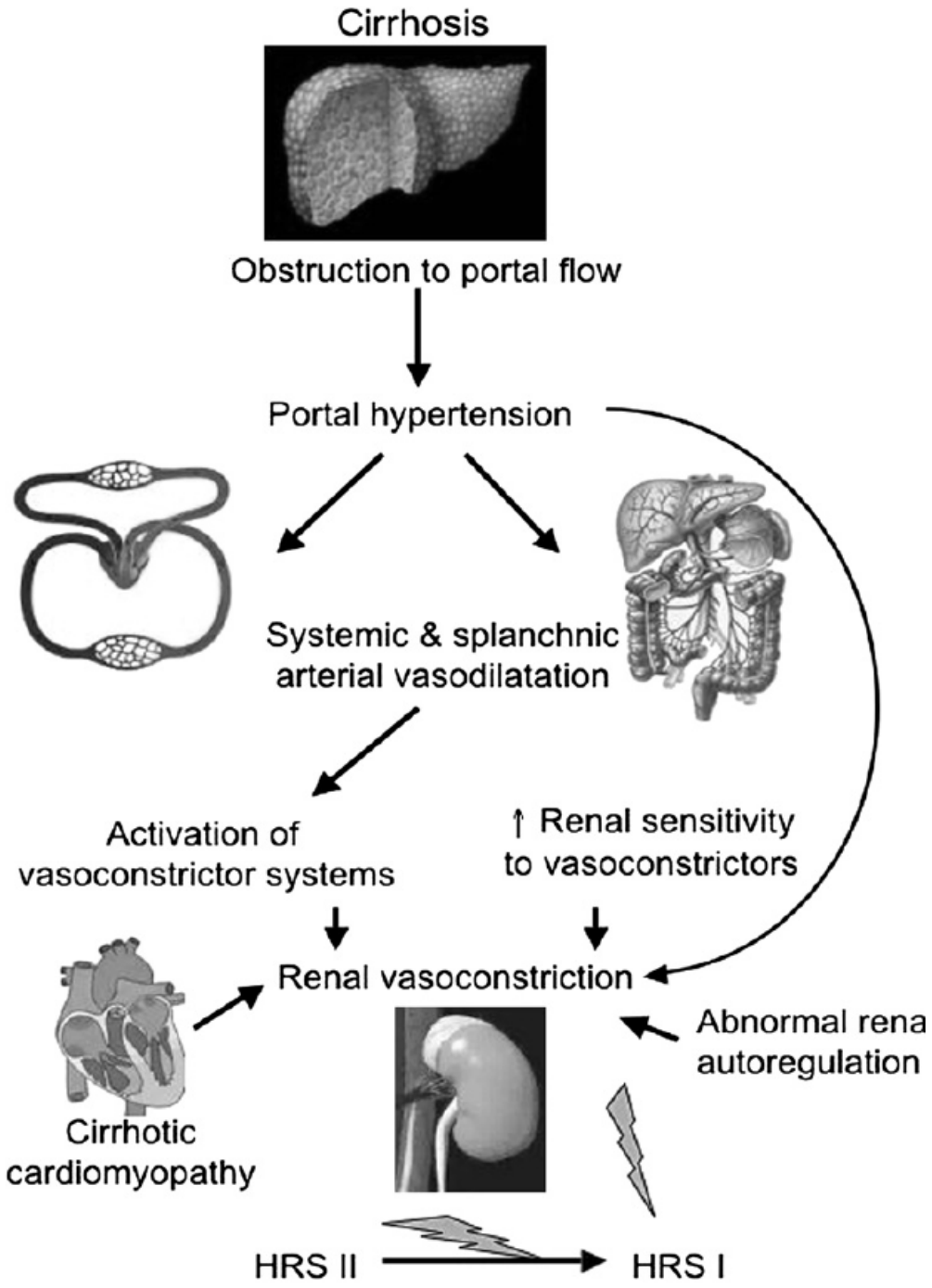
Management of oliguria in cirrhosis

Oliguria & Liver disease

- Acute liver failure
  - AKI
  - Direct paracetamol tubular toxicity
- Hepatobiliary and liver trauma
  - AKI
  - Elevated IAP
- Cirrhosis
  - AKI
  - CKD ± AKI
  - HRS

- Pre Renal
  - Actual volume loss : over diuresis, bleed, paracentesis ….
  - Effective volume loss
    - Cirrhosis : splanchnic hypervolaemia, central hypovolaemia
  - Impaired renal blood flow
    - decreased RBF as part of cirrhosis : rationale re NSAI
    - intra-abdominal hypertension
- Renal
  - Glomerulonephritis : viral / autoimmune
  - IgA nephropathy
  - Hypertension, diabetes, intersitial nephritis,
  - Contrast -volume depletion also
  - Immunosupressant induced renal injury
- Post Renal


Cirrhosis
Obstruction to portal flow
Portal hypertension
Systemic & splanchnic
arterial vasodilatation
Activation of
vasoconstrictor systems
↑ Renal sensitivity
to vasoconstrictors
Renal vasoconstriction
Abnormal rena
autoregulation
Cirrhotic
cardiomyopathy
HRS II
HRS I

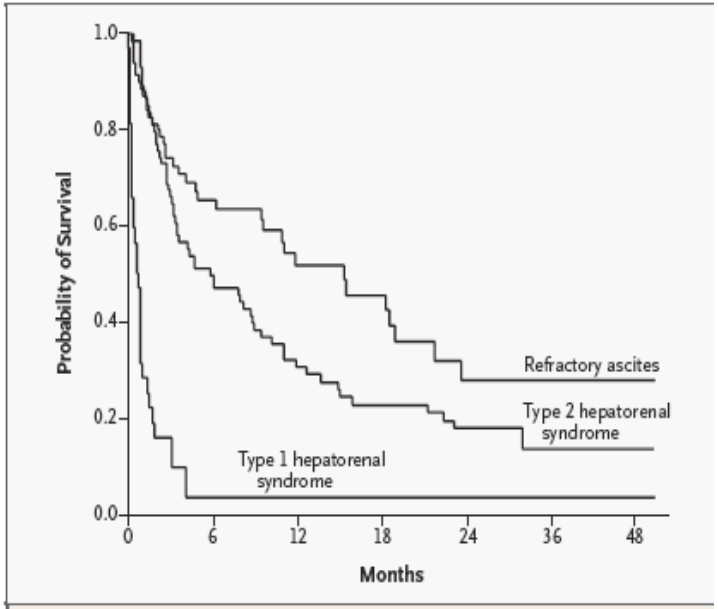


Figure 2. Probability of Survival among Patients with Cirrhosis, Refractory Ascites, and the Hepatorenal Syndrome.

Type 1 hepatorenal syndrome is a progressive impairment in renal function, defined by a doubling of the initial serum creatinine concentration in less than two weeks to a value greater than 2.5 mg per deciliter (221 μmol per liter). Type 2 hepatorenal syndrome is a stable or slowly progressive impairment in renal function that does not meet the criterion for type 1 hepatorenal syndrome.

Box 1 International Ascites Club (IAC) proposed diagnostic criteria for hepatorenal syndrome[10]

- Cirrhosis with ascites
- Serum creatinine >133 μmol/l (1.5 mg/dl)
- No improvement in serum creatinine (decrease to a level of ≤133 μmol/l or 1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg body weight/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, microhaematuria (>50 red blood cells/high power field) and/or abnormal renal ultrasonography

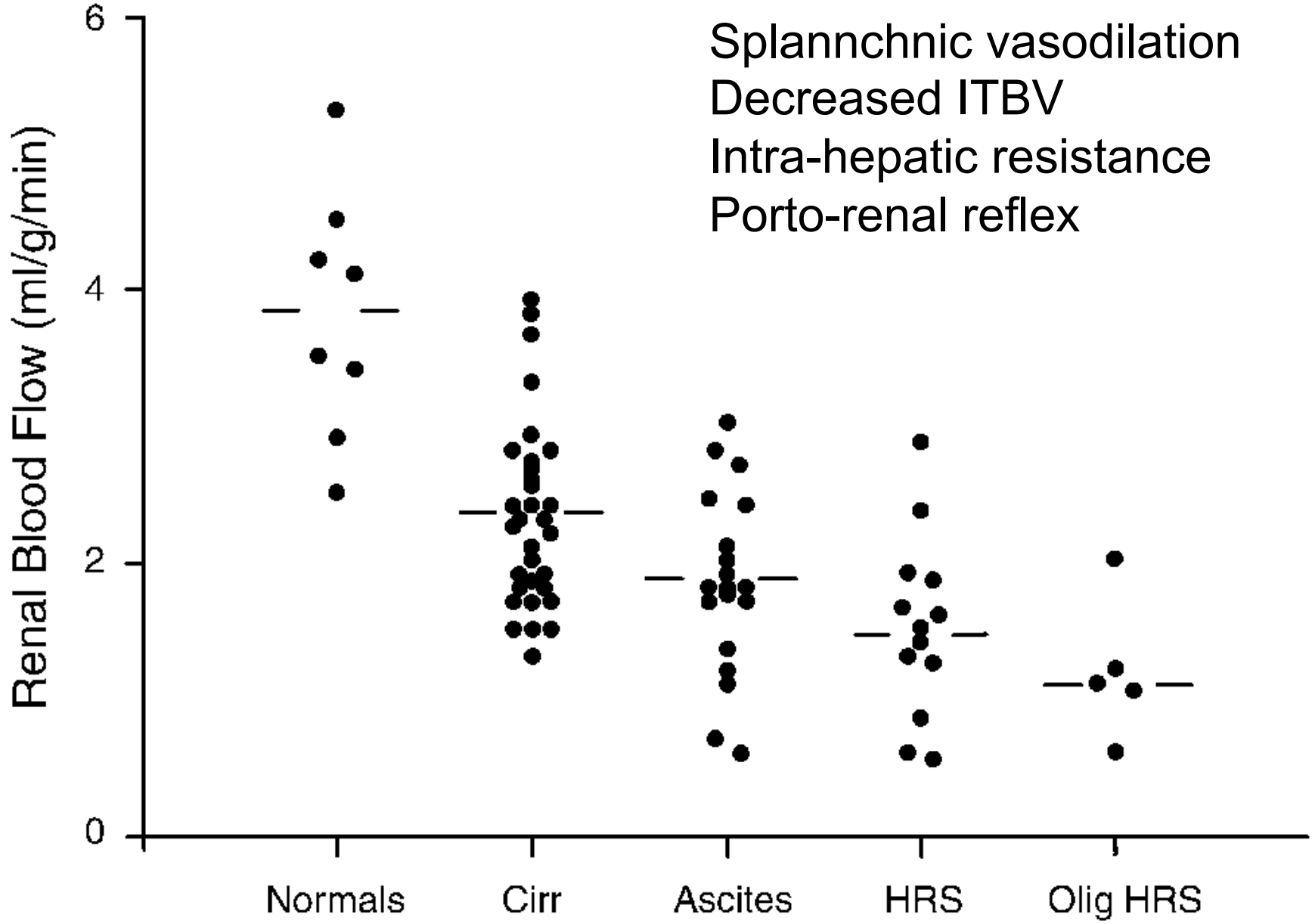
Issues :
Not even eGFR
Creatine is produced in the liver
Woman vs men
Ethnic diversity
Decreased muscle mass in cirrhosis

N Engl J Med 2004;350:1646-54.

Management of Cirrhosis and Ascites

Pere Ginès, M.D., Andrés Cárdenas, M.D., Vicente Arroyo, M.D., and Juan Rodés, M.D.

Consider acute renal dysfunction in cirrhosis : RIFLE



Ring-Larsen et al.

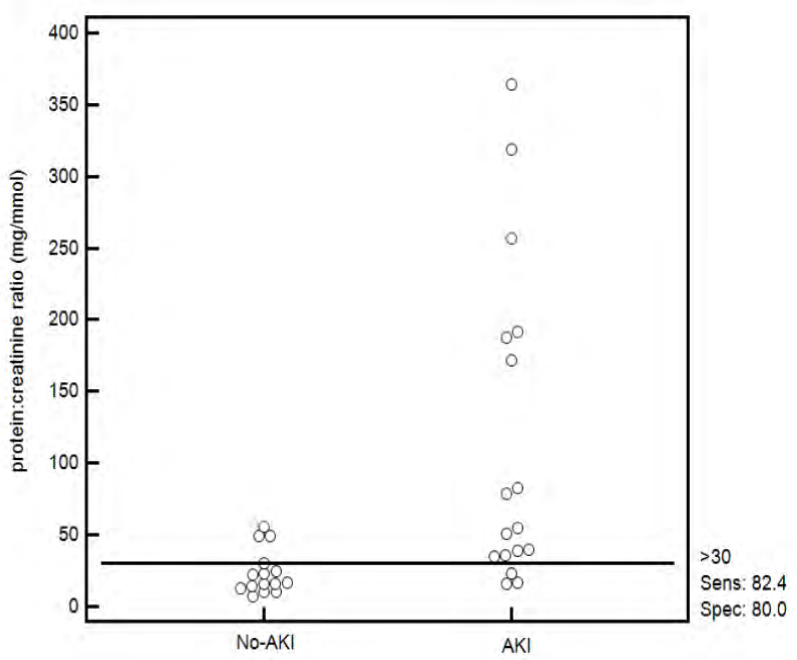
Prediction and earlier Rx of AKI

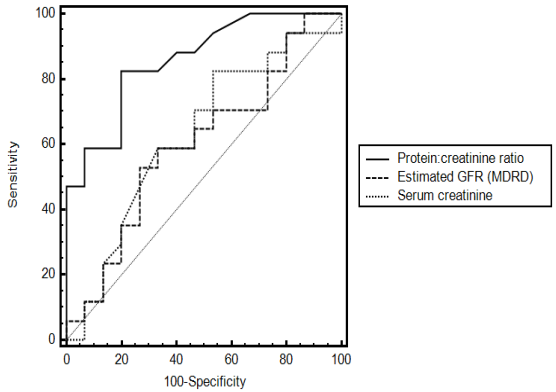
Inappropriate recognition of renal dysfunction

- Creatine
- Muscle mass

Recent review poor correlation of eGFR and iohexol or isotope methods

- eGFR only predicted 30% of those with GRF of < 60
- Proteinuria appeared highly predictive of development





Creatinine cut off for abnormal renal function 65 µmol/L

Slack et al Aliment Pharmacol Ther. 2013 May;37(10): 989-97

Table 2b. Summary Statistics for Urine Biomarkers by Diagnosis

	PRA N=55	HRS N=16	ATN N=39	p
Tubular injury markers				
NGAL (ng/ml)	54 (17-180)	115 (51-373)	565 (76-1000)***, ##	<0.001
IL-18 (pg/ml)	15 (15-49)	37 (15-90)	124 (15-325)***, #	<0.001
KIM-1 (ng/ml)	4.4 (1.8-11.7)	7.6 (4.5-10.1)	8.4 (4.1-18.3)**	0.03
L-FABP (ng/ml)	9 (4-18)	14 (6-20)	27 (8-103)***	0.002
Tubular function marker				
FENa (%)	0.27 (0.13-0.58)	0.10 (0.02-0.23)**	0.31 (0.12-0.65)##	0.01
Glomerular injury marker				
Albumin (mg/dL)	21 (4-70)	24 (13-129)	92 (44-253)***, #	<0.001

Abbreviations: PRA, pre-renal azotemia; HRS, hepatorenal syndrome; ATN, acute tubular necrosis; NGAL, neutrophil gelatinase associated lipocalin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; FENa, fractional excretion of sodium

Table 4. Association Between Biomarker Panel and the Diagnosis of ATN

	Relative Risk*
0 Markers Positive	1.00
1 Marker Positive	4.63 (1.29-16.61)
2 Markers Positive	6.98 (2.14-22.75)
3 Markers Positive	9.78 (3.10-30.86)
4 Markers Positive	13.33 (4.40-40.39)

Abbreviations: ATN, acute tubular necrosis

Biomarker cutoffs: NGAL, 365 ng/ml; IL-18, 85 pg/mL; L-FABP, 25 ng/mL; Albumin 44 mg/dL

*Unadjusted

Table 2b. Summary Statistics for Urine Biomarkers by Diagnosis

	PRA N=55	HRS N=16	ATN N=39	p
Tubular injury markers				
NGAL (ng/ml)	54 (17-180)	115 (51-373)	565 (76-1000)***, ##	<0.001
IL-18 (pg/ml)	15 (15-49)	37 (15-90)	124 (15-325)***, #	<0.001
KIM-1 (ng/ml)	4.4 (1.8-11.7)	7.6 (4.5-10.1)	8.4 (4.1-18.3)**	0.03
L-FABP (ng/ml)	9 (4-18)	14 (6-20)	27 (8-103)***	0.002
Tubular function marker				
FENa (%)	0.27 (0.13-0.58)	0.10 (0.02-0.23)**	0.31 (0.12-0.65)##	0.01
Glomerular injury marker				
Albumin (mg/dL)	21 (4-70)	24 (13-129)	92 (44-253)***, #	<0.001

Abbreviations: PRA, pre-renal azotemia; HRS, hepatorenal syndrome; ATN, acute tubular necrosis; NGAL, neutrophil gelatinase associated lipocalin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; FENa, fractional excretion of sodium

Table 4. Association Between Biomarker Panel and the Diagnosis of ATN

	Relative Risk*
0 Markers Positive	1.00
1 Marker Positive	4.63 (1.29-16.61)
2 Markers Positive	6.98 (2.14-22.75)
3 Markers Positive	9.78 (3.10-30.86)
4 Markers Positive	13.33 (4.40-40.39)

Abbreviations: ATN, acute tubular necrosis

Biomarker cutoffs: NGAL, 365 ng/ml; IL-18, 85 pg/mL; L-FABP, 25 ng/mL; Albumin 44 mg/dL

*Unadjusted

Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis

Florence Wong, *Gut* 2011;**60**:702–709.

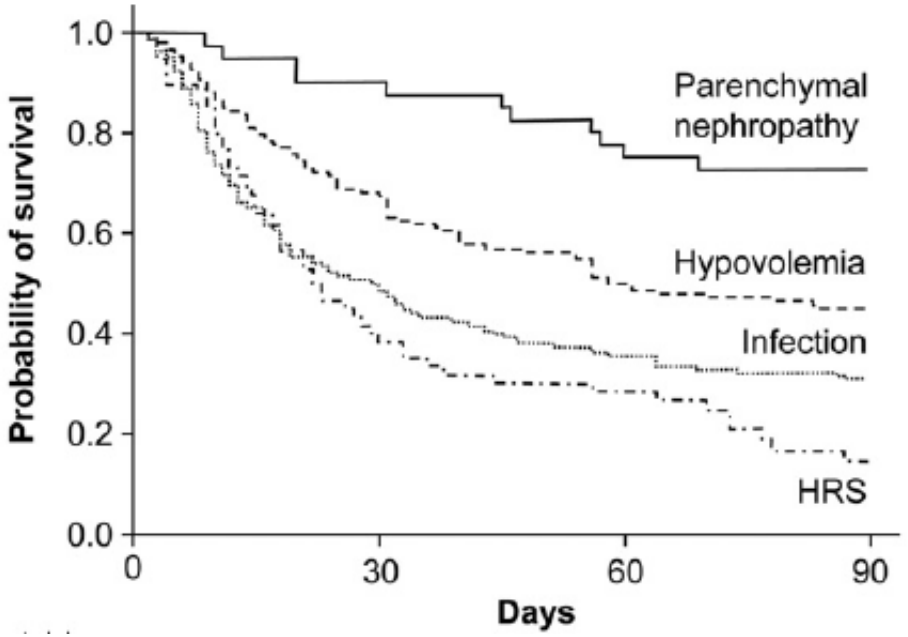
Table 2 Proposed diagnostic criteria of kidney dysfunction in cirrhosis

Diagnosis	Definition
Acute kidney injury	Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h HRS type 1 is a specific form of acute kidney injury
Chronic kidney disease	Glomerular filtration rate of <60 ml/min for >3 months calculated using MDRD6 formula HRS type 2 is a specific form of chronic kidney disease
Acute-on-chronic kidney disease	Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h in a patient with cirrhosis whose glomerular filtration rate is <60 ml/min for >3 months calculated using MDRD6 formula

Prognostic Importance of the Cause of Renal Failure in Patients With Cirrhosis

GASTROENTEROLOGY 2011;140:488–496

MARTA MARTÍN-LLAHÍ,



Creatinine >1 .5 mg/dl
463 patients over 6 years
Single centre

	Odds ratio	*P*	95% confidence interval
Hypovolemia-related	2.32	.049	1.00–5.36
Bacterial infections	2.61	.027	1.11–6.11
Hepatorenal syndrome	6.88	.001	2.19–21.55
MELD score at diagnosis	1.13	.0005	1.08–1.18
Serum sodium at diagnosis	0.96	.020	0.92–0.99
Hepatic encephalopathy at diagnosis[a]	1.94	.005	1.22–3.09

3 month mortality

A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis

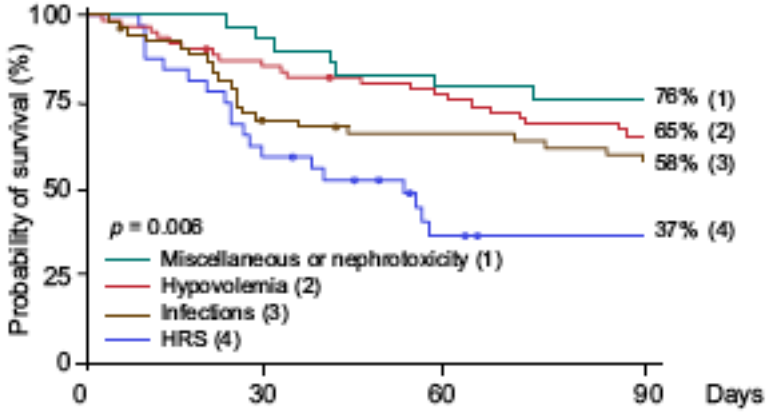
Claudia Fagundes

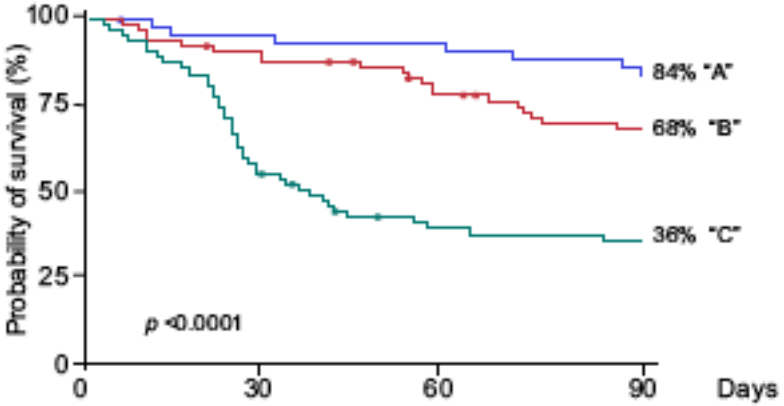
Journal of Hepatology **2013** vol. 59 | 474–481

Table 2. Comparison of patients who developed AKI classified according to progression or lack of progression of AKI. Variables are those obtained at diagnosis of AKI Only patients with AKI stage 1 or 2 were considered for the analysis (n = 156).

	No progression (n = 125)	Progression (n = 31)	*p* value
Age (yr)	62 ± 12	59 ± 13	0.24
Sex, male (n)	82 (66%)	18 (58%)	0.93
Alcoholic etiology, (n)	66 (53%)	16 (52%)	0.89
Treatment with beta-blockers, (n)	28 (22%)	3 (10%)	0.06
Chronic kidney impairment	34 (27%)	2 (7%)	0.016
HRS type II	9	0	
Intrinsic nephropathy	20	1	
Unknown	15	1	
Presence of ascites	93 (74%)	25 (81%)	0.30
Presence of encephalopathy	42 (34%)	18 (58%)	0.007
Serum bilirubin (mg/dl)	5 ± 7	13 ± 10	<0.0001
Serum albumin (g/L)	26 ± 5	26 ± 5	0.99
INR	1.6 ± 0.6	2.0 ± 0.6	0.004
Serum creatinine (mg/dl)	1.8 ± 0.8	1.6 ± 0.5	0.047
Serum sodium (mEq/L)	133 ± 6	129 ± 8	0.024
Serum potassium (mEq/L)	4.5 ± 1.0	4.5 ± 0.9	0.76
Mean arterial pressure (mmHg)	79 ± 14	74 ± 13	0.039
Heart rate (bpm)	77 ± 18	87 ± 15	0.007
Leukocyte count (10^9/L)	7.9 ± 4.3	9.5 ± 6.0	0.007
C-reactive protein (mg/dl)	4.0 ± 4.6	5.0 ± 5.8	0.38
Child-Pugh score	9 ± 2	11 ± 2	0.001
MELD score	20 ± 6	26 ± 6	<0.0001

Claudia Fagundes

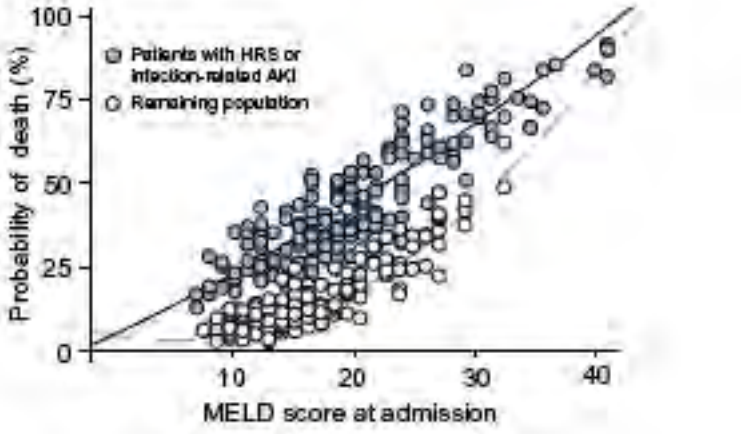




A (n = 44)	41	39	37
B (n = 66)	57	48	40
C (n = 67)	36	23	21

serum creatinine ⩽1.5 mg/dl;

AKI stage 1 with a peak value of serum creatinine >1.5 mg/dl



stage C, patients meeting the criteria of AKI stage 2 or 3.

Terlipressin and albumin vs albumin

Martin-Llahi M Gastroenterology 2008:134

- 1-2 mg 4hrly
- Albumin daily 1g/kg
- N=23 each grp
- Improved renal function 43 vs 8%
- No difference in 2 mnth survival
- CVS complications
  - 4 Alb vs 10 T + Alb

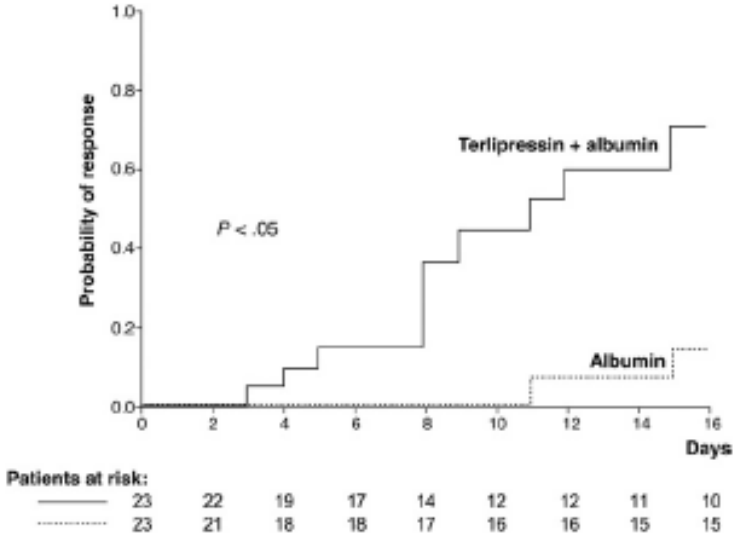
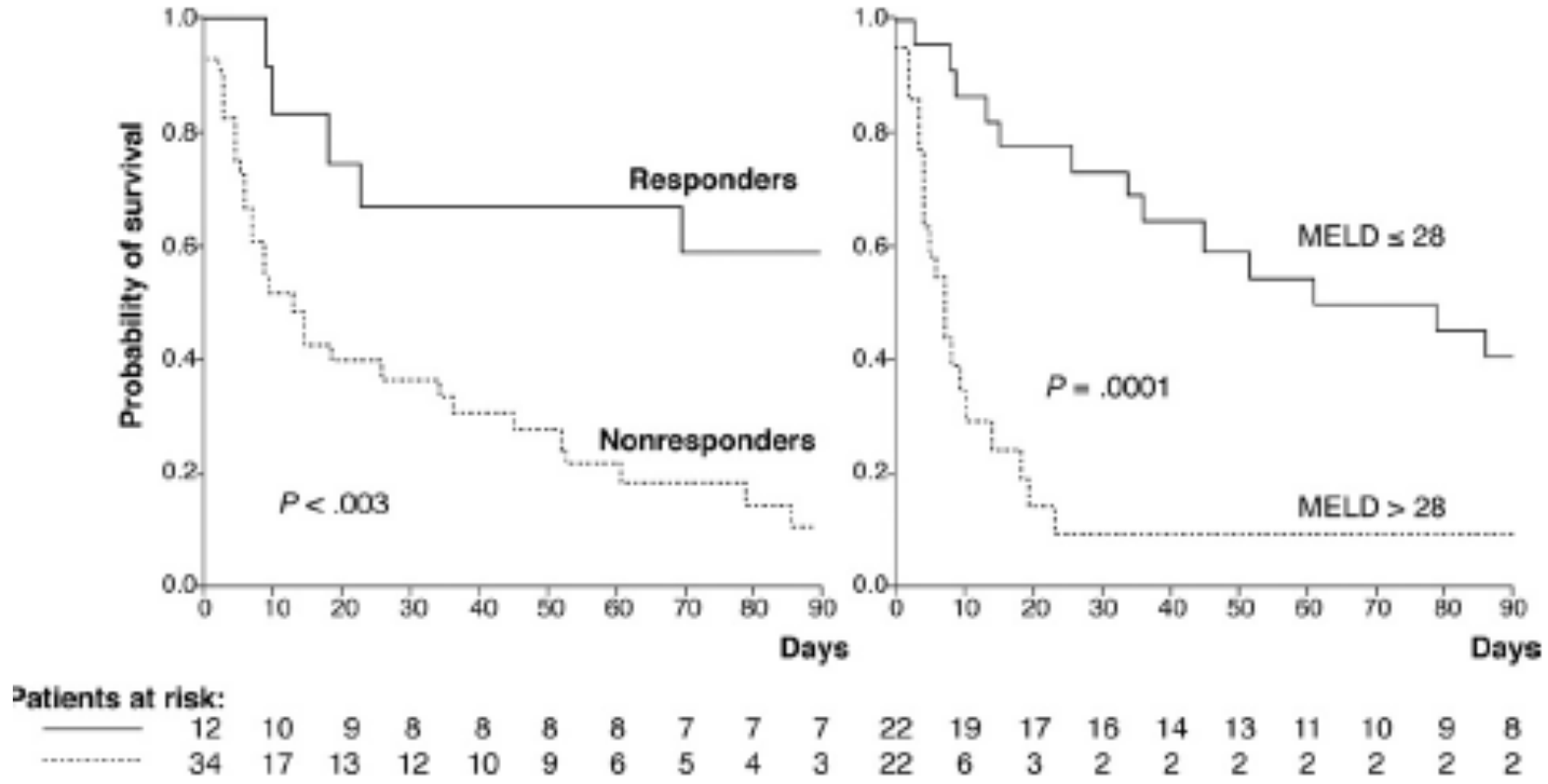


Table 2. Independent Predictive Factors of Response to Treatment

Variable	Responders (n = 12)	Nonresponders (n = 34)	*P* value
Assigned to terlipressin + albumin therapy (*n*)	10 (83%)	13 (38%)	.005
Serum creatinine (*μmol/L*)	256.4 ± 70.7	369.4 ± 194.5	.000
Urine volume (*mL/day*)	880 ± 440	496 ± 419	.005
White cell (*per mm*^{3})	6649 ± 3556	10932 ± 8107	.001

NOTE. Plus-minus values are means ± SD.
P values result from the multivariate analysis.



Previous studies CP score 11

Martin-Llahi M Gastroenterology 2008:134

RCT Terlipressin in Type I HRS

Sanyal A Gatroenterology 2008 :134:1360

1 mg 6 hrly vs placebo

Success defined as creatinine < 1.5 mg/dl for 48 hrs by Day 14

Rx success : 25 vs 12.5 %

Baseline to day 14

decrease in creatinine

0.7 vs 0 mg/dl

Table 2. Treatment Outcomes

End point	Terlipressin n (%)	Placebo n (%)	*P* value
All patients	(n = 56)	(n = 56)	
Treatment success at day 14	14 (25.0)	7 (12.5)	.093
HRS reversal	19 (33.9)	7 (12.5)	.008
Patients who received >3 days of treatment	(n = 36)	(n = 39)	
Treatment success at day 14	14 (38.9)	7 (17.9)	.046
HRS reversal	19 (52.8)	7 (17.9)	.002

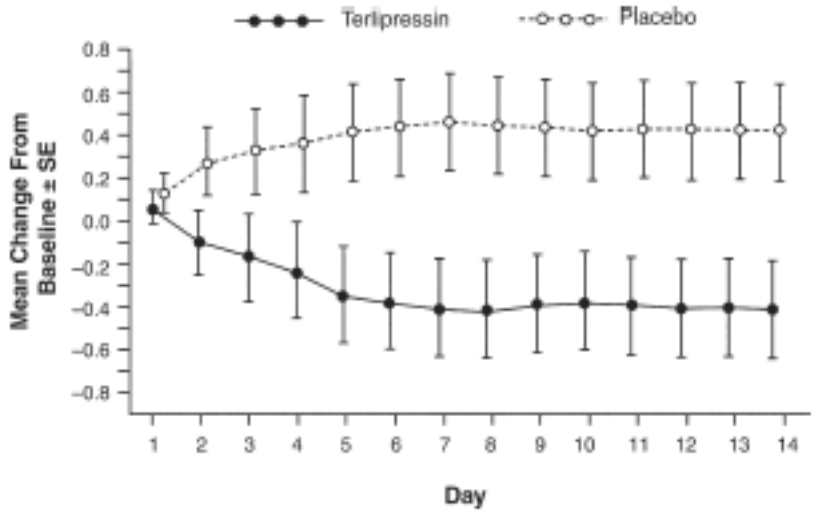


Figure 2. Mean change from baseline in SCr (mg/dL) to end of treatment. Data include all patients in the ITT population at each time point.

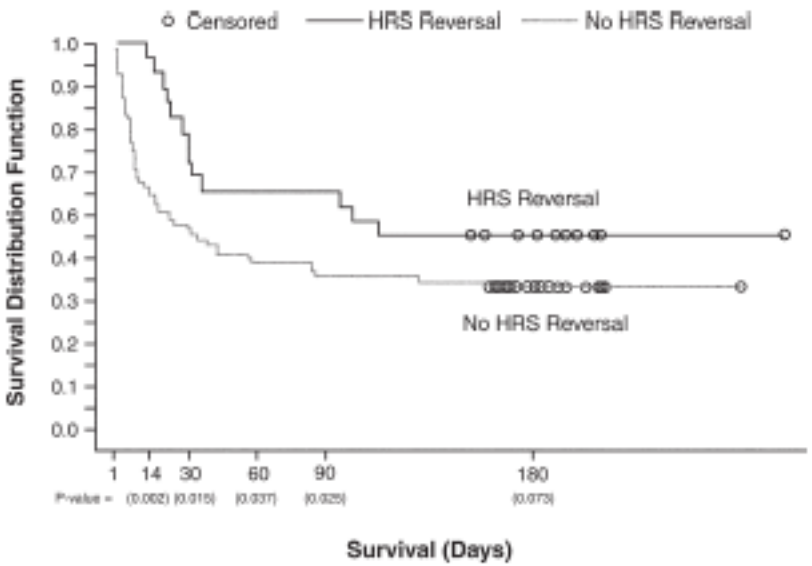
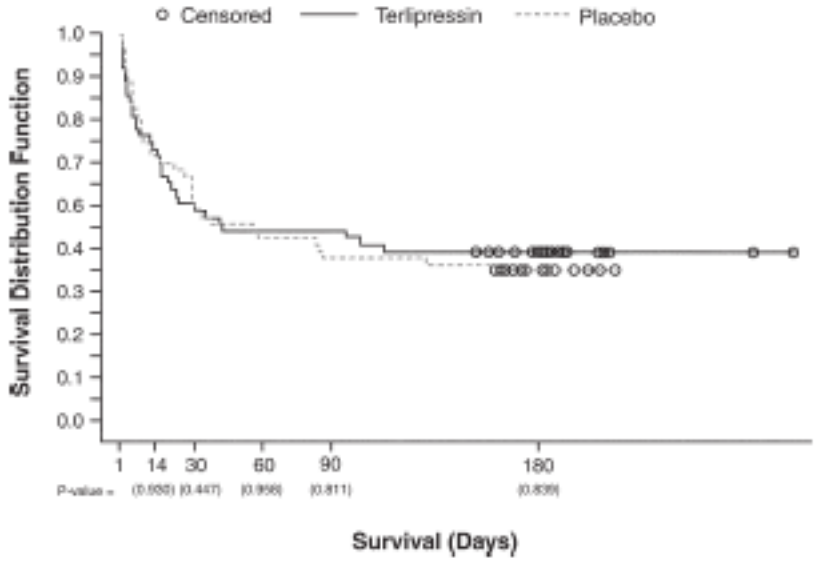


Table 3. Overview of Safety Data

Safety parameter (number of patients with AE)	Terlipressin (n = 56) n (%)	Placebo (n = 55) n (%)
AEs up to 7 days posttreatment		
All	52 (92.9)	49 (89.1)
Related	18 (32.1)	12 (21.8)
Serious AEs up to 30 days posttreatment		
All	37 (66.1)	36 (65.5)
Related	5 (8.9)	1 (1.8)
Deaths up to 30 days posttreatment		
All	27 (48.2)	27 (49.1)
Related	0 (0.0)	0 (0.0)
Withdrawals because of AEs up to 7 days		
All	3 (5.4)	2 (3.6)
Related	3 (5.4)	0 (0.0)



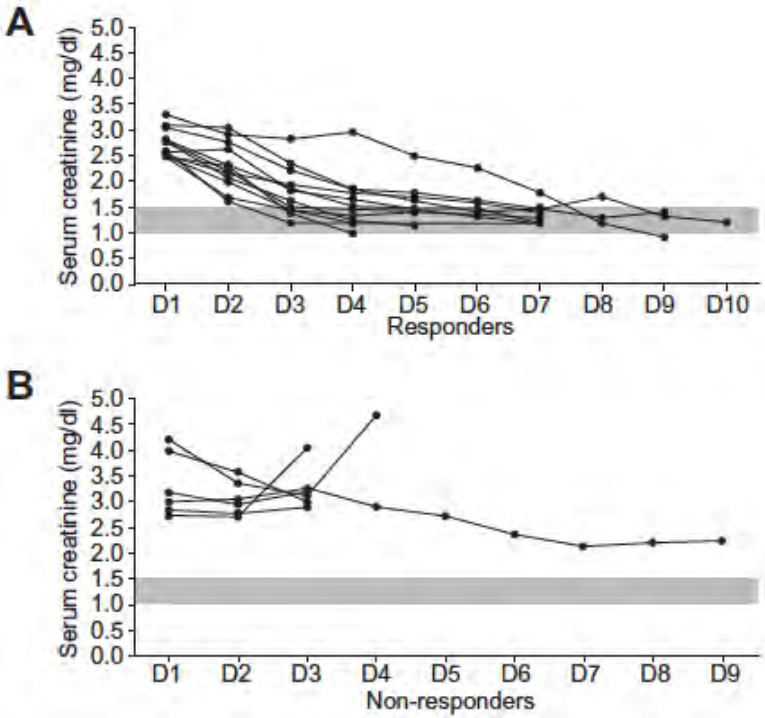
Sanyal A Gatroenterology 2008 :134:1360

Terlipressin and albumin for type-1 hepatorenal syndrome associated with sepsis

Ezequiel Rodríguez,

Journal of Hepatology 2014

Grade		
I	10	2
II	2	-
III	-	4
Type of organ/system failure		
Kidney	12	6
Liver	1	2
Cerebral	-	2
Coagulation	1	2
Circulation	-	-
Respiratory	-	2
CLIF-SOFA Score**	8 ± 1	14 ± 3



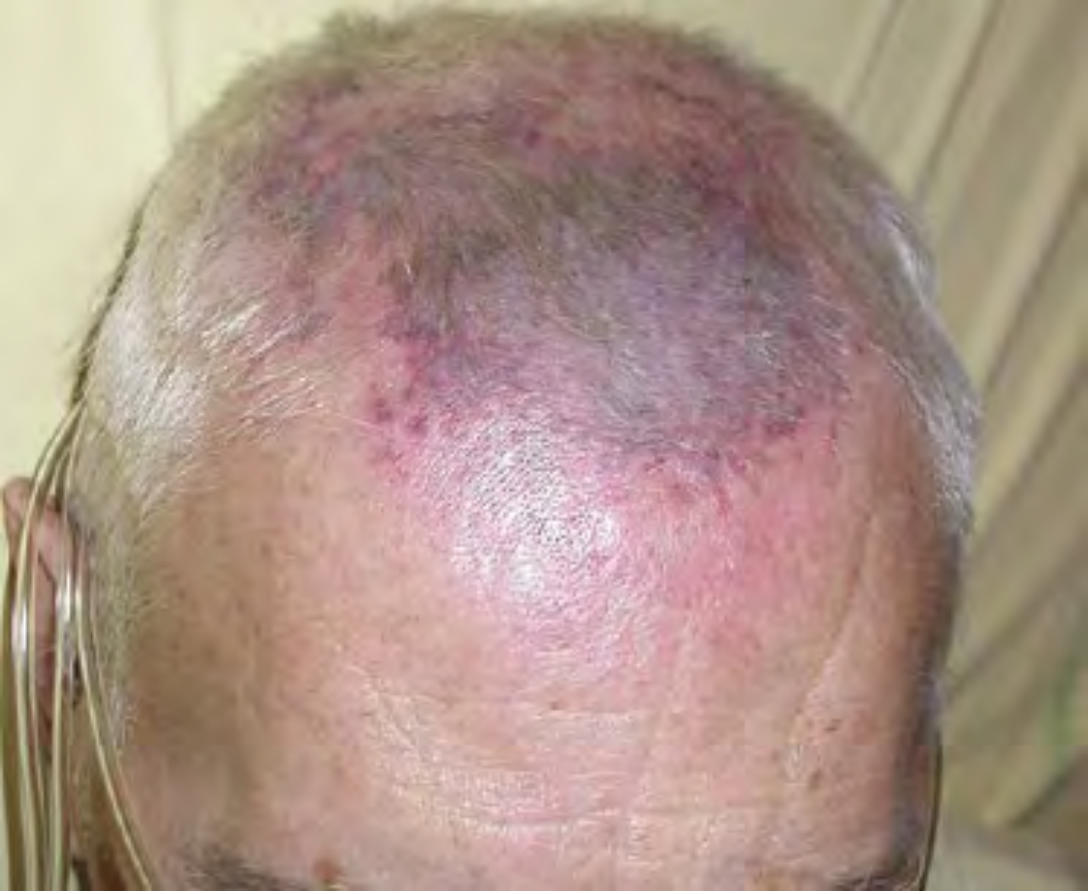
	During treatment	After treatment
Likely related to treatment		
Patients with complications	8	-
Type of complication		
Circulatory overload[a]	3	-
Bradycardia[b]	2	-
Abdominal pain[c]	3	-
Ischemia of the scrotum[d]	1	-

Definition of organ failure

Modified SOFA score for Cirrhosis (The SOFA-CLIF SCORE)

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤1.9	≥2 - ≤5.9	≥6 - <12	≥12
Kidney (Creatinine (mg/dL)	<1.2	≥1.2 - ≤ 1.9	≥2 - <3.5	≥3.5 - <5	≥5
			or use of renal-replacement therapy		
Cerebral (HE grade)	No HE	1	2	3	4
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/L
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO/FiO2:	>400	>300 - ≤400	>200 - ≤300	>100 - ≤200	≤100
or			>214 - ≤357		
SpO2/FiO2	>512	>357 - ≤512		>8 - ≤214	≤89

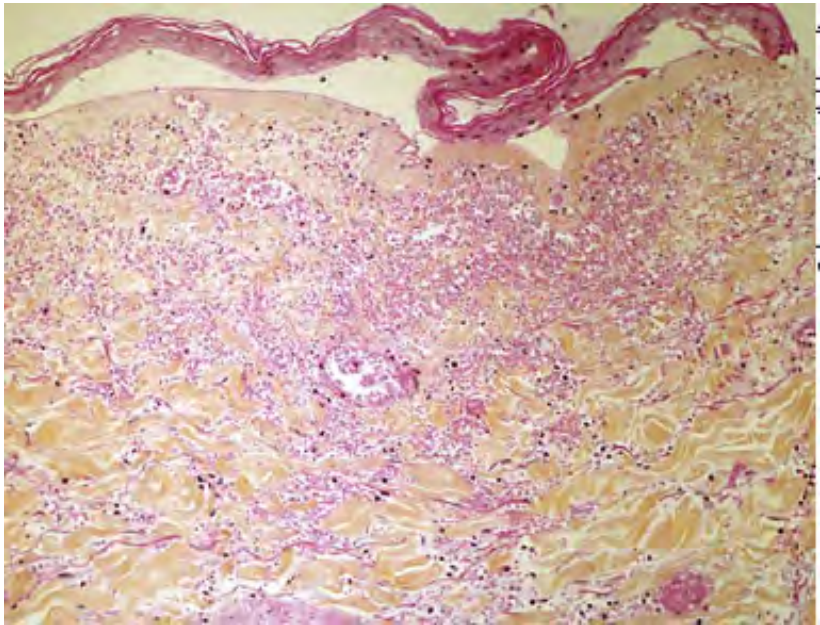
GASTROENTEROLOGY 2013;144:1426–1437



Blue fingers and toes

Myocardial events

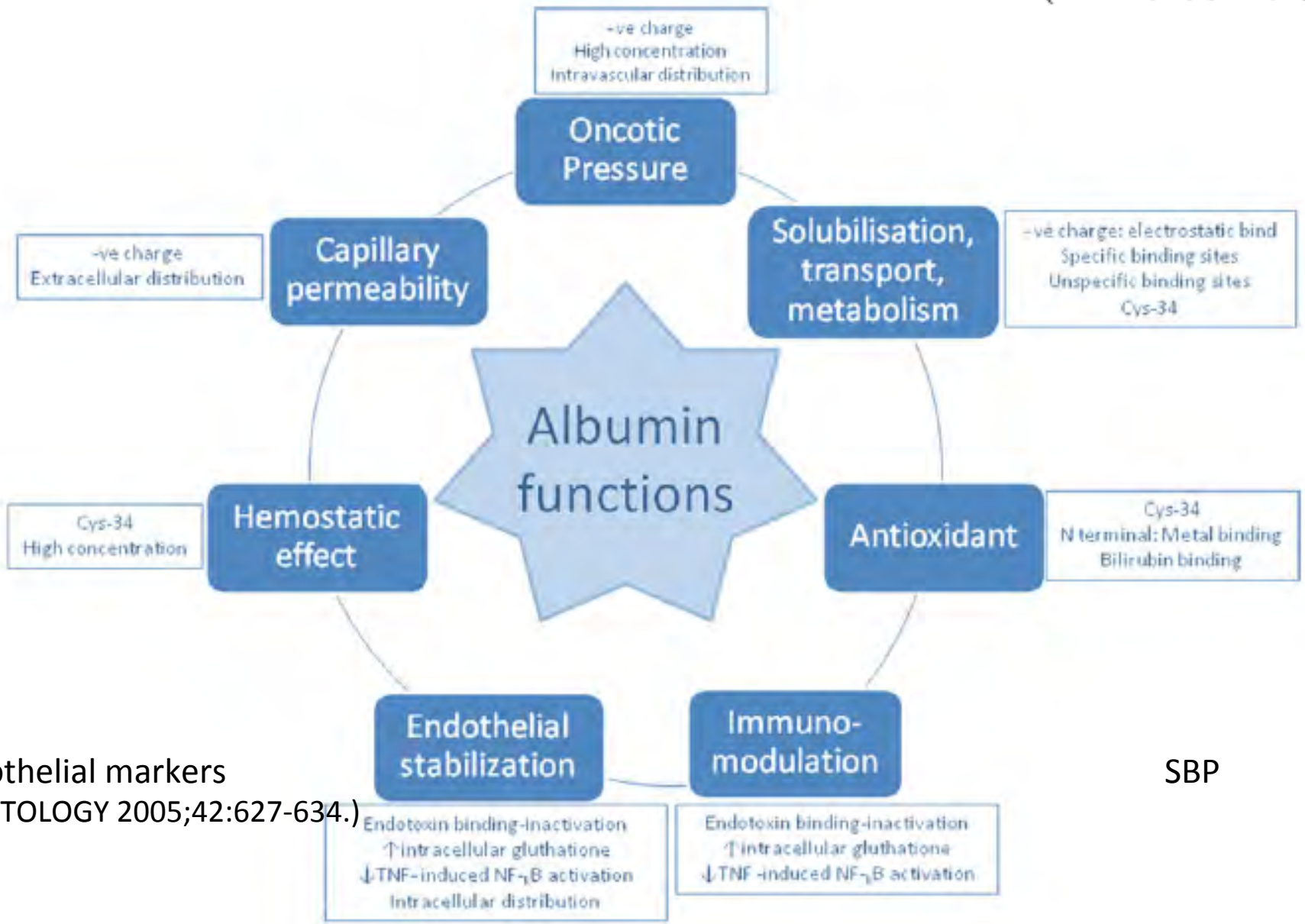
Diarrhoea - almost inevitable



Albumin: Pathophysiologic Basis of Its Role in the Treatment of Cirrhosis and Its Complications

Rita Garcia-Martinez

(HEPATOLOGY 2013;



Endothelial markers

HEPATOLOGY 2005;42:627-634.)

SBP

Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study.

- *J Hepatol. 2012 Oct;57(4):759-65.*

- Non SBP infections 100 patients
- Antibiotics ± albumin at diagnosis and day 3 (1.5 and 1 g/kg)
- No difference in survival at 3 mnths
- Improved creatinine and circulation markers – no difference in HRF (1 vs 3)

Norepinephrine for the treatment of HRS ?

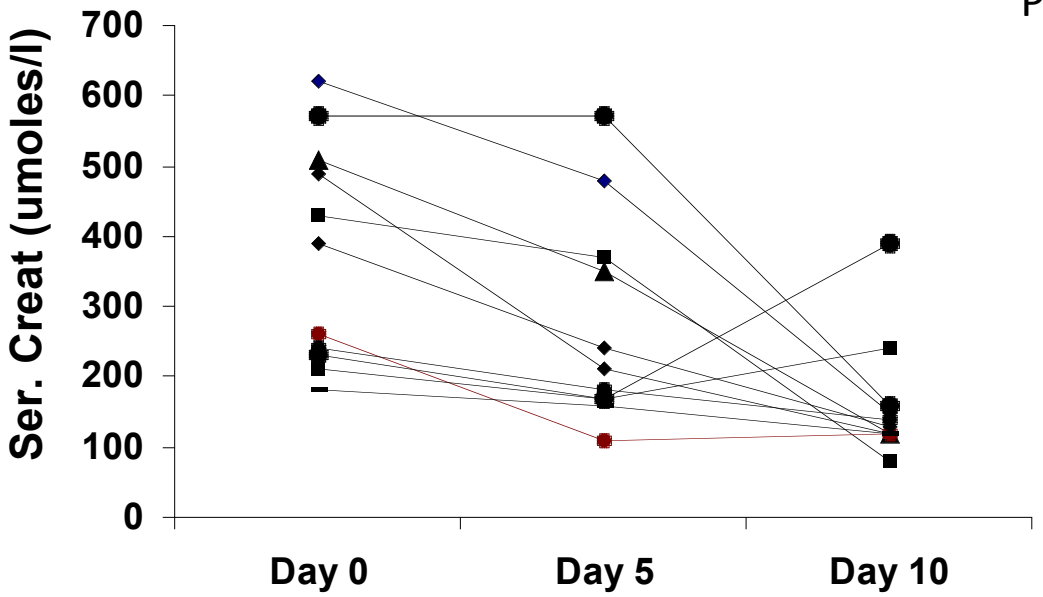
Duvoux et al. Hepatology 2002

Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol 2008;103:1689-1697.

Terlipressin vs NE *n=40*

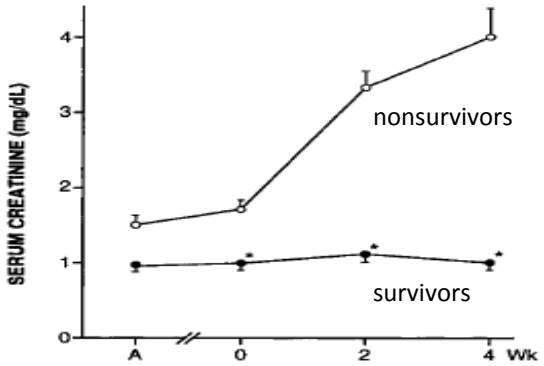
Predictors of outcome :

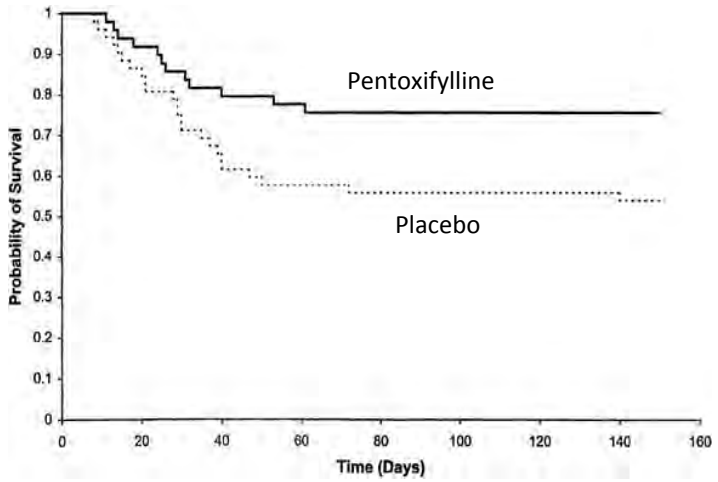
- Creatinine clearance
- MAP
- Renin



NA 0.5-3mg/h
MAP >100mmHg increaase
or U.O >50ml/h

Pentoxifylline and Alcoholic Hepatitis





PTX 12/49 (24.5%) died

Placebo 24/52 (46.1%) died

p=0.037

40% reduction in mortality

65% reduction in HRS

Steroid non responders do not benefit from switch to Ptx

Louvet et al J Hep 2008;48:465

E Akriviadas Gastroenterology 2000

Glucocorticoids plus *N*-Acetylcysteine in Severe Alcoholic Hepatitis

N Engl J Med 2011;365:1781-9.

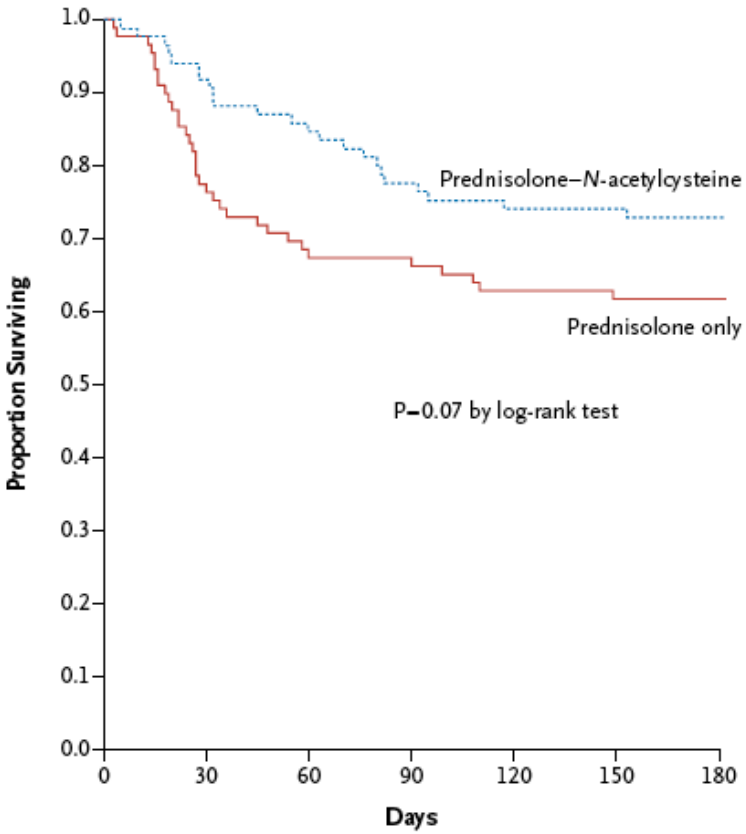


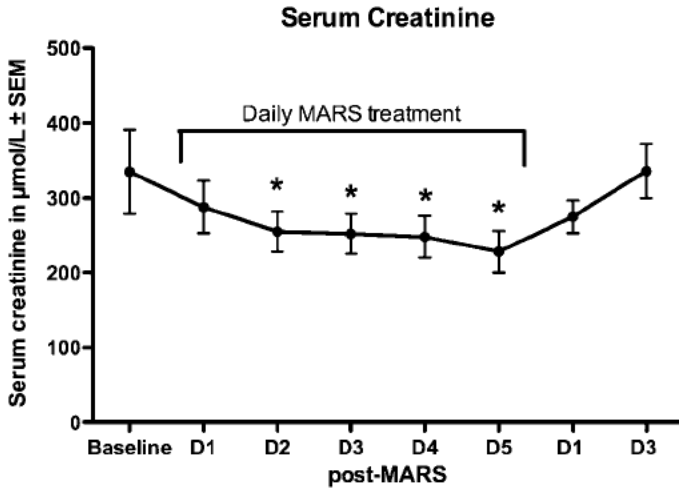
Figure 2. Kaplan–Meier Curves for 6-Month Survival in the Intention-to-Treat Population.

Mortality at 1 mnth 8 vs 24%
3 mnth 22 vs 34 and
6 mnth 27 vs 38

Less HRF 9 vs 22 %

Decreased infection

	Pre-MARS	Post-MARS
Renin (normal 6.4—23.8 ng/l)	76.92±16.45	61.24±21.74
Aldosterone (normal 27—444 pmol/l)	2295±1141	1443±841
Norepinephrine (normal 0.8—3.4 nmol/l)	4.08±0.58	4.80±0.72
Atrial natriuretic factor (normal 23—52 pg/ml)	113.0±28.5	106.2±19.8
Tumour necrosis factor α (normal <2.1 pg/ml)	5.86±1.24	6.96±1.11
Interleukin-6 (normal 0.4—8.9 pg/ml)	110.6±23.7	145.2±20.7



Midronine to identify responders and these then offered TIPS

Hepatology 2004

Gut 2010 59: 381-386

Molecular adsorbent recirculating system is ineffective in the management of type 1 hepatorenal syndrome in patients with cirrhosis with ascites who have failed vasoconstrictor treatment

Florence Wong,

Terlipressin + Albumin vs Albumin

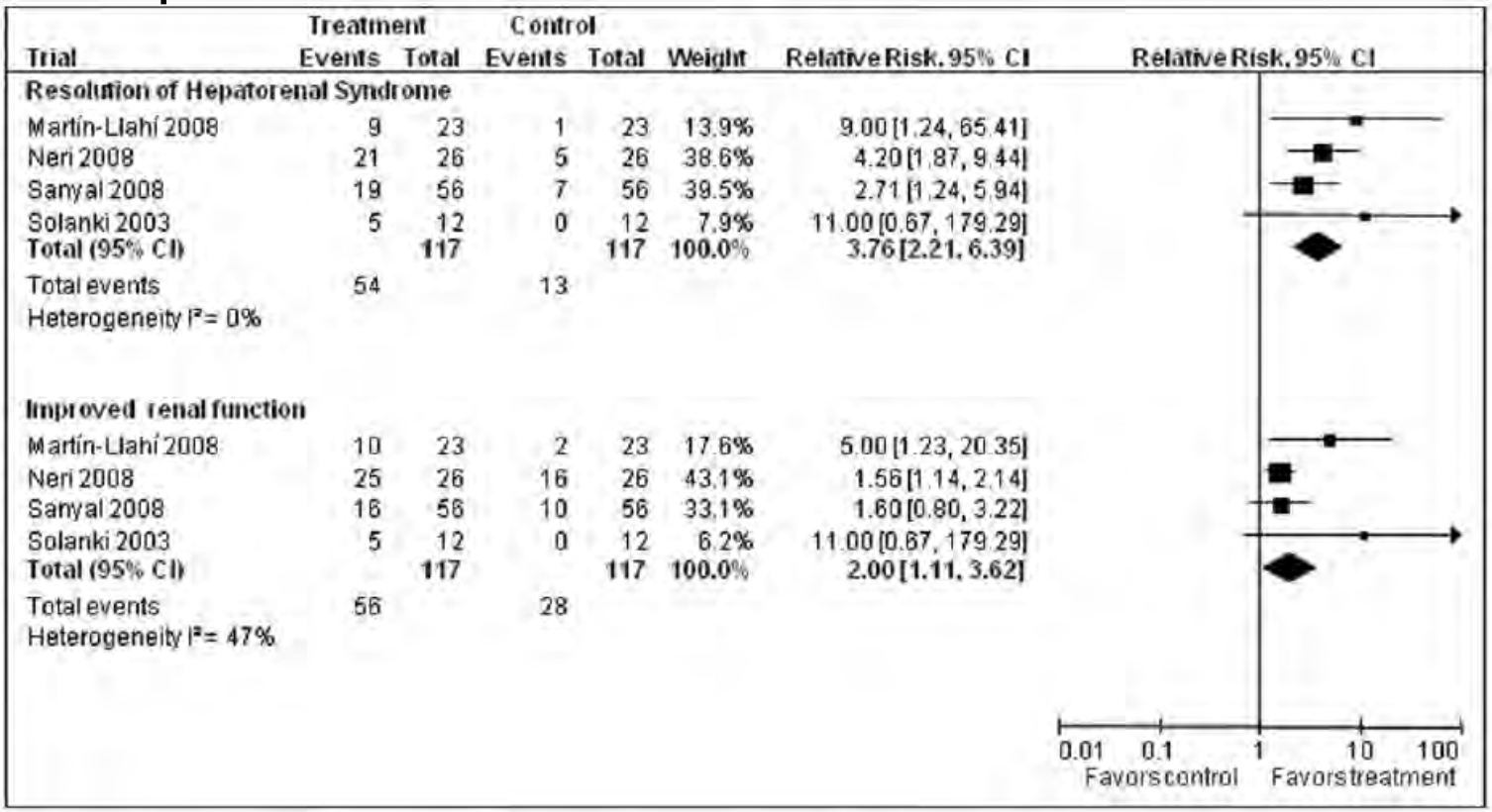


Fig. 3. Forest plots of random effects meta-analyses on terlipressin plus albumin versus albumin for patients with HRS. The outcome measures are reversal of HRS and improved renal function. The included patients received terlipressin alone or with albumin versus no intervention or albumin.

Vasoconstrictors + Alb : Effect on mortality at 15 days but not at 30, 90 or 180 days RR 0.6 (0.37-0.97)

Terlipressin + Albumin vs Albumin : decreased mortality in type I RR 0.83 (0.65-1.05)

Predictors of Response to Therapy with Terlipressin and Albumin in Patients with Cirrhosis and Type 1 Hepatorenal Syndrome

André Nazar

Hepatology 2010;51:219-226

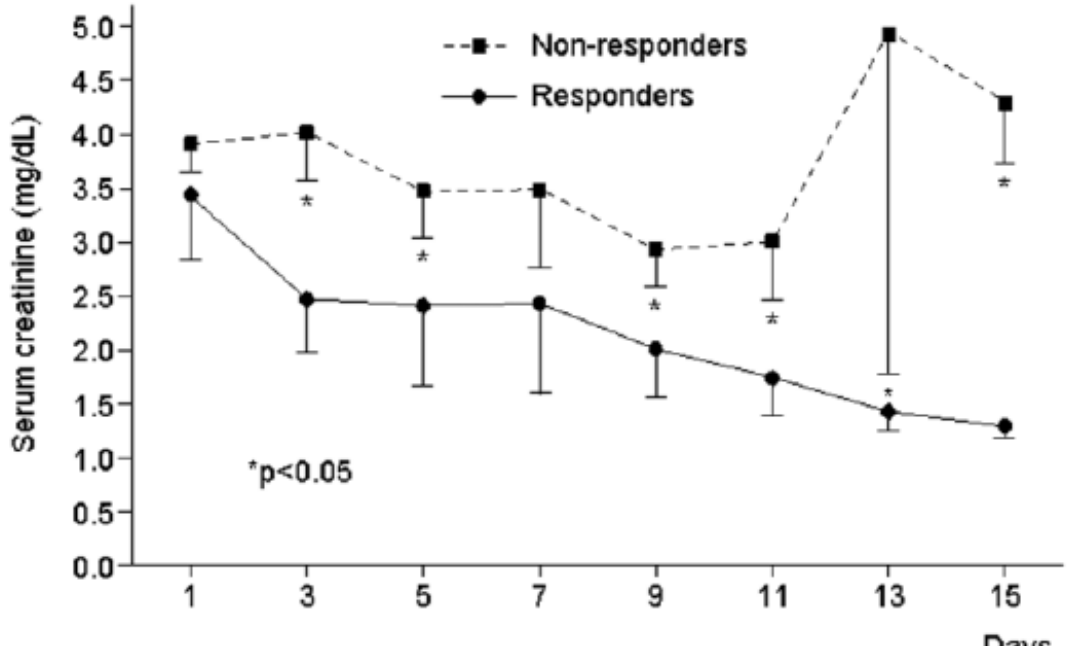


Table 4. Variables with Independent Predictive Value of Response to Treatment with Terlipressin and Albumin in Patients with Type 1 HRS

Variables	Odds Ratio	95% Confidence Interval	*P*
Baseline serum bilirubin	0.901	0.834–0.974	0.009
Δ MAP at day 3 ≥5 mm Hg	9.482	1.007–89.316	0.049

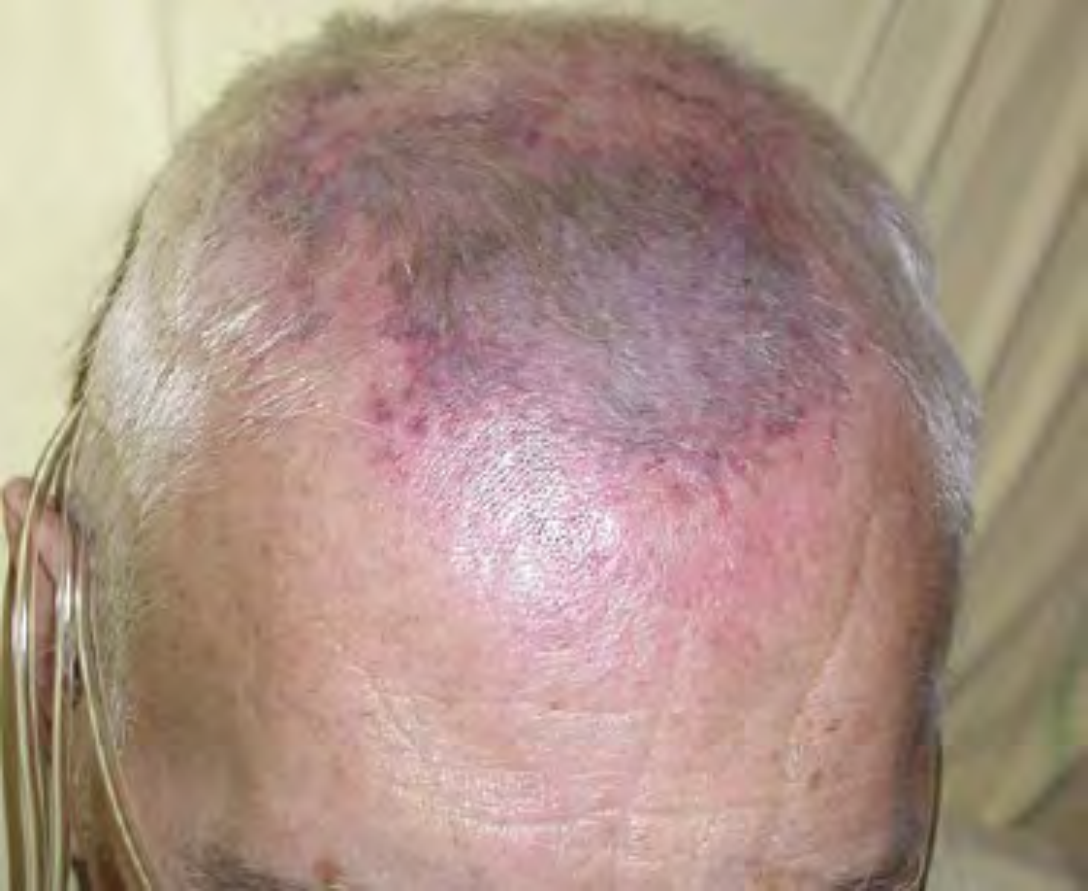
Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: Relationship of serum creatinine to hemodynamics

Thomas D. Boyer Terlipressin Study Group

Table 1. Summary of the effects of baseline characteristics on HRS reversal and survival (univariate analysis, ITT population).

Baseline parameter	HRS Reversal			Survival		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Treatment group	2.71	1.24-5.94	0.009	0.93	0.58-1.51	0.782
Alcoholic hepatitis	0.97	0.49-1.92	0.890	2.29	1.41-3.72	<0.001
Gender	0.57	0.31-1.08	0.055	1.00	0.59-1.69	0.963
MELD score	0.95	0.91-0.99	0.017	1.05	1.01-1.10	0.030
Child-Pugh score	0.87	0.75-1.02	0.065	1.15	1.00-1.32	0.051
Serum creatinine	0.65	0.46-0.93	0.021	1.40	1.22-1.60	<0.001
Bilirubin	1.00	0.97-1.02	0.805	1.01	1.00-1.03	0.087
MAP	0.99	0.96-1.02	0.459	1.02	0.99-1.04	0.216
Serum sodium	0.99	0.95-1.04	0.730	0.99	0.95-1.03	0.519

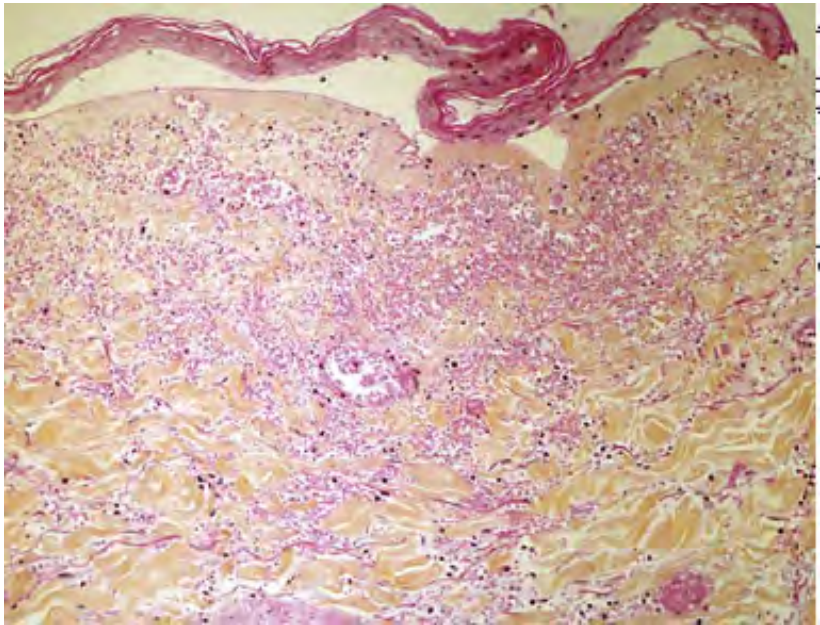
Journal of Hepatology **2011** vol. 55 | 315–321



Blue fingers and toes

Myocardial events

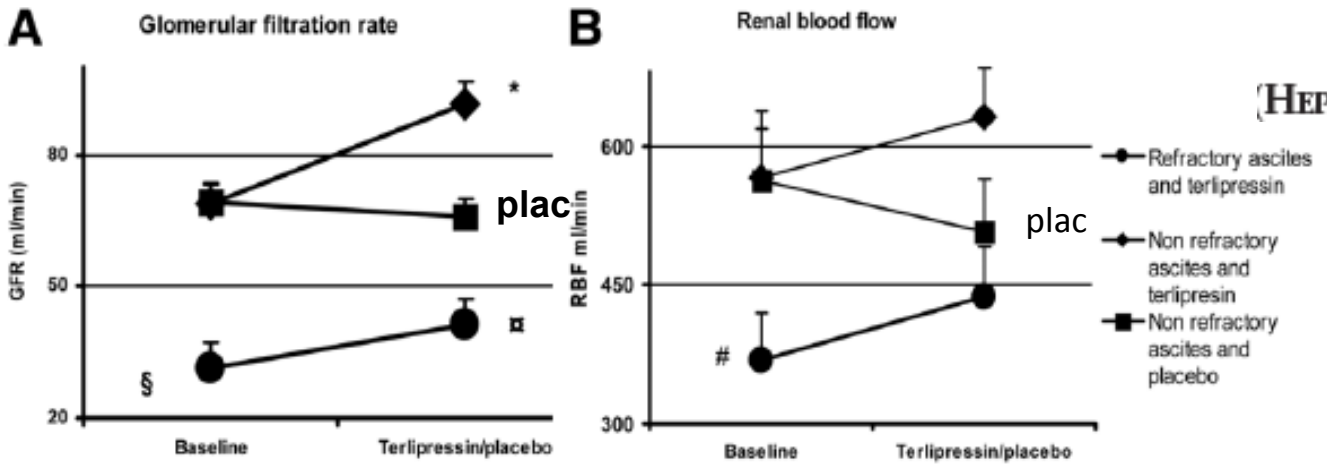
Diarrhoea - almost inevitable



Terlipressin Improves Renal Function in Patients with Cirrhosis and Ascites Without Hepatorenal Syndrome

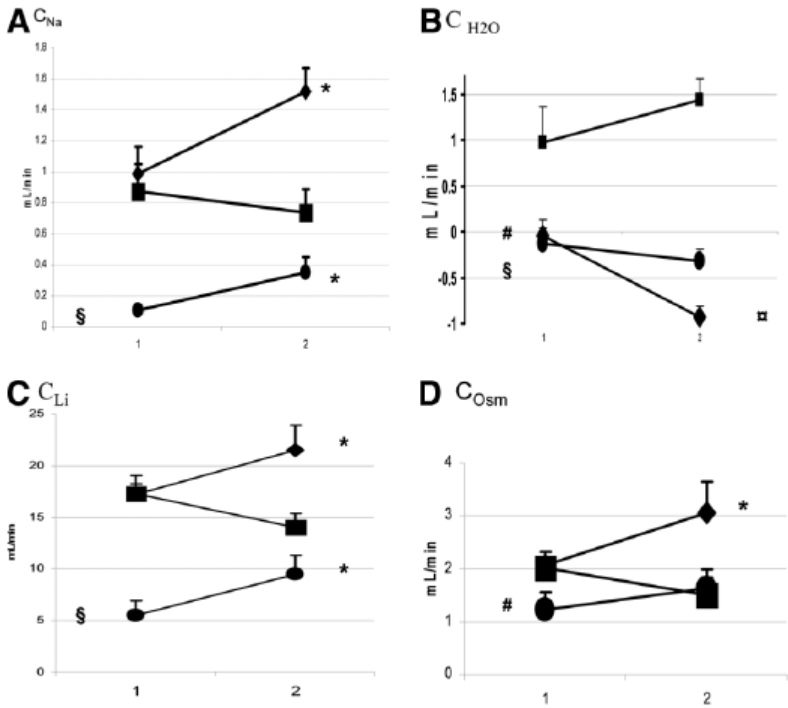
Aleksander Krag.

(Hepatology 2007;46:1863-1871.)



MAP no relationship to changes in GFR

Reversal of RAA, NE levels



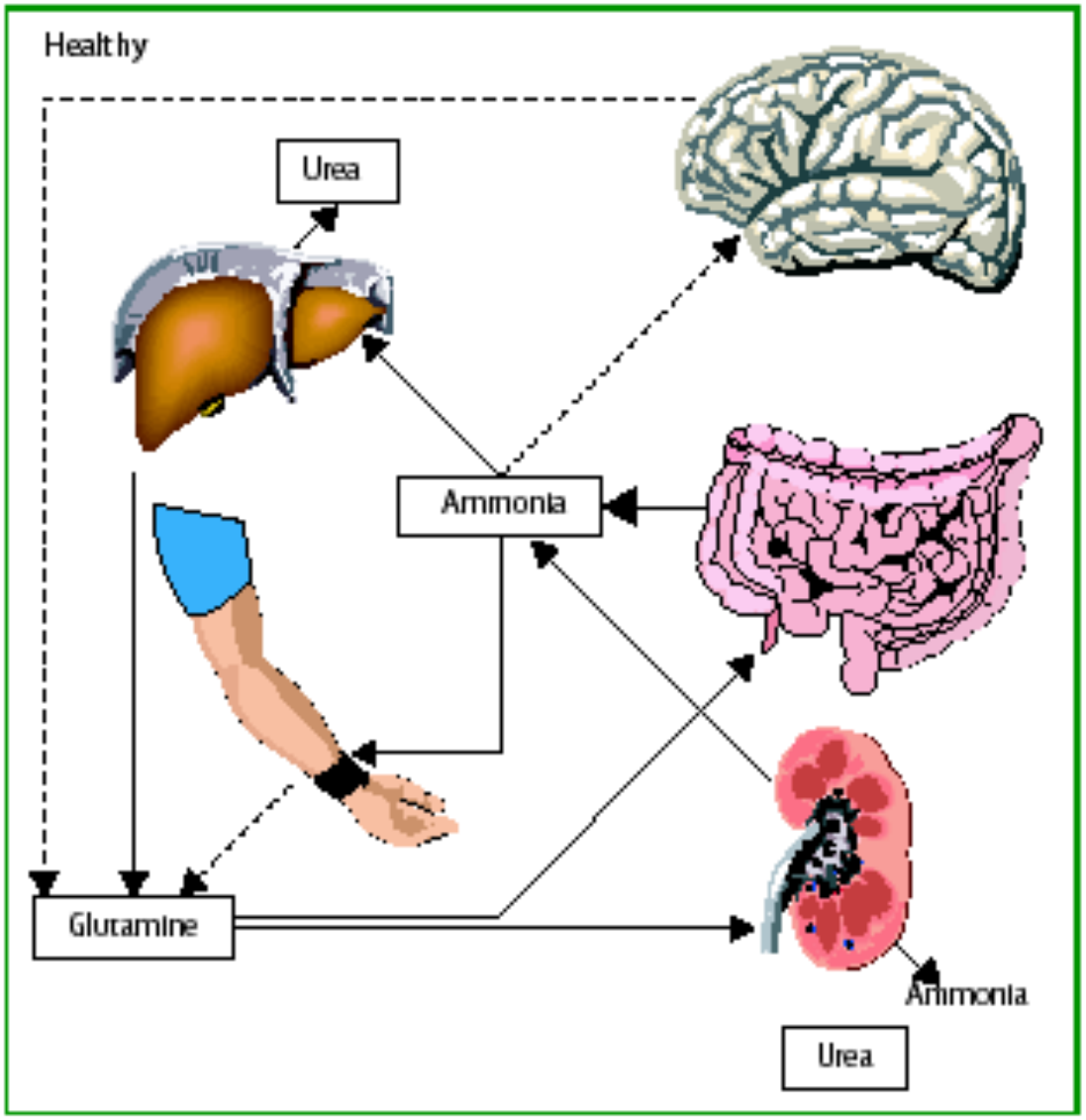
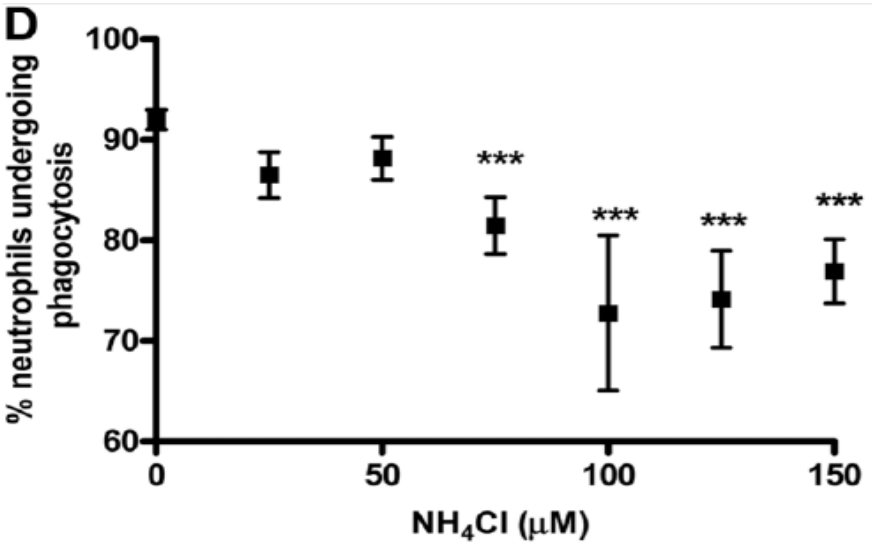


Figure: Interorgan trafficking of ammonia in health and in cirrhosis
In healthy individuals, liver removes ammonia by detoxification into urea. In patients with cirrhosis, metabolic capacity of liver is reduced, resulting in hyperammonaemia: muscle becomes important organ of ammonia detoxification into glutamine. Glutamine acts as temporary buffer that can both regenerate ammonia (enterocytes) and excrete ammonia (kidneys).

(HEPATOLOGY 2008;48:1202-1212.



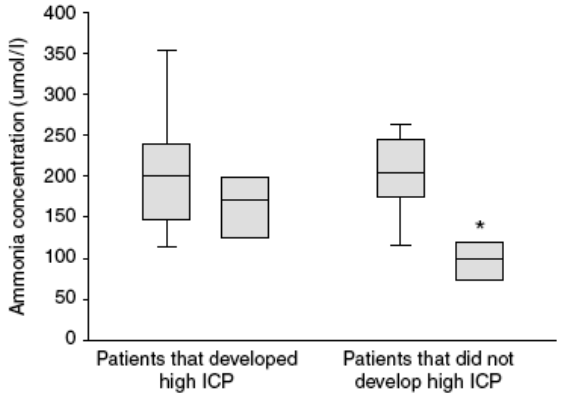
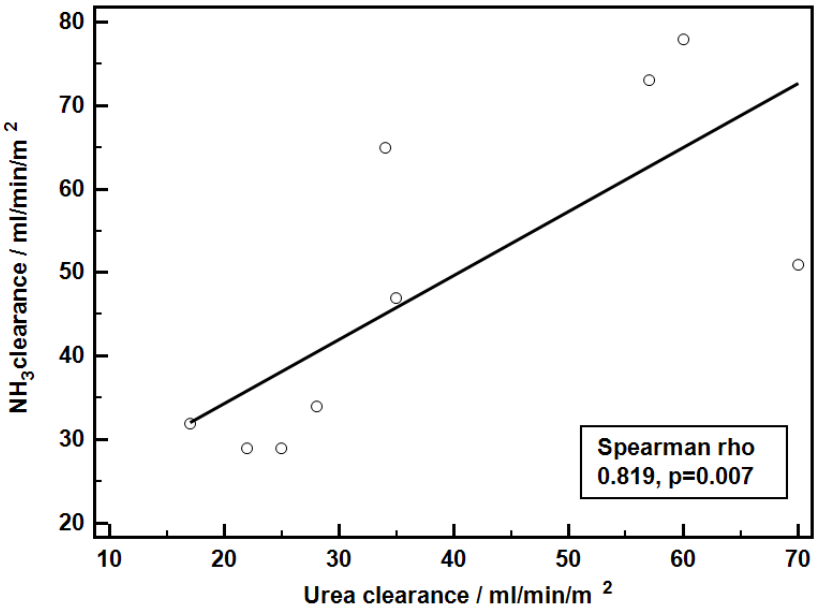
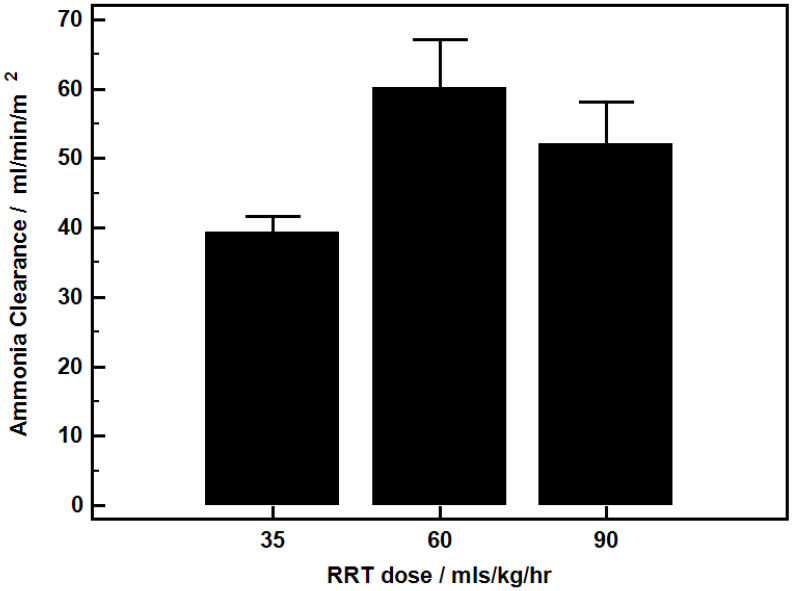


Figure 1 Arterial ammonia concentration (μmol/L) in two groups of patients with fulminant hepatic failure (FHF): patients who did develop high ICP and patients who did not. For each group, baseline values and values taken later during FHF are given. *$P<0.05$ versus baseline values in both groups.

CVHF Arterial NH4 > 100

Liver Int. 2013 May 17 Slack et al





Continuous renal replacement therapy (CRRT) in patients with liver disease: Is circuit life different?☆

Journal of Hepatology 51 (2009) 504–509

Retrospective chart study in patients undergoing RRT without initial anticoagulation

Coagulation data

Renal function and coagulation status prior to initiation of CRRT.

Parameter	ALF	ACLD	Post-LTx	Sepsis	Haematological
Urea mmol/l	16 (11.7)	23.6 (16.3)	15.9 (8.4)	22.0 (10.4)	25.1 (13.5)
Creatinine μmol/l	313.5 (147)	319.2 (340)	236.1 (87)	386.8 (273)	304 (155)
INR	5.66 (3.1)[a]	2.67 (0.74)	2.82 (0.97)	2.05 (0.89)	1.75 (0.29)
APTT (s)	120.6[b] (48.7)	104.4 (54.4)	67.5 (28.6)	53.9 (21.7)	52.5 (12.9)
Platelet count 10^9/l	109.5 (97.7)	80.4 (51.1)	71.3 (35.2)	204.6 (136)	53.5 (56.7)

Circuit life

Duration of continuous renal replacement (CRRT) circuits.

Parameter	ALF	ACLD	Post-LTx	Sepsis	Haematological
Mean filter life in hours – 1st–3rd filter	10.4 (8.6)	11.1 (7.8)	8.1 (6.2)	11.6 (11.4)	21.7 (19.7)*
Number of filters used/48 h	4.3 (1.3)	4.2 (2.1)	5.3 (1.5)	4.6 (1.5)	2.4 (1.1)**
Number of filter clots the 1st 3 CRRT circuit	2.1 (0.7)	1.9 (1.1)	1.9 (1.1)	2.1 (1.1)	1.8 (1)
Number of PRBC transfusion	4.8 (4.2)	4.2 (4.16)	2.2 (2.1)	3.0 (1.6)	1.2 (1.3)

Anticoagulation added to a sub group and filter life increased from 5.6 to 19 hours

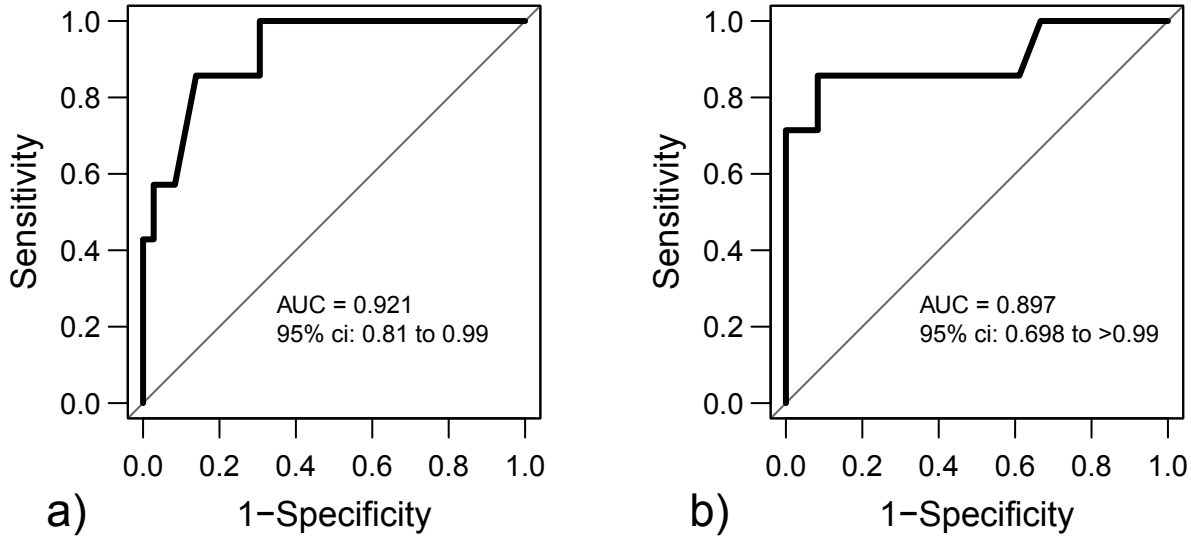
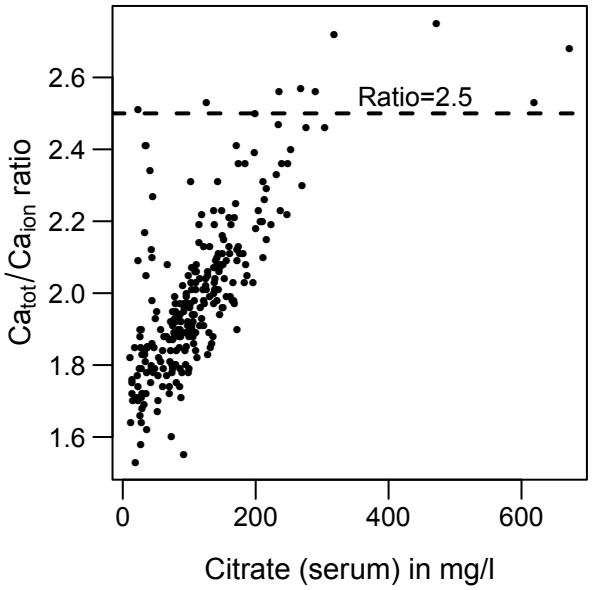


Figure 2 Predictive capabilities of prothrombin time and serum lactate regarding citrate accumulation. Baseline **(a)** prothrombin time and **(b)** serum lactate showed highest areas under the curve (AUC) in receiver operating characteristic analysis, therefore having best predictive capability for citrate accumulation in terms of a total calcium/ionized calcium ratio ≥2.5. ci, confidence interval.

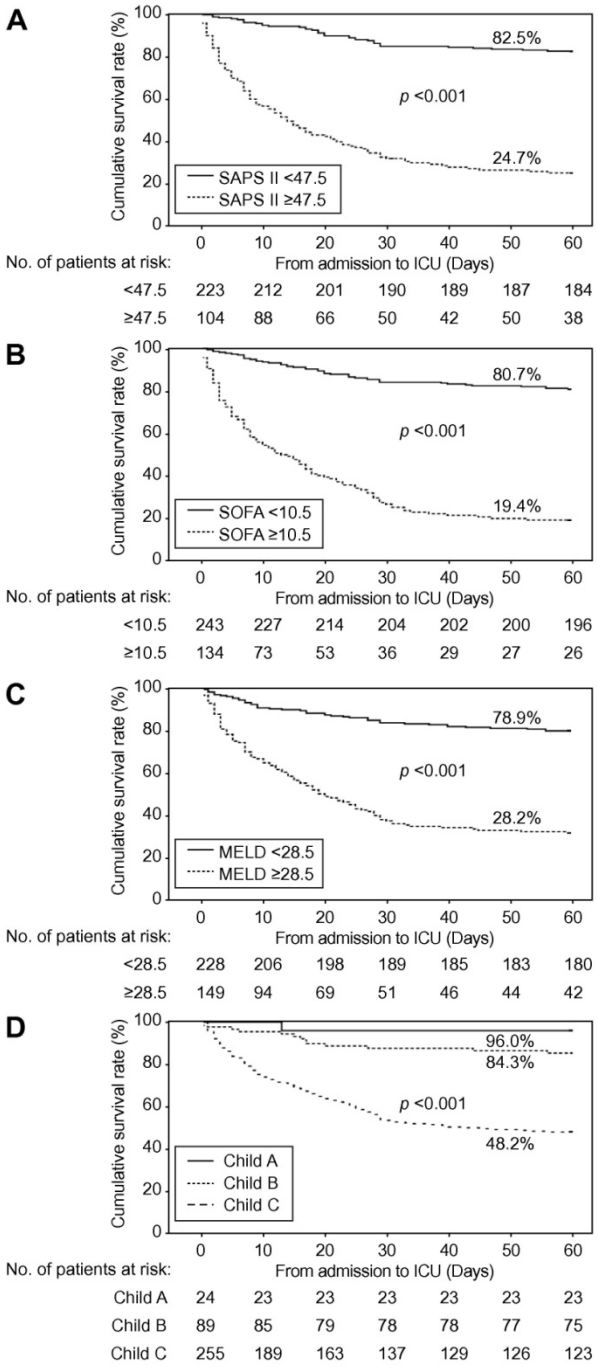
Schultheiss C et al Crit Care 2012 16:R162

Decreased citrate clearance in cirrhosis 340 ml/min
Vs 710 ml/min in normals
Krammer et al 2003

? Option of CVVHD vs CVVHF the former allowing lower blood flow and greater clearance of citrate

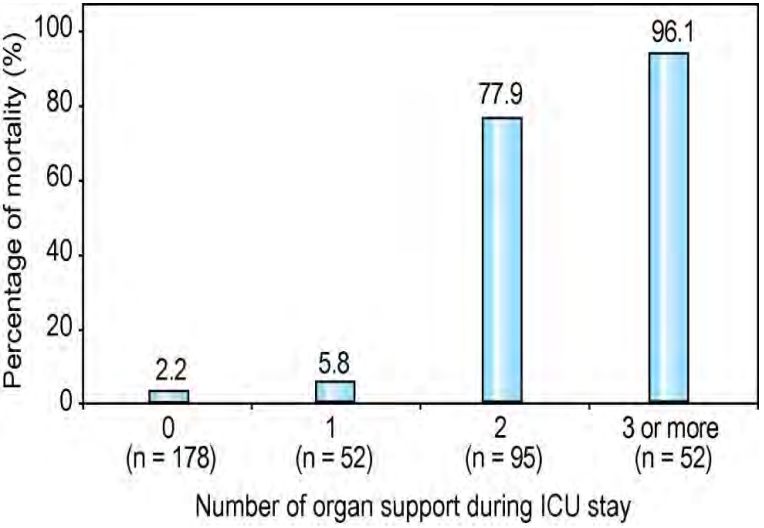


Acute on chronic liver failure: Prognostication based on scores

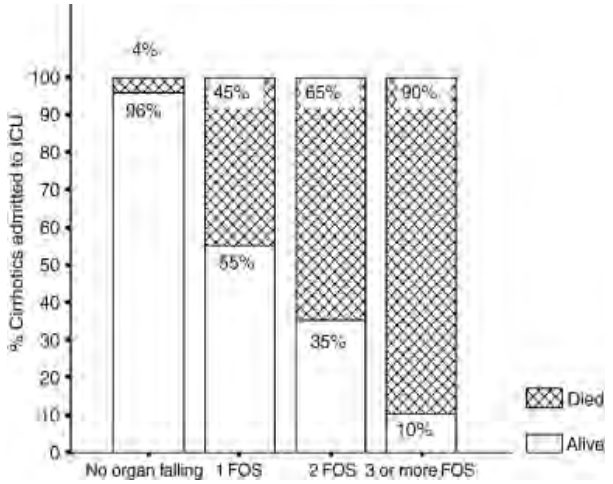


Levesque E et al. J Hepatology 2012, n = 377

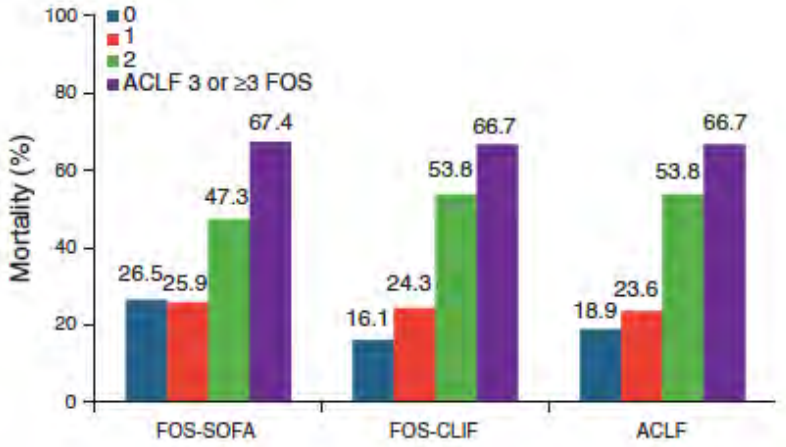
Acute on chronic liver failure: Prognostication based on number of organ failures



Levesque E et al. J Hepatology 2012



Cholongitas E et al. Aliment Pharmacol & Therap 2006



Theocharidou

The American Journal of GASTROENTEROLOGY 2014

Figure 3. Mortality according to number of failing organ system (FOS, according to SOFA and chronic liver failure-SOFA (CLIF-SOFA) criteria) and acute-on-chronic-liver-failure (ACLF) classification.

What do I do for oliguria

- Assess volume status – echo / pulse contour
- Look for sepsis : blood/ chest/ ascites
- Look at delta creatinine
- Urinalysis and consider other diagnoses than HRF
- Rx antibiotics and volume …
- Early use of terlipressin (oliguria / hyponatraemia)
  - 0.25 to 0.5 mg 6 hourly and review and increase every 2 days
- Measure IAP
  - If > 20-25 consider paracentesis
  - Data supports use of volume replacement if large volume or unstable
  - Can also use terlipressin 1 mg x 3 doses 8 hourly


Treat the kidneys early
Large blood volume - all
in the wrong space !
THE LIVER
IS EVIL AND
MUST BE
PUNISHED
Kronenbourg
1664
COLD
première
Premium
Extra Cold
ARCHERS
HADRIAN & BORDER
Festival

Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients

Crit Care Med 2003 Vol. 31, No. 10

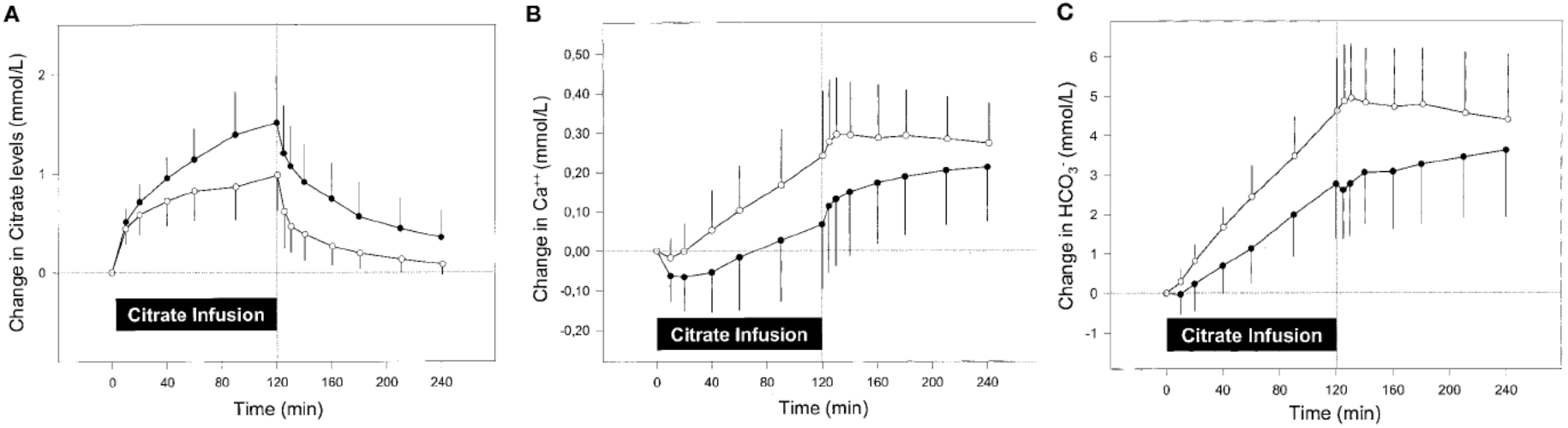
Ludwig Kramer

Table 3. Citrate pharmacokinetics

	Cirrhotic Patients	Control Group	*p* Value
Total dose, mmol	77 ± 21	72 ± 10	.40
$C_{baseline}$, mmol/L	0.51 ± 0.13	0.06 ± 0.13	<.001
C_{max}, mmol/L	1.60 ± 0.50	1.01 ± 0.39	.007
T_{max}, mins	115 ± 12	114 ± 16	.93
AUC, mmol × min/L	282 ± 130	131 ± 68	<.001
$t_{1/2}$, mins	69 ± 33	36 ± 18	.001
Vd_z	27 ± 9	29 ± 10	.52
Vd_{ss}	23 ± 6	21 ± 6	.34
Clearance, mL/min	340 ± 185	710 ± 397	.002

NaCitrate @ 0.5 mg/kg/hr
CaCa 0.17 ml/kg/hr

Increase citrate
No citrate side effects



Closed circles cirrhotics

CVVHD + regional citrate in liver failure – observational study *Schultheiss C et al Crit Care 2012 16:R162*

Critical ratio of 2.5 exceeded 10 times (of 273) in 7 of 43 runs; seen at 12 hours(3), 24 hours (6) and 1 at 72 hours

- Equalization of acid base was possible
- Standard laboratory values did not correlate with citrate accumulation or ratio > 2.5
- Lactate > 3.5 mmol/L or prothrombin ratio < 26% predict ratio Ca_{tot}/ Ca_{ion} > 2.5
- sensitivity 86% for both and specificity of 86% for lactate and 92% for prothrombin) AUROC : 0.92 and 0.9
- AUROC for AST 0.71, 0.49 ALT, 0.67 for bilirubin, 0.73 cholinesterase, 0.54 ICG
- Accumulation in citrate correlated with an increase in Ca_{tot}/Ca_{ion}

- Specific diseases
  - Alcoholic hepatitis : steroids and NAC
- Decreased GCS / encephalopathy and oliguria
- Measure arterial ammonia
- Consider RRT early vs late
- Aggressive early support of organ failures and then review at a few days

- Which fluids
  - ????

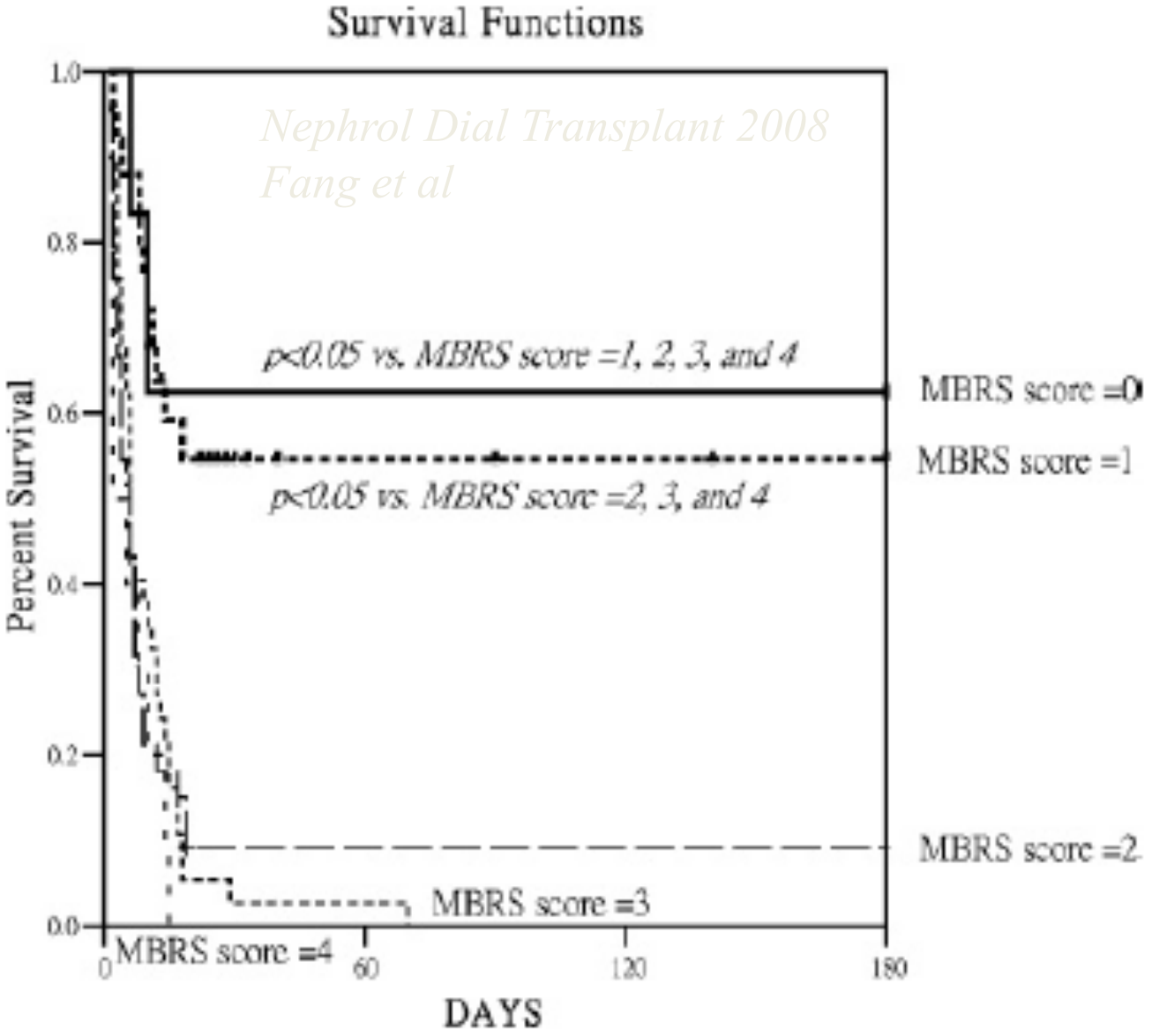


Fig. 1. Cumulative survival in 111 critical ill cirrhotic patients with acute renal failure according to their MBRS score after the first day of admission to a specialized hepatogastroenterology intensive care unit.

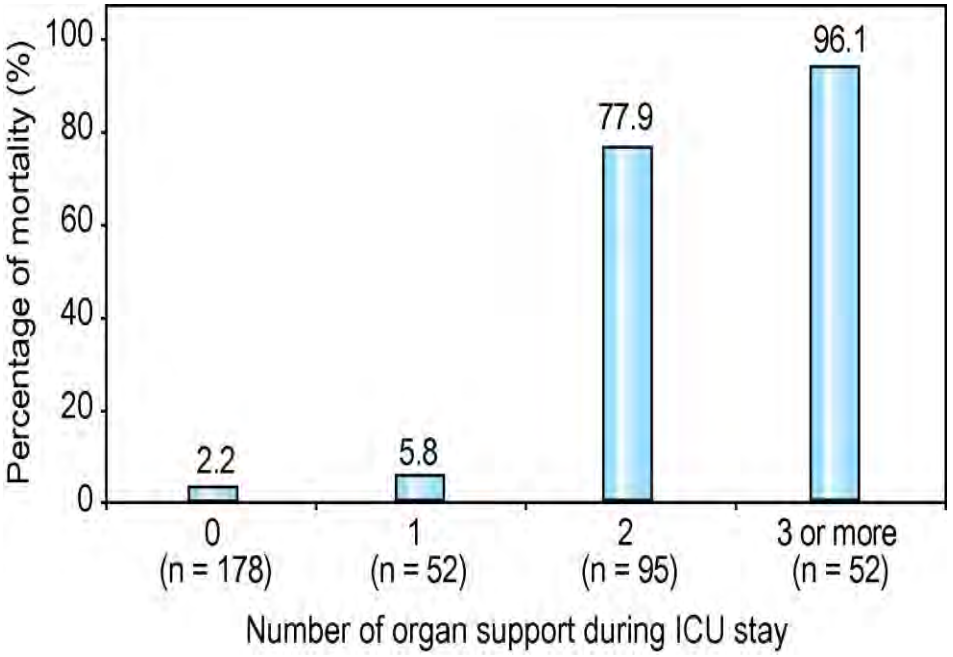
111 patients
ITU admissions
with cirrhosis +
ARF

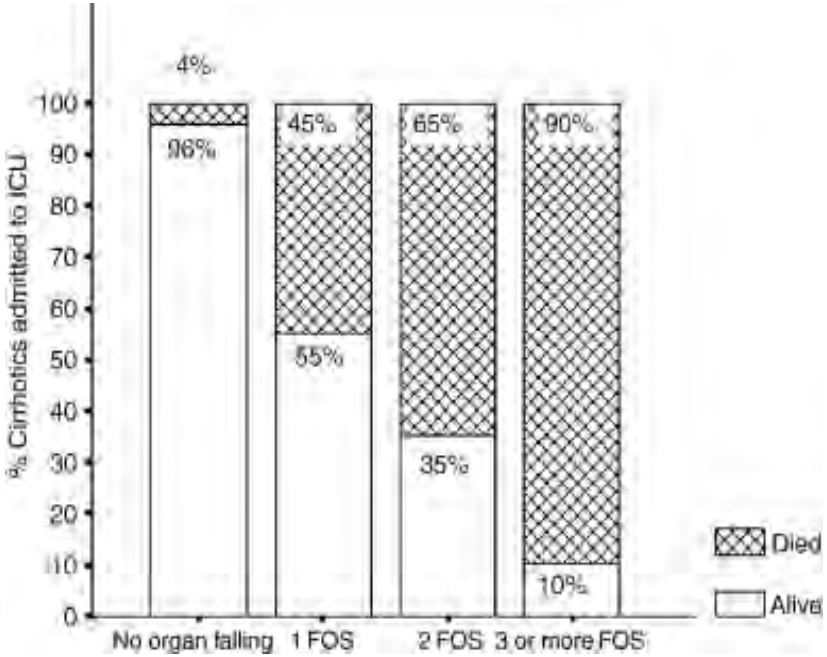
2003-2005

Scoring system
MAP 80
Bili 80
Resp failure
Sepsis

ROC 0.89
mortality > 90%
if score > 2

Acute on chronic liver failure: Prognostication based on number of organ failures



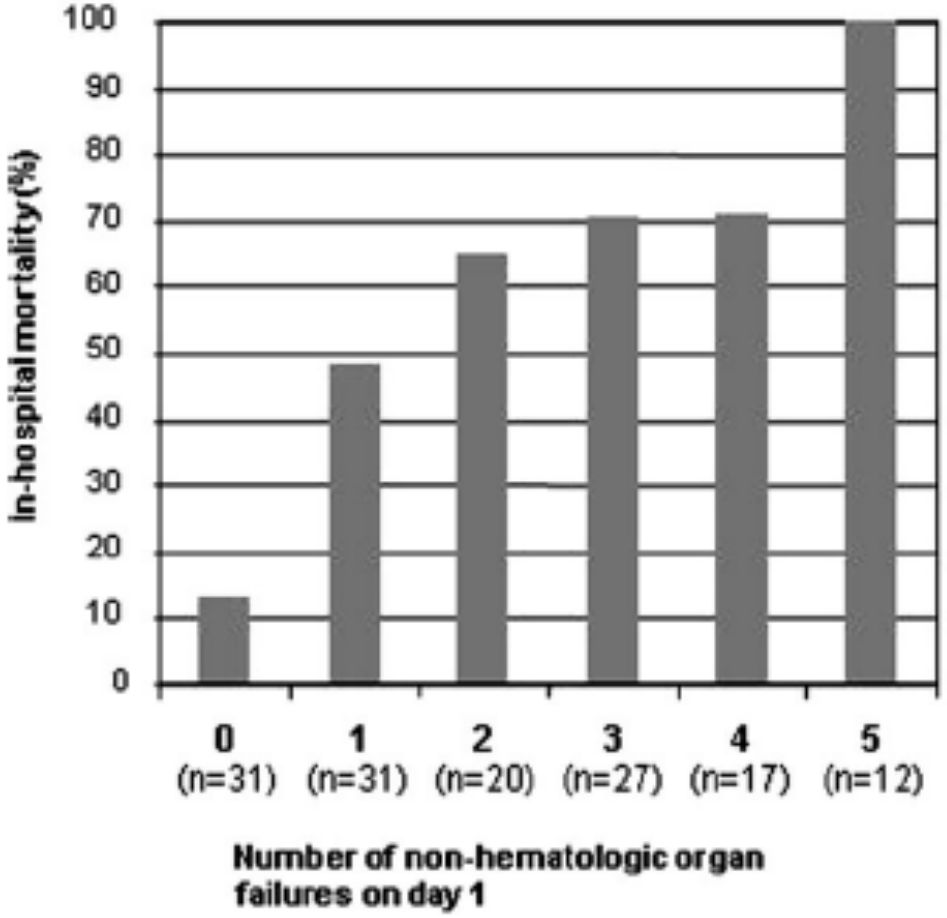


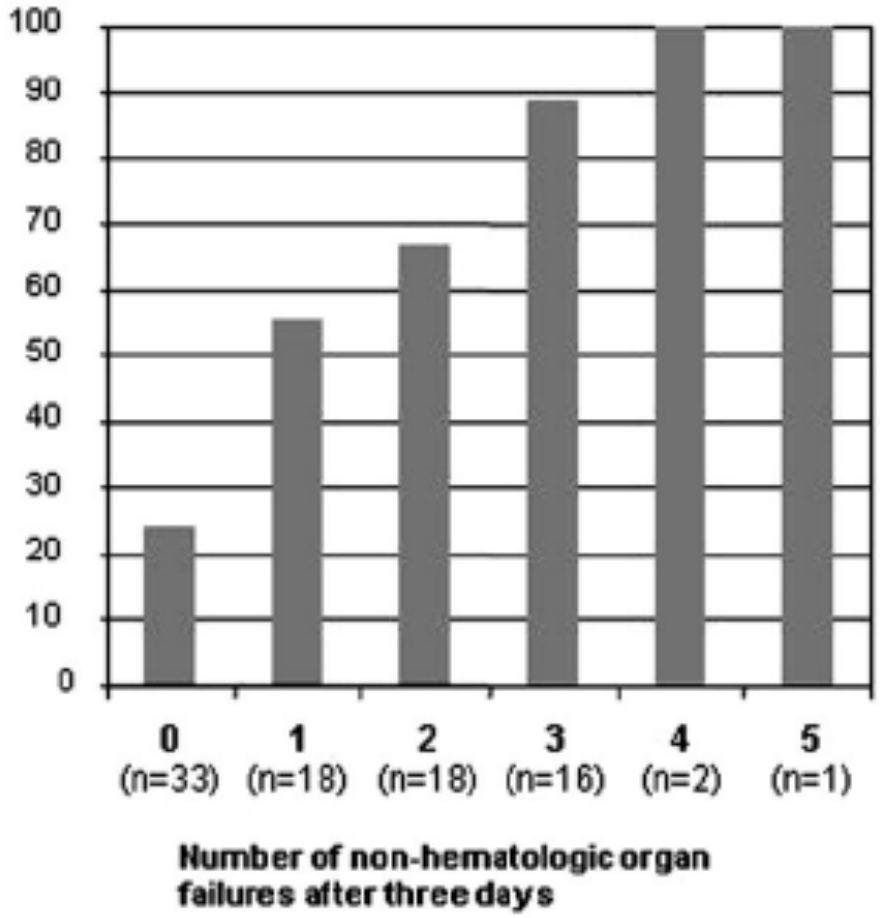
Levesque E et al. J Hepatology 2012

Cholongitas E et al. Aliment Pharmacol & Therap 2006

Cirrhotic patients in the medical intensive care unit: Early prognosis and long-term survival*

Vincent Das,
Crit Care Med 2010; 38:2108–2116)

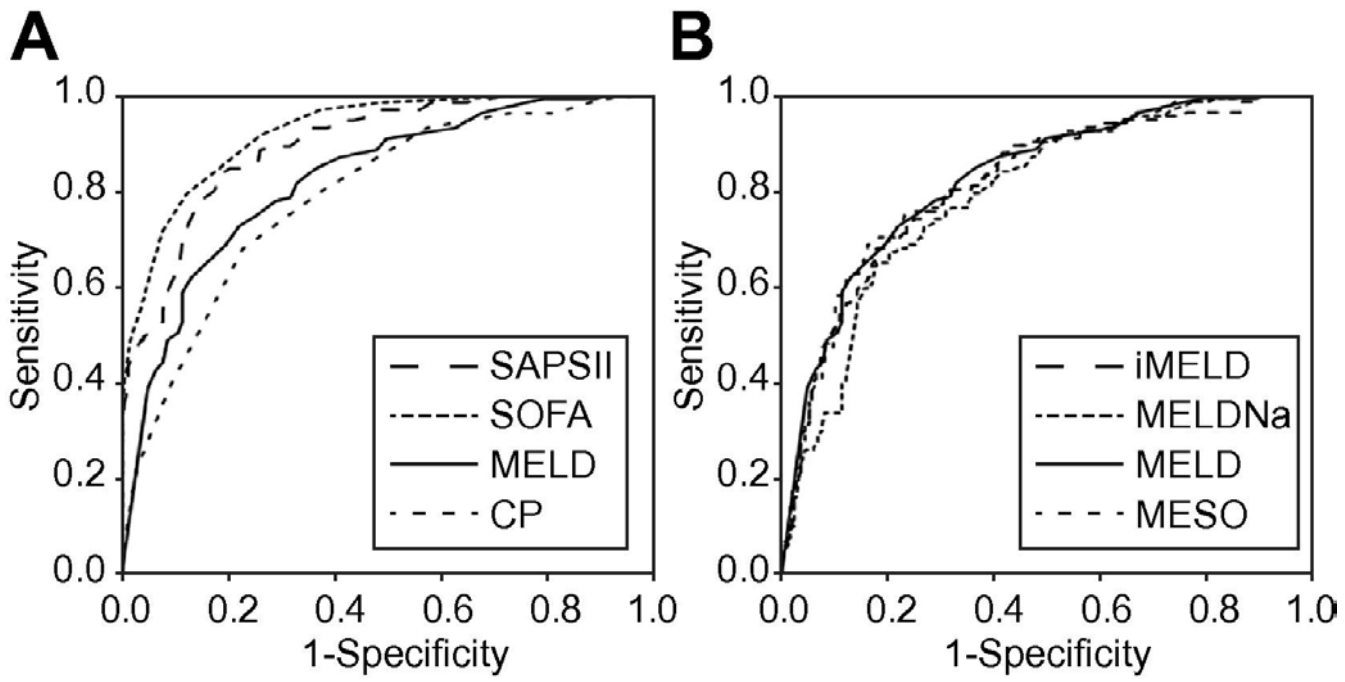




20-40% of patients discharged who had required organ support on admission : 6 month survival of 40%

Acute on chronic liver failure: Prognostication based on scores

45% I&V
40% pressors
12% RRT



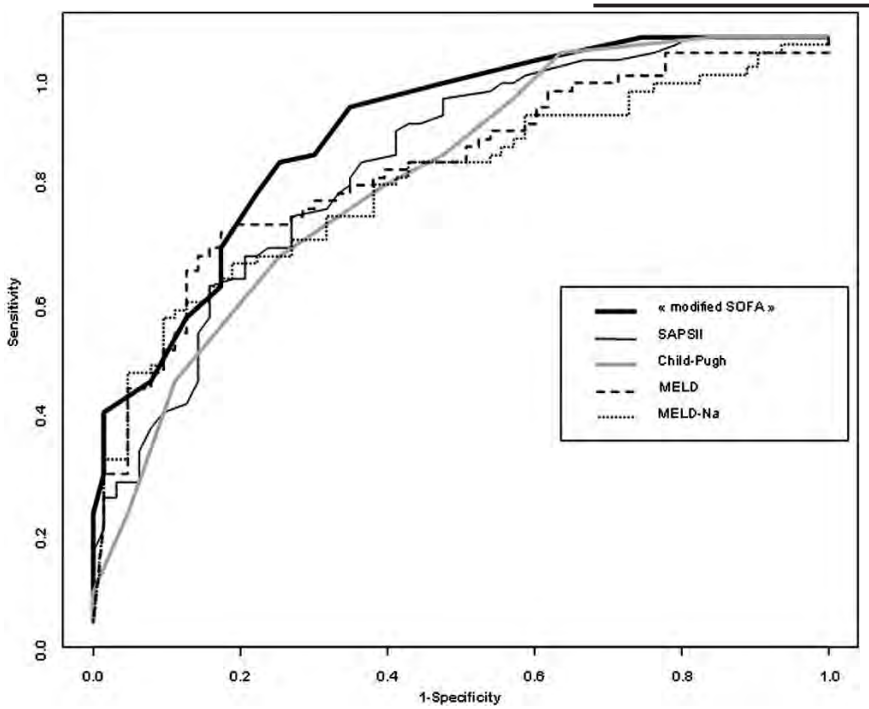
Scoring system	Cut-off point	Youden Index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SOFA	10.5	0.67	79	87	78	88
MELD	28.5	0.50	72	78	63	84
SAPS II	47.5	0.65	83	81	70	91

Levesque E et al. J Hepatology 2012, n =377

Cirrhotic patients in the medical intensive care unit: Early prognosis and long-term survival*

Table 4. Risk factors on day 1 for inhospital mortality: Results of multivariate analysis

Characteristic	Odds Ratio (95% Confidence Interval)	*p*
Age		.002
<50	1	
>50	6.6 (2.2–23.2)	
Serum albumin (per 5 g/L)	0.7 (0.5–0.96)	.035
International normalized ratio (per 0.1 additional units)	1.1 (1.0–1.2)	.05
Modified Sequential Organ Failure Assessment score (per 1 additional unit)	1.3 (1.2–1.5)	<.0001



Crit Care Med 2010; 38:2108–2116)

Vincent Das,

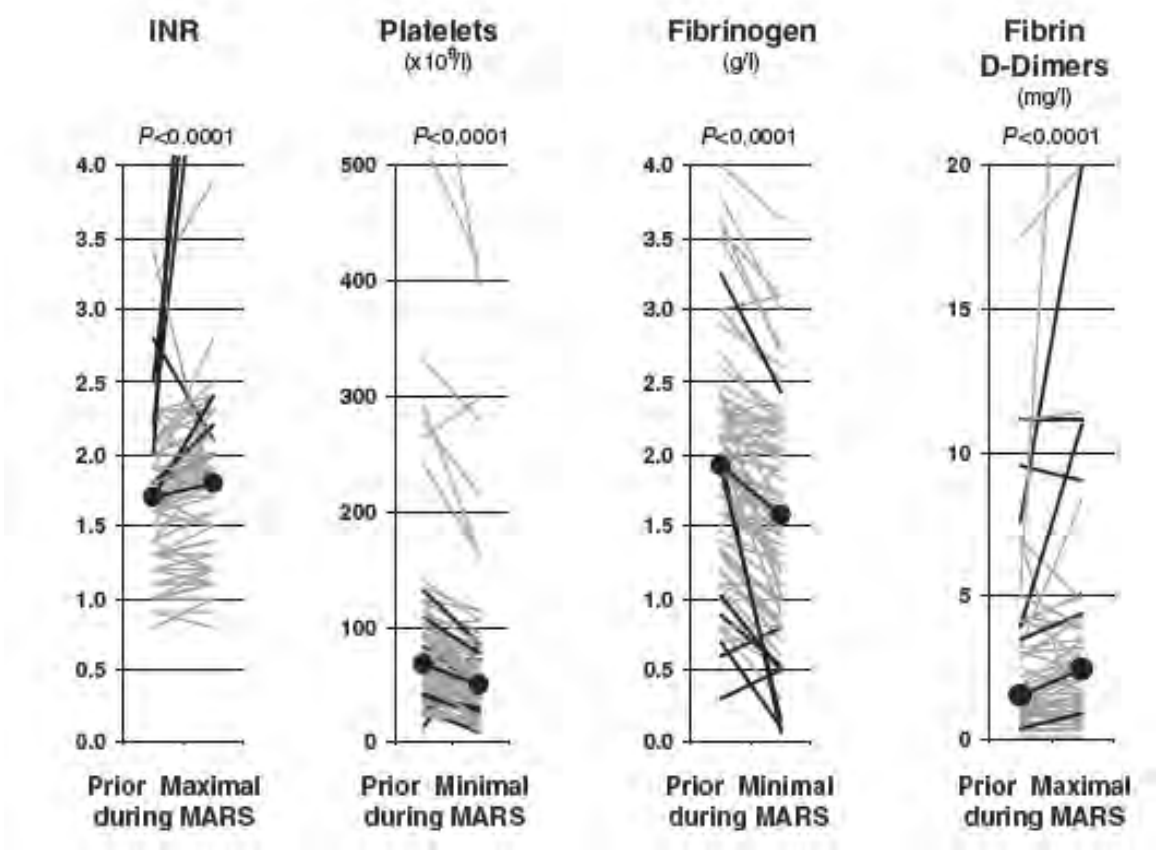
Data 2000-2008 : KCH

- 478 admissions with cirrhosis
- Excluded anyone transplanted on that ITU admission
- 253 received RRT 225 did not
  - 22% ITU discharge 13% hospital discharge
  - Sepsis commonest cause for deterioration

- Scores on admission
  - CP 12 vs 11, MELD 32 vs 17, SOFA 13 vs 11
  - SOFA – R 9 vs 7
  - No difference for early vs late RRT
  - No vent or pressors but RRT 78% ITU and 48% hospital discharge

Artificial liver support with the molecular adsorbent recirculating system: activation of coagulation and bleeding complications Liver International (2007)

Esther B. Bachli[1*†], Reto A. Schuepbach[1*], Marco Maggiorini[1,2], Reto Stocker[3], Beat Müllhaupt[4] and Eberhard L. Renner[4‡]



Doria et al
Clinical Transplantation 2004;18:365

Significant worsening of PT, all TEG variables, factor VIII, von WB, DDimers

Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study *Critical Care* 2006, 10:R24 Peter Faybik[1],

Statistical decrease in platelets and fibrinogen and other TEG functions but no evidence of clot lysis / fibrinolysis however

Acute kidney injury in patients admitted to a liver intensive therapy unit with ALF . *O'Riordan A*

Nephrol Dial Transplant (2011) 26: 3501–3508

Period 2000-2007 : 302 ALF managed without OLT

21% did not develop AKI : all survived

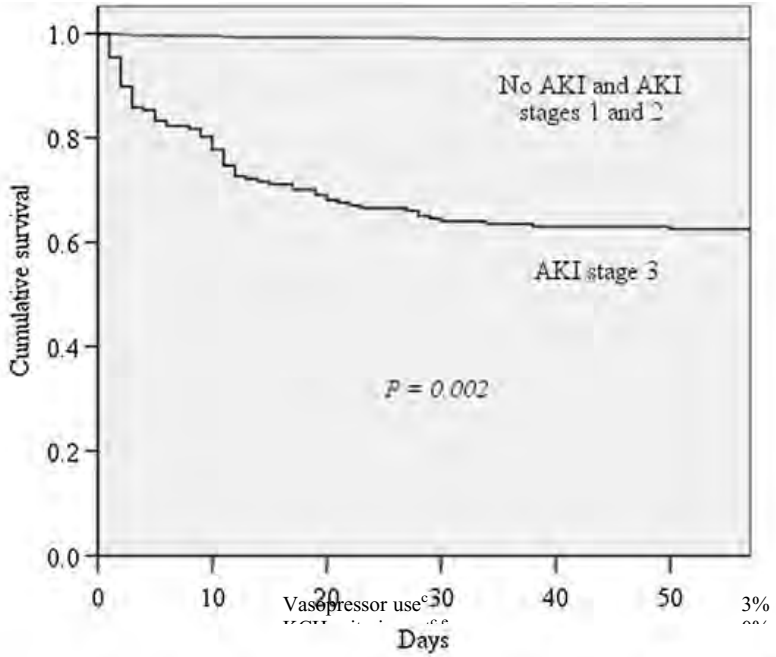
239 with AKI of whom 164 survived

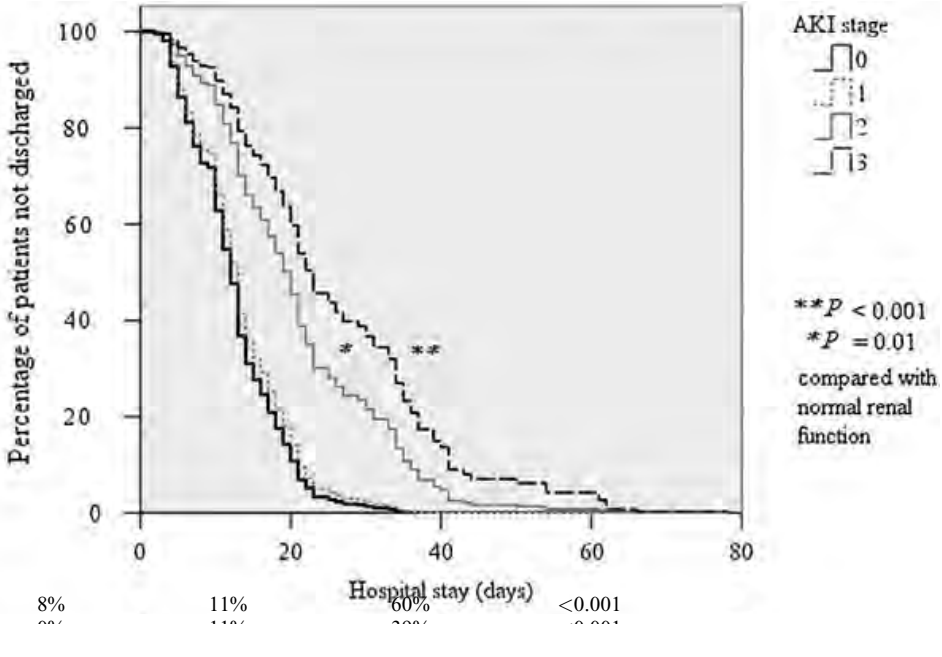
Lactate 2-7
INR 2-5

51% return of normal renal function
eGFR > 60 discharge

7% required on going haemodialysis at time of discharge
At 30 days post discharge of this group eGFR was 20
At 90 days none dialysis dependant and eGFR > 60
AKI does not impact on outcome om mutivariate analysis

Nephrol Dial Transplant. 2011 Nov;26(11): 3501-8.





Vasopressor use[c]	3%	8%	11%	60%	<0.001

	AKI stage				
Variables	0 ($n = 63$)	1 ($n = 25$)	2 ($n = 19$)	3 ($n = 195$)	P for trend[b]
Lactate (mmol/L)	2 (2–3)	3 (2–3)	2 (2–3)	4 (2–7)	<0.001
International normalized ratio	3 (2–4)	4 (2–5)	2 (2–4)	4 (3–5)	<0.001

On multivariate analysis AKI not significant vs prognostic models

Examining those in receipt of RRT

	survivors	non survivors
RRT alone	17	5
NA + RRT	4	9
Vent +RRT	8	18
NA+RRT+ vent	28	166

50% of cases require RRT : 22% survival overall

Differences between S and NS

Duration of Rx 6 (3-12) vs 8 (3-14)
D1 urine output 500 (10-1000) vs 285 (0-1000)
D1 lactate 2.2 (1.6-4) vs 3.1(1.8 - 5.5)
D3 lactate 1.8 (1.3-2.5) vs 2.6 (1.8-4.8)