

Corso di aggiornamento Sezione regionale SIFO - Campania

La filiera dei farmaci plasmaderivati

Napoli, 13 Settembre, 2019

**LINEE GUIDA SULL'USO DELL'ALBUMINA:
FOCUS SULLA GESTIONE DEL PAZIENTE CIRROTICO**

Paolo Caraceni



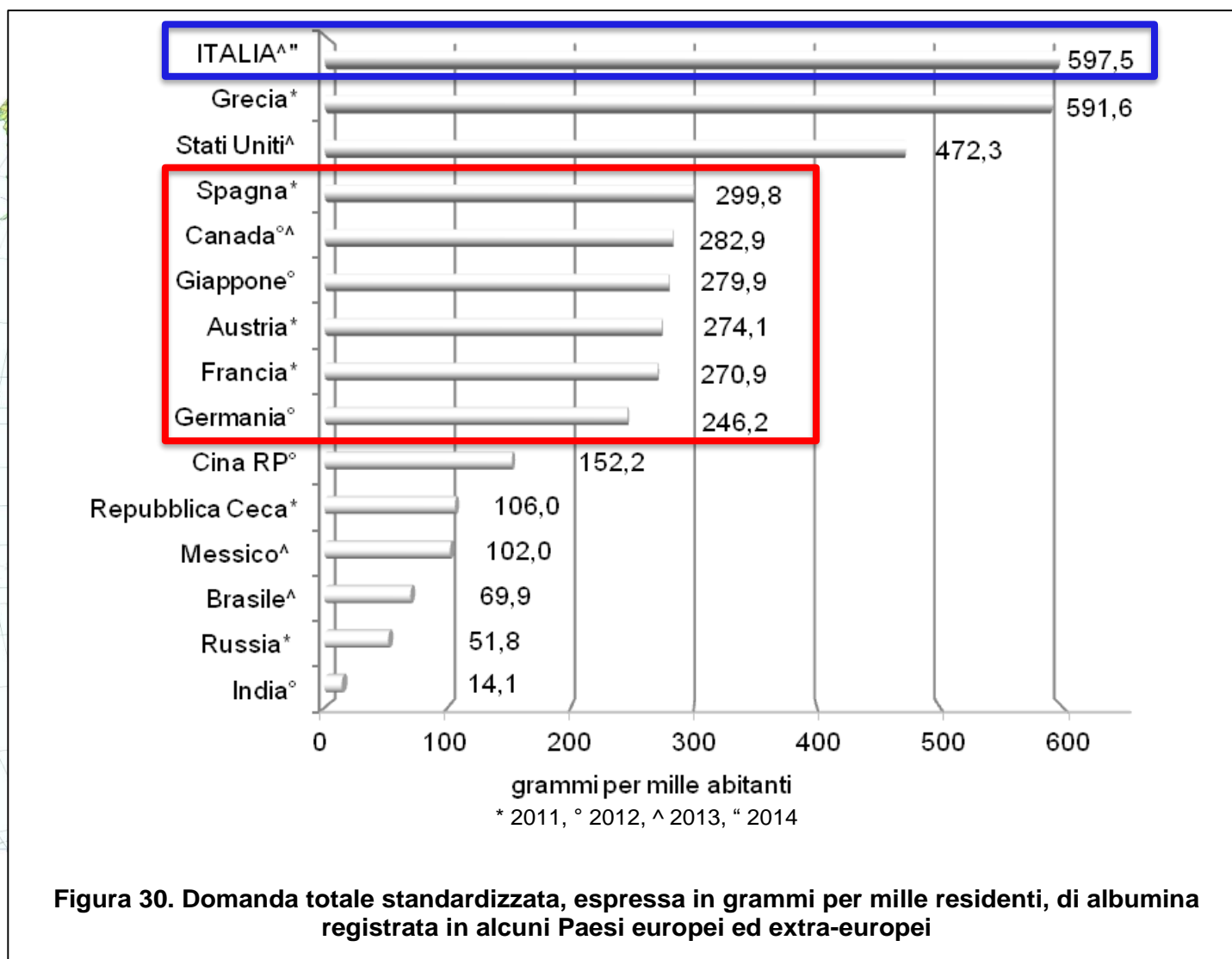
*Alma Mater Studiorum Università di Bologna
Dipartimento di Scienze Mediche e Chirurgiche
Centro di Ricerca Biomedica Applicata (CRBA)*



LIMITAZIONI NELL'USO DI ALBUMINA

- Disponibilità finita (emoderivato)
- Costo elevato
- Alternative più economiche (cristalloidi, colloidi sintetici)
- Limiti alla prescrivibilità (farmacie, centri trasfusionali)

CONSUMO DI ALBUMINA NEL MONDO



CONSUMO DI ALBUMINA IN ITALIA

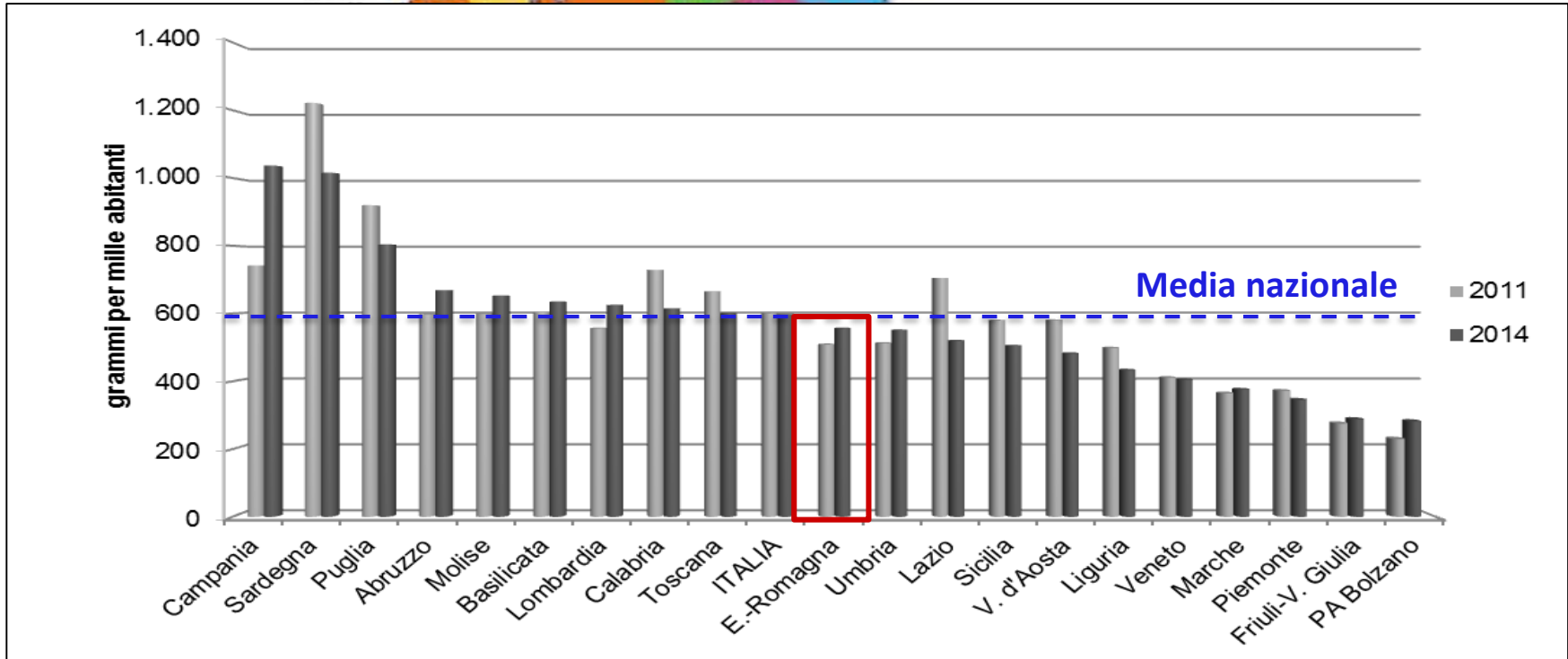


Figura 5. Domanda nazionale e regionale (a carico SSN e privata) espressa in grammi per mille residenti di albumina. Confronto 2011 rispetto a 2014 (Elaborazioni CNS su fonte Tracciabilità del farmaco)



INAPPROPRIATE USE OF ALBUMIN

- Use of albumin Padua Hospital: **inappropriate in 68% of cases**

Favaretti et al, Qual Assur Health Care 1993

- Use of albumin in two Spanish hospitals: **inappropriate in 90% of cases**

Vargas et al, Eur J Clin Pharmacol 1997

- Use of albumin in Tenon hospital, Paris: **inappropriate in 38.5% of cases**

Debrix et al, Pharm Word Sci 1999

- Use of albumin in 53 VHA, USA: **inappropriate in 58% of cases**

Tanzi et al, Am J Health Syst Pharm 2003

- Use of albumin in a urban academic center, USA: **inappropriate in 45% of cases**

Castillo et al, Pharm Pract 2018



INAPPROPRIATE USE OF ALBUMIN

22 public hospitals in Spain (3 non consecutive days - 5 month period)

Use of albumin deemed inappropriate in 76% of cases

Main reasons for inappropriate use:

- nutritional intervention
- hypoalbuminemia *per se*
- palliation
- nephrotic syndrome
- wound healing

USO INAPPROPRIATO DI ALBUMINA

RELAZIONE CLINICA di DIMISSIONE

██████████ Lì, 03/01/2019

Dimettiamo in data odierna la sua paziente Sig.ra ██████████ di anni 104 ██████████ con diagnosi di: **"Emorragia digestiva superiore trattata con terapia endoscopica iniettiva. Disonia. Decadimento psico-organico"**.

Al momento della dimissione la paziente sta effettuando la seguente terapia endovenosa:

- sacca in infusione continua a 43 cc/h con soluzione glucosata 250 cc e aminoacidi ramificati 500 cc
- Pantorc 40 mg 5 fiale in 50 cc di soluzione fisiologica, in pompa a 2.1 cc/h
- Rocefin fl 2 g: 1 h 8 (iniziato dal 24/12)
- Albumina umana 20% flaconi: 1 h 8 e 1 h 20

Non edemi all'esame obiettivo all'ingresso
Albuminemia 3.2 g/dl



Medico/Decisore



**Appropriatezza
terapeutica**

Solide evidenze scientifiche di efficacia

Studi di farmacoeconomia

Raccomandazioni/linee guida condivise





SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

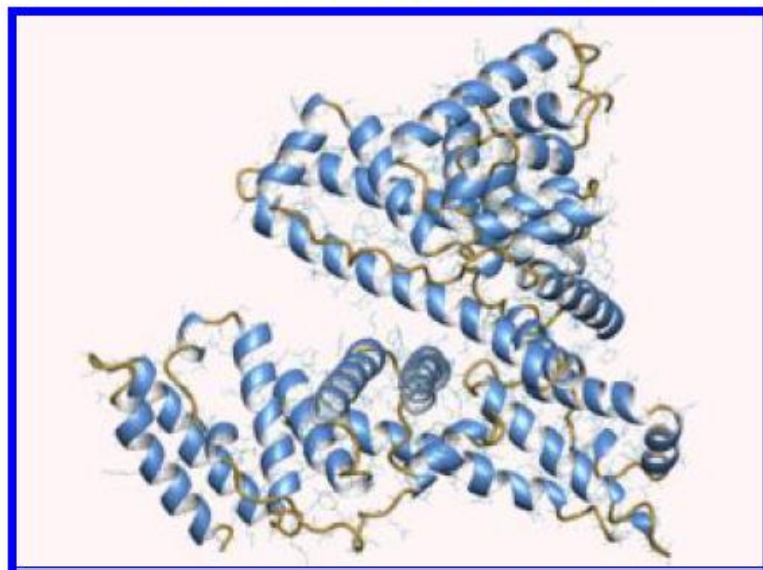
Policlinico S. Orsola-Malpighi



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

COMITATO PER IL BUON USO DEL SANGUE

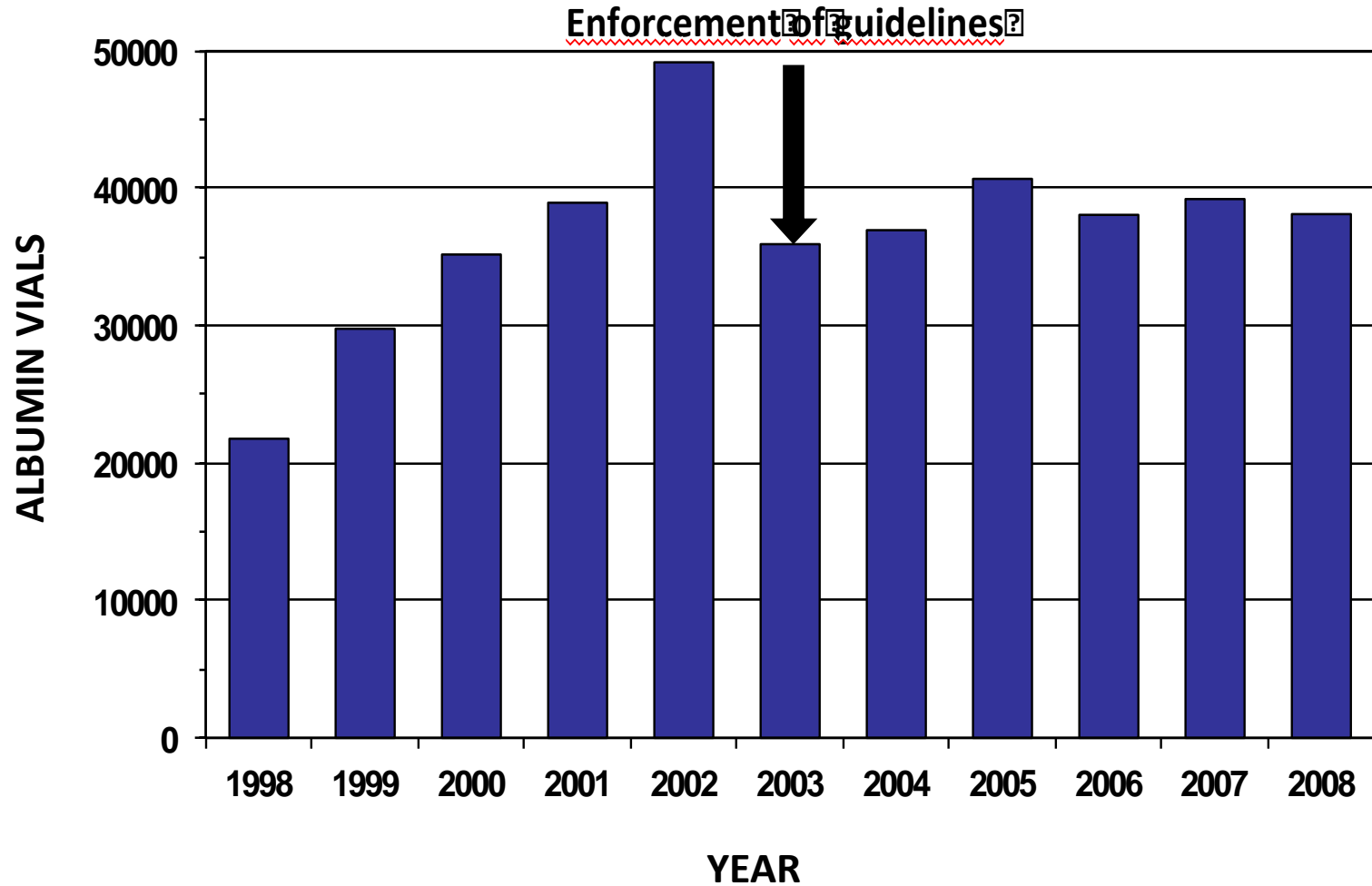
Protocollo Aziendale



USO APPROPRIATO DELL'ALBUMINA

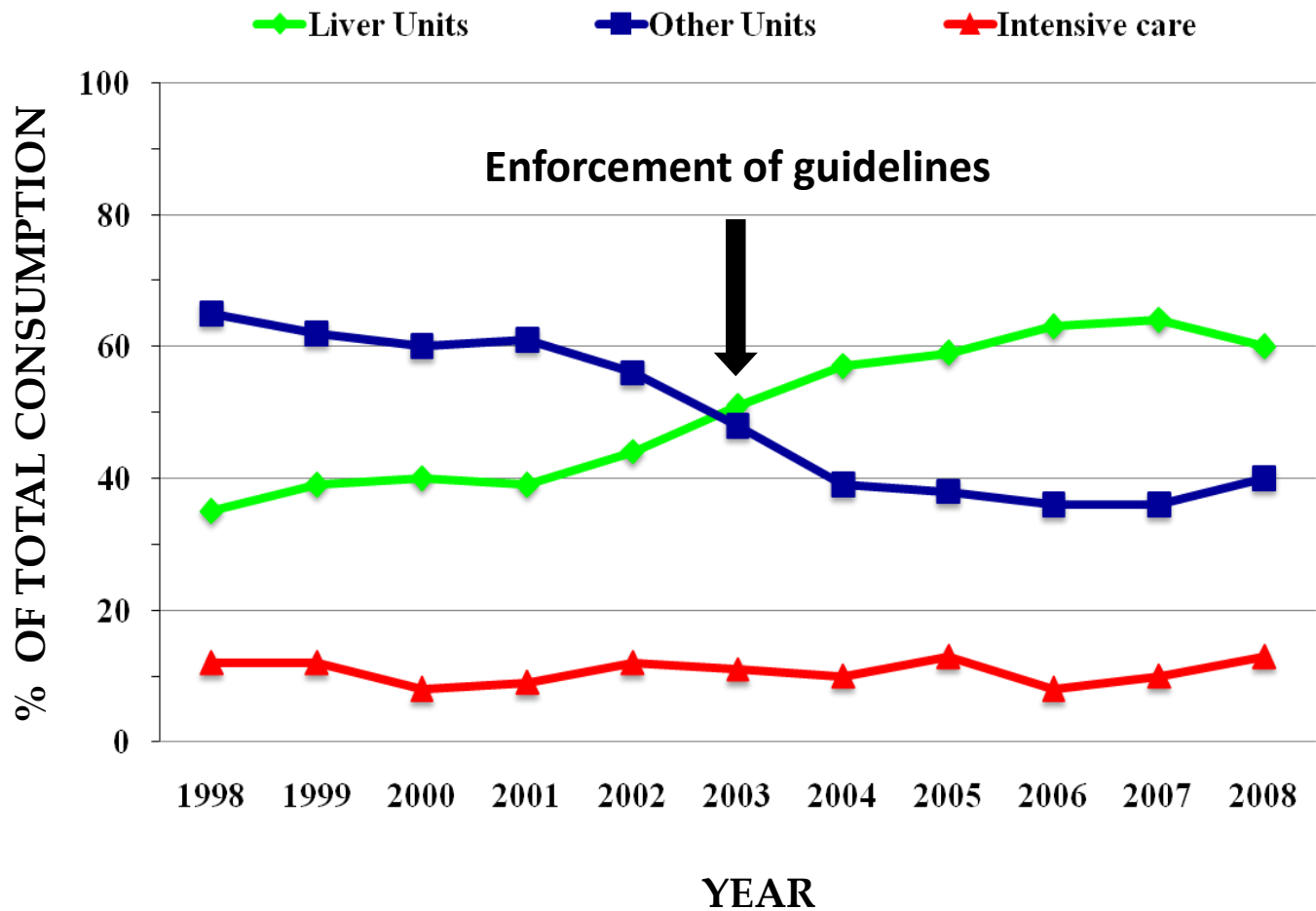
POLICLINICO S. ORSOLA-MALPIGHI

IMPACT OF GUIDELINES ON ALBUMIN CONSUMPTION



POLICLINICO S. ORSOLA-MALPIGHI

DISTRIBUTION OF CONSUMPTION AMONG UNITS



AREE DI UTILIZZO APPROPRIATO DELL'ALBUMINA

- Paziente critico in terapia intensiva
- Interventi di cardiocirurgia
- **Cirrosi epatica scompensata**
- Specifiche condizioni patologiche



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Position Paper

AISF-SIMTI Position Paper: The appropriate use of albumin in patients with liver cirrhosis



Italian Association for the Study of the Liver (AISF)
Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

RECOMMENDATION

AISF-SIMTI position paper: the appropriate use of albumin in patients with liver cirrhosis

Paolo Caraceni¹, Paolo Angeli², Daniele Prati³, Mauro Bernardi¹, on behalf of the Italian Association for the Study of the Liver (AISF); Giancarlo M. Liumbruno⁴, Francesco Bennardello⁵, Pierluigi Piccoli⁶, Claudio Velati⁷, on behalf of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

¹Department of Medical and Surgical Sciences, University of Bologna, Bologna; ²Department of Medicine, University of Padua, Padua; ³Department of Transfusion Medicine and Hematology, "Alessandro Manzoni" Hospital, Lecco; ⁴Italian National Blood Centre, National Institute of Health, Rome; ⁵Immunohaematology and Transfusion Medicine Centre, Provincial Health Authority n. 7, Ragusa - "R. Guzzardi" Hospital, Vittoria; ⁶Transfusion Medicine Unit, University Hospital of Verona, Verona; ⁷Transfusion Medicine and Immunohaematology Department of Bologna Metropolitan Area, Bologna, Italy

AISF-SIMTI RECOMMENDATIONS

CLINICAL CONDITION		DOSES AND SCHEDULES OF ADMINISTRATION	INDICATION FOR THE USE OF HA	QUALITY OF EVIDENCE STRENGTH OF RECOMMENDATION
Prevention of post-paracentesis circulatory dysfunction	Paracentesis ≥ 5 L	6-8 g per L of removed ascites	Mandatory in all patients	A1
	Paracentesis < 5 L		Preferred if concerns regarding use of synthetic colloids or crystalloids	B1
Prevention of renal failure after SBP	High-risk patients	1.5 g/kg at diagnosis + 1 g/kg on the 3 rd day	Mandatory in all patients	A1
	Low-risk patients*		Consider in individual patients	B1
Diagnosis of hepatorenal syndrome		1 g/kg/die for 2 consecutive days	To be used regularly	D1
Treatment of type I hepatorenal syndrome (in association with vasoconstrictors)		1 g/kg at diagnosis + 20-40 g/die until vasoconstrictors are stopped	Mandatory in all patients	A1
Long-term treatment of ascites		To be defined	Consider in difficult-to-treat ascites	C1
Treatment of severe hyponatraemia		To be defined	Consider if no response to standard measures	D1
Prevention of renal failure after non-SBP bacterial infections		-----	Not indicated at present	B1
Treatment of septic shock		To be defined	Consider in all patients	C1
Treatment of hepatic encephalopathy		-----	Not indicated at present	B1

SHORT-TERM USE OF ALBUMIN IN DECOMPENSATED CIRRHOSIS

Evidence-based clinical indications

1. Prevention of post-paracentesis circulatory dysfunction

8 g/L of tapped ascites for >4-5 L paracentesis

2. Prevention of renal failure induced by spontaneous bacterial peritonitis

1.5 g/Kg b.w. at diagnosis

1 g/Kg b.w. on day 3

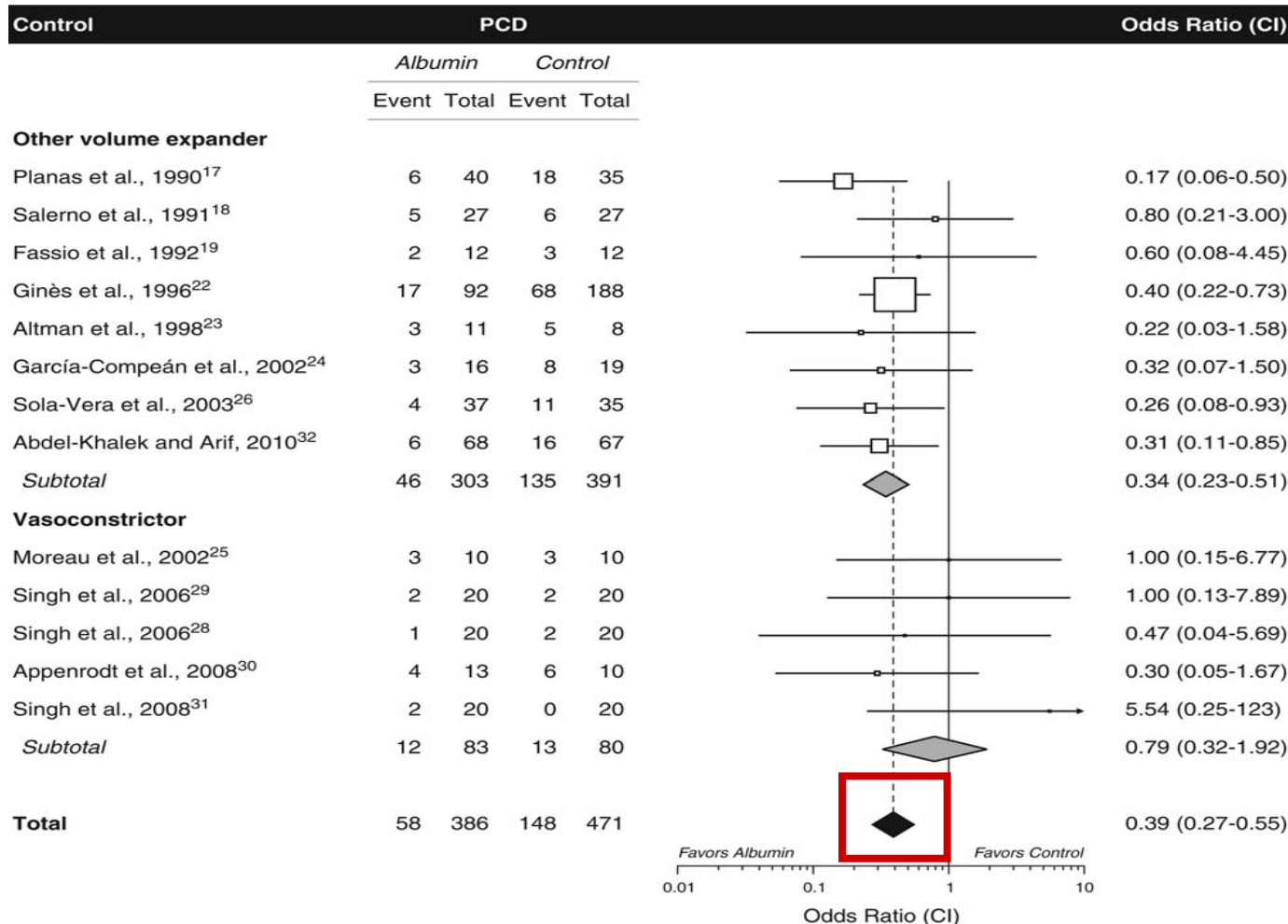
3. Treatment of hepatorenal syndrome with vasopressors

1 g/Kg b.w. at diagnosis

20-40 g/day thereafter until vasoconstrictors are stopped

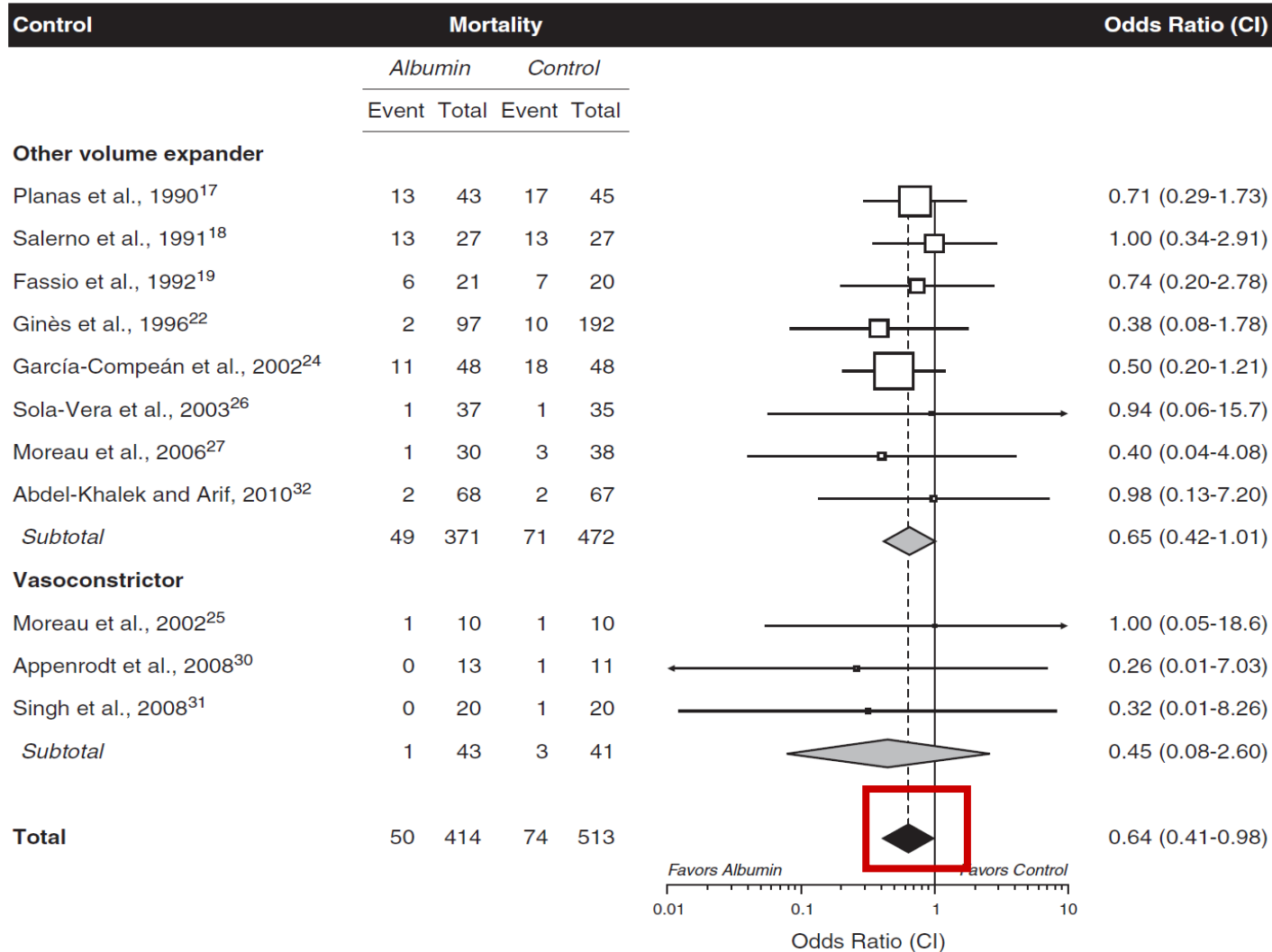
PREVENTION OF POST-PARACENTESIS CIRCULATORY DYSFUNCTION

Albumin vs other plasma-expanders and/or vasoconstrictors



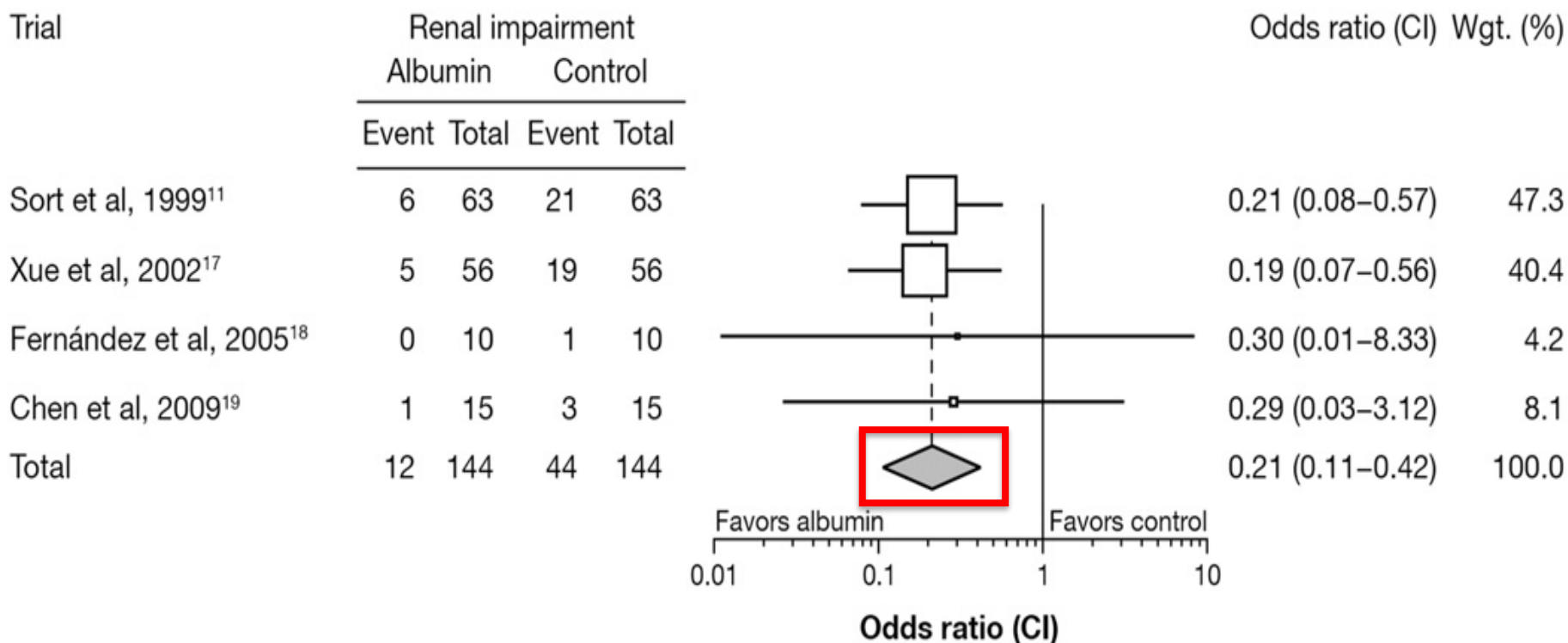
PREVENTION OF MORTALITY AFTER PARACENTESIS

Albumin vs other plasma-expanders and/or vasoconstrictors



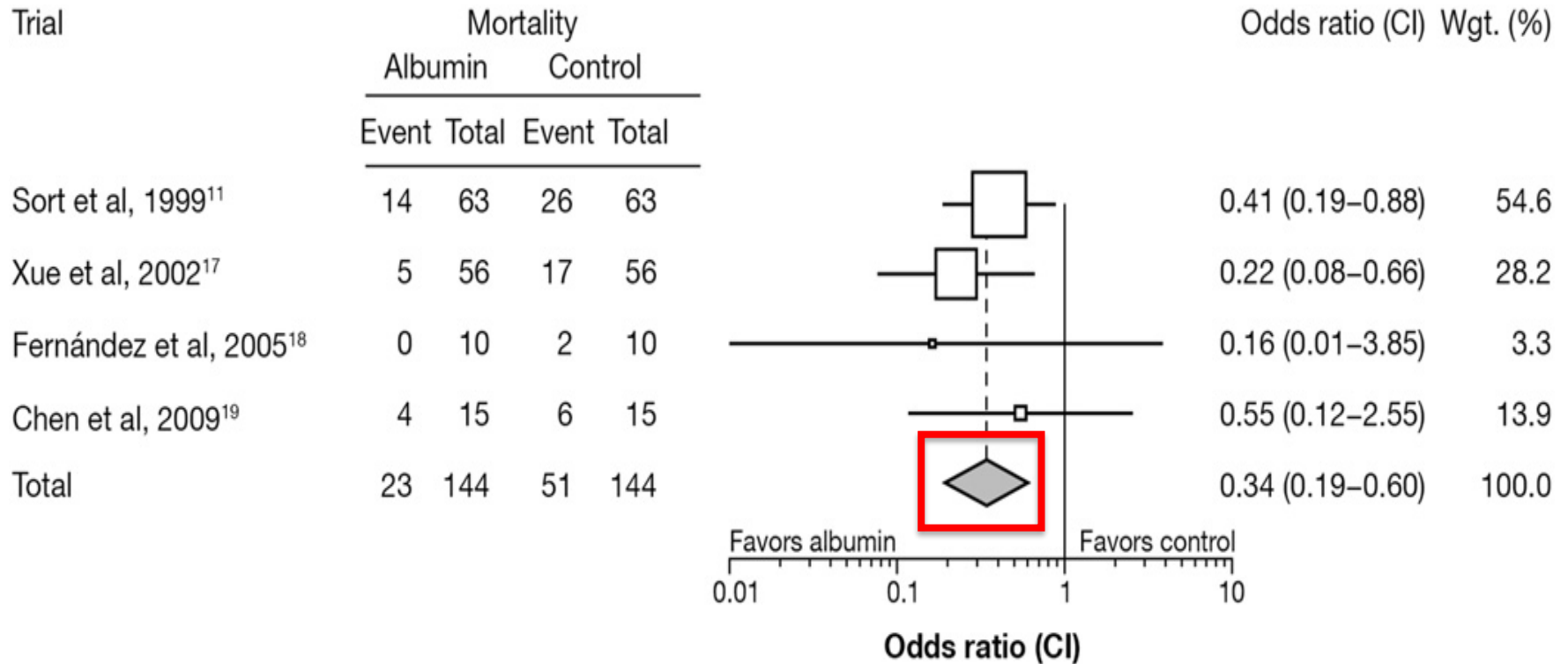
PREVENTION OF RENAL FAILURE AFTER SPONTANEOUS BACTERIAL PERITONITIS

Effect of albumin administration



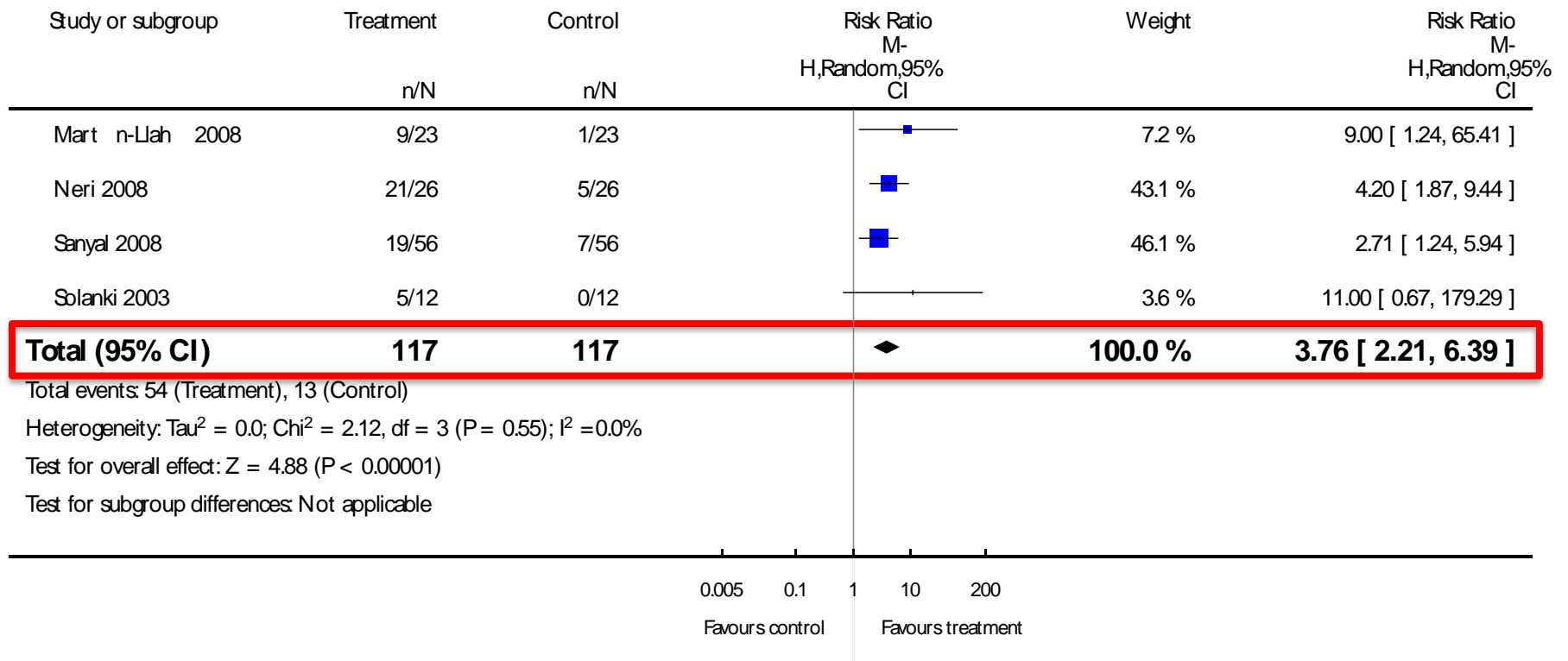
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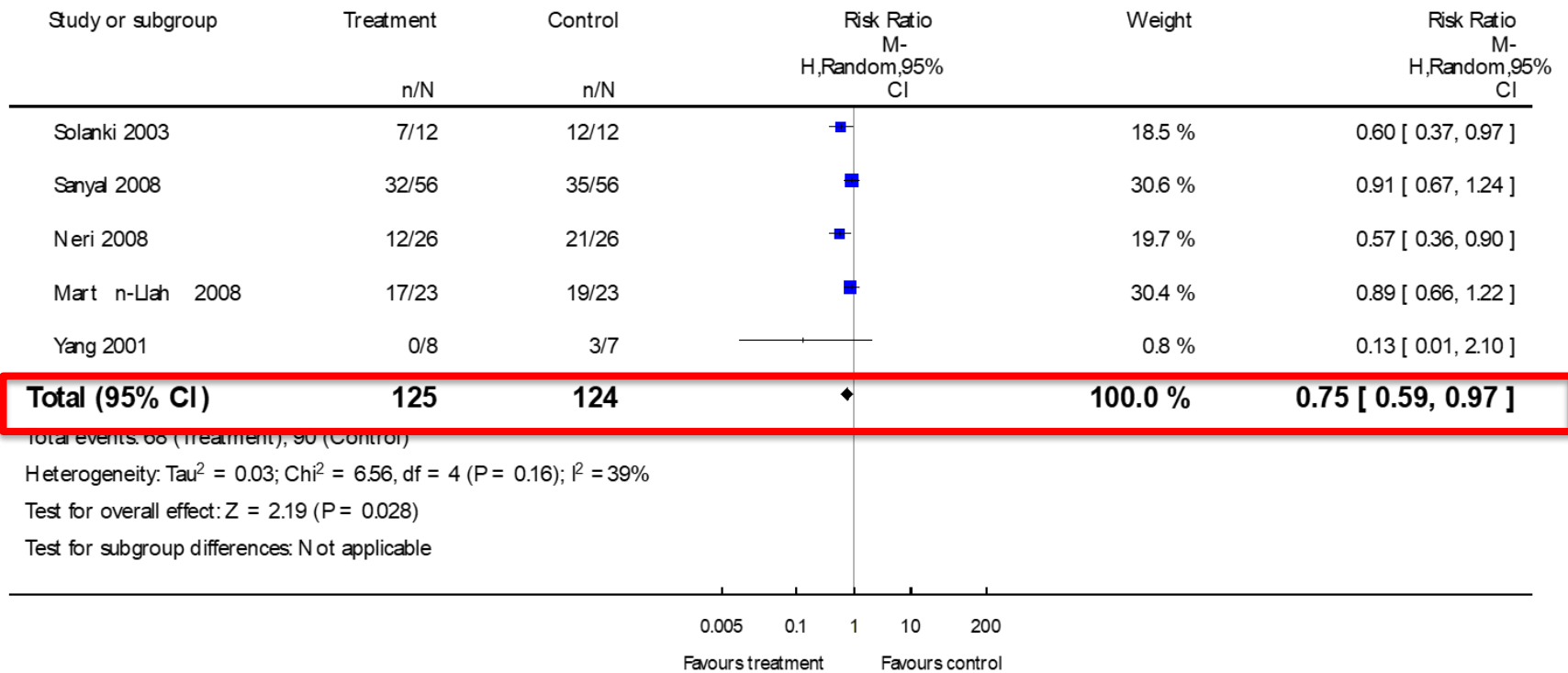
REVERSAL OF HEPATORENAL SYNDROME

Terlipressin + Albumin



PREVENTION OF MORTALITY AFTER HEPATORENAL SYNDROME

Terlipressin + Albumin



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NOTA 15 AIFA

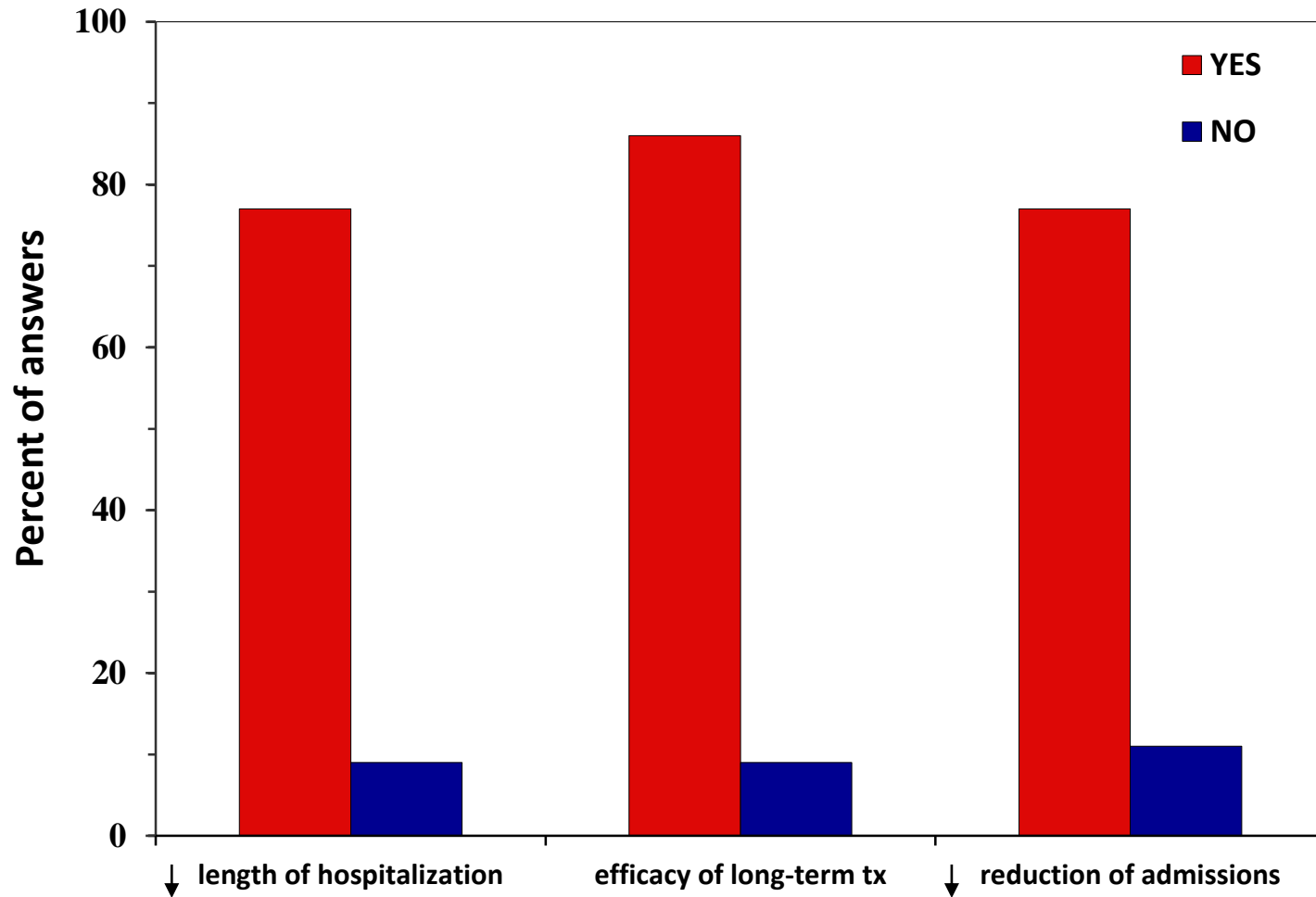
(2005)

La prescrizione a carico del SSN, su diagnosi e piano terapeutico di strutture specialistiche delle Aziende Sanitarie, è limitata alle seguenti condizioni:

- dopo paracentesi evacuativa di grande volume nella cirrosi epatica
- **grave ritenzione idrosalina nella cirrosi ascitica**, nella sindrome nefrosica o nelle sindromi da malassorbimento (ad es. intestino corto post-chirurgico o da proteino-dispersione), **non responsiva a un trattamento diuretico appropriato, specie se associata ad ipoalbuminemia ed in particolare a segni clinici di ipovolemia**

LONG-TERM ALBUMIN FOR ASCITES TREATMENT

A DELPHI STUDY AMONG ITALIAN HEPATOLOGISTS



**NO-PROFIT STUDY SPONSORED BY
THE ITALIAN DRUG AGENCY (A.I.F.A.)**

**The use of human Albumin for the treatment of ascites
in patients With hepatic cirrhosis:
a multicenter, open-label randomized clinical trial.**



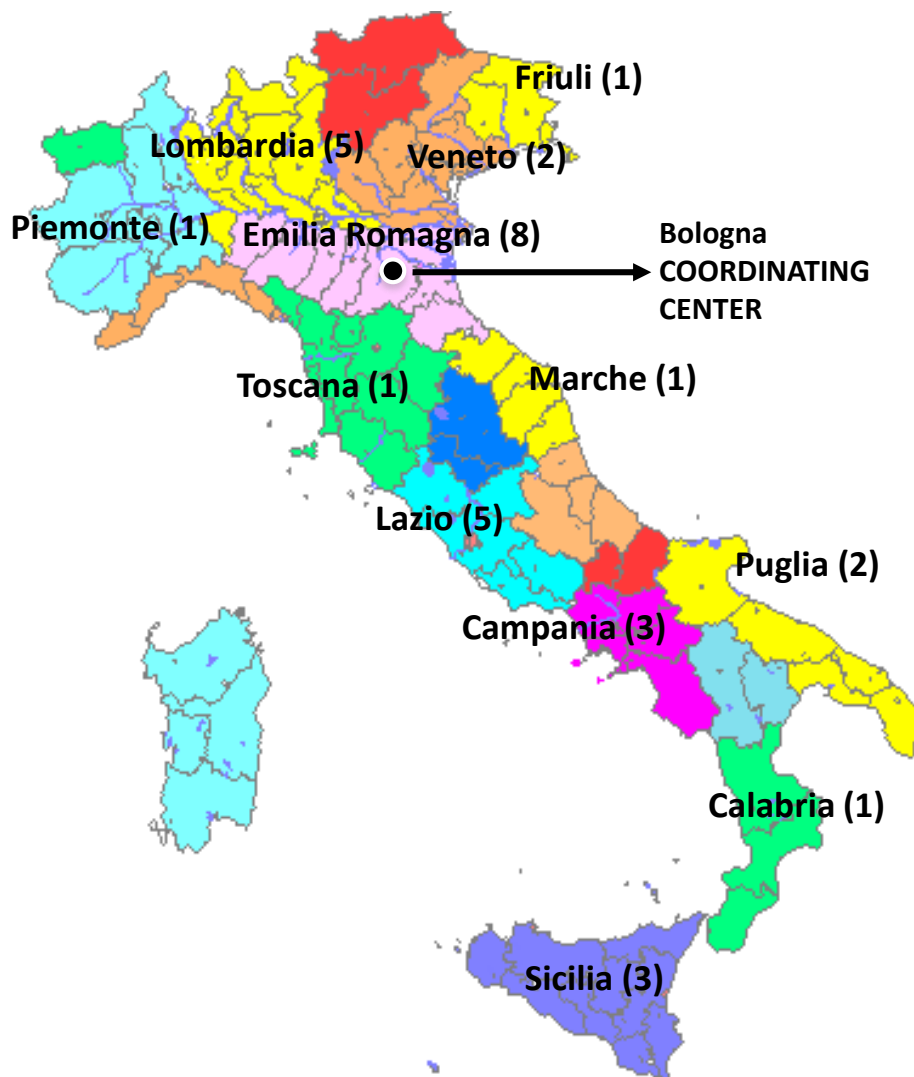
**The ANSWER study
NCT01288794**

Endorsed by

Italian Association for the Study of the Liver (AISF) – Italian Association of Gastroenterology (SIGE)
• *Italian Association of Gastroenterologist Hospitalists (AIGO)* •



The ANSWER study group

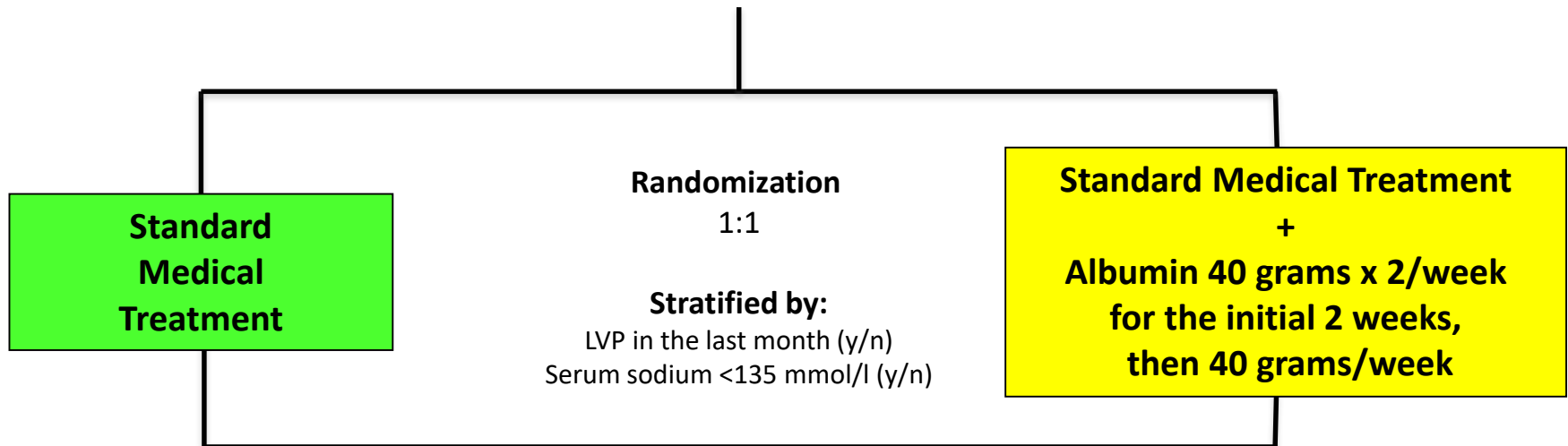


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32. G. RAIMONDO
33. S. NERI

DESIGN OF THE STUDY

440 PATIENTS WITH CIRRHOSIS and NON COMPLICATED ASCITES

ongoing treatment with anti-aldosteronic drug (≥ 200 mg/day) and furosemide (≥ 25 mg/day)



Causes of study termination:

- Transjugular Intra-hepatic Porto-systemic Shunt (TIPS)
- Liver transplantation
- 3 large paracentesis per month

End follow-up: 18 months



ALBUMIN INFUSION

SETTING

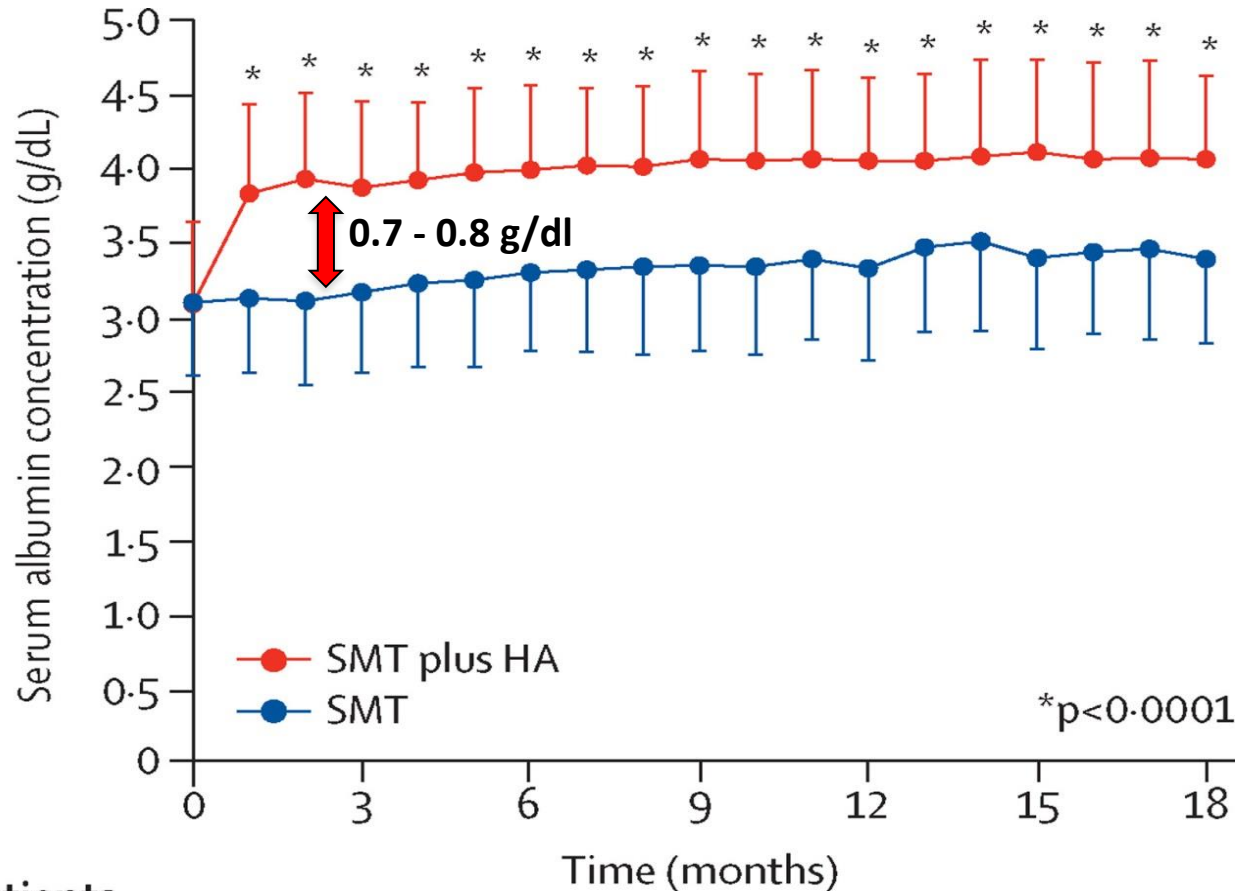
- Hospital outpatient clinics (majority)
- Out-of-hospital outpatient clinics
- Home-care assistance (few cases)
- During hospitalization for other causes

PROCEDURE

- Intravenous infusion of 4 vials (50 cc each) 20% human albumin via a peripheral vein in about 30-60 minutes



EFFECT ON SERUM ALBUMIN CONCENTRATION



Number of patients

SMT	213	115	84	76	53	52	51
SMT plus HA	218	153	123	109	103	88	86



END POINTS

PRIMARY END-POINT

- 18-month overall survival

SECONDARY END-POINTS

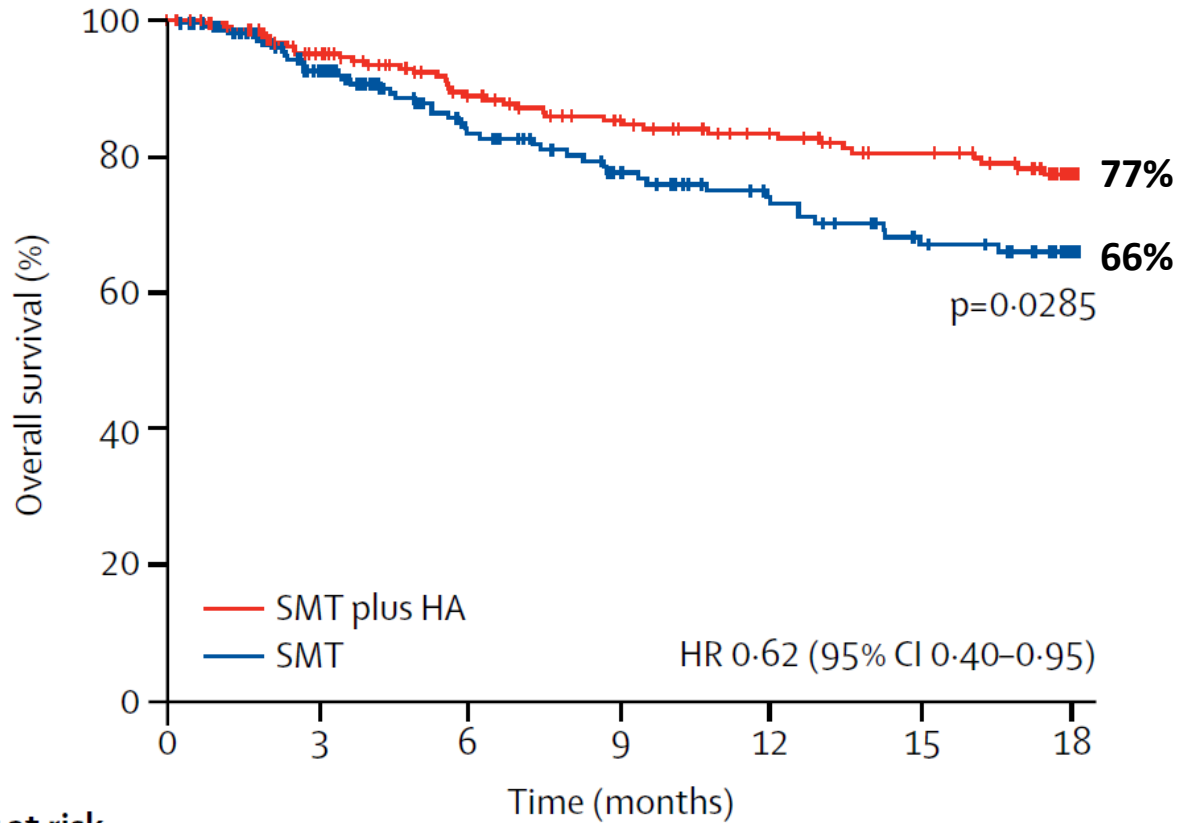
- Number of paracentesis
- Incidence of refractory ascites (ICA criteria)
- Number of patients reaching the indication to TIPS (3 paracentesis/month)
- Incidence of clinical complications of cirrhosis (*SBP and other bacterial infections, renal failure, GI bleeding, grade III and IV HE*)
- Incidence of diuretic-related side-effects
- Quality of life (EQ-5D and SF-36 questionnaires)
- Cost-effectiveness analysis

PRIMARY END-POINT





OVERALL SURVIVAL



Number at risk

	0	3	6	9	12	15	18
SMT	213	157	110	90	76	65	28
SMT plus HA	218	183	153	135	121	109	43

38% reduction in the mortality HR (0.62 [95% CI: 0.40-0.95])

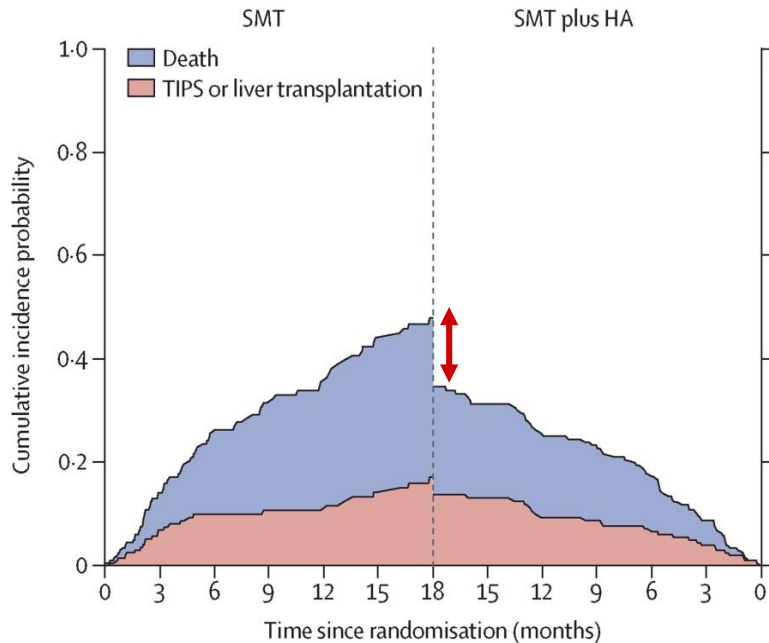
Log-rank test: p = 0.031



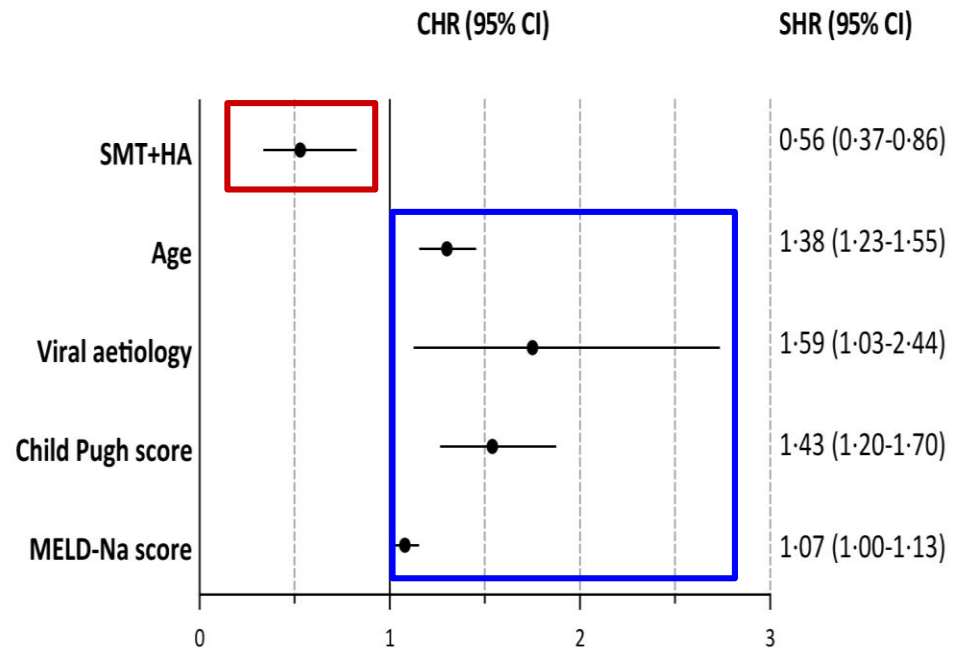
MORTALITY

Competing Risk Analysis

A Cumulative incidence of death and TIPS or liver transplantation



Multivariable competing risk model





NUMBER NEEDED TO TREAT (NNT)

Multivariate estimates

Follow-Up timepoints	Intent-to-Treat Population
	NNT(B) * [95%CI]
3 months	28.7 [20, 75]
6 months	13.3 [9, 35]
9 months	10.1 [7, 27]
12 months	8.5 [6, 23]
15 months	7.1 [5, 19]
18 months	7.0 [5, 19]

SECONDARY END-POINTS

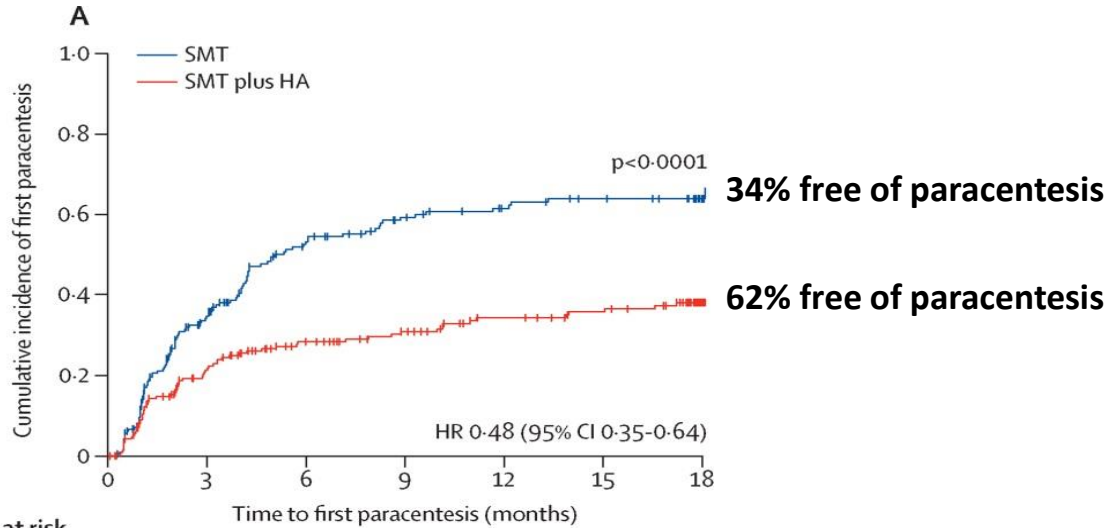


MANAGEMENT OF ASCITES



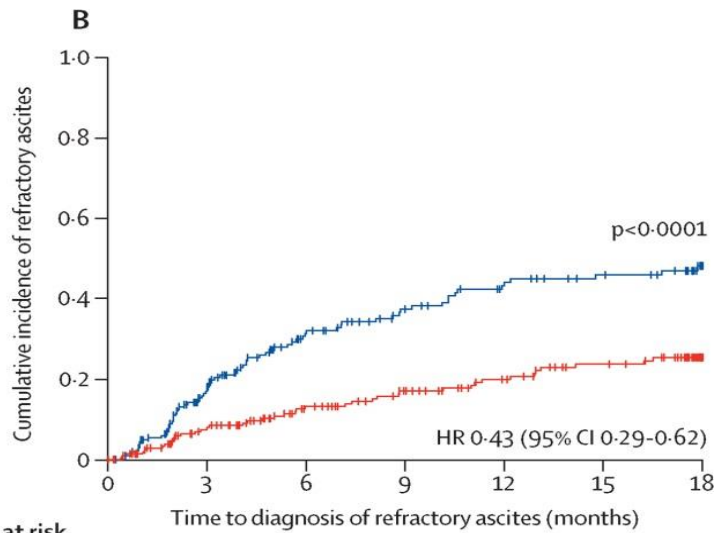


MANAGEMENT OF ASCITES



Number at risk

SMT	213	118	74	57	48	42	20
SMT plus HA	218	150	121	108	92	84	32



Number at risk

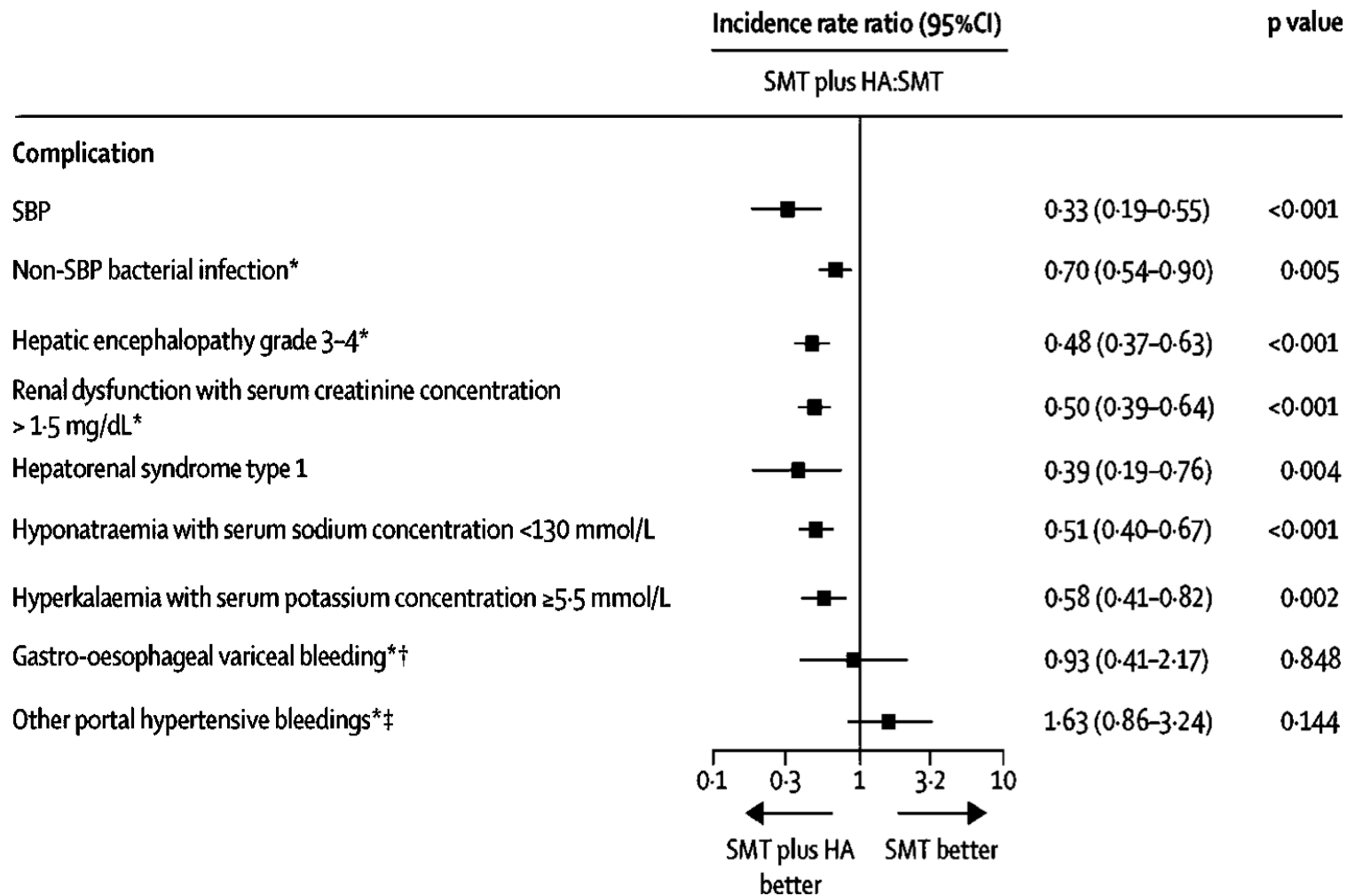
SMT	213	147	98	78	65	57	26
SMT plus HA	218	175	142	125	109	95	39

COMPLICATIONS OF CIRRHOSIS





INCIDENCE OF COMPLICATIONS



HOSPITALIZATIONS





HOSPITALIZATIONS

	Incidence rate <i>number/patient/year</i>		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

QUALITY OF LIFE





QUALITY OF LIFE METHODS

EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D)

1. Mobility
2. Self-care
3. Usual activities
4. Pain/discomfort
5. Anxiety/depression

No problems

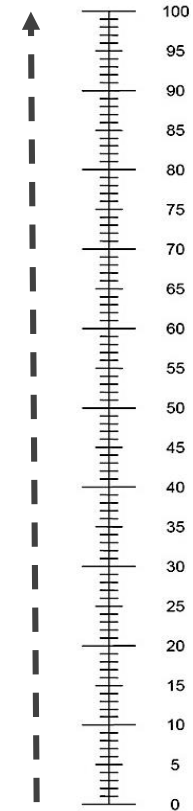
Some problems

Extreme problems

Utility index*

Visual Analogue Scale (VAS)

The best health you can imagine



The worst health you can imagine



QUALITY OF LIFE

RESULTS

EQ-5D utility index & VAS score changes during follow-up

		SMT	SMT+HA	
		Δ from baseline	Δ from baseline	p value
Month 3	EQ-5D utility index	-0.07 (0.21)	-0.02 (0.20)	0.012
	EQ-VAS	-5.0 (17.2)	-2.2 (18.7)	0.075
Month 6	EQ-5D utility index	-0.10 (0.25)	-0.04 (0.22)	0.004
	EQ-VAS	-6.8 (20.0)	-1.7 (21.8)	0.021
Month 12	EQ-5D utility index	-0.14 (0.32)	-0.05 (0.24)	0.024
	EQ-VAS	-10.7 (26.8)	-1.8 (24.1)	0.016
Month 18	EQ-5D utility index	-0.12 (0.33)	-0.06 (0.25)	0.499
	EQ-VAS	-6.0 (23.4)	-2.4 (26.3)	0.283

HEALTHCARE COSTS



Graduate School of Health Economics and Management

Catholic University, Rome

DIRECT HEALTHCARE COSTS

METHODS

Items included in the analysis and cost estimation according to the payer perspective
(Italian National Health System [NHS])

Liver-related hospitalization

According to the NHS diagnosis-related group (DRG) "cirrhosis"

€ 4,013 per hospitalization plus
€ 185 per day when the length of hospitalization exceeds 27 days

Indirect costs were not estimated

Paracentesis

According to NHS tariffs for medical and outpatient services

€ 34.86 per paracentesis

Albumin administration

Albumin cost

According to the ex-factory price in the Italian Official Journal

€ 2.63 per gram

Infusion cost (SMT+HA arm)

According to NHS tariffs for medical and outpatient services

€ 10.66 per infusion

DIRECT HEALTHCARE COSTS

Cost driver	SMT	SMT + HA
Liver-related hospitalizations (€/patient/year)	6,765	3,981
Paracentesis (€/patient/year)	122	54
Albumin infused for evidence-based indications* (€/patient/year)	388	151
Albumin infused per protocol (€/patient/year)	-	5,065
Accesses for albumin infusion per protocol (€/patient/year)	-	512
Total cost/patient/year (€)	7,275	9,763

*Evidence-based indications include:

- prevention of paracentesis-induced circulatory dysfunction
- prevention of SBP-induced renal dysfunction
- diagnosis and treatment of type 1 hepatorenal syndrome

COST-EFFECTIVENESS ANALYSIS



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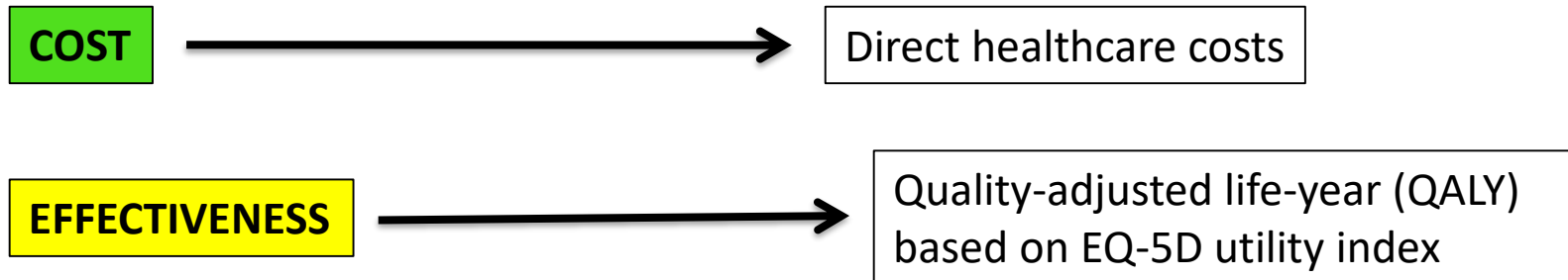


COST-EFFECTIVENESS ANALYSIS

Methods

INCREMENTAL COST-EFFECTIVENESS RATIO (ICER)

$$\text{ICER} = \frac{\text{cost (new treatment - current treatment)}}{\text{effectiveness (new treatment - current treatment)}}$$



QUALY: a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life.

1 QALY is equal to 1 year of life in perfect health*

* From the National Institute for Health and Care Excellence (NICE) glossary

COST-EFFECTIVENESS ANALYSIS

Incremental Cost-Effectiveness Ratio (ICER)

	SMT	SMT + HA
Total cost/patient/year (€)	7,275	9,763
→ Incremental cost/patient/year (€)	2,488	
QALY gain/year*	0.392	0.509
→ Incremental QALY/year	0,117	
→ ICER (€/QALY)	21,265	

*Based on the EQ-5D utility index

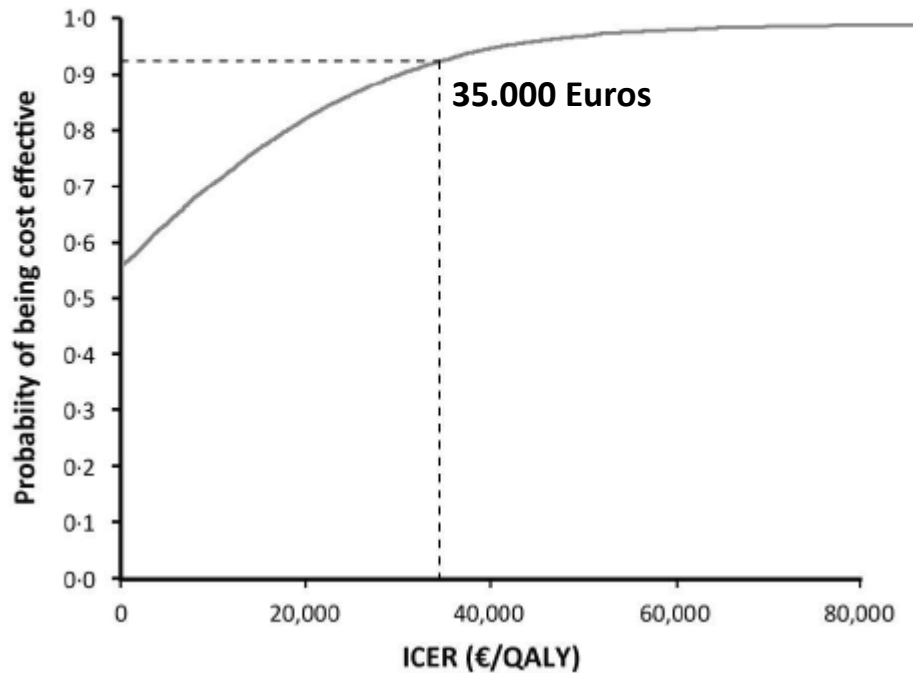
NICE threshold to consider a treatment cost-effective: 35,000 €



COST-EFFECTIVENESS ANALYSIS

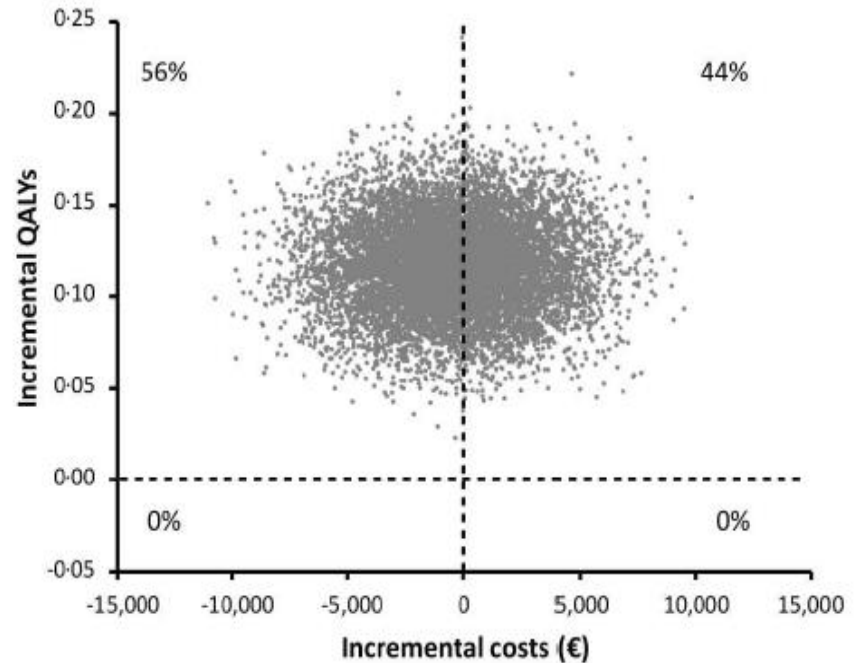
Sensitivity analysis

Cost-effectiveness acceptability curve



92% of 10.000 simulations are cost-effective

Bootstrap simulation



56% of 10.000 simulations are cost-saving



THE ANSWER STUDY

SUMMARY OF THE RESULTS

Long-term albumin administration to patients with cirrhosis and ascites:

- Improves 18-month overall survival
- Facilitates the management of ascites
- Reduces the incidence of severe complications of cirrhosis
- Reduces the number of hospitalizations
- Improves quality of life
- Is cost-effective
- Is safe

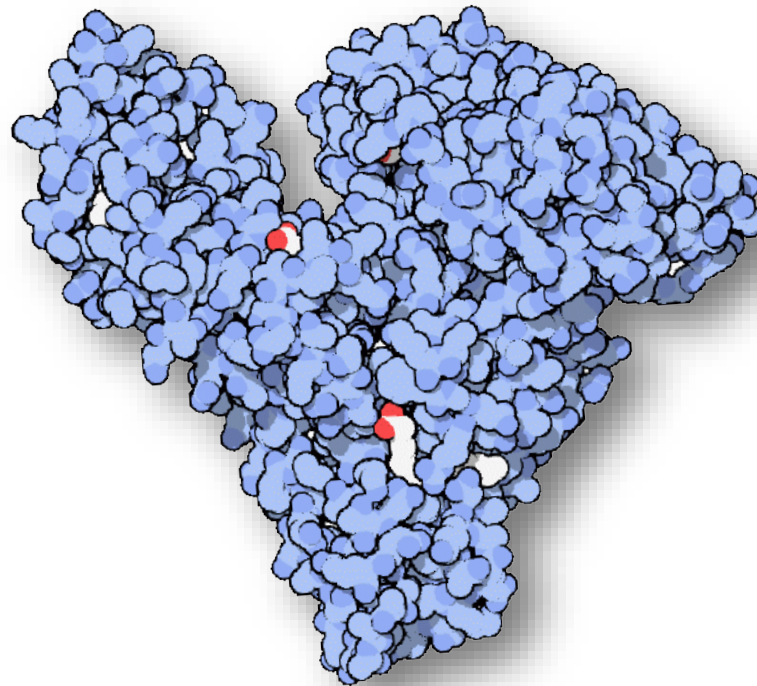
Albumin is a disease-modifying agent in decompensated cirrhosis

THE ALBUMIN MOLECULE

PROPERTIES

**Regulation of
fluid distribution**

*Negative net charge
High molecular weight
High plasma concentration*



ONCOTIC

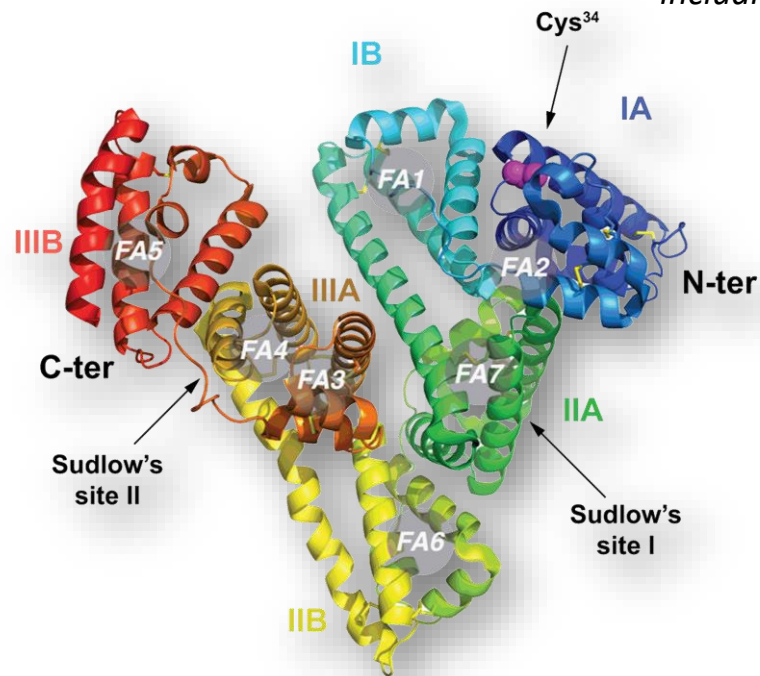
THE ALBUMIN MOLECULE

PROPERTIES

Regulation of fluid distribution

Negative net charge
High molecular weight
High plasma concentration

ONCOTIC



Binding and transport

Many endogenous and exogenous compounds including drugs

Antioxidant

Free radical and metal ion scavenging

Endothelial stabilization

Immunomodulation and antioxidant properties

Hemostatic effect

NO binding at Cys-34

Regulation of extracellular pH

Binding of H⁺

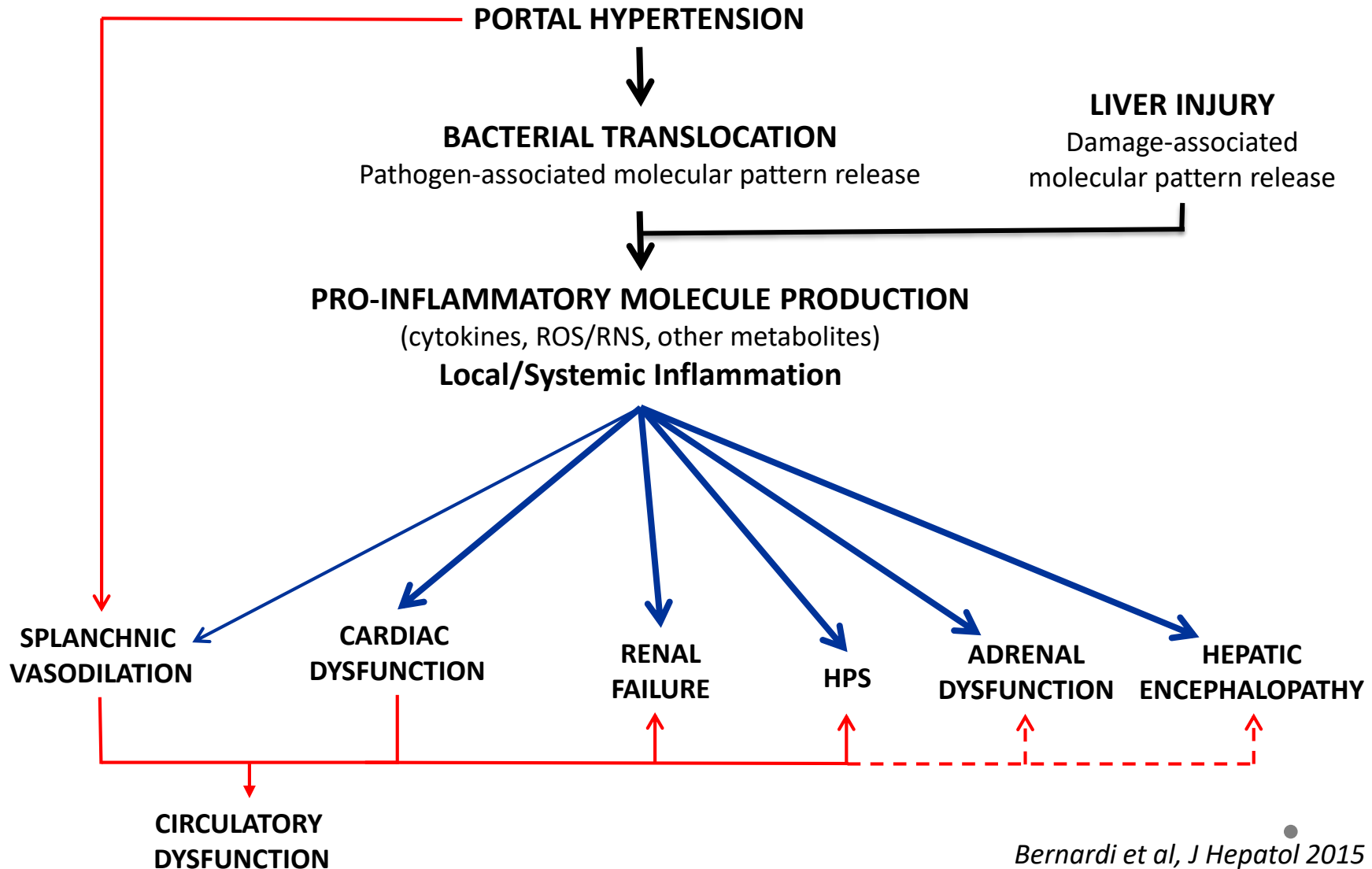
Modulation of immune/inflammatory responses

LPS binding, modulation of intracellular redox state, TNF α inhibition, PGE binding

NON-ONCOTIC

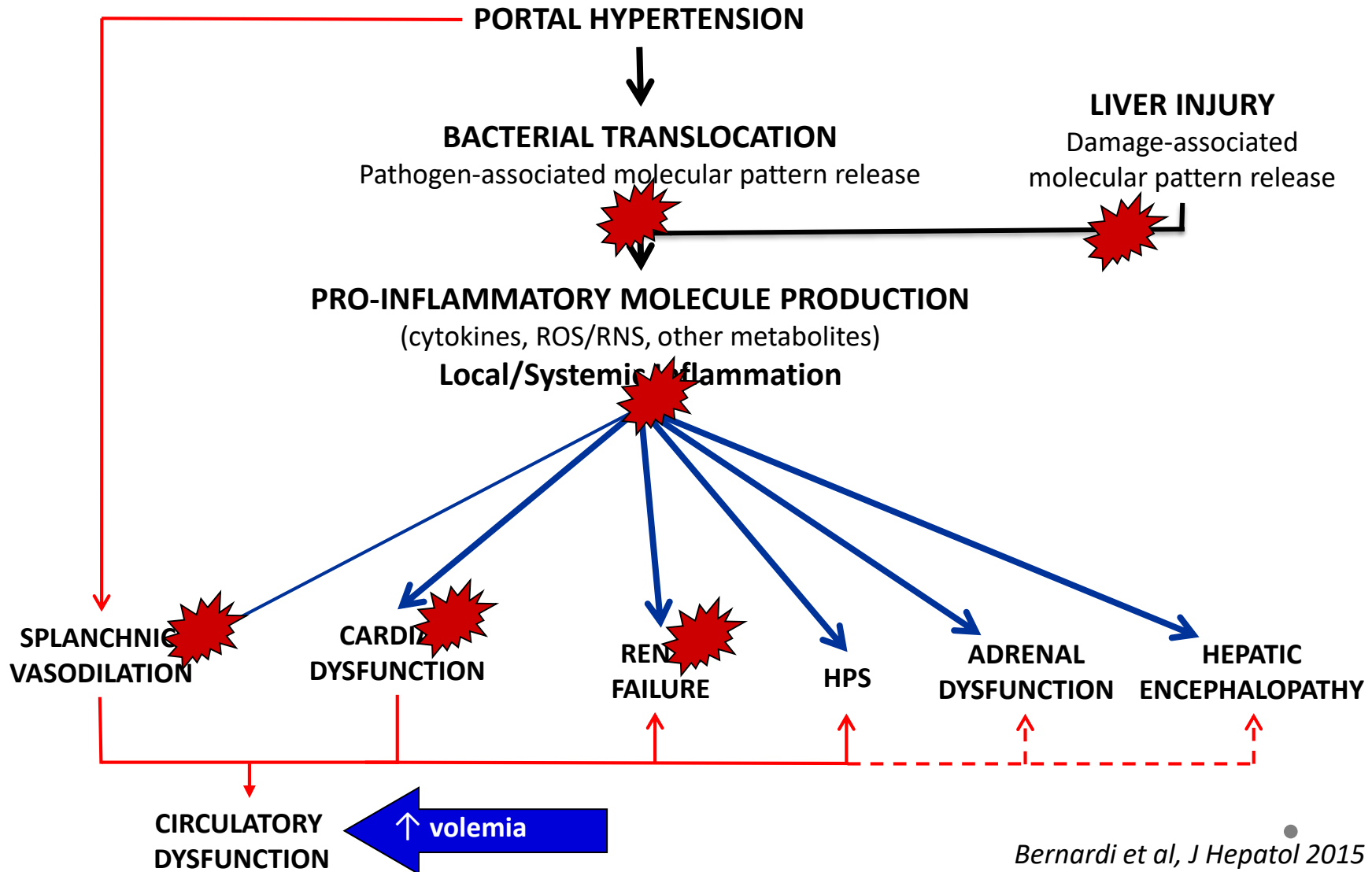
PATHOPHYSIOLOGY OF DECOMPENSATED CIRRHOSIS

The systemic inflammation hypothesis



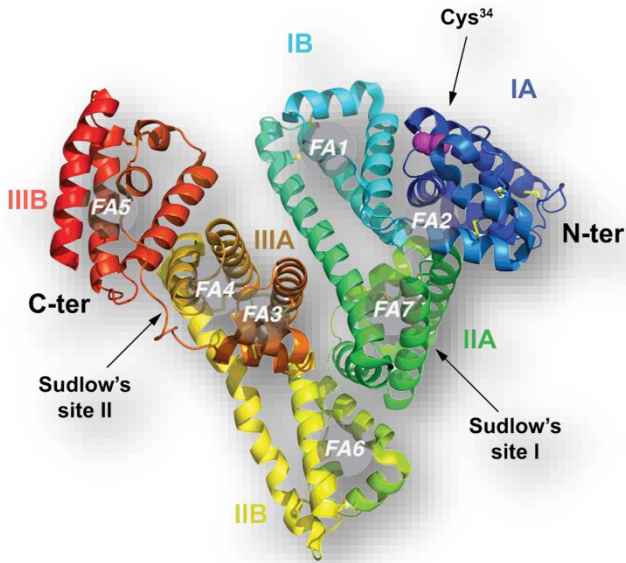
PATHOPHYSIOLOGY OF DECOMPENSATED CIRRHOSIS

Potential targets for albumin actions



HUMAN ALBUMIN

A "DISEASE-MODIFYING AGENT IN CIRRHOSIS" (DMAC)



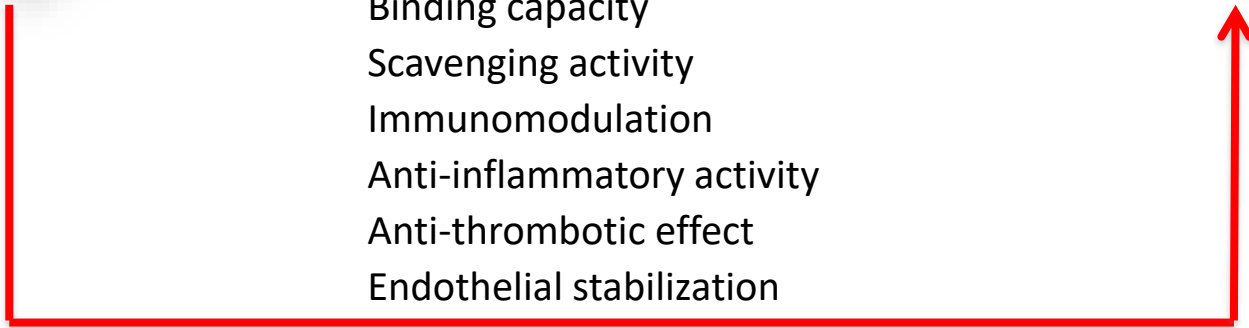
ONCOTIC PROPERTIES

Plasma volume expansion



NON-ONCOTIC PROPERTIES

Binding capacity
Scavenging activity
Immunomodulation
Anti-inflammatory activity
Anti-thrombotic effect
Endothelial stabilization



ASCITES
RENAL FAILURE
ENCEPHALOPATHY
BACTERIAL INFECTION
ORGAN FAILURE
ACLF
MORTALITY

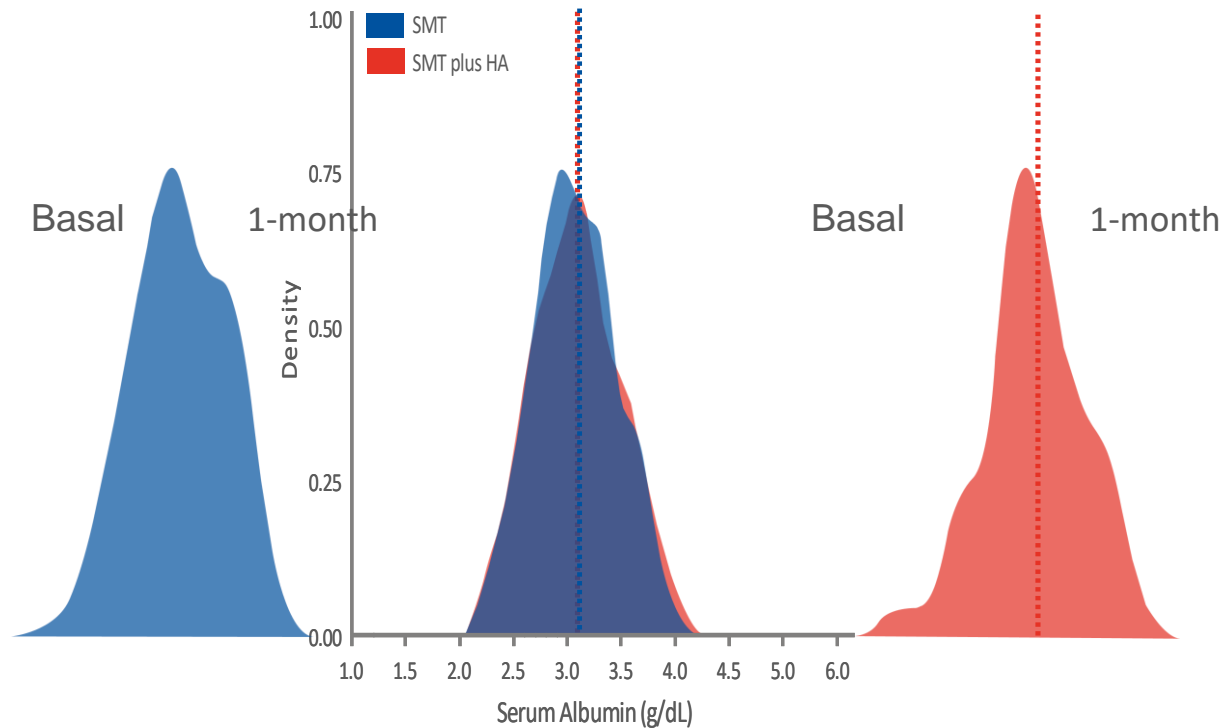
ONGOING POST-HOC ANALYSIS OF THE ANSWER STUDY

From the clinical trial to the real-world clinical practice

- **Serum albumin concentration as a guide of treatment**
- Tailoring treatment in terms of dosage, duration, frequency and criteria for discontinuation
- Identification of patient sub-groups to apply personalized treatment

RESULTS

1-month serum albumin levels in the SMT and SMT+HA arms



SMT: Standard Medical Treatment (n = 161)

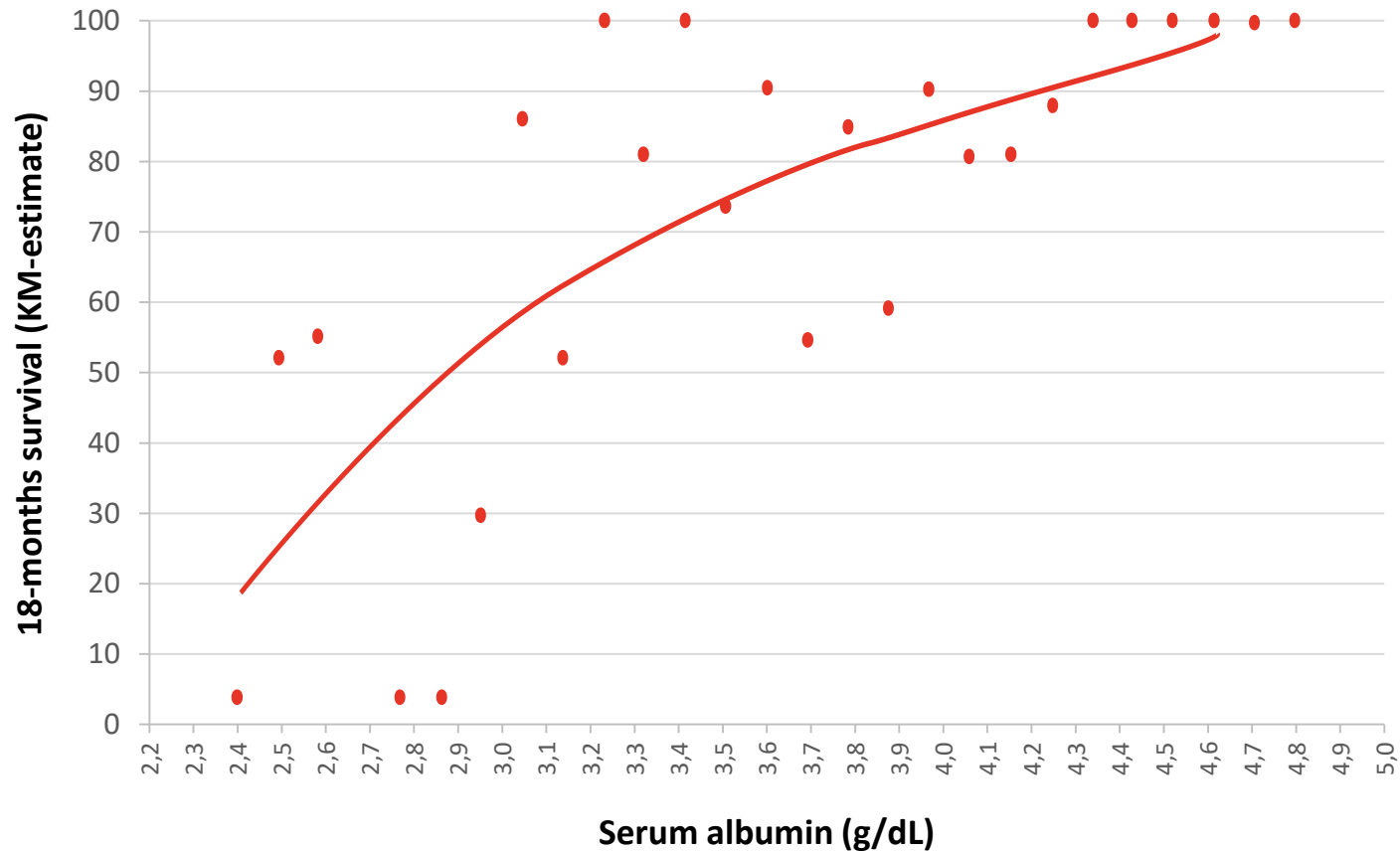
SMT+HA: SMT + Human Albumin (n = 181)



1-MONTH SERUM ALBUMIN TARGET LEVEL

18-month probability of survival according to the target level

THIRD-ORDER POLYNOMIAL REGRESSION ANALYSIS

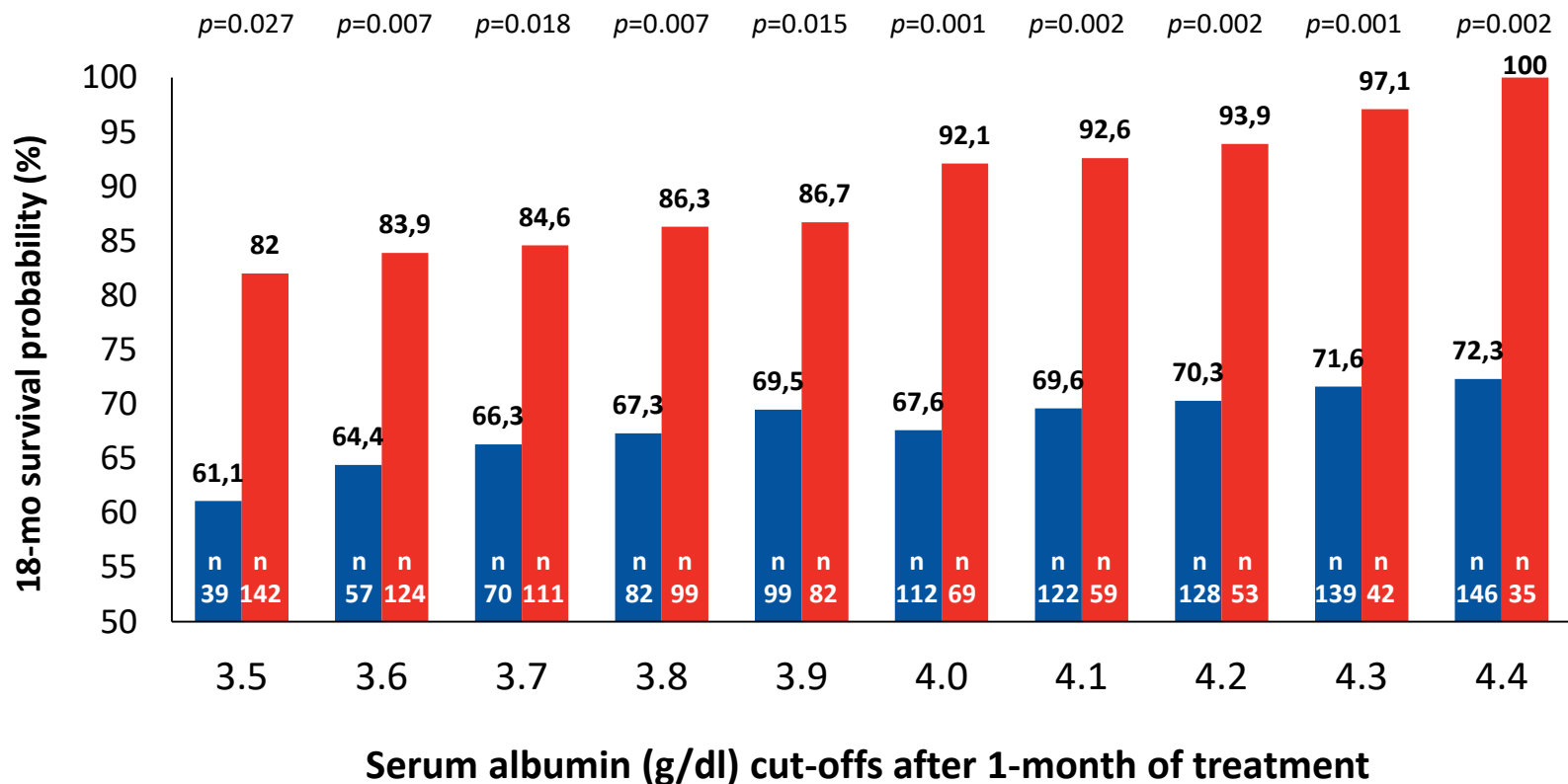


 SMT + HA: Standard Medical Treatment + Human Albumin (n=181)

1-MONTH SERUM ALBUMIN TARGET LEVEL

18-months survival of patients stratified according to serum albumin levels reached after at 1-month of treatment

KAPLAN MEIER SURVIVAL ESTIMATES



Best cut-off to discriminate probability of survival: 4.0 g/dL





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