemia, worsening inflammation, macrovascular dysfunction, or promoting bile salt-related direct tubular damage [3, 6, 7].

Vasoconstrictor therapy (specially terlipressin) with volume expansion (with albumin) is the recommended treatment of choice for hepatorenal syndrome (HRS)-AKI to counteract systemic arterial vasodilation and hypovolemia. However, there are limited studies assessing the role of terlipressin in patients with ACLF and HRS-AKI [8-11]. Furthermore, none of the studies have highlighted the course of AKI in these sick patients and the outcomes of terlipressin non-responders [12].

Terlipressin is associated with adverse events in about 25-40% of patients with ACLF, and approximately 40% of those patients require treatment discontinuation [9, 11]. In addition, ischemic complications and volume overload are common in patients with ACLF and high model for end-stage liver disease (MELD) score [13, 14]. Continuous infusion of terlipressin leads to sustained suppression of portal pressure with a lower total dose as compared to intermittent bolus therapy [7]. This low dose infusion protocol maintains a high mean arterial pressure (MAP) with a concomitant reduction in adverse events due to terlipressin [7, 15, 16]. However, a detailed evaluation of adverse events with continuous infusion and the outcomes and implications of the adverse events have not been studied in a prospective real-world study [7, 12]. Furthermore, the incidence of HRS recurrence and progression to chronic

kidney disease (CKD) is unknown in patients with ACLF. Here we aimed to analyze the outcomes and course of HRS-AKI in patients with ACLF treated with continuous terlipressin infusion in a real-world cohort. We also evaluated the differences in response to terlipressin in patients with ACLF across two definitions, EASL and APASL (Asian Pacific Association for the Study of the Liver), which has not been studied to date as the differential use of criteria also affects outcomes [17].

Methods

This was a prospective cohort study conducted at the Asian Institute of Gastroenterology hospital, Hyderabad, India, from 14 October 2019 and completed on 24 July 2020. We included consecutive ACLF patients aged 18-75 years treated with terlipressin infusion for HRS-AKI. We recorded the baseline clinical, demographic, and biochemical data. We excluded AKI patients treated with other vasoconstrictors (octreotide/midodrine or noradrenaline), patients with CKD, hepatocellular carcinoma (HCC), and those who refused to participate.

Written informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The institutional human research ethics committee (Institutional Ethics Committee-Asian Institute of Gastroenterology [IEC-AIG]) approved the study vide letter number AIG/IEC34/07.19-16 and was registered at clinical trials registry-India (CTRI/2019/10/021737). All authors had access to the study data and reviewed and approved the final manuscript.

Objectives: The primary objective was to assess the incidence of adverse effects. The secondary objectives were to evaluate the response to terlipressin, determine the course of AKI, assess the predictors of terlipressin non-response, and lastly, determine transplant-free survival (TFS) at day 30, 90 in patients with ACLF and HRS-AKI. We compared the outcomes for each objective for EASL and APASL subgroups.

Definitions: We included both APASL and EASL definitions of ACLF [18, 19]. Patients with HRS only were graded as ACLF I; patients with HRS and one extrarenal organ failure were graded as ACLF II, and patients who had HRS with ≥ 2 organ failures were graded as ACLF III [9].

AKI was defined as a rise in serum creatinine (sCr) by 0.3mg/dl or $\geq 50\%$ rise in sCr, which is presumed or known to have occurred in the previous seven days. Patients satisfying the International Club of Ascites (ICA) criteria of HRS were classified as HRS-AKI [20]. Responders (reversal of AKI) were classified as either complete or partial responders. Complete response was defined as a reversal in the stage of AKI with a final sCr value of ≤ 0.3 mg/dL of the baseline. Partial response was defined as regression in the stage of AKI with a final sCr > 0.3 mg/dL above the baseline and non-responder if the sCr did not decrease or increased from the baseline [20]. Patients with glomerular filtration rate (GFR) < 60 ml/min per 1.73 m^2 for more than three months were considered CKD patients. Sepsis was defined as per SEPSIS-3 criteria [21].

Management of AKI

Standard therapy was initiated, i.e., withdrawal of diuretics and volume expansion with intravenous 20% albumin infusion at a dose of 1g/kg for all patients. Terlipressin infusion was initiated at 2 mg/day in the absence of shock and response to volume expansion at 48 hours, provided the renal ultrasonography, urinary protein-creatinine ratio, urine examination were normal, as per the International Club of Ascites (ICA) diagnostic criteria of HRS. The clinical and biochemical data after 48 hours of volume expansion (at the time of initiation of terlipressin therapy) was considered baseline data and enrolled for the study. The dose of terlipressin was doubled every 48-hours in

case the sCr did not decrease by 25% [20]. Terlipressin 2mg (10ml = 1mg) was diluted in 30ml of normal saline and infused over 24 hours at a rate of 2.1 ml/hour. Electrocardiogram and echocardiography were done for all patients before initiating terlipressin. Daily clinical evaluation of the enrolled patients was done by two independent investigators (STR and AVK). Patients were followed up for 90 days to observe the recurrence of HRS and outcome (transplant-free survival).

Withdrawal of terlipressin therapy was decided based on the response to treatment and the development of adverse events. Standard care of management as per institution protocol was provided to all patients. For mild adverse events, the drug dose was reduced and monitored. Severe adverse effects requiring the withdrawal of terlipressin therapy were defined as previously suggested by Cavallin *et al.* [16]. The second line of therapy included either octreotide with midodrine or noradrenaline. The timing and modality of renal replacement therapy (RRT) was planned as per the multidisciplinary team's (involving hepatologists, nephrologists, and intensivists) decision on a case-to-case basis.

Statistical analysis: The data is analyzed using SPSS version 25.0 (IBM Corp, NY, USA). Descriptive statistics will be expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) for parametric or non-parametric continuous data, respectively, and number (%) for categorical data. We used the student's t-test for comparison of means between the two groups. The categorical data are compared using Pearson's Chi-square test (or Fisher's exact test when required). The predictors of adverse events and terlipressin non-response are derived using stepwise multivariate logistic regression analysis involving parameters that have $P < 0.1$ on univariate logistic regression analysis and is expressed as odds ratio (OR). The predictors of mortality are derived using stepwise multivariate Cox regression analysis involving parameters that have $P < 0.1$ on univariate analysis and is expressed as hazard ratio (HR). The adjusted hazard ratio (aHR) was also calculated to counter the differences between the groups. Further, to find the different cut-off points for terlipressin non-response and mortality, receiver operating characteristic (ROC) curve analysis was also carried out. All statistical tests with $P < 0.05$ were considered significant.

Results

During the study period, 141 patients with ACLF were diagnosed with HRS-AKI. Of them, twenty-five patients were excluded (reasons: received midodrine and octreotide-9; CKD-8; HCC-4, refusal to participate-4). Thus, a total of 116 patients with ACLF received terlipressin therapy for HRS-AKI. The mean age in the cohort was 48.31 ± 9.01 years. Ninety-four percent were males. Alcohol was the most common acute precipitant (51%), followed by sepsis (20%). The mean MELD-sodium (MELD NA) was 31.37 ± 7.36 in the whole cohort. Baseline characteristics of the included patients are shown in **Table 1**.

All the patients in the cohort met EASL criteria. We compared those meeting only EASL criteria (n=51) against those satisfying APASL criteria (n=65). Patients in APASL group also satisfied EASL criteria. Patients in the APASL ACLF subgroup were younger with higher total leucocyte counts (TLC), serum bilirubin, and lower serum albumin. Though alcohol was the most common etiology of underlying liver disease in both groups, the acute precipitants differed. (**Table 1**) Sepsis was the common cause of acute precipitation in the EASL subgroup, while in the APASL subgroup, alcohol (77%) followed by hepatitis B virus reactivation (12.3%) was the cause. Though 57% of patients at inclusion had sepsis in the APASL subgroup, it is not considered a precipitating event for ACLF as per the APASL definition. Baseline sCr was similar in both groups. Severity scores including, MELD NA, CLIF- C (Chronic Liver Failure-Consortium) ACLF, and APASL ACLF Research Consortium (AARC) scores, were higher in the APASL group

than the EASL group. Furthermore, a greater number of patients in the APASL group belonged to grade II/III ACLF than the EASL subgroup.

Forty-five percent in the EASL subgroup and 57% in the APASL subgroup had sepsis at baseline ($P = 0.2$). The most common source of sepsis was urinary tract infection, bloodstream infection (BSI), and spontaneous bacterial peritonitis (**Supplementary Table 1**). Culture was positive in 68% of patients. Seventy-four percent in the EASL group and 65% of patients in the APASL group had culture positivity ($P=0.46$). The most common organisms isolated were *Escherichia coli* and *Klebsiella pneumonia* (**Supplementary Table 2**).

Drug therapy: The mean dose of albumin infused (per day) for the first two days was 44.48 ± 17.56 g/day in the whole cohort. The mean dose of albumin infused was similar in both the subgroups (EASL- 43.13 ± 17.71 and APASL- 45.53 ± 17.5 g/day; $P = 0.46$). The mean dose of terlipressin was 2.75 ± 0.93 mg/day for a mean duration of 5.28 ± 3.51 days in the whole cohort. The dose and duration of terlipressin therapy were similar in both groups (dose: EASL- 2.6 ± 0.82 vs. APASL- 2.86 ± 0.99 mg/day; $P = 0.11$; duration: EASL- 5.22 ± 3.22 vs. APASL- 5.34 ± 3.76 ; $P = 0.85$).

Primary Endpoint: Incidence of Adverse Events

A total of 20.7% (95% CI, 13.76-29.2) developed adverse effects to terlipressin in the whole cohort. Twelve percent of patients had to discontinue terlipressin due to adverse events. The incidence of adverse events in the EASL subgroup was 11.76% (95% CI, 4.45-23.8), while 27.7% (95% CI, 17.3-40.2) in the APASL group developed adverse effects ($P = 0.03$). (**Table 2**) Six percent in the EASL group and 17% in the APASL group had to discontinue the therapy due to adverse events ($P = 0.08$). Diarrhea and abdominal pain were the most common adverse events. Of the 24 patients who developed adverse effects, 54.2% expired, 12.5% underwent liver transplant, and 33.34% were alive at day 90 in the whole cohort ($P = 0.03$). (**Supplementary Table 3**) The incidence of ischemic adverse events were higher in APASL group (13.8%, 9/65) than EASL group (6%, 3/51; $P = 0.13$). The incidence of mortality at day 90 in patients who developed ischemic adverse events was 91.7% (EASL-2/3 vs. APASL-9/9; $P = 0.25$). MELD NA score was higher in patients who developed adverse events (MELD NA adverse events group- 34.46 ± 5.49 vs. no adverse events- 30.57 ± 7.59 ; $P = 0.02$). Presence of sepsis at baseline (OR, 4.2 [1.41-12.4]; $P = 0.01$) and baseline serum bilirubin (OR, 1.07 [1.02-1.12]; $P = 0.002$) were predictors of adverse events to terlipressin on multivariate stepwise logistic regression analysis. (**Supplementary Table 4**)

Secondary endpoints:

Efficacy of terlipressin in patients with ACLF and HRS-AKI and the course of AKI

Sixty-five percent (95%CI, 55.23-73.3) of the patients responded to terlipressin. Complete response was noted in 39.7% (46/116) and partial response in 25% (29/116). The mean time to reversal of AKI was 4.8 ± 2.64 days. Terlipressin increased the mean arterial pressure (MAP) on day 3 by 5.23 ± 3.13 mmHg and urine output by 193.41 ± 145.65 ml/day. Twenty-six percent of patients (30/116) required RRT. Nearly 22% developed recurrence of HRS, and 5.2% progressed to HRS-CKD (**Figure 1: flow of patients in the whole cohort**).

Response to terlipressin was higher in the EASL subgroup (78.43%) than the APASL subgroup (53.84%; $P = 0.006$). Complete response was noted in 53% and partial response in 25.5% in EASL subgroup while in the APASL subgroup 29.2% had complete response and 24.6% had partial response (complete response- $P = 0.01$; partial response- $P = 0.91$) (**Figure 2: flow of patients in EASL and APASL subgroup**). The mean time to reversal of AKI

was similar in both the subgroups (EASL- 4.9 ± 2.41 days vs. APASL- 4.68 ± 2.9 days; $P = 0.72$). Terlipressin increased the MAP on day 3 by 4.3 ± 2.9 mmHg in the EASL subgroup and 5.98 ± 3.12 mmHg in the APASL subgroup ($P = 0.004$). Terlipressin increased the urine output by 223.4 ± 140.3 ml/day and 170 ± 147.26 ml/day on day 3 in the EASL and APASL subgroups, respectively ($P = 0.05$). Ten percent of patients (5/51) in the EASL subgroup and 38.5% (25/65) in APASL subgroup required RRT ($P < 0.001$). There was no significant difference in the HRS recurrence, normalization of kidney function, and CKD development amongst both subgroups (P -ns).

(Figure 2)

Predictors of terlipressin non-response

On multivariate stepwise logistic regression analysis, baseline sCr (OR-2.24 [1.41-3.57]; $P = 0.001$), ACLF grade (Grade II-OR, 4.98 [1.5-16.5]; $P = 0.009$; Grade III- OR, 7.61 [1.91-30.16]; $P = 0.004$) and change in MAP at day 3 (OR, 0.73 [0.57-0.92]; $P = 0.009$) were predictors of terlipressin non-response in the whole cohort (**Table 3**). Baseline sCr > 3.02 predicted terlipressin non-response with a sensitivity of 75.6%, specificity of 84% with an AUROC of 82.2 (74.1-90.4; $P < 0.001$) (**Supplementary Figure 1A**). A change in MAP by 4.5 mmHg at day 3 predicted terlipressin response with a sensitivity of 62.7%, specificity of 67.6%, and an AUROC of 71.2 (61.5-80.9; $P < 0.001$) (**Supplementary Figure 1B**).

Change in MAP at day 3 remained significant at predicting terlipressin non-response in EASL (OR, 0.17 [0.03-0.91]; $P = 0.03$) and APASL subgroup (OR, 0.67 [0.47-0.95]; $P = 0.02$). In addition, baseline sCr (OR, 13.85 [3.15-60.8]; $P < 0.001$) predicted terlipressin non-response in APASL subgroup (**Supplementary Table 5**).

Transplant-free survival at day 30, 90

TFS in whole cohort was 70.4% (81/116) at day 30 and 57.8% at day 90. TFS at day 30 in EASL subgroup was 86% while TFS in APASL subgroup was only 58.5% ($P = 0.001$). Similarly, at day 90 TFS was 78.4% in EASL subgroup and 41.5% in APASL subgroup ($P < 0.001$). (**Figure 3**) Compared to EASL criteria, patients satisfying APASL criteria had higher mortality at day 30 (HR, 3.63 [1.46-7.72]; $P = 0.004$) and day-90 (HR, 3.53 [1.8-6.92]; $P < 0.001$). Four patients in the EASL subgroup underwent transjugular intrahepatic portosystemic shunt (TIPS) at day 90 for refractory ascites, while none in the APASL subgroup underwent TIPS.

Predictors of mortality: On multivariate stepwise Cox regression analysis terlipressin non-response (HR, 3.49 [1.85-6.57]; $P < 0.001$) and MELD NA score (HR, 1.12 [1.06-1.18]; $P < 0.001$) predicted mortality at day-90 in the whole cohort (**Table 4**). Ischemic adverse events to terlipressin predicted mortality on univariate analysis but not on multivariate analysis. On adjusting for age, serum albumin, and severity scores, terlipressin non-response retained to be a significant predictor of mortality in both the EASL (aHR, 6.35 [1.15-35.13]; $P = 0.03$) and APASL subgroups (aHR, 3.07 [1.47-6.4]; $P = 0.003$) (**Supplementary Table 6**).

Discussion

Terlipressin with albumin is an effective treatment for patients with ACLF and HRS-AKI [9, 11]. This study has demonstrated that: a) the overall incidence of adverse events due to terlipressin was 21% in ACLF patients with a higher incidence in the APASL subgroup than EASL subgroup; b) sepsis and baseline bilirubin levels predict the adverse events in patients with ACLF; c) only 1/3rd of patients who developed adverse events were alive (without transplant) at day 90; d) 65% of patients with ACLF responded to terlipressin with higher response in EASL subgroup (53%) than APASL subgroup (29.2%); e) the risk of recurrence of HRS was 21.5%; f) change in MAP at

day 3 predicted terlipressin response; g) TFS was 70.4% with higher survival in EASL subgroup than APASL subgroup h) terlipressin non-response predicted mortality in patients with ACLF and HRS-AKI regardless of the definition used.

The main strength of our study is the prospective collection of data of both EASL and APASL ACLF subgroups. There are no studies comparing the response to terlipressin in EASL and APASL ACLF patients with HRS-AKI [17]. Adverse events to terlipressin have been reported in earlier studies [22, 23]. However, none of the studies have reported the implications and outcomes associated with it [12]. Our data is the first prospective study to report the outcomes related to adverse events due to terlipressin. MELD score was higher in patients who developed adverse events, and high MELD is known to be associated with ischemic adverse effects and, thereby, mortality [13]. Patients with adverse effects had poorer TFS in both subgroups. A small trial has reported fewer ischemic complications with terlipressin, even in the presence of sepsis [8]. But the study included only 18 patients with sepsis and HRS-AKI, and there was no comparator arm. Though sepsis was associated with higher adverse events, the response to terlipressin was unaltered by the presence of sepsis akin to the previous studies [8, 11]. Hyperbilirubinemia is well known to be associated with poor prognosis and terlipressin response in patients with ACLF [24, 25]. We noted hyperbilirubinemia to be predictive of adverse events, probably indicating the effect of cholemic injury in patients with ACLF [6].

EASL and APASL definitions have advantages and limitations. Patients in EASL subgroup had better TFS, implying EASL criteria might identify ACLF in an earlier stage and aid in prioritization for liver transplant/TIPS [26]. Conversely, higher serum bilirubin in patients with APASL ACLF led to higher incidence of adverse events and poorer response to terlipressin infusion. In addition, mortality was higher in the APASL subgroup due to higher severity scores at baseline in the included patients. The possible reason is a dominant liver failure in the APASL subgroup and high cut-off variables in the APASL subgroup [27, 28]. However, change in MAP at day 3 was a significant predictor of terlipressin response in both the subgroups of ACLF [7, 9, 11].

Terlipressin therapy is associated with a mortality benefit [11]. The adverse events of terlipressin are of great concern. Terlipressin increases the afterload and end-diastolic volume with a concurrent reduction in cardiac index [7, 29]. This may unmask the pre-existing cardiac dysfunction in cirrhosis and lead to volume overload and pulmonary edema, particularly if large amounts of albumin are administered concomitantly. The CONFIRM study recently highlighted the risk of pulmonary edema in patients treated with terlipressin and albumin [14]. In contrast, we did not note any pulmonary overload due to significantly lower dose of terlipressin and albumin than the dose used in the CONFIRM trial. Furthermore, continuous infusion of low dose terlipressin may have prevented cardiac dysfunction in our patients.

Randomized trials with low dose terlipressin or alternate day terlipressin therapy may be utilized to reduce the adverse effects of terlipressin in patients with ACLF. Endothelin-1/Nitric oxide ratio aid in predicting response to terlipressin therapy [30]. Serum endothelin levels, nitric oxide, lactate dehydrogenase levels may be used to monitor and predict the ischemic adverse events of terlipressin. Another unexplored area is a combination therapy of vasoconstrictors. Low-dose terlipressin, in addition to midodrine or noradrenaline, may be explored to assess the safety and efficacy in patients with ACLF and HRS-AKI.

There are certain limitations to our study. The sample size is considerably small to compare two major definitions. Secondly, patients with APASL ACLF (due to inherent criteria of bilirubin > 5mg/dl) were a sicker group at inclusion with higher severity scores, which may skew our results. Patients may satisfy criteria for both the EASL and APASL

definitions, and this study was not designed to assess the same. Lastly, the use of intermittent bolus therapy was not assessed in this real-world cohort, and the results of infusion-based vs. bolus-based protocols in different study settings may skew results regarding adverse effects. Future data should also assess the role of cirrhotic cardiomyopathy as a confounder as this may also alter outcomes and renal response in HRS-AKI [31].

In conclusion, our novel study shows the course and outcomes of patients with ACLF and HRS-AKI. The outlying of adverse events and their effect on outcomes opens an avenue for future randomized trials, including patient selection, dosing, and alternatives. In addition, our data is the first to compare two criteria for defining ACLF and their role in the management of patients with HRS-AKI.

Abbreviations

ACLF, acute-on-chronic liver failure

aHR, adjusted hazard ratio

AKI, acute kidney injury

APASL, *Asian Pacific Association for the Study for the Liver*

AARC, APASL ACLF research consortium

CLIF-C, Chronic Liver Failure Consortium acute-on-chronic liver failure score

EASL, European Association for the Study of the Liver

HR, hazard ratio

HRS, hepatorenal syndrome

IAC, International ascites club

OR, odds ratio

sCr, serum creatinine

TFS, transplant-free survival

Declarations

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Tables

TABLE 1: BASELINE CHARACTERISTICS OF THE INCLUDED PATIENTS

Variables	All ACLF (n=116)	EASL ACLF (n=51)	APASL ACLF (n=65)	<i>P-value for only EASL vs. APASL</i>
Age (years)	48.31±9.01	50.22±8.82	46.82±8.95	0.04
Males	109 (94%)	46 (90.2%)	63 (96.9%)	0.13
Etiology of liver disease (alcohol/NASH/HBV/Unknown/HCV) (n)	82/20/11/2/1	30/16/3/1/1	52/4/8/1/0	0.01
Precipitant (alcohol/HBV/DILI/HEV/sepsis/unknown) (n)	59/10/4/1/23/19	9/2/0/0/23/17	50/8/4/1/0/2	0.001
MAP (mmHg) at inclusion	68.66±6.65	69.33±6.2	68.14±6.99	0.34
Urine output at inclusion (ml/day)	825.95±232.92	850±252.81	807.23±216.2	0.33
Hemoglobin (g/dL)	9.14±1.94	9.01±2.07	9.24±1.85	0.51
Total leucocyte counts (x10 ³ per cmm)	13.01±8.36	9.9±7.13	15.4±8.5	<0.001
Platelets (x10 ³ per cmm)	130.11±57.23	124.27±52.66	134.7±60.58	0.33
Total bilirubin (mg/dl)	11.5±11	2.96±1.91	18.18±10.54	<0.001
Serum albumin (g/dL)	2.69±0.39	2.78±0.39	2.62±0.37	0.02
Blood urea (mg/dl)	101.06±55.09	107.51±53.73	96±56.02	0.26
Serum Creatinine (mg/dL)	3.07±1.36	3.1±1.51	3.03±1.23	0.76
Serum sodium (meq/dL)	129.72±6.71	131.24±7.2	128.52±6.1	0.03
Serum potassium (meq/dL)	4.46±0.73	4.45±0.64	4.47 ±0.81	0.9
INR	2.04±0.78	1.54±0.41	2.44±0.78	<0.001
Arterial lactate	1.1±0.6	1.09±0.57	1.11±0.62	0.85
Presence of sepsis at baseline	60 (51.7%)	23 (45.1%)	37 (56.9%)	0.2
HE at baseline (Yes)	64 (55.2%)	22 (43.1%)	42 (64.6%)	0.02
West Haven HE grade (0,1-2,3-4)	52 (44.8%)/45 (38.8%)/19 (16.4%)	29(57%)/14(27.3%)/8 (15.7%)	23 (35.4%)/31 (47.7%)/11 (17%)	0.05
MELD NA	31.37±7.36	26.02±6.24	35.57±5.12	<0.001
CLIF-C ACLF score	47.31±10.39	44±9.83	49.91±10.14	0.002
AARC score	7.76±2.43	6.24±1.64	8.95±2.31	<0.001
AARC grading (I/II/III)	21 (18.1%)/ 48	18 (35.3%)/23	3 (4.6%)/25	<0.001

	(41.4%)/47 (40.5%)	(45.1%)/10 (19.6%)	(38.5%)/37 (57%)	
ACLF grade (I/II/III)	62 (53.4%)/33 (28.4%)/21 (18.1%)	41 (80.4%)/7 (13.7%)/3 (5.9%)¶	21 (32.3%)/26 (40%)/18 (27.7%)	<0.001

EASL-European association for the study of the liver; ACLF-acute-on-chronic liver failure; APASL-Asian pacific association for the study of the liver;HBV-hepatitis B virus; DILI-drug induced liver injury; HEV-hepatitis E virus; HCV-hepatitis C virus;MAP-mean arterial pressure; INR-international normalized ratio; HE-hepatic encephalopathy; MELD NA-model for end-stage liver disease sodium; CLIF-C ACLF- Chronic Liver Failure Consortium acute-on-chronic liver failure score; AARC- APASL ACLF research consortium

TABLE 2: ADVERSE EFFECTS RELATED TO TERLIPRESSIN THERAPY.

Adverse effects	All ACLF (n = 116)	EASL ACLF (n = 51)	APASL ACLF (n = 65)	<i>P-value for only EASL vs. APASL</i>
Total	24 (20.7%)	6 (11.76%)	18 (27.7%)	0.03
Abdominal pain	2 (1.72%)	0	2 (3.07%)	0.5
Diarrhea	9 (7.75%)	3 (5.88%)	6 (9.2%)	
Abdominal pain and diarrhea	4 (3.45%)	2 (4%)	2 (3.07%)	
Cyanosis	3 (2.58%)	0	3 (4.61%)	
Myocardial ischemia	1 (0.08%)	1 (2%)	0	
Ischemic skin necrosis	1 (0.08%)	0	1 (1.53%)	
Cyanosis + arrhythmia	1 (0.08%)	0	1 (1.53%)	
Hypertension	3 (2.5%)	0	3 (4.61%)	0.08
Discontinuation of drug	14 (12.07%)	3 (5.88%)	11 (16.92%)	

EASL-European association for the study of the liver; ACLF-acute-on-chronic liver failure; APASL-Asian pacific association for the study of the liver. Nine events in APASL subgroup and three events in EASL subgroup were ischemic events.

TABLE 3: PREDICTORS OF TERLIPRESSIN NON-RESPONSE ON UNIVARIATE AND MULTIVARIATE STEPWISE LOGISTIC REGRESSION ANALYSIS FOR WHOLE COHORT.

Parameters	Univariate OR (95%CI)	<i>P</i>	Multivariate OR* (95%CI)	<i>P</i>
Age	1.005 (0.96-1.04)	0.82		
MAP at inclusion	0.9 (0.83-0.97)	0.007		
Change in MAP at day 3	0.72 (0.6-0.86)	<0.001	0.73 (0.57-0.92)	0.009
Presence of sepsis at baseline	2.89 (1.3-6.45)	0.009		
Hemoglobin	1 (0.82-1.22)	0.97		
Total leucocyte counts	1	0.001		
Platelets	1 (0.99-1.009)	0.47		
Total bilirubin	1.05 (1.01-1.08)	0.006		
Serum albumin	0.62 (0.23-1.67)	0.34		
Blood urea	1.01(1-1.01)	0.007		
Serum Creatinine	2.83 (1.81-4.43)	<0.001	2.24 (1.41-3.57)	0.001
Serum sodium	0.93 (0.87-0.99)	0.02		
Serum potassium	1.08 (0.64-1.82)	0.75		
INR	1.7 (1.03-2.8)	0.03		
HE at baseline	3.28 (1.43-7.52)	0.005		
MELD NA	1.17 (1.08-1.26)	<0.001		
CLIF-C ACLF	1.06 (1.02-1.11)	0.004		
AARC score	1.38(1.16-1.65)	<0.001		
ACLF grade II vs. I	4.36 (1.69-11.21)	0.002	4.98 (1.5-16.5)	0.009
ACLF grade III vs. I	9.27 (3.03-28.33)	<0.001	7.61 (1.91-30.16)	0.004

*change in MAP at day 3, ACLF grade, Creatinine, Sepsis, TLC, HE, MAP day 1, blood urea, sodium, INR, Total bilirubin, AARC score, CLIF-C score, MELD NA score.

OR-odds ratio, EASL-European association for the study of the liver; ACLF-acute-on-chronic liver failure; APASL-Asian pacific association for the study of the liver;MAP-mean arterial pressure; INR-international normalized ratio; HE-hepatic encephalopathy; MELD NA-model for end-stage liver disease sodium; CLIF-C ACLF- Chronic Liver Failure Consortium acute-on-chronic liver failure score; AARC- APASL ACLF research consortium

TABLE 4: PREDICTORS OF MORTALITY ON UNIVARIATE AND MULTIVARIATE STEPWISE COX REGRESSION ANALYSIS FOR WHOLE COHORT.

Parameters	Univariate HR (95%CI)	<i>P</i>	Multivariate HR (95%CI)	<i>P</i>
Age	0.99 (0.96-1.02)	0.51		
MAP at baseline	0.97 (0.93-1.02)	0.33		
Change in MAP at day 3	0.85 (0.76-0.96)	0.009		
Presence of sepsis at baseline	1.4 (0.79-2.48)	0.24		
Hemoglobin	1.05 (0.91-1.2)	0.48		
Total leucocyte counts	1	<0.001		
Platelets	0.99 (0.99-1.003)	0.5		
Total bilirubin	1.03 (1.01-1.06)	0.001		
Serum albumin	0.53 (0.25-1.1)	0.09		
Blood urea	1.005(1-1.009)	0.03		
Serum Creatinine	1.38 (1.18-1.62)	<0.001		
Serum sodium	0.95 (0.91-0.99)	0.01		
Serum potassium	0.98 (0.66-1.44)	0.92		
INR	1.42 (1.06-1.9)	0.01		
HE at baseline	2.55 (1.37-4.74)	0.003		
Terlipressin non-response	5.67 (3.13-10.3)	<0.001	3.49 (1.85-6.57)	<0.001
Ischemic adverse events	2.95 (1.5-5.82)	0.002		
MELD NA	1.14 (1.09-1.2)	<0.001	1.12 (1.06-1.18)	<0.001
APASL vs. EASL	3.53 (1.79-6.92)	<0.001		
CLIF-C ACLF	1.03 (1.01-1.06)	0.005		
AARC score	1.34 (1.2-1.49)	<0.001		
ACLF grade II vs. I	3.18 (1.59-6.36)	0.001		
ACLF grade III vs. I	5.83 (2.81-12.06)	<0.001		

* Change in MAP at day 3, ACLF grade, terlipressin non-response, Creatinine, TLC, HE, blood urea, sodium, Total bilirubin, Albumin, AARC score, CLIF-C score, MELD NA score.

HR-hazard ratio, EASL-European association for the study of the liver; ACLF-acute-on-chronic liver failure; APASL-Asian pacific association for the study of the liver; MAP-mean arterial pressure; INR-international normalized ratio; HE-hepatic encephalopathy; MELD NA-model for end-stage liver disease sodium; CLIF-C ACLF- Chronic Liver Failure Consortium acute-on-chronic liver failure score; AARC- APASL ACLF research consortium.

Figures

Figure 1

The course of HRS-AKI in the whole cohort.

Of the 116 patients, 75 were responders, and 41 were non-responders. In the responder group, 46 patients achieved a complete response, and 29 patients achieved a partial response. Of the 41 non-responders, 29 required renal replacement therapy, and those requiring RRT succumbed. Nine patients of the non-responders were treated with octreotide and midodrine, and the rest were treated with noradrenaline.

Footnotes: HRS-AKI-hepatorenal syndrome acute kidney injury; CR-complete response; PR-partial response; LT-liver transplantation; TFS-transplant free survival; TIPS-transjugular intrahepatic portosystemic shunt; OCT/MID-octreotide with midodrine; CKD-chronic kidney disease.

Figure 2

The course of HRS-AKI in the EASL and APASL subgroups.

Of the 51 patients in EASL subgroup, 40 were responders and 11 were non-responders. In the responder group, 27 achieved CR and 13 achieved partial response. Of the non-responders, five required RRT and 3 responded to OCT/MID and 3 to noradrenaline. In the EASL subgroup, 21.56% (11/51) developed recurrence, 62.74% (32/51) had complete normalization of renal functions and 5.8% (3/51) progressed to CKD.

Of the 65 patients in APASL subgroup, 35 patients were responders, and 30 patients were non-responders. Nineteen achieved a complete response, and 16 had a partial response. Of the non-responders, 24 required RRT, and of them, one patient underwent liver transplant and the other six responded to OCT/MID. In the APASL subgroup, 21.53% (14/65) developed HRS recurrence, 30.7% (24/65) had complete normalization of kidney function, and 4.61% (3/65) progressed to CKD at three months.

Footnotes: EASL- European association for the study of the liver; APASL- Asian pacific association for the study of the liver; CR-complete response; PR-partial response; LT-liver transplantation; TFS-transplant free survival; TIPS-transjugular intrahepatic portosystemic shunt; OCT/MID-octreotide with midodrine; CKD-chronic kidney disease.

Figure 3

Kaplan Meier curve showing transplant-free survival in both the subgroups.

TFS was better at days 30 and 90 in EASL subgroup than APASL subgroup.

EASL- European association for the study of the liver; APASL- Asian pacific association for the study of the liver.

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