SINGAPORE HEPATOLOGY CONFERENCE

ADVANCED LIVER DISEASE SERIES

December 7th, 2020

LONG TERM ALBUMIN REPLACEMENT: A PANACEA FOR DECOMPENSATED CIRRHOSIS ?

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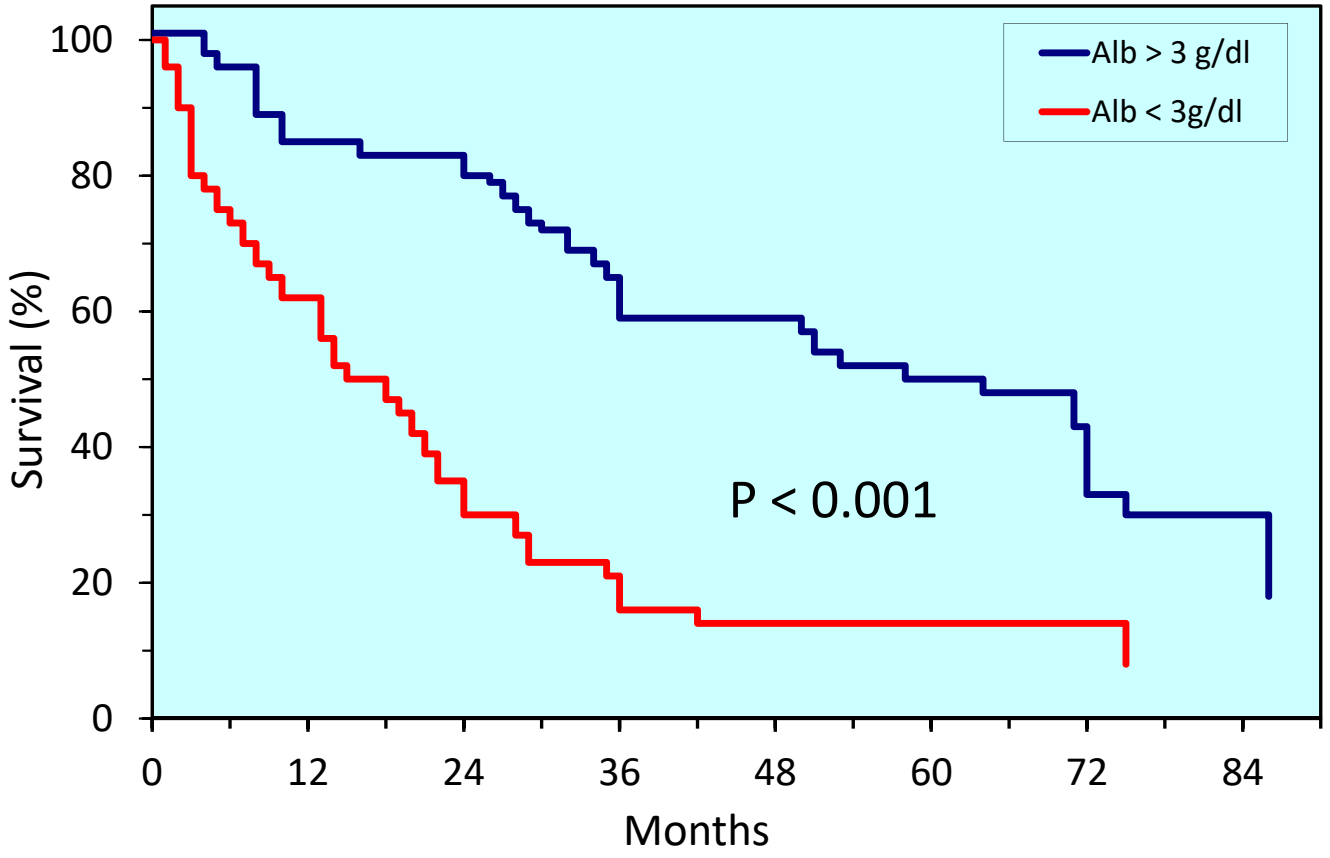
DISCLOSURE

CLS Behring GmbH	consultant
	speaker
Takeda Pharmaceuticals	consultant
	speaker
Grifols SA	consultant
	speaker
Martin Pharmaceuticals	consultant
PPTA	speaker
Octapharma AG	speaker
Gilead Sciences	speaker
AbbVie Italia	speaker

SERUM ALBUMIN

PROGNOSTIC POWER IN PATIENTS WITH CIRRHOSIS



Salerno et al, Am J Gastroenterol 1983

WHY AND HOW DO WE USE ALBUMIN IN DECOMPENSATED CIRRHOSIS?

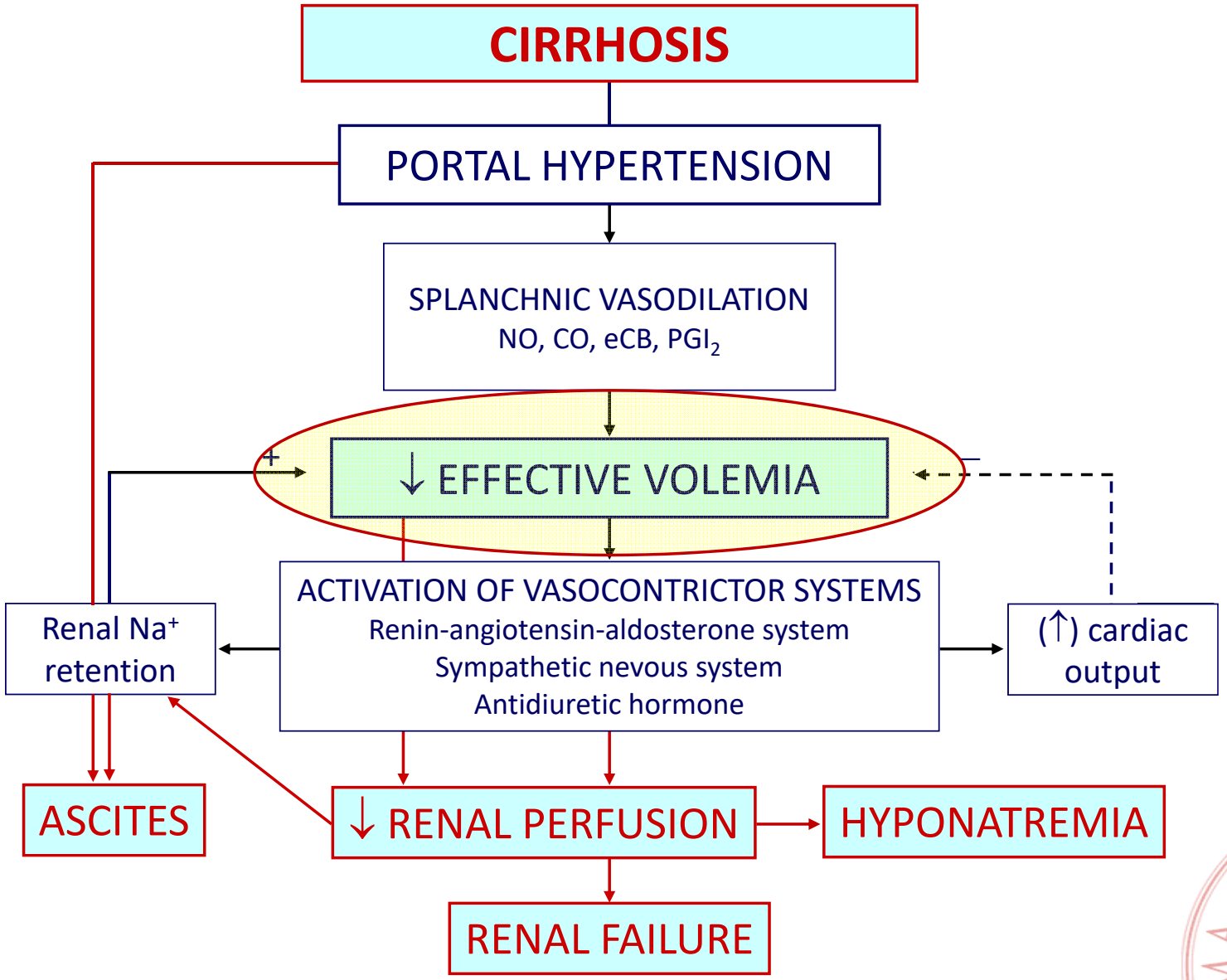
0270-9139/88/0805-1151$02.00/0
HEPATOLOGY

Vol. 8, No. 5, pp. 1151–1157, 1988
Printed in U.S.A.

Special Article

Peripheral Arterial Vasodilation Hypothesis: A Proposal for the Initiation of Renal Sodium and Water Retention in Cirrhosis

ROBERT W. SCHRIER, VICENTE ARROYO, MAURO BERNARDI, MURRAY EPSTEIN, JENS H. HENRIKSEN AND JOAN RODÉS



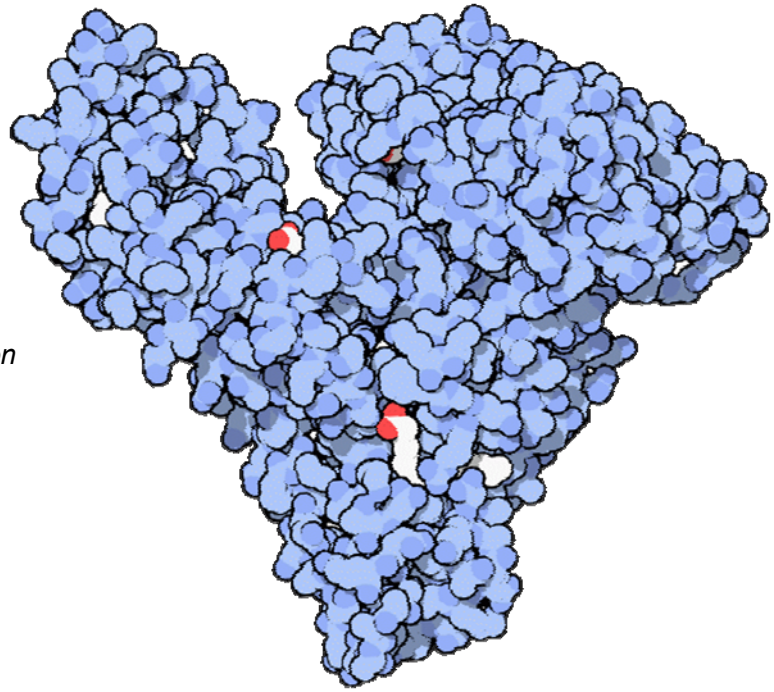
Schrier, Arroyo, Bernardi, Epstein, Henriksen, Rodés, Hepatology 1988

ALBUMIN MOLECULE

ONCOTIC PROPERTIES

Regulation of fluid distribution

High plasma concentration
High molecular weight
Negative net charge



ONCOTIC

PERIPHERAL ARTERIAL VASODILATION HYPOTHESIS

IMPACT ON CLINICAL PRACTICE

Pathophysiology of paracentesis-induced circulatory dysfunction

↓

Prevention by albumin infusion

Pathophysiology of PBS-induced renal dysfunction

↓

Prevention by albumin infusion

Pathophysiology of hepatorenal syndrome

↓

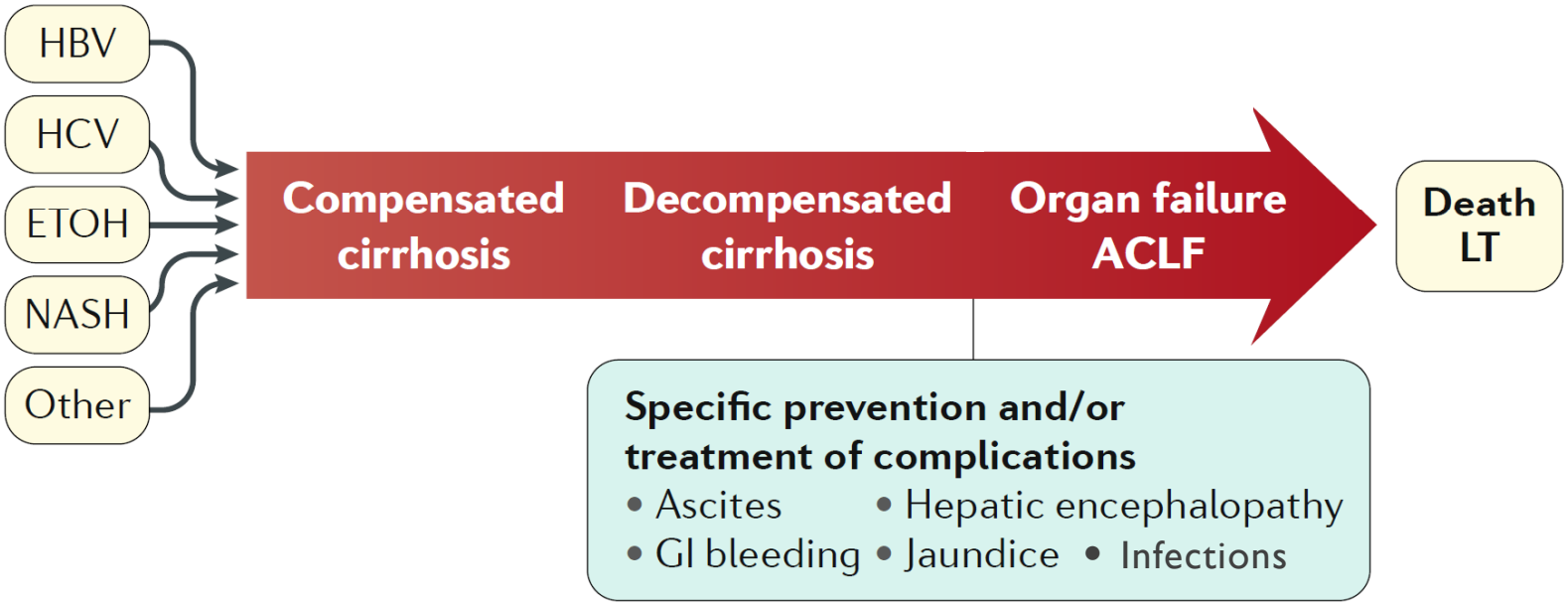
Treatment with vasoconstrictors + albumin

Sort et al, NEJM 1999
Sanyal et al, Gastroenterology 2008
Martin-Llahi et al, Gastroenterology 2008

Ginés et al, Gastroenterology 1996
Bernardi et al, Hepatology 2012

MANAGEMENT OF DECOMPENSATED CIRRHOSIS

CURRENT APPROACH



Bernardi and Caraceni, Nat Rev Gastroenterol Hepatol 2018

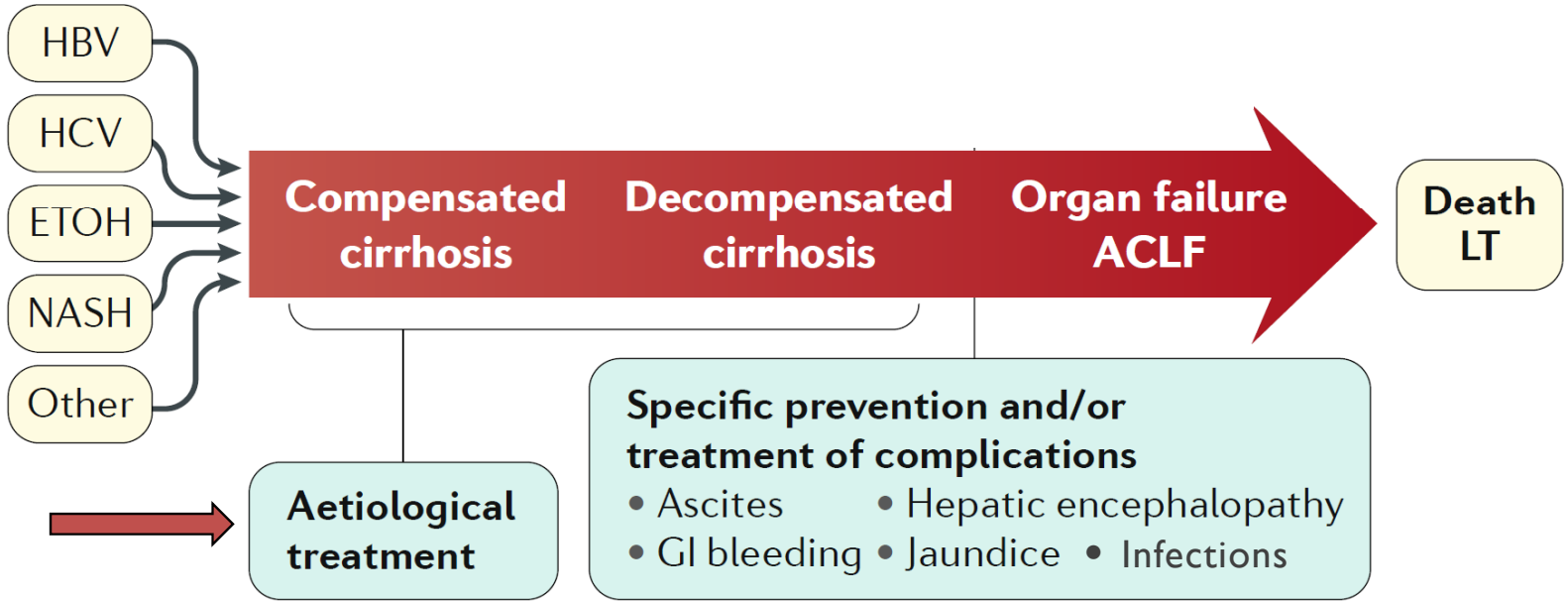
MANAGEMENT OF DECOMPENSATED CIRRHOSIS

PREVENT / TREAT SPECIFIC COMPLICATIONS → MANAGE THE DISEASE

- Modify the natural history of the disease
- Prevent organ failure and ACLF
- Reduce hospitalizations & the burden on heathcare
- Improve survival and quality of life

MANAGEMENT OF DECOMPENSATED CIRRHOSIS

MODIFYING THE NATURAL HISTORY OF THE DISEASE



Bernardi and Caraceni, Nat Rev Gastroenterol Hepatol 2018

DISEASE MODIFYING AGENTS

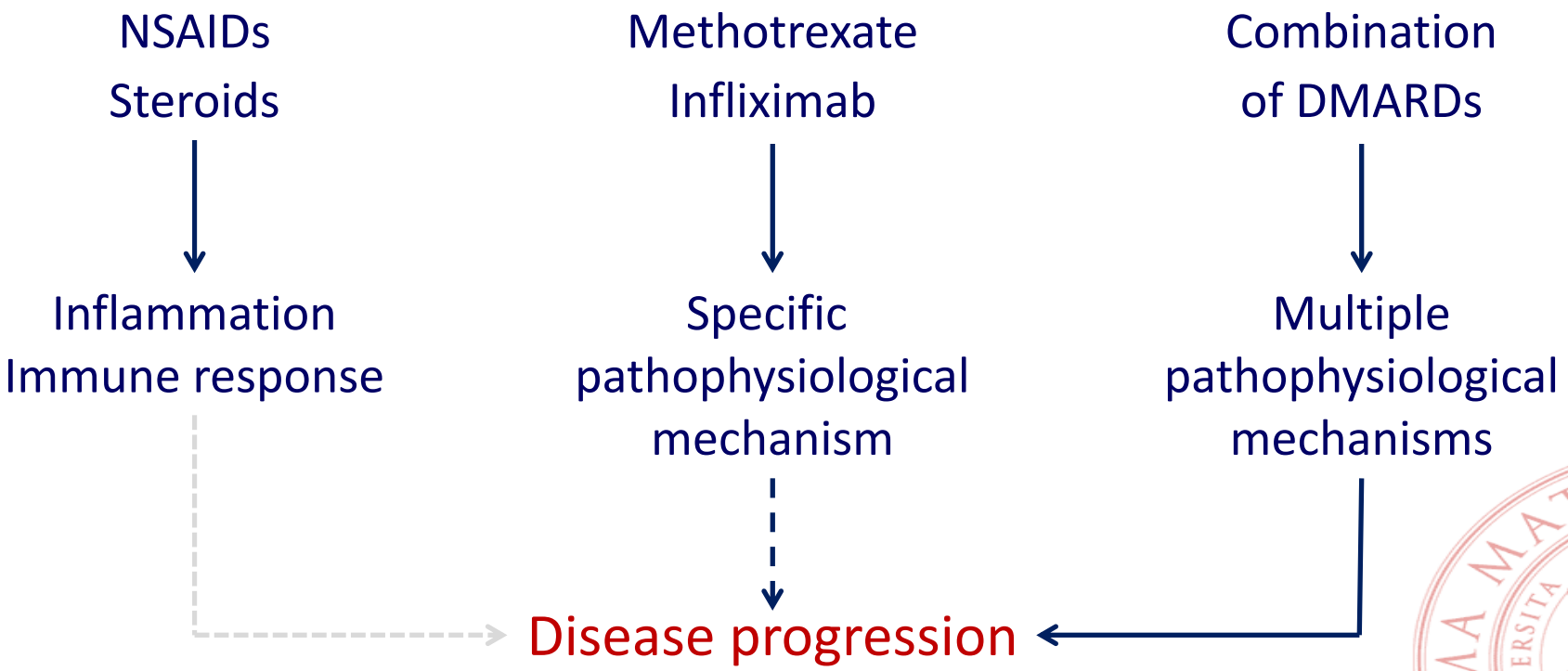
THE CONCEPT

Disease modification can be defined as treatments or interventions that affect **the underlying pathophysiology** and have a **beneficial outcome** on the **course of a disease**

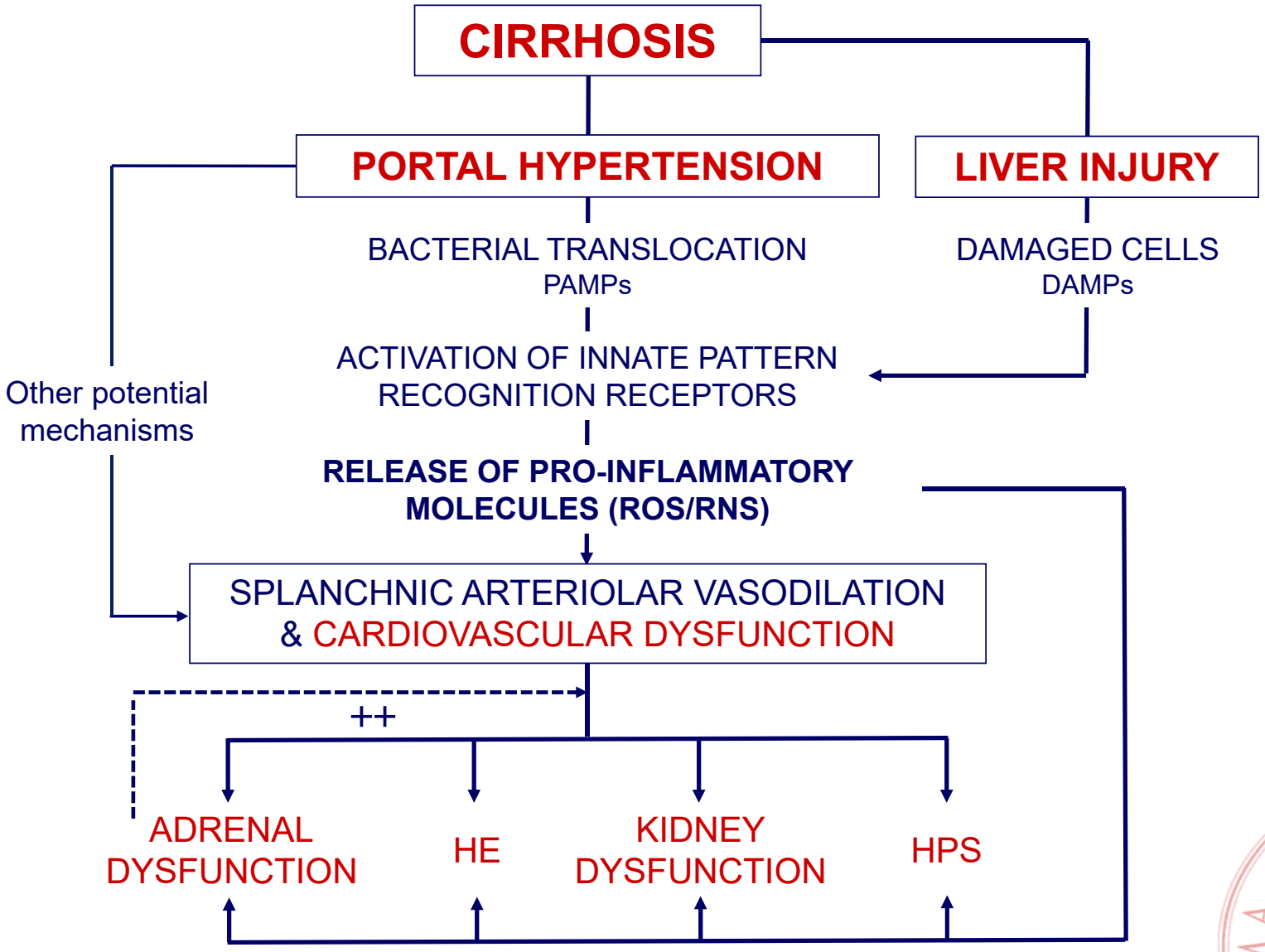
DISEASE MODIFYING AGENTS

THE CONCEPT

Disease-modifying antirheumatic drugs (DMARDs)



TRANSLATING THE DMARDs CONCEPT TO DECOMPENSATED CIRRHOSIS



Bernardi, Moreau, Angeli, Schnabl, Arroyo, J Hepatol 2015

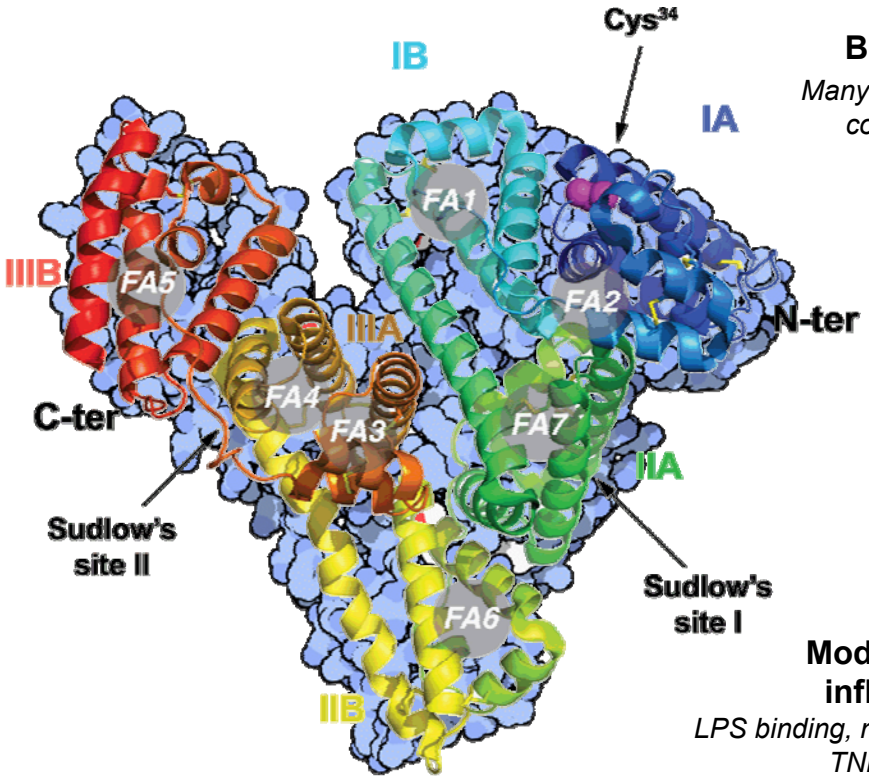
HE: hepatic encephalopathy
HPS: hepato-pulmonary syndrome

THE ALBUMIN MOLECULE

PLEIOTROPIC EFFECTS

Regulation of fluid distribution

High plasma concentration
High molecular weight
Negative net charge



Binding and transport

Many endogenous and exogenous compounds including drugs

Antioxidant

Free radical and metal ion scavenging

Endothelial stabilization

Immunomodulation and antioxidant properties

Regulation of extracellular pH

Binding of H^+

Hemostatic effect

NO binding at Cys-34

Modulation of immune and inflammatory responses

LPS binding, modulation of intracellular redox state, TNFα inhibition, PGE binding

ONCOTIC

NON-ONCOTIC

Modified from Bernardi et al, Gut 2020

NON-ONCOTIC ALBUMIN PROPERTIES

CURRENT EVIDENCE IN PATIENTS WITH CIRRHOSIS

Albumin infusion in patients with SBP increases PVR and cardiac work

Fernandez et al, J Hepatol 2004; Hepatology 2005

Albumin restores heart contractility in cirrhotic rats with ascites

Bortoluzzi et al, Hepatology 2012

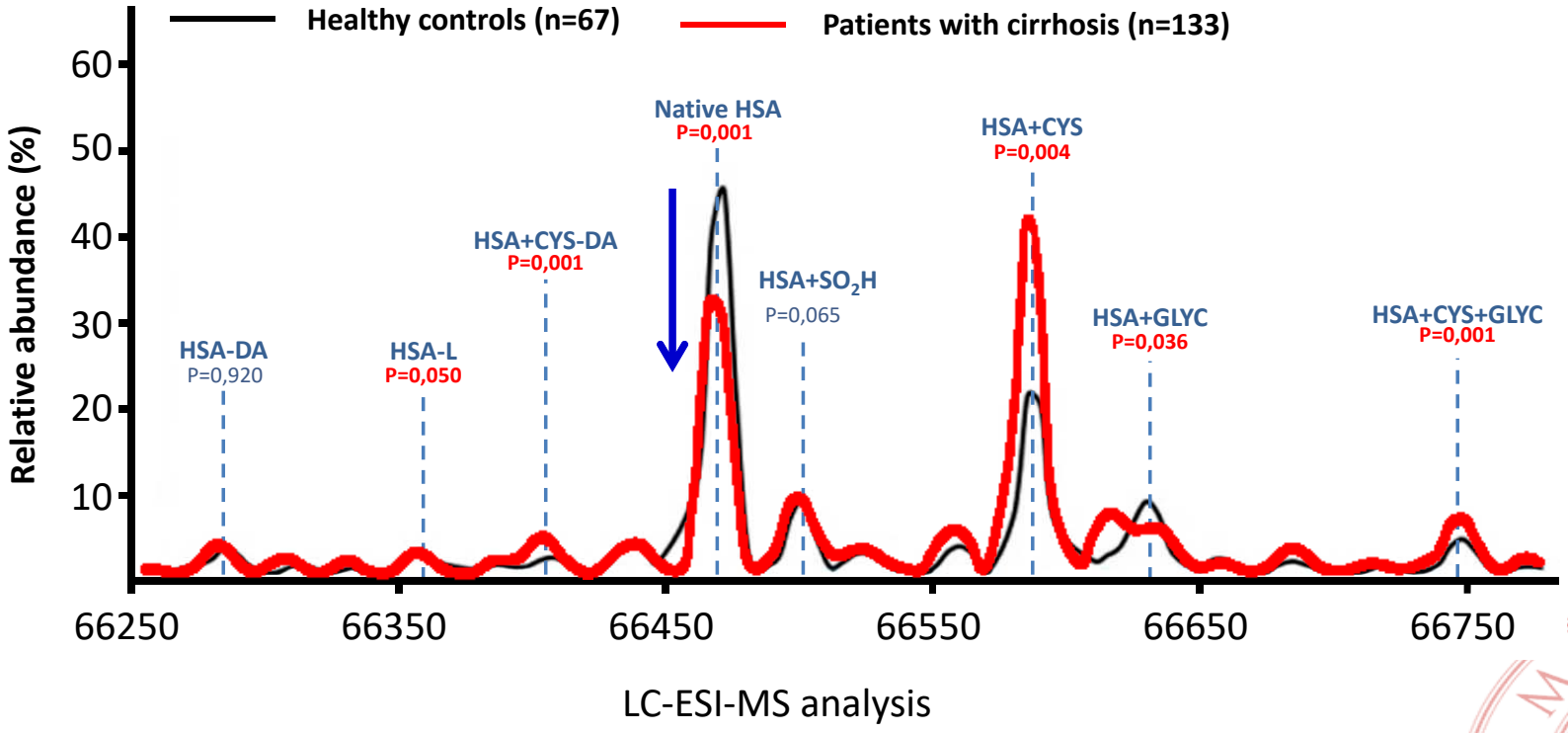
Albumin as toxin adsorbent in liver dialysis devices (*MARS, Prometheus, SPAD*)

Albumin restores immunocompetence by binding PGE2

O'Brien et al, Nature Med 2014

ALBUMIN IN CIRRHOSIS: STRUCTURAL ALTERATIONS

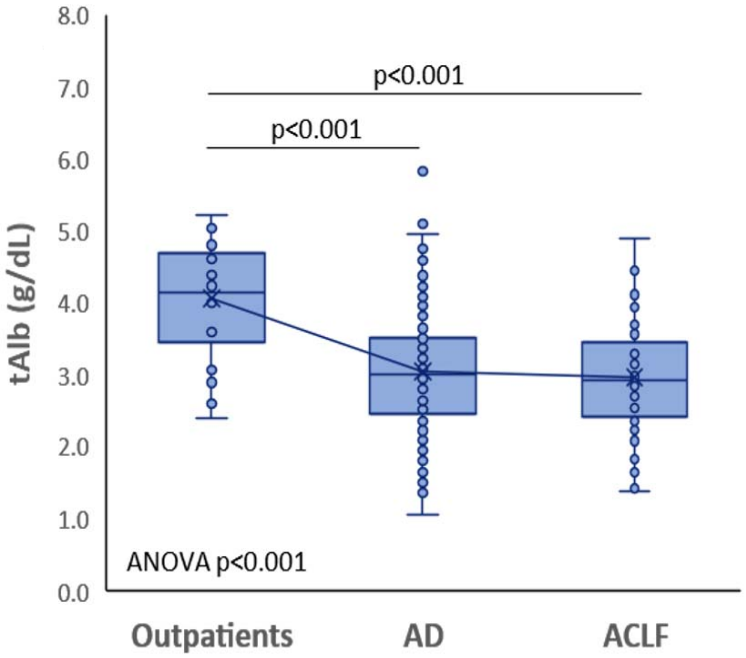
ALBUMIN ISOFORMS IN HEALTHY CONTROLS AND PATIENTS WITH CIRRHOSIS

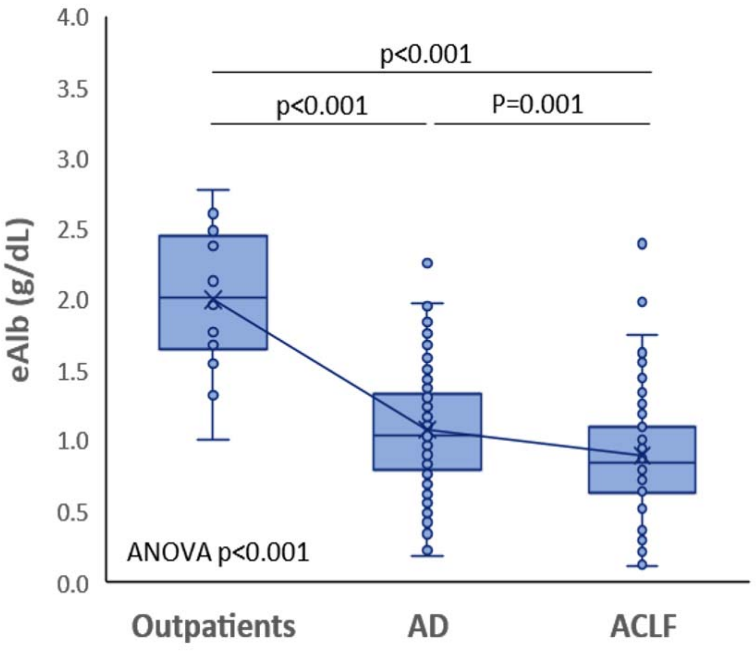


Domenicali et al., Hepatology 2014

ALBUMIN ABNORMALITIES IN CIRRHOSIS

SERUM "EFFECTIVE ALBUMIN" CONCENTRATION



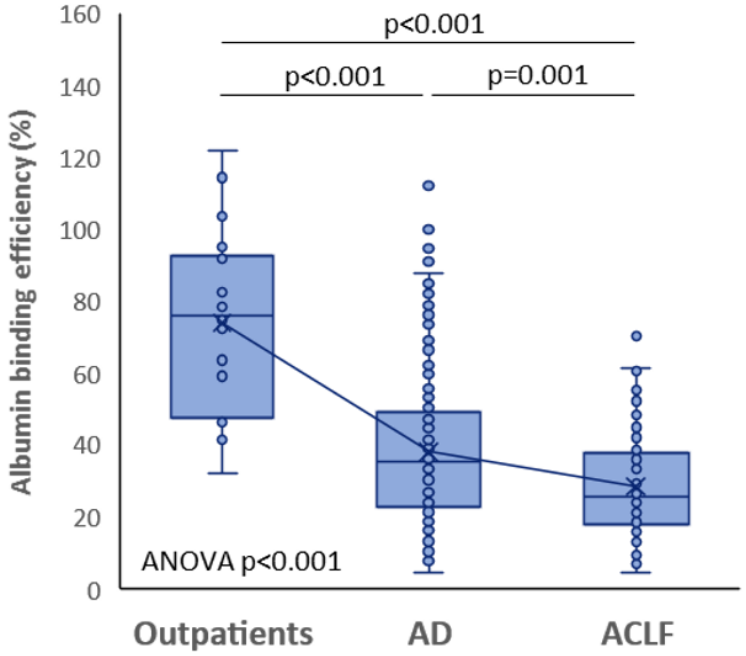


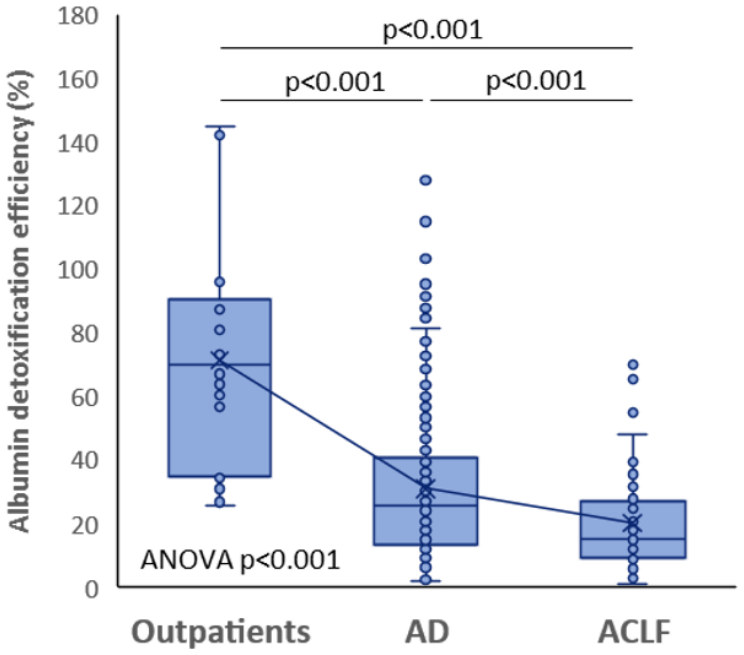
$$eAlb\ (g/dL) = \frac{tAlb\ (g/dL) \times nAlb\ (\%)}{100}$$

Baldassarre et al, submitted

ALBUMIN ABNORMALITIES IN CIRRHOSIS

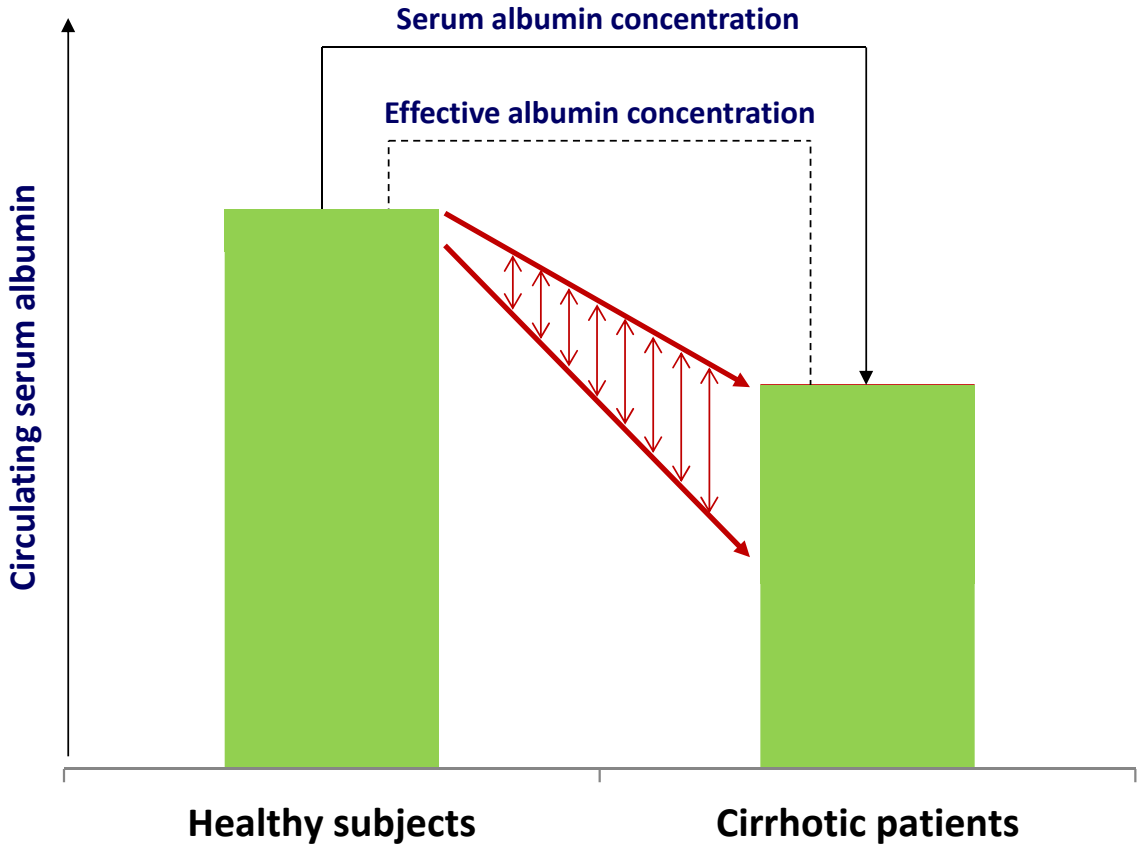
DYSFUNCTION OF BINDING AND DETOXIFICATION EFFICIENCY





Baldassarre et al, submitted

THE EFFECTIVE ALBUMIN CONCENTRATION



ALTERED HSA

HNA1

HNA2

Glycosilated

N-terminal truncated

C-terminal truncated

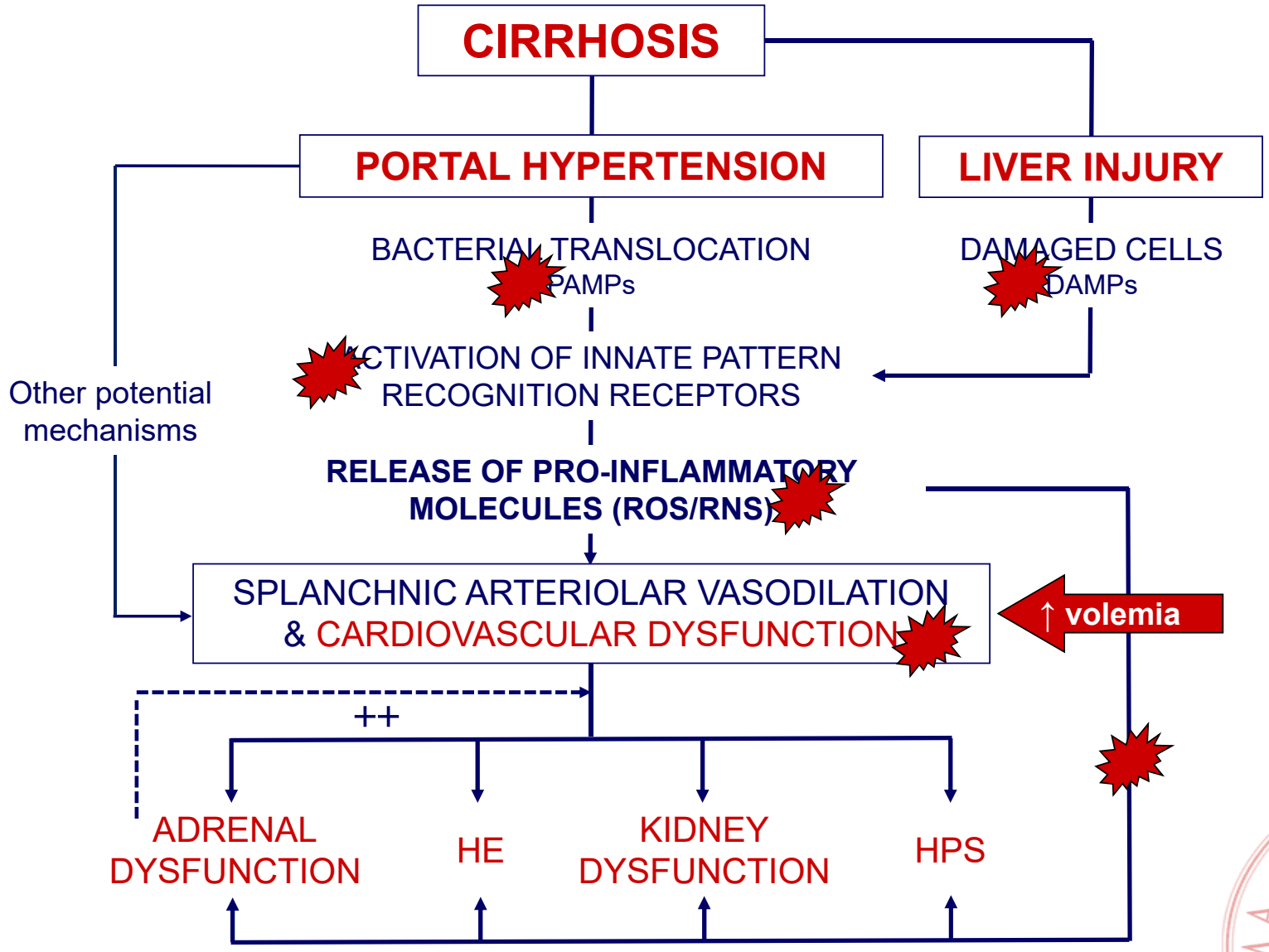
IMA

Others

NATIVE HSA

Fully preserved

structure and fuction



Bernardi, Moreau, Angeli, Schnabl, Arroyo, J Hepatol 2015

HE: hepatic encephalopathy
HPS: hepato-pulmonary syndrome

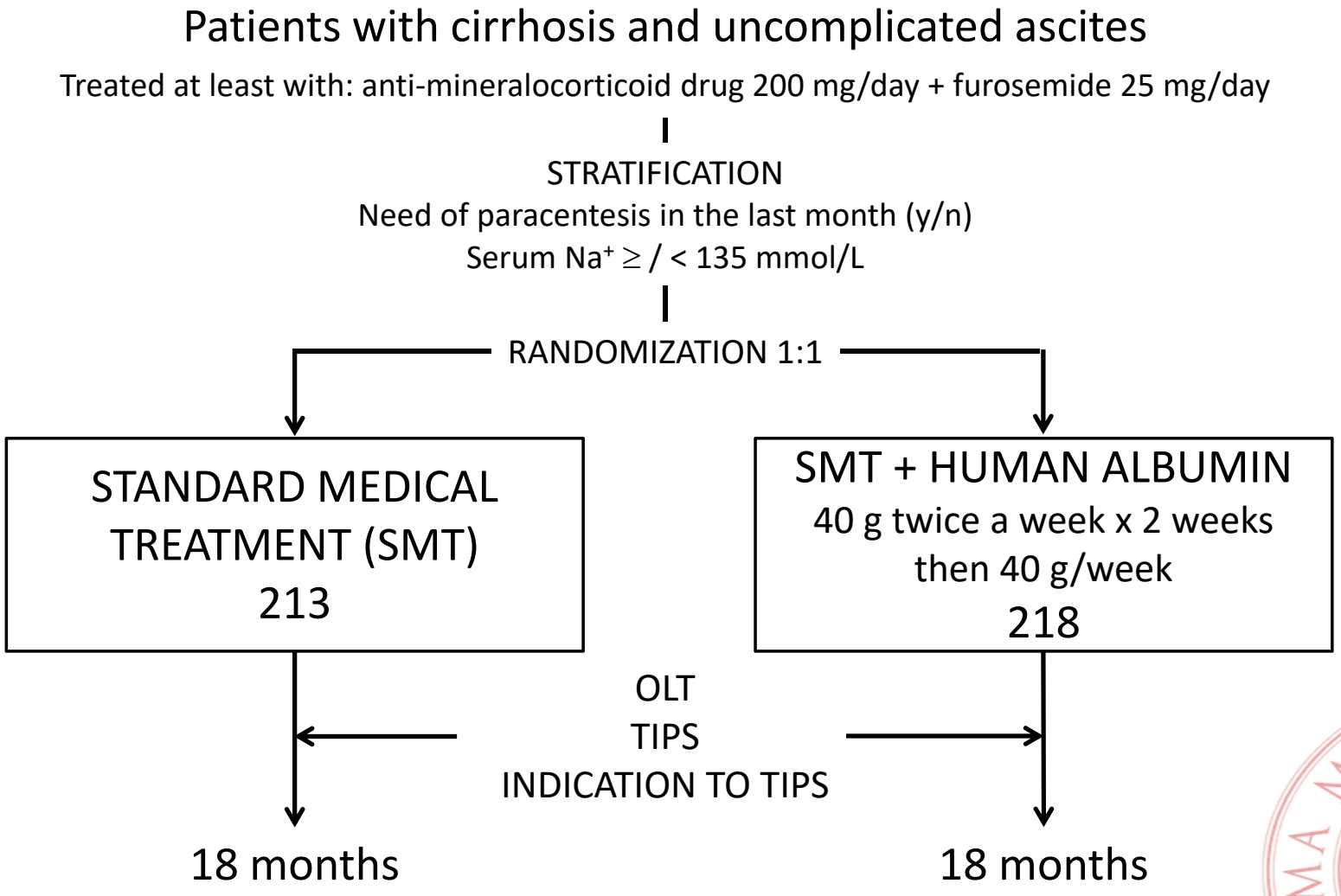
NOVEL PERSPECTIVES ON THE USE OF ALBUMIN IN CIRRHOSIS: LONG-TERM ADMINISTRATION

Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial

*Paolo Caraceni, Oliviero Riggio, Paolo Angeli, Carlo Alessandria, Sergio Neri, Francesco G Foschi, Fabio Levantesi, Aldo Airoldi, Sergio Boccia, Gianluca Svegliati-Baroni, Stefano Fagiuoli, Roberto G Romanelli, Raffaele Cozzolongo, Vito Di Marco, Vincenzo Sangiovanni, Filomena Morisco, Pierluigi Toniutto, Annalisa Tortora, Rosanna De Marco, Mario Angelico, Irene Cacciola, Gianfranco Elia, Alessandro Federico, Sara Massironi, Riccardo Guarisco, Alessandra Galioto, Giorgio Ballardini, Maria Rendina, Silvia Nardelli, Salvatore Piano, Chiara Elia, Loredana Prestianni, Federica Mirici Cappa, Lucia Cesarini, Loredana Simone, Chiara Pasquale, Marta Cavallin, Alida Andrealli, Federica Fidone, Matteo Ruggeri, Andrea Roncadori, Maurizio Baldassarre, Manuel Tufoni, Giacomo Zaccherini, Mauro Bernardi, for the ANSWER Study Investigators**

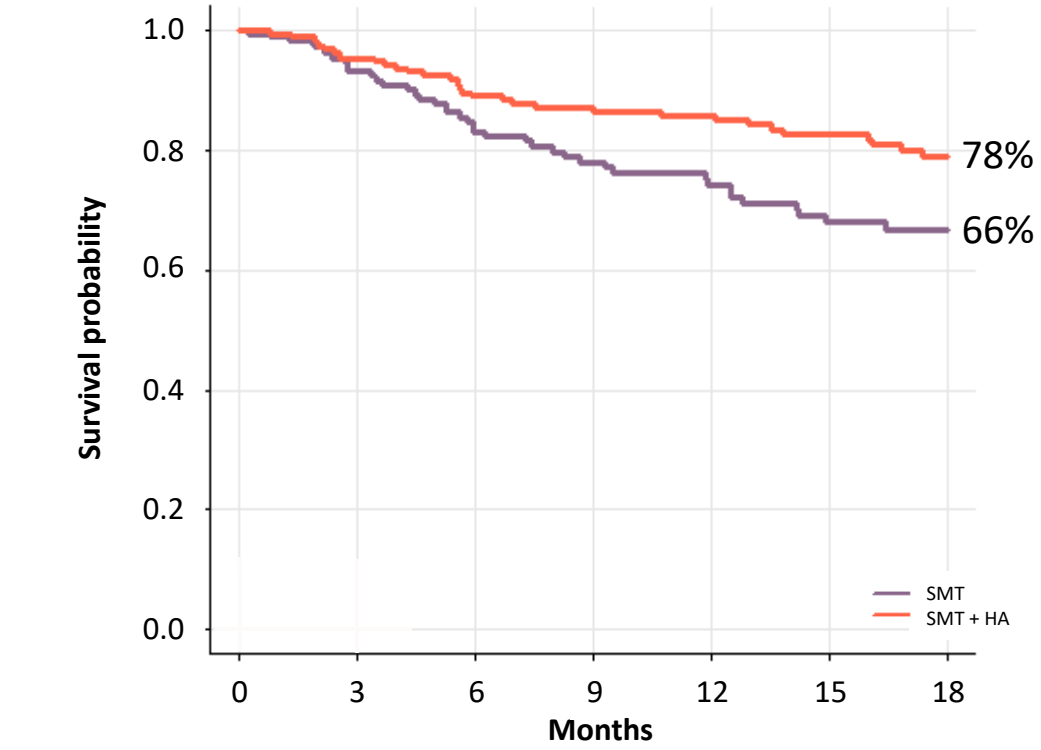
Lancet 2018; 391: 2417–29

STUDY PROTOCOL



Caraceni et al, Lancet 2018

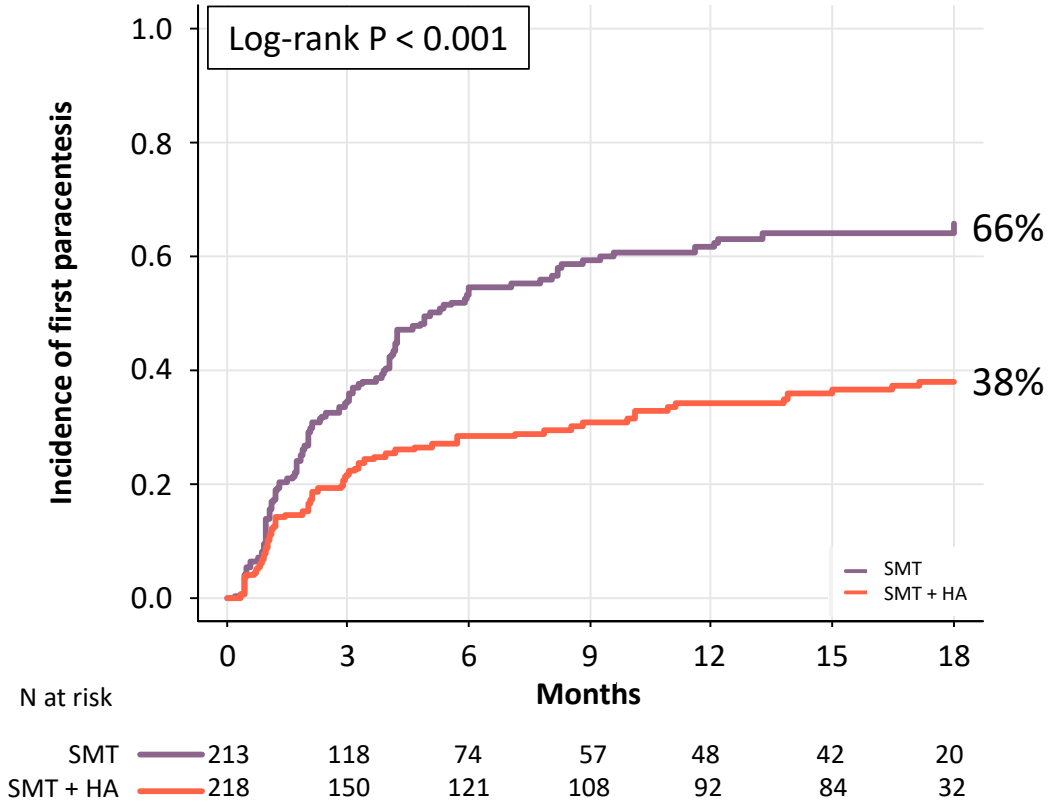
OVERALL SURVIVAL



Hazard Ratio (HA+SMT vs SMT)	Log-rank P value
0.62 (95% CI 0.40-0.95) (–38%)	**0.0285**

Caraceni et al, Lancet 2018

PARACENTESIS

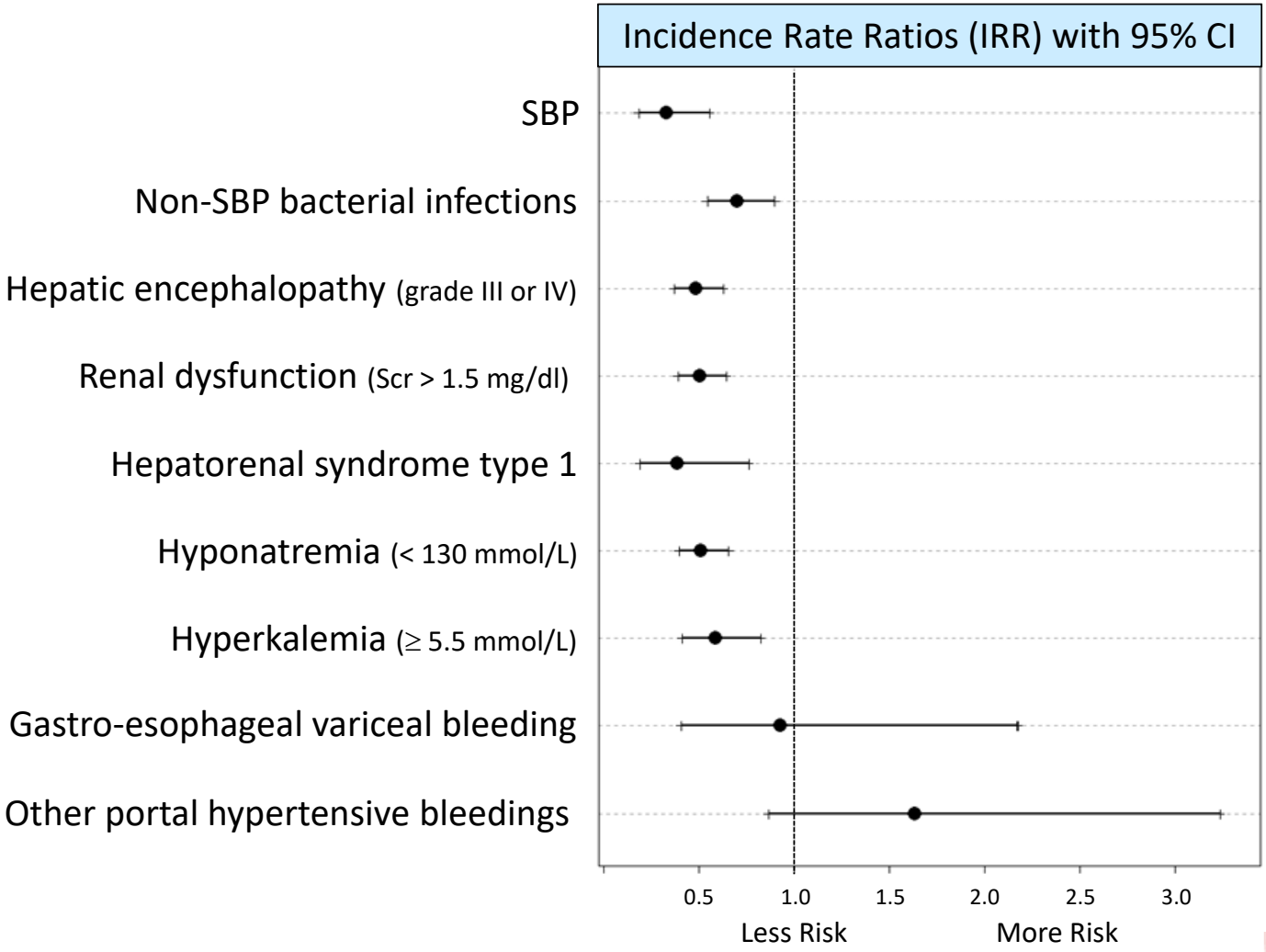


Cumulative number of paracentesis

IR SMT	IRR (HA+SMT/SMT) - Poisson rates test	P value
3.50 (95% CI 3.21-3.80)	**0.46 (– 54%)** (95% CI 0.40-0.53)	**< 0.0001**

Caraceni et al, Lancet 2018

INCIDENCE OF COMPLICATIONS



Caraceni et al, Lancet 2018

HOSPITALIZATIONS

	Incidence rate *number/patient/year*		Incidence rate ratio	P value
	SMT+HA group	**SMT group**	**SMT+HA/SMT**	
Hospitalizations				
- All cause	1.19 (1.05-1.35)	1.83 (1.62-2.05)	0.65 (0.55-0.77)	<0.001
- Liver-related	0.98 (0.85-1.12)	1.65 (1.46-1.86)	0.59 (0.49-0.71)	<0.001
- Non liver-related	0.22 (0.16-0.29)	0.18 (0.12-0.26)	1.22 (0.75-2.03)	0.481
Days in hospital	10.70 (10.27-11.15)	19.39 (18.71-20.09)	0.55 (0.52-0.58)	<0.001

Caraceni et al, Lancet 2018

COST-EFFECTIVENESS OF LONG-TERM ALBUMIN ADMINISTRATION

NICE* threshold for cost-effectiveness: ICER = € 35,000
Long-term albumin administration: ICER = € 21,265

ANSWER study bootstrap analysis (10,000 simulated cases)
Long-term albumin administration is cost-effective in 92.5% of cases
Long-term albumin administration is cheaper than STM in 56% of cases

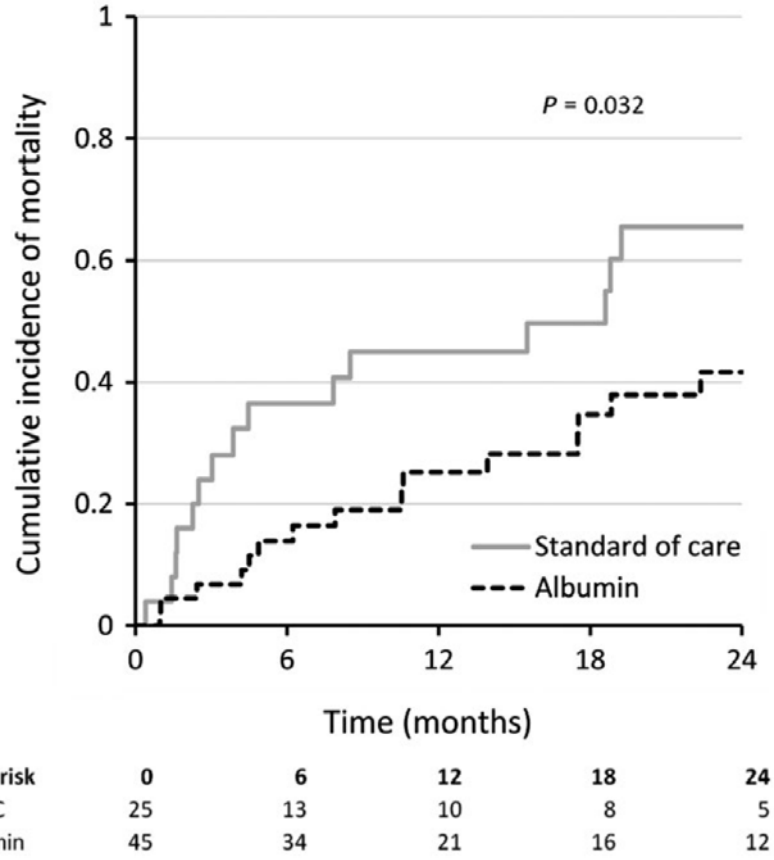
** National Institute for Health and Care Excellence*

Caraceni et al, Lancet 2018
McCabe et al, 2008

LONG-TERM ALBUMIN IN REFRACTORY ASCITES

IMPACT ON COMPLICATIONS

45 pts → albumin 20 g x 2/w
25 pts → SOC



PTS at risk	0	6	12	18	24
SOC	25	13	10	8	5
Albumin	45	34	21	16	12

Predictors of mortality

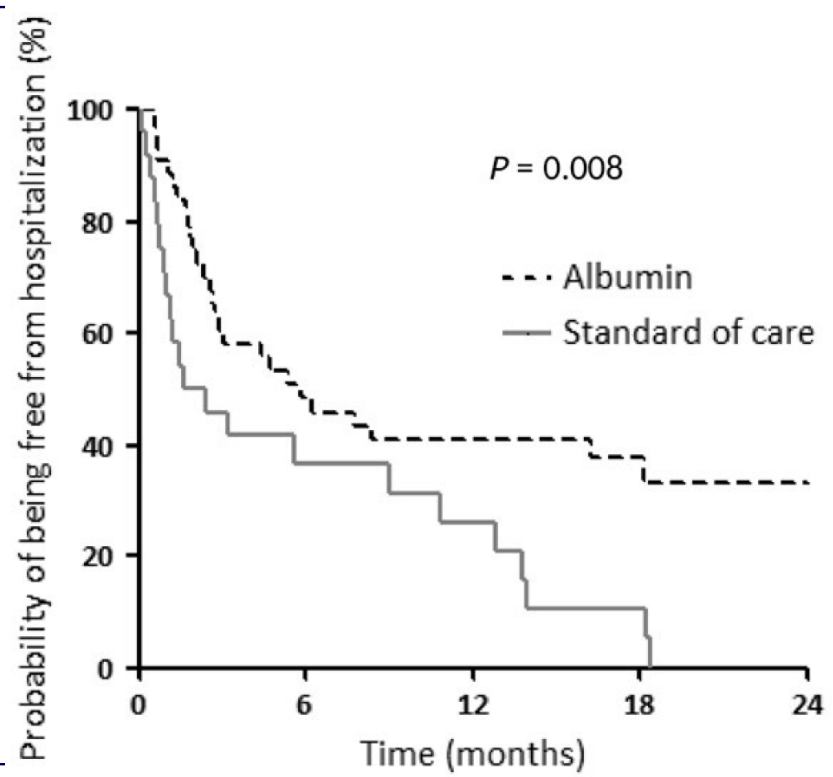
Multivariate analysis			
Treatment with albumin	0.49	0.24-0.99	0.047
Age, y	1.05	1.02-1.08	0.004
Baseline MELD	1.08	1.01-1.15	0.017

Di Pascoli et al, Liver Int 2019

LONG-TERM ALBUMIN IN REFRACTORY ASCITES

IMPACT ON COMPLICATIONS

Hepatic encephalopathy
Ascites
SBP
Non-SBP bacterial infections
(HRS)



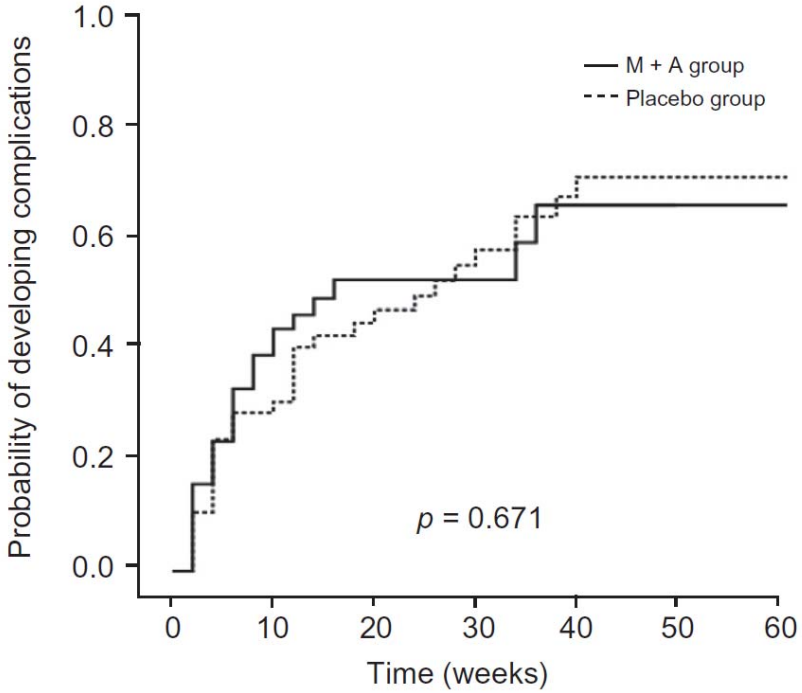
PTS at risk	0	6	12	18	24
SOC	25	7	5	2	0
Albumin	45	20	14	8	5

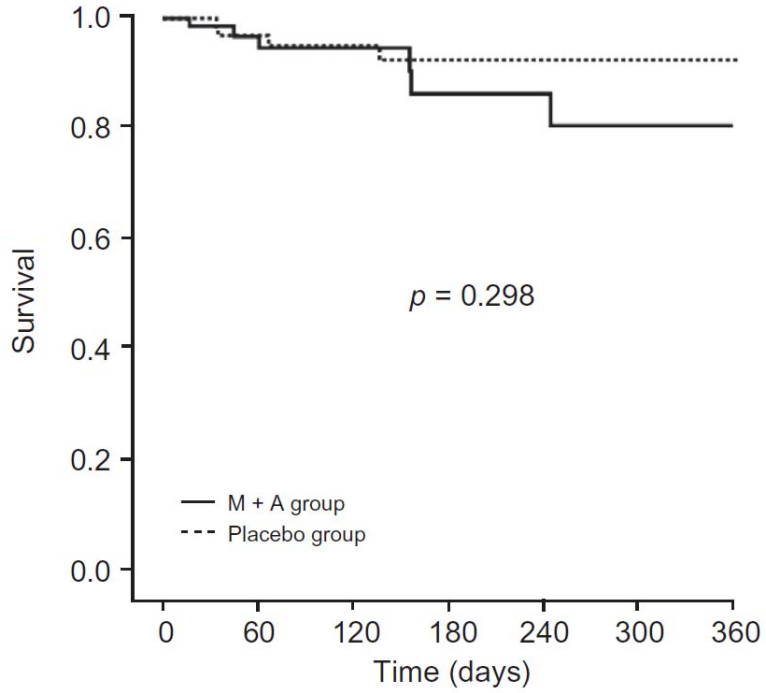
Pascoli et al, Liver Int 2019

LONG-TERM ALBUMIN IN DECOMPENSATED CIRRHOSIS

THE MACTH STUDY

87 pts: albumin: 40 g/15 days
midodrine: 15-30 mg/day
86 pts: placebos





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

Solà at al, J Hepatol 2018

LONG-TERM ALBUMIN IN DECOMPENSATED CIRRHOSIS

COMPARISON OF CONTROLLED STUDIES

	ANSWER	Di Pascoli	MACHT

** Reverse Kaplan-Meier method*

CONCLUSIONS (1)

Long-term albumin administration to pts with decompensated cirrhosis:

- Improves survival
- Facilitates the management of ascites
- Reduces the incidence of severe complications of cirrhosis
- Ameliorates the quality of life and reduces the need of hospitalization
- Is cost-effective

Provided that:

- Leads to a sustained increase in serum albumin concentration
- Treatment lasts for a sufficient time to exert its effects

PERSPECTIVES

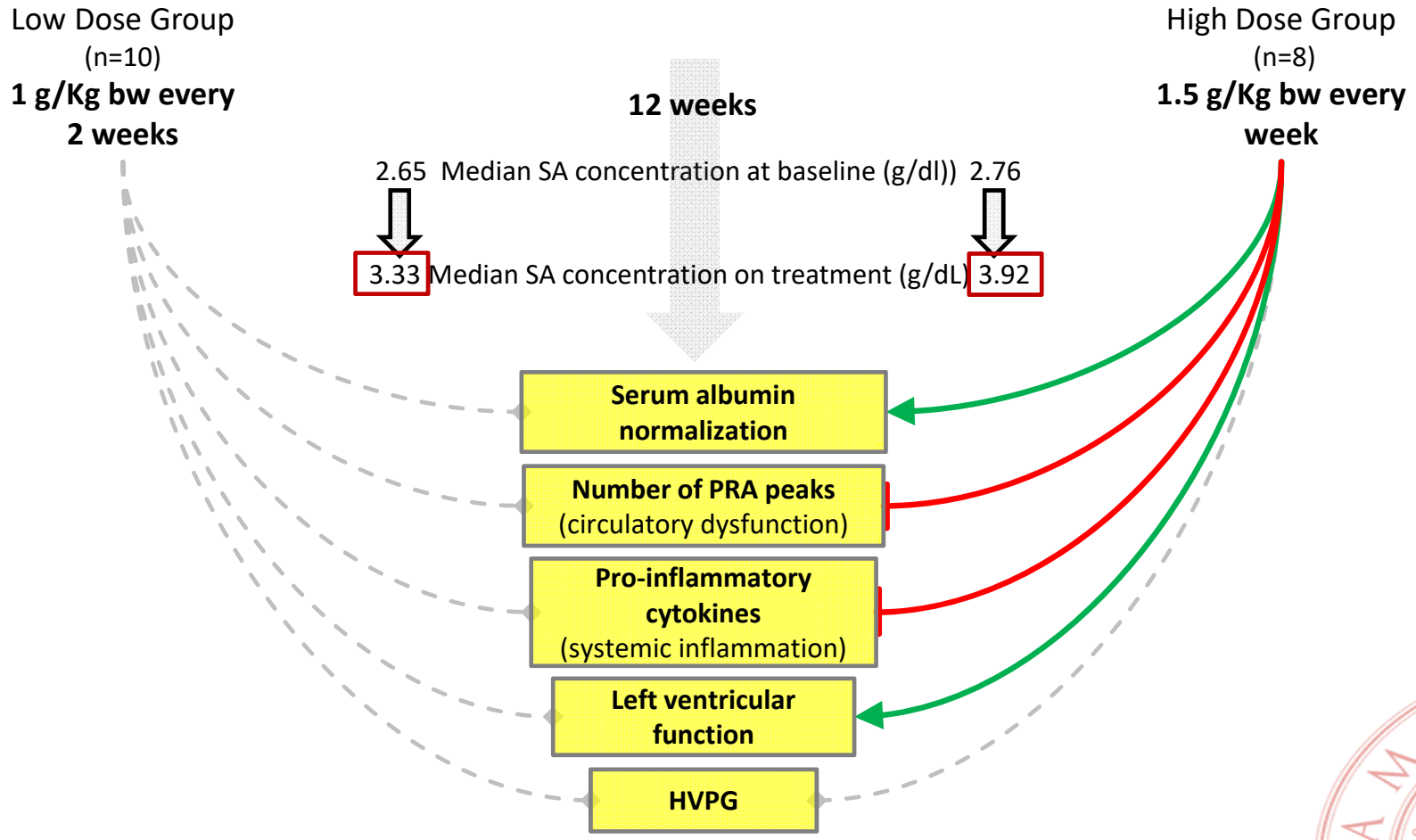
What still needs to be ascertained:

- Patient sub-populations (if any) who would benefit most from long-term albumin administration
- Target levels of serum albumin concentration to be reached to obtain favorable results
- Optimal duration of treatment
- Optimal dose(s) and administration schedule(s) of albumin (individualized therapy)

HOW MUCH SHOULD WE INCREASE SERUM ALBUMIN CONCENTRATION TO OBTAIN BENEFICIAL EFFECTS?

THE PILOT-PRECIOSA STUDY

EFFECTS OF DIFFERENT ALBUMIN DOSES

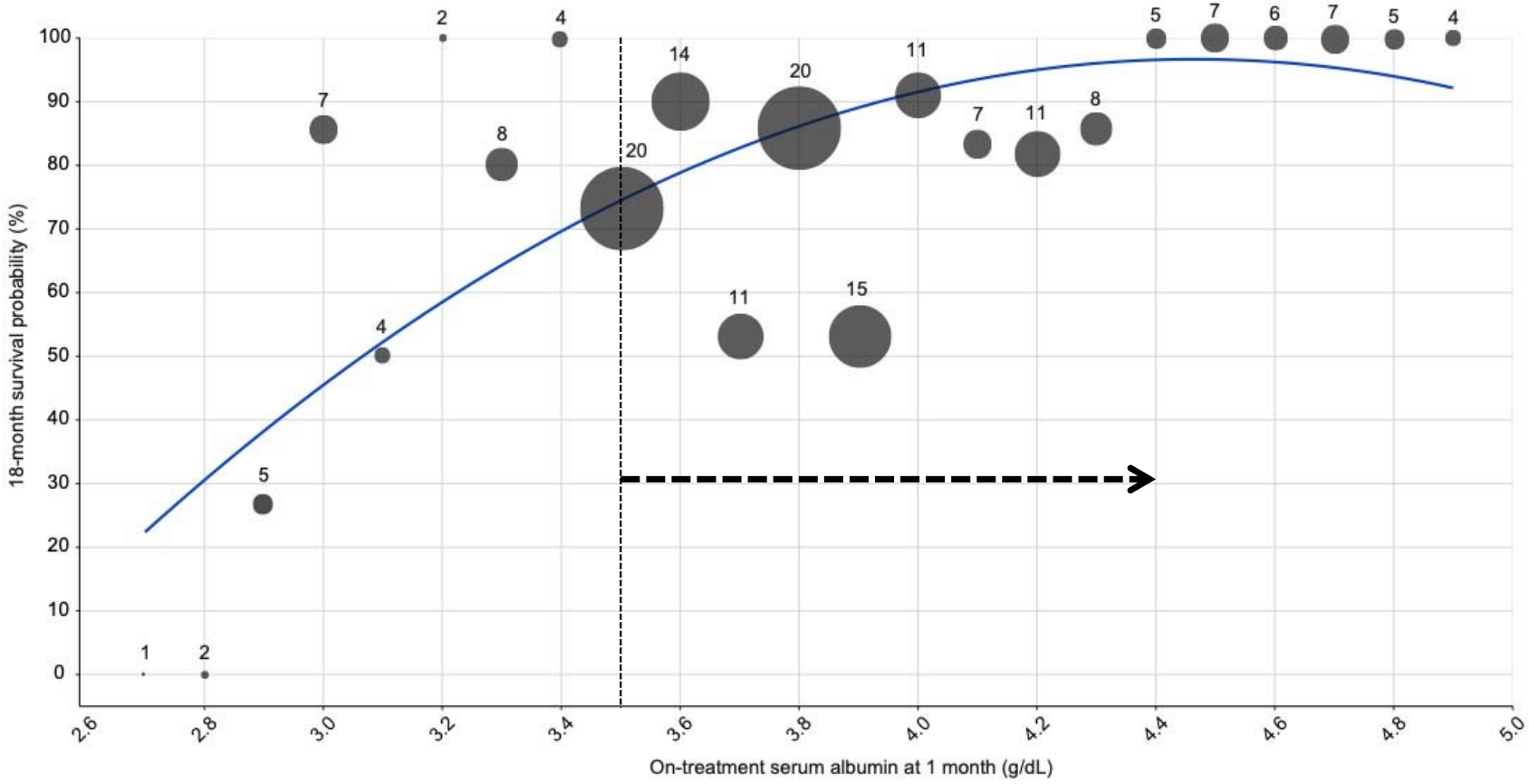


Fernandez et al, Gastroenterology, 2019

ANSWER STUDY

POST-HOC ANALYSIS OF THE DATABASE

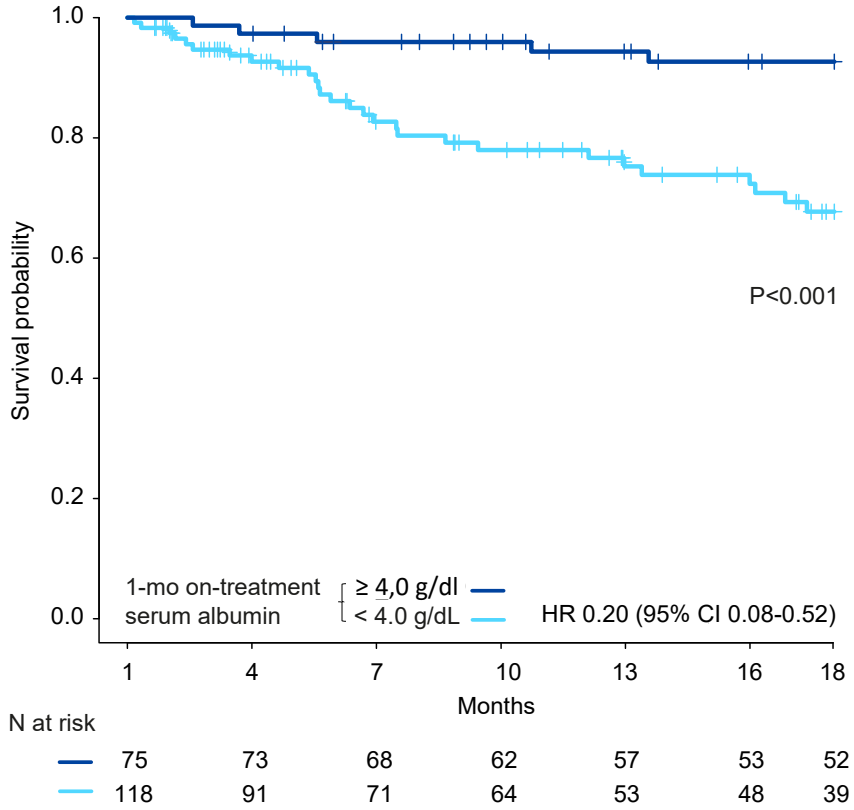
SECOND-ORDER POLYNOMIAL REGRESSION ANALYSIS



Caraceni et al, J Hepatol 2020

ANSWER STUDY

POST-HOC ANALYSIS OF THE DATABASE



Serum albumin of 4.0 g/dl may be the ideal on-treatment (1-mo) target to be reached to ensure optimal outcomes

Caraceni et al, J Hepatol 2020

ANSWER STUDY

POST-HOC ANALYSIS OF THE DATABASE

Baseline predictors of the probability of reaching serum albumin of 4.0 g/dl after 1 month of treatment

MULTIVARIABLE MODEL	HR	95% CI	P value
Serum albumin *	1.147	1.021–1.149	< 0.001
MELD score **	0.903	1.120–1.322	0.04

* *Death risk for any 0.1 g/dl increase*

** *Death risk for any point decrease*

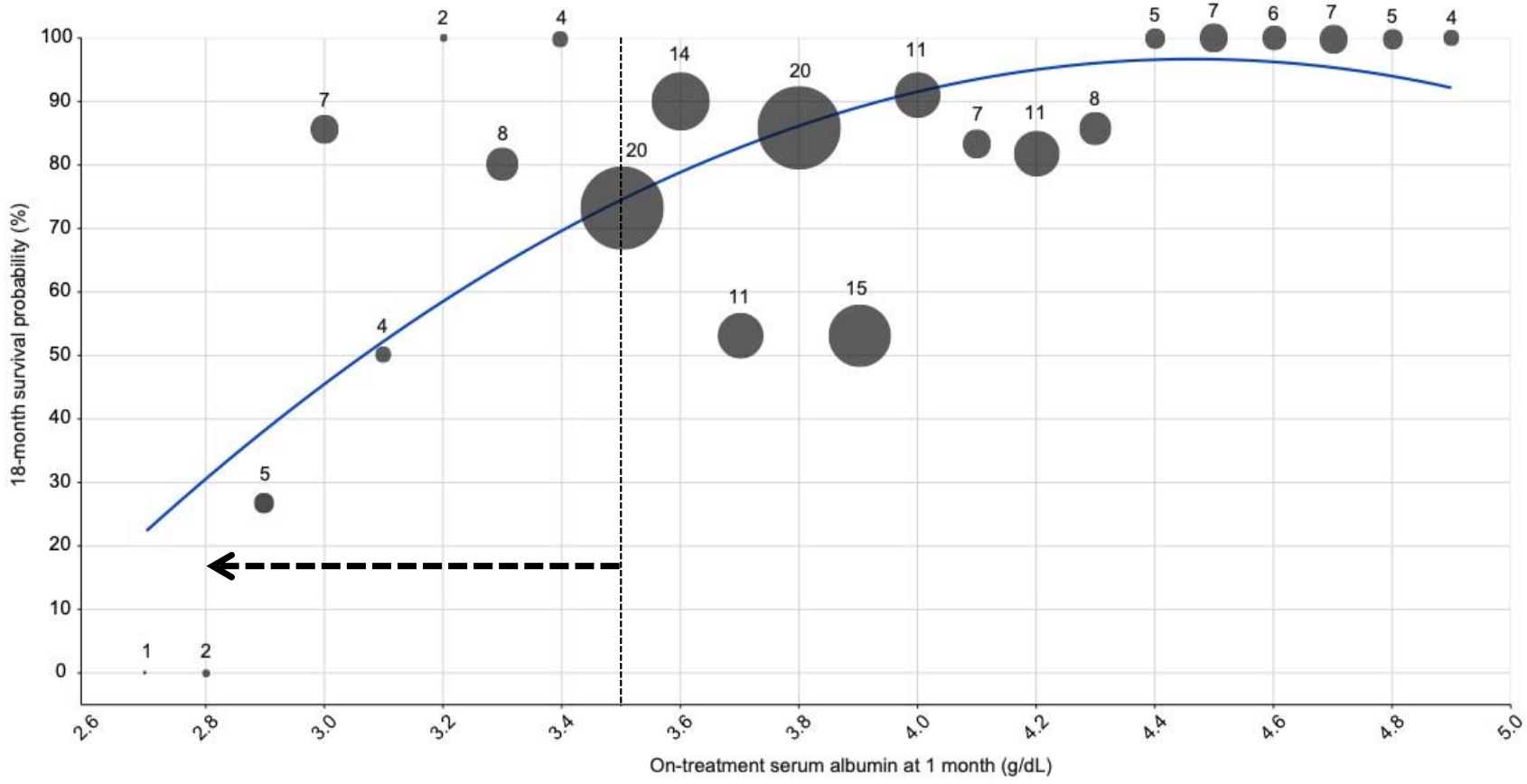
Patients with very low serum albumin and/or high MELD score likely need greater amounts of albumin to reach an optimal on-treatment (1-mo) serum albumin level

Caraceni et al, J Hepatol 2020

ANSWER STUDY

POST-HOC ANALYSIS OF THE DATABASE

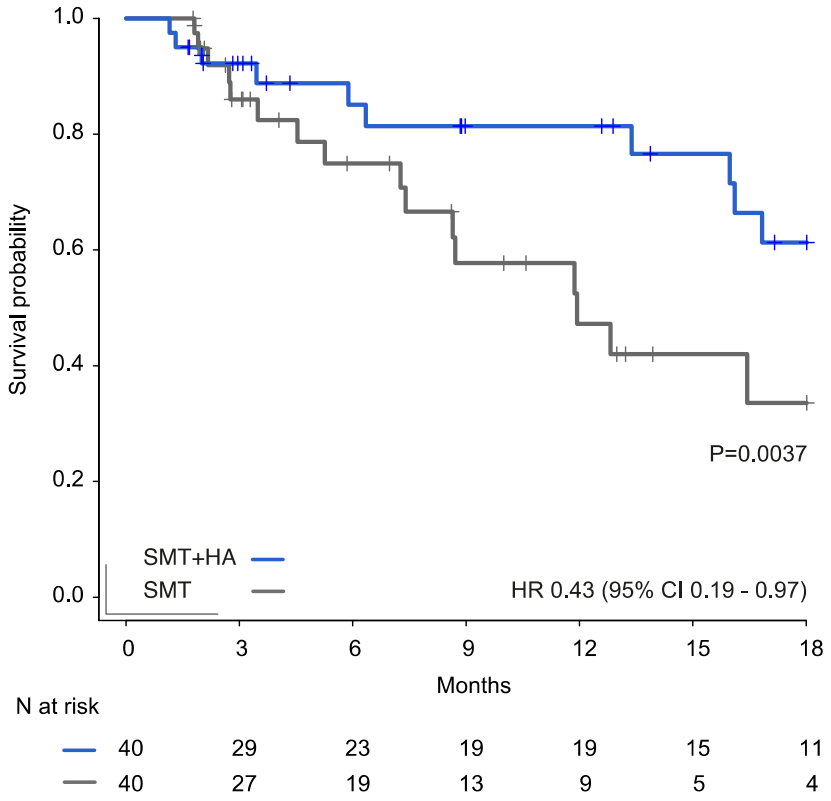
SECOND-ORDER POLYNOMIAL REGRESSION ANALYSIS



Caraceni et al, J Hepatol 2020

ANSWER STUDY

POST-HOC ANALYSIS OF THE DATABASE



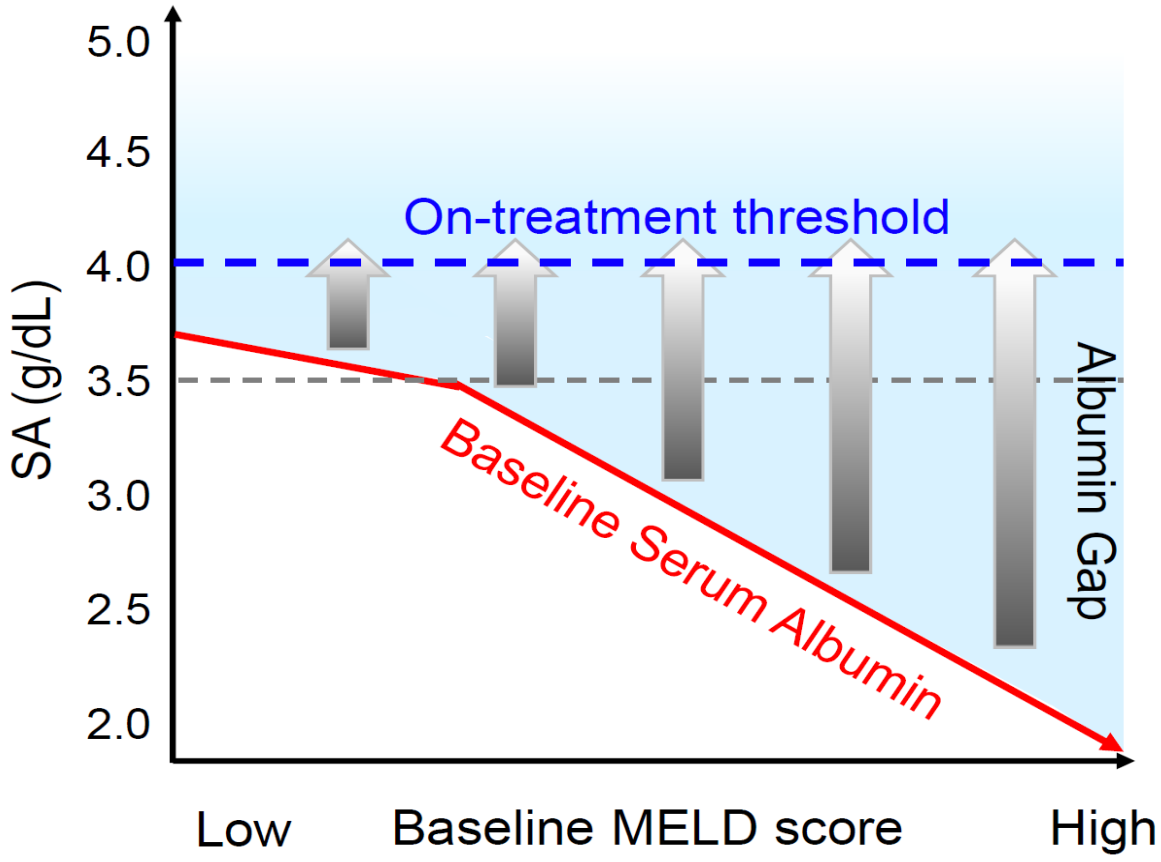
Even patients with on-treatment (1-mo) serum albumin < 3.5 g/dl benefit from long-term albumin administration

Caraceni et al, J Hepatol 2020

CONCLUSIONS (2)

- On-treatment serum albumin at 1-month predicts outcomes and can be used to guide therapy
- We propose 4 g/dl as the optimal serum albumin concentration target to be reached
- Even patients who fail to normalize serum albumin at 1-mo of treatment benefit from long-term albumin administration

TOWARDS A PERSONALIZED LONG-TERM ALBUMIN ADMINISTRATION



FILL THE ALBUMIN GAP !

Caraceni et al, J Hepatol 2020