Hepato-Renal Syndrome

Vasanthi Balaraman M.D

Assistant Professor, Division of Transplant Surgery

Transplant Nephrologist

Medical Director, Living Donor Kidney Transplant Program

Methodist Transplant Institute, Methodist University Hospital

University of Tennessee Health Science Center

1211 Union Ave, Suite 340

Memphis, TN-38104

Disclosures

- No disclosures

Learning objectives..

Define the classification, prevalence and manifestations of hepatorenal syndrome (HRS).

Review the Pathophysiology of hepatorenal syndrome (HRS).

Review updated HRS guidelines and recommendations, including treatment goals in HRS.

Discuss the new International Club of Ascites criteria for the diagnosis and management of acute kidney injury (AKI) in cirrhosis and apply these criteria in clinical practice.

Discuss appropriate albumin management and other therapeutic options in patients with cirrhosis.

Case scenario

- 65 year old female with h/o Cirrhosis presents with tense ascites and a creatinine of 2.1 mg/dl.

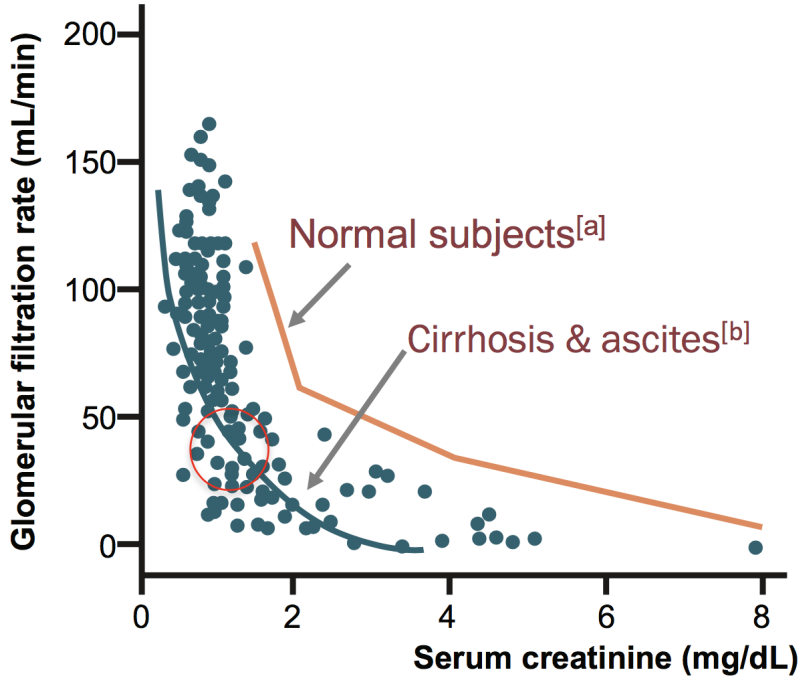
  PMH includes DM type II and HTN.

  BP 108/65 mm Hg, BMI is 32, She has 2+ edema,
  She is on Lasix 40 mg , Lisinopril 10 mg and Metoprolol 25 BID.

  LABS
  Na+ is 130, K+ 5.0, Bilirubin is 3.6, INR is 1.6 , HbA1c is 6.2 ,Hb is 10.3, PLT 78 , Serum Creatinine is 2.1 mg/dl (was 1.2 mg/dl, 2 weeks ago) , Urine Protein Creatine Ratio is normal , BNP is 400 .

Relationship Between Serum Creatinine and GFR in Patients with Cirrhosis

- Serum creatinine of 1.5 mg/dL corresponds to GFR of ~30 mL/min in cirrhosis.
- Due to low muscle mass in cirrhosis, SCr overestimates renal function



- *Arroyo V, et al. Zakim and Boyer's Hepatology: A Textbook of Liver Disease. 2006.*

Differential Diagnosis of AKI

- **Prerenal**

– Hypovolemia: diuretics, GI bleeding, diarrhea

– Hepatorenal syndrome.

- **Intrinsic renal disease**

– Acute tubular necrosis.

– Glomerulonephritis

– Interstitial nephritis.

- **Obstructive**

- **HRS AKI vs. ATN AKI**
- Among the most promising are urinary biomarkers, interleukin-18 (IL-18), kidney injury molecule-1(KIM-1), liver type fatty acid-binding protein (L- FABP) and neutrophil gelatinase- associated lipocalin (NGAL).

Graupera I et al. Clin Liver Dis. 2013;2:128-131.

Diagnosis and Stages of AKI

The Kidney Disease: Improving Global Outcomes (KDIGO)

1) increase in sCr by ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hr or

2) increase in sCr to ≥1.5x baseline, which is known or presumed to have occurred within the prior 7 days or

3) urine volume <0.5 ml/kg/h for 6 h.

- "More recently it was observed that adding the urine output (UO) diagnostic criteria of AKI to the assessment of critically ill patients with chronic liver disease, in the intensive care unit improved the identification of patients with AKI, as well as of those with stage 2–3 AKI.
- Additionally, patients identified based on UO criteria without sCr elevation had a significantly higher mortality."

AKI Stages	Description
1	Increase of creatinine ≥0.3 mg/dL up to 2-fold of baseline
2	Increase in creatinine between 2-fold and 3-fold of baseline
3	Increase in creatinine >3-fold of baseline or creatinine >4 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dL (26.5 µmol/L) or initiation of RRT

Criteria to diagnose HRS-AKI

Cirrhosis with ascites.
Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury† criteria (Increase in serum creatinine ≥0.3 mg/dL from baseline within 48 hours or a percent increase in serum creatinine of ≥50% which is known or presumed to have occurred within the preceding 7 days.)
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography .

Biggins SW et al. Hepatology. 2021;74:1014-1048

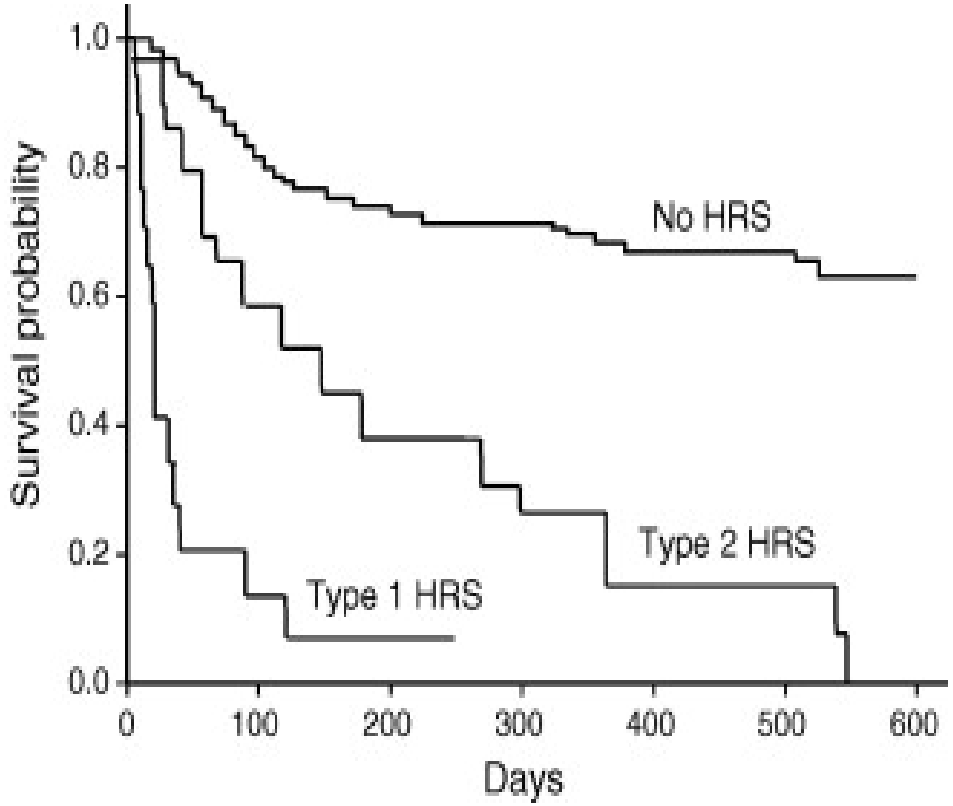
Revised HRS definition
No more Type 1 and Type 2

Old Classification	New Classification		Criteria
HRS-1*	HRS-AKI		1. Absolute increase in sCr ≥0.3 mg/dl within 48h and/or 2. Urinary output ≤0.5 ml/kg B.W. ≥6h* or 3. Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2*	HRS-NAKI	HRS-AKD	1.eGFR <60 ml/min per 1.73 m2 for <3 months in the absence of other (structural) causes 2.Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value
		HRS-CKD	eGFR <60 ml/min per 1.73 m2 for ≥3 months in the absence of other(structural) causes

Angeli P et al. J Hepatol. 2019; 71:811.

Burden of HRS-AKI

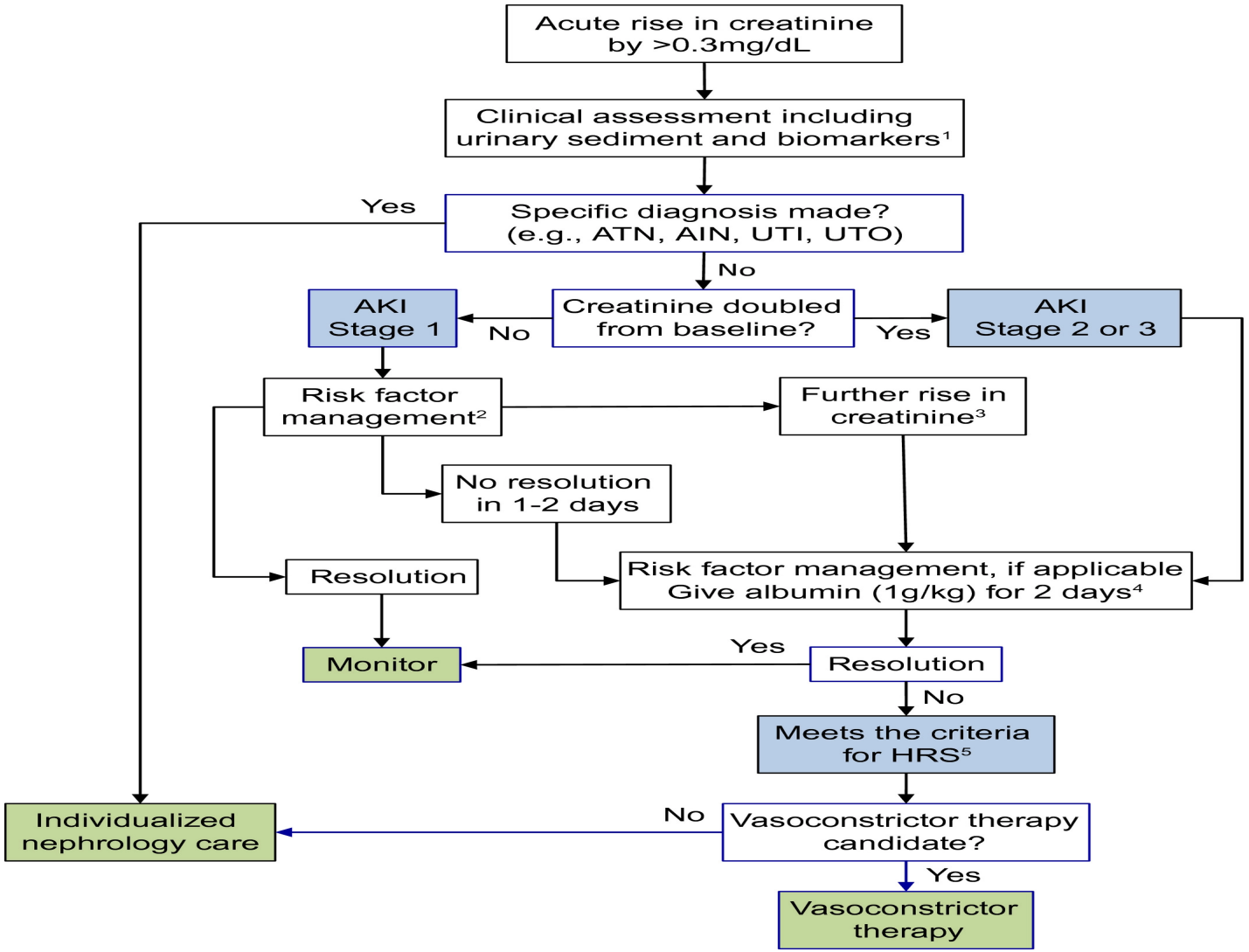
- Prevalence of AKI in hospitalized patients with decompensated cirrhosis is ~27% to 53%
- Affects >3500 patients in the US annually.
- AKI associated with 30-day mortality of 29% to 44% .
- AKI is an independent negative predictor of transplant free survival and post liver transplant outcomes.



Biggins SW et al. Hepatology. 2021;74:1014-1048

- *Arroyo et al. J Hepatol. 2007.*

AASLD proposed algorithm for diagnosis and management of AKI in cirrhosis.



Biggins SW et al. Hepatology. 2021;74:1014-1048

Case scenario

- 65 year old female with h/o Cirrhosis presents with tense ascites and a creatinine of 2.1 mg/dl.

  PMH includes DM type II and HTN.

  BP 108/65 mm Hg, BMI is 32, She has 2+ edema,
  She is on Lasix 40 mg , Lisinopril 10 mg and Metoprolol 25 BID.

  LABS
  Na+ is 130, K+ 5.0, Bilirubin is 3.6, INR is 1.6 , HbA1c is 6.2 ,Hb is 10.3, PLT 78 , Serum Creatinine is 2.1 mg/dl (was 1.2 mg/dl, 2 weeks ago) , Urine Protein Creatine Ratio is normal , BNP is 400 .

Pharmacologic therapy of HRS-AKI

➢IV Albumin

- Albumin is infused at a dose of 1 g/kg on day 1 of therapy followed by 40-50 g/day, continued for the duration of Vasoconstrictor therapy.

Plus

➢Vasoconstrictors
  - Midodrine + octreotide
  - Norepinephrine
  - Terlipressin.

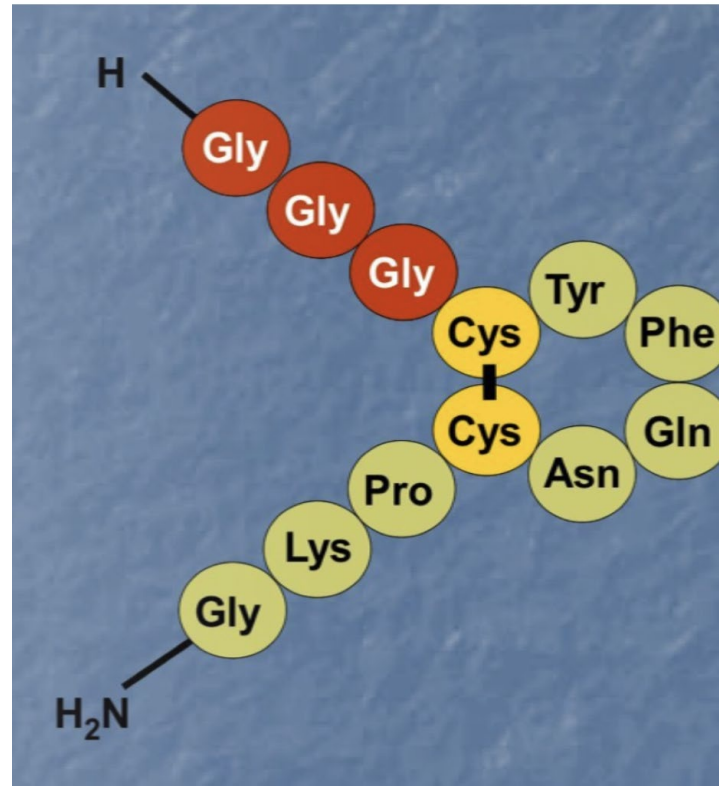
Biggins SW et al. Hepatology. 2021;74:1014-1048.

Terlipressin

- Now approved in the US.
- Synthetic 12 amino acid peptide
- Pro-drug
- Constrictive activity via **V-1 receptors**
- – Vascular and extra vascular smooth muscle cells
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
  – Increases effective blood volume – Reduces renin and angiotensin

- **Can lead to renal vasodilation**
- **Can lead to improvement in serum creatinine**

- V-2 agonist activity
  – Could possibly cause hyponatremia



Terlipressin plus Albumin vs Albumin Alone for HRS-1 (CONFIRM Study)

- Randomized, placebo-controlled study in 300 patients

2:1 to Terlipressin (1 mg IV every 6 hours) or placebo, plus albumin in both groups.

- Treatment for up to 14 days unless one of the following occurred:

➢ Verified HRS reversal(VHRSR) (decrease in SCr to ≤ 1.5mg/dL)

➢ Renal replacement therapy(RRT).

➢ Liver transplantation(LT)or

➢ SCr at or above baseline(BL) at Day4

- Primary Endpoint

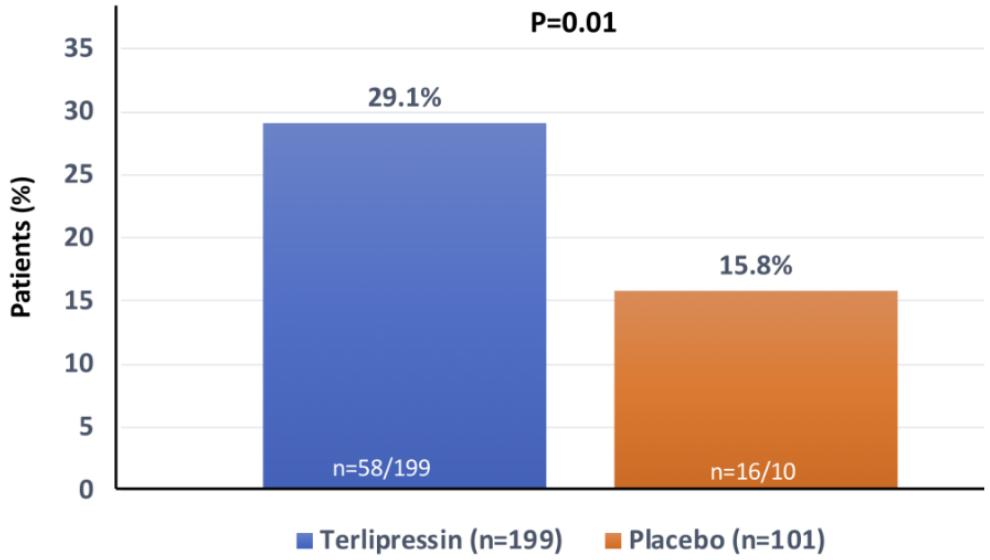
➢ VHRSR defined as 2 consecutive SCr values ≤ 1.5mg/dL, at least 2 hours apart, with patient alive without RRT for ≥10 days after the second SCr ≤1.5 mg/dL.

Wong F et al. N Engl J Med. 2021;384:818-828.

Primary Endpoint (CONFIRM Study)

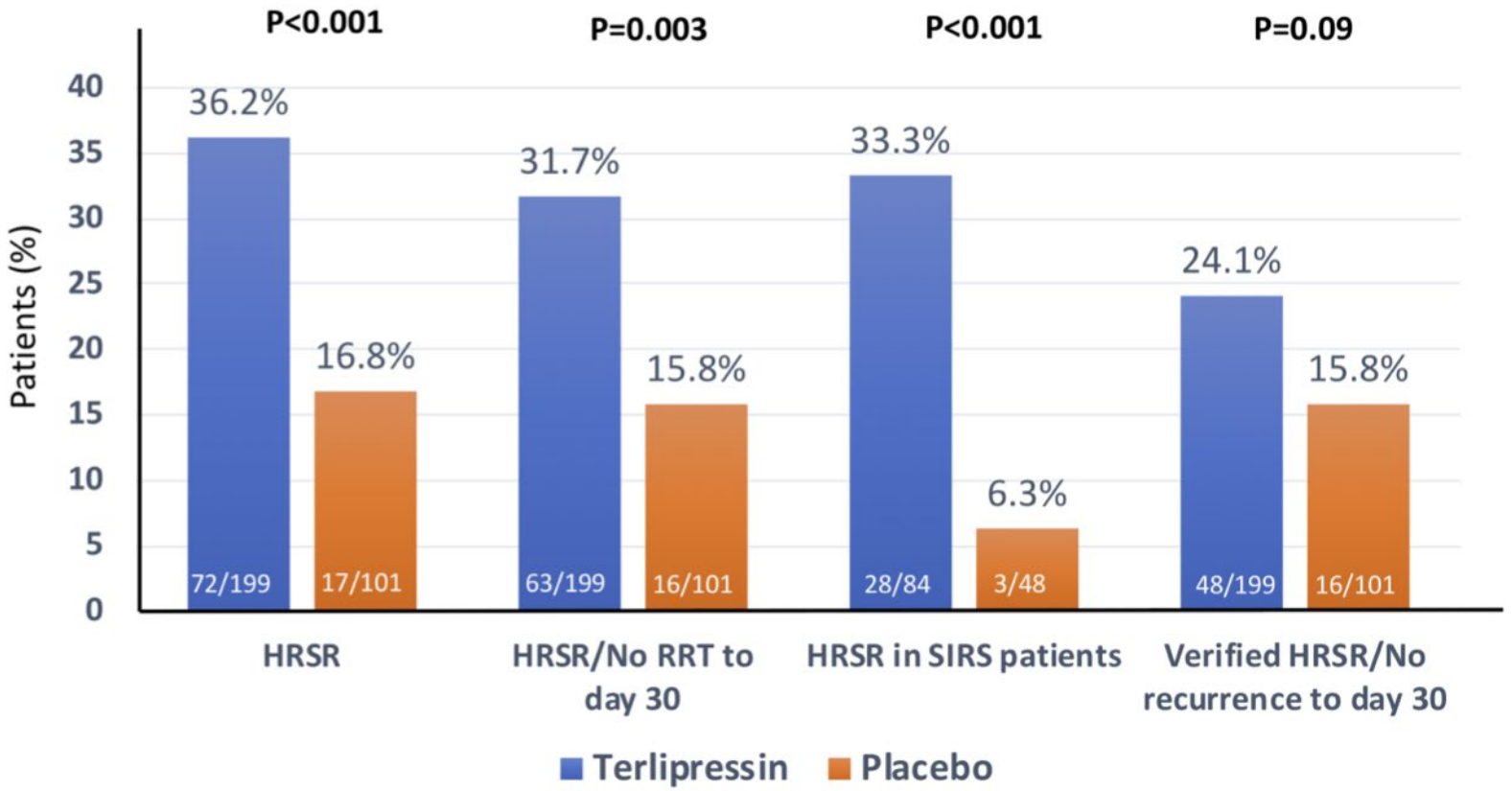
Figure S4: Primary and Secondary End Points as per Pre-specified Analysis Plan

A: Verified HRS Reversal



Wong F et al. *N Engl J Med*. 2021;384:818-828.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)



Wong F et al. *N Engl J Med*. 2021;384:818-828.

Incidence of Adverse Events (>10% Terlipressin Patients) (CONFIRM Study)

Adverse effects	Terlipressin (N=200)[b] % (n)	Placebo (N=99)[b] % (n)
Abdominal pain	19.5 (39)	6.1 (6)
Nausea	16.0 (32)	10.1 (10)
Diarrhea	13.0 (26)	7.1 (7)
Dyspnea	**12.5 (25)**	**5.1 (5)**
Respiratory failure	**10.5 (21)**	**5.1 (5)**
Hepatic encephalopathy	10.0 (20)	13.1 (13)

Wong F et al. N Engl J Med. 2021;384:818-828.

Caveats for Terlipressin use per the FDA

INDICATIONS AND LIMITATION OF USE

- Indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.
- Patients with a serum **creatinine >5 mg/dL** are unlikely to experience benefit.

ISSUES WITH USE

- **Ineligibility for Liver Transplant:** Adverse reactions (respiratory failure, ischemia) may make a patient ineligible for liver transplantation, if listed. For patients with high prioritization for liver transplantation (e.g., MELD ≥35), the benefits may not outweigh its risks.

CONTRA-INDICATIONS

- In patients experiencing hypoxia or worsening respiratory symptoms.
- In patients with ongoing coronary, peripheral, or mesenteric ischemia.

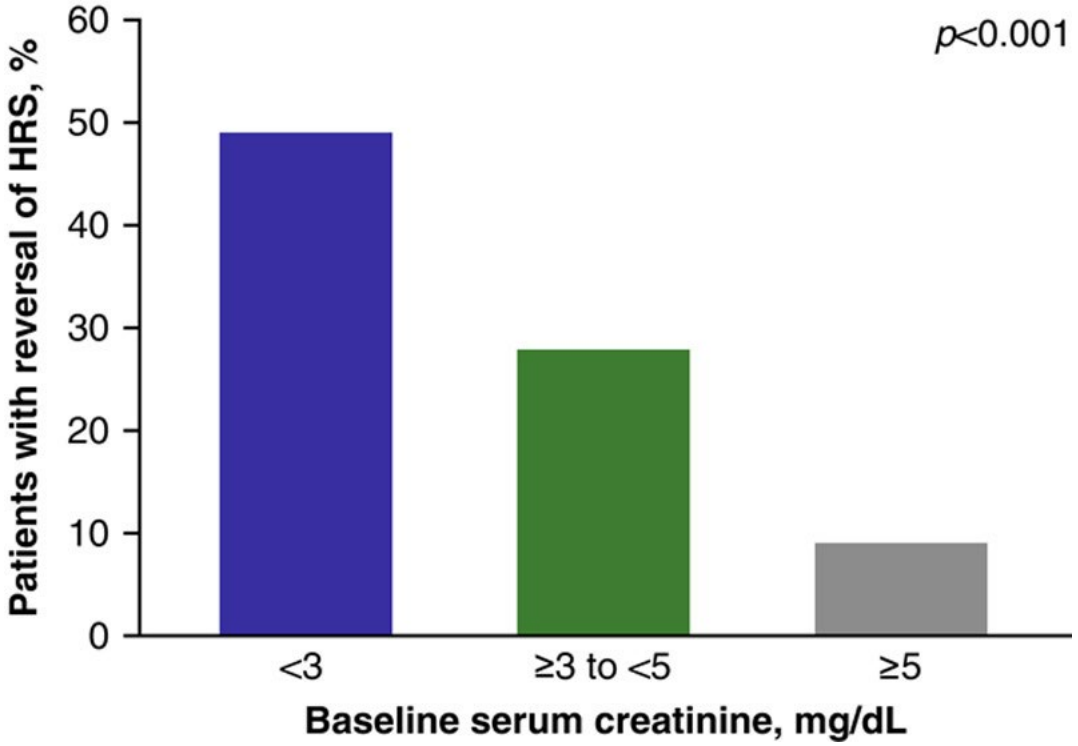
Warning:

- May cause serious or fatal respiratory failure. Patients with volume overload or with acute-on-chronic liver failure (ACLF) Grade 3 are at increased risk.
- Do not initiate it in patients experiencing hypoxia (e.g., SpO2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue it if SpO2 decreases below 90%.

Vasoconstrictor Dosing and Administration for HRS-AKI

Drug	Dosing and Administration
Terlipressin	Vasopressors of choice and currently approved in the US. Day 1-3, 0.85 mg IV every 6 hours Day 4, If Scr drops >30 % from baseline, continue the same dose If Scr drops by <30% from baseline, increase the dose to 1.7 mg IV every 6 hrs If Scr is =/>baseline, discontinue therapy. Continue Terlipressin until 24 hrs after 2 consecutive Scr < 1.5 mg/dl at least 2 hours apart or a max of 14 days.
Norepinephrine	Given as continuous IV infusion, typically in an intensive care unit setting, starting at 0.5 mg/hour to achieve an increase in mean arterial pressure of at least 10 mm Hg or an increase in urine output of >200 mL/4 hours. If at least one of these goals is not achieved, the dose of norepinephrine is increased every 4 hours in increments of 0.5 mg/hour up to a maximum of 3 mg/hour
Midodrine in combination with Octreotide	Midodrine 5 to 15 mg q8 hours Octreotide 100-200mcg q8hrs.

Timely recognition and treatment.



Curry P, et al. Hepatol Commun. 2023 Jan 3;7(1):e1307

HRS and Liver Transplantation

- HRS not responding to treatment can only be reversed by Liver Transplantation with RRT as bridge to transplant

- HRS patients have a higher priority for liver transplant due to impact of high creatinine in the MELD score

- Reversal of HRS could delay Liver Transplant

- Best option Severe HRS AKI is for Liver Transplantation

- Simultaneous Liver Kidney Transplant may be an option for some patients on prolonged RRT.

Eligibility Criteria for SLK

1. AKI ≥6 consecutive weeks with one or a combination of both (weekly documentation)

- Dialysis
- eGFR/CrCl ≤25 mL/min

2. CKD with GFR ≤60 mL/min for >90 days with one of the following:

- End-stage renal disease
- eGFR/CrCl ≤30 mL/min at the time or after registration on kidney waiting list

3. Metabolic diseases- Hyperoxaluria, aHUS from mutation in factor H or factor I, Familian non neuropathic systemic amyloidosis, methylmalonic aciduria.

Safety net:

- Any patient who is registered on the kidney waitlist between 60 and 365 days after LT and is either on chronic hemodialysis or has an eGFR <20 mL/min will qualify for increased priority

Summary and Conclusions

- HRS is a significant cause of morbidity/mortality and early recognition and intervention is needed.
- Current classification expedites the recognition of HRS-AKI and allows for potential earlier intervention.
- Volume expansion is the first step in management of HRS AKI.
- Once HRS AKI is diagnosed, Vasoactive agents (terlipressin) should be considered.
- Terlipressin should be avoided in patients with creatinine of >5mg/dl, those with advanced Acute on Chronic Liver Failure CLF (Grade 3), those with hypoxia.
- Early Referral to a liver Transplant center is critical.

THANK YOU