Ascites and Complications: Focus on AKI in Cirrhosis

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Background: AKI in Cirrhosis

- A common and serious clinical problem
  - ~20% of hospitalized cirrhotic patients
  - Increased risk of short-term mortality
- AKI redefined by the International Ascites Club[1]:
  - Abrupt rise in serum creatinine ≥ 0.3mg/dL within 48h
  - Or increase by >50%
    - Within presumed 7 days
    - Baseline creatinine within 3 months
- AKI – 3 general types:
  - (1) Prerenal (includes HRS), also known as "Functional";
  - (2) Intrinsic (includes ATN, GN, AIN), "Structural";
  - (3) Post-renal - obstructive
- How to diagnose?
  - Careful history and physical exam
  - Fluid/Albumin challenge, U/A, renal US, Urine electrolytes, Urine Eos
  - FeNa – out of favor given confounding with diuretics, sepsis, sodium avid state
  - FeUrea[2] – less affected by diuretics

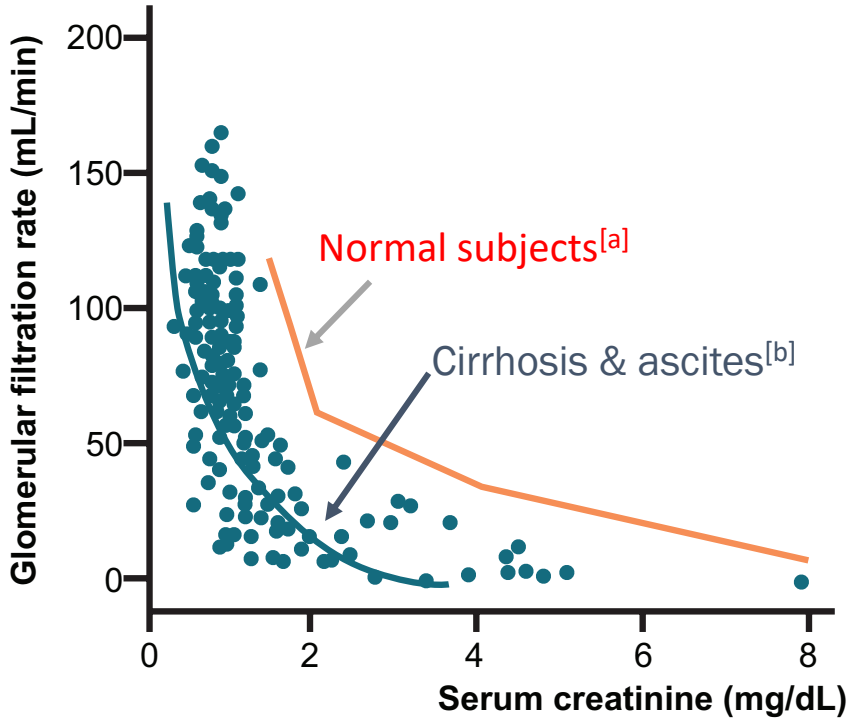
Stage AKI[1]	Criteria
Stage 1*	Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2-fold from baseline[#]
Stage 2	Increase in SCr >2- to 3-fold from baseline
Stage 3	Increase of SCr >3-fold from baseline or SCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of RRT

*Stage 1A: < 1.5mg/dL; Stage 1B: ≥ 1.5mg/dL
[#]Baseline: within 3 months

1. Angeli P, et al. *J Hepatol.* 2015; 2. Patidar KR et al. Hepatology 2018; 3. EASL Guidelines. *J Hepatol.* 2018

Relationship between serum creatinine (SCr) and GFR in patients with cirrhosis

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



a. Inker LA, Perrone R. UpToDate.
b. Arroyo V, et al. *Zakim and Boyer's Hepatology: A Textbook of Liver Disease.* 2006.

AKI – How to differentiate?

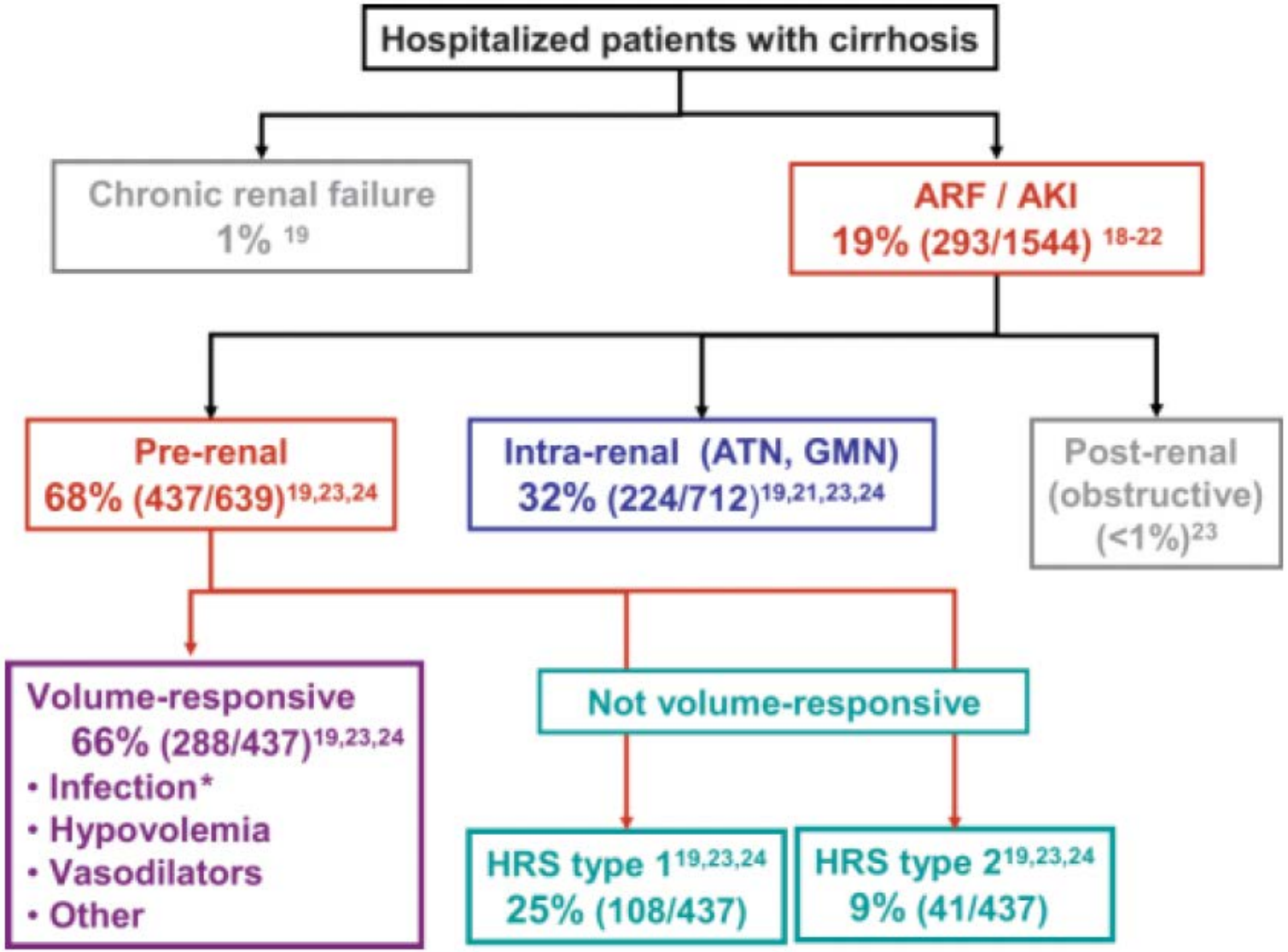
	Pre-renal (non-HRS)	Intrarenal (ATN or other)	Hepatorenal (HRS)
Urine Volume	Low (<500ml)	Low to High	Low (<500ml)
Urine Sodium	Low (<20)	Moderate to High (>40)	Low (<20)
Response to Fluid?	Yes	No	No
Urine Sp Gravity	>1.020	≤1.010	>1.020
FeNa*	<1%	>2%	<1%
FeUrea[1]	<35%	>33%	<33%
Urine Osm	>500	<350	>500
Urine Sediment	Bland/Normal, Few granular or hyaline casts	Cellular cast, "muddy brown" casts, RBC casts	Bland to few granular casts
BUN/Cr	>20	<15	>20
Proteinuria	None to trace	Mild to moderate	None to trace
Urine NGAL[#2]	Low	High	Low-Moderate

Additional clues for HRS: Cirrhosis with portal HTN, Ascites, Hyponatremia

*Caution if taking diuretics; #NGAL, neutrophil gelatinase-associated lipocalin

1. Patidar et al. Hepatology 2018;
2. Huelin et al. Hepatology 2019

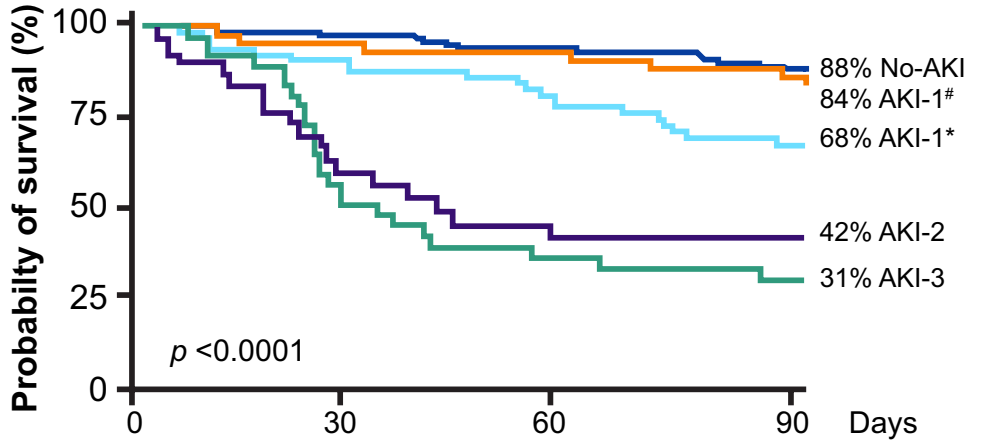
Etiology of AKI in Cirrhosis

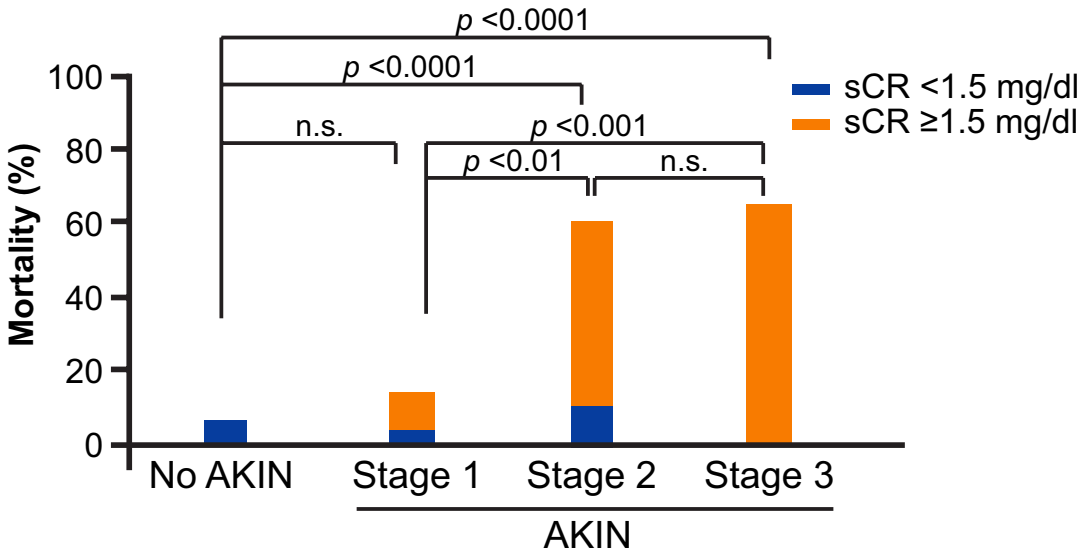


Garcia-Tsao et al. Hepatology 2008

AKI and Cirrhosis - Implications

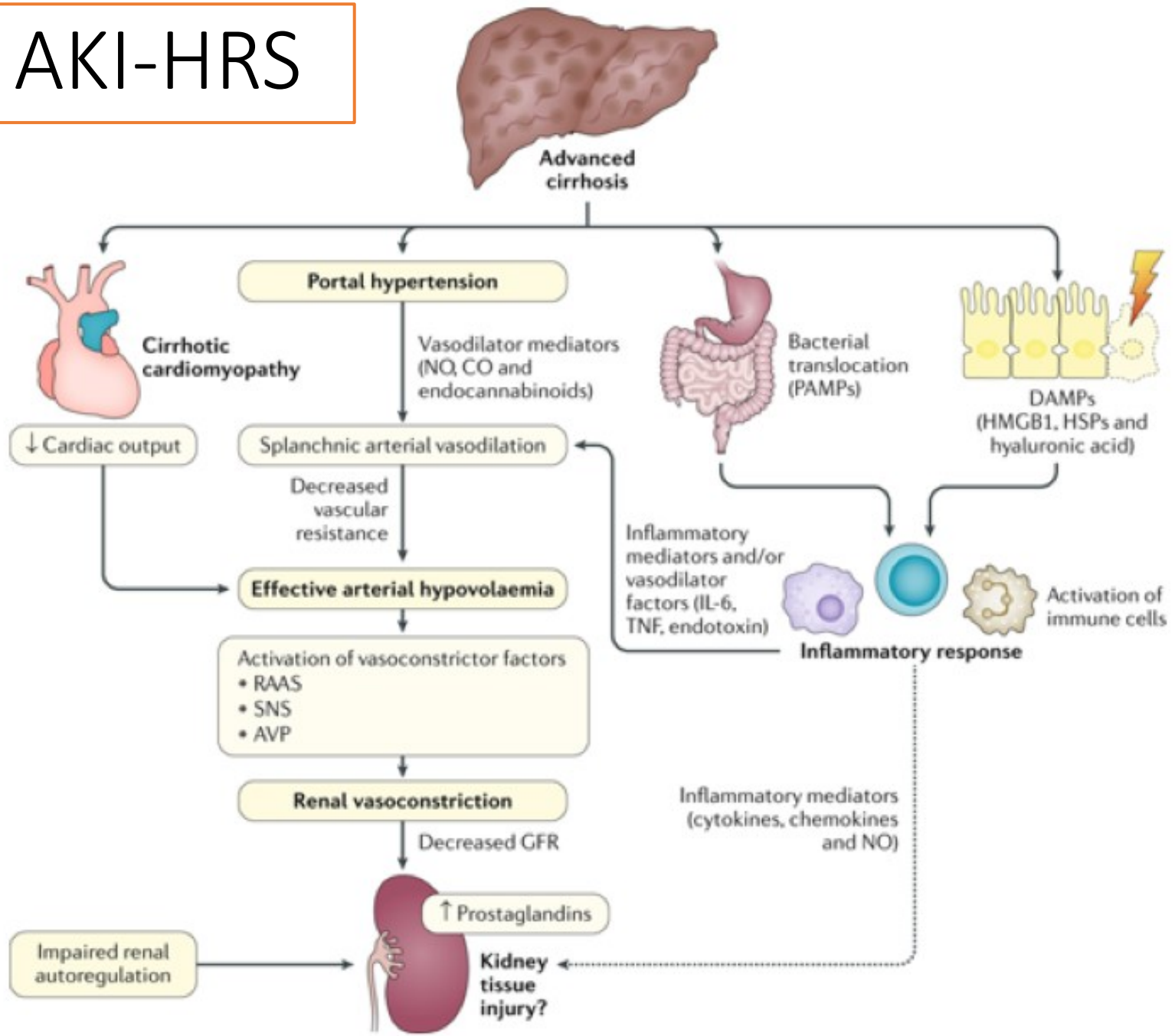
- AKI diagnosed with AKIN criteria associated with increased mortality in patients with cirrhosis[1]
- Progression through stages strongly correlates with increased mortality[2]
- However, serum creatinine cutoff of 1.5 mg/dL is still prognostic[3]
  - Identifies patients at increased risk of mortality
- New AKI-HRS criteria enable earlier treatment (by 4 days) at lower creatinine (1 mg/dL lower)[4]
  - Baseline serum creatinine is a predictor of response to therapy





1. Piano S, et al. *Hepatology.* 2013;57:753-762; 2. Belcher JM, et al. *Hepatology.* 2013;57:753-762;
3. Fagundes C, et al. *J Hepatol.* 2013;59:474-481; 4. Wong F. et al. Journal Hepatology 2019;70(1)Supp.

Pathophysiology AKI-HRS



Ginès P, et al. *Nat Rev Dis Primers.* 2018;4:23.

Hepatorenal syndrome (HRS) - Defined

- Extreme prerenal AKI associated with severe liver disease and portal HTN
  - Baseline ascites
  - Hyperdynamic circulation with low systemic vascular resistance (SVR)
  - Frequent underlying cirrhotic cardiomyopathy
- Not reversible with volume resuscitation (48 hours, IV albumin +/- saline)
- No intrinsic renal injury (no proteinuria, hematuria); normal renal ultrasound
- May or may not identify precipitating event
- Diagnosis of exclusion

Old Classification of HRS:

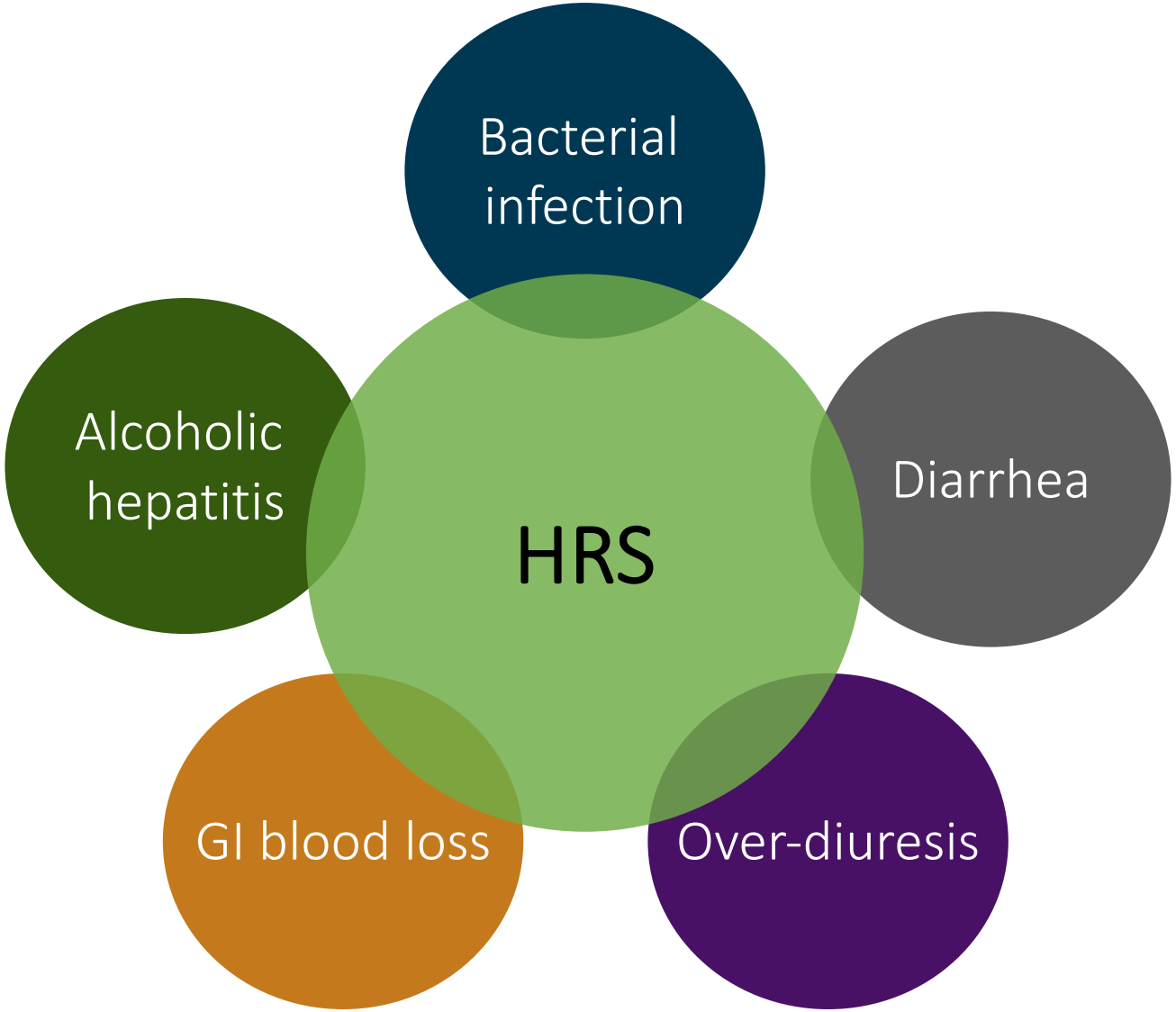
- HRS Type 1:
  - Rapid progression
  - Creatinine > 2.5 mg/dL in < 2 weeks
- HRS Type 2:
  - Slowly progressive course
  - Creatinine > 1.5 mg/dL

New Classification:

HRS-1 → AKI-HRS (Stage 2-3)
HRS-2 → CKD-HRS

1. Angeli P, et al. *J Hepatol.* 2015;62:968-974; 2. *J Hepatol.* 2018;69:406-460.

Common Precipitating Factors of HRS



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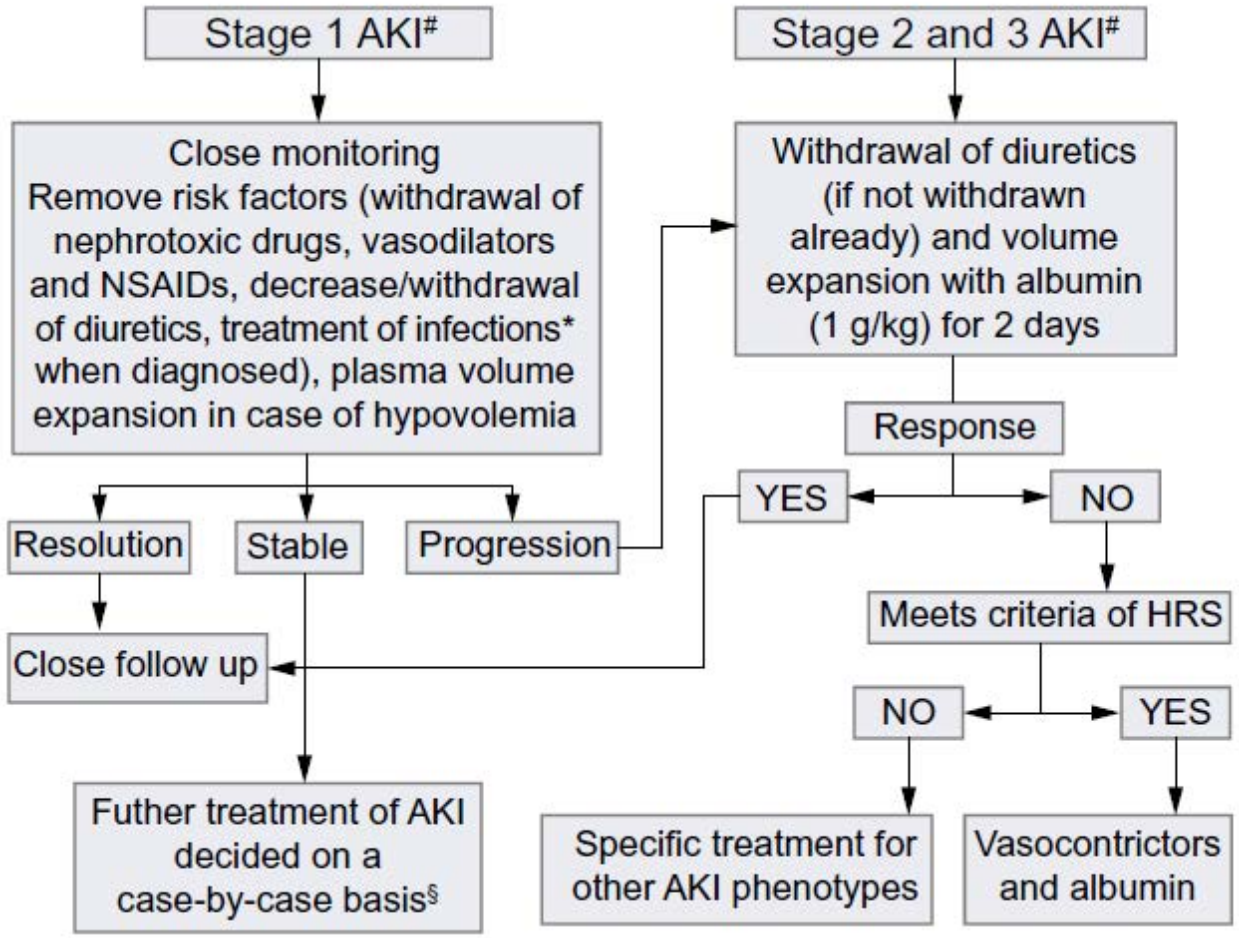
Initial Management

- Early identification
- Assess and treat bacterial infection
  - Blood, urine, ascitic fluid culture, CXR
- Avoid large-volume paracentesis (diagnostic OK)
- Stop β-blockers
- Stop nephrotoxic medications: NSAIDs, diuretics
- Volume expansion



Tapper EB, et al. *Am J Med.* 2016;129:461-467.
Angeli P et al. J Hepatology 2015

Pharmacologic Therapy for HRS

Albumin

- 0.5-1gm/kg (max 100gm/d) for resuscitation; then
- 25 to 50 g/day

Plus

Vasoconstrictors

- Midodrine (Alpha-1 agonist) +/- Octreotide (Glucagon inhibitor)
- Norepinephrine (Alpha-1/2, Beta-1/3 agonist)
- Vasopressin or analogues (Terlipressin) (V1>V2 agonist)

Ginès P, et al. *Nat Rev Dis Primers.* 2018;4:23

**Midodrine Plus Octreotide: Dosing

Midodrine: initially 7.5 mg oral 3 times daily

- Titrate to maximum of 12.5 mg 3 times daily

Octreotide: 100 µg SC 3 times daily

- Maximum dose 200 µg SC 3 times daily
- Titrate to achieve increase of MAP by 15 mmHg

**Note this is off-label treatment for HRS but recommended by AASLD Practice Guidelines

Runyon BA. *Hepatology.* 2013;57:1651-1653.

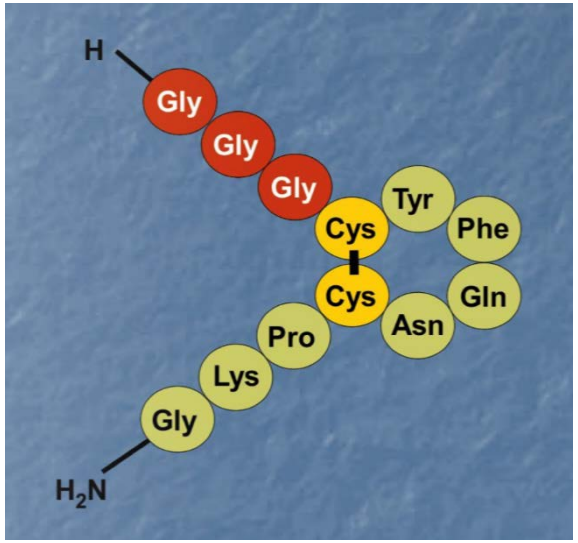
Comparative Efficacy of Midodrine and Norepinephrine: Systematic Review and Network Meta-Analysis

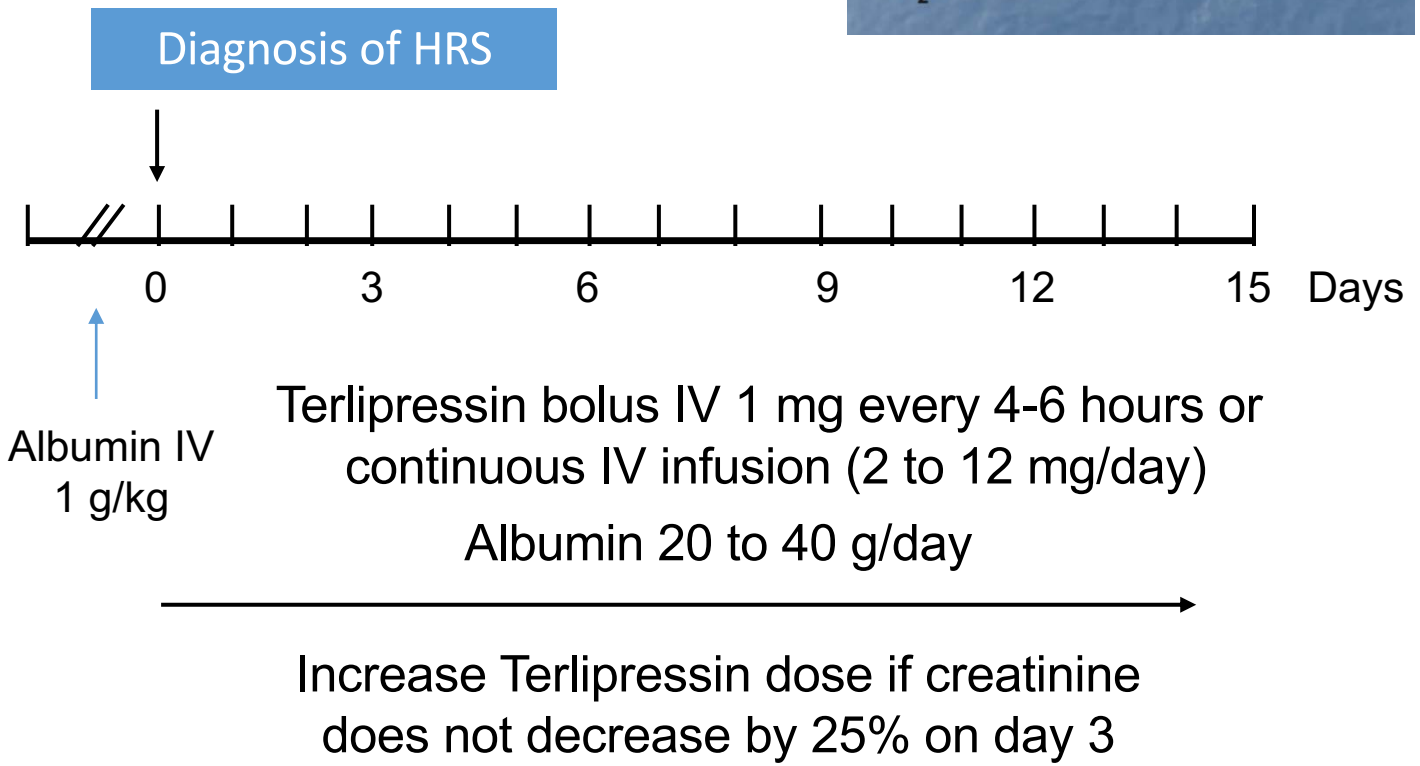
	Short-Term Mortality		Reversal of HRS	
	OR (95% CI)	Quality of Evidence	OR (95% CI)	Quality of Evidence
Efficacy vs. Placebo				
Midodrine + octreotide	0.61 (0.19, 1.93)	Low (network)	0.44 (0.06, 3.23)	Low (network)
Noradrenaline	0.75 (0.32, 1.76)	Low (network)	**4.17 (1.37, 12.50)**	Low (network)
Efficacy vs. Midodrine + Octreotide				
Noradrenaline	1.50 (0.60, 3.78)	Low (network)	**10.00 (1.49, 50.00)**	Low (network)

Facciorusso A, et al. *Lancet Gastroenterol Hepatol.* 2017;2:94-102.

Terlipressin and Albumin

- Vasopressin analogue
- Prodrug with longer half-life (~3h)
- Selective V1a > V1b or V2 activity
- Splanchnic and portal vasoconstriction
- Reduces renin-angiotensin-aldosterone
  - Promote renal arterial vasodilation
- Requires IV Albumin for HRS treatment





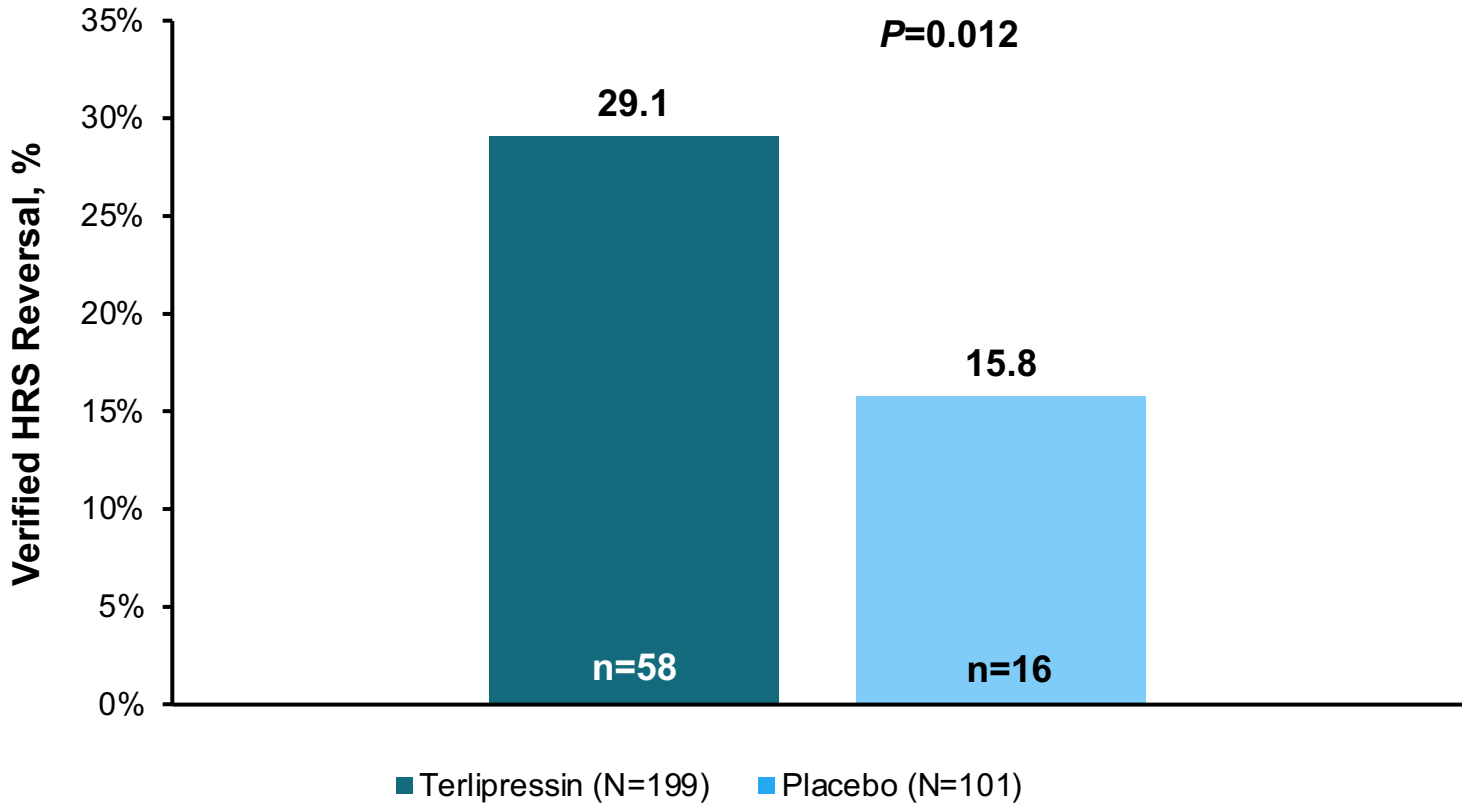
Solà E, et al. *Curr Opin Organ Transplant.* 2013;18:265-270.

Terlipressin + 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
- Primary Endpoint
  - Verified HRS reversal (VHRSR): 2 consecutive SCr values ≤1.5 mg/dL, at least 2 hours apart, with patient alive without RRT for ≥10 days after the second SCr ≤1.5 mg/dL
- Treatment for up to 14 days unless one of the following occurred:
  - VHRSR (sustained decrease in SCr to ≤1.5 mg/dL)
  - Renal replacement therapy (RRT)
  - Liver transplantation (LT) or
  - SCr at or above baseline (BL) at Day 4

Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

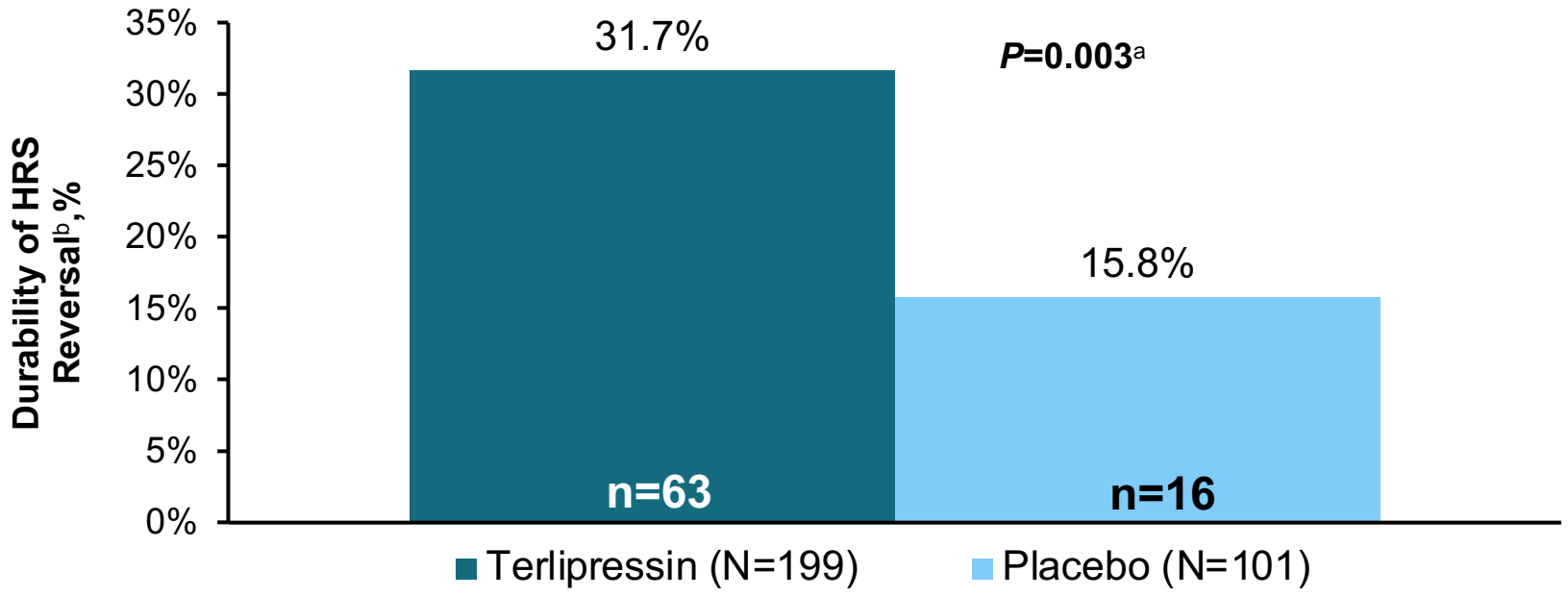
Primary Endpoint: Verified HRS Reversal (CONFIRM Study)



Z score=2.52618. The final analysis is successful if the score is >1.97743.

Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)

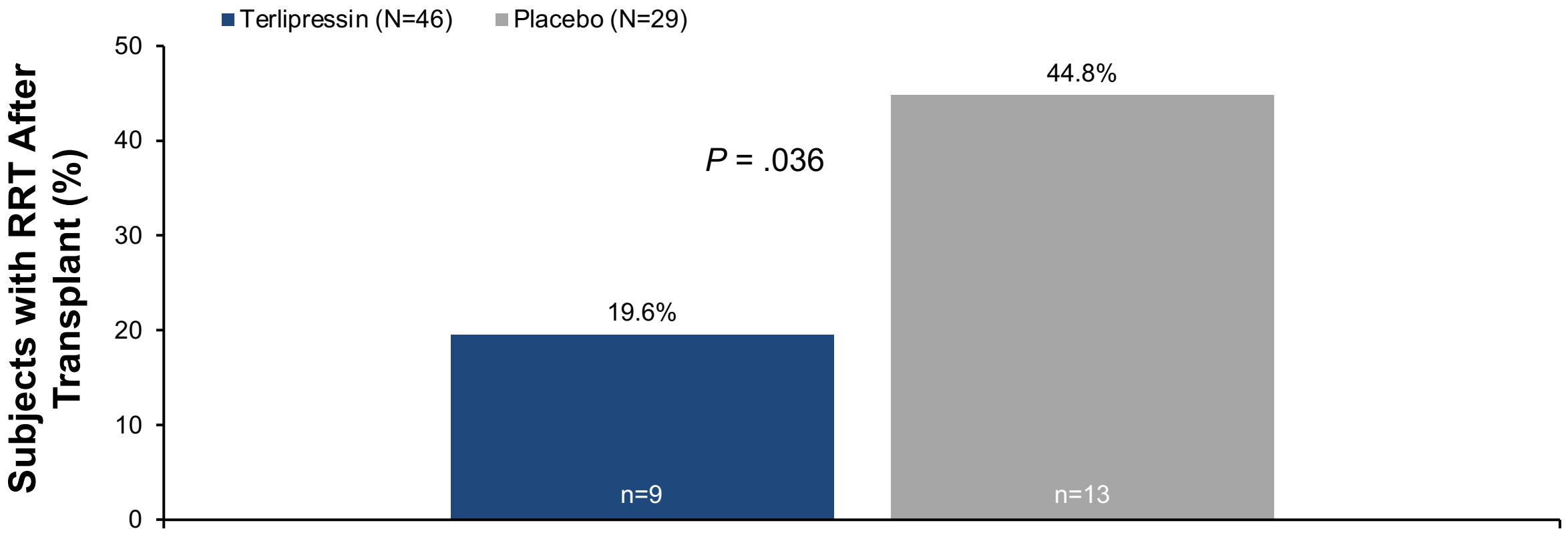


[a]From a CMH Test stratified by qualifying serum creatinine (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least one single event of ≥4 vs <4 L).
[b]Percentage of subjects with HRS reversal without RRT to day 30.

Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Incidence of RRT Post Liver Transplant

CONFIRM Study (ITT Population)



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

Preferred Term[a]	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)

Respiratory Failure higher in both cohorts in CONFIRM than REVERSE trial; REVERSE T 5.4% vs P 2.1%; none of the respiratory failure were reported as related to study drug.

AEs, adverse events; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group.

[a]Up to 7 days posttreatment. [b]Subjects experiencing multiple episodes of a given adverse event are counted once within each preferred term.

Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Most Common Serious Adverse Events (≥5%)

Integrated Studies (Safety Population)

Preferred Term* †	Terlipressin N=349 %	Placebo N=249 %
Total with any SAEs	65.0	59.8
Respiratory failure	8.3	2.4
Multiple organ dysfunction syndrome	7.4	3.2
Chronic hepatic failure	6.0	6.0
Hepatic failure	6.0	9.2
Sepsis	5.2	1.6

*Up to 30 days posttreatment. †Subjects with multiple AEs of one preferred term are counted once.

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Improvement in Renal Function: TERLI vs MID/OCT

RCT (non-blinded)

n=49 (27 Terli; 22 Mid/Oct)

HRS-1 or severe HRS-2 (Scr>2.5mg/dL)

Terlipressin by continuous infusion

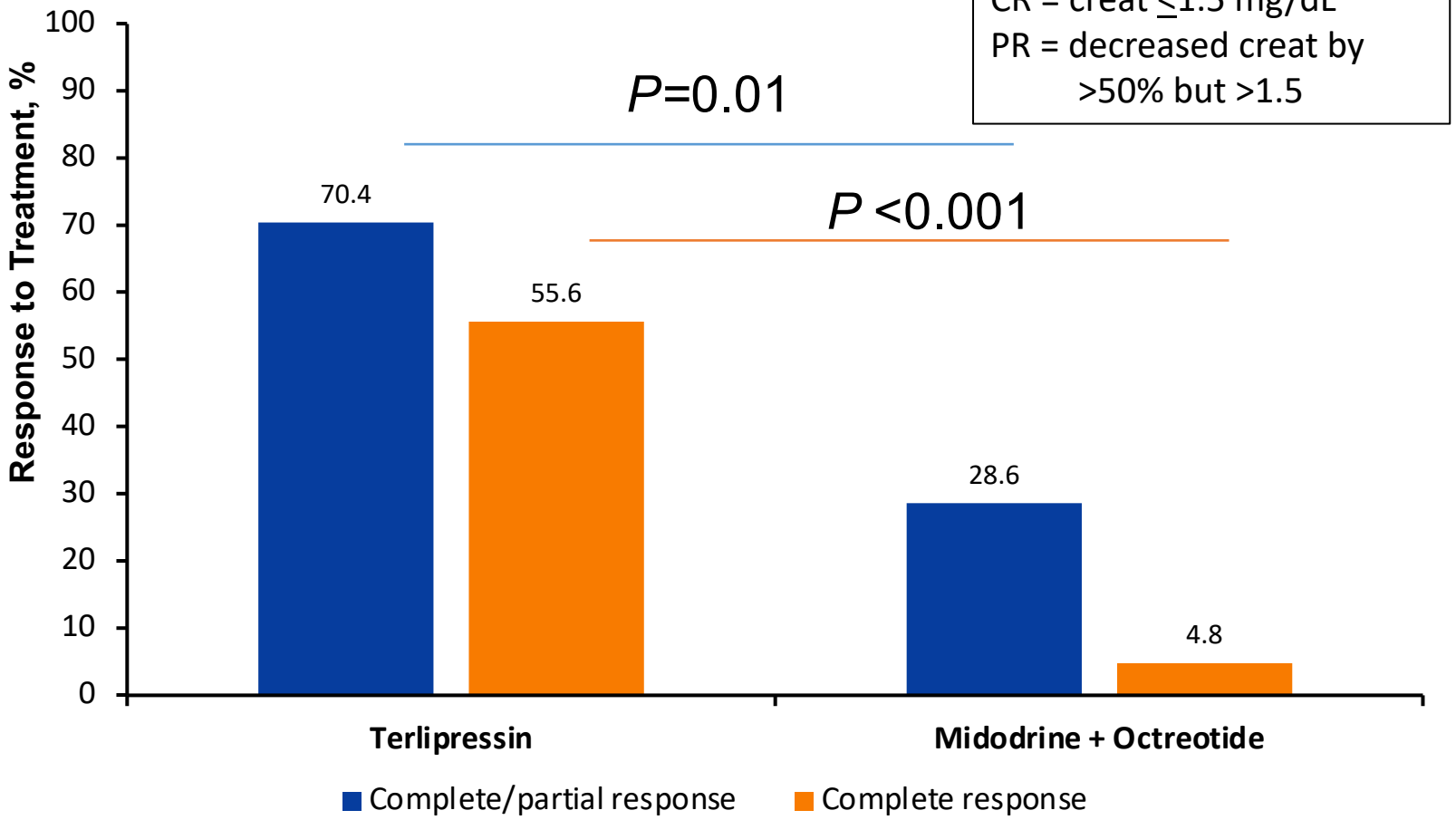
- Titrated 3mg/24h -> 12mg/24h

Midodrine (PO)/Octreotide (SQ)

- Titrated 7.5mg TID -> 12.5mg TID
- Titrated 100mcg TID -> 200mcg TID

Albumin 1g/kg D1, 20-40g/d after

CR = creat ≤1.5 mg/dL
PR = decreased creat by >50% but >1.5



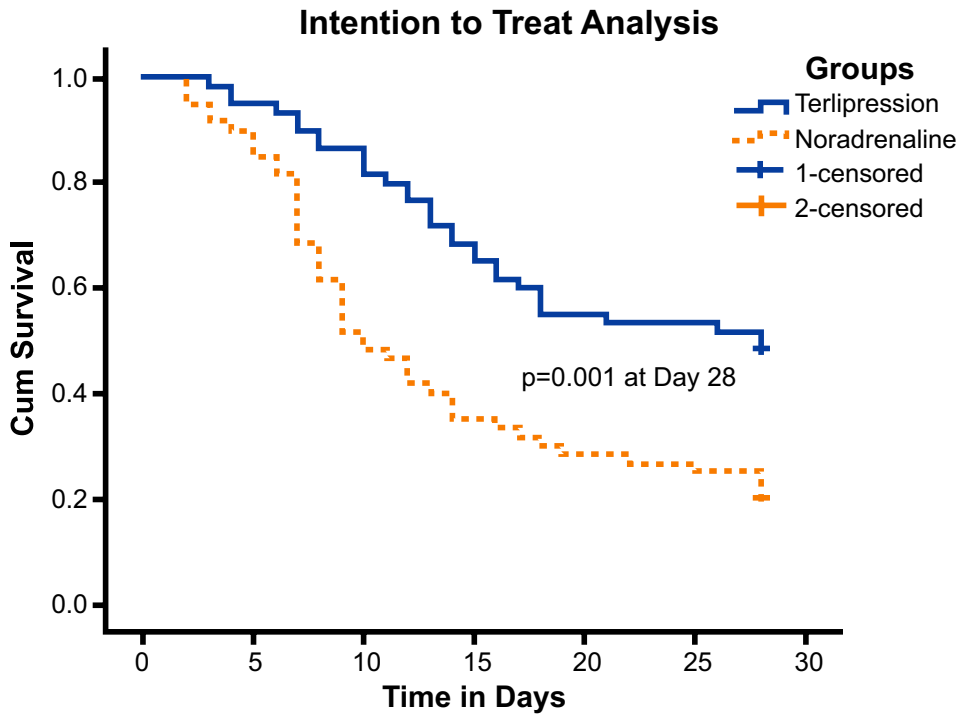
Cavallin M, et al. *Hepatology.* 2015;62:567-574.

RCT (Open Label): Terlipressin vs Norepinephrine in Patients with ACLF and HRS-AKI

Continuous IV infusion of terlipressin (2 to 12 mg/day) vs. norepinephrine (0.5 to 3 mg/hour)

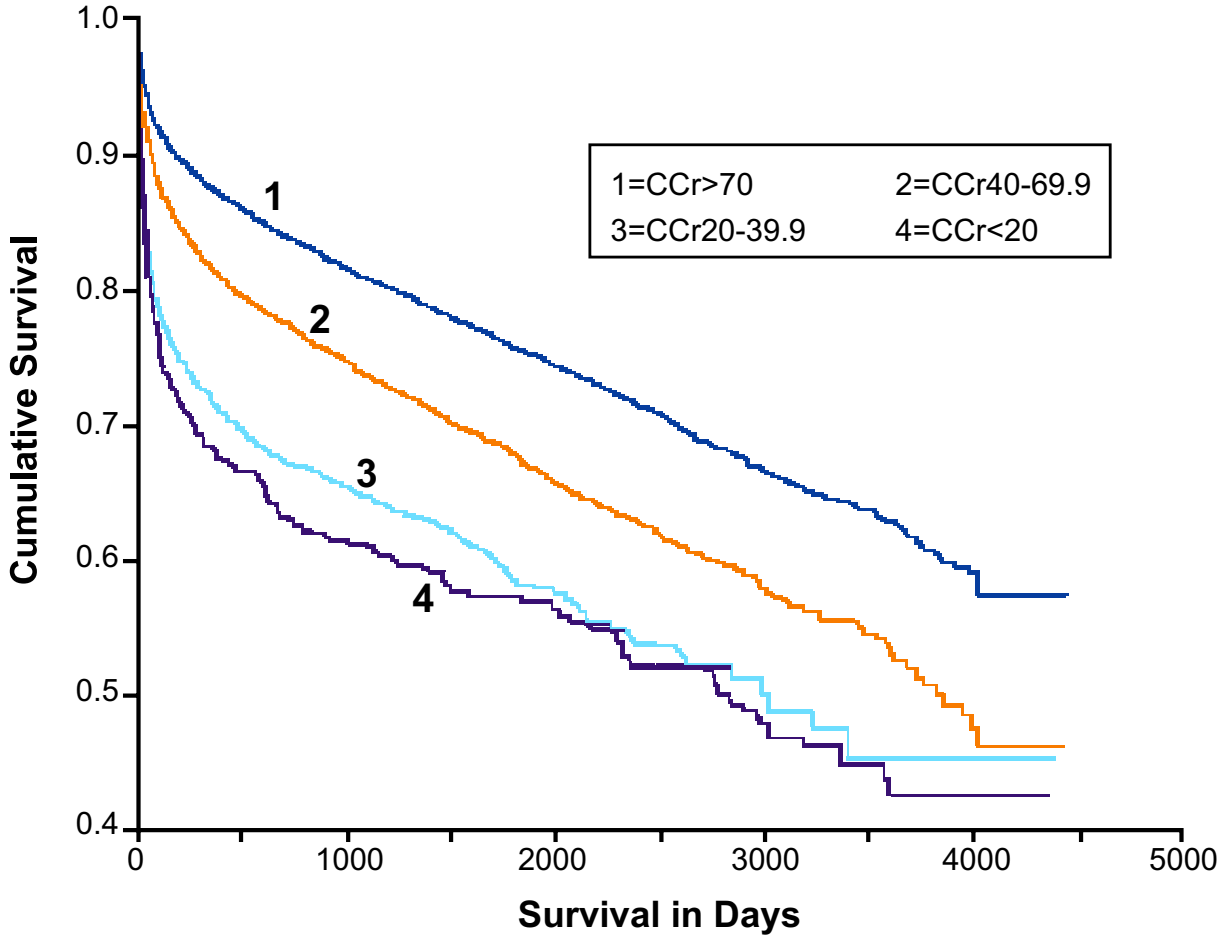
	Response Rate, n/N (%)		
	Norepinephrine	Terlipressin	P Value
Day 4	7/60 (11.7%)	16/60 (26.7%)	0.03
Day 7	12/60 (20%)	25/60 (41.7%)	0.01
Reversal of HRS-AKI (Day 14)	10/60 (16.7%)	24/60 (40%)	0.004

- Terlipressin reduced need for RRT
- Terlipressin improved survival



Arora V, et al. *Hepatology.* 2019; 0:1-11.

Renal Function Predicts Post-LT Outcomes

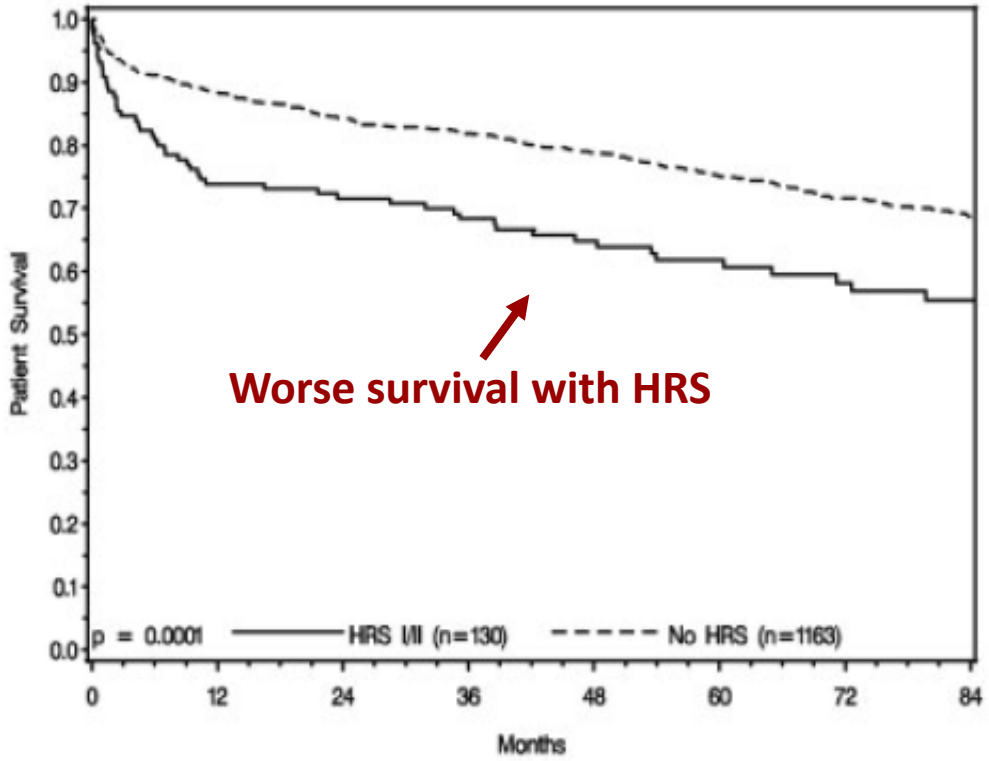


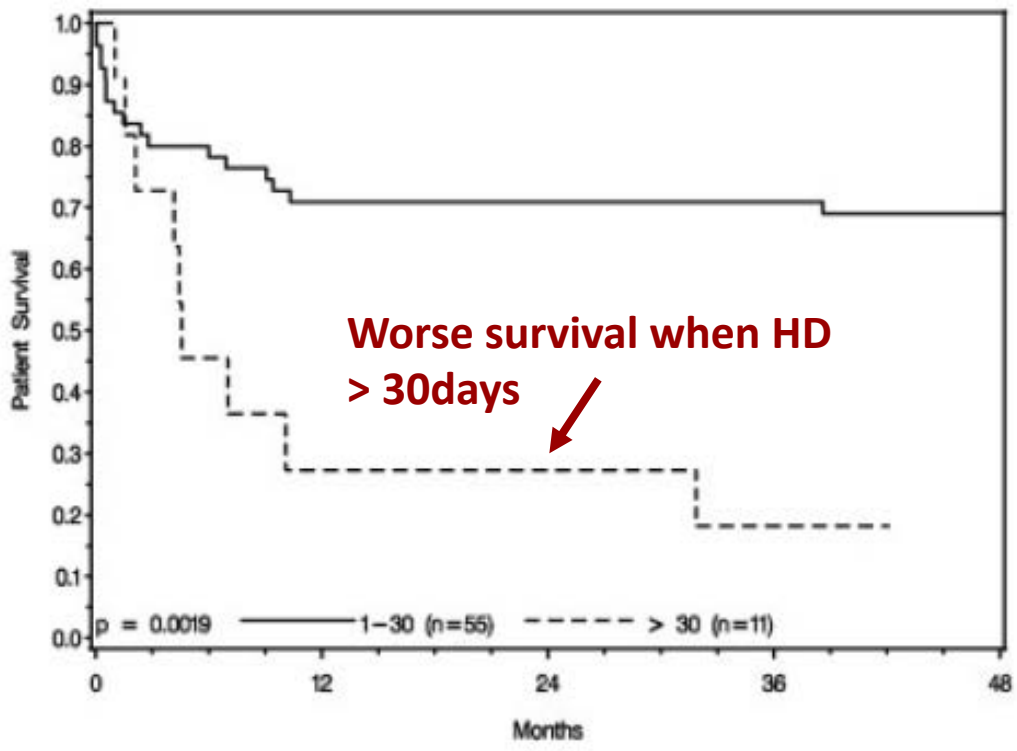
- UNOS Database
- GFR < 40 predicted worse graft and patient survival post liver transplant

Nair, et al. *Hepatology.* 2002.

HRS and prolonged dialysis-dependency worsen post liver transplant outcomes

- Retrospective study of 130 patients (122 HRS-2, only 8 HRS-1)
- Rate of ESRD post Liver Tx: 6% (HRS) vs 0.34% (no HRS)





Ruiz et al, Liver Transplantation 2007

Summary - AKI in Cirrhosis

- New diagnostic criteria to be familiar with
  - Allows for earlier diagnosis, earlier treatment
- Consider the differential diagnosis of AKI
  - Not all AKI in cirrhosis is HRS
  - More than one cause may be contributing

Stage AKI[1]	Criteria
Stage 1	Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2-fold from baseline
Stage 2	Increase in SCr >2- to 3-fold from baseline
Stage 3	Increase of SCr >3-fold from baseline or SCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy

Summary - Hepatorenal Syndrome (AKI-HRS)

- Devastating complication of cirrhosis and ACLF
- Early recognition essential to improve outcomes; new diagnostic criteria offer promise
- Currently available treatment in the US has limited efficacy
- Terlipressin may be superior to other vasoconstrictors in reversing HRS
- In suitable patients, liver transplantation is the best treatment option
- Improving renal function reduces short-term mortality and need for RRT and may improve post-liver transplant outcomes