

## **SUPPLEMENTARY MATERIAL**

### **Real-world use of terlipressin in cirrhosis and acute kidney injury: frequent use beyond hepatorenal syndrome**

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## Supplementary methods

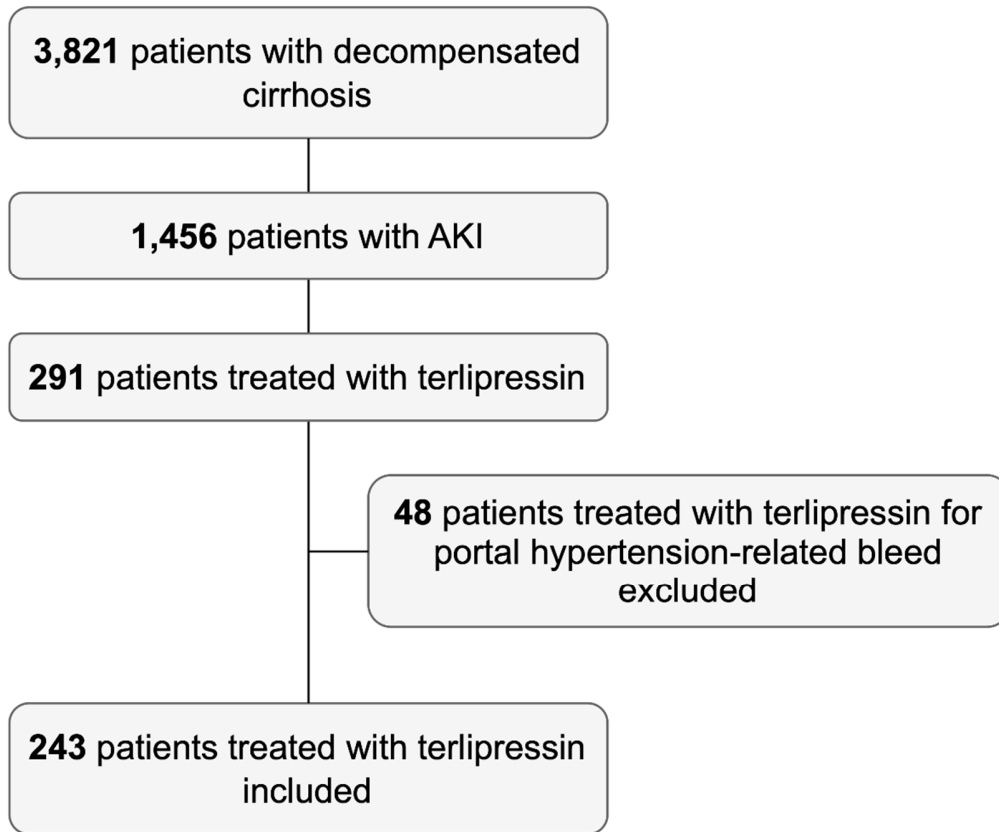
### *Definitions*

Acute kidney injury was defined according to the International Club of Ascites (ICA) criteria<sup>1</sup>. AKI staging followed the ICA definition of stages 1, 2, 3<sup>1</sup>. Community-acquired AKI was defined as AKI diagnosed at admission, while hospital-acquired AKI was defined as AKI that developed during admission. AKI resolution was defined as a return of serum creatinine to within 0.3 mg/dL of baseline value during admission. The following precipitating events of AKI were considered: volume loss/excessive diuretic use, spontaneous bacterial peritonitis (SBP), non-SBP infection, gastrointestinal bleeding, nephrotoxic drugs (including nonsteroidal anti-inflammatory drugs, contrast media), other causes, and no identifiable precipitant. AKI phenotype was classified as hypovolemia-induced when there was a history of excessive fluid losses (i.e. excessive diuresis due to diuretic therapy with loss of body weight >500 g/day or 1,000 g/day in patients without and with edema, respectively; severe diarrhea) or bleeding in the days preceding AKI, and improving with fluid administration. Hepatorenal syndrome-AKI (HRS-AKI) was defined as per 2015 ICA criteria<sup>1</sup>. Acute tubular necrosis (ATN) was defined as the presence of at least three out of six of the following criteria: a) fractional excretion of sodium >2%; b) urinary osmolality <400 mOsm/L; c) urinary sodium >40 mEq/L; d) presence of shock or use of nephrotoxic drugs; e) urine sediment showing granular/epithelial casts; f) urine sediment showing renal tubular epithelial cells. AKI not meeting the above phenotype definitions were classified as Other AKI.

### **Supplementary methods references**

- <sup>1</sup> Angeli P, Ginès P, Wong F, *et al.* Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015; **62**: 968–74.

**Supplementary Figure S1. Flow diagram of included patients**



*Legend:* AKI, acute kidney injury

**Supplementary Table S1** Sensitivity analysis for predictors of AKI resolution, excluding patients who died or underwent liver transplantation by 28 days without achieving AKI resolution

	OR (95% CI)	p value
<b>Age</b>	1.05 (1.00 – 1.09)	0.041
<b>Female sex</b>	1.30 (0.46 – 3.67)	0.618
<b>AKI Phenotype</b> (vs. HRS-AKI)		
Hypovolemia-induced	1.71 (0.55 – 5.35)	0.354
ATN	2.20 (0.54 – 8.96)	0.271
Other	0.91 (0.14 – 6.08)	0.920
<b>Hospital-acquired AKI</b> (vs. community-acquired)	1.57 (0.52 – 4.72)	0.422
<b>AKI stage at diagnosis</b> (vs. stage 1)		
Stage 2	1.35 (0.39 – 4.58)	0.636
Stage 3	5.02 (1.26 – 20.00)	0.022
<b>ACLF grade</b> (vs. no ACLF)		
1	2.59 (0.69 – 9.71)	0.157
2	1.13 (0.26 – 5.02)	0.867
3	2.80 (0.28 – 27.65)	0.378

Multivariable analysis performed with a logistic model.

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; HRS, hepatorenal syndrome; OR, odds ratio.

**Supplementary Table S2** Univariable analysis for predictors of 28-day mortality

	sHR (95% CI)	p value
<b>Age</b>	1.01 (0.99 - 1.04)	0.069
<b>Female sex</b>	1.09 (0.69 - 1.72)	0.710
<b>Etiology of cirrhosis</b>		
Alcohol-related	1.01 (0.66 - 1.57)	0.948
MASLD	0.57 (0.31 - 1.04)	0.068
HCV	1.43 (0.74 - 2.74)	0.291
HBV	1.03 (0.37 - 2.87)	0.954
Other	1.08 (0.64 - 1.83)	0.773
<b>Ascites</b>	4.40 (1.07 - 18.10)	0.040
<b>Hepatic encephalopathy</b>	1.29 (0.85 - 1.96)	0.233
<b>MAP</b>	1.00 (0.98 - 1.02)	0.965
<b>Baseline creatinine</b>	0.79 (0.48 - 1.30)	0.348
<b>Serum creatinine</b>	0.89 (0.72 - 1.09)	0.254
<b>Sodium</b>	0.99 (0.96 - 1.03)	0.678
<b>Bilirubin</b>	1.03 (1.01 - 1.05)	0.002
<b>Albumin</b>	0.67 (0.47 - 0.94)	0.019
<b>INR</b>	1.77 (1.45 - 2.17)	<0.001
<b>WBC</b>	1.03 (1.00 - 1.06)	0.042
<b>MELD-Na</b>	1.06 (1.03 - 1.08)	<0.001
<b>AKI precipitant</b>		
Volume loss/excessive diuretic use	0.83 (0.54 - 1.28)	0.411
Infection	1.94 (1.26 - 2.99)	0.003
Gastrointestinal bleed	1.04 (0.50 - 2.16)	0.921
Nephrotoxic drugs	0.66 (0.21 - 2.12)	0.489
Other	1.39 (0.45 - 4.36)	0.572
No identifiable precipitant	0.70 (0.37 - 1.31)	0.265
<b>Hospital-acquired AKI (vs community-acquired)</b>	2.71 (1.79 - 4.10)	<0.001
<b>ACLF</b>	1.16 (0.73 - 1.84)	0.529
<b>ACLF grade (vs. no ACLF)</b>		
1	0.68 (0.38 - 1.23)	0.210
2	1.22 (0.70 - 2.12)	0.489
3	2.48 (1.36 - 4.55)	0.003
<b>Albumin use (in first 48h)</b>	0.79 (0.45 - 1.38)	0.401
<b>Crystalloids use (in first 48h)</b>	1.44 (0.94 - 2.20)	0.101
<b>AKI stage at diagnosis (vs. stage 1)</b>		
Stage 2	1.29 (0.82 - 2.02)	0.281
Stage 3	0.72 (0.41 - 1.28)	0.274
<b>AKI phenotype (vs. hypovolemic)</b>		
HRS-AKI	1.22 (0.71 - 2.10)	0.482
ATN	2.05 (1.08 - 3.89)	0.027
Other	0.98 (0.40 - 2.41)	0.961

AKI, acute kidney injury; ALCF, 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.

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