Management of hepatorenal syndrome

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Hepatology Day

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Definitions of kidney injury in cirrhosis

Acute Kidney Injury Network

- AKI
  - A rise of serum creatinine of 50% above baseline
  - A rise of 0.3 mg/ml per day in less than 48 hours
- CKD
  - eGFR less than 60 ml/min for more than 3 months
- Acute on CKD
  - A rise of serum creatinine of 50% above baseline
  - A rise of 0.3 mg/ml per day in less than 48 hours in a person with CKD

Causes of AKI in cirrhosis

- Prerenal azotemia: the most common (45%)
- Intrarenal (structural kidney disease):
  - ATN
  - Glomerulopathies
- Obstructive uropathy
- HRS (23%)
  - ***Møller et al, Liver International 2014 Sep;34(8):1153-63***

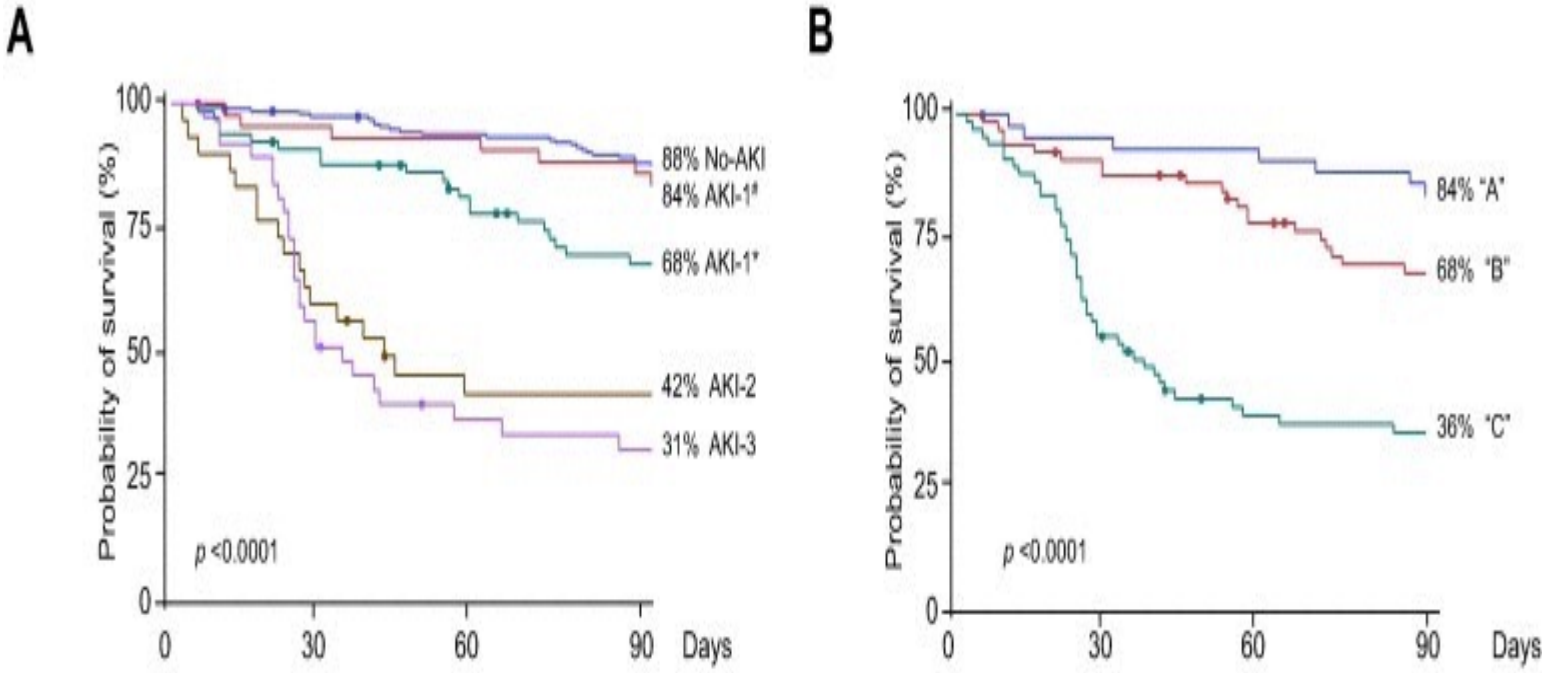
HRS: definition

- Progressive, functional, reversible, oliguric renal failure in cirrhosis or acute hepatic failure
- Absence of other triggers of renal disease
- Lack of response to volume expansion *and* withdrawal of diuretics over 2 days

Stages of AKI

	Change in serum level of creatinine	Urine output
Stage 1	Increase of ≥ 26.4 µmol/L or 150%–200% from baseline	< 0.5 mL/kg hourly for > 6 h
Stage 2	Increase > 200%–300% from baseline	< 0.5 mL/kg hourly for > 12 h
Stage 3	Increase > 300% from baseline or ≥ 354 µmol/L with an acute increase of ≥ 44 µmol/L	< 0.3 mL/kg hourly for > 24 h or anuria for > 12 h

Survival is directly related to stage of AKI

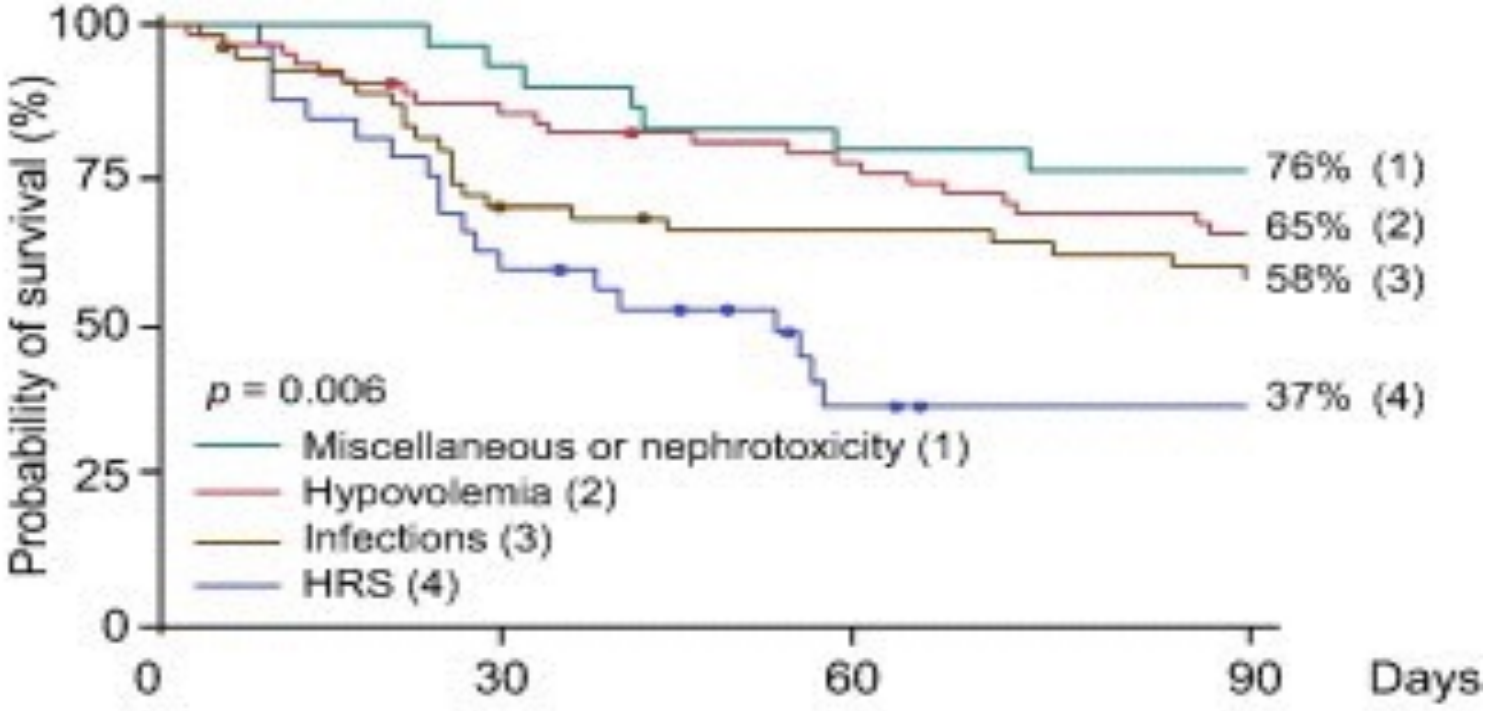


No AKI (n = 198)	191	182	172
AKI-1*(n = 44)	41	39	37
AKI-1*(n = 66)	57	48	40
AKI-2 (n = 30)	18	11	11
AKI-3 (n = 37)	18	12	10

A (n = 44)	41	39	37
B (n = 66)	57	48	40
C (n = 67)	36	23	21

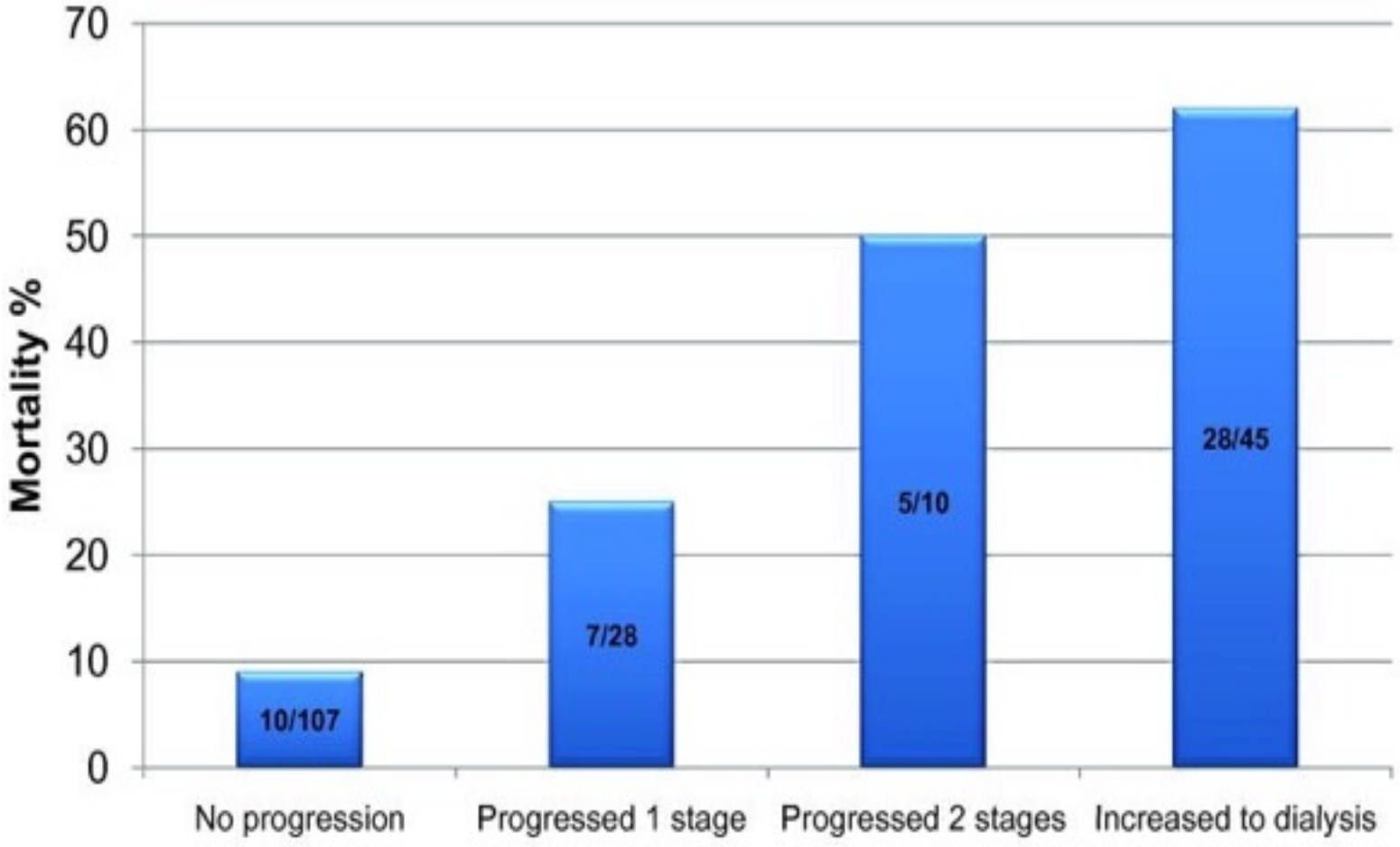
Survival is directly related to type of AKI

Fagundes C et al, J Hepatol, 2013

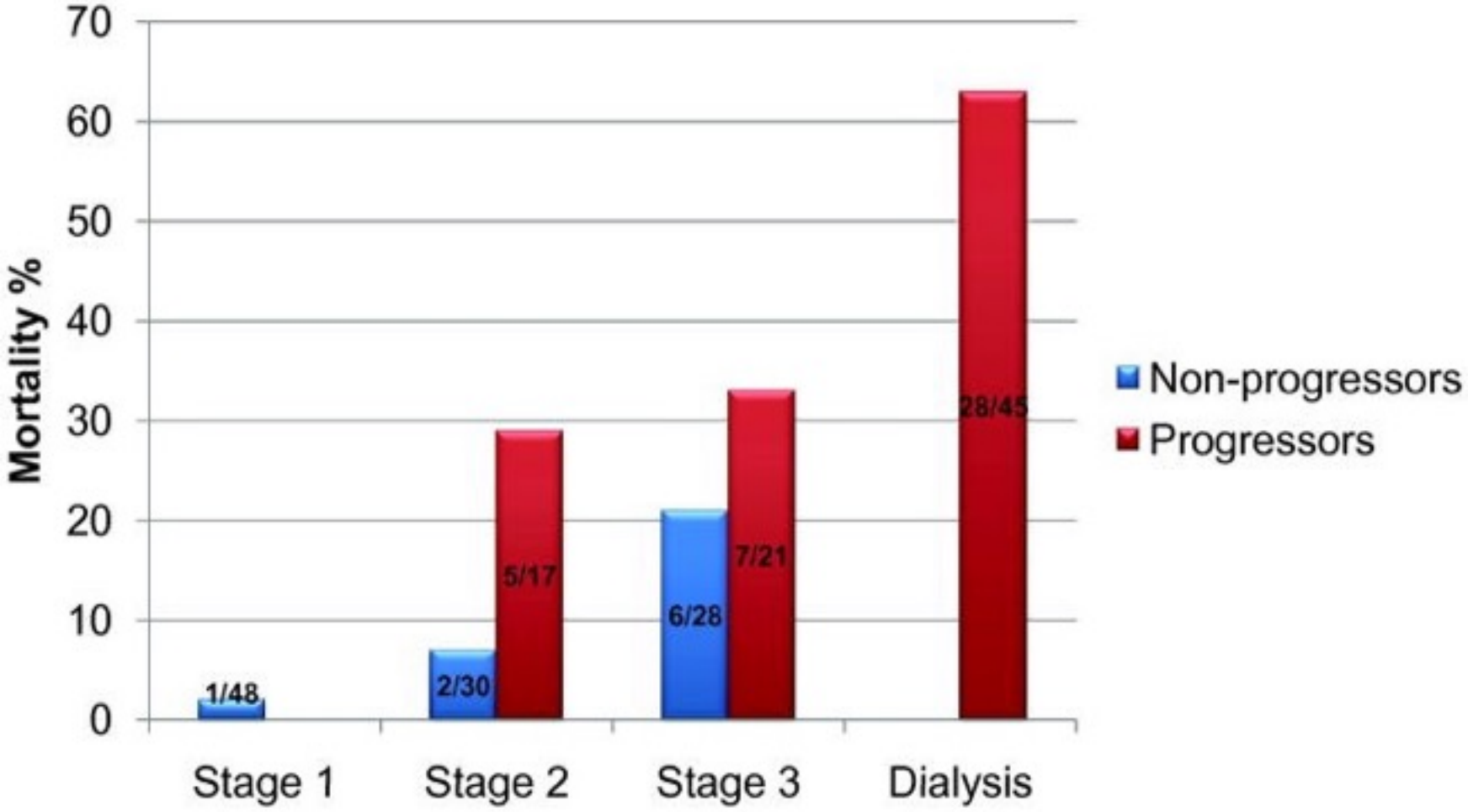


1 (n = 29)	27	23	22
2 (n = 62)	52	45	39
3 (n = 54)	36	33	30
4 (n = 32)	19	9	7

A prospective study of 192 patients with cirrhosis and AKI



Progression of AKI is an independent predictor of mortality



Criteria for diagnosis of HRS EASL guidelines 2010

- Cirrhosis with ascites
- Serum creatinine >133 µmol/l (1.5 mg/dl)
- No improvement of serum creatinine (decrease to a level of ≤133 µmol/l) after at least two days of diuretic withdrawal and volume expansion with albumin
- The recommended dose of albumin is 1 g/kg body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/ day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography

TYPES OF HRS

- **HRS TYPE 1**
  - Cr>2.5 mg/dl or GFR<20 ml/min within 2 weeks
  - Acute decrease in GFR
  - Precipitating event
  - Grave prognosis
  - Associated with multiorgan failure
- **HRS TYPE 2**
  - Cr>1.5 mg/dl or GFR<40 ml/min
  - Chronic decrease in GFR
  - Spontanous
  - Associated with refractory ascites
  - Better prognosis

AKI and HRS are common

- AKI occurs in 20% of hospitalized patients with cirrhosis
- HRS occurs in 39% of cirrhotics 5 years after the appearance of ascites

Precipitating factors of AKI and HRS are the same

- Large volume paracentesis
- Increased diuretic use
- SBP and other infections
- IV contrast
- GIB

Hepatorenal syndrome is invariably associated with ascites *and* extreme circulatory dysfunction.

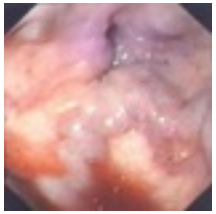
Pathophysiology of ascites and hepatorenal syndrome

Progression of liver failure and portal hypertension

Increase in splanchnic arterial vasodilation

Decrease in cardiac output

Reduction in effective arterial blood volume



Moderate

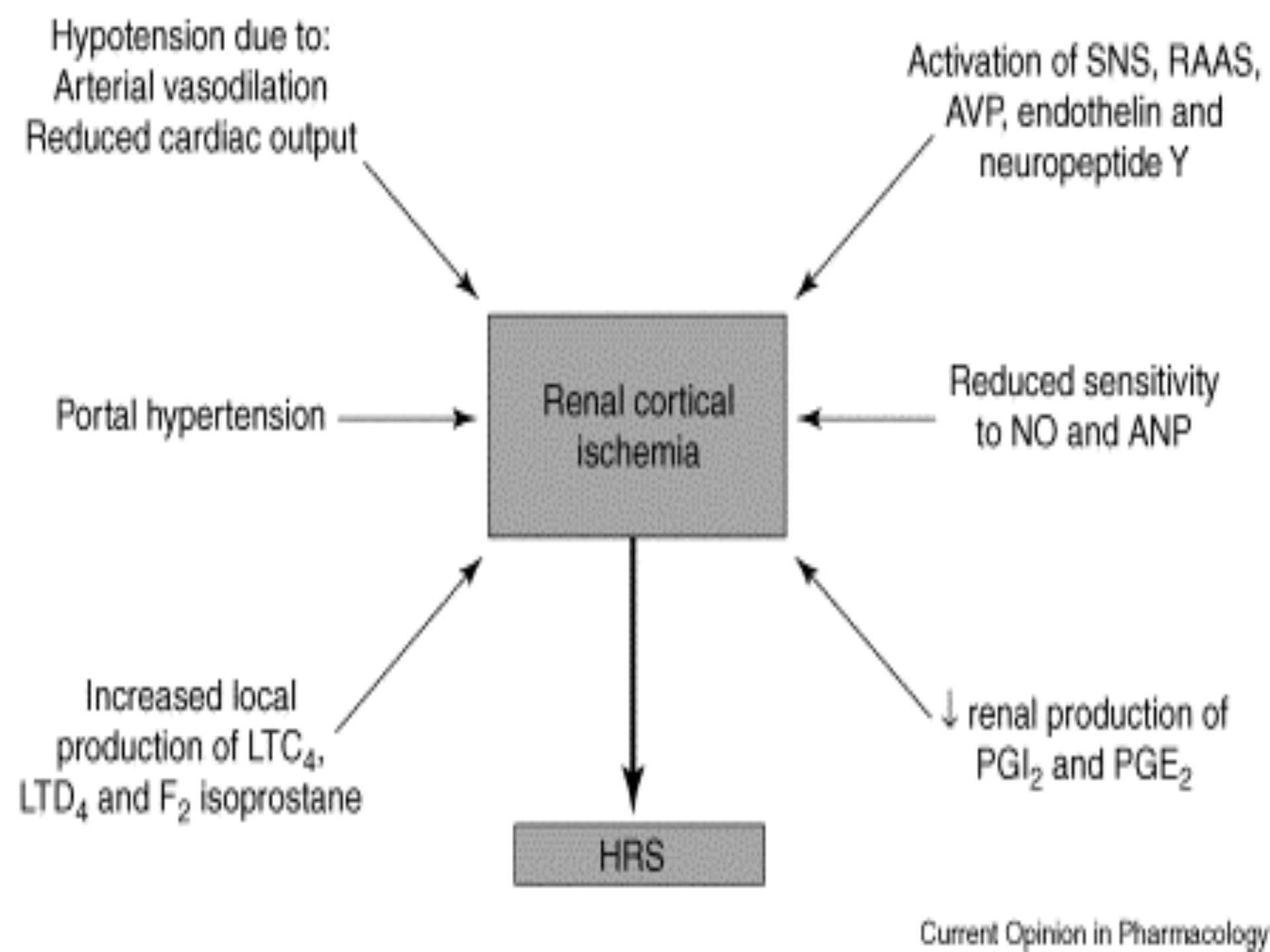
Severe

Extreme

Sodium retention

Water retention Hyponatermia

Type-2 Hepatorenal syndrome



Current Opinion in Pharmacology

Factors that reduce renal blood flow precipitate or aggravate HRS

- Cardiac chronotropic and ionotropic incompetence (cirrhotic cardiomyopathy)
  - Should B-blockers be discontinued in advanced cirrhosis?
- Relative adrenal insufficiency with impaired ACTH and CRH release
- Infections, particularly SBP, which aggravate splanchnic vasodilatation

Typical Urinary Findings in Renal Failure in Patients with Ascites

Parameter	Osmolarity mosm/kg	Urine (Na) mmol/L	Sediment	Protein mg/day
Prerenal				
Hypovolemia	>500	<20	Normal	<500
Hepatorenal syndrome	>500	<10	Normal	<500
Renal	<350	>40	Granular Casts	500-1500
Acute tubular necrosis	<350	>40	WBC eosinophils	500-1500
Interstitial nephritis	Variable	Variable	Red cell casts	Often >1500
Glomerular disease				

Treatment of AKI in cirrhosis

- Stop ACE and NSAIDs
- Stop diuretics
- Do large volume paracentesis
  - Reduces pressure on the IVC and improves cardiac output
  - Reduces pressure on the renal veins

Treatment of HRS

- Fluid challenge over 2 days
  - Albumin at 1 g/Kg/day, with a maximum of 100 g/day
- Correction and treatment of triggering factors
- Vasoconstrictors
  - Terlipressin
  - Midodrine
  - norepinephrine

Terlipressin for HRS
EASL practice guidelines, 2010

- Start at 0.5-1mg every 4-6 hours IV
- Increase to 2 mg every 4-6 hours IV if no improvement in 3 days
- Albumin at 1g/Kg on day 1 followed by 40 g/ day
- Reversal of HRS occurs in 40-50% of patients
- Improved survival
  - RR 0.76 [95% confidence interval (CI) 0.61–0.95]
  - Survival improves in patients whose HRS is reversed
- Main side effect is ischemia

Midodrine

- Midodrine (up to 12.5 mo tid) plus albumin (10-20 g/day) plus octreotide 100 microgram tid or 25 microgram/hour
  - Reversal of HRS in majority of patients in three small studies

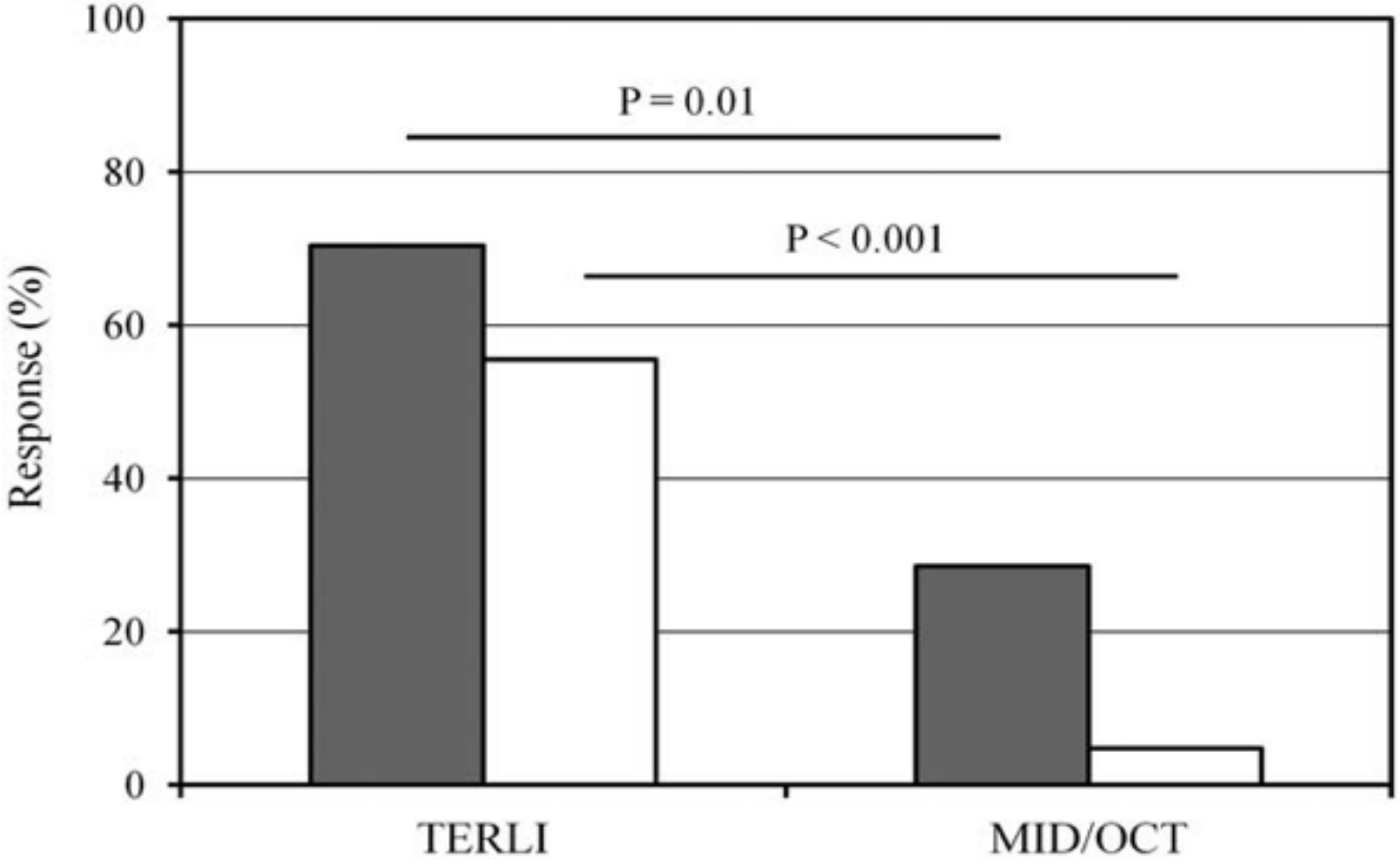
Norepinephrine

- 0.5 mg/hour IV and increased to achieve a 10 mm Hg increase in MAP
  - In a study on NE plus albumin plus furosemide, reversal of HRS in 83% of patients
  - Ischemic complications in 17%

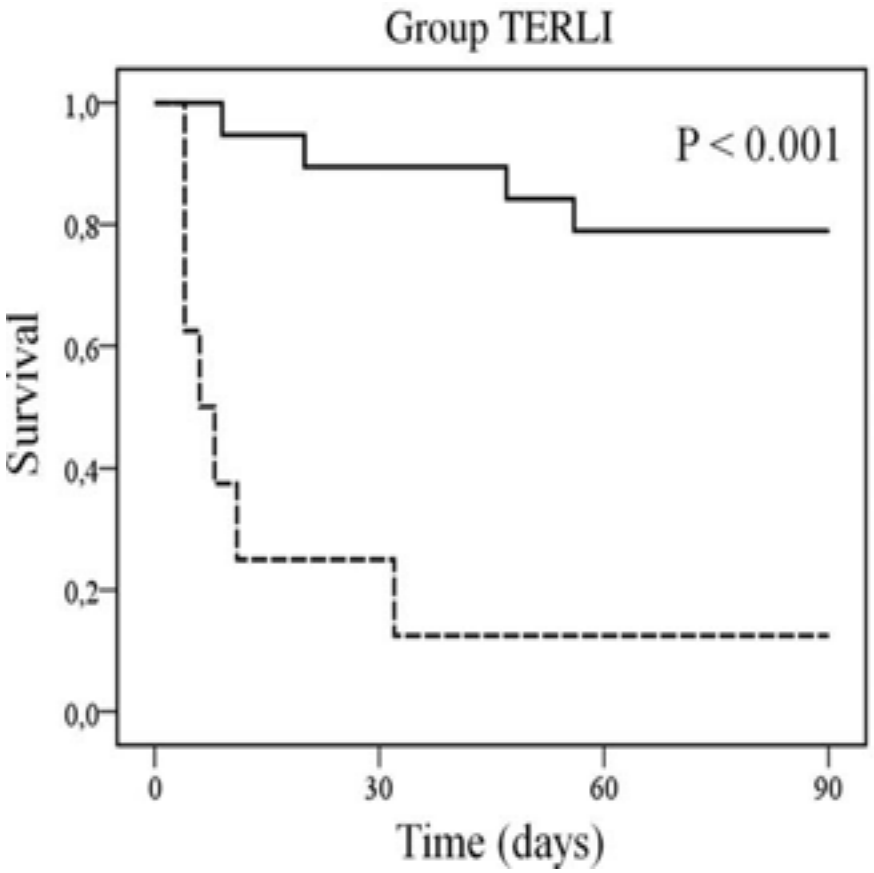
Terlipressin Plus Albumin Versus Midodrine and Octreotide Plus Albumin in the Treatment of Hepatorenal Syndrome: A Randomized Trial

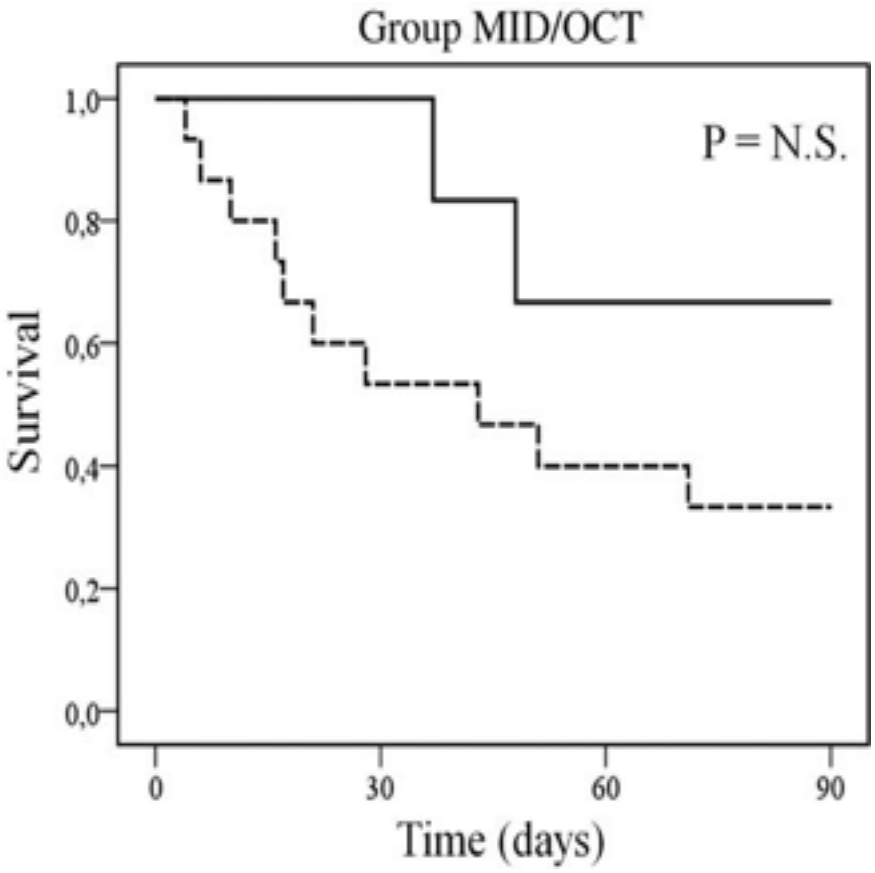
Cavallin M et al, Hepatology. 2015 Jan 16. doi: 10.1002/hep.27709. [Epub ahead of print]

Terlipressin is superior in terms of partial and full response



Only terlipressin use was associated with improved survival

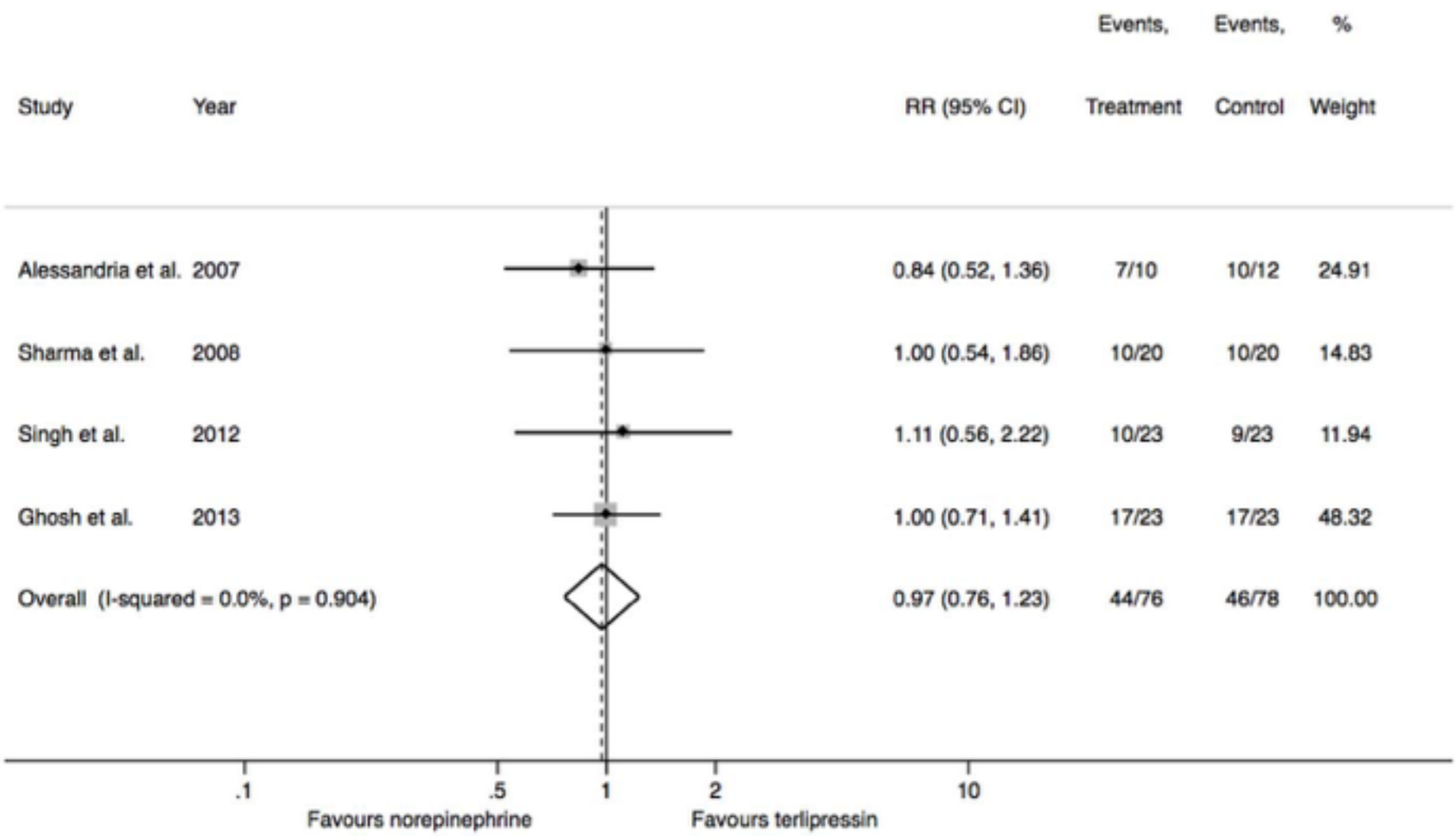




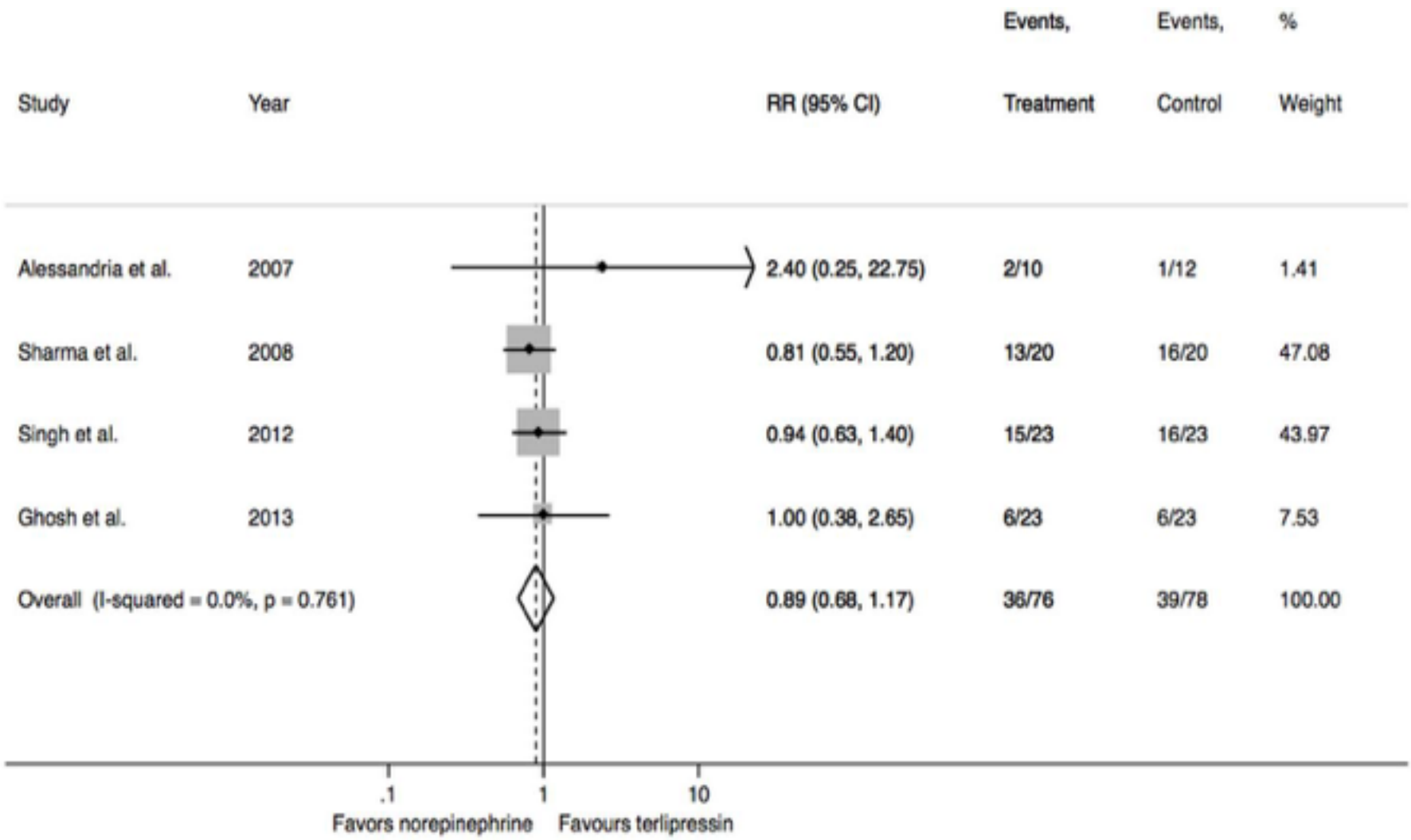
Terlipressin versus Norepinephrine in the Treatment of Hepatorenal Syndrome: A Systematic Review and Meta-Analysis

Antonio Paulo Nassar Junior et al,
PLoS One. 2014 Sep 9;9(9):e107466

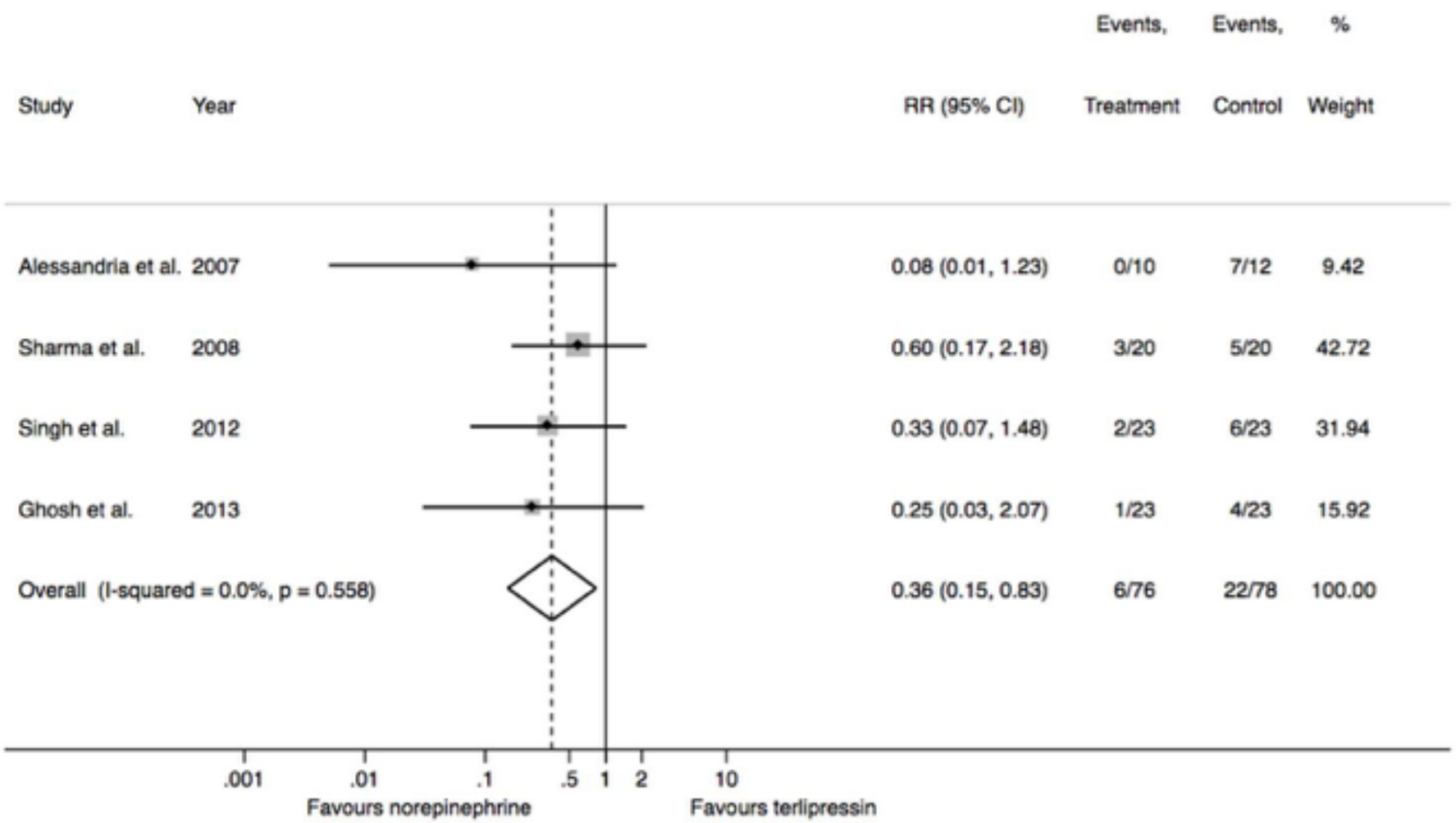
Reversal of HRS was similar in the two groups



Mortality rates at 30 days were similar



Adverse events were lower with NE



HRS management summary

- Avoid AKI of any type in cirrhosis as it might progress to HRS
- Recognize and treat infections promptly
- Administer albumin when doing LVP
- Discontinue ACE, NSAIDs and diuretics
- Consider discontinuing B blockers
- Challenge your patient with AKI with albumin
- Administer a vasoconstrictor


Thank
you