Real-world Use of Terlipressin in Cirrhosis and Acute Kidney Injury: Frequent Use Beyond Hepatorenal Syndrome

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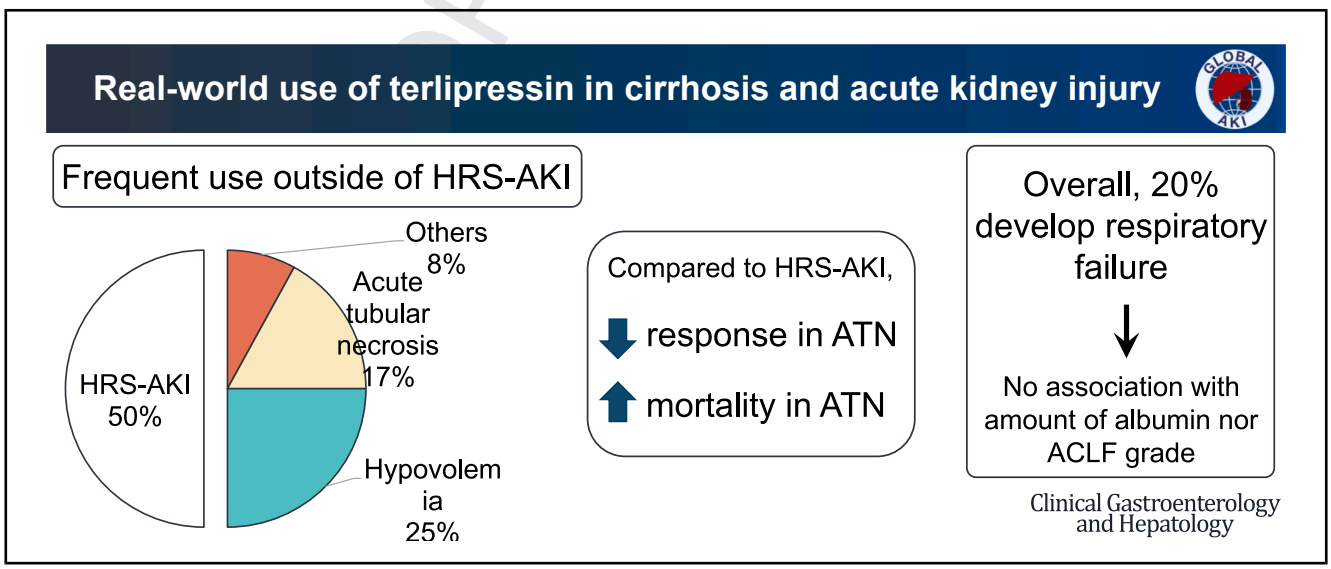
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Abbreviations used in this paper: ADQI, Acute Disease Quality Initiative; AKI, acute kidney injury; ACLF, acute-on-chronic liver failure; ATN, acute tubular necrosis; CI, confidence interval; CKD, chronic kidney disease; eCRF, electronic case report form; FIO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; ICA, International Club of Ascites; IQR, interquartile range; MELD, Model for End-stage Liver Disease; Na, sodium; NGAL, neutrophil gelatinase-associated lipocalin; OR, odds ratio; PaO_2, partial pressure of arterial oxygen; SBP, spontaneous bacterial peritonitis; sHR, subdistribution hazard ratio; SPO_2, pulse oximetric saturation; V1A, vasopressin 1A.

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BACKGROUND & AIMS: **Terlipressin is indicated to treat hepatorenal syndrome (HRS)-acute kidney injury (AKI) but is likely used outside this primary indication in clinical practice. We aimed to investigate real-world practice patterns on the use of terlipressin in AKI in cirrhosis.**

METHODS: **International prospective study including patients hospitalized for decompensated cirrhosis. This was a subgroup analysis of patients who received terlipressin to treat AKI. Primary outcome was AKI resolution. Secondary outcomes were respiratory failure and 28-day mortality.**

RESULTS: **Among 1456 patients with AKI, 243 (17%) received terlipressin. Terlipressin was predominantly administered as a continuous infusion (75%). The AKI phenotype was HRS-AKI in 50%, acute tubular necrosis (ATN) in 17%, hypovolemic in 25%, and other in 8%. AKI resolution occurred in 49% of the patients, and was lowest in ATN (29%), followed by HRS-AKI (51%) and hypovolemic (63%). ATN was independently associated with lack of AKI resolution (odds ratio, 2.77; 95% confidence interval, 1.24–6.54; $P = .02$). De novo respiratory failure occurred in 20% of patients. There were no significant differences in the amount of albumin received nor acute-on-chronic liver failure grade between those who did and did not develop respiratory failure. The presence of pneumonia independently predicted respiratory failure (odds ratio, 7.80; 95% confidence interval, 2.43–26.95; $P < .001$). Mortality rate at 28 days was 36%; ATN and hospital-acquired AKI independently predicted 28-day mortality.**

CONCLUSIONS: **Terlipressin is often used for treatment of AKI outside its primary indication of HRS-AKI. Compared with patients with HRS-AKI, response to terlipressin is significantly lower in patients with ATN, in whom the risks may outweigh the benefits. Respiratory failure is common but does not seem to be driven by the amount of albumin received nor acute-on-chronic liver failure grade.**

Keywords: Hepatorenal Syndrome; Mortality; Respiratory Failure; Vasoconstrictor.

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Patients with cirrhosis can develop portal hypertension, which is characterized by splanchnic arterial vasodilation and reduction of effective circulating volume. Initially, compensatory mechanisms such as activation of endogenous vasoconstrictors system and increased cardiac output can maintain renal perfusion.[1,2] However, when these compensatory mechanisms no longer suffice, patients can develop hepatorenal syndrome-acute kidney injury (HRS-AKI), a predominantly functional form of AKI characterized by intrarenal vasoconstriction.[3] Terlipressin is a selective vasopressin-1A (V1A) receptor agonist that counteracts the pathological splanchnic arterial vasodilation that occurs in the setting of severe portal hypertension. Terlipressin, in combination with albumin, has been shown to be an effective treatment of HRS-AKI,[4–8] and is recommended as first-line therapy.[9,10] However, some off-label use in patients with cirrhosis and with AKI, but not meeting the strict definition of HRS-AKI, likely occurs in clinical practice. Recently, a consensus conference held by the International Club of Ascites (ICA) and Acute Disease Quality Initiative (ADQI) proposed an updated, broadened definition of HRS-AKI. In this consensus, HRS-AKI may also occur in the presence of tubular injury, proteinuria, and/or pre-existing chronic kidney disease (CKD),[1] thus broadening the potential use of terlipressin even further.

Concerns have been raised regarding adverse events related to terlipressin use, including ischemic events and respiratory failure.[11,12] As such, evaluating how terlipressin is being used globally in a real-world setting is crucial to measure the benefits and risks of terlipressin therapy in patients with cirrhosis in general, including in non HRS-AKI settings. Therefore, we aimed to evaluate practice patterns on the use of terlipressin in AKI in cirrhosis in a post hoc analysis of the ICA-GLOBAL AKI study.[13] We specifically aimed to assess AKI resolution in patients treated with terlipressin.

Methods

The study protocol is available at https://clinicaltrials.gov/study/NCT05387811. This study is reported in accordance with the STROBE checklist.

Patient Population

The GLOBAL AKI study was an international prospective cohort study including patients admitted to the hospital for decompensated cirrhosis at 65 centers on 5 continents between July 2022 and May 2023.[13] Inclusion criteria were adult patients with cirrhosis admitted to the hospital for the treatment of a complication of liver

disease (ascites, gastrointestinal bleeding, hepatic encephalopathy [HE], bacterial infections, AKI, jaundice, etc) who provided informed consent. Exclusion criteria were pregnancy, hepatocellular carcinoma outside Milan criteria, extrahepatic malignancy other than non-melanoma skin cancer within last 5 years, previously known severe extrahepatic diseases (eg, chronic renal failure requiring hemodialysis, severe congestive heart disease [New York Heart Association class $\geq$3], severe chronic obstructive pulmonary disease [GOLD class $\geq$3], psychiatric disorders), previous solid organ transplantation, human immunodeficiency virus infection with CD4 $\leq$250/μL, lack of informed consent, and no legal surrogate decision maker. Individual centers received approval from their local Research and Ethics Board. This study was undertaken in accordance with the Declaration of Helsinki.

The current study was a subgroup analysis of patients with AKI who received terlipressin for treatment of AKI, excluding those who received it for portal hypertension-related bleeding.

What You Need to Know

Background

Terlipressin is indicated to treat hepatorenal syndrome. Real-world practice patterns on its use in patients with cirrhosis and acute kidney injury are unknown.

Findings

In this international prospective study including 243 patients treated with terlipressin, terlipressin was used outside of hepatorenal syndrome in 50% of cases. Acute tubular necrosis was independently associated with lack of acute kidney injury resolution.

Implications for patient care

Terlipressin is often used for treatment of acute kidney injury outside its primary indication of hepatorenal syndrome. The use of terlipressin in patients with acute tubular necrosis should be carefully considered, with risks that may outweigh the benefits.

Study Design

Patients were included only once in the study, and only the first episode of AKI was considered. Included patients were followed during admission until liver transplantation, death, or 90 days from AKI diagnosis, whichever occurred first. Data collected included demographic, clinical, and biochemical information, such as AKI severity and phenotype, along with management of AKI. Respiratory failure (see Definitions) was a predetermined outcome collected. Data were registered by individual sites on an electronic case report form (eCRF) using the Research Electronic Data Capture Software REDCap hosted at the Department of Medicine of the University of Padova (Italy).

Outcomes

The primary outcome of this study was AKI resolution, defined as return of serum creatinine to within 0.3 mg/dL of baseline value during the hospitalization. Secondary outcomes were de novo respiratory failure and 28-day mortality.

Definitions

Definitions of AKI, AKI staging, AKI resolution, AKI phenotype, and AKI precipitants have previously been reported[13] and are presented in the Supplementary Methods. In particular, HRS-AKI was defined as per the 2015 ICA criteria.[14] De novo respiratory failure was defined as: (1) a partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio of $\leq$ 200, or a pulse oximetric saturation (SpO_2) to FiO2 ratio $\leq$214 (CLIF-C acute-on-chronic liver failure [ACLF] criteria[15]); and (2) that was not present at time of AKI diagnosis.

Statistical Analyses

Non-normally distributed continuous variables were reported as median and interquartile range (IQR) and compared with the Mann-Whitney test or the Kruskal-Wallis test. Categorical variables were reported as count and percentage and compared with the χ^2 test or Fisher's exact test, when appropriate. Variables that were judged as clinically relevant according to available literature were included in multivariable models. Collinearity of variables was assessed using Spearman or Pearson correlation, as appropriate, and variables with collinearity above 0.5 were not introduced together in multivariable models to avoid multicollinearity. Multivariable binary logistic regression model was used to identify factors associated with lack of AKI resolution and de novo respiratory failure. The odds ratios (ORs) and their 95% confidence intervals (CI) were calculated. Covariates included in the multivariable model for lack of AKI resolution were age, sex, AKI stage, hospital-acquired AKI, ACLF grade, and AKI phenotype. Patients who died or underwent liver transplant without achieving AKI resolution were considered to have lack of AKI resolution. A sensitivity analysis for lack of AKI resolution was performed excluding patients who died or underwent liver transplant by 28 days without

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achieving AKI resolution. Covariates included in the multivariable model for de novo respiratory failure included age, sex, AKI precipitant, peak AKI stage, hospital-acquired AKI, ACLF grade, SpO_2, and AKI phenotype. Cumulative incidence functions of mortality were developed through competing risks analysis and compared with Gray's test. Liver transplant was considered a competing risk for mortality. Univariable and multivariable analysis of predictors of mortality were performed using the Fine and Gray subdistribution hazard model. Subdistribution hazard ratio (sHR) and their 95% CIs were reported. Covariates included in the multivariable model were age, sex, AKI phenotype, and hospital-acquired AKI, in addition to Model for End-stage Liver Disease-Sodium (MELD-Na) in Model 1 or ACLF grade in Model 2. All tests were 2-tailed, and $P < .05$ values were considered significant. Statistical analyses were performed using R software (version 4.2.1).

Results

In total, 1456 patients had AKI, of which 291 were treated with terlipressin. After excluding the 48 patients who received terlipressin to treat portal hypertension-related bleeding, we included 243 patients (17% of all patients with AKI) (Supplementary Figure 1) from 44 centers. Most terlipressin-treated patients were from Europe (47%), followed by Asia (27%) and Latin America (15%).

Terlipressin Regimen and AKI Characteristics

Characteristics of patients treated with terlipressin are presented in Table 1. They had a median age of 59 years (IQR, 50–65 years), were predominantly male (76%), and mostly had alcohol-related liver disease (68%). The most common AKI precipitants were non-spontaneous bacterial peritonitis (SBP) infections and volume loss. Patients had advanced liver disease, with a median MELD-Na score of 30. The AKI stage at diagnosis was stage 1 in 42%, stage 2 in 30%, and stage 3 in 28%. Most patients were started on terlipressin by 48 to 72 hours from AKI diagnosis (70.4%), and most received albumin within the same time frame (79.8%). Patients received a median maximum dose of terlipressin of 3.0 mg/24 hours (IQR, 2.0–4.0 mg/24 hours), for a median duration of 5 days (IQR, 3–8 days). Terlipressin was predominantly administered in continuous infusion form (75.9%) and in combination with albumin (74.9%). The AKI phenotype in terlipressin-treated patients was HRS-AKI in 50%, hypovolemia-induced in 25%, acute tubular necrosis (ATN) in 17%, and others in 8%. During the hospital stay, 38 patients (15.6%) required renal replacement therapy.

Primary Outcome: AKI Resolution

Overall, 49% achieved AKI resolution. Patients without AKI resolution had significantly higher MELD-Na score, AKI stage, and ACLF grade compared with those with AKI resolution (Table 1). AKI resolution was lowest in ATN (29%), followed by HRS-AKI (51%) and hypovolemia-induced AKI (63%; $P = .005$ across groups). On multivariable analysis adjusted for age, sex, AKI stage, and ACLF grade, ATN was independently associated with lack of AKI resolution (OR, 2.77; 95% CI, 1.24–6.54; $P = .016$) compared with HRS-AKI (Table 2). AKI stage 3 and ACLF grades 2 and 3 were also associated with lack of AKI resolution. In the sensitivity analysis excluding patients who had died or underwent liver transplant by 28 days without achieving AKI resolution (n = 69 and n = 8, respectively), only age and AKI stage 3 at diagnosis remained significantly associated with lack of AKI resolution. These results are presented in Supplementary Table 1.

Respiratory Failure

Twenty-two patients already had respiratory failure at AKI diagnosis, whereas de novo respiratory failure occurred in 45 of 221 patients (20.4%) treated with terlipressin. There were no significant differences in the amount of albumin received, the maximum daily dose of terlipressin, and the mode of terlipressin administration (continuous infusion vs intermittent bolus) in those who did and did not develop respiratory failure (Table 3). The AKI phenotype did not significantly differ between those who did and did not develop respiratory failure. Patients developing respiratory failure had lower prevalence of volume loss as precipitating factor, a higher prevalence of non-SBP infections (in particular, pneumonia), lower oxygen saturation, and higher MELD-Na score. The grade of ACLF and baseline mean arterial pressure were not significantly different between the 2 groups. On multivariable analysis, only the presence of pneumonia (OR, 7.80; 95% CI, 2.43–26.95; $P < .001$) and absence of fluid loss before AKI (OR, 2.79; 95% CI, 1.18–7.24; $P = .025$) were independent predictors of respiratory failure (Table 4).

Mortality

At 28 days, 88 patients (36%) who received terlipressin had died, whereas 16 (6.5%) had undergone liver transplantation. The 28-day cumulative incidence of death was 39% (95% CI, 33%–46%). Patients with ATN had higher 28-day cumulative incidence of death than those with HRS-AKI, although this did not reach statistical significance (53%; 95% CI, 36%–67% vs 39%; 95% CI, 30%–49%; $P = .051$) (Figure 1), with a sHR of

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Table 1. Baseline Characteristics of Patients Treated With Terlipressin

	Overall (n = 243)	No AKI resolution (n = 123)	AKI resolution (n = 120)	*P* value
Age, *years*	59 (50–65)	59 (51–65)	57 (48–64)	.174
Male sex	184 (76)	85 (72)	95 (79)	.276
Geographical area				.036
Africa	4 (2)	2 (2)	2 (2)	
Asia	65 (27)	39 (31)	26 (22)	
Europe	114 (47)	49 (40)	65 (54)	
Latin America	38 (15)	17 (14)	21 (17)	
North America	22 (9)	16 (13)	6 (5)	
Race				
White	148 (61)	68 (55.3)	80 (67)	.162
Black	4 (2)	1 (0.8)	3 (2.5)	
Asian	67 (27)	40 (32.5)	27 (22.5)	
Other	24 (10)	14 (11.4)	10 (8)	
Chronic kidney disease	21 (9)	9 (7)	12 (10)	.606
Diabetes	75 (31)	43 (35)	30 (25)	.120
Hypertension	73 (30)	38 (31)	37 (31)	.999
Etiology of cirrhosis[a]				
Alcohol-related	165 (68)	78 (63)	87 (73)	.168
MASLD	45 (18.5)	18 (15)	27 (23)	.158
HCV	23 (9)	15 (6)	8 (3)	.210
HBV	11 (4.5)	6 (5)	5 (4)	.998
Other	37 (15)	17 (14)	20 (17)	.661
Reason for admission[a]				
Hepatic encephalopathy	82 (34)	41 (33)	41 (34)	.999
Portal hypertension-related bleed	23 (9)	6 (5)	17 (14)	.024
Ascites/anasarca	151 (62)	80 (65)	71 (59)	.417
Infection	75 (31)	41 (33)	34 (28)	.481
AKI	114 (47)	57 (46)	57 (47)	.958
AKI precipitant[a]				
Volume loss/excessive diuretics	91 (37)	45 (36)	46 (38)	.882
SBP	33 (13.5)	18 (15)	15 (13)	.766
Non-SBP infection[b]	97 (40)	51 (42)	46 (38)	.714
GI bleed	30 (12)	13 (11)	17 (14)	.511
Nephrotoxic drugs	11 (4.5)	7 (6)	4 (3)	.539
Other	7 (3)	4 (3)	3 (2)	.999
No identifiable precipitant	34 (14)	16 (13)	18 (15)	.793
Ascites	223 (92)	115 (94)	108 (90)	.448
Hepatic encephalopathy	135 (56)	71 (58)	64 (53)	.576
MAP, *mm Hg*	76 (68–88)	77 (70–89)	76 (68–87)	.403
Baseline serum creatinine, *mg/dL*	0.92 (0.78–1.16)	0.97 (0.79–1.22)	0.90 (0.76–1.12)	.463
Biochemical values at AKI diagnosis				
Serum creatinine, *mg/dL*	2.04 (1.61–3.01)	2.31 (1.76–3.21)	1.94 (1.53–2.68)	.002
Bilirubin, *mg/dL*	5.8 (2.2–14.8)	6.8 (2.4–20.0)	5.1 (2.2–10.5)	.074
Albumin, *g/dL*	2.8 (2.4–3.3)	2.8 (2.4–3.3)	2.8 (2.3–3.2)	.382
Sodium	132 (127–136)	132 (127–136)	132 (128–136)	.814
INR	1.8 (1.5–2.3)	1.9 (1.5–2.4)	1.8 (1.4–2.2)	.135
Platelet, $\times 10^9$/L	90 (61–145)	90 (58–108)	90 (63.5–135)	.974
WBC, $\times 10^9$/L	9.8 (6.0–13.6)	10.0 (6.0–14.3)	9.5 (6.2–13.3)	.975
MELD-Na score	30 (24–34)	31 (27–36)	29 (24–33)	.001
AKI stage at diagnosis				.009
Stage 1	103 (42)	42 (34)	61 (51)	
Stage 2	72 (30)	37 (30)	35 (29)	
Stage 3	68 (28)	44 (36)	24 (20)	

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Table 1. Continued

	Overall (n = 243)	No AKI resolution (n = 123)	AKI resolution (n = 120)	*P* value
AKI peak stage				< .001
Stage 1	52 (21)	8 (6)	44 (36)	
Stage 2	72 (30)	34 (28)	38 (32)	
Stage 3	119 (49)	81 (66)	38 (32)	
Child Pugh score				.716
A	3 (1.3)	1 (1)	2 (2)	
B	73 (30)	39 (32)	34 (28)	
C	161 (67)	80 (67)	81 (68)	
ACLF grade				< .001
No ACLF	62 (25.5)	19 (15)	43 (36)	
Grade 1	80 (33)	40 (33)	40 (33)	
Grade 2	61 (25)	36 (29)	25 (21)	
Grade 3	40 (16.5)	28 (23)	12 (10)	
Hospital-acquired AKI	87 (36)	44 (36)	43 (36)	.999
AKI phenotype				.005
Hypovolemia-induced	60 (25)	22 (18)	38 (32)	
HRS-AKI	123 (50)	60 (49)	63 (52)	
ATN	41 (17)	29 (24)	12 (10)	
Others	19 (8)	12 (10)	7 (6)	
Method of administration of terlipressin				.742
Continuous infusion[c] (n = 195)	148 (76)	77 (77)	71 (75)	

NOTE. Data are presented as number (%) or median (interquartile range).
NOTE. Values are collected at time of AKI diagnosis, unless otherwise specified.
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HRS, hepatorenal syndrome; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-stage Liver Disease; Na, sodium; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; WBC, white blood cell count.
[a]More than one can apply.
[b]Pneumonia (n = 23), urinary tract infection (n = 23), bacteremia (n = 19), other (n = 29), missing (n = 3).
[c]Missing in 48.

Table 2. Multivariable Analysis for Predictors of Lack of AKI Resolution

	OR (95% CI)	*P* value
Age	1.02 (1.00–1.05)	.059
Female sex	1.92 (1.01–3.74)	.050
AKI phenotype (vs HRS-AKI)		
Hypovolemia-induced	0.60 (0.29–1.20)	.153
ATN	2.77 (1.24–6.54)	.016
Other	1.58 (0.55–4.85)	.406
Hospital-acquired AKI (vs community-acquired)	1.56 (0.85–2.90)	.158
AKI stage at diagnosis (vs stage 1)		
Stage 2	1.50 (0.76–2.95)	.241
Stage 3	2.17 (1.02–4.70)	.045
ACLF grade (vs no ACLF)		
1	2.12 (0.98–4.70)	.060
2	3.18 (1.40–7.42)	.006
3	4.39 (1.67–12.10)	.003

NOTE. Multivariable analysis performed with a logistic model.
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; CI, confidence interval; HRS, hepatorenal syndrome; OR, odds ratio.

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Table 3. Baseline Characteristics of Patients, by Development of De Novo Respiratory Failure

	No respiratory failure (n = 176)	Respiratory failure (n = 45)	*P* value
Age, *years*	58 (49–65)	60 (52–64)	.71
Male sex	140 (80)	33 (73)	.48
Etiology[a]			
Alcohol-related	124 (70)	31 (69)	.98
MASLD	33 (19)	3 (7)	.08
HCV	12 (7)	6 (13)	.22
HBV	9 (5)	2 (4)	.99
Other	25 (14)	9 (20)	.47
Chronic kidney disease	16 (9)	4 (9)	.99
Hypertension	56 (32)	9 (20)	.17
Diabetes	50 (28)	11 (24)	.73
Ascites	161 (91)	44 (98)	.20
Hepatic encephalopathy	91 (52)	28 (62)	.27
AKI precipitant[a]			
Volume loss/excessive diuretics	71 (40)	8 (18)	.008
SBP	25 (14)	7 (16)	.999
Non-SBP infection	63 (36)	25 (56)	.025
Gastrointestinal bleed	21 (12)	6 (13)	.999
Nephrotoxic drugs	10 (6)	1 (2)	.469
Other	7 (4)	0	.349
No identifiable precipitant	26 (15)	7 (16)	.999
Infections (both SBP and non-SBP infections)			
Other infections	75 (91)	20 (65)	.001
Pneumonia	7 (9)	11 (35)	
SpO2, %	98 (96–99)	96 (95–98)	.035
MAP, *mm Hg*	77 (68–88)	78 (70–91)	.482
Bilirubin, *mg/dL*	4.6 (2.1–13.2)	11.2 (5.7–20.0)	.001
Albumin, *g/dL*	2.8 (2.4–3.3)	2.9 (2.6–3.2)	.643
INR	1.7 (1.4–2.2)	1.9 (1.6–2.6)	.024
WBC, $\times 10^9$/*L*	9.1 (6.0–13.0)	11.2 (7.0–16.4)	.066
MELD-Na	29 (24–34)	32 (28–35)	.041
Serum creatinine at AKI diagnosis, *mg/dL*	2.05 (1.67–3.05)	1.94 (1.50–2.87)	.18
Serum creatinine at 48 hours, *mg/dL*	1.98 (1.45–2.97)	1.95 (1.40–2.40)	.77
Maximum serum creatinine, *mg/dL*	2.79 (2.00–3.75)	3.03 (2.20–4.18)	.43
Albumin received in first 48 hours	154 (88)	40 (89)	.99
Albumin dose in first 48 hours, *grams*	80 (50–130)	80 (40–120)	.71
Albumin dose received beyond 48 hours, *grams*	120 (60–240)	80 (25–160)	.13
Crystalloids use in first 48 hours	93 (53)	29 (64)	.22
Volume of crystalloids given in first 48 hours, *mL*	2500 (1000–4000)	1750 (700–4750)	.50
Methods of administration of terlipressin			.18
Continuous infusion[b]	103/139 (74)	35/40 (88)	
Maximum terlipressin dose per 24 hours, *mg*	3 (2–4)	2 (2–4)	.43
AKI phenotype			.14
Hypovolemia-induced	41 (23)	5 (11)	
HRS-AKI	95 (54)	24 (54)	
ATN	28 (16)	10 (22)	
Others	12 (7)	6 (13)	

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Table 3. Continued

	No respiratory failure (n = 176)	Respiratory failure (n = 45)	*P* value
AKI stage at diagnosis			.08
Stage 1	74 (42)	20 (44)	
Stage 2	48 (27)	18 (40)	
Stage 3	54 (31)	7 (16)	
AKI peak stage			.14
Stage 1	41 (23)	5 (11)	
Stage 2	51 (29)	18 (40)	
Stage 3	84 (48)	22 (49)	
Presence of ACLF	124 (70)	35 (78)	.43
ACLF grade			.81
0	52 (29.6)	10 (22)	
1	60 (34)	17 (38)	
2	44 (25)	12 (27)	
3	20 (11)	6 (13)	

NOTE. Data are presented as number (%) or median (interquartile range).
NOTE. Twenty-two patients with respiratory failure at time of AKI diagnosis were excluded from this analysis.
NOTE. Values are collected at time of AKI diagnosis, unless otherwise specified.
AKI, acute kidney injury; ACLF, acute-on-chronic liver failure; ATN, acute tubular necrosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HRS, hepatorenal syndrome; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-stage Liver Disease; Na, sodium; SBP, spontaneous bacterial peritonitis; WBC, white blood cell count.
[a]More than one can apply.
[b]Missing in 42.

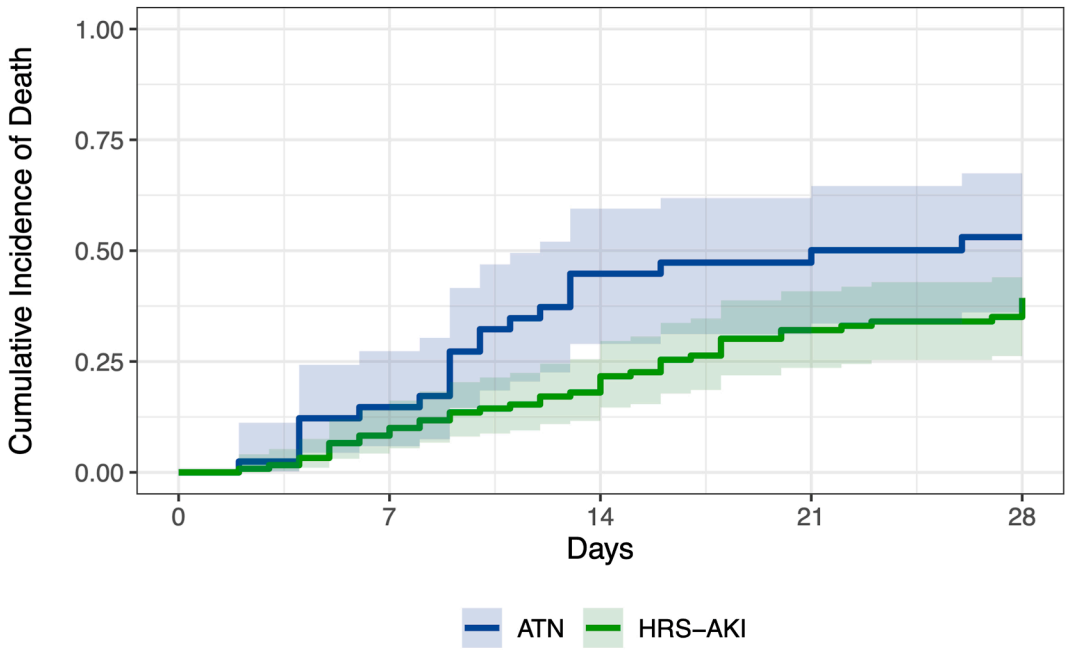
1.69 (95% CI, 0.99–2.86; $P = .052$). Univariable analysis for predictors of 28-day mortality are presented in Supplementary Table 2. On multivariable analysis adjusted for age, sex, and MELD-Na, the ATN phenotype and hospital-acquired AKI were independent predictors of 28-day mortality (Table 5, Model 1). Using ACLF

Table 4. Multivariable Analysis for Predictors of Respiratory Failure in Terlipressin-treated Patients

	OR (95% CI)	*P* value
Age	1.01 (0.98–1.04)	.681
Female sex	1.88 (0.77–4.52)	.161
AKI precipitant		
Absence of volume loss/excessive diuretic use	2.79 (1.18–7.24)	.025
Pneumonia	7.80 (2.43–26.95)	< .001
AKI phenotype (vs HRS-AKI)		
Hypovolemia-induced	0.79 (0.22–2.45)	.699
ATN	1.18 (0.42–3.14)	.747
Other	1.33 (0.35–4.53)	.655
Hospital-acquired AKI (vs community-acquired)	1.50 (0.67–3.35)	.319
AKI peak stage (vs stage 1)		
Stage 2	3.12 (0.92–12.37)	.081
Stage 3	1.97 (0.59–7.72)	.294
ACLF grade (vs no ACLF)		
1	1.44 (0.55–3.91)	.463
2	0.94 (0.30–2.93)	.917
3	1.35 (0.34–5.03)	.657
SpO_2	0.90 (0.78–1.05)	.173

NOTE. Multivariable analysis performed with a logistic model.
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; CI, confidence interval; HRS, hepatorenal syndrome; OR, odds ratio; SpO2, peripheral oxygen saturation.

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ATN					
At Risk	41	34	21	18	14
Events	0	6	18	20	21
HRS–AKI					
At Risk	123	105	85	62	51
Events	0	12	25	36	43

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Figure 1. Cumulative incidence of death in terlipressin-treated patients by AKI phenotype, in the subgroup of patients with either ATN or HRS-AKI. Including 164 patients (41 with ATN, 123 with HRS-AKI). The 28-day cumulative incidence of death for ATN was 0.53 (95% CI, 0.36–0.67) and for HRS-AKI 0.39 (95% CI, 0.30–0.49); Gray test *P* value = .051. The shaded area represents 95% CI.

grade instead of MELD-Na in the model did not significantly change results (Table 5, Model 2).

Discussion

This is the largest prospective cohort study to report on real-world use of terlipressin in patients with cirrhosis and AKI. The first important finding is that terlipressin is often used outside its primary indication of HRS-AKI. Second, lack of AKI resolution and 28-day mortality is significantly higher in patients with ATN than those with HRS-AKI. Therefore, clinicians need to weigh the risks vs the expected benefit of terlipressin in those with ATN. Third, respiratory failure in the setting of terlipressin use is common, occurring in 1 in 5 patients, but does not appear to be driven by mode of terlipressin administration, amount of albumin given, or ACLF grade.

In the current study, the fact that one-half of the patients who received terlipressin did not meet HRS-AKI criteria likely reflects 2 phenomena: (1) clinicians may be starting terlipressin before obtaining all clinical/biochemical information to determine the phenotype, to avoid delays in treatment initiation; and (2) important challenges remain in differentiating between HRS-AKI and ATN in clinical practice, despite the fairly stringent definition of HRS-AKI from 2015 used in the current study. The recent proposed changes to the diagnostic criteria of HRS-AKI will likely result in a larger proportion of patients being diagnosed with HRS-AKI and therefore receiving treatment with vasoconstrictors, earlier in the course of the disease.[1] However, our study demonstrates that clinicians are already treating many patients who do not meet the definition of HRS-AKI, and further expansion of criteria may lead to exposing patients to potential side effects of terlipressin, while deriving little benefit, particularly in the case of patients who are ultimately diagnosed with ATN. Therefore, an adequate workup for the differential diagnosis of AKI is key before initiating terlipressin and albumin. The use of urinary biomarkers of tubular

Table 5. Multivariable Analysis for Predictors of 28-day Mortality

	sHR (95% CI)	*P* value
Model 1		
Age	1.03 (1.01–1.05)	.005
Female sex	1.13 (0.68–1.88)	.643
AKI phenotype (vs HRS-AKI)		
Hypovolemia-induced	0.83 (0.46–1.49)	.534
ATN	1.94 (1.12–3.36)	.019
Others	0.88 (0.35–2.23)	.781
Hospital-acquired AKI	3.32 (2.05–5.08)	< .001
MELD–Na	1.09 (1.04–1.13)	< .001
Model 2		
Age	1.02 (1.00–1.05)	.023
Female sex	1.22 (0.76–2.96)	.412
AKI phenotype (vs HRS-AKI)		
Hypovolemia-induced	0.78 (0.45–1.35)	.384
ATN	2.04 (1.22–3.42)	.007
Others	0.88 (0.34–2.27)	.801
Hospital-acquired AKI	3.65 (2.32–5.74)	< .001
ACLF grade (vs no ACLF)		
1	0.90 (0.50–1.63)	.729
2	1.86 (1.06–3.24)	.029
3	4.82 (2.48–9.37)	< .001

NOTE. Multivariable analysis of predictors of mortality performed using the Fine and Gray subdistribution hazard model, with liver transplant considered a competing event.
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; CI, confidence interval; HRS, hepatorenal syndrome; sHR, subdistribution hazard ratio.

damage such as neutrophil gelatinase-associated lipocalin (NGAL) could improve the differential diagnosis of AKI in these patients.[16,17] Moreover, urinary NGAL may predict response to terlipressin and albumin[17] and mortality risk in patients with HRS-AKI, being able to identify subclinical tubular damage, and its use deserves implementation on a large scale.

The proportion of patients who developed respiratory failure in our study is higher than those observed in patients with AKI in general (12%)[18] and slightly higher than that found in the CONFIRM trial, a randomized trial comparing treatment of patients with type 1 HRS with terlipressin vs placebo, in which significantly higher rates of respiratory failure, including fatal cases, were observed in the terlipressin group (14.0% vs 5.1%, respectively).[6] In particular, the presence of ACLF grade 3 (on univariable analysis) and lower SpO_2 (on multivariable analysis) at baseline were predictive of respiratory failure.[19] In our study, however, we found that neither ACLF grade nor SpO_2 predicted the development of respiratory failure on multivariable analysis. There are 2 important differences worth mentioning, apart from study design, which may explain this discrepancy: (1) the patient population in this real-world study was not comprised exclusively of patients with HRS-AKI and had lower serum creatinine at study entry (2.0 mg/dL vs 3.5 mg/dL); and (2) the total amount of albumin used was significantly lower in the current study (200 g vs 500 g). We could not ascertain whether fatal cases of respiratory failure occurred, as this was not a predetermined outcome collected. We found however that the presence of pneumonia was the strongest predictor of de novo respiratory failure, highlighting that patients should be screened for pneumonia prior to starting terlipressin, and those with confirmed pneumonia should be closely monitored, given the increased risk of adverse effects. In addition, patients without history of fluid loss were at higher risk of respiratory failure, likely reflecting a predisposition to develop circulatory overload following treatment with terlipressin and albumin.

Our study has several limitations. Due to the observational nature of this study, we could not compare the efficacy of terlipressin vs other vasoconstrictors head-to-head. This was in fact not a primary outcome of interest in this real-world study on the use of terlipressin specifically. Next, the AKI phenotype was ascertained by investigators locally. We, however, used predetermined diagnostic criteria for these phenotypes in the study protocol, which would minimize variability between centers. We also integrated flags in the eCRF to minimize errors, such as the presence of ascites as a prerequisite for the HRS-AKI phenotype. In addition, the cause of respiratory failure was not collected; therefore, inferences on the mechanism linking terlipressin to respiratory failure could not be made. Moreover, the use of SpO_2/FiO_2 to define respiratory failure may have led to an overestimation of its incidence.[20] Data on active alcohol use were not collected either. The presence of alcohol-associated hepatitis did not significantly impact the efficacy of terlipressin in HRS-AKI in the CONFIRM trial.[6] It was, however, an independent predictor of mortality in HRS-AKI in a recent retrospective study from the United States.[21] Moreover, data on cardiac function, such as NT-proBNP, were not available. Assessment of cardiac function and volume status is notoriously challenging in patients with decompensated cirrhosis, and no single biomarker has yet been validated in this setting. Furthermore, biomarkers such as urinary NGAL, which has been shown to be useful in the differential diagnosis of AKI in cirrhosis, were not readily available in most participating centers. Again, this is a real-world study, and given that urinary NGAL is not widely available, our results reflect clinical decision-making at its current state, without the support of such biomarkers, therefore increasing the generalizability of findings.

Conclusions

In summary, terlipressin is often used for treatment of AKI outside its primary indication of HRS-AKI. Compared with patients with HRS-AKI, response to terlipressin is significantly lower in patients with ATN. Therefore, in this setting, the potential benefits of

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terlipressin need to be weighed against its potential risks. Moreover, a thorough differential diagnosis of AKI workup remains essential before initiating terlipressin and albumin. Respiratory failure occurs in 1 of 5 patients but does not seem to be driven by the amount of albumin received nor ACLF grade. Conversely, caution should be exercised when using terlipressin in patients with pneumonia.

Supplementary Material

NOTE: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.08.031.

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CRediT Authorship Contributions Q6
■■■

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Conflicts of interest Q3

These authors disclose the following: Kavish R. Patidar received advisory board fees from Madrigal Pharmaceuticals; and has received consulting fees from Mallinckrodt Pharmaceuticals. Christian M. Lange received speakers honoraria and advisory board fees from AbbVie, Gilead, Falk, Eisai, Norgine, CSL Behring, Boston Scientific, AstraZeneca, Shionogi, Roche, and Sobi. Maria Papp received funding from the Ministry of Innovation and Technology of Hungary from the National Research, Development, and Innovation Fund. Douglas A. Simonetto consulted for Mallinckrodt, BioVie, Evive, Resolution Therapeutics, PharmaIN, AstraZeneca, and Iota. Puria Nabilou received research grants from Novo Nordisk and Takeda Pharma. Paolo Caraceni received speaking fees from Grifols SA, Octapharma SA, and CSL Behring SA; research grants from Grifols SA and Octapharma SA; and advisory board fees from CSL Behring. Manuela Merli received speaker honoraria from Gore. Aleksander Krag has served as speaker for Novo Nordisk, Norgine, Siemens, and Nordic Bioscience; participated in advisory boards for Norgine, Siemens, Resalis Therapeutics, Boehringer Ingelheim, and Novo Nordisk, all outside the submitted work; received research support from Norgine, Siemens, Nordic Bioscience, Astra, and Echosense; and is a board member and co-founder of Evido. Tony Bruns received speaking fees, consulting fees, or travel support from Abbvie, Gilead, SOBI, CSL Behring, Merck, Gore, and Advanz. Brian Wentworth received advisory board and consulting fees from Ipsen; and consulting fees from GSK and Luna Labs USA. Yu Jun Wong received speaking fees from Gilead and AbbVie. Nikolaos T. Pyrsopoulos received research grants from Salix, OCERA, Grifols, CytoSorbents, Intercept, and Gilead; speaking fees from Ipsen and Madrigal; and advisory board fees from Salix, Ipsen, and OCERA. Andrew S. Allegretti has received consulting fees from Mallinckrodt Pharmaceuticals, Ocelot Bio, Sequana Medical, Bioporto, and Motric Bio. Pere Ginés received research funding from Gilead and Grifols; has consulted or attended advisory boards for Gilead, RallyBio, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Behring, Roche Diagnostics International, Boehringer Ingelheim, and Astra-Zeneca; and has received speaking fees from Pfizer. Paolo Angeli received grant/research support from Grifols and CSL Behring; held a patent with Biovie; and served as consultant for Sequana Medical. Salvatore Piano served as consultant for Plasma Protein Therapeutics Association, Boehringer Ingelheim, and Resolution Therapeutics; and received speaking fees from Grifols, Ferring, and Medscape. The remaining authors disclose no conflicts.

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Data Availability

The individual data collected will not be made available due to restrictions from both ethics committees and individual data sharing agreements between the sponsor and the centers.

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