



CONTROVÉRSIAS EM CUIDADOS INTENSIVOS E COMPLICAÇÕES DA CIRROSE – UMA ABORDAGEM BASEADA EM CASOS CLÍNICOS

O QUE MUDOU NO TRATAMENTO DA ASCITE E DA ENCEFALOPATIA HEPÁTICA



Sociedade Brasileira de Hepatologia
Desde 1967



AMIB
ASSOCIAÇÃO DE MEDICINA
INTENSIVA BRASILEIRA



CONTROVÉRSIAS EM CUIDADOS INTENSIVOS E COMPLICAÇÕES DA CIRROSE – UMA ABORDAGEM BASEADA EM CASOS CLÍNICOS

José Eymard Moraes de Medeiros Filho



Professor Associado III da Universidade Federal da Paraíba

Doutor em Gastroenterologia pela FMUSP

Coordenador Clínico do Grupo de Transplante de Fígado do Estado da Paraíba

Coordenador da UTI Pós Operatória do Hospital Unimed João Pessoa

Coordenador do Ambulatório de Hepatologia do Hospital Universitário Lauro Wanderley da UFPB

Coordenador do Grupo de Interesse em Hepatointensivismo da Sociedade Brasileira de Hepatologia



Sociedade Brasileira de Hepatologia

Desde 1967



CONFLITO DE INTERESSES:

- Não há conflitos de interesse em relação ao tema.



CASO CLÍNICO

Homem, 62 anos, com Ascite e encefalopatia hepática

JCPM, 62 anos, masculino, cirrótico de etiologia alcoólica, abstinência há 2 anos, Professor.

Ascite de difícil controle há 2 anos.

HDA Varicosa há 5 anos (primeira manifestação da doença)

Ativo, apesar de perda de massa muscular e ascite de moderado – grande volume.

Transferido de UPA – Unidade de Pronto Atendimento para Hospital Universitário após tratamento inicial de Hemorragia Digestiva Alta varicosa há 4 dias.

Resumo de transferência para enfermagem: Hemorragia Digestiva Alta Varicosa com instabilidade hemodinâmica submetido à Ligadura elástica de varizes gástricas (5 bandas) + Terlipressina (4º dia de tratamento).

CASO CLINICO

Homem, 62 anos, com Ascite e encefalopatia hepática

JCPM, 62 anos, masculino, cirrótico de etiologia alcoólica, abstinência há 2 anos, Professor.

Resumo de transferência para enfermagem: Hemorragia Digestiva Alta Varicosa com instabilidade hemodinâmica submetido à Ligadura elástica de varizes gástricas (5 bandas) + Terlipressina (4º dia de tratamento).

Problemas:

Admitido na UTI após 24 horas da admissão hospitalar por confusão mental e agitação seguida de rebaixamento progressivo do nível de consciência . Apresenta-se com dispneia restritiva.

Hipóteses diagnósticas:

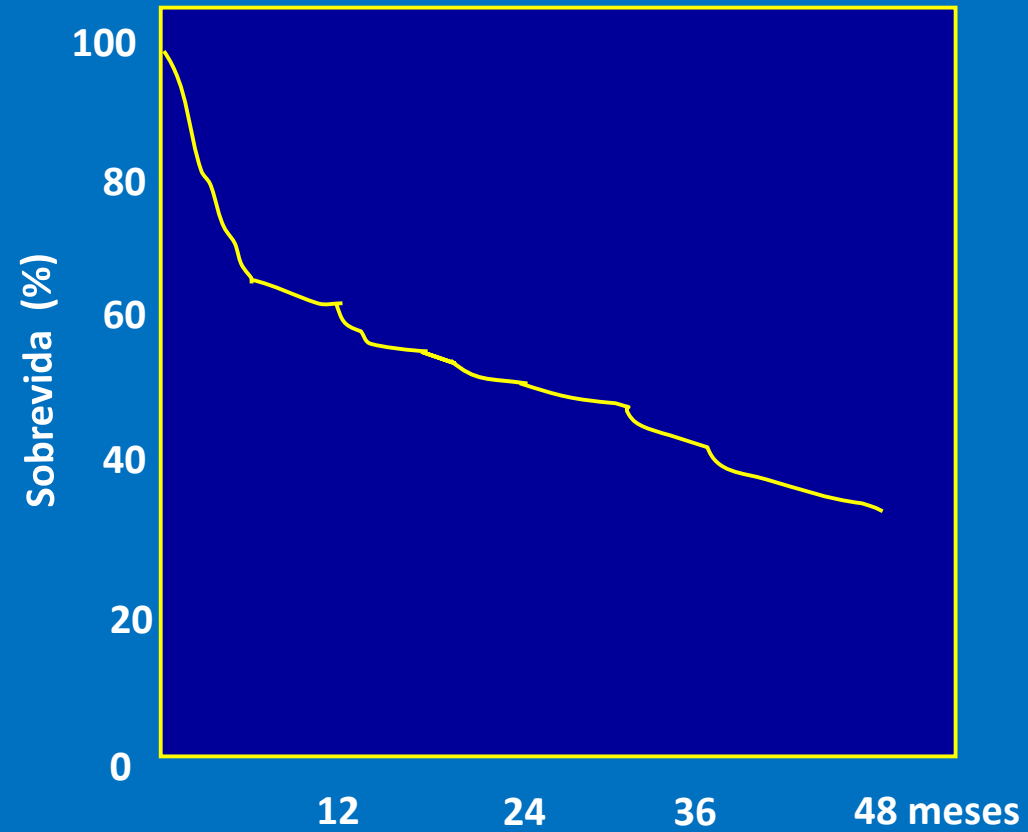
Encefalopatia Hepática

Ascite de grande volume

ASCITE E CIRROSE

PROGNÓSTICO

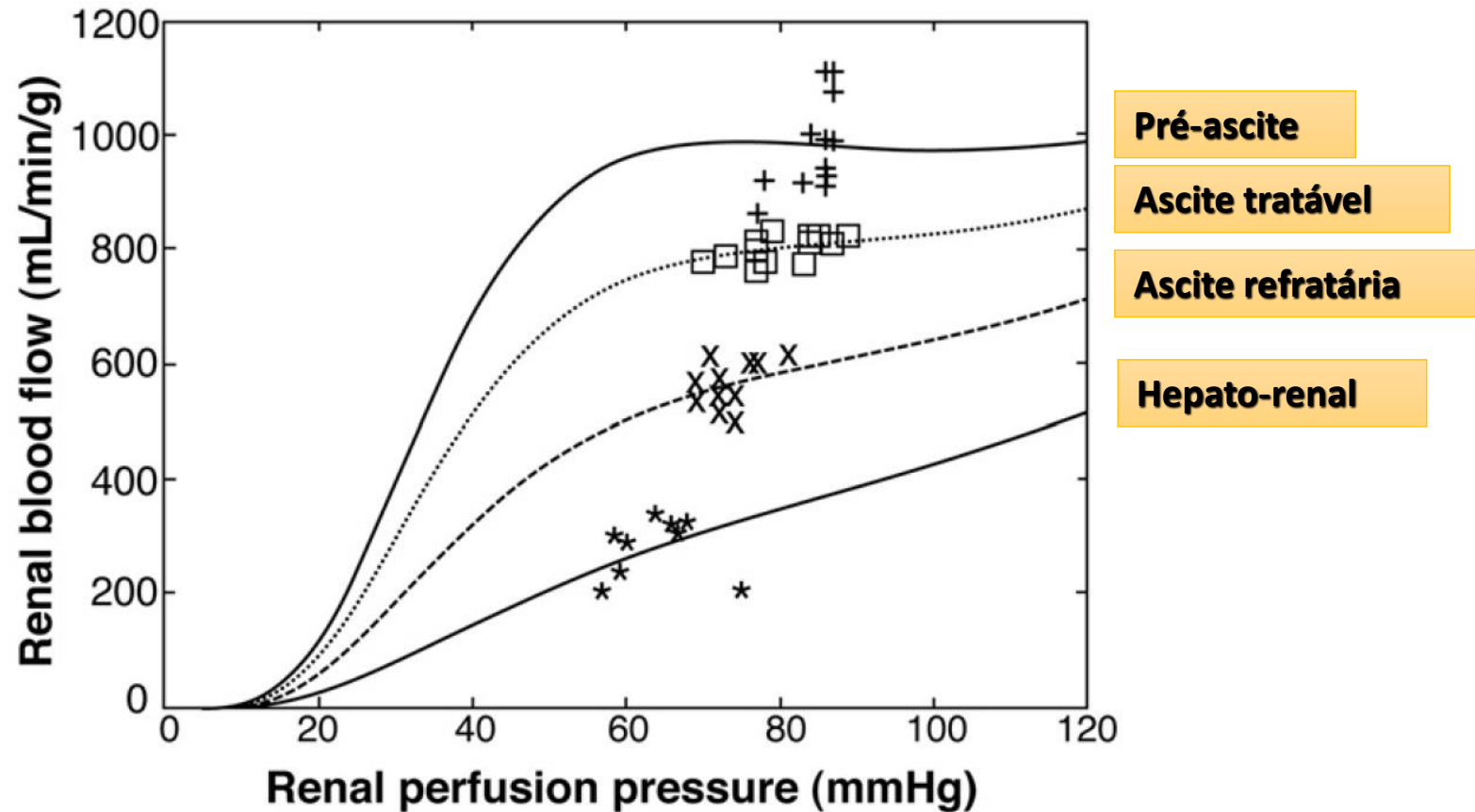
Mediana de sobrevida: 24 meses



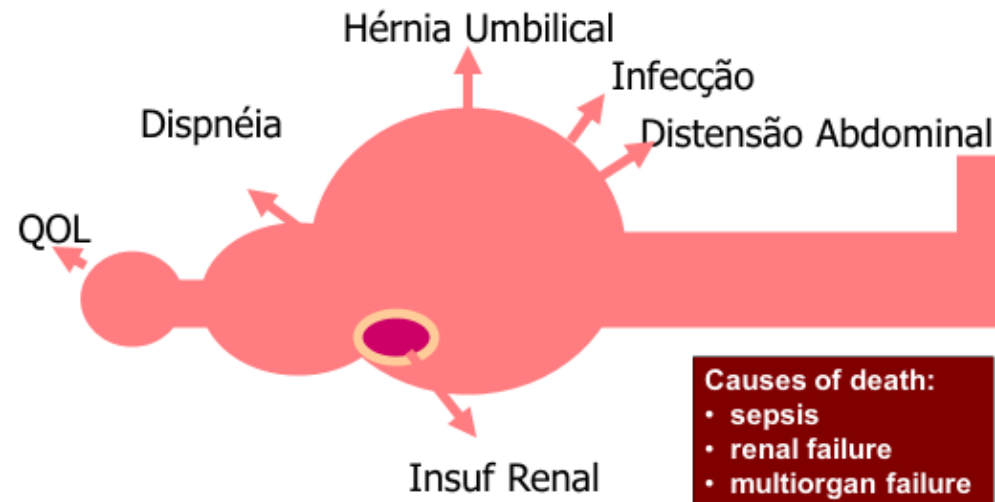
Ascite x perfusão renal

Autorregulação renal no cirrótico

(fluxo renal inversamente proporcional a pressão portal e adrenalina)



Efeito da Ascite sobre o Paciente



ASCITE GRAU 3

TRATAMENTO



ASCITE GRAU 3 TRATAMIENTO

	Paracentese (n = 58)	Diurético (n = 59)	p
Patients with complications	10	36	<0.001
Hyponatremia	3	18	<0.001
Encephalopathy	6	17	<0.002
Renal impairment	2	16	<0.001
Hyperkalemia	1	7	NS
GI bleeding	2	6	NS
Peritonitis	0	4	NS
Bacteremia	2	0	NS
Others	0	4 ^a	NS

Tratamento

Síndrome de disfunção circulatória pós paracentese (*paracentesis induced circulatory disfunction – PICD*)

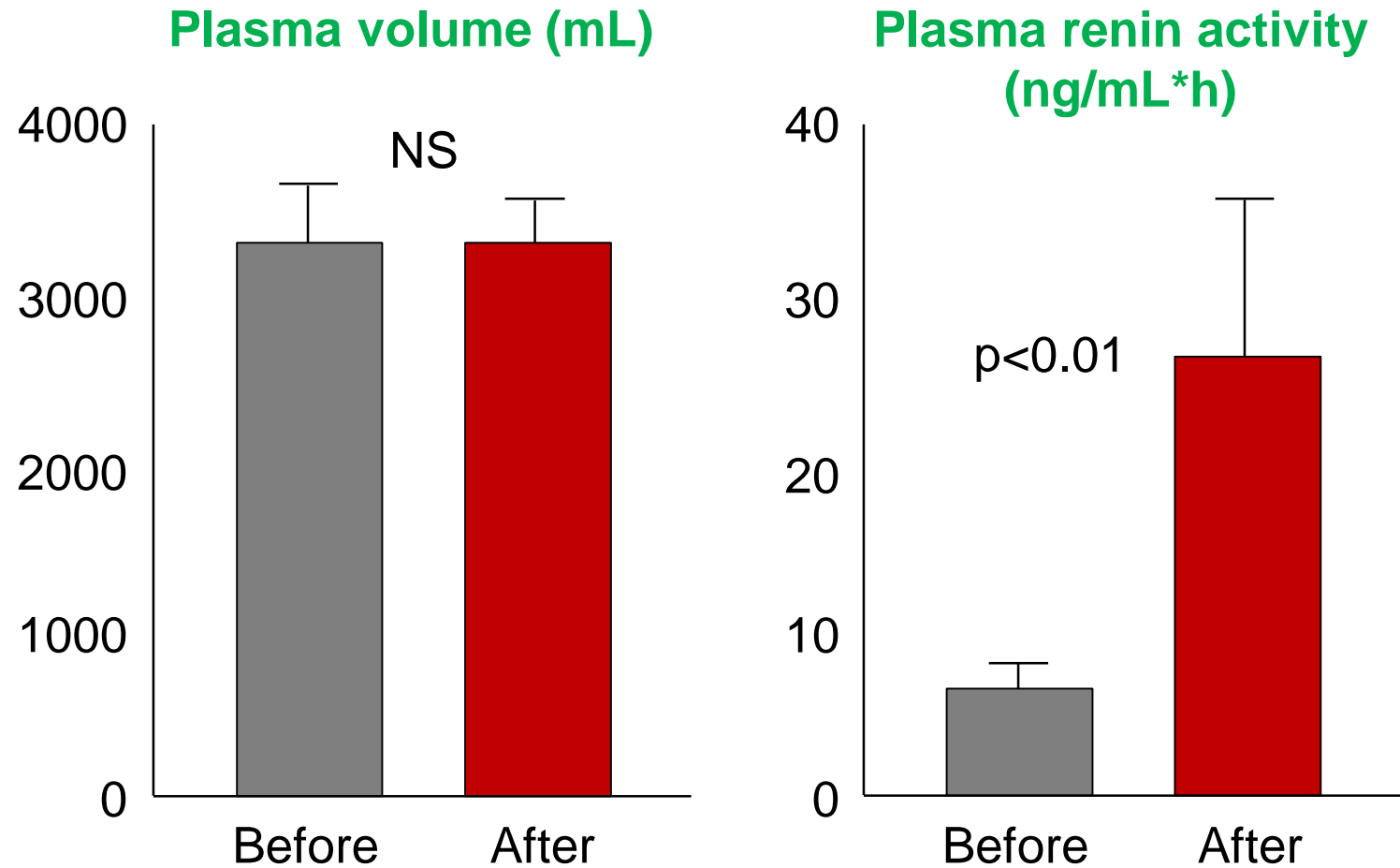
Definição: aumento na atividade de renina plasmática >50% em relação ao valor pre-tratamento, com valor final (6º dia pós paracenteses) > 4 ng/ml/h.

Incidência: 27-71%

variável segundo o volume de líquido retirado e tipo de expansão plasmática utilizada.

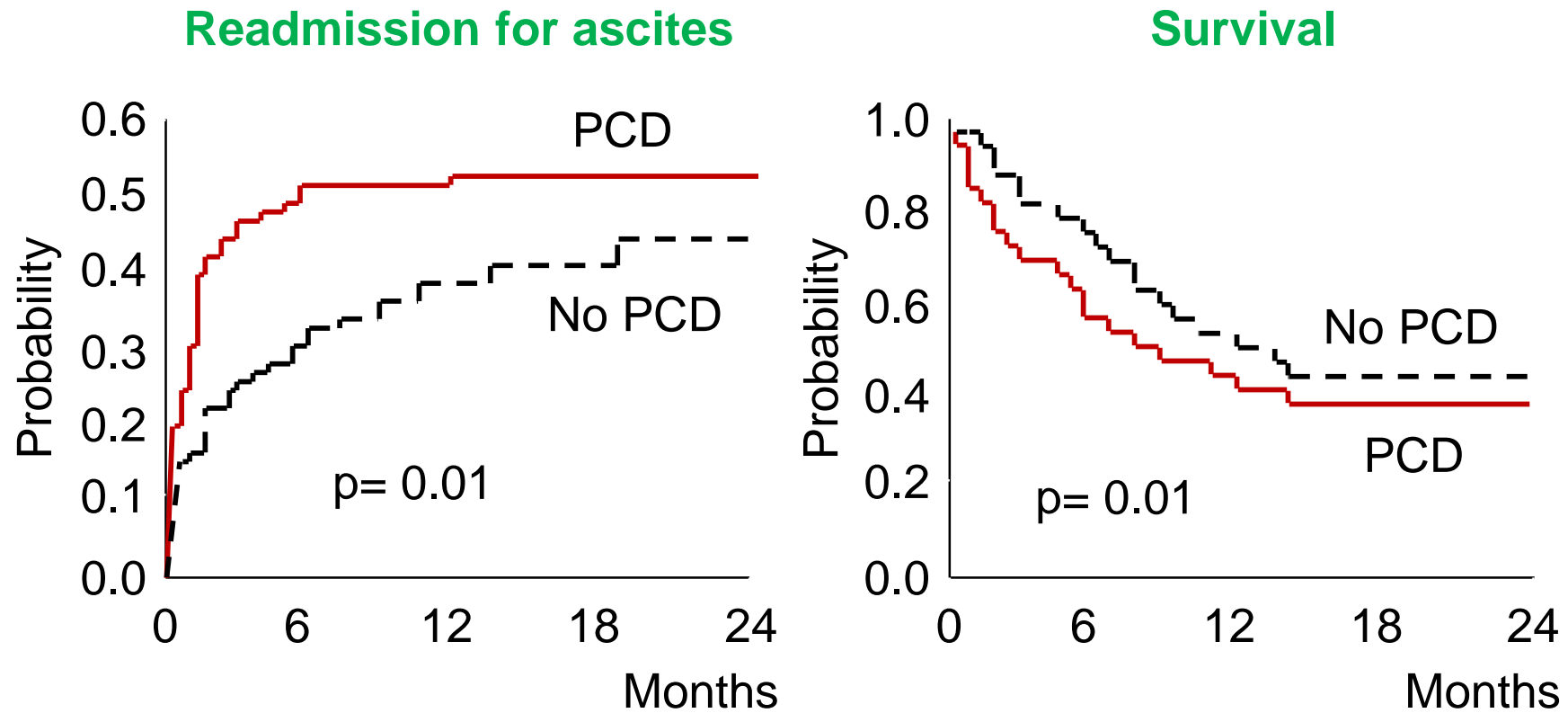
PARACENTESIS-INDUCED CIRCULATORY DYSFUNCTION

Effects on plasma volume and renin-angiotensin system



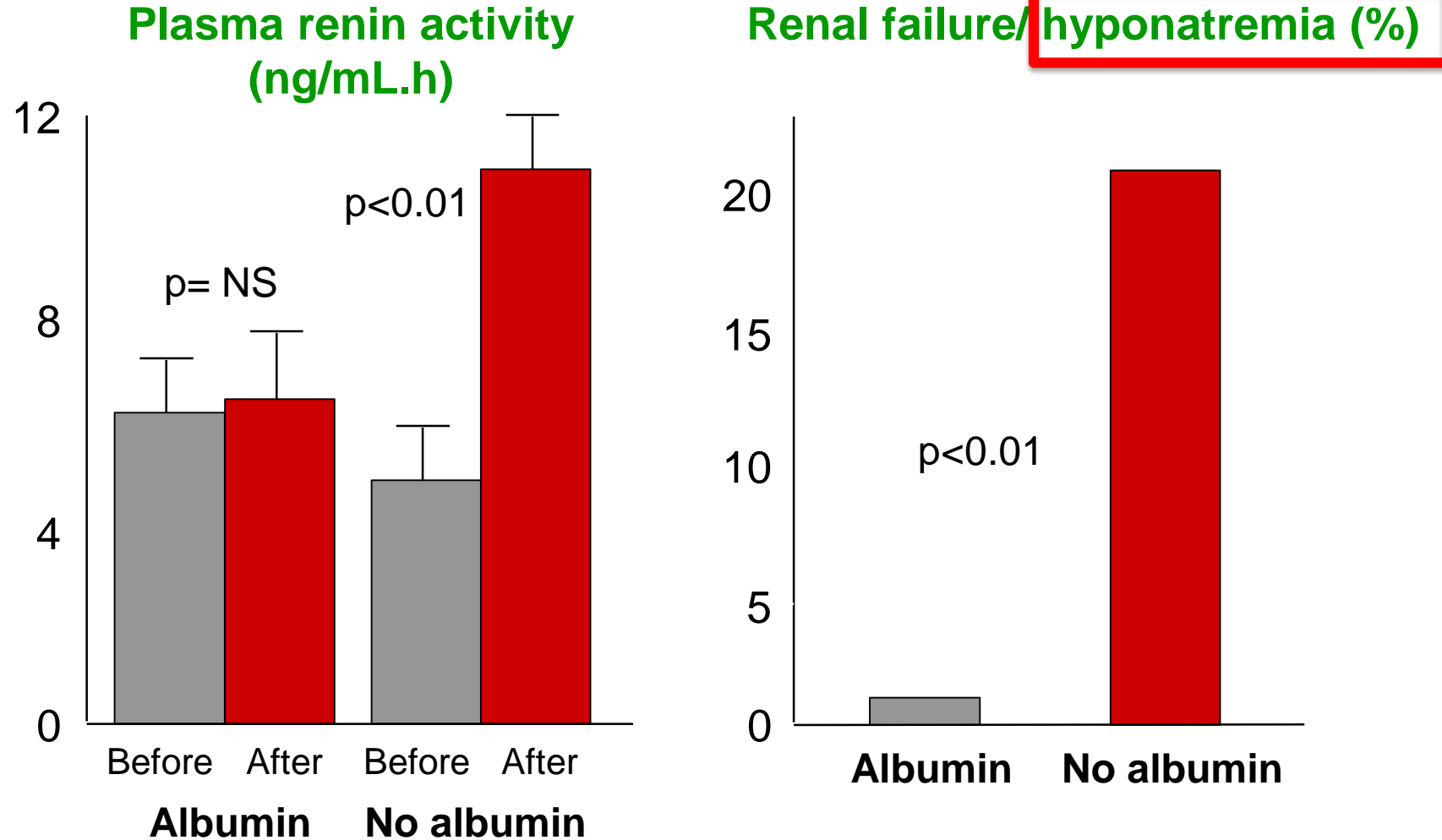
PARACENTESIS-INDUCED CIRCULATORY DYSFUNCTION

Effects on ascites reformation and survival

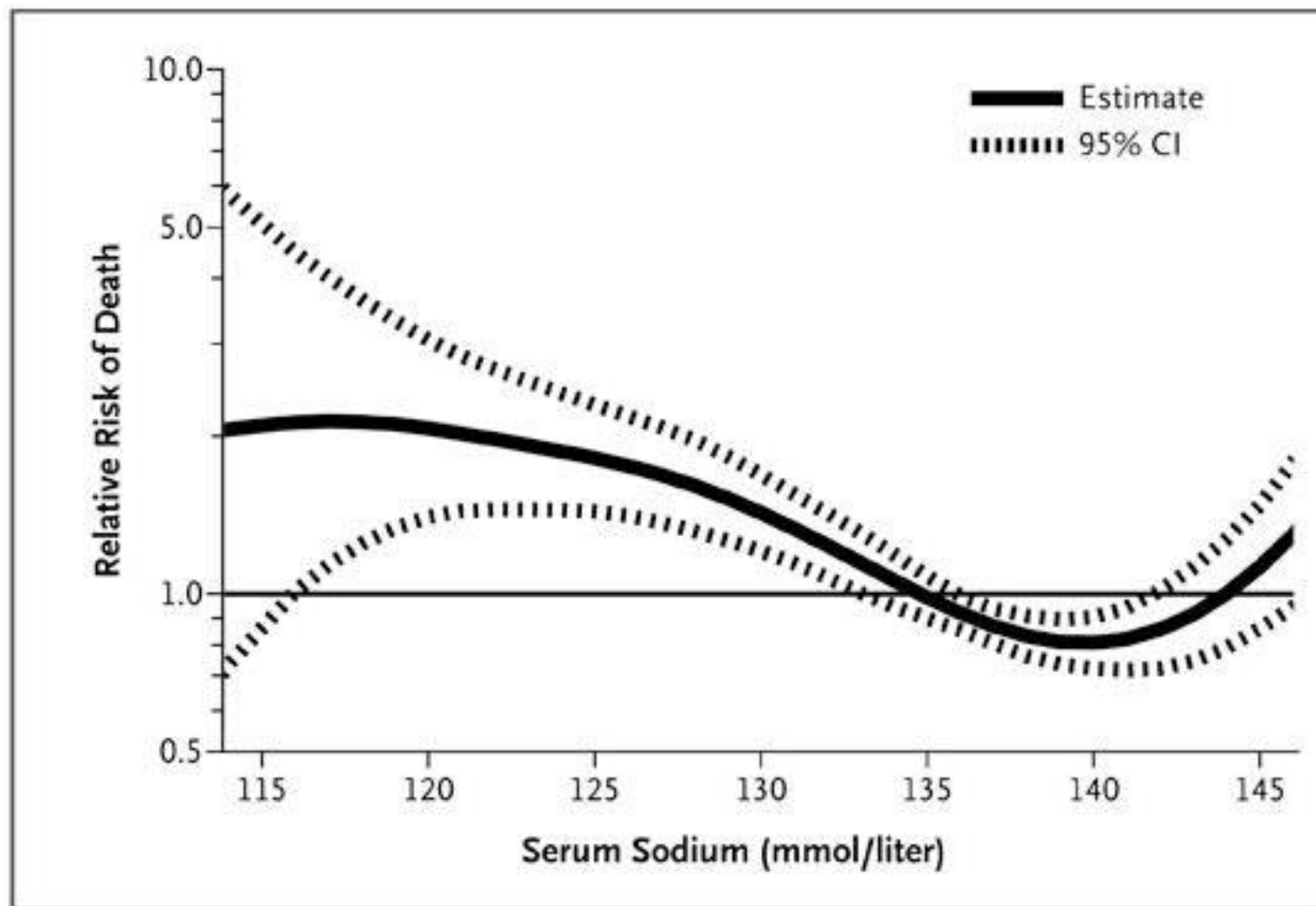


PARACENTESIS-INDUCED CIRCULATORY DYSFUNCTION

Albumin vs No albumin



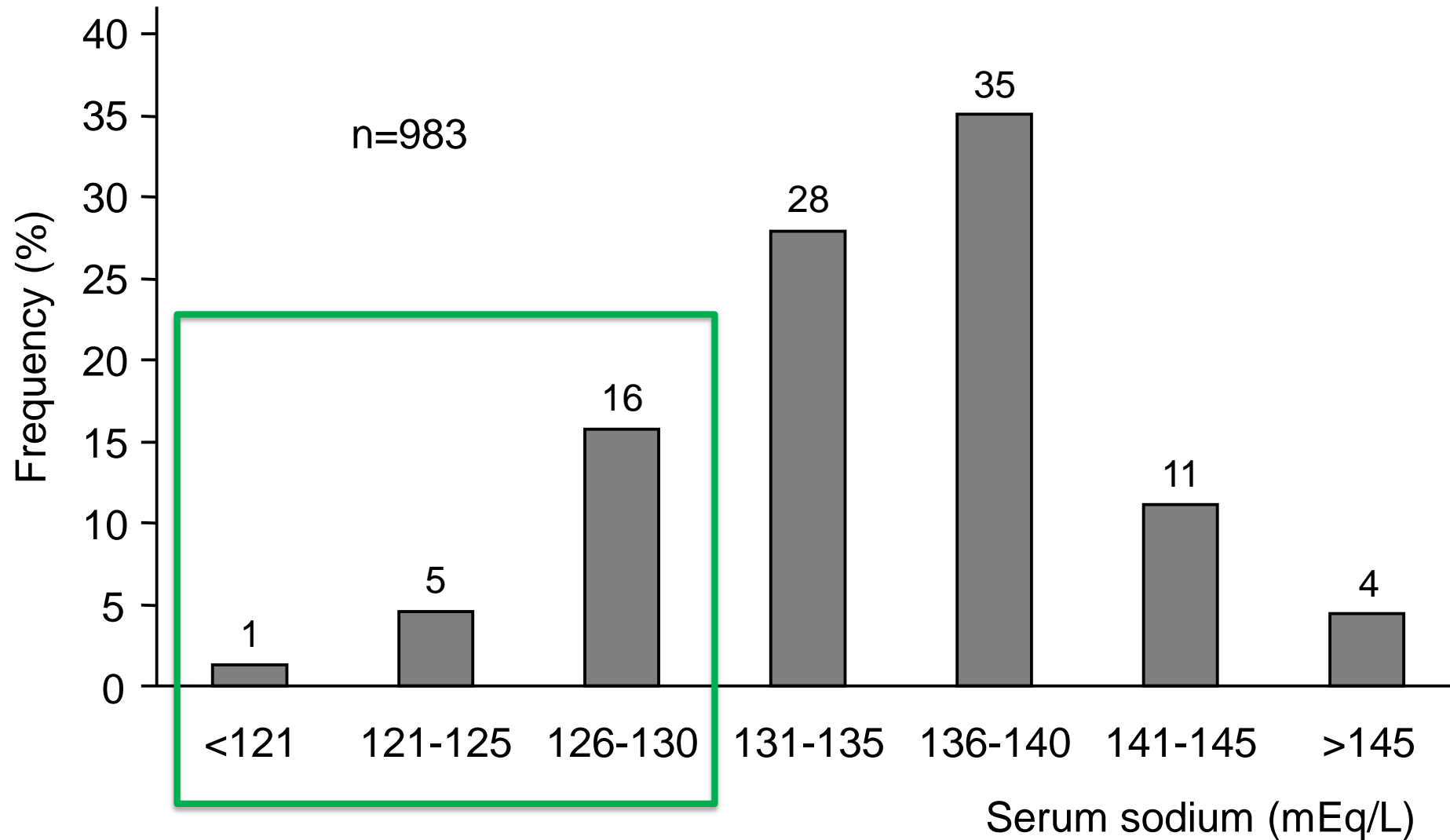
Sódio Sérico e mortalidade em pacientes cirróticos



Kim WR et al. N Engl J Med 2008;359:1018-1026.

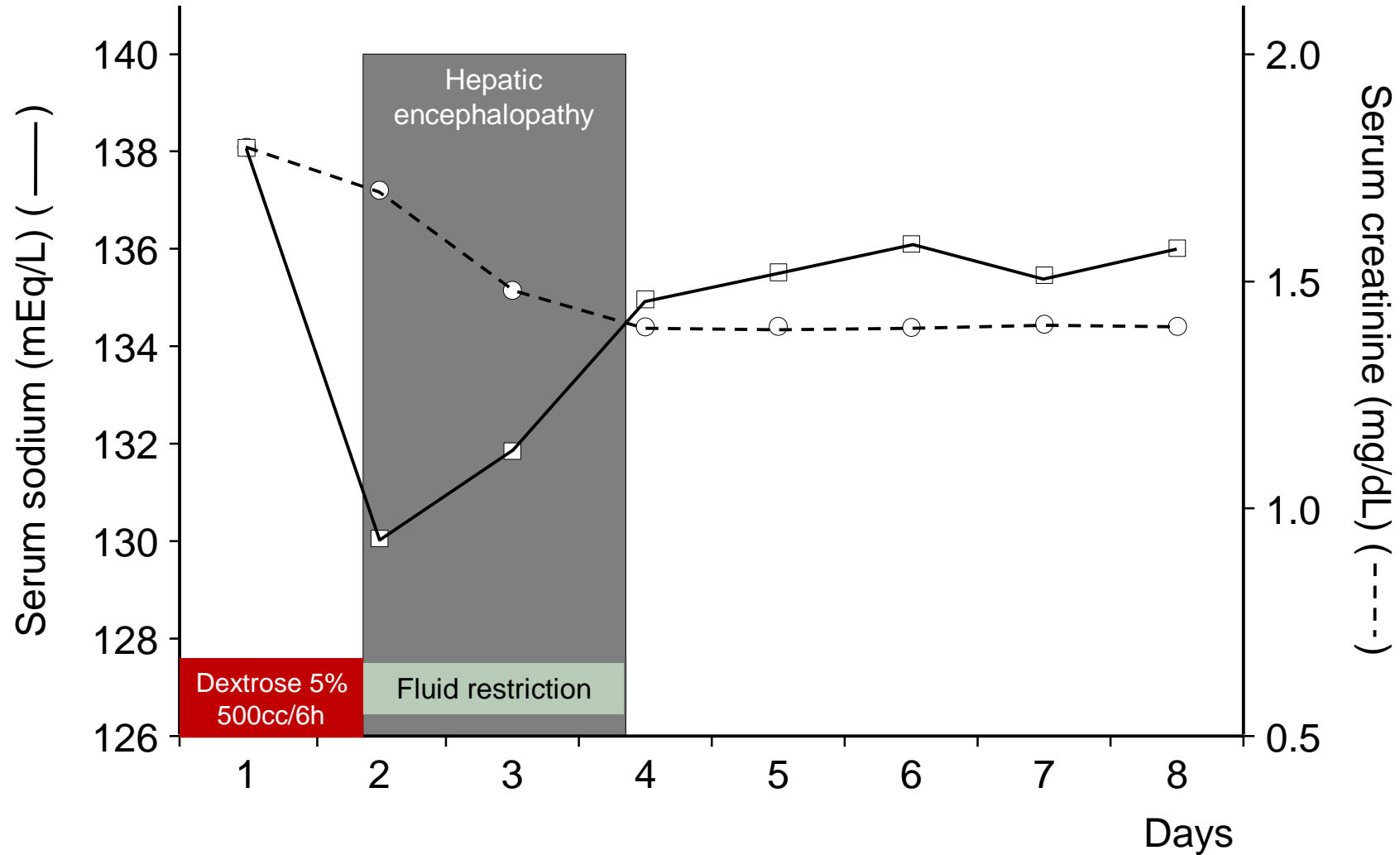
HIPONATREMIA EM CIRRÓTICOS COM ASCITE

Prevalência



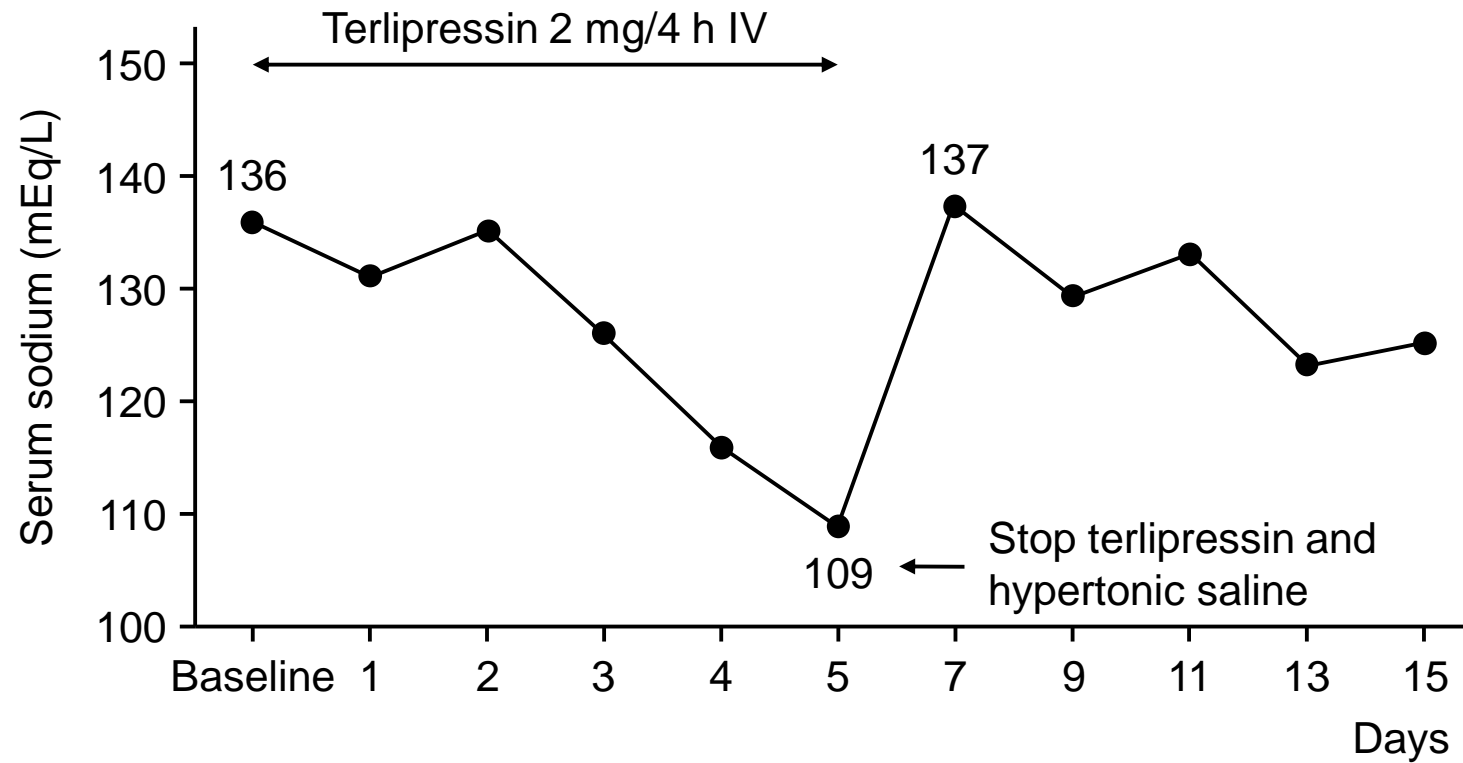
HYPERVOLEMIC HYPONATREMIA

Fluid-induced



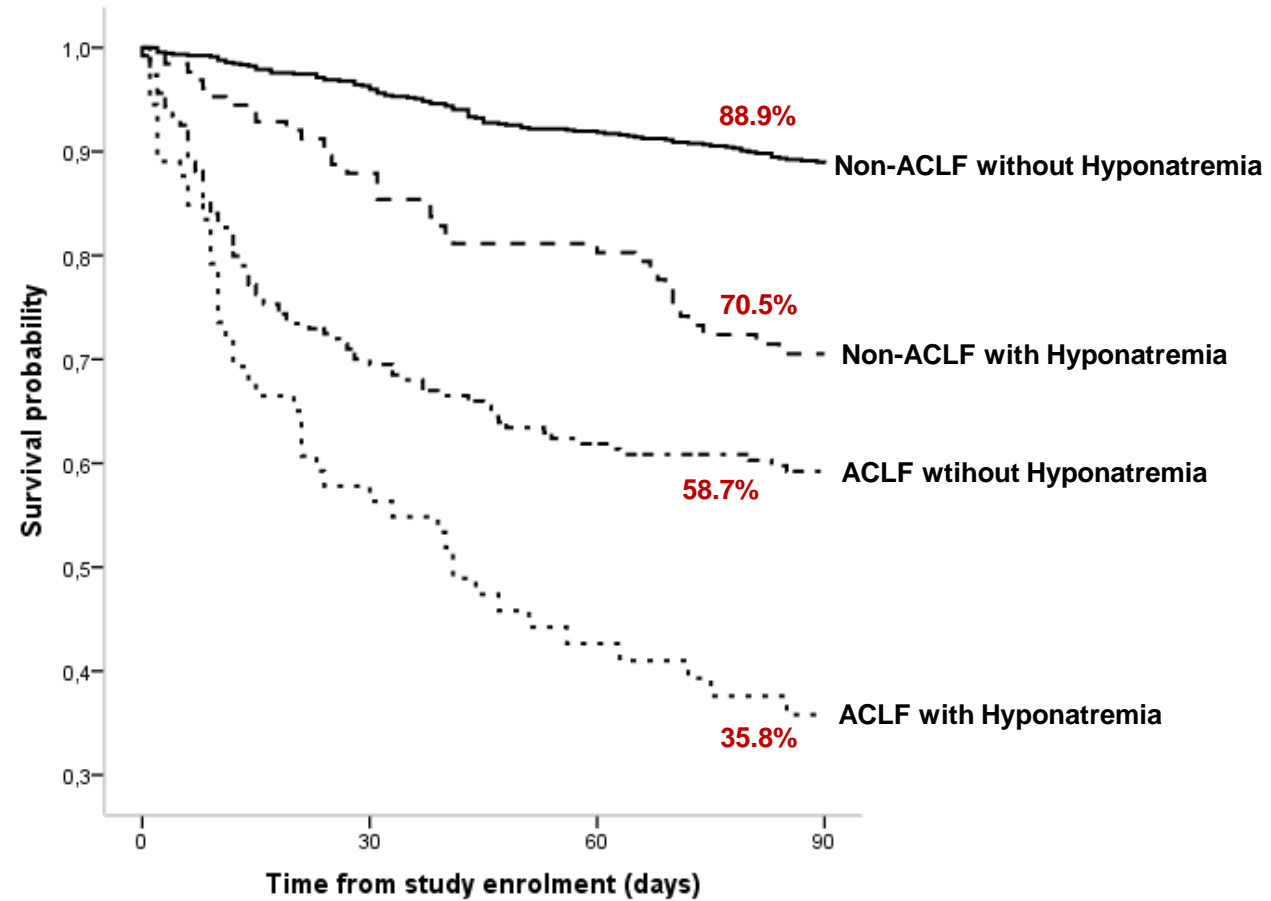
HYPERVOLEMIC HYPONATREMIA

Terlipressin-induced

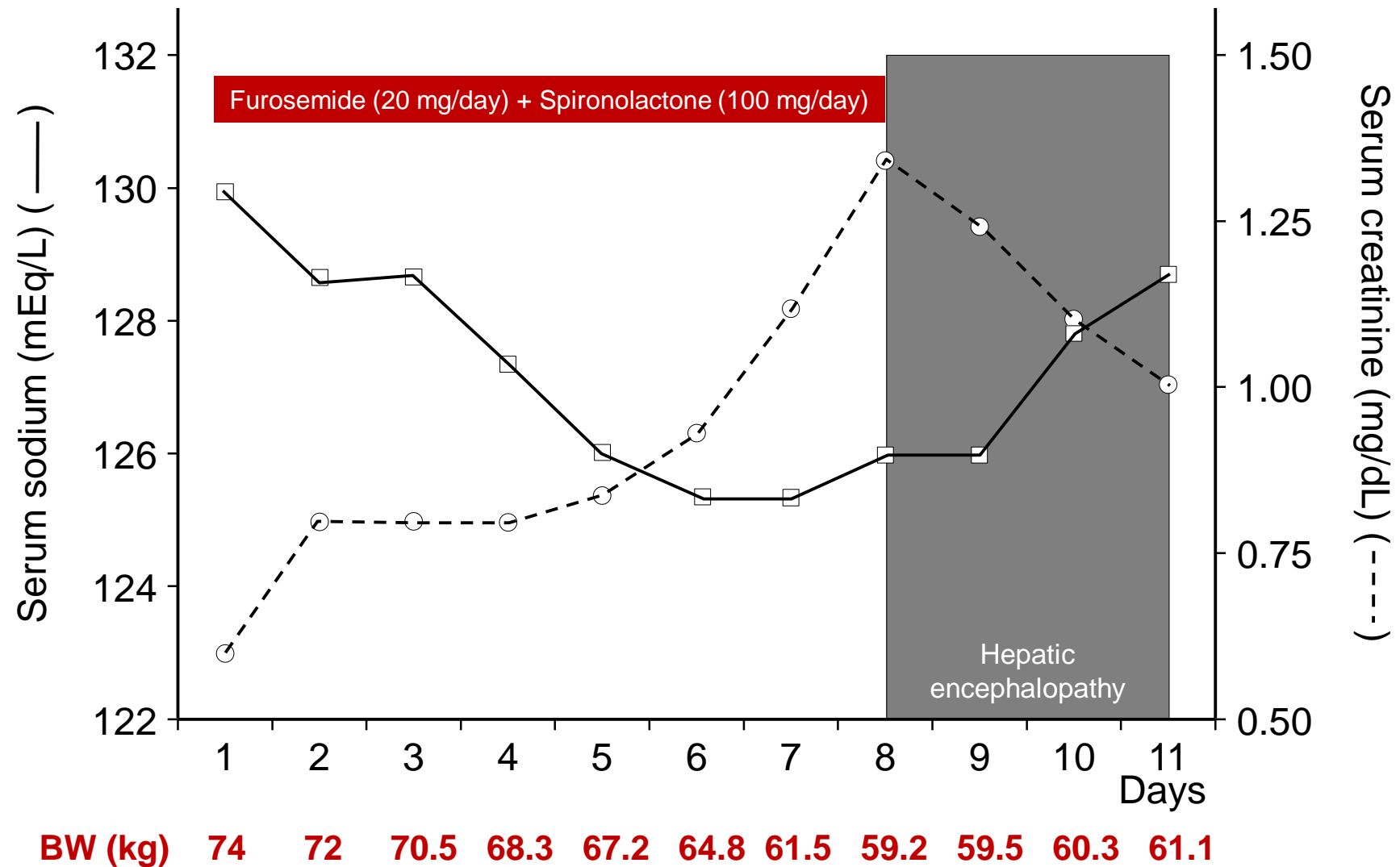


HYPONATREMIA IN CIRRHOSIS

Prognosis in patients with Acute-on-Chronic Liver Failure



HYPOVOLEMIC HYPONATREMIA DUE TO OVERDIURESIS



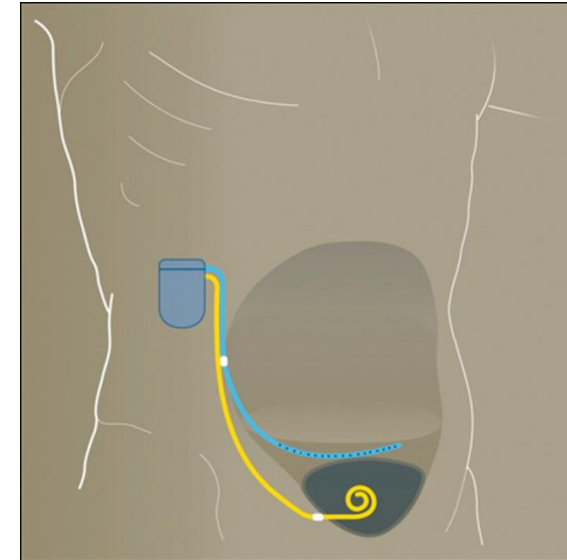
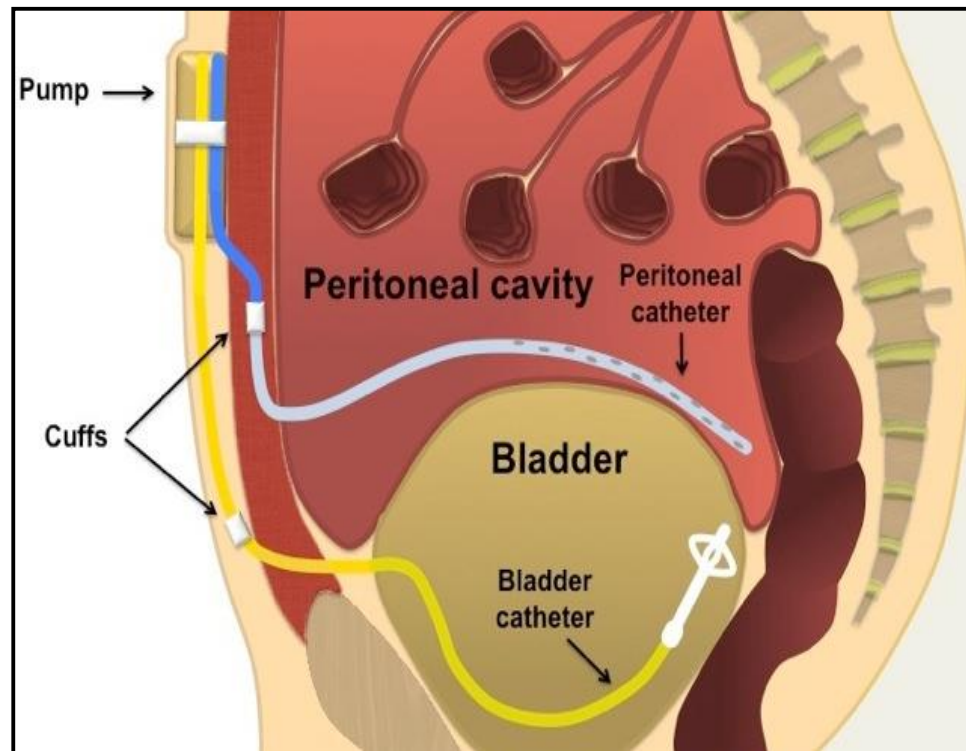
QUALITY OF IN CIRRHOSIS WITH ASCITES

Independent predictive factors

Physical component score			Mental component score		
Variable	Coefficient	p-value	Variable	Coefficient	p-value
Alcoholic cirrhosis	2.7	0.031	Serum sodium	0.21	0.01
Ascites	-1.3	0.06	Lactulose/lactitol		
Previous hepatic encephalopathy	-2.7	0.002	treatment*	-3.0	0.004
Falls within the last month	-3.6	0.01			
Serum sodium	0.3	<0.0001			
Leg edema	-3.6	<0.0001			

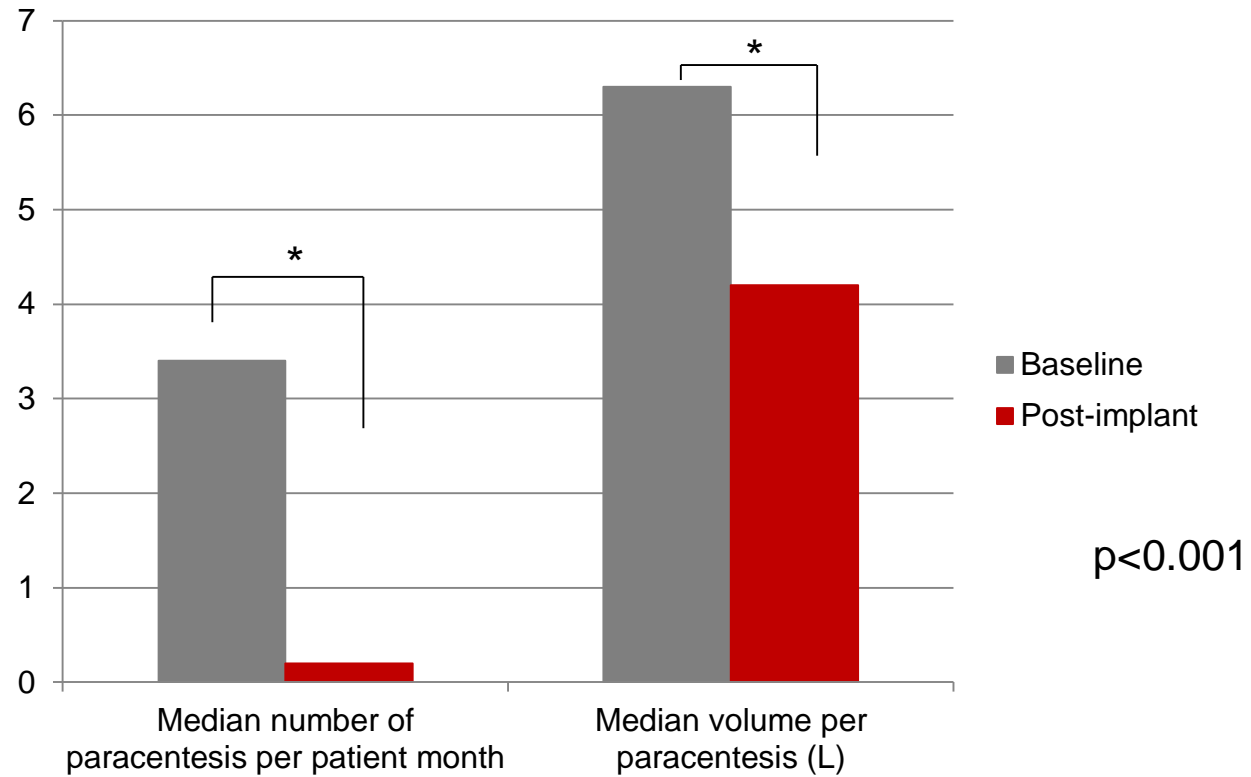
OTHER THERAPIES

AUTOMATED LOW-FLOW ASCITES (ALFA) PUMP SYSTEM



ALFAPUMP SYSTEM

Safety and efficacy study



ALFAPUMP

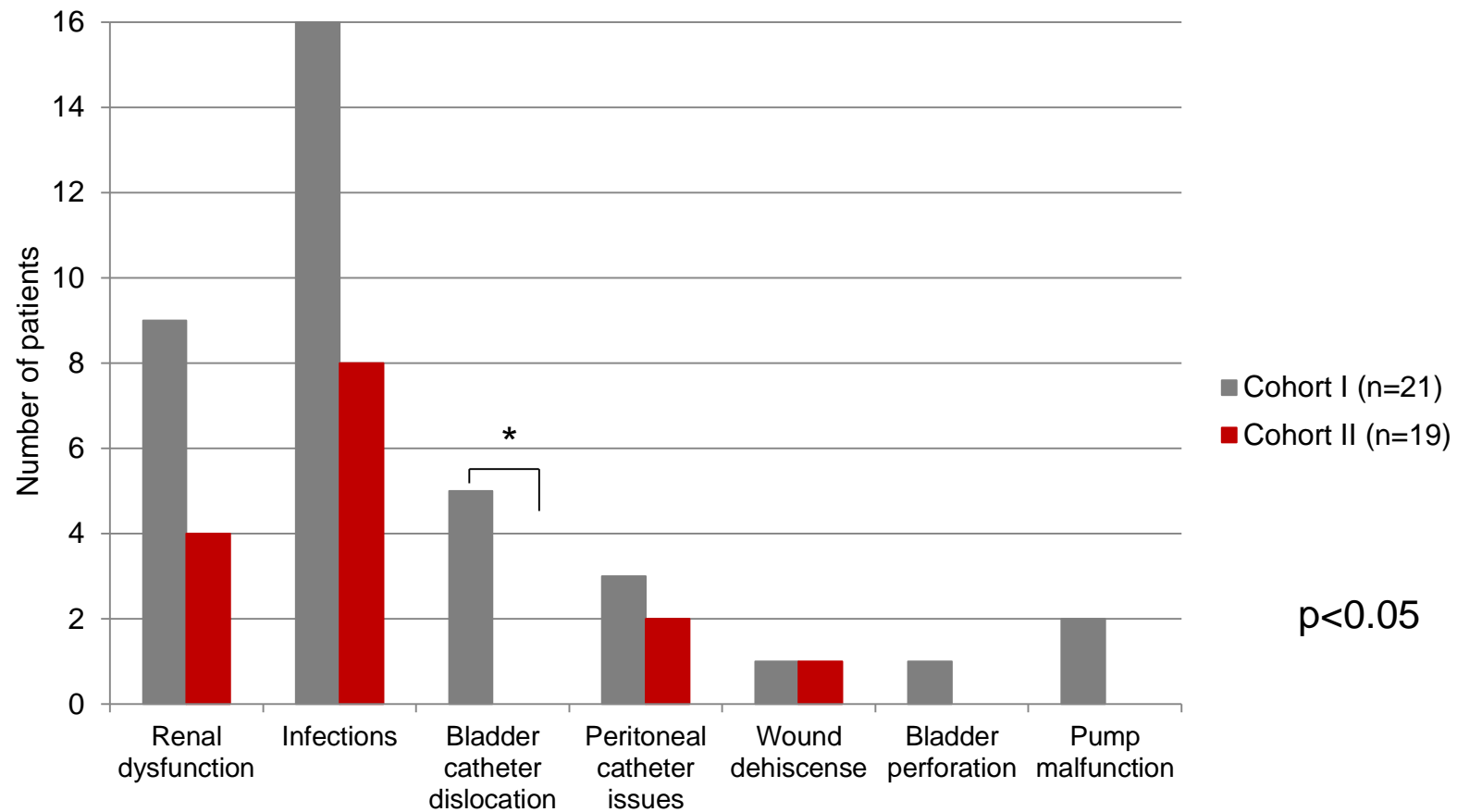
Pioneer study

Effects of Alfapump system on renal, circulatory and liver function

(number of patients)	Baseline (40)	Month 1 (37)	Month 3 (31)	Month 6 (14)
MAP (mmHg)	85.1 ± 10.3 (40)	83.7 ± 12.4 (36)	80.1 ± 20.3 (29)	86.8 ± 12.0 (14)
MELD score	12.6 ± 4.0 (40)	13.5 ± 5.2 (33)	13.2 ± 6.3 (28)	11.7 ± 4.0 (11)
Child-Pugh score	8.5 ± 1.1 (40)	9.0 ± 1.0 (34)	9.0 ± 0.8 (26)	8.6 ± 0.8 (10)
INR ⁽¹⁾	1.37 ± 0.26 (40)	1.33 ± 0.22 (35)	1.36 ± 0.29 (29)	1.24 ± 0.16 (12)
Serum bilirubin (μmol/L)	31.9 ± 16.6 (40)	30.1 ± 18.5 (34)	26.2 ± 20.3 (28)	25.3 ± 23.7 (11)
Serum albumin (g/L) ⁽²⁾	31.9 ± 5.0 (40)	30.0 ± 3.9 (36)	28.2 ± 4.6 (28)	27.2 ± 4.9 (11)
Serum sodium (mEq/L)	136 ± 5 (40)	133 ± 6 (35)	133 ± 7 (29)	134 ± 5 (12)
Serum creatinine (μmol/L)	106 ± 33 (40)	123 ± 63 (35)	127 ± 59 (29)	105 ± 27 (12)

ALFAPUMP SYSTEM

Safety and efficacy study



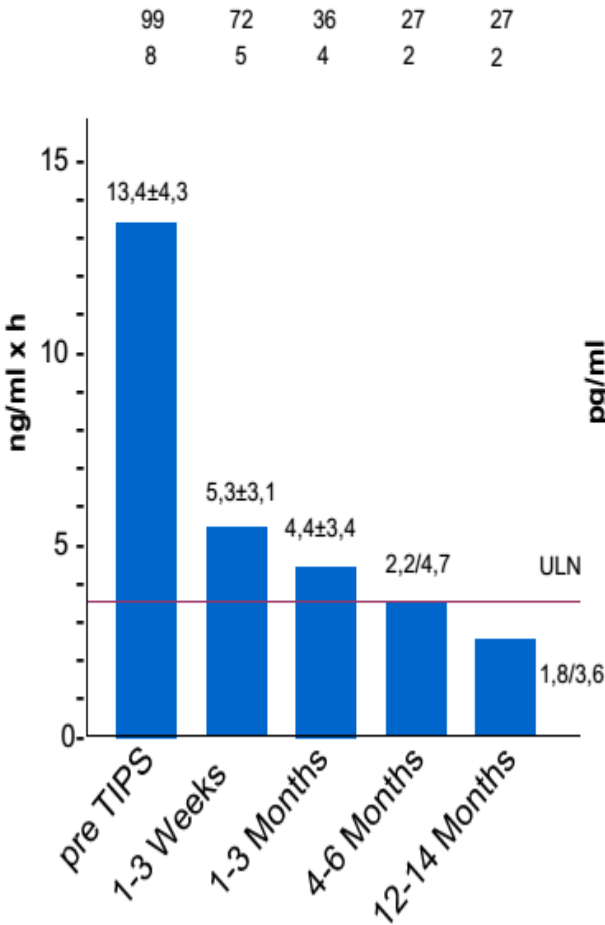
Transjugular Intrahepatic Portosystemic Shunt



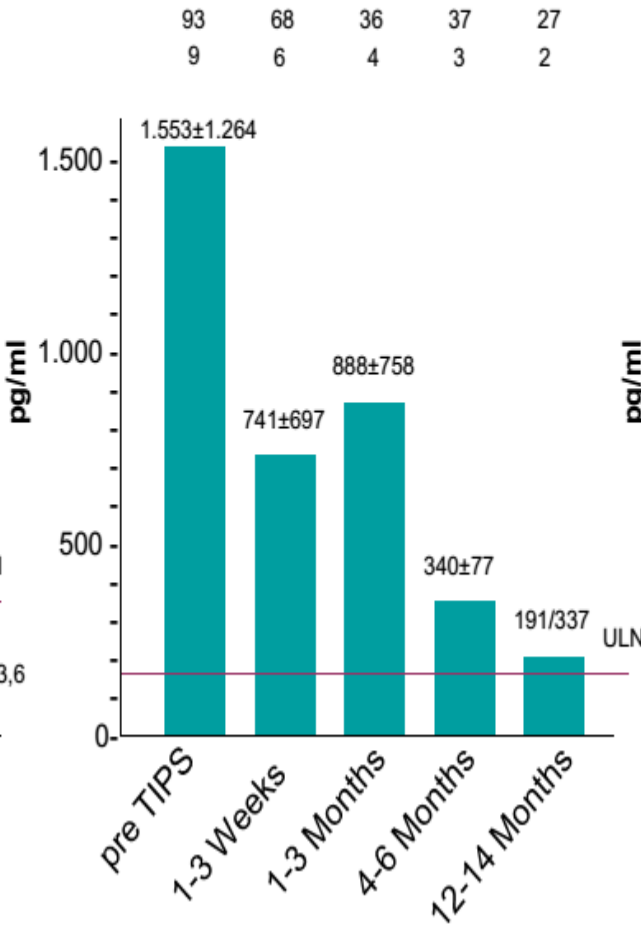
Summary of published data of plasma renin activity, aldosterone and noradrenalin concentrations before and after TIPS-implantation. Values normalized within 1 year demonstrating improvement of systemic hemodynamics.

Journal of Hepatology (2013)

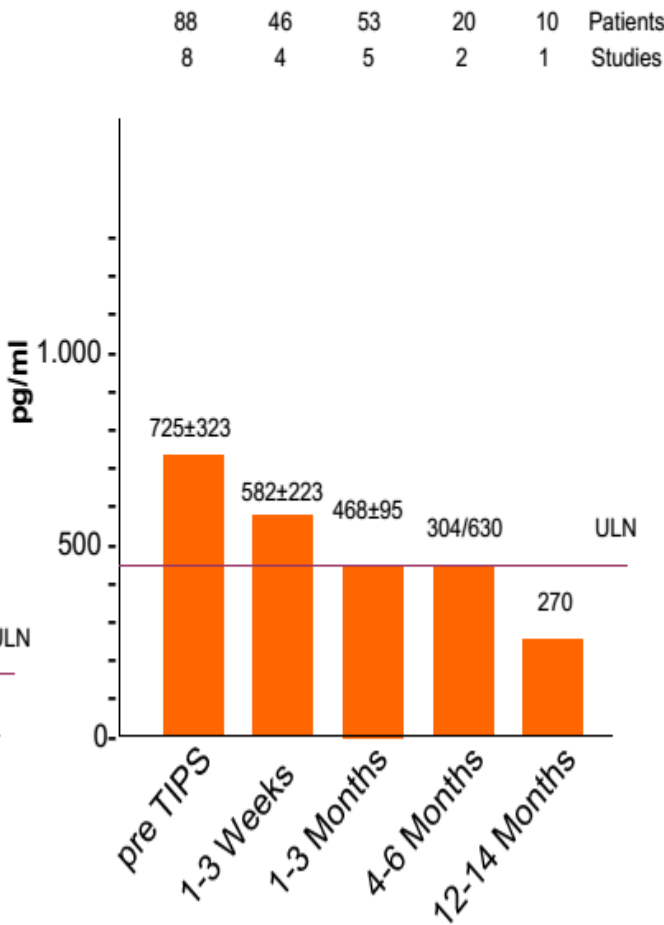
Plasma-Renin-Activity



Plasma-Aldosteron-Concentration

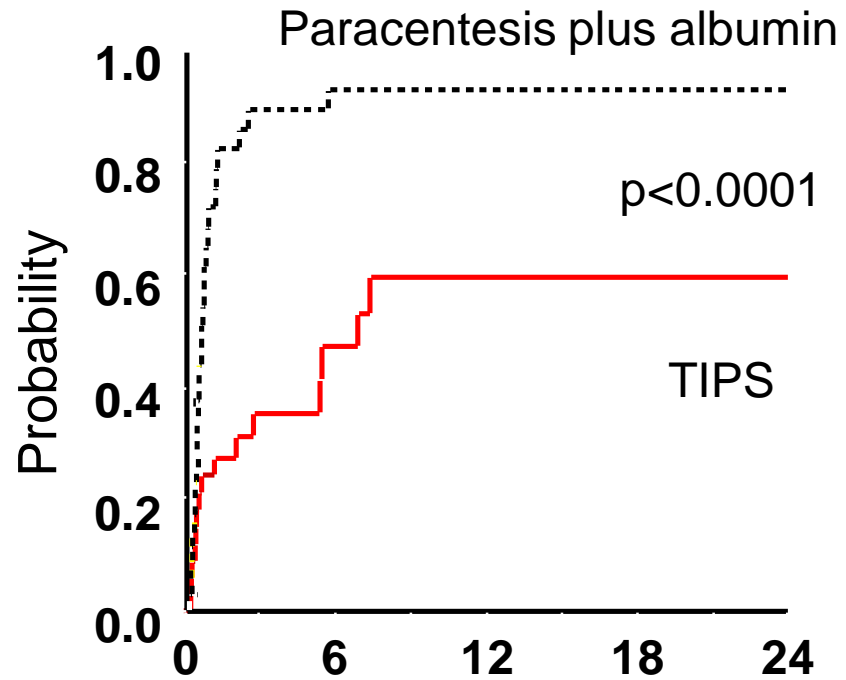


Plasma-Noradrenalin-Concentration

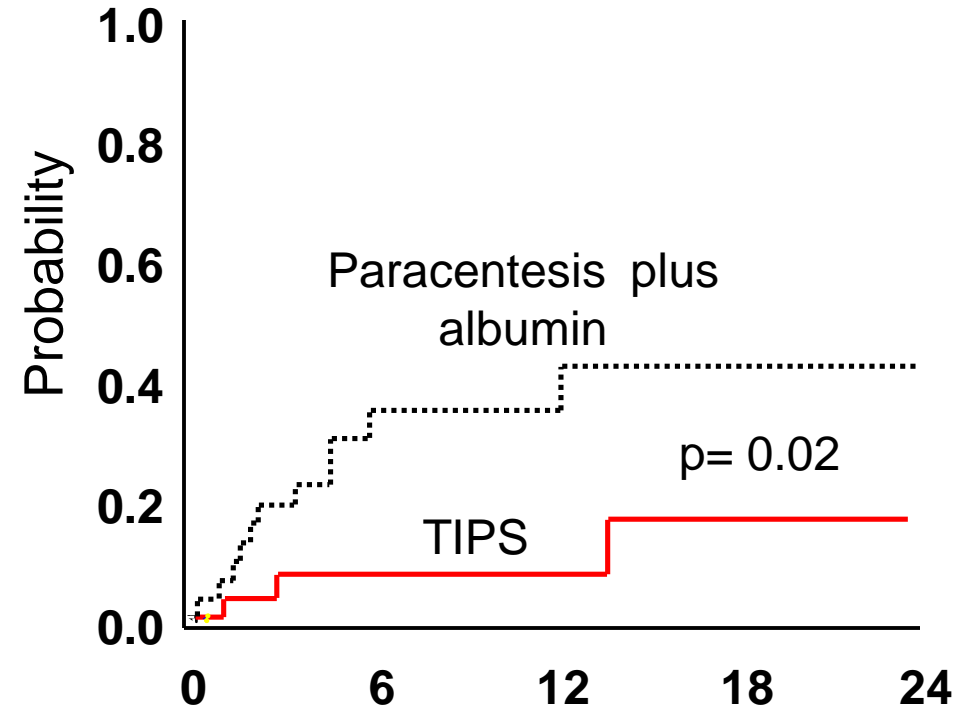


TIPS vs. PARACENTESIS FOR REFRACTORY ASCITES

Ascites recurrence



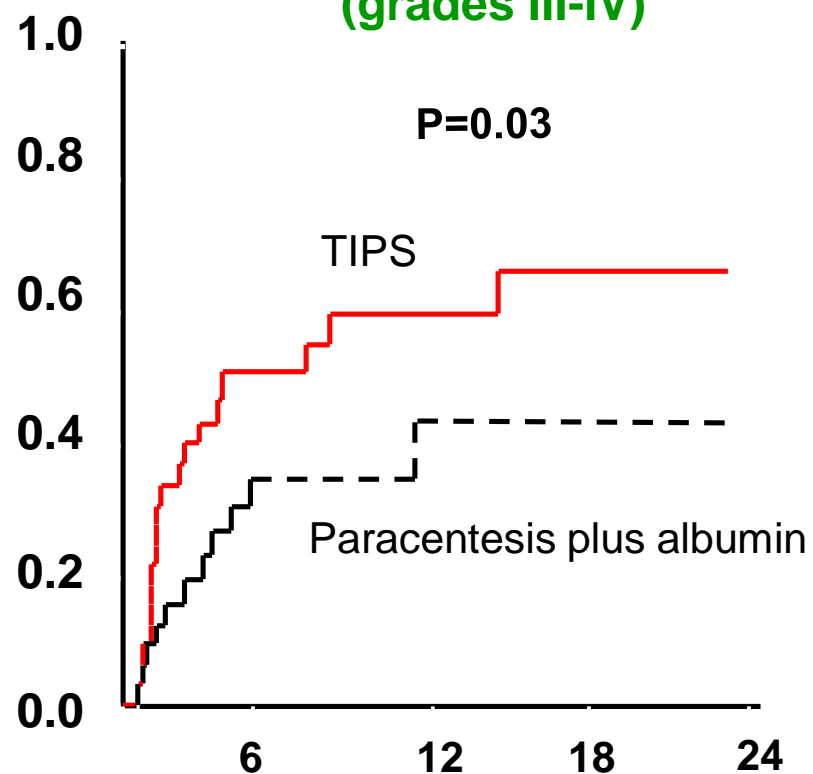
Type 1 Hepatorenal syndrome



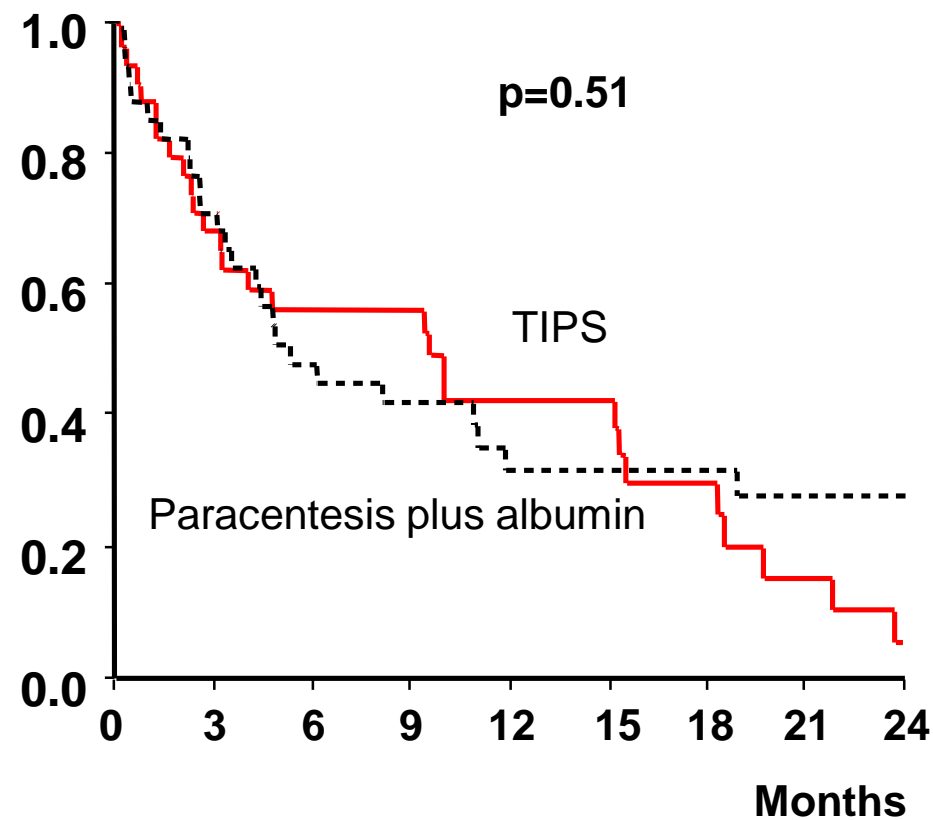
TIPS vs. PARACENTESIS FOR REFRACTORY ASCITES

Severe Hepatic Encephalopathy

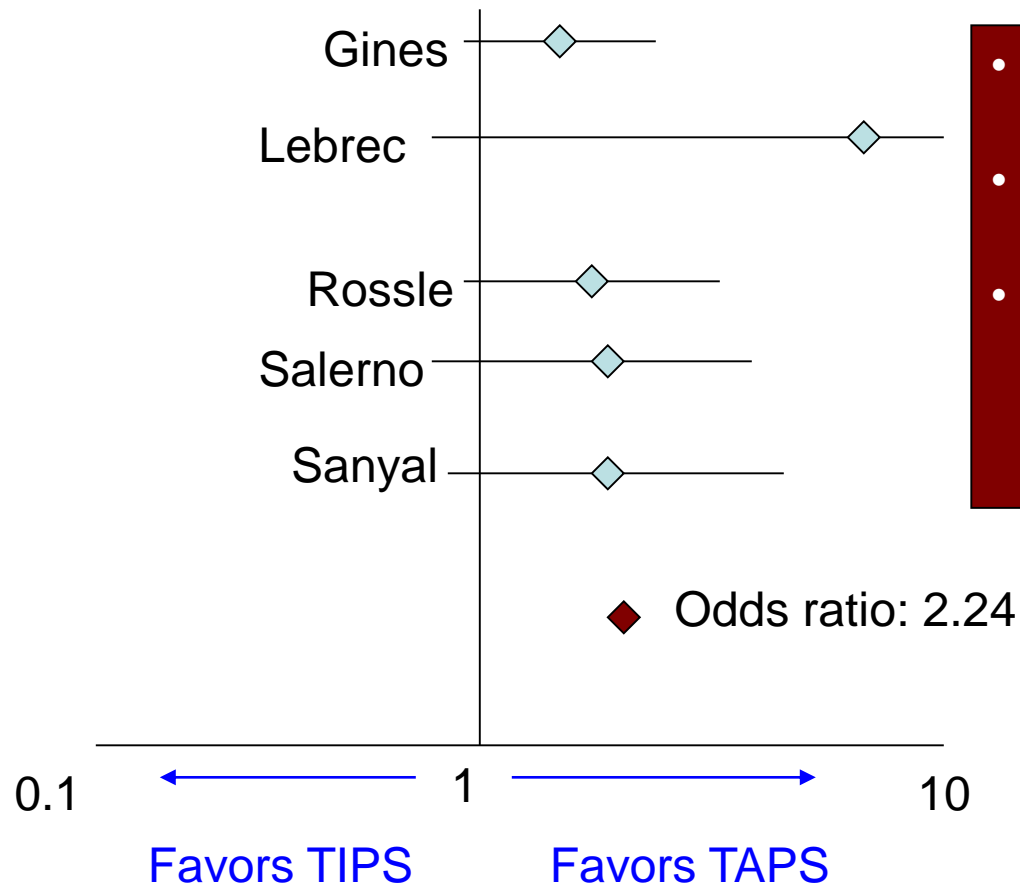
(grades III-IV)



Survival

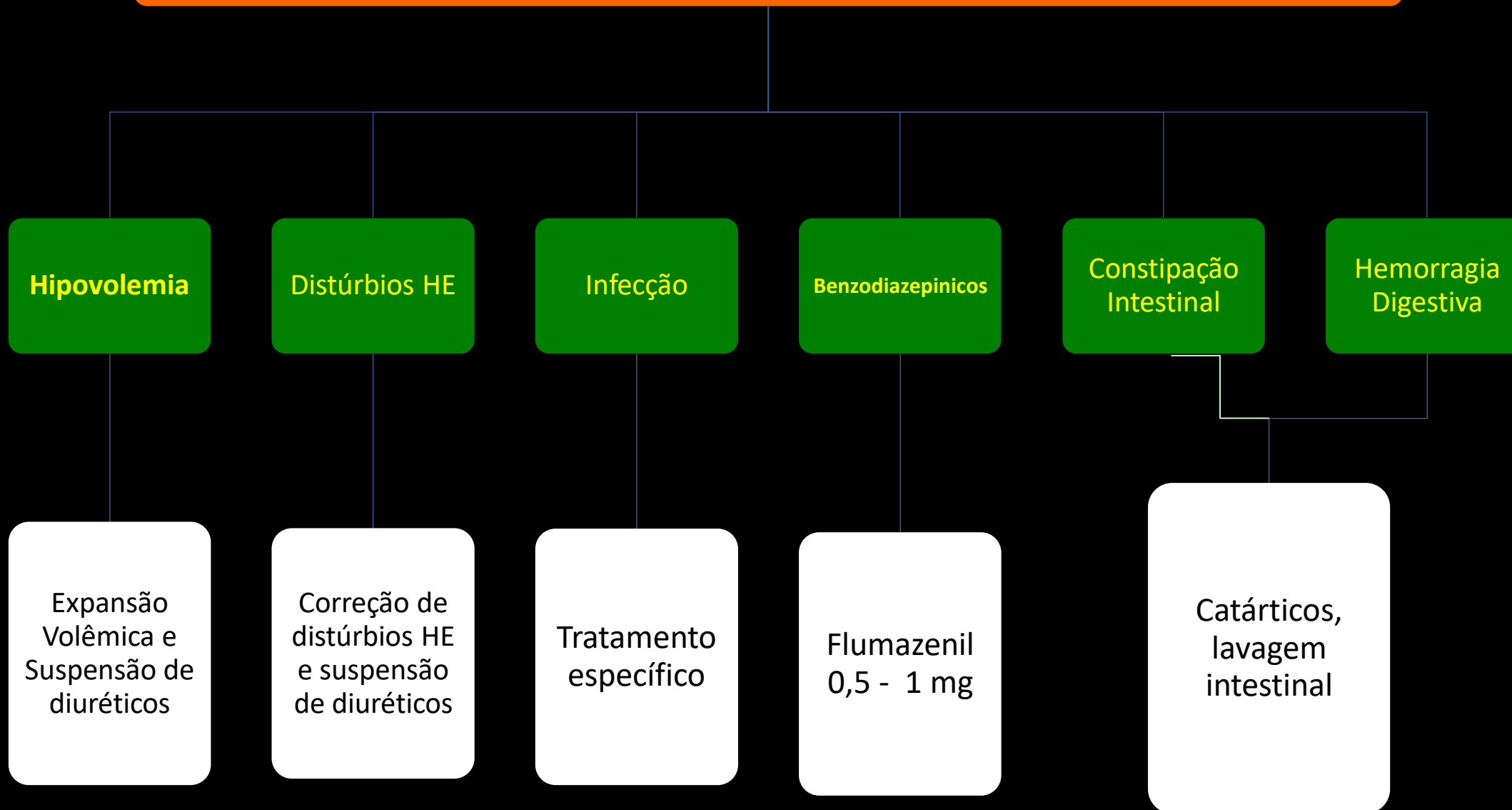


TIPS vs Paracentese (Impacto na encefalopatia)



- All studies showed similar trend
- Not powered to test for this endpoint
- Overall increased PSE after TIPS
 - Age
 - Shunt size
 - liver function

Identificação e tratamento dos fatores precipitantes



ASSOCIATION BETWEEN MALNUTRITION IN PATIENTS WITH LIVER CIRRHOSIS AND THE PRESENCE OF OVERT HEPATIC ENCEPHALOPATHY

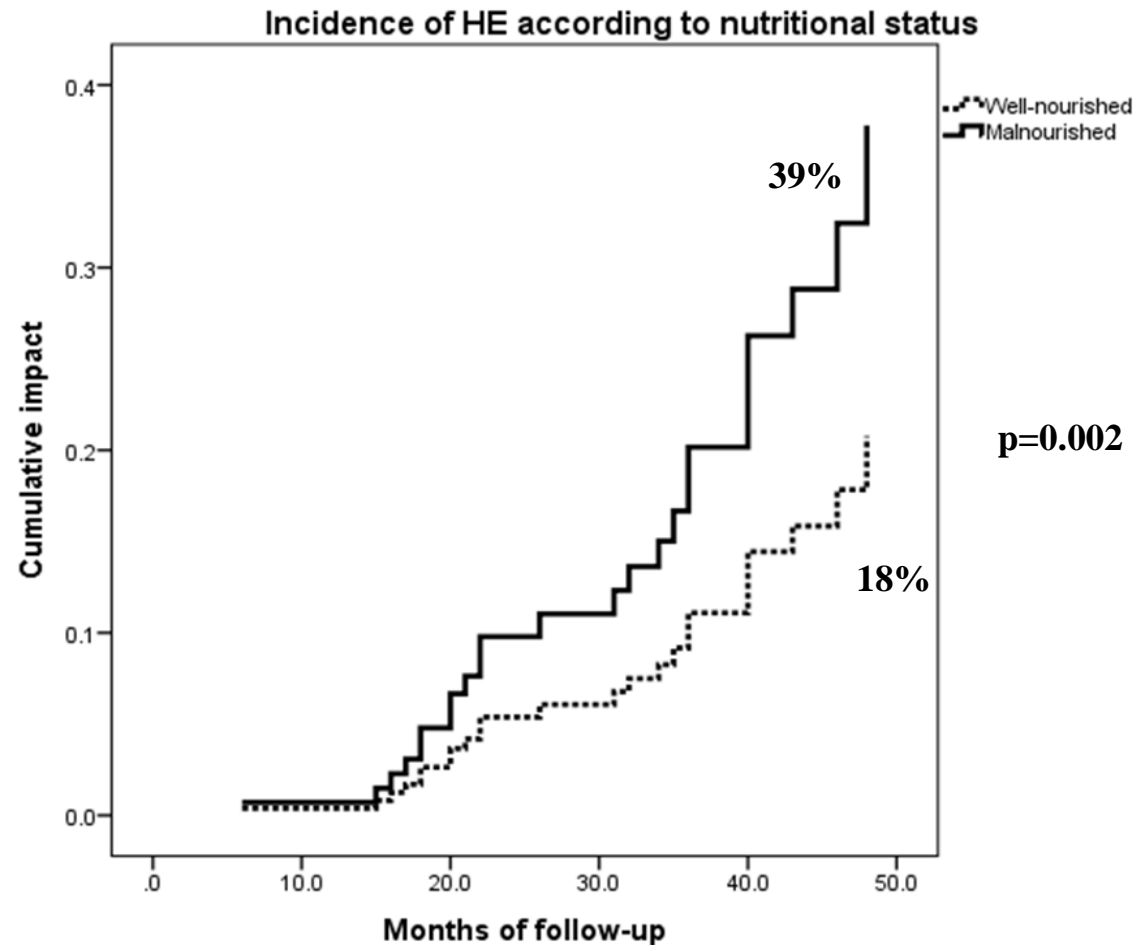
Table 1. Clinical and demographic characteristics of the study population according to the presence of HE.

	W/o HE (173)	With HE (47)	P value	Total (220)
Age (years)	53 (45-60.25)	53 (47-60)	0.505	53 (43-60)
Gender Female/male (%)	54.6/45.4	56.5/43.5	0.816	55/45
Months of follow up	40 (22-47)	35.5 (19.8-47.2)	0.361	36 (22-47)
BMI (Kg/m ²)	27.4 (24-30.5)	26.4 (21.3-30.7)	0.185	27.1 (23.4-30.3)
Child-Pugh A/B/C (%)	42.8/48/9.2	2.3/43.2/54.5	0.000	34.6/47/18.4
Child-Pugh (points)	7 (5-8)	10 (8-11)	0.000	7 (6-9)
MELD score	11 (8-14)	14 (12-17)	0.000	11 (8.3-14)
Phase angle (°)	5.2 (4.4-5.8)	4.41 (3.8-5.5)	0.001	5 (4.3-5.8)
Ammonia (µg)	64.4 (40.5-94.7)	94.3 (54.4-153.3)	0.002	70 (45-100.1)
Etiology VHC/PBC (%)	35.6/17.2	37/15.2	0.111	35.9/16.8

HE= Hepatic encephalopathy, BMI= Body mass index, VHC = Hepatitis C virus C, PBC = Primary biliary cirrhosis

Ruiz-Margáin A, Gastroenterology. 2014 Suppl 1

ASSOCIATION BETWEEN MALNUTRITION IN PATIENTS WITH LIVER CIRRHOSIS AND THE PRESENCE OF OVERT HEPATIC ENCEPHALOPATHY



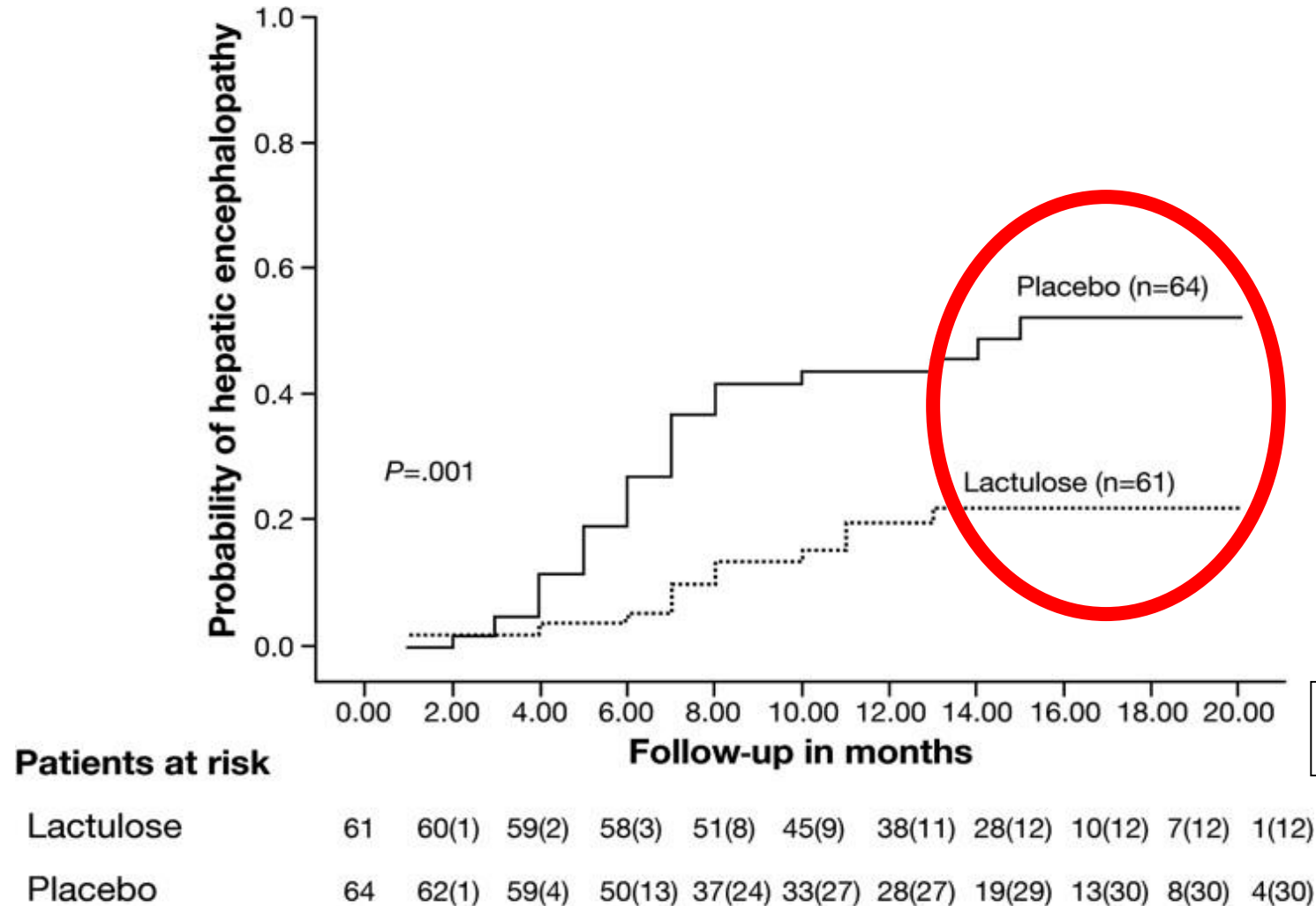
- ✓ Inibição da produção de amônia:
- ✓ Dissacarídeos não-absorvíveis: lactulose e lactitol
 - ✓ Já bastante estudados, mas vários ensaios clínicos com pequenas casuísticas

Table 1 Comparison of Non-absorbable Disaccharides and Placebo or No Treatment for Hepatic Encephalopathy.

Trial	Study design	Patients	No	Treatment	Assessment	Efficacy
Simmons et al ¹³	Parallel	AHE + CHE	26	Lactulose/glucose	Clinical grading, ammonia, stool production	Lactulose = glucose
Uribe et al ¹⁴	Parallel	AHE	15	Lactulose enema	Mortality, clinical grading	Lactulose > placebo
Lanthier et al ¹⁵	Crossover	CHE	5	6 months	Clinical examination, psychometric tests, ammonia levels, EEG, cerebral blood flow	Lactulose = lactitol
Heredia et al ¹⁶	Parallel	AHE	40	5 days	Mortality, clinical grading, PSE grade, adverse events	Lactulose = lactitol
Riggio et al ¹⁷	Parallel	CHE + MHE	31	6 months	PSE index, new episodes of HE, adverse events	Lactulose = lactitol

AHE: acute hepatic encephalopathy; CHE: Chronic hepatic encephalopathy; MHE: Minimal hepatic encephalopathy; EEG: Electroencephalography.

Treatment of Overt HE: Lactulose



Sharma et al
Gastro 2009

Predictors of Failed Response to Lactulose

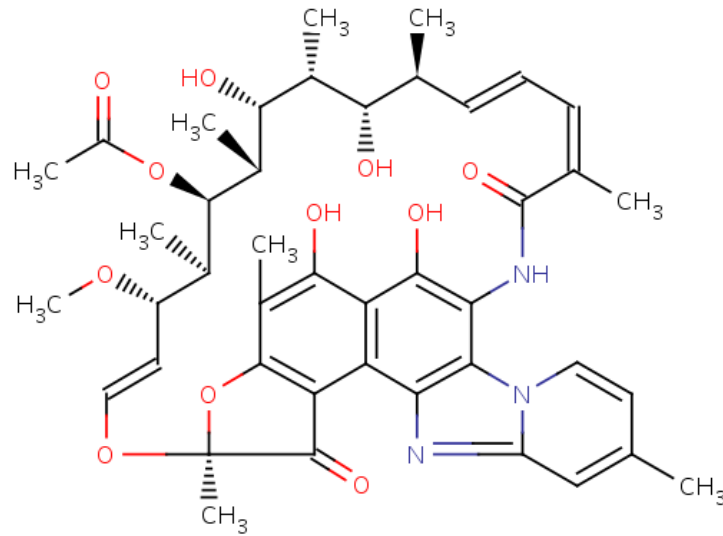
- 231 patients with liver cirrhosis and HE treated with lactulose dosed so patients had 2 to 3 semi-formed stools per day
- 51 patients (22%) did not respond to lactulose therapy

Baseline factor predicting lack of response in multivariate analysis*	<i>P</i> value
Leucocyte count $\geq 7350/\text{mm}^3$	0.04
Serum sodium ≤ 130.5 mmol/L	0.006
MELD score ≥ 21	0.006
Mean arterial pressure < 79.0 mmHg	0.01
Hepatocellular carcinoma	0.002

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HE = hepatic encephalopathy; Hg = mercury;
MELD = model for end-stage liver disease.

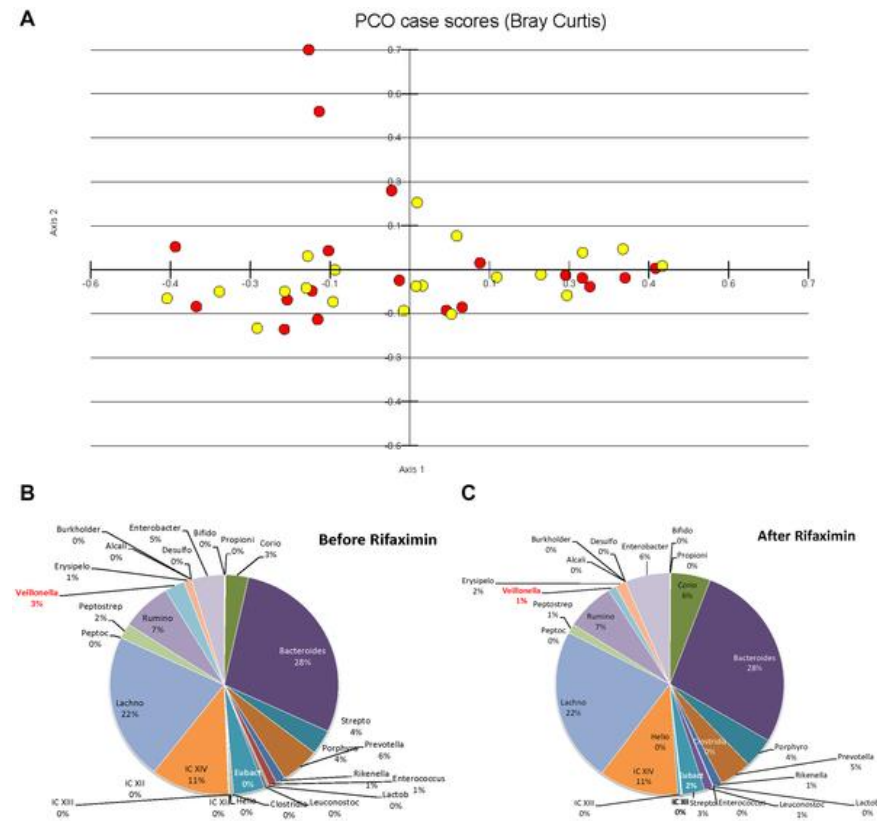
*Sharma et al. *Eur J Gastroenterol Hepatol.* 2010;22:526-531.

Rifaximin



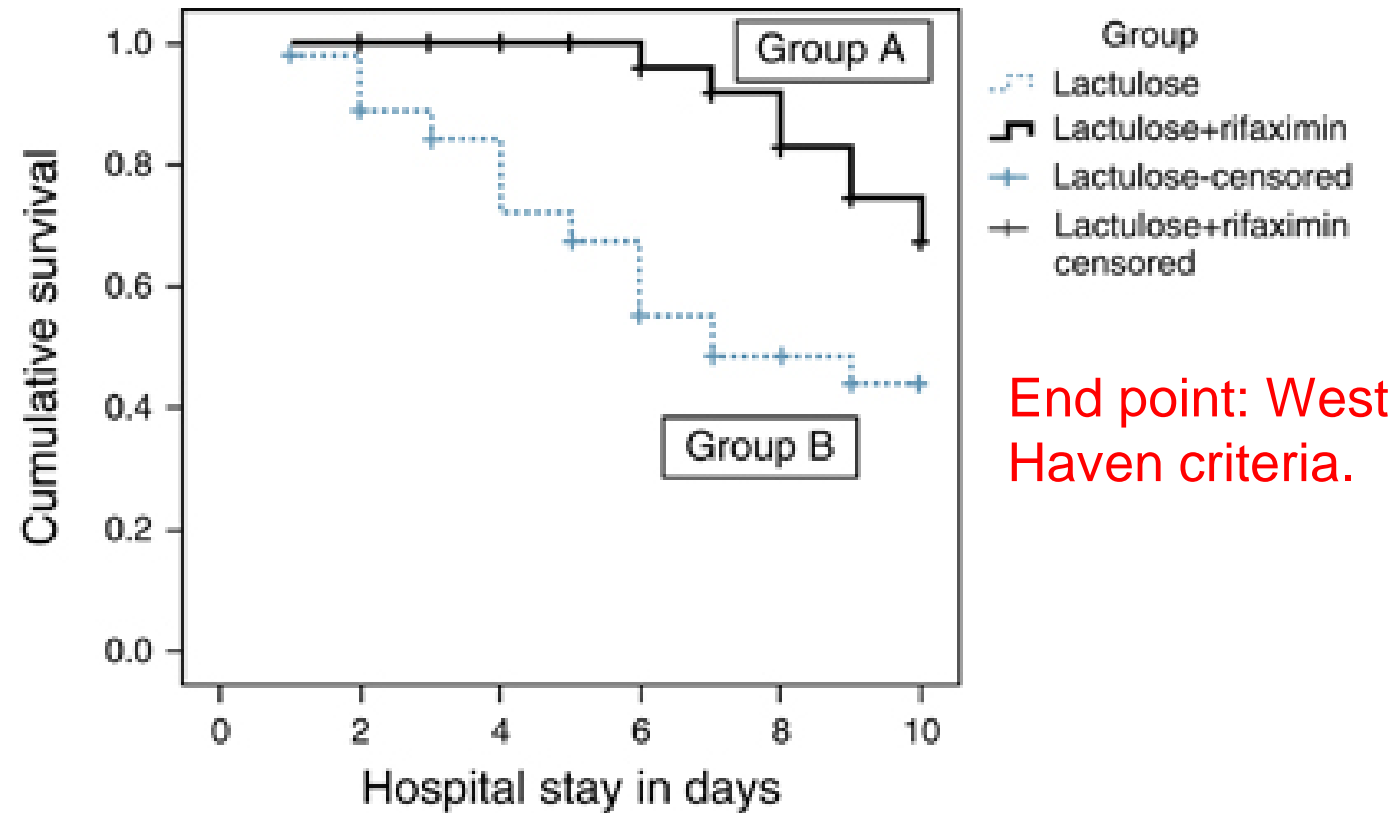
- nonabsorbable antibiotic
- inhibits bacterial RNA synthesis
- PXR inhibitor
- inhibits NFkb
- 97% recovery in stool
- half-life 6 hrs

Rifaximin does not produce major changes in gut microbial composition



Bajaj et al, 2013, PLoS ONE, 8(4) e60042

Inpatient study of rifaximin vs. lactulose in overt HE



Sharma et al Am J Gastroenterol 2013

Rifaximin Significantly Reduced the Risk of Complications of Cirrhosis

Complication	Patients, %		<i>P</i> value
	Rifaximin 1200 mg/d (n=23)	Control (n=46)	
Variceal bleeding	35	60	0.01
HE	32	47	0.03
SBP	6	46	0.03
HRS	5	51	0.04

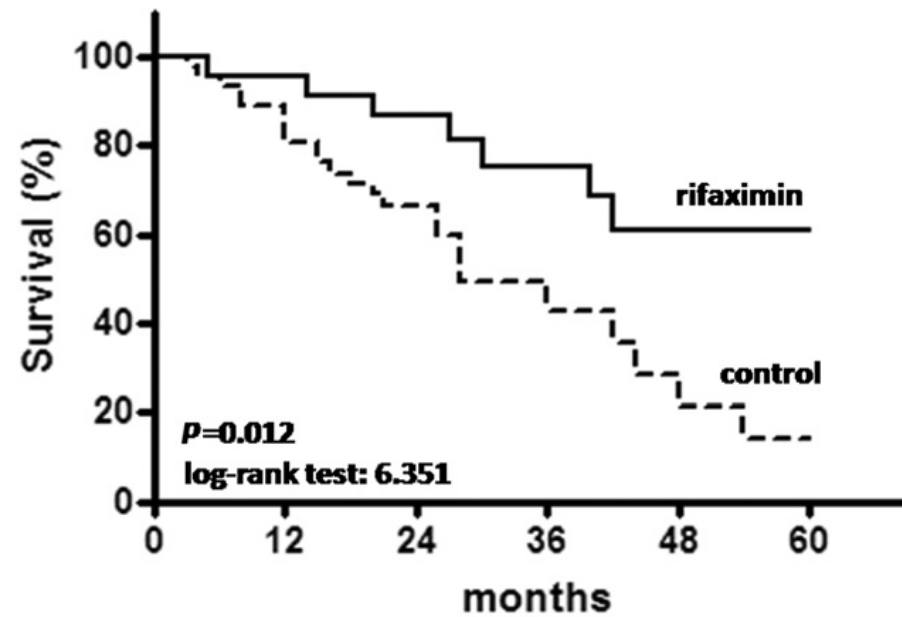
- In multivariate analysis, rifaximin was independently associated with lower risk of developing variceal bleeding, HE, SBP, and HRS

Journal of Gastroenterology and Hepatology

[Volume 28, Issue 3](#), pages 450-455, 26 FEB 2013 DOI: 10.1111/jgh.12070

<http://onlinelibrary.wiley.com/doi/10.1111/jgh.12070/full#jgh12070-fig-0001>

Rifaximin improved survival



Patients at risk

Rifaximin	23	22	18	15	10	9
Control	46	41	24	13	9	6

Journal of Gastroenterology and Hepatology

Volume 28, Issue 3, pages 450-455, 26 FEB 2013 DOI: 10.1111/jgh.12070

<http://onlinelibrary.wiley.com/doi/10.1111/jgh.12070/full#jgh12070-fig-0001>

✓ **Remoção da amônia: LOLA**

✓ **LOLA:**

- ✓ **reduz [amônia plasmática] proporcionando substratos para a conversão intracelular de amônia para glutamina e uréia**
- ✓ **Dose: Infusão EV 20 g (5g/amp)/d; 3 a 6 g (1 a 2 env) VO 3x/d**
- ✓ **RCTs: reduz amônia; benefícios em EH crônica leve a moderada**
- ✓ **LOLA em infusão EV 20g/d por 7 dias vs placebo (N=126):**
 - ✓ **↓ amônia**
 - ✓ **↑ *status* mental**
 - ✓ **↑ *PSE index***

✓ Remoção da amônia: LOLA

✓ Bai M, 2013: metanálise de 8 estudos

✓ 4 estudos: suplementação oral; 4 estudos: infusão EV

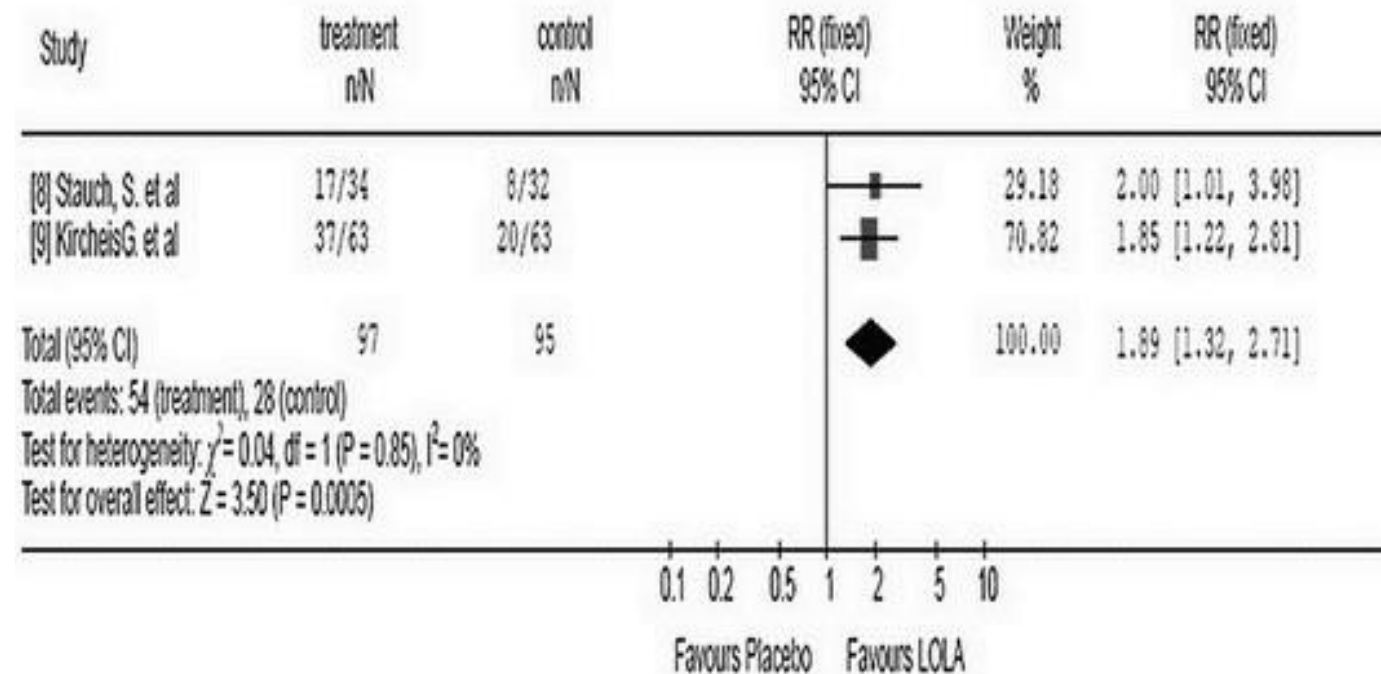
Table 1 Characteristics of included studies

Study	Interventions		Patient eligible criteria	Diagnosis criteria		Randomized patients	Centers	Study duration
	LOLA	Control		MHE	OHE			
Kircheis <i>et al.</i> 1997 ⁸	Infusion, 20 g, qd, 7 days	Placebo (riboflavin)	Cirrhosis, hyperammonemia (> 50 µg/dL), and MHE or grade I–II HE, without precipitating factors	NCT-A	West Haven	126	> 1	7 days
Stauch <i>et al.</i> 1998 ¹⁷	Oral, 6 g, tid, 14 days	Placebo (fructose)	Cirrhosis, hyperammonemia (> 50 µg/dL), MHE or grade I–II HE, without gastrointestinal bleeding, without peritonitis	NCT-A	West Haven	66	> 1	14 days
Poo <i>et al.</i> 2006 ²³	Oral, 3–6 g, tid, 14 days	Lactulose	Cirrhosis, hyperammonemia (> 60 µg/dL), grade I–II HE, without gastrointestinal bleeding, without active infection	NR	West Haven	20	1	14 days
Ahmad <i>et al.</i> 2008 ¹⁸	Infusion, 20 g, qd, 5 days	Placebo (distilled water)	Cirrhosis, hyperammonemia (> 50 µg/dL), grade I–III HE, without major complications of portal hypertension, without infection	NR	West Haven	80	1	5 days
Schmid <i>et al.</i> 2010 ¹⁹	Infusion, 20 g, qd, 8 days	Placebo (unclear)	Cirrhosis (Child–Pugh B/C), MHE, or grade I–II HE, without precipitating factors	NCT-A and B, DST, LTT, SDT	West Haven	40	1	9 days
Mittal <i>et al.</i> 2011 ²²	Oral, 6 g, tid, 3 months	Probiotics/ lactulose/blank	Cirrhosis, MHE, without recent gastrointestinal bleeding, without active infection	NCT-A and B, FCT-A and B	NR	160	1	3 months
Abid <i>et al.</i> 2011 ²⁰	Infusion, 20 g, qd, 3 days	Placebo (distilled water)	Cirrhosis, hyperammonemia (> 60 µmol/L), MHE, or grade I–IV HE, without active gastrointestinal bleeding, without septicemia	NCT-A	West Haven	120	1	3 days
Ndraha, <i>et al.</i> 2011 ²¹	Oral, 6 g, tid, 14 days	Placebo (unclear)	Cirrhosis, MHE (CFF < 39 Hz), malnutrition, without gastrointestinal bleeding, without active infection	CFF	NR	34	1	14 days

CFF, critical flicker frequency; DST, digit symbol test; FCT, figure connection test; HE, hepatic encephalopathy; LOLA, L-ornithine-L-aspartate; LTT, line tract test; MHE, minimal HE; NCT, number connection test; NR, not reported; OHE, overt HE; qd, one time per day; SDT, serial dotting test; tid, three times per day.

Other Drugs for HE: L-ornithine-L-aspartate

Review: L-Ornithine-L-Aspartate in the Management of Hepatic Encephalopathy: a Meta-analysis
Comparison: LOLA versus placebo
Outcome: LOLA in the management of Chronic HE—overall effect



Jiang et al, J Gastroenterol Hepatol. 2009 Jan;24(1):9-14.

Conclusão:

- Ascite e Encefalopatia são complicações frequentes no paciente cirrótico crítico
- Compreensão da fisiopatologia e observação de fatores precipitantes prováveis e condições clínicas subjacentes permitem não apenas tratamento do evento atual como evitar iatrogenias.