

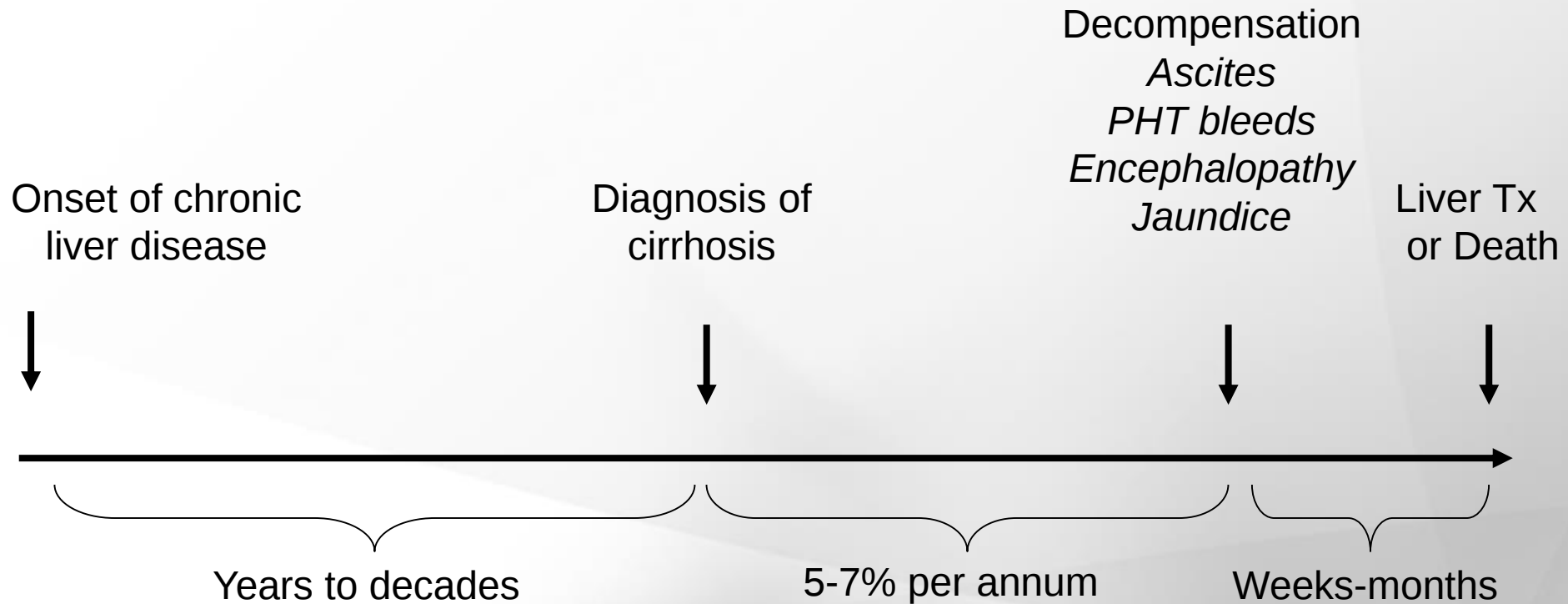
Updates on Ascites and Hepatorenal Syndrome

Florence Wong
University of Toronto

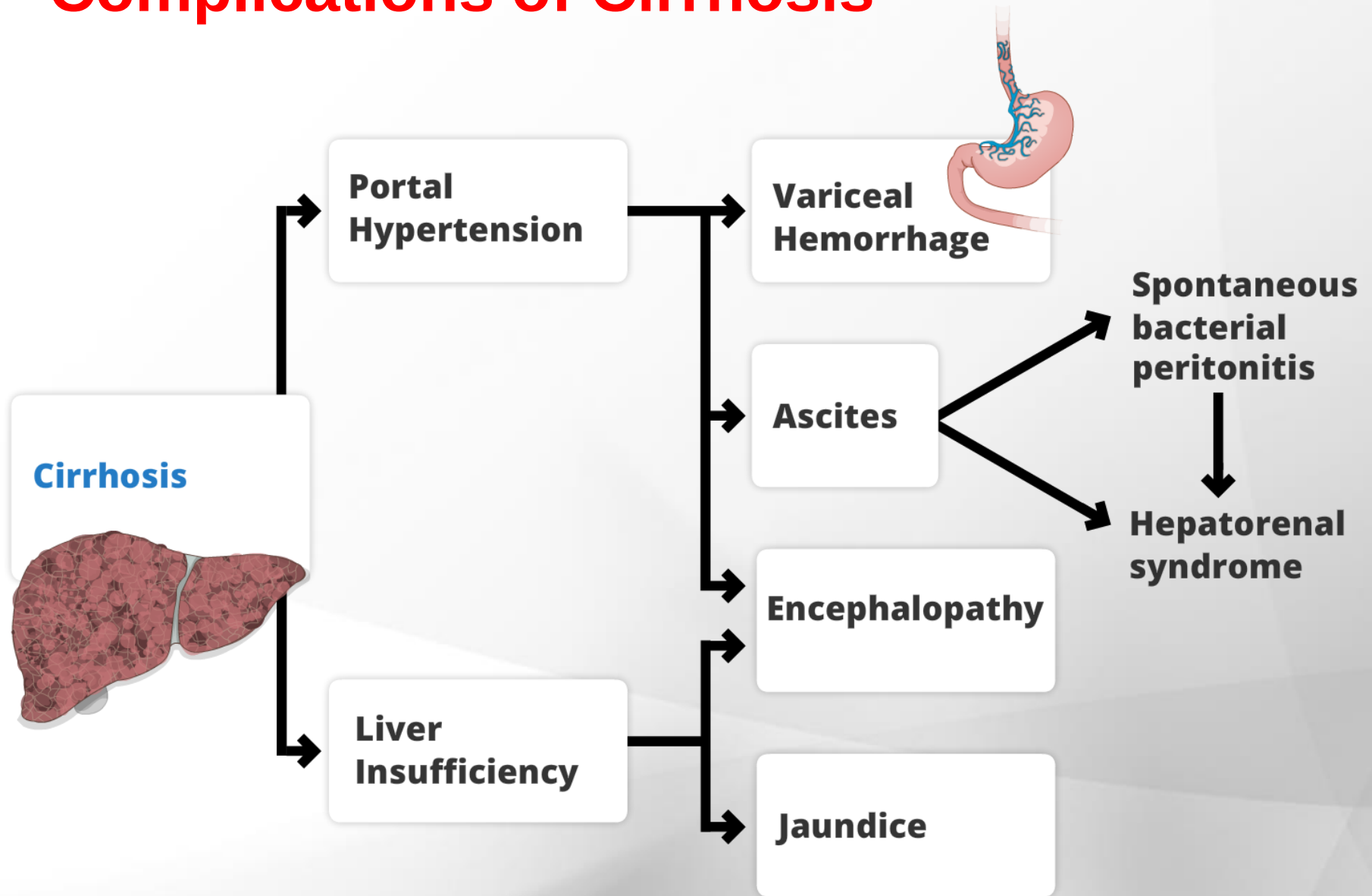
May 26, 2019



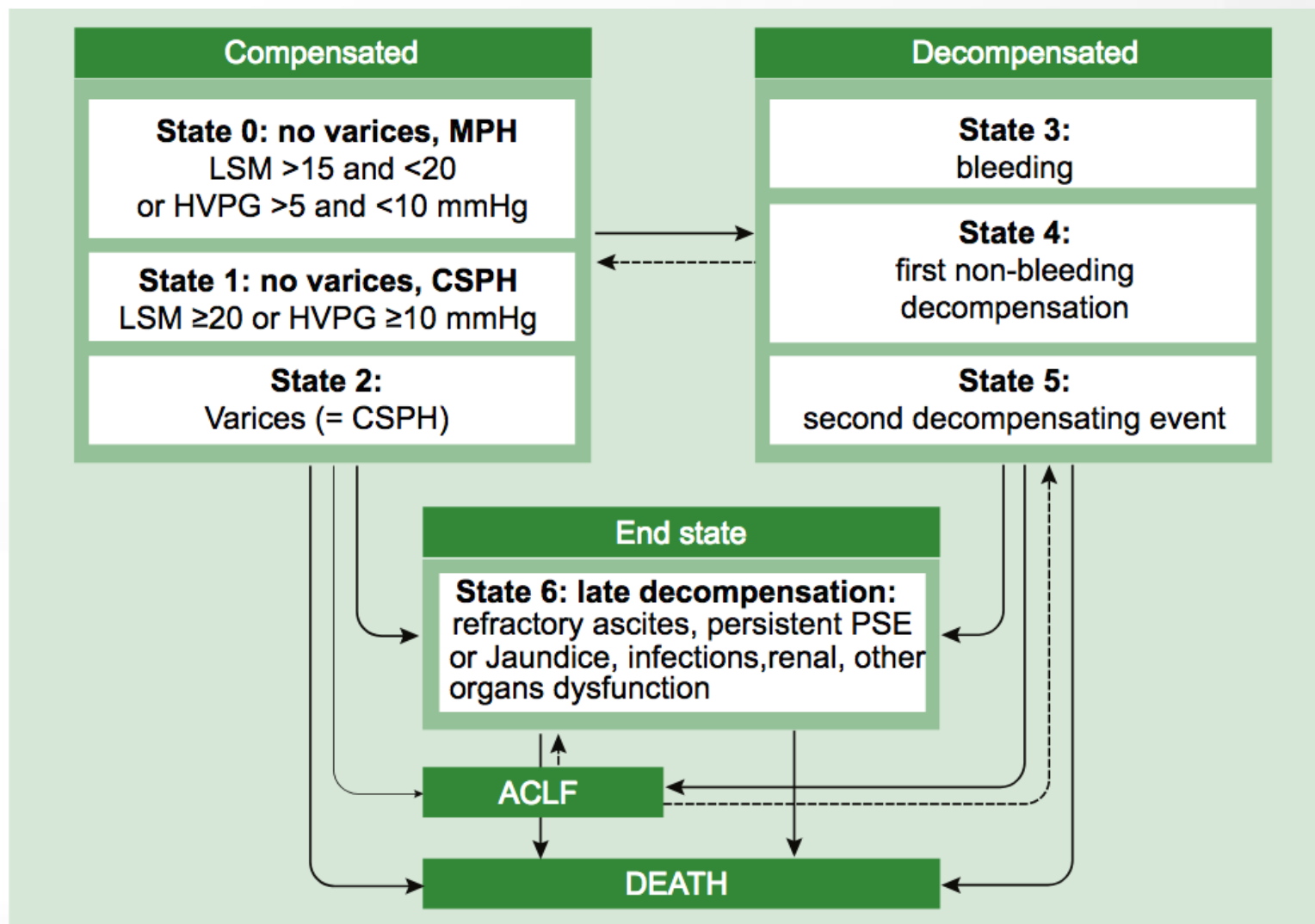
Natural History of Liver Disease



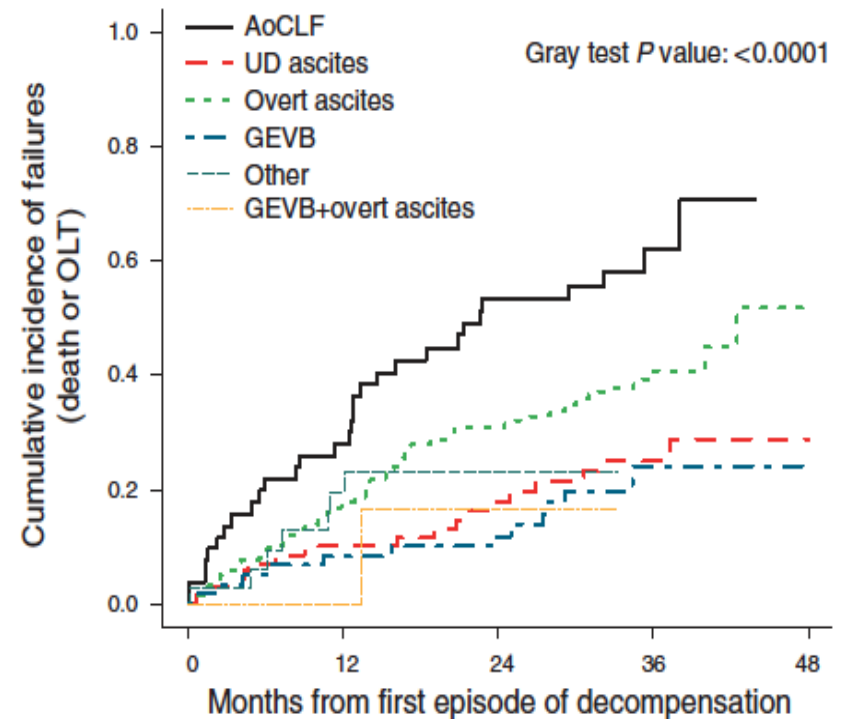
Complications of Cirrhosis



Stages of Cirrhosis



Poor Survival After Decompensation



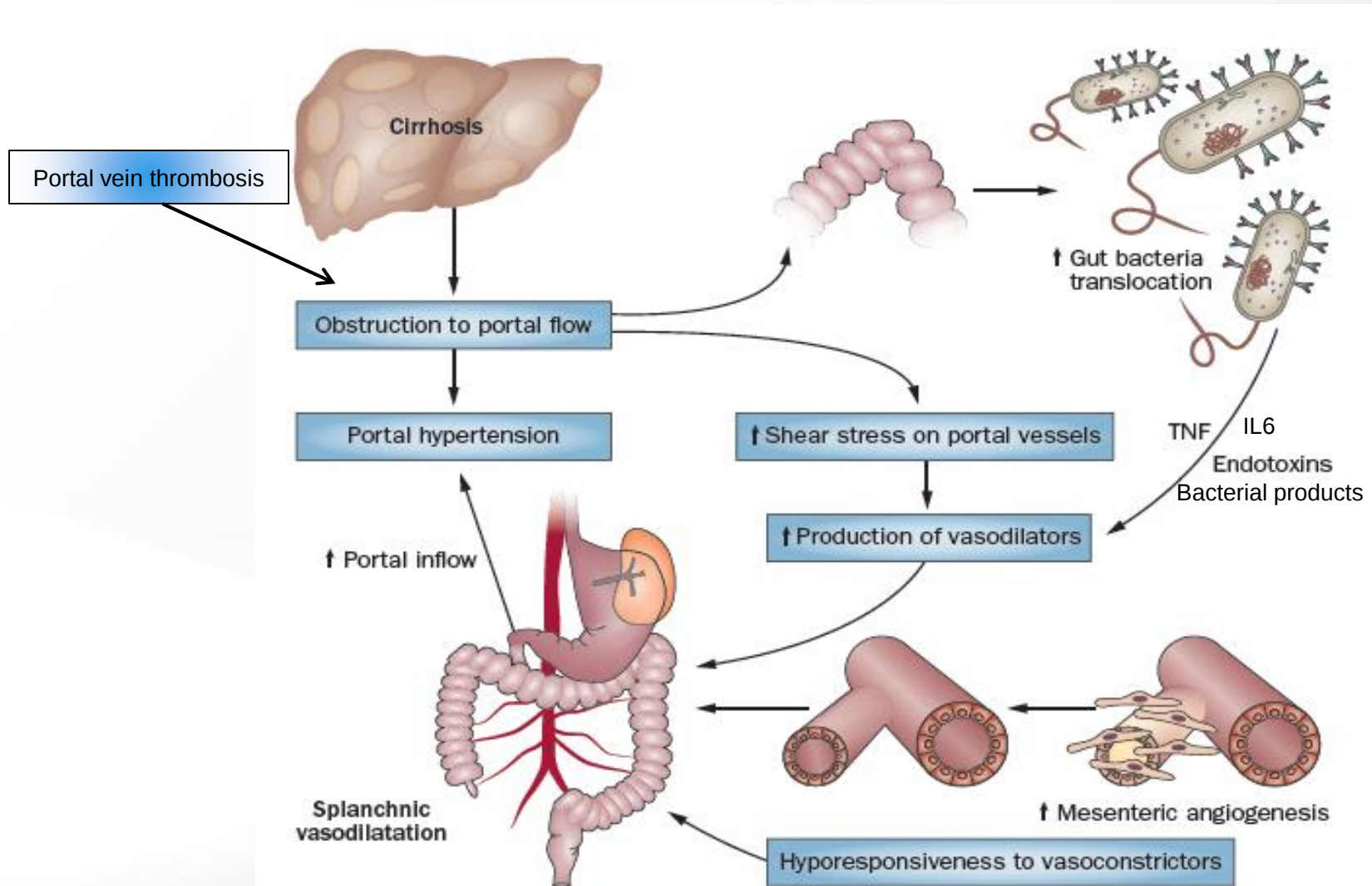
AoCLF	53	33	20	7	
UD ascites	71	60	46	21	2
Overt ascites	230	161	109	25	1
GEVB	60	50	43	11	2
Other*	33	21	13		
GEVB+Overt asc.	8	6	2		



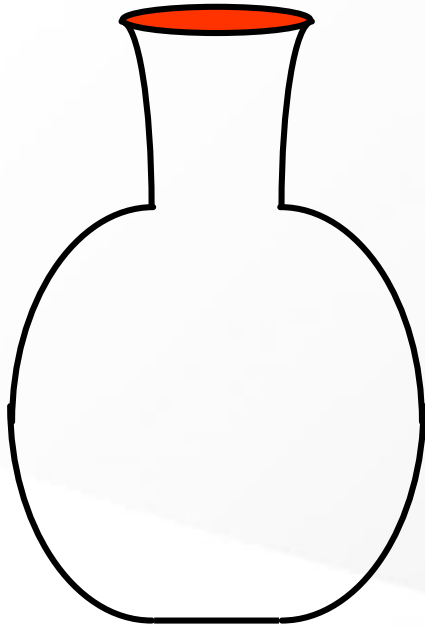
18th Century Patient with Ascites



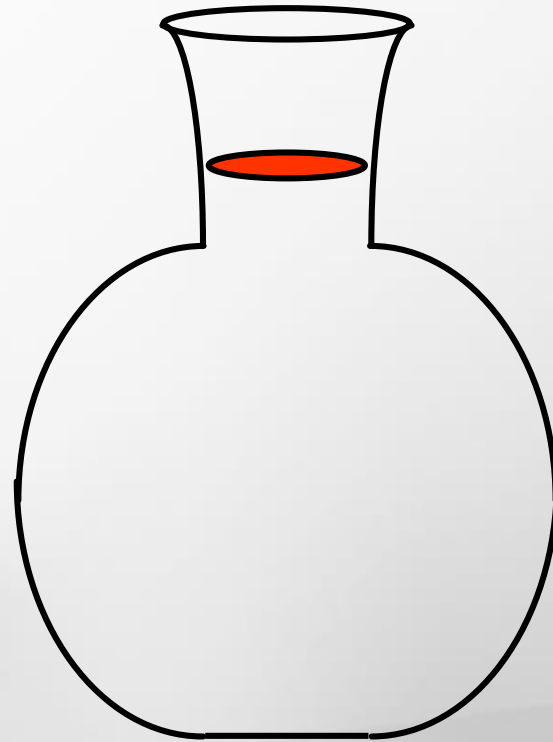
Increased Portal Flow & Splanchnic Vasodilatation



Vasodilatation & Reduction in EABV



Normal



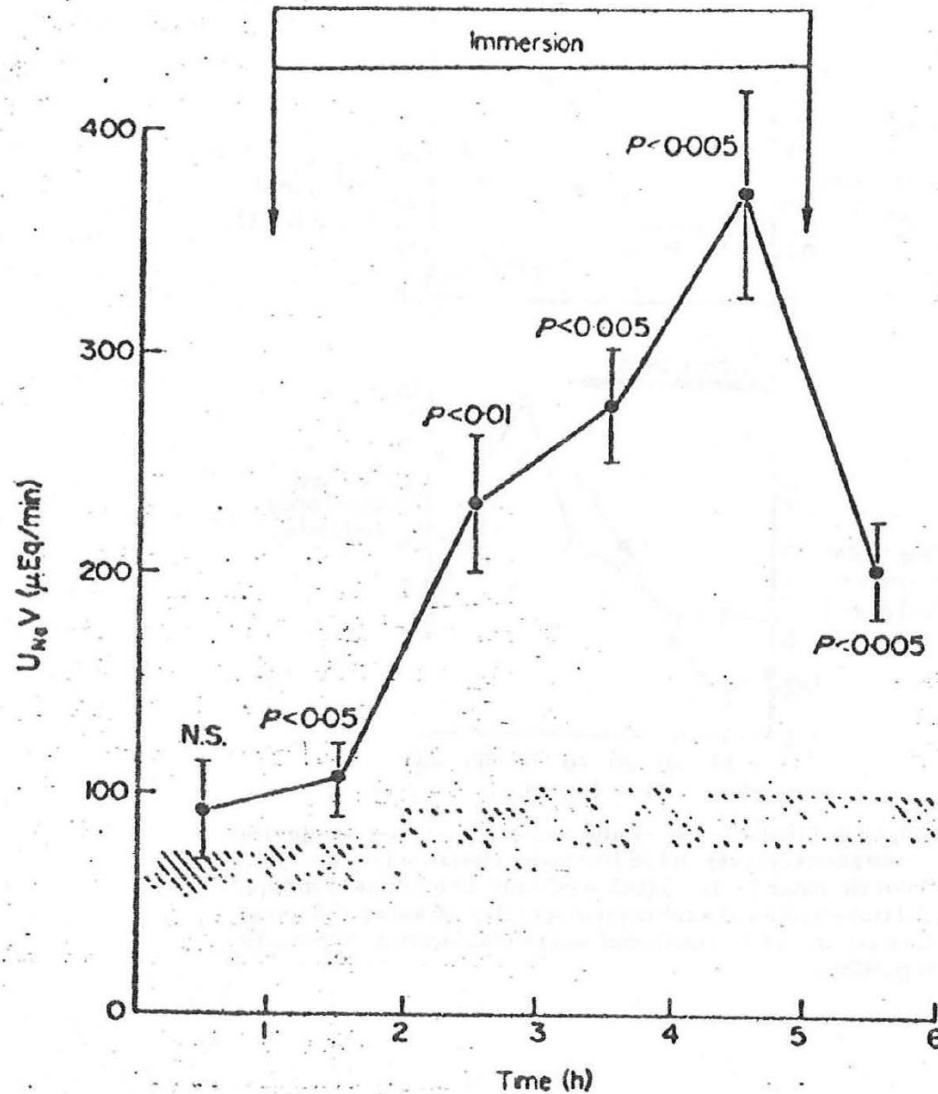
Cirrhosis with ascites

Head-Out-Water Immersion

- Exerts hydrostatic pressure on vascular columns of the body
- Forces the blood from the lower extremities into the intrathoracic vascular compartment
- Lowers the levels of Na retaining neurohormonal systems
- Pressure exerted increases by 22.4mmHg for every foot depth of water
- Net results is a natriuresis & diuresis



Head-Out-Water Immersion

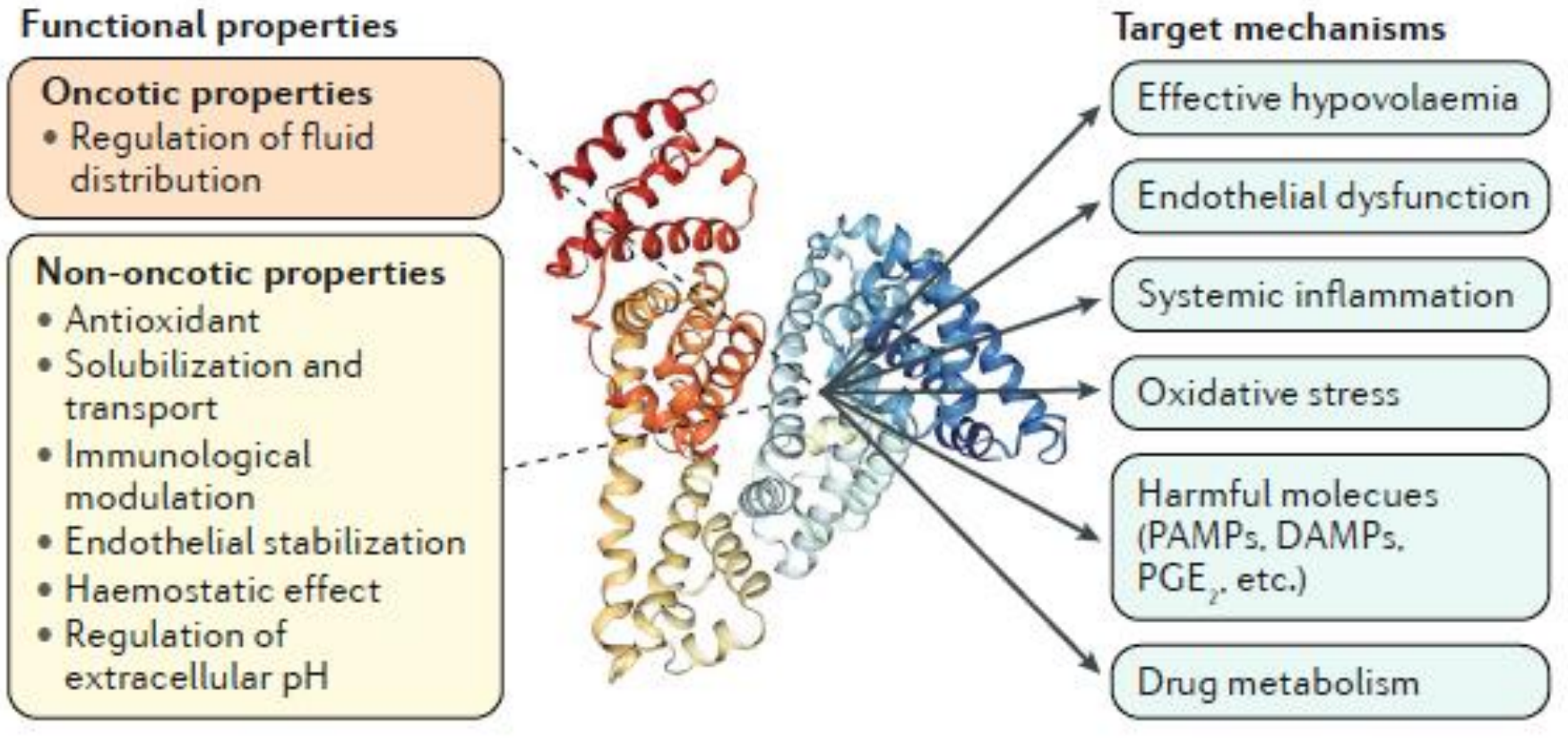


(Epstein M, Clin Sci 1972)

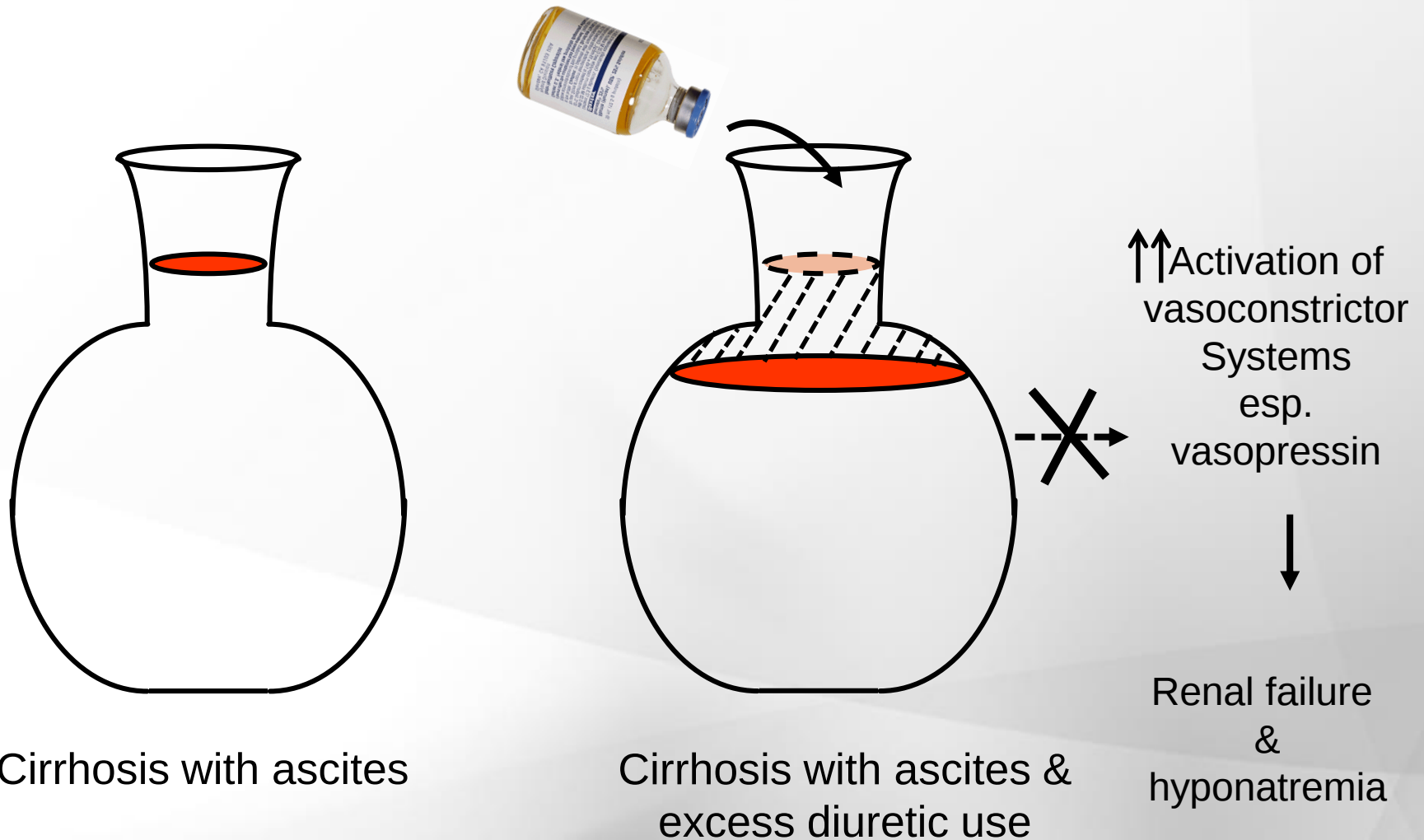
The Comforts of Bath, England



The Use of Albumin

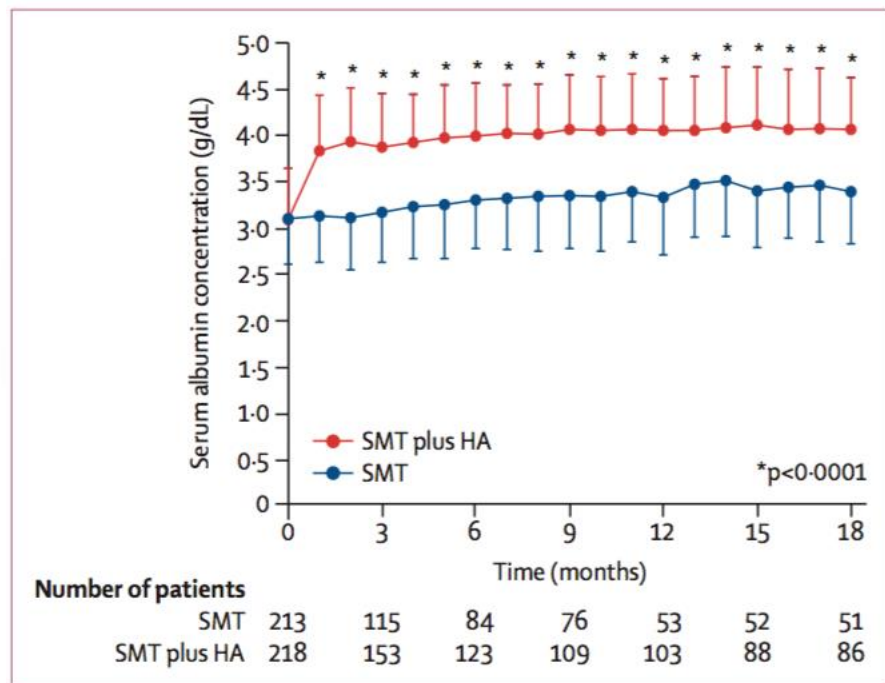


Albumin Can Improve The Intravascular Volume

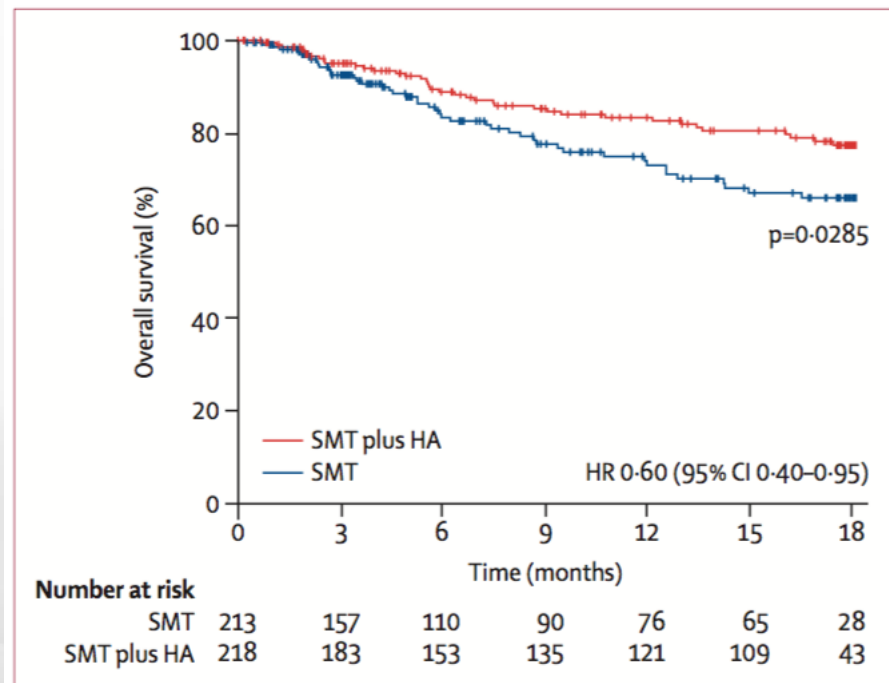


The Italian ANSWER Study

Serum Albumin Levels



Overall Survival

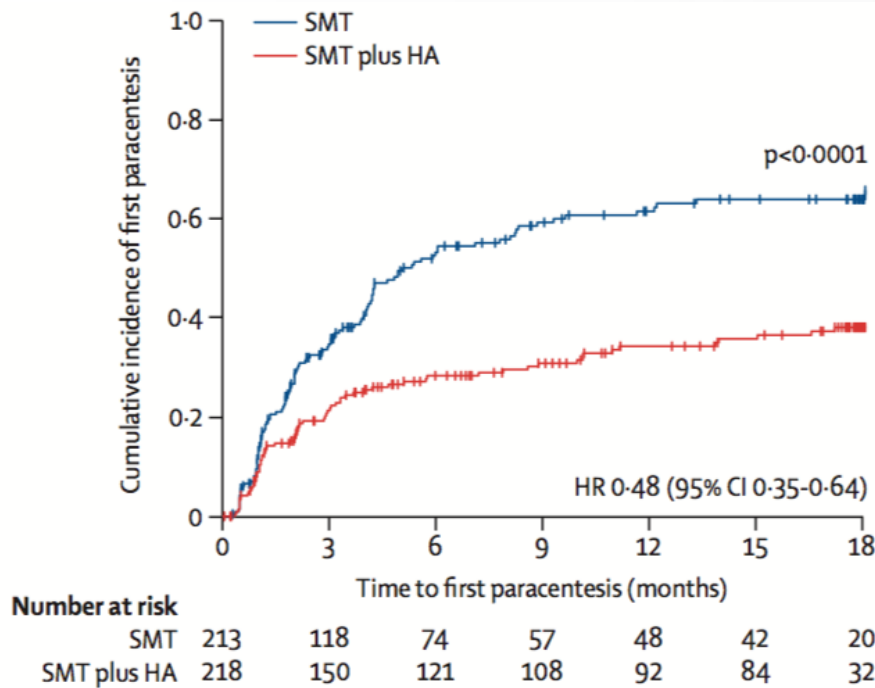


Albumin dose: 40gm 2X weekly for 2 weeks, then 40gm weekly

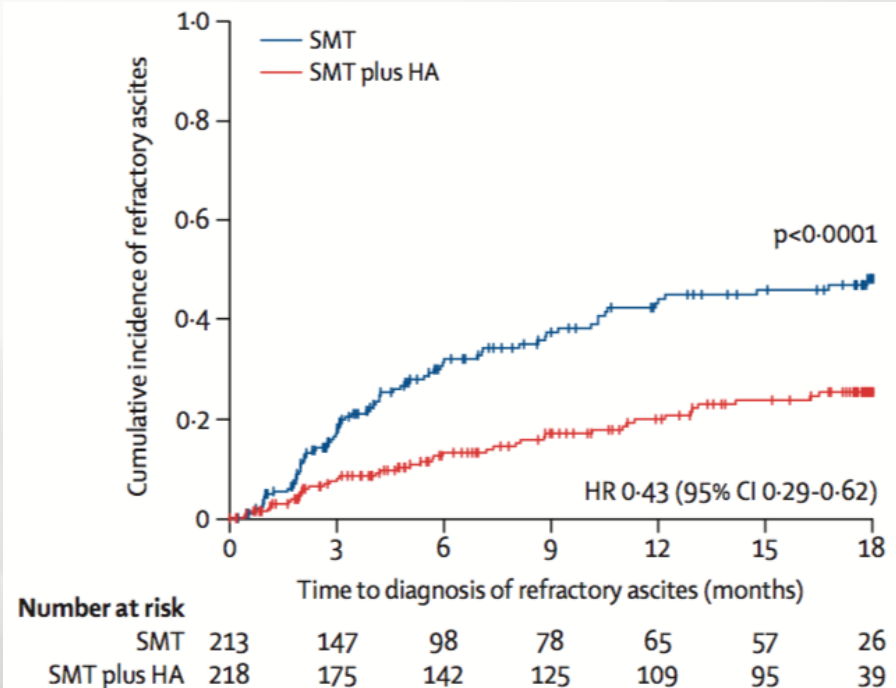


The Italian ANSWER Study

Time to First Paracentesis



Incidence of Refractory Ascites

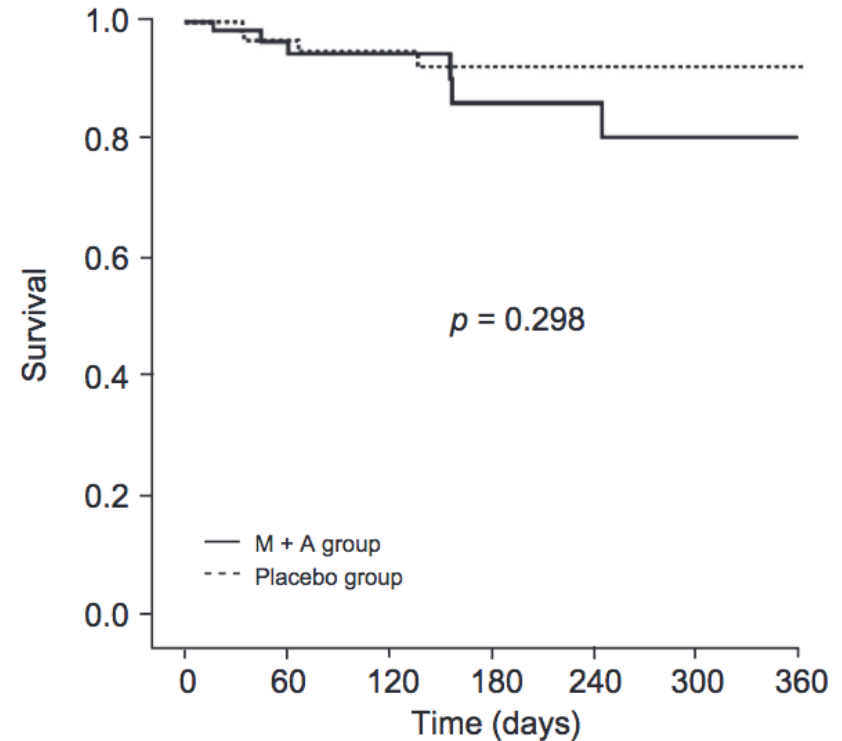
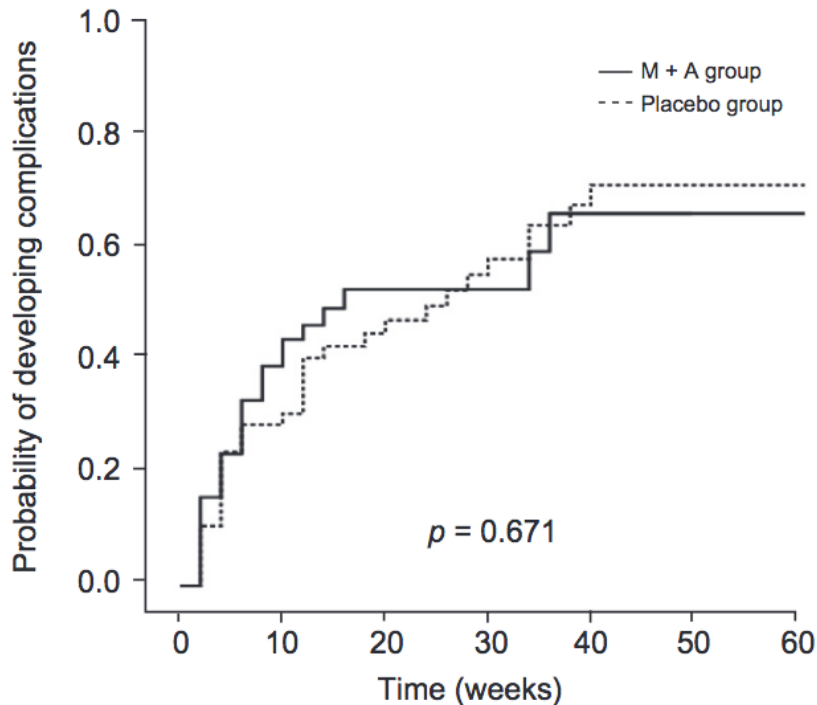


Albumin dose: 40gm 2X weekly for 2 weeks, then 40gm weekly



(Caraceni P, et al. Lancet 2018)

The Spanish MACHT Study



N M&A	87	49	38	19	14	10	9
N Placebo	86	55	46	35	28	22	21

Median dose of Midodrine 23mg/day, albumin dose: 40gm every 2 weeks



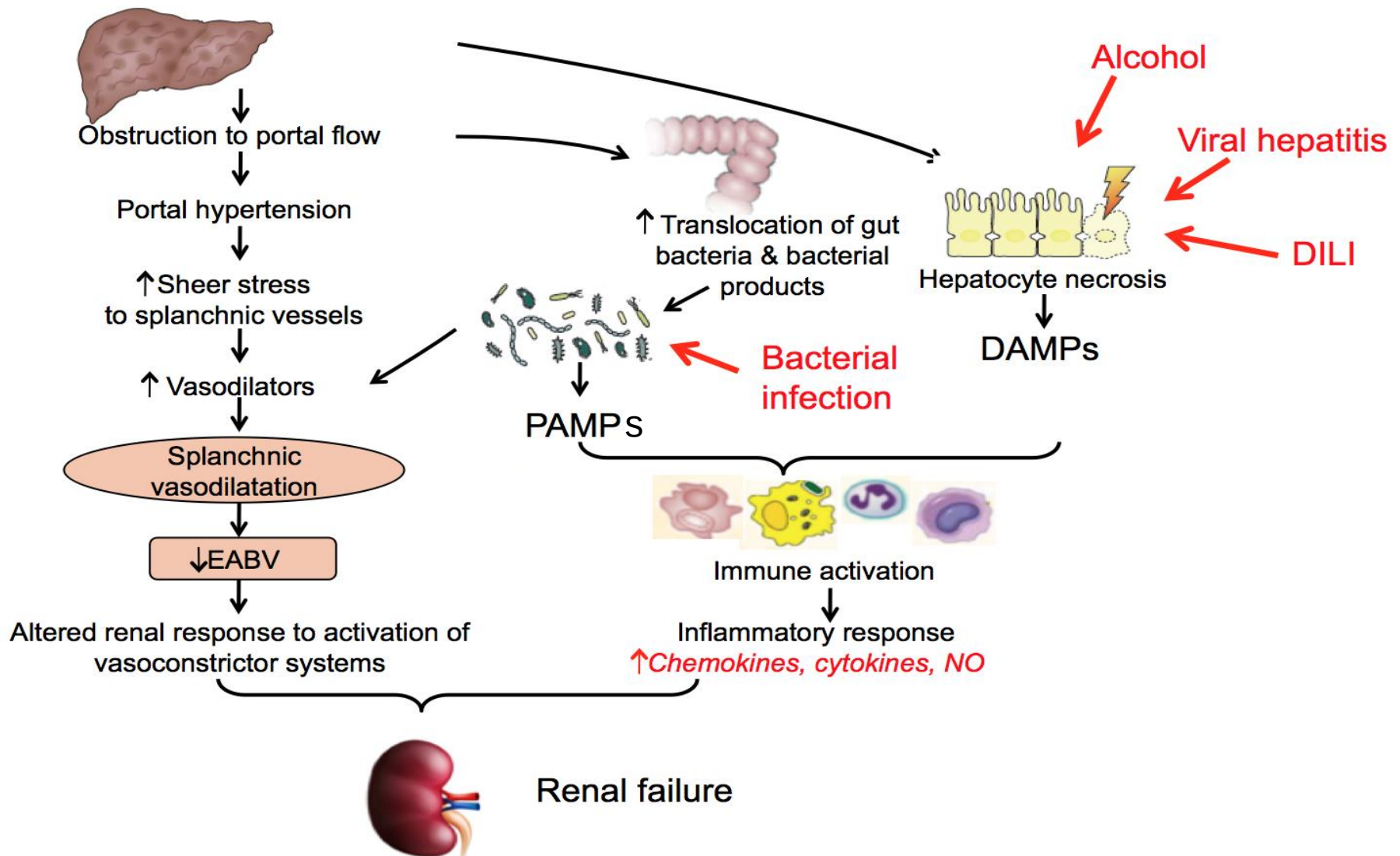
(Sola E, et al. J Hepatol 2018)

Why the Discrepancies

- Patients in the ANSWER study had a median MELD of 12-13, While those in MACHT study had a median MELD of 16-17
- Different doses of albumin used
- Shorter follow-up with the MACHT study
- Will await the American PRECIOSA study



Non-Oncotic Properties of Albumin

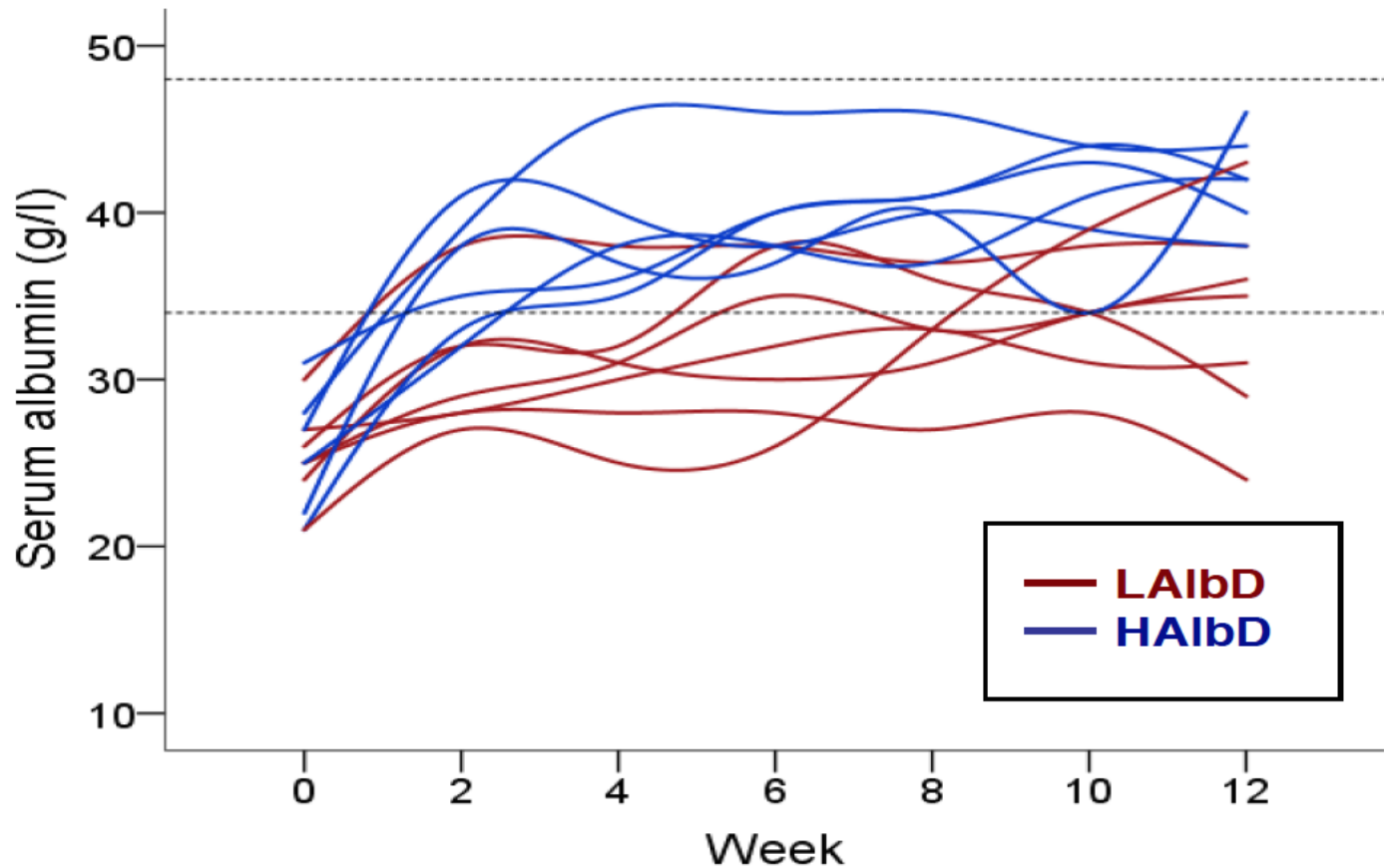


Anti-inflammatory Effects of Albumin

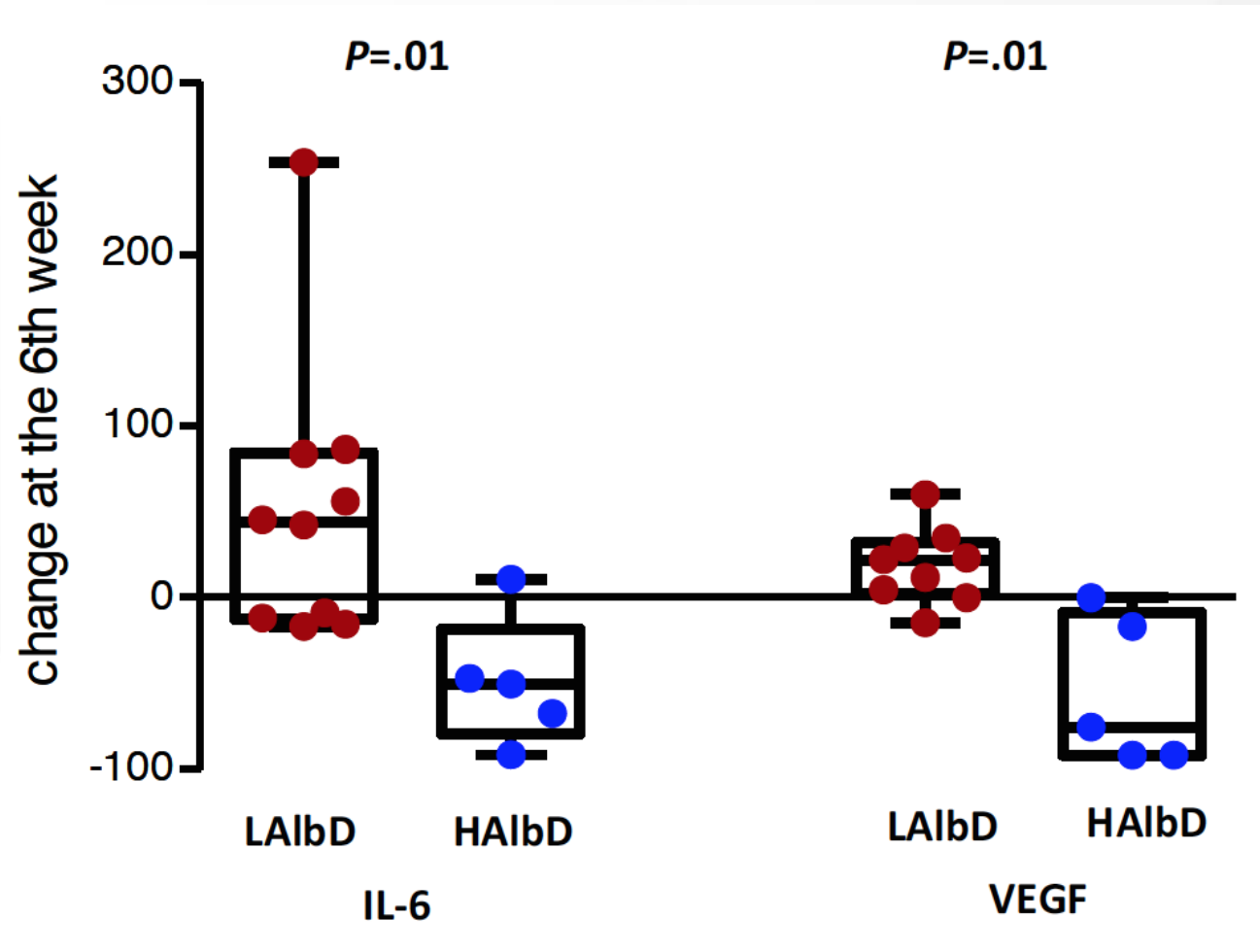
- Patients with decompensated cirrhosis & renal dysfunction
- 12 week infusion of albumin in non-infected patients
- Low dose (1gm/kg of body weight/2 weeks) versus high dose (1.5gm/kg of body weight/week)
- Assess effects on
 - serum albumin
 - plasma renin
 - cardiocirculatory function
 - portal pressure
 - plasma cytokine levels



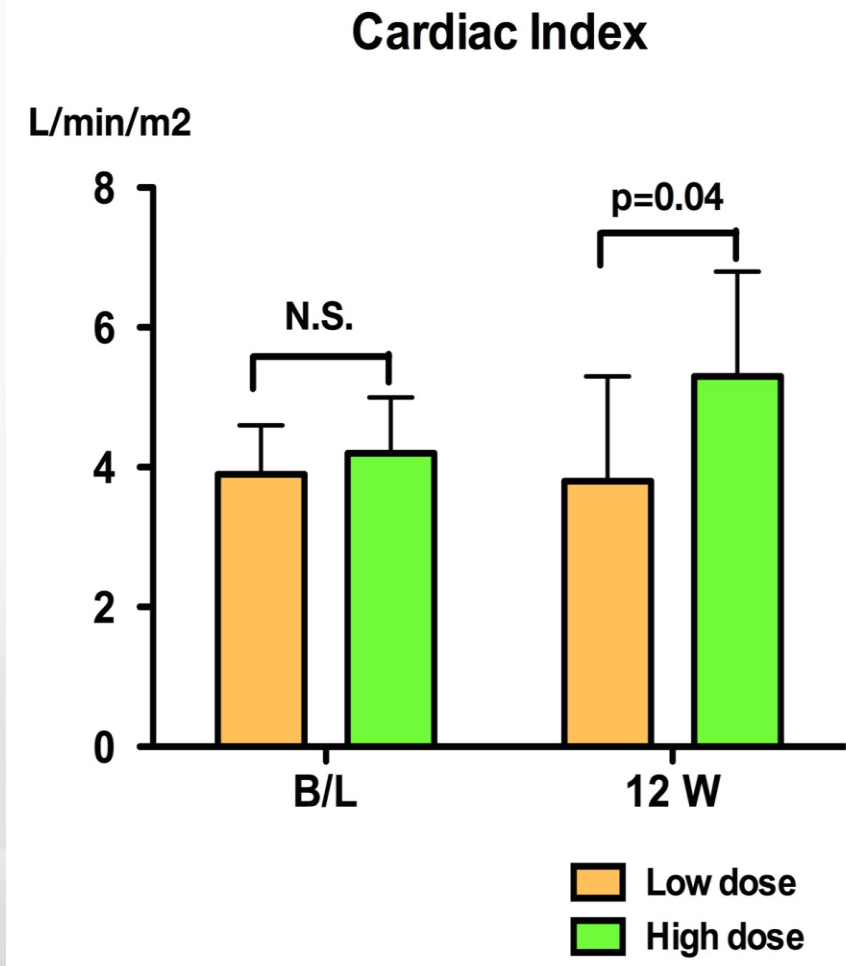
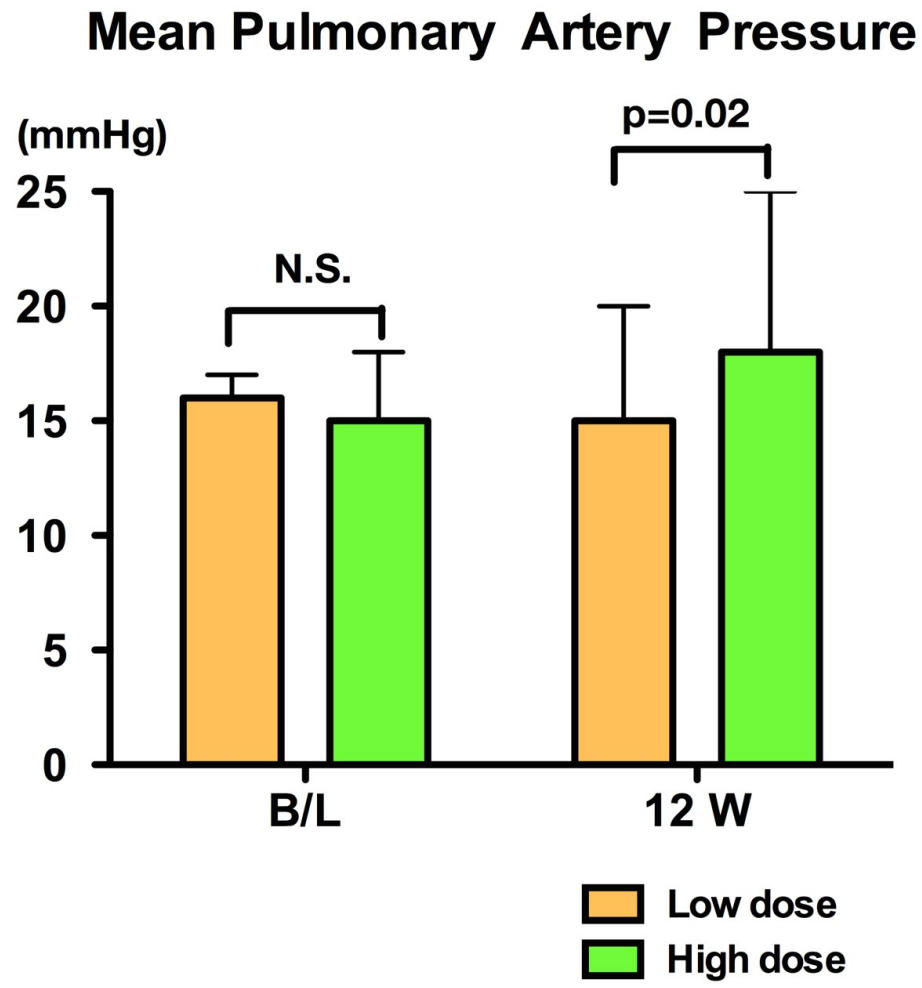
Effects of Infused Albumin on Serum Albumin



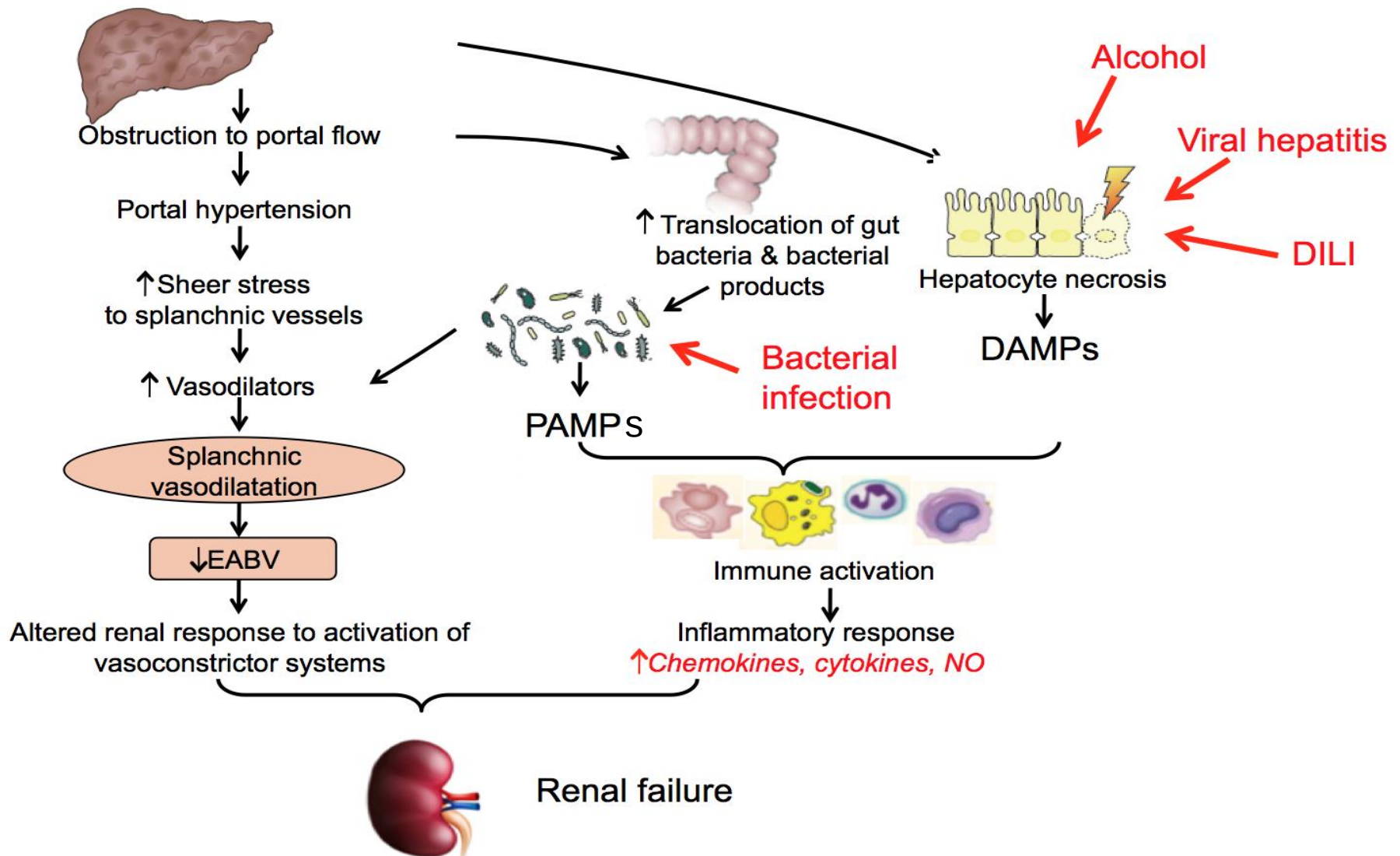
Effects of Infused Albumin on Inflammatory Markers



Effects of Infused Albumin on Inflammatory Markers



Non-Oncotic Properties of Albumin



Use of Albumin in Management of Ascites

- Dose of albumin seems important
- Dampening down inflammation may improve ascites control
- Need to monitor serum albumin
- Excessively high serum albumin may be counter-productive



What about Patients With Difficult to Control Ascites

- The elderly >65 years of age
- Patients with prior spontaneous hepatic encephalopathy
- MELD >18
- Portal vein thrombosis
- Pulmonary hypertension
- Heart failure

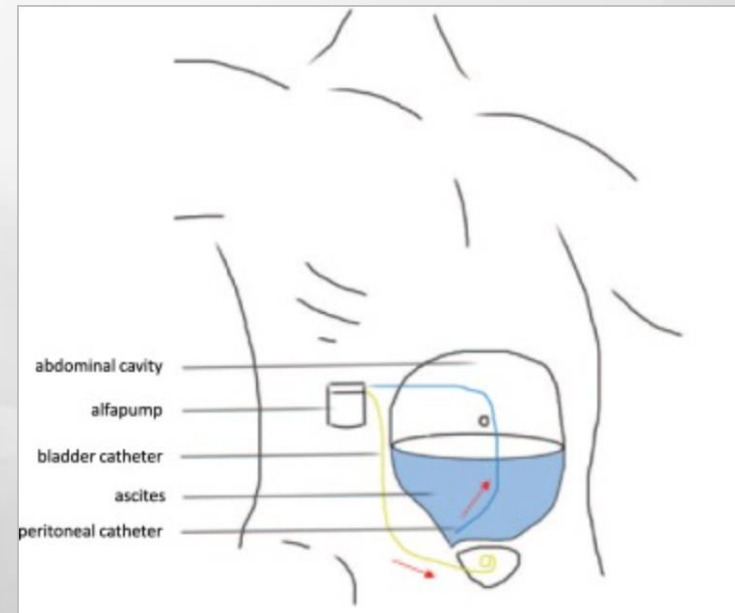


The Solution

The alfapump[®] System

Automatically and continually moves ascites from the abdominal cavity to the bladder, where it is excreted naturally from the body.

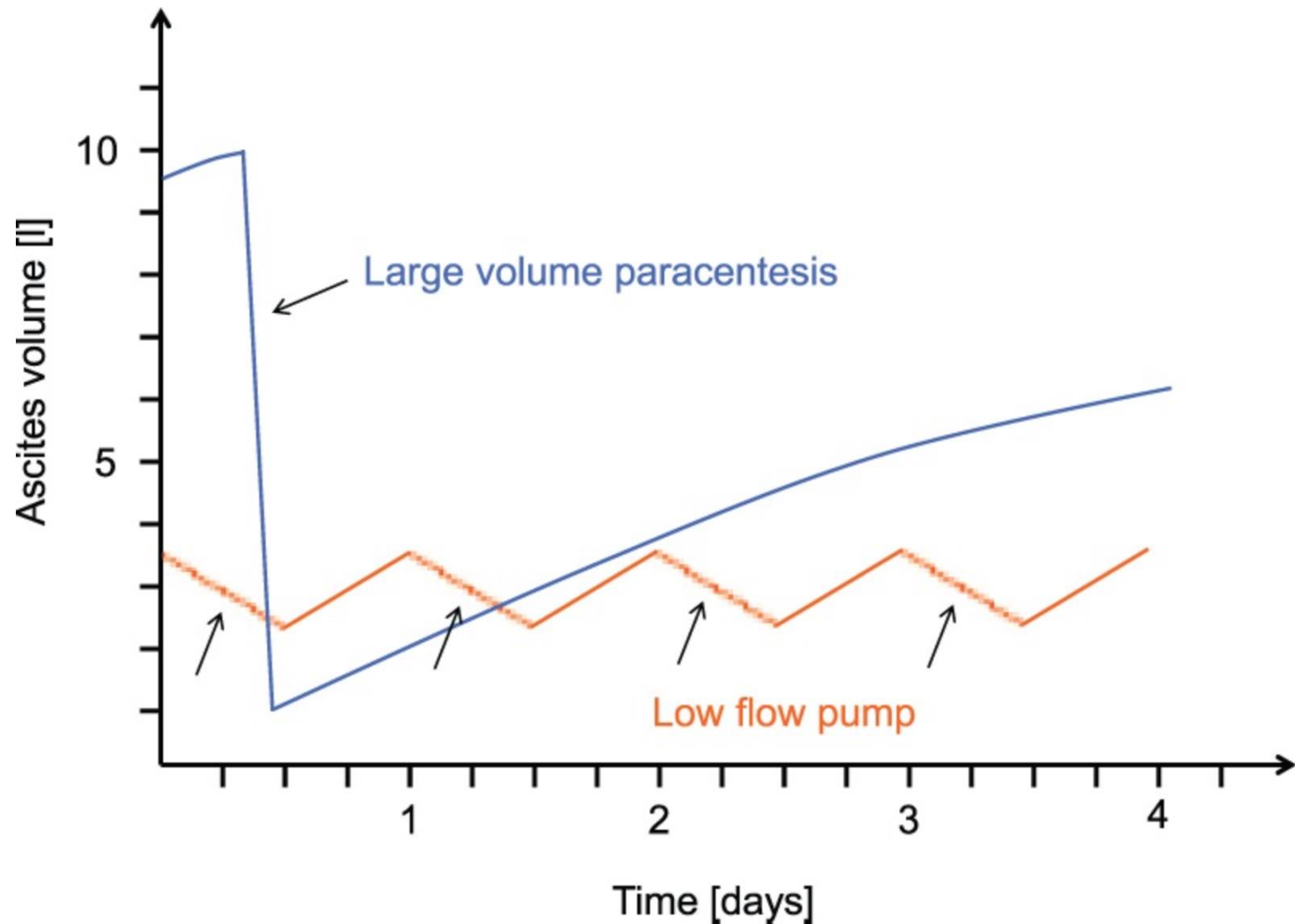
- Significantly reduces the need for paracentesis
- Improves patient quality of life
- Avoids the risks of current therapeutic options



Pump in situ



ALFA pump provides continuous small volume ascites drainage



ALFA Pump Report

Pump serial no.: **6285**

Days since implant: **47**

Total volume of fluid removed: **36.2 liters**

Average daily volume of the last 7 complete days: **861.8 ml**

The **alfapump** is functioning very well and has been adequately charged.

Please find below the daily statistics from the last 8 days for this **alfapump**.



Date	Target Daily Volume [ml]	Total Volume transported [ml]	% Target Daily Volume Transported	Effective Pump Charging Time [min:sec]
25.02.2019	900	861	96	26:52
26.02.2019	900	867	96	12:46
27.02.2019	900	859	95	19:59
28.02.2019	900	858	95	16:22
01.03.2019	900	865	96	30:05
02.03.2019	900	856	95	27:10
03.03.2019	900	866	96	03:32
04.03.2019 (incomplete) data from 00:00 to 06:40	900	0	0	00:00



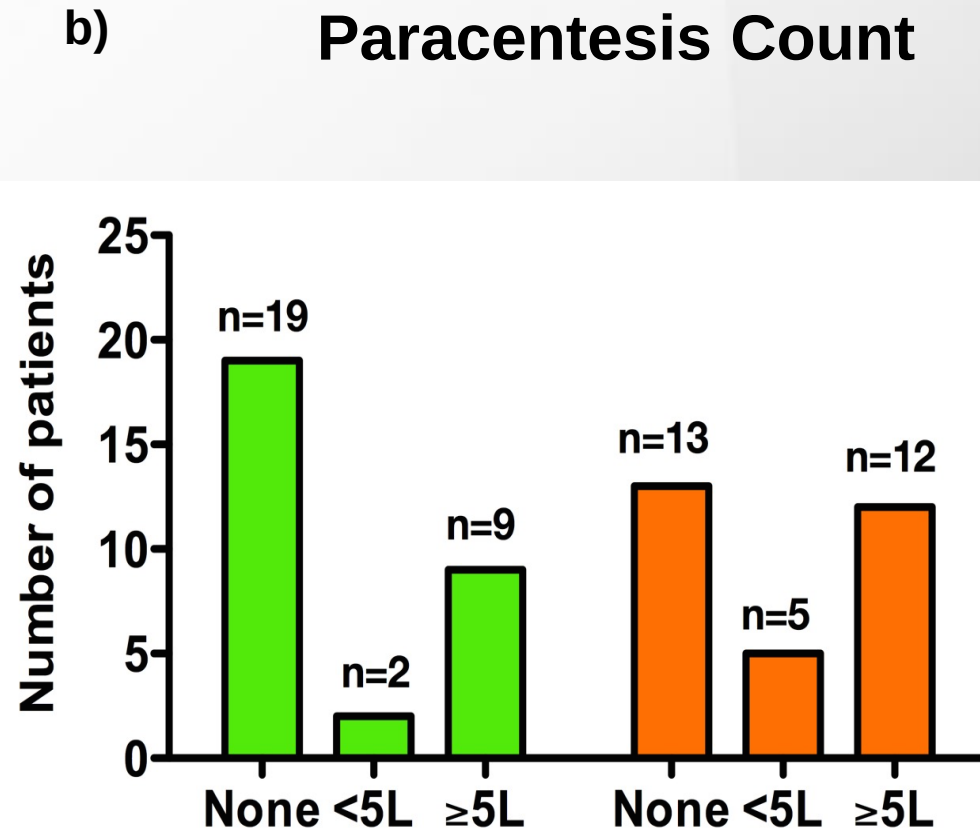
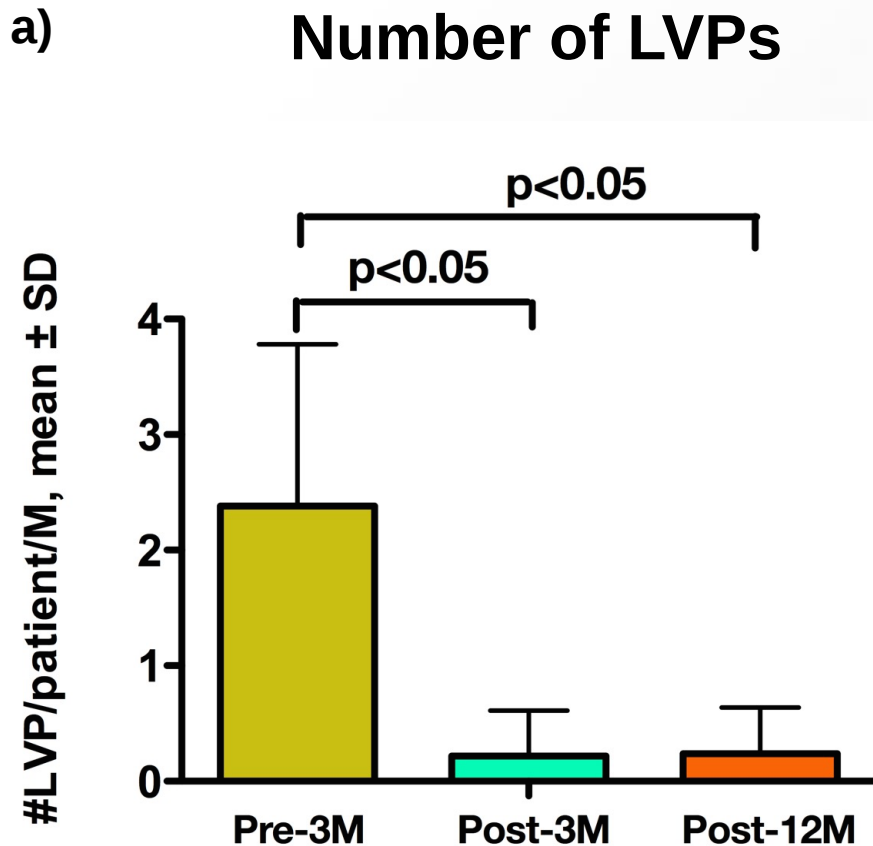
Control of Ascites

- Pump is set to work from 0800-2200 hours
- Average volume per pump cycle: ~6ml
- Average time between pump cycles: 5-6 minutes
- Median follow-up time of 30 patients in North America: 361 days (27-764)
- Total ascites removed in 12 months: 317.9 ± 121.9 litres/patient (=53 large volume paracenteses of 5 litres each)

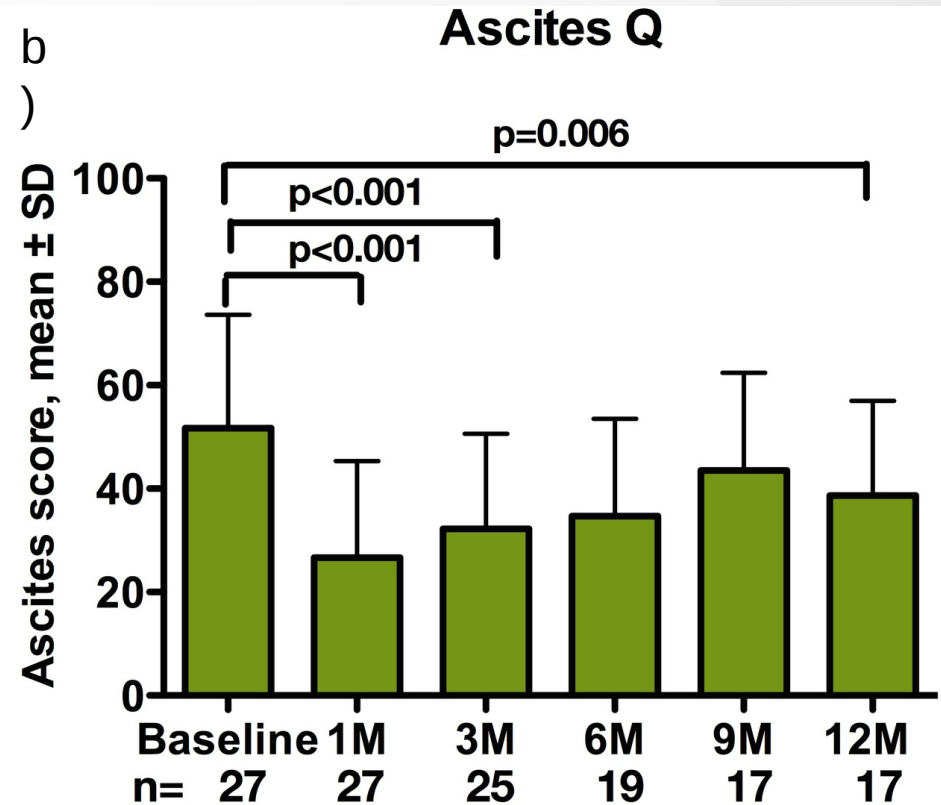
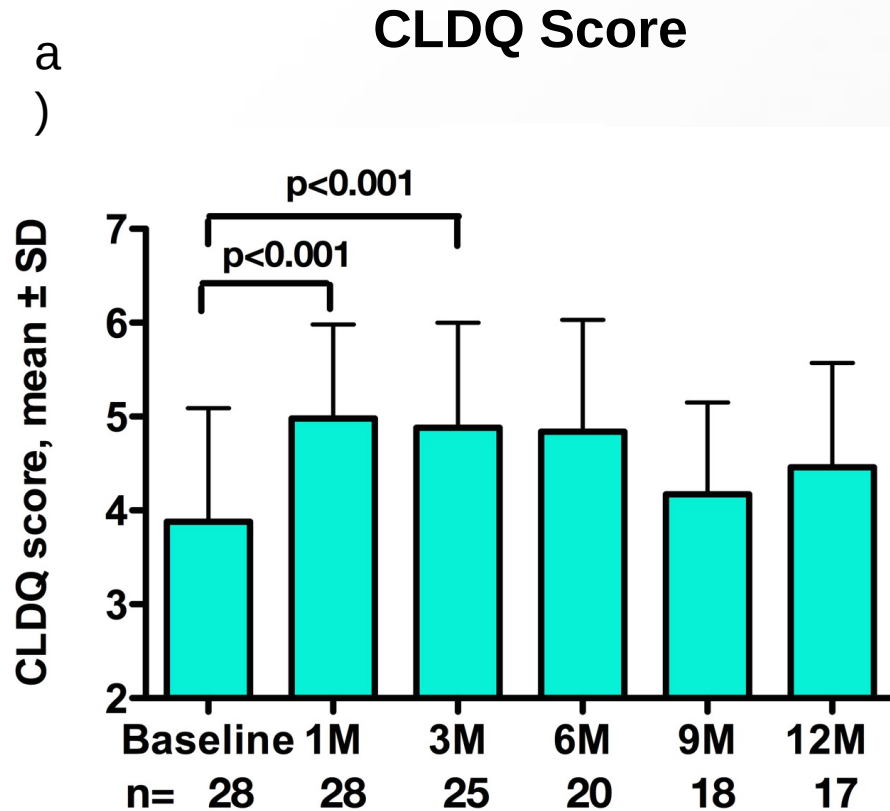
Average daily ascites volume removed: 883 ± 338 ml



Control of Ascites with alfapump

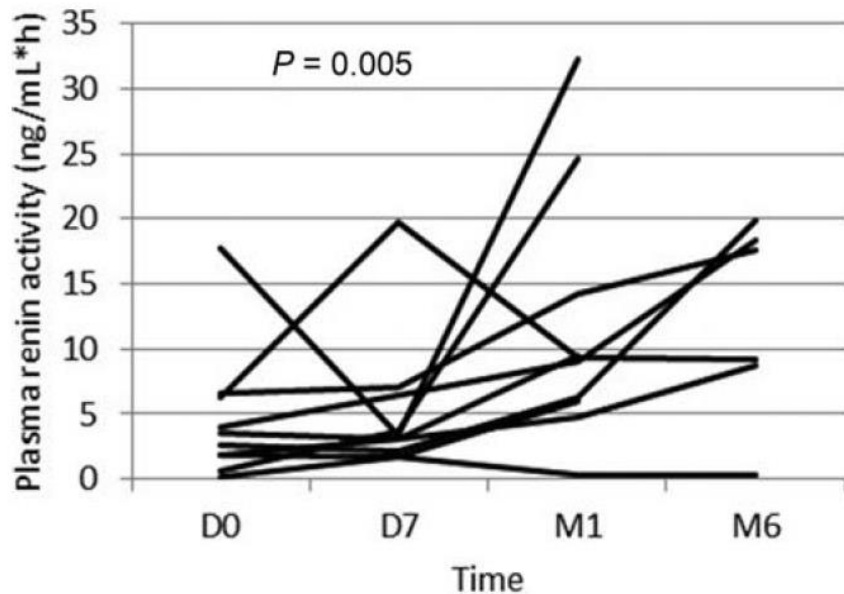


Quality of Life Changes

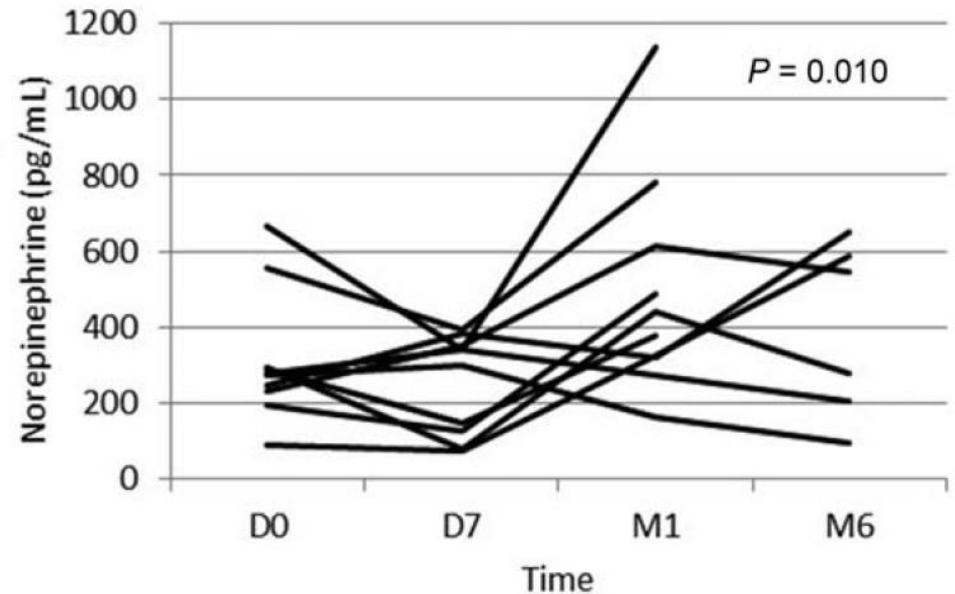


Vasoconstrictor activities post-pump insertion

Plasma renin activity



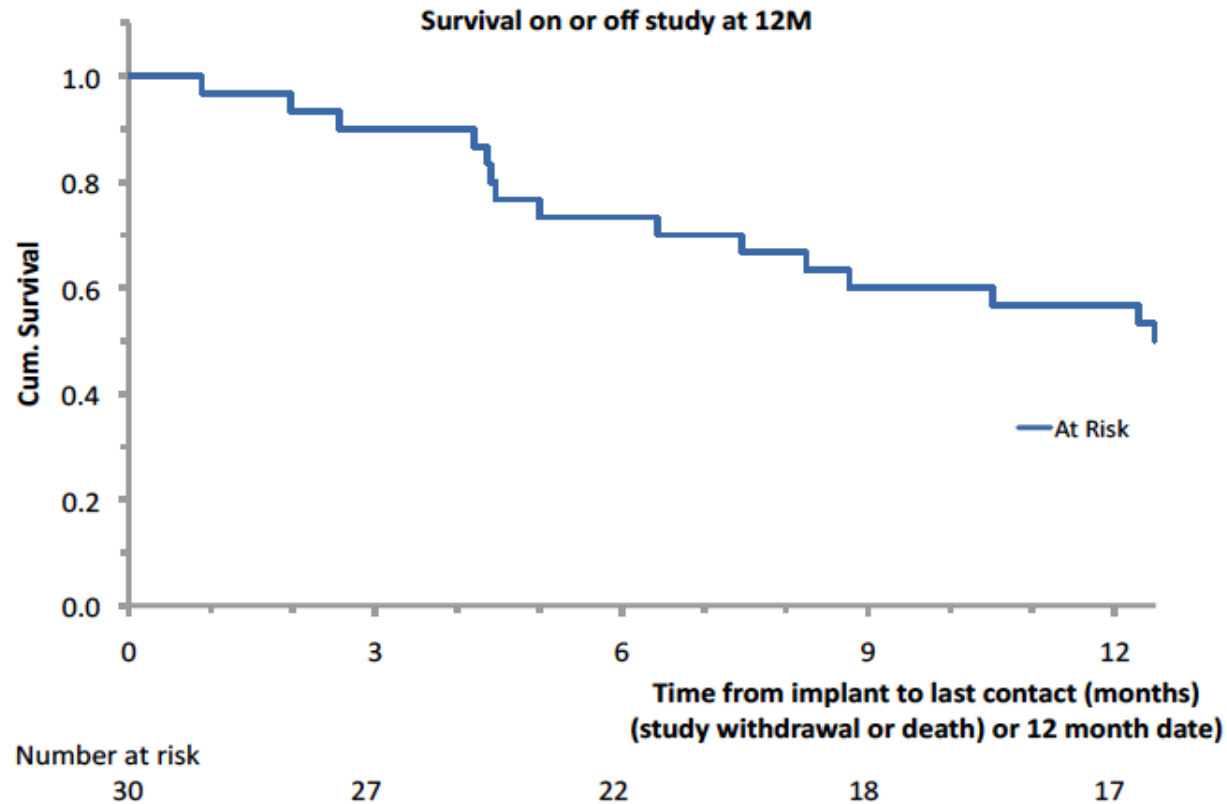
Norepinephrine



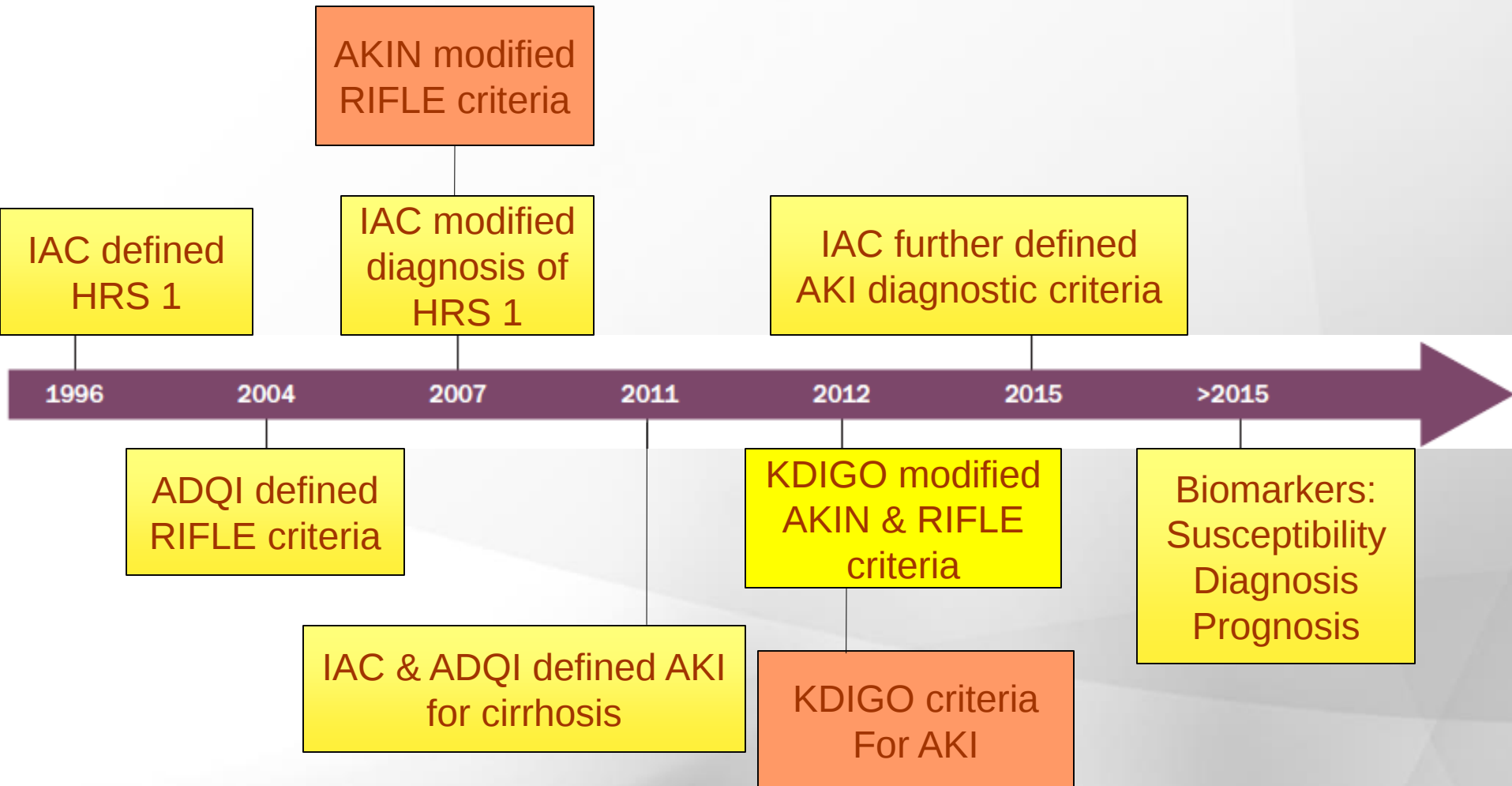
Continued monitoring of renal function and intermittent albumin infusions may be required



Survival post-pump insertion



The Evolving Concept of Renal Dysfunction in Cirrhosis



Acute Kidney Injury (AKI) in Cirrhosis

Parameter	Definition
Baseline SCr	Stable SCr ≤ 3 months If not available, a stable SCr closest to the current one If no previous SCr at all, use admission SCr
Definition of AKI	$\uparrow$ in SCr $\geq 26.5 \mu\text{mol/l}$ (0.3 mg/dL) ≤ 48 hours, or $\uparrow 50\%$ from baseline
Staging	Stage 1: $\uparrow$ SCr $\geq 26.4 \mu\text{mol/L}$ (0.3 mg/dL) or $\uparrow$ SCr $\geq 1.5 - 2.0 \times$ from baseline Stage 2: $\uparrow$ SCr $> 2.0 - 3.0 \times$ from baseline Stage 3: $\uparrow$ SCr $> 3.0 \times$ from baseline, or SCr $\geq 352 \mu\text{mol/L}$ (4.0 mg/dL) with an acute $\uparrow$ of $\geq 26.4 \mu\text{mol/L}$ (0.3 mg/dL), or Initiation of renal replacement therapy



AKI – Hepatorenal Syndrome

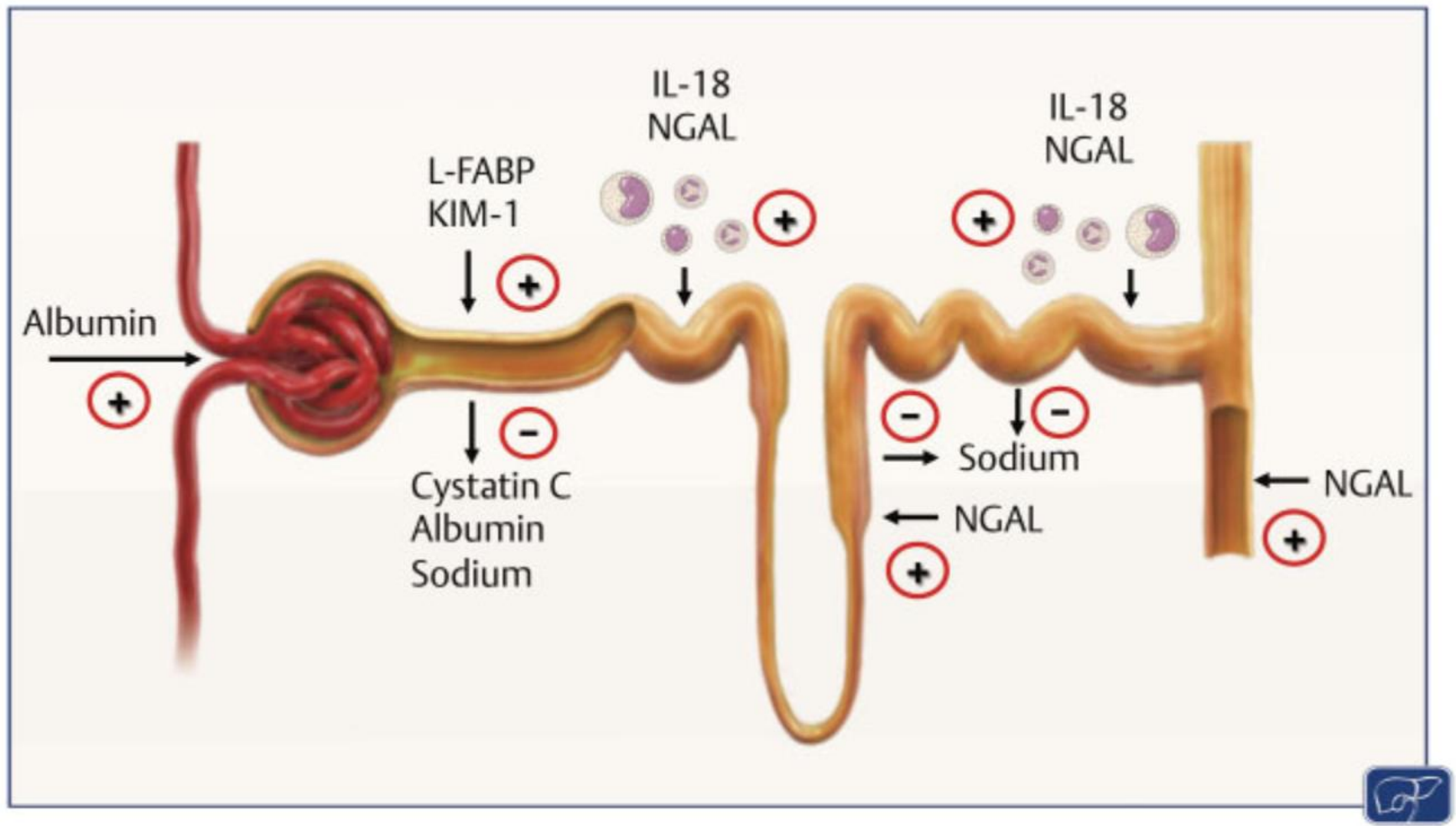
Diagnostic Criteria

1. Cirrhosis and ascites;
2. Stage 2 or 3 AKI;
3. No improvement of serum creatinine (decrease of creatinine $\leq$ 0.3mg/dl of baseline) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (1 g/kg b.w./day for 2 days);
4. Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure;
5. No current or recent treatment with nephrotoxic drugs;
6. Proteinuria <500 mg/day and no microhematuria (<50 RBCs/ml).



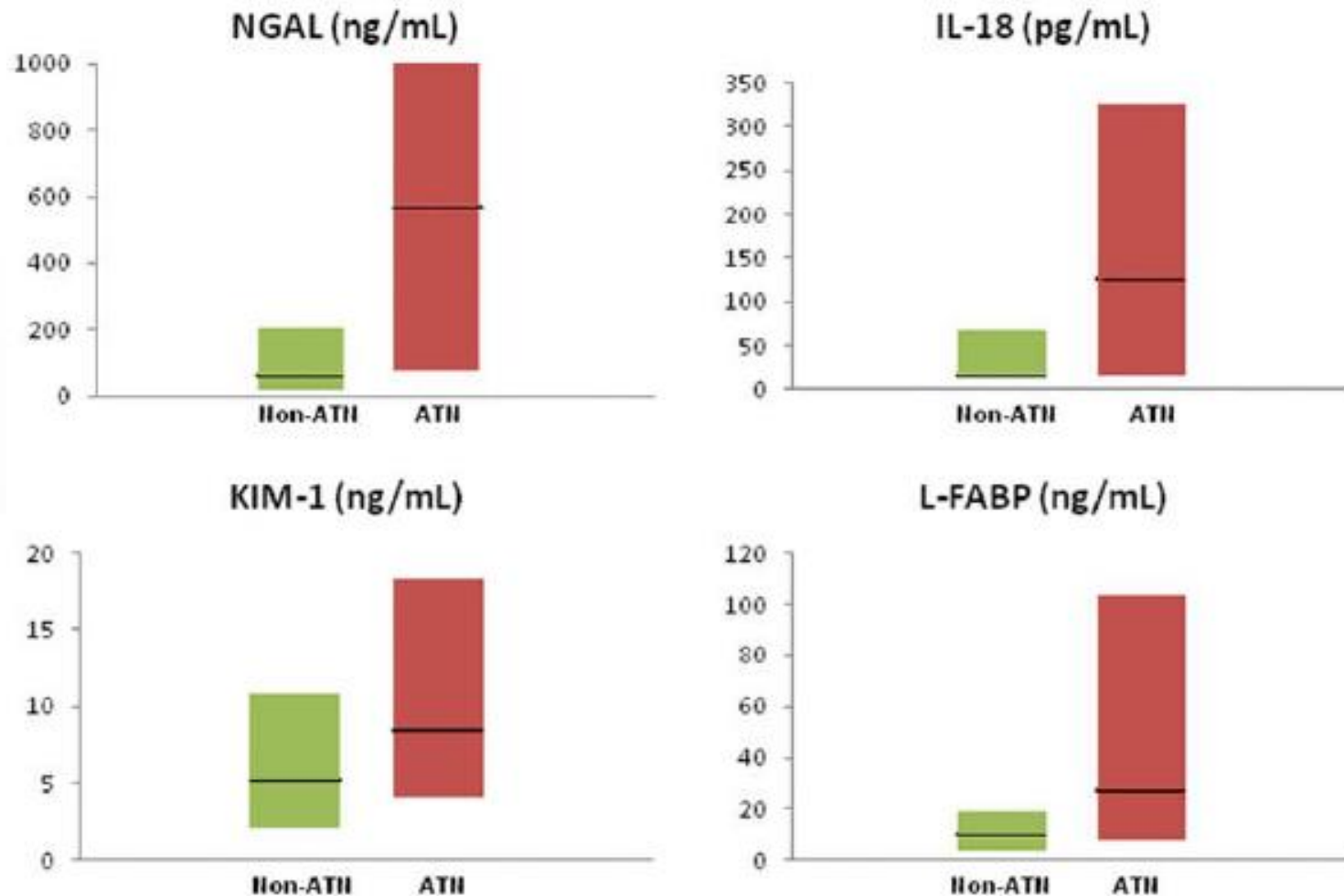
Diagnosis of AKI in Cirrhosis

Role of Biomarkers



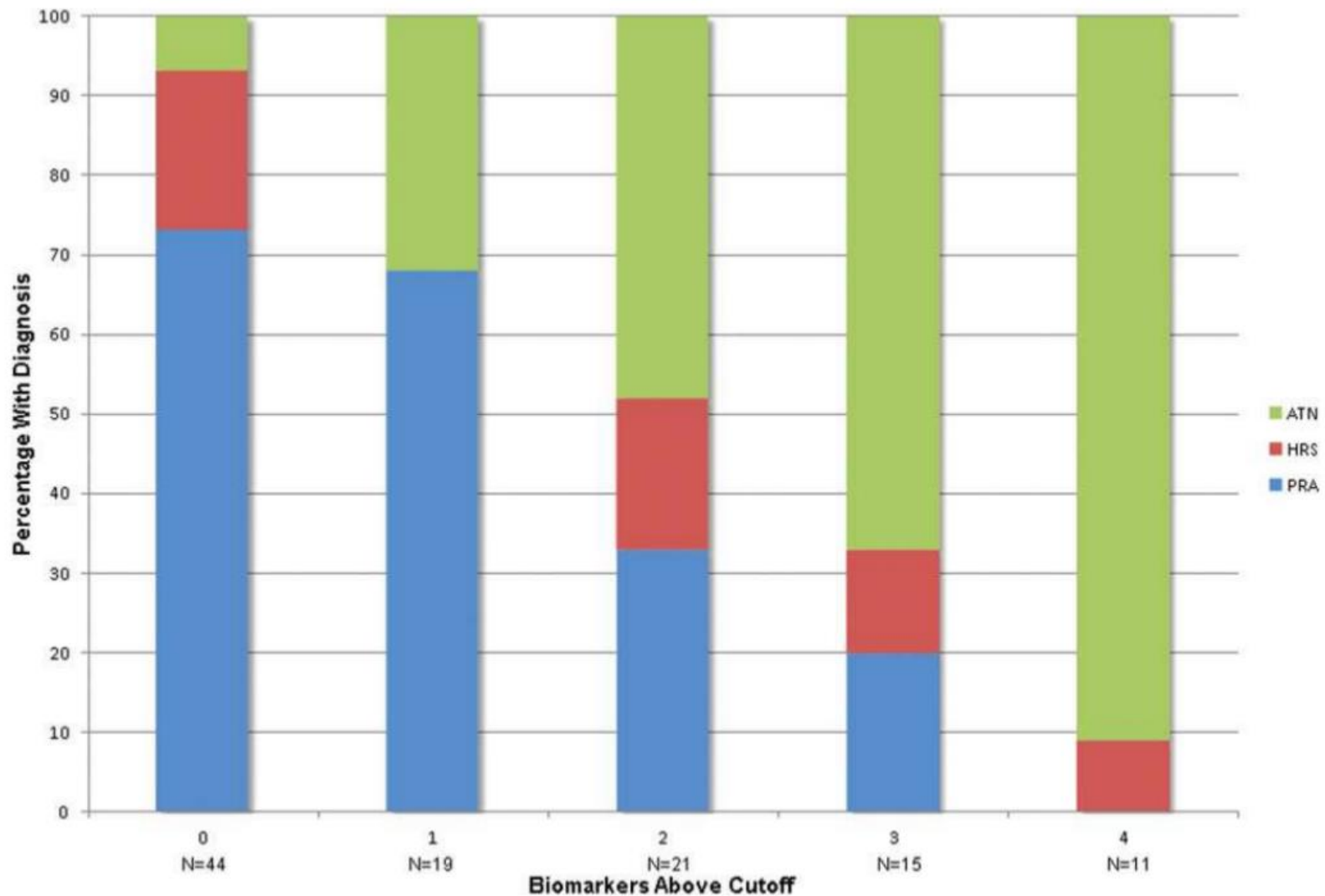
Diagnosis of AKI in Cirrhosis

Role of Biomarkers

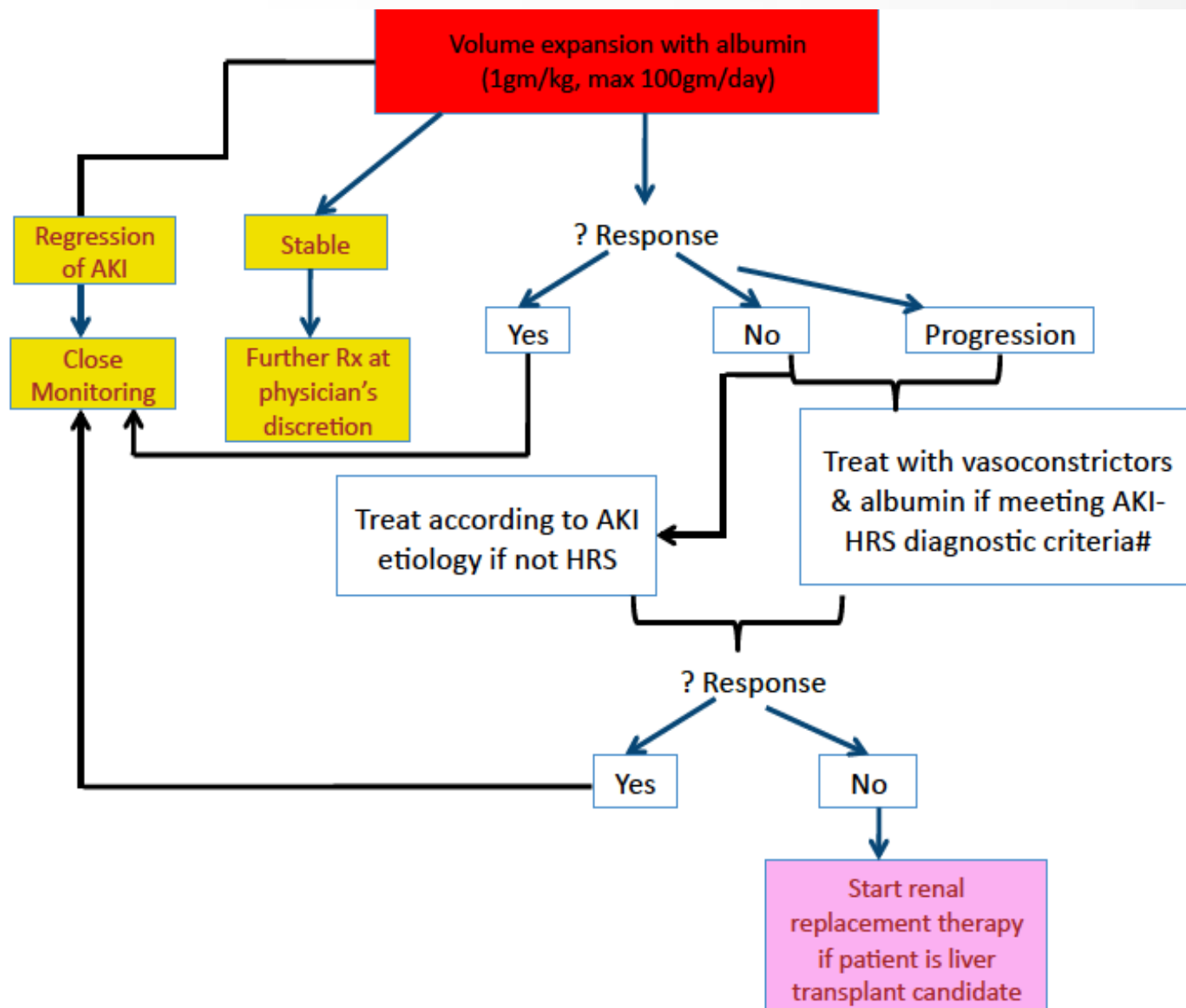


Diagnosis of AKI in Cirrhosis

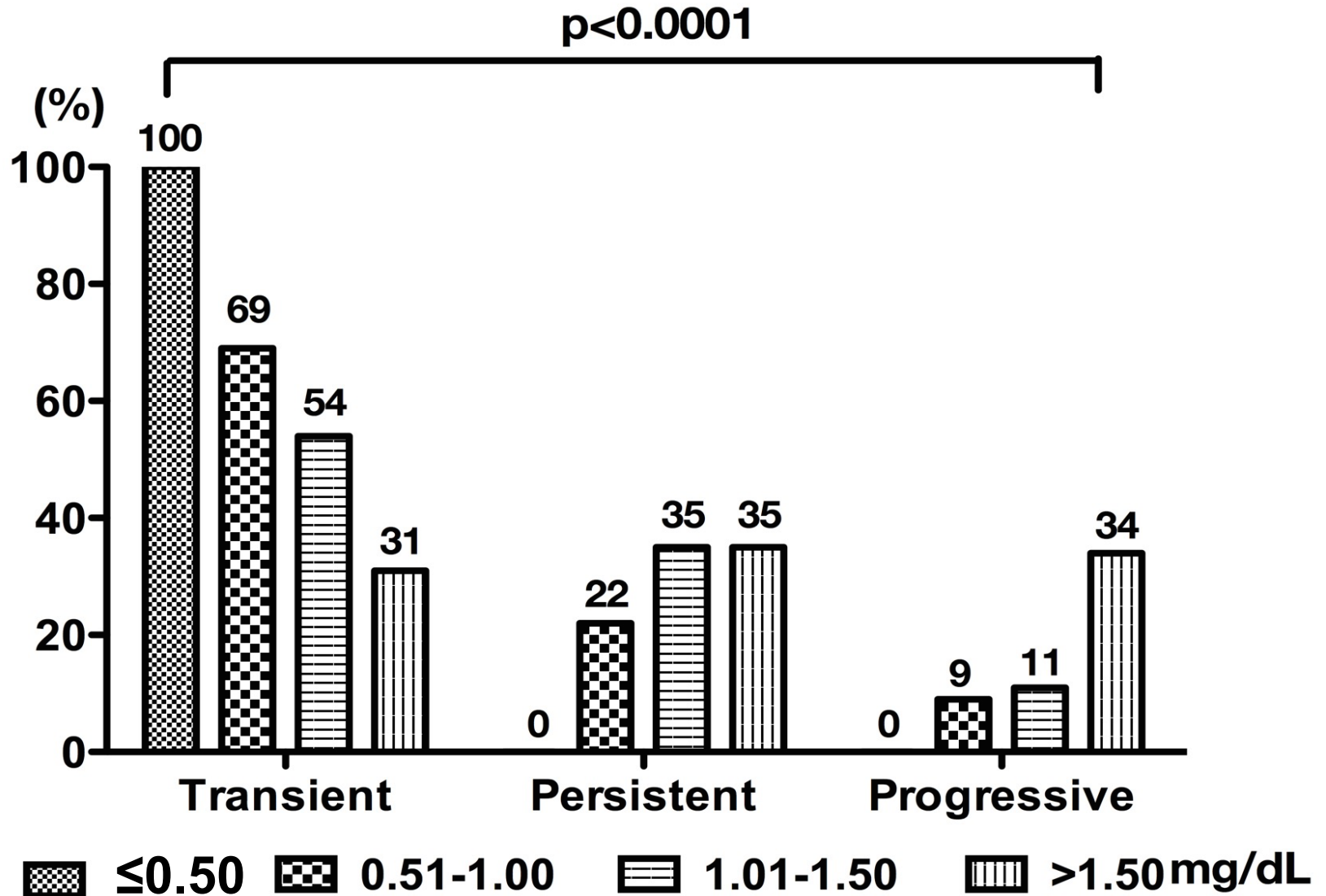
Role of Biomarkers



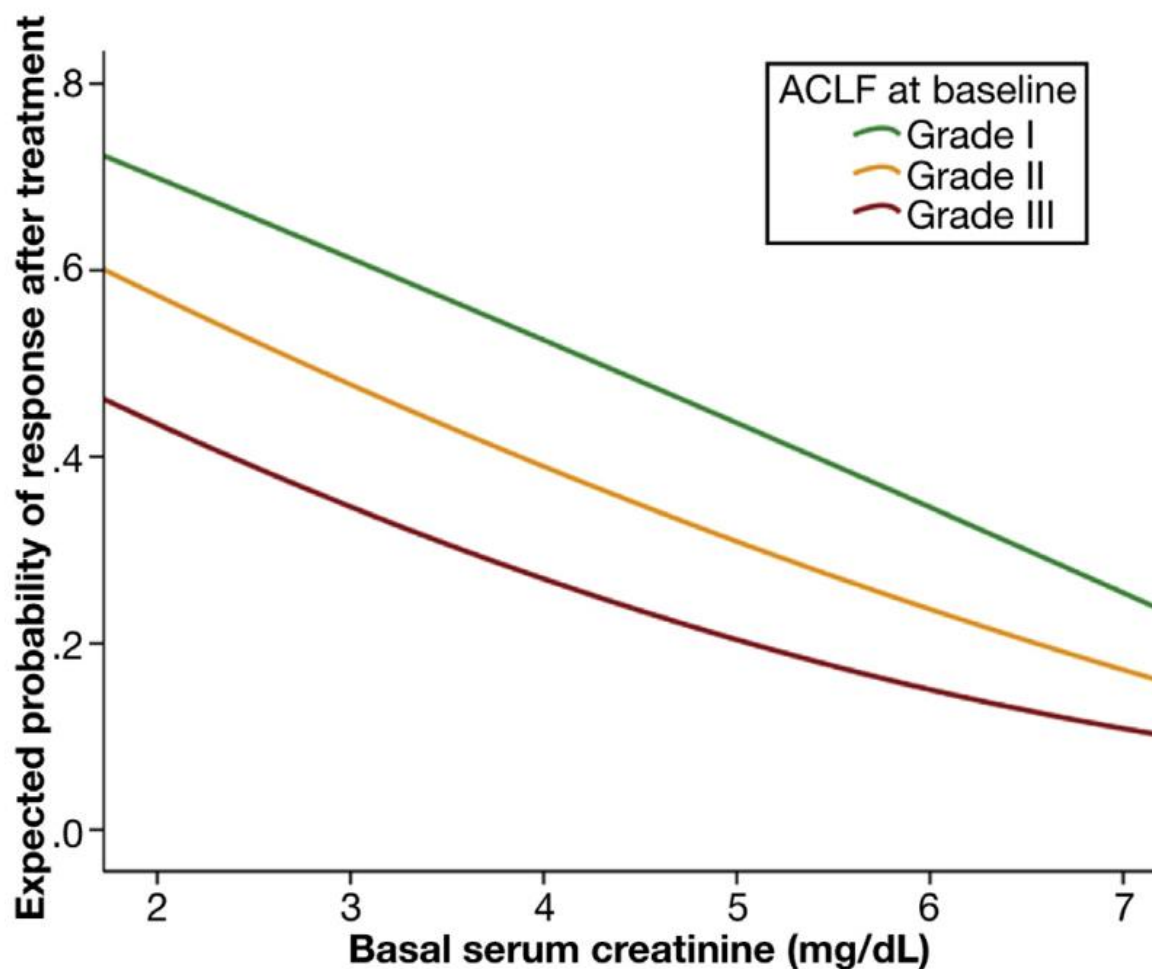
Management of AKI in Cirrhosis



Baseline Serum Creatinine Matters

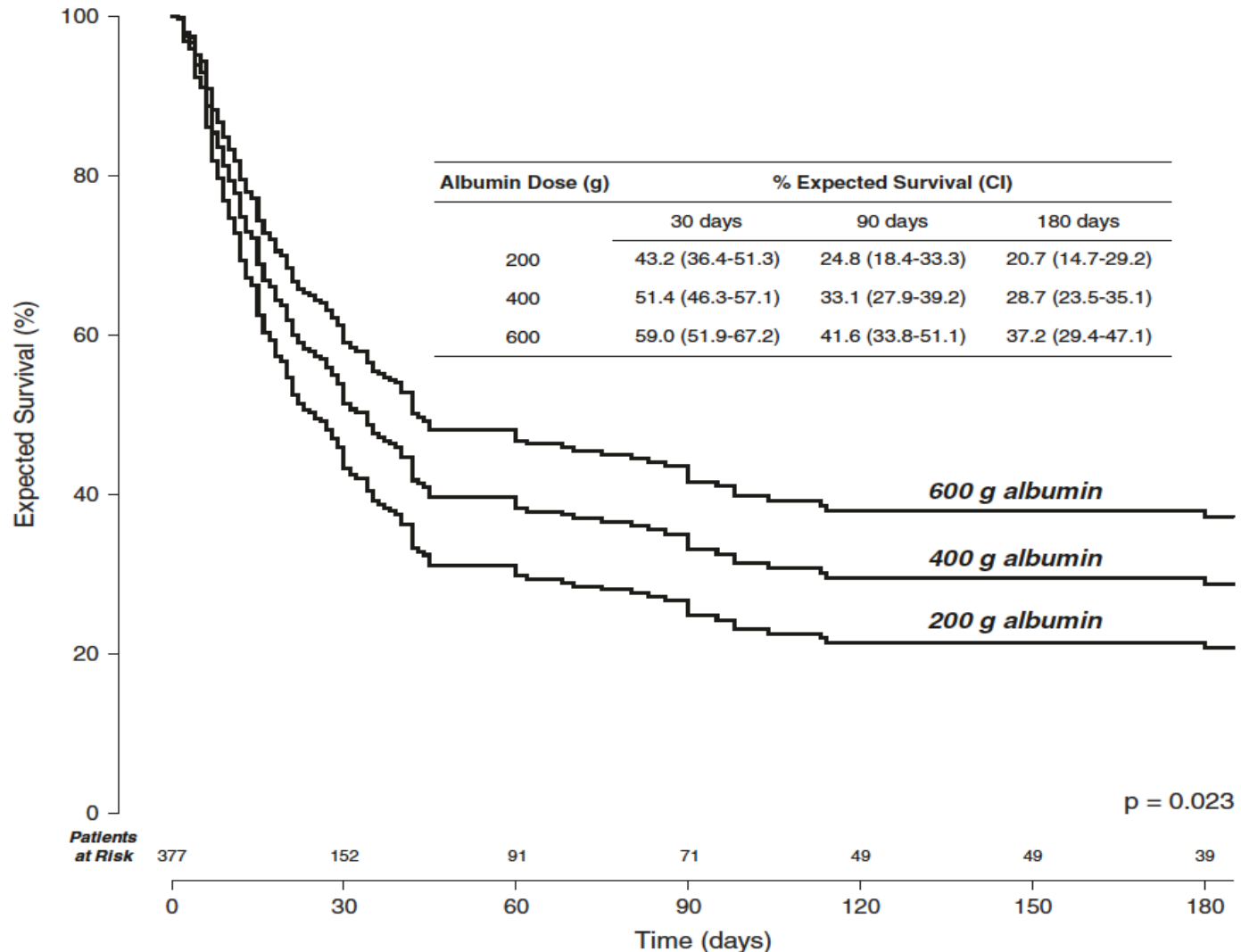


Severity of Liver Dysfunction Matters

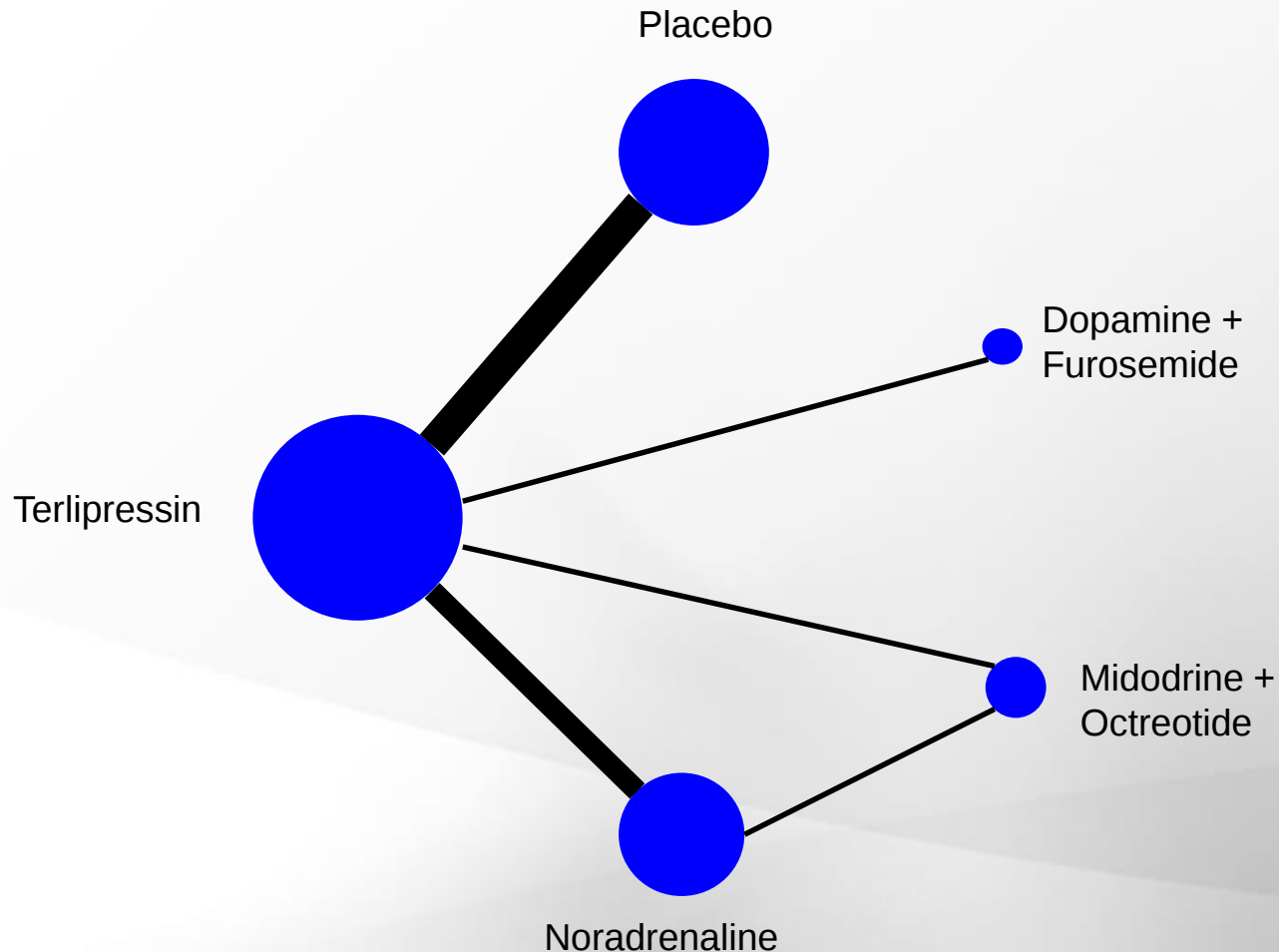


(Piano S. et al, Clin Gastro Hepatol 2018)

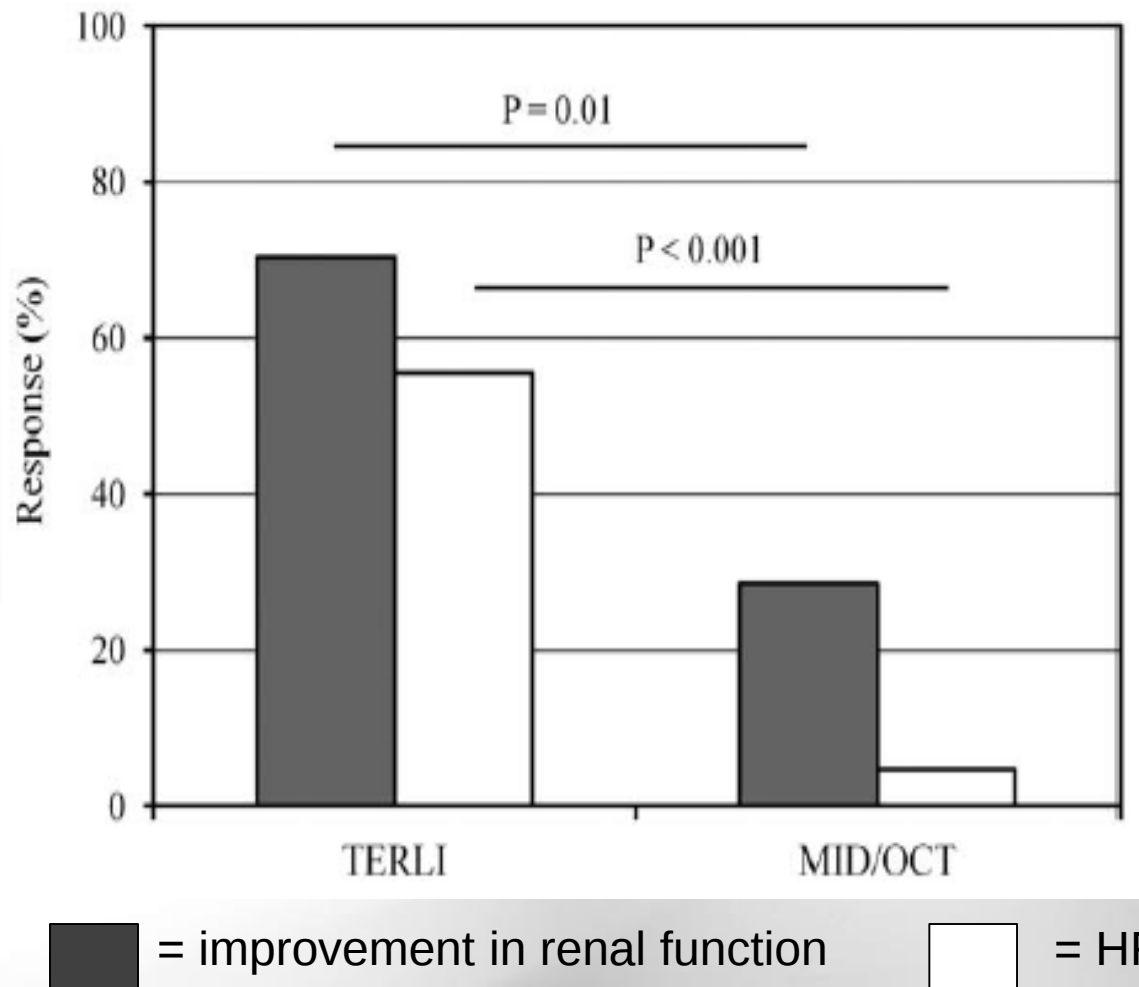
Dose Response to Albumin in AKI



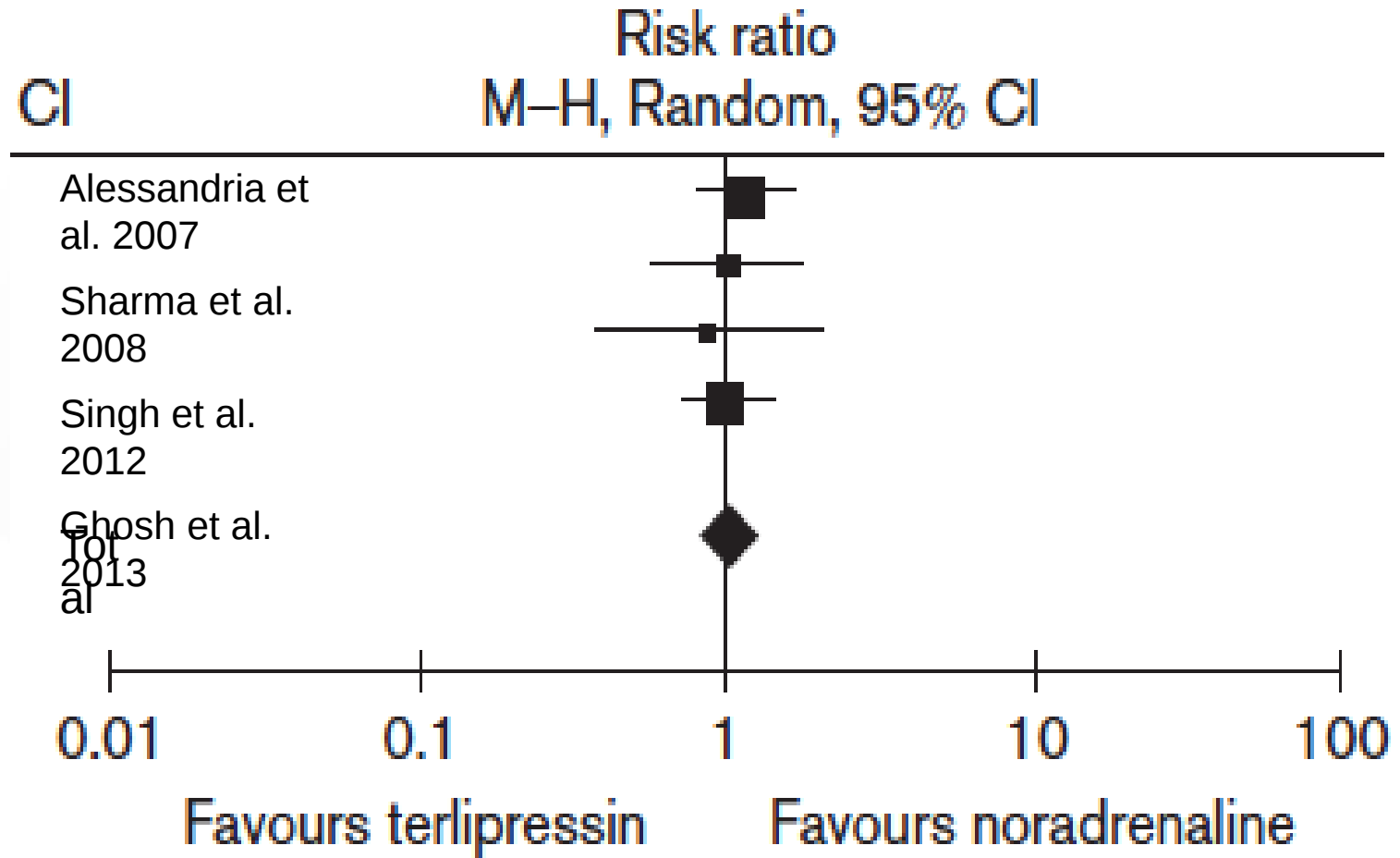
Terlipressin is the most commonly studied drug for HRS1



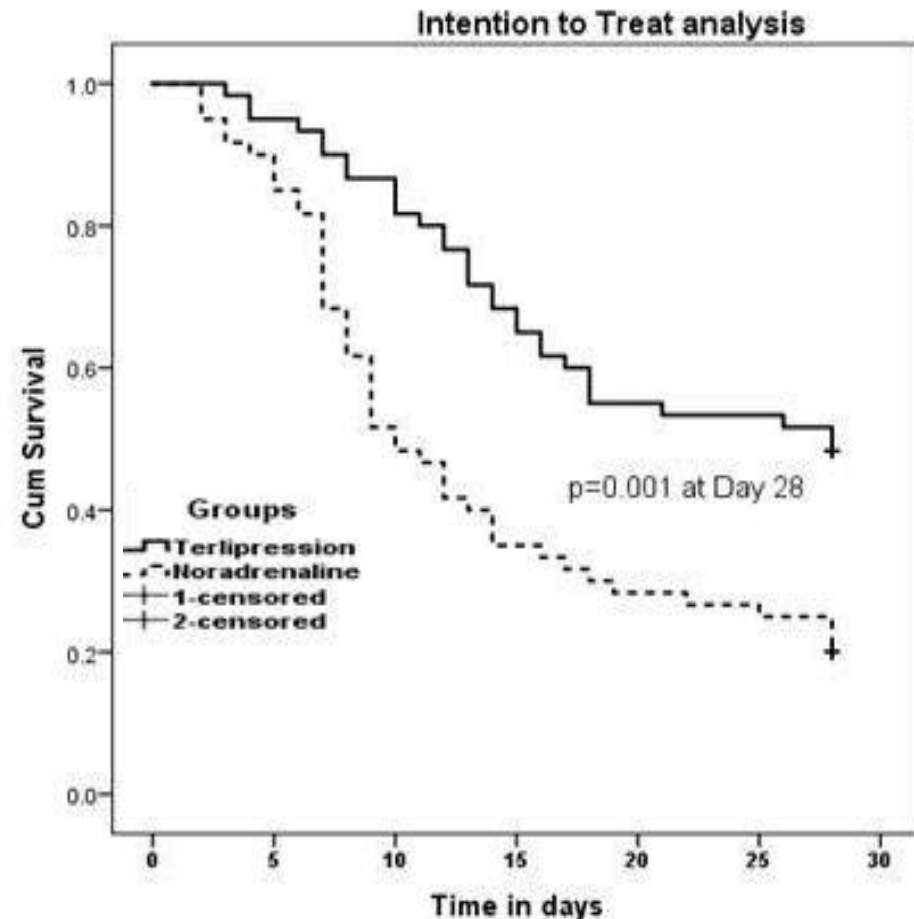
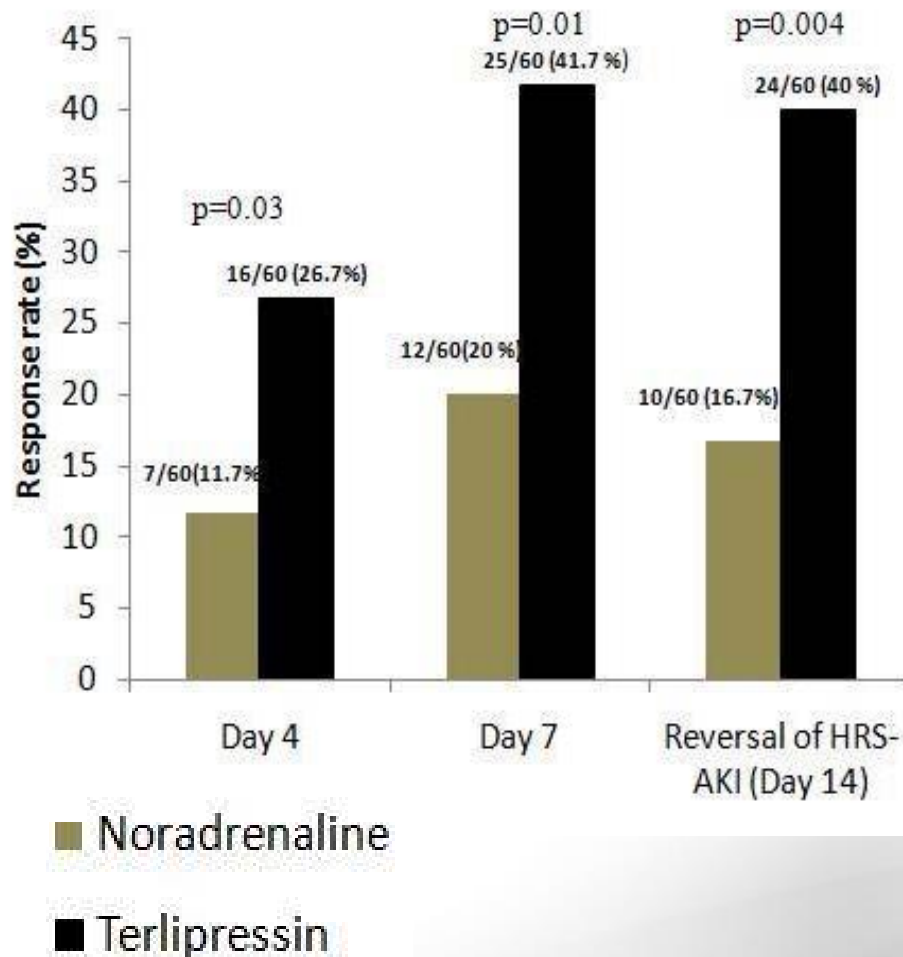
Terlipressin vs. Midodrine/Octreotide for HRS1



Terlipressin versus Norepinephrine for HRS1 Meta-analysis

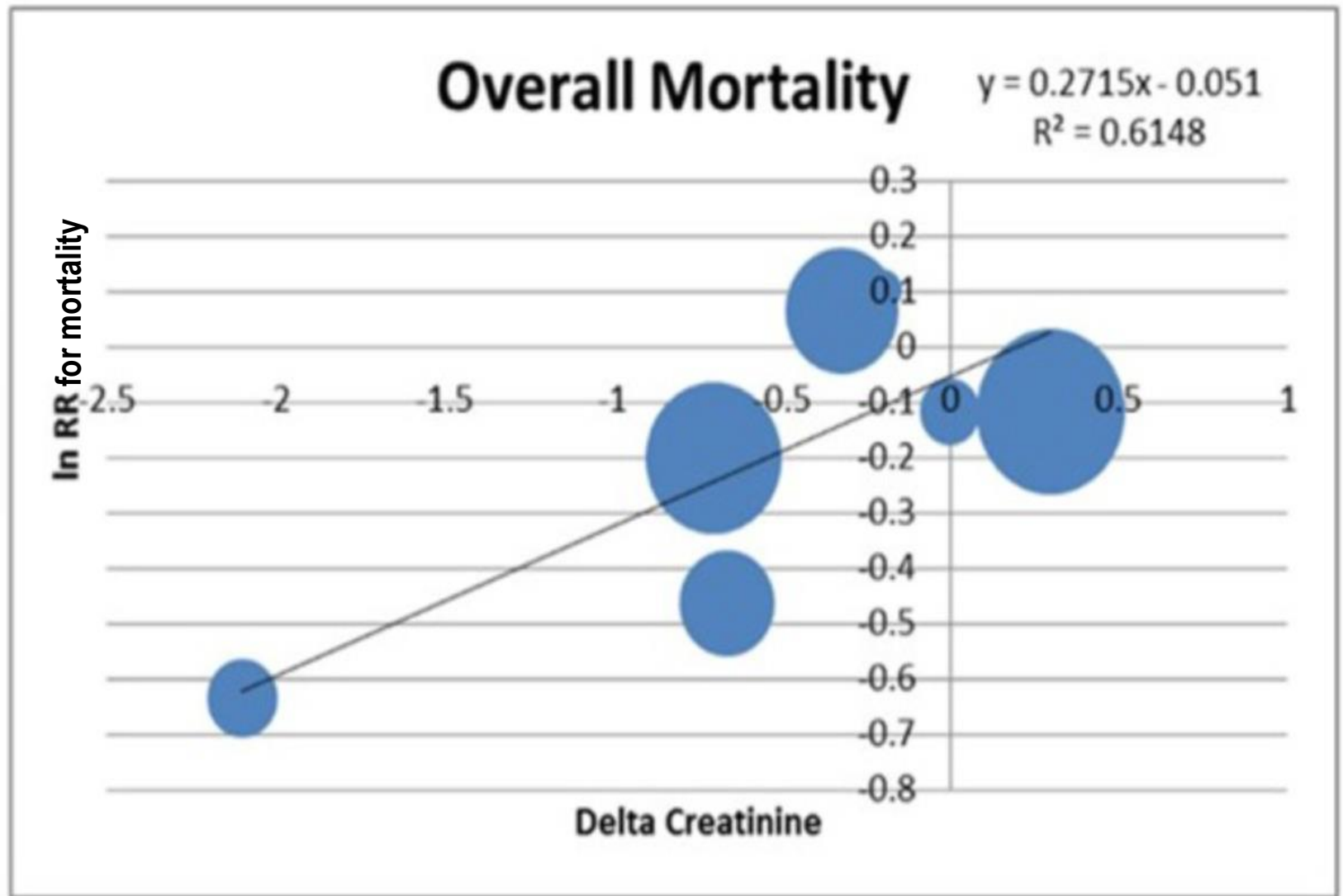


Terlipressin versus Norepinephrine in the Context of ACLF



ACLF=bilirubin >5mg/dl + INR >1.5 plus ascites ± HE in <4 weeks

Small reduction in serum creatinine with treatment can improve survival



Summary

- Renal failure is the most common organ failure in decompensated cirrhosis
- Need to recognize it early in order to initiate timely treatment
- Terlipressin is the most commonly used vasoconstrictor worldwide for AKI in cirrhosis
- Small improvement in serum creatinine with treatment is beneficial
- Refer for consideration for liver transplant early
- Early transplantation is associated with improved outcomes



The Future - Biomarkers

