

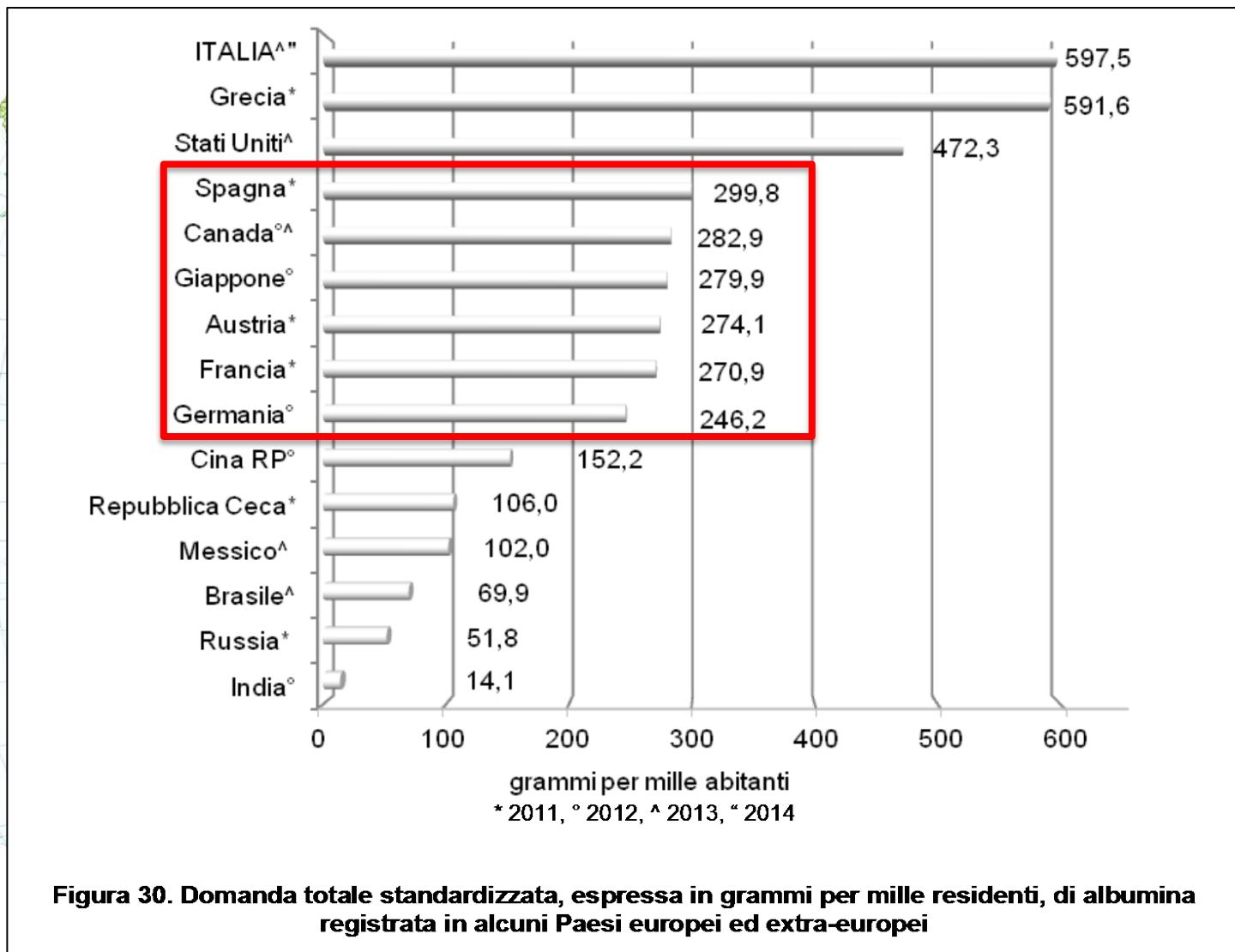


Le indicazioni cliniche per l'utilizzo dell'albumina

Paolo Caraceni

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Alma Mater Studiorum Università di Bologna*

ALBUMIN CONSUMPTION WORLDWIDE



ALBUMIN CONSUMPTION IN ITALY

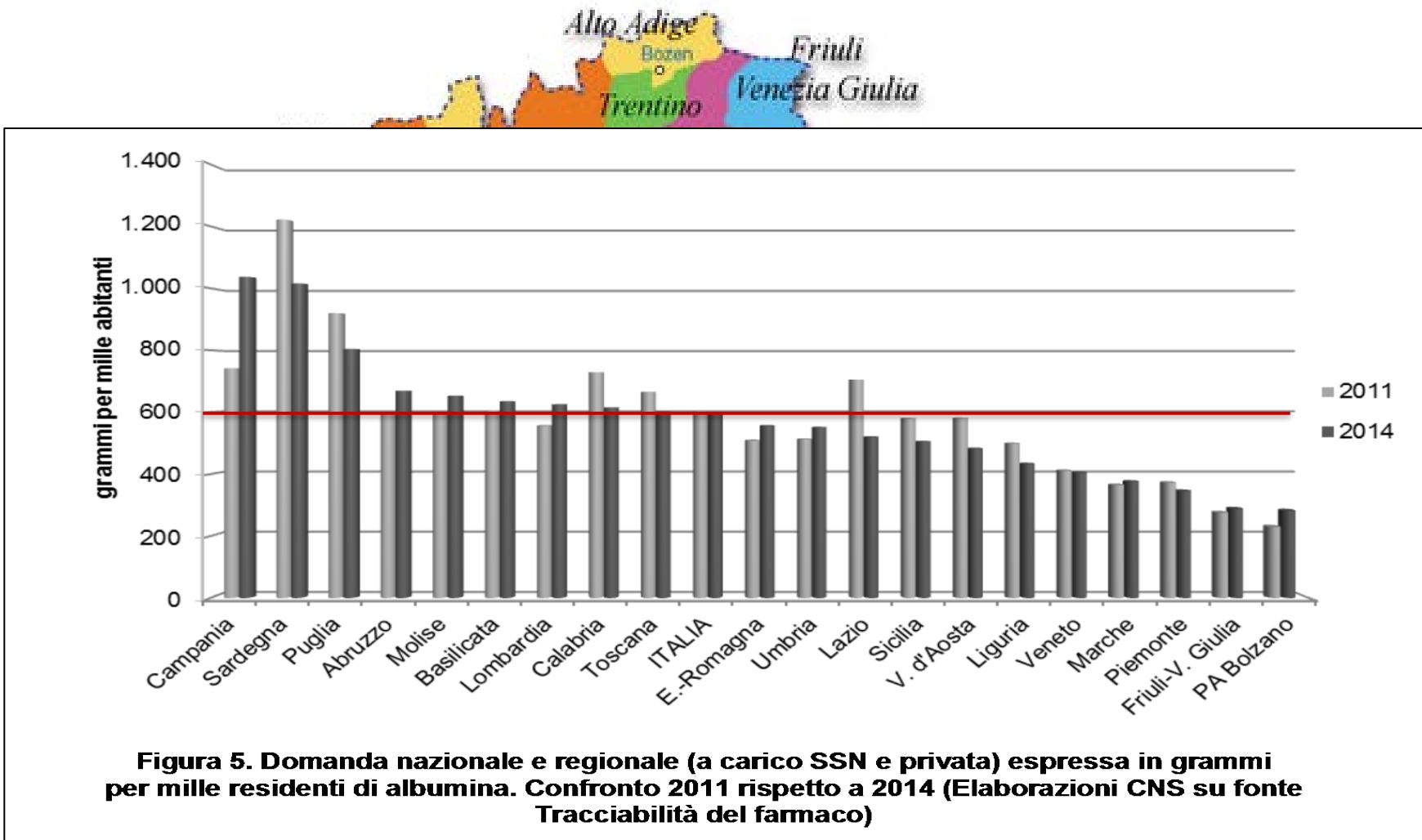


Figura 5. Domanda nazionale e regionale (a carico SSN e privata) espressa in grammi per mille residenti di albumina. Confronto 2011 rispetto a 2014 (Elaborazioni CNS su fonte Tracciabilità del farmaco)



RESTRAINTS FOR ALBUMIN USE

- Limited solid scientific evidence
- High cost
- Availability of cheaper alternatives
- Limited availability
- Fear of transmission of viral infection



FIGHTING THE SCARCITY OF RESOURCES



The NEW ENGLAND JOURNAL *of* MEDICINE

Perspective
MAY 24, 2012

From an Ethics of Rationing to an Ethics of Waste Avoidance

Howard Brody, M.D., Ph.D.

VIEWPOINT

Why the Ethics of Parsimonious Medicine Is Not the Ethics of Rationing

Jon C. Tilburg, MD

Christine K. Cassel, MD

JAMA 2013; February 27, 2013



Medico/Decisore



Appropriatezza terapeutica

Solide evidenze scientifiche di efficacia

Studi di farmacoeconomia

Raccomandazioni/linee guida condivise



UTILIZZO DELL'ALBUMINA NELLA PRATICA CLINICA

OUTLINE

- Complicanze della cirrosi epatica
- Paziente critico
- Altre condizioni patologiche

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COMPLICANZE DELLA CIRROSI EPATICA

USO DELL'ALBUMINA

Elevata prevalenza della cirrosi in Italia

- Europa: 170.000 morti per anno (1.8% dei decessi totali)
- Italia: 15-20.000 morti per anno (\approx 3% dei decessi totali)

Solido presupposto fisiopatologico

- Espansione plasmatica → ipovolemia efficace
- Proprietà non-oncotiche → infiammazione cronica e disfunzione immunitaria

Disponibilità di solide evidenze scientifiche

- Trials randomizzati
- Metanalisi





Contents lists available at [ScienceDirect](#)

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)

RACCOMANDAZIONI AISF-SIMTI

CLINICAL CONDITION		DOSES AND SCHEDULES OF ADMINISTRATION	INDICATION FOR THE USE OF HA	QUALITY OF EVIDENCE STRENGTH OF RECOMMENDATION
Prevention of PPCD	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 HRS		1 g/kg/die for 2 consecutive days	To be used regularly	D1
Treatment of type I HRS (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

TREATMENT OF ASCITES

LONG-TERM ALBUMIN ADMINISTRATION

PROs

Pathophysiological rationale

Endorsed by Italian hepatologists

Gentilini et al, Dig Liv Dis, 2002

CONS

Lack of solid scientific evidences

No mention in the International guidelines

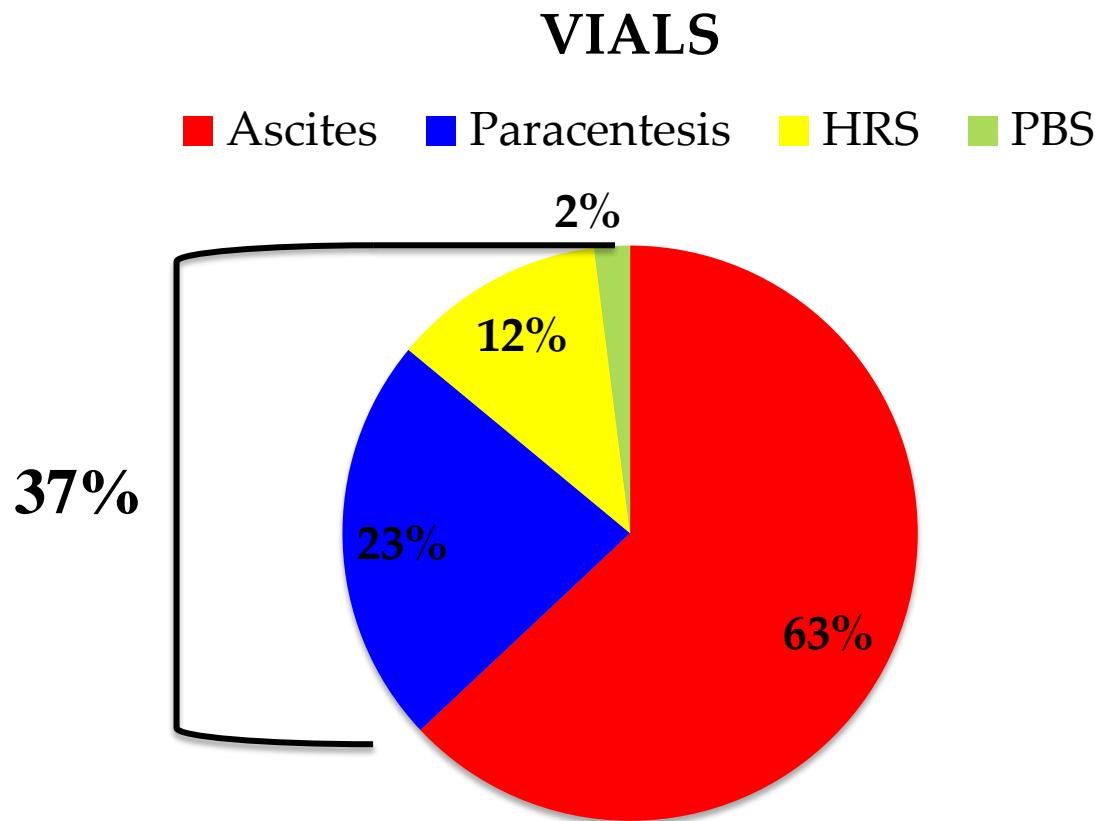
EASL, 2010; AASLD, 2012

NOTA 15 AIFA

Classe A, limitatamente alle seguenti indicazioni:

- *grave ritenzione idrosalina nella cirrosi ascitica, nella sindrome nefrosica o nelle sindromi da malassorbimento non responsiva a un trattamento diuretico appropriato, specie se associata ad ipoalbuminemia ed in particolare a segni clinici di ipovolemia.*

ALBUMIN USE AMONG PATIENTS WITH CIRRHOSIS AT S. ORSOLA-MALPIGHI HOSPITAL



**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

Associazione Italiana per lo Studio del Fegato (AISF) - Società Italiana di Gastroenterologia (SIGE)
Associazione Italiana Gastroenterologi Ospedalieri (AIGO)



AKNOWLEDGEMENT

UNRESTRICTED SUPPORT

- **Baxter**
- **Biostest**
- **CSL Behring**
- **Grifols**
- **Kedrion**

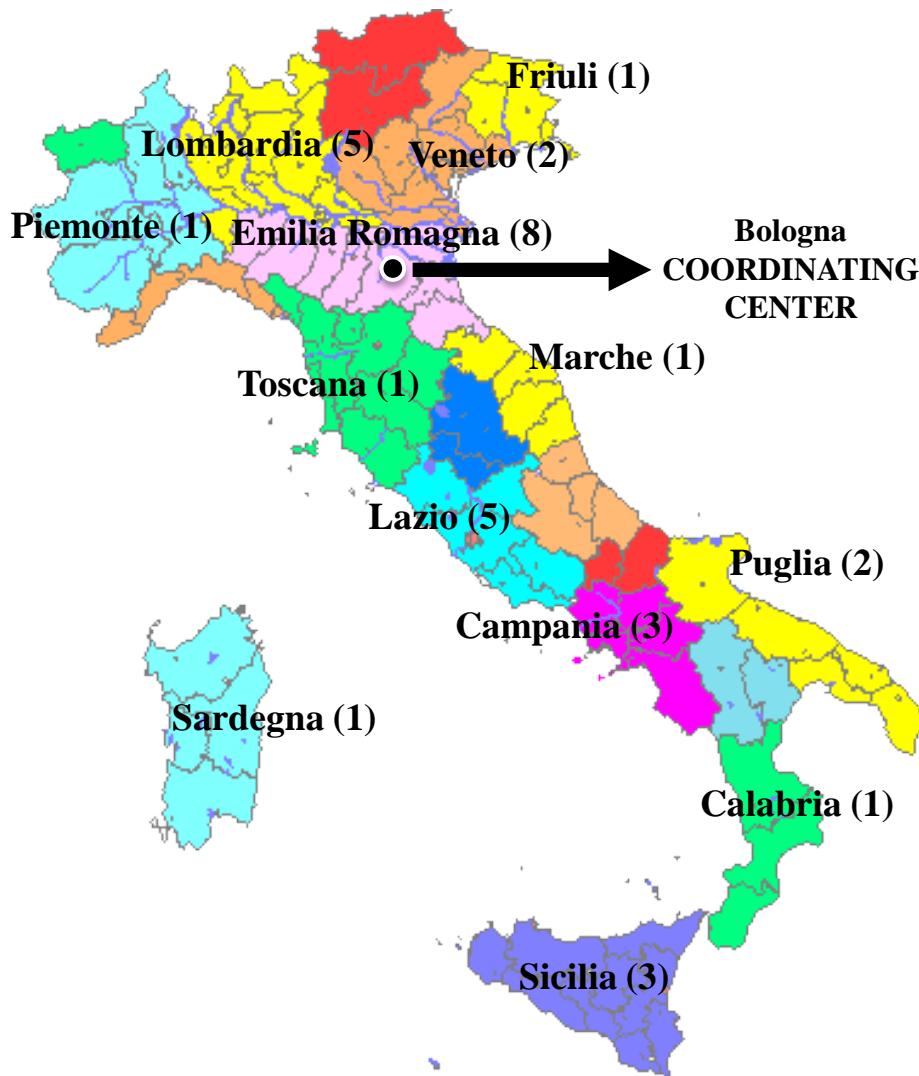


DECRETO 17 dicembre 2004.

Prescrizioni e condizioni di carattere generale, relative all'esecuzione delle sperimentazioni cliniche dei medicinali, con particolare riferimento a quelle ai fini del miglioramento della pratica clinica, quale parte integrante dell'assistenza sanitaria.



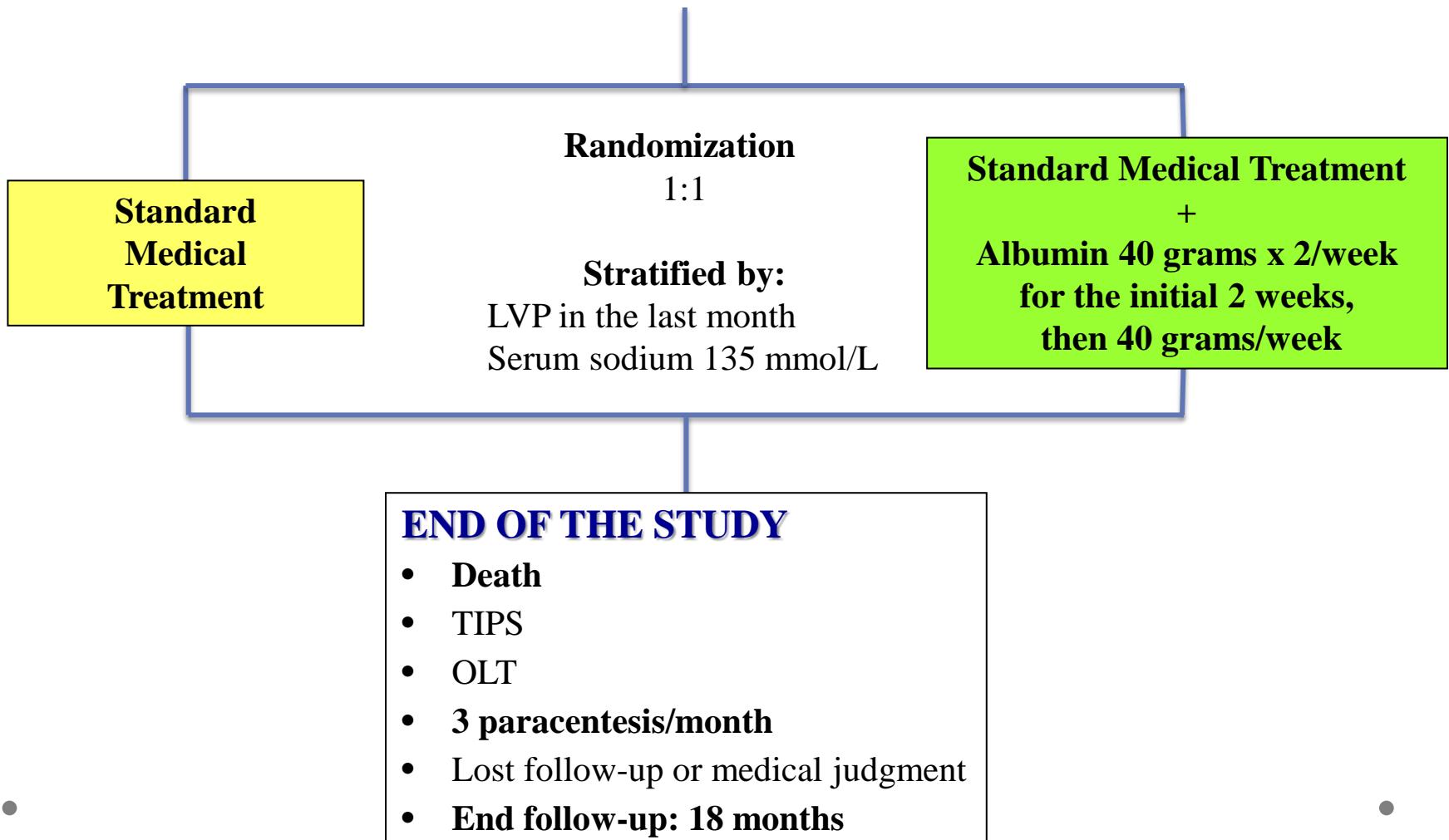
The ANSWER Study Group



- | | |
|----|----------------|
| 1 | M. RIZZETTO |
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| 3 | A. AIROLDI |
| 4 | F. SALERNO |
| 5 | G. SPINZI |
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| 13 | E. VILLA |
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| 29 | R. COZZOLONGO |
| 30 | A. DI LEO |
| 31 | P. LEO |
| 32 | V. DI MARCO |
| 33 | G. RAIMONDO |
| 34 | S. NERI |

DESIGN OF THE STUDY

420 PATIENTS WITH CIRRHOSIS and NON COMPLICATED ASCITES
ongoing treatment with anti-aldosteronics (≥ 200 mg/day) and furosemide (≥ 25 mg/die)



END-POINTS

PRIMARY END-POINT

- 18-month 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, hepatic encephalopathy)
- Quality of life (SF-36 and EQ 5D questionnaires)
- Cost-effectiveness analysis



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EFFECTS OF ALBUMIN IN CRITICAL ILLNESSES

Hypovolemia, burns, hypoalbuminemia

Albumin administration increases the risk of death (pooled relative risk: 1.68)

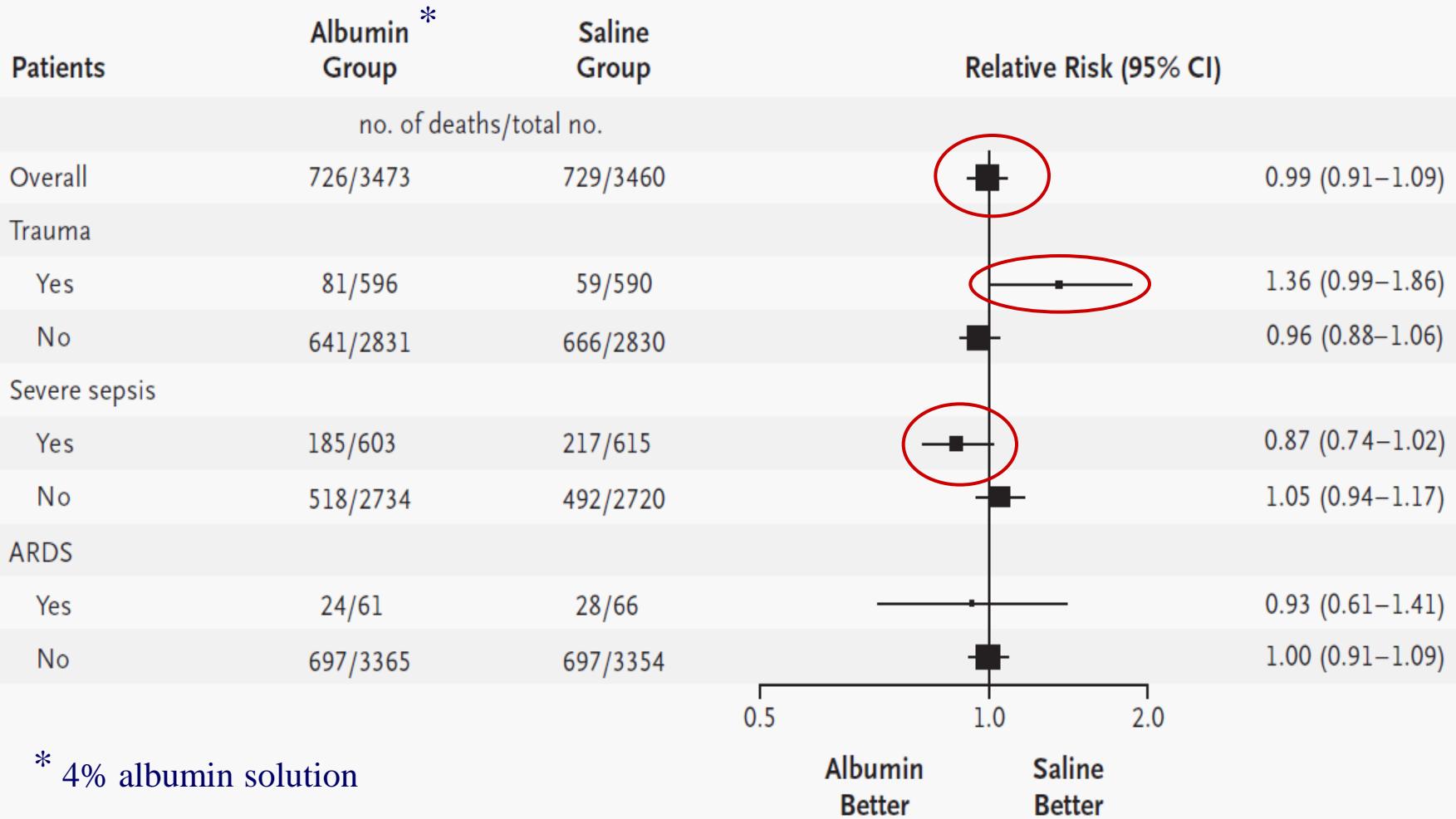
Cochrane review - BMJ 1998

Surgery or trauma, burns, hypoalbuminemia, ascites, high-risk neonates

Albumin administration does not increase the risk of death (pooled relative risk: 1.11)

Wilkes & Navickis - Ann Int Med 2001

EFFECTS OF ALBUMIN IN CRITICAL ILLNESSES



* 4% albumin solution

No influence by baseline serum albumin concentration

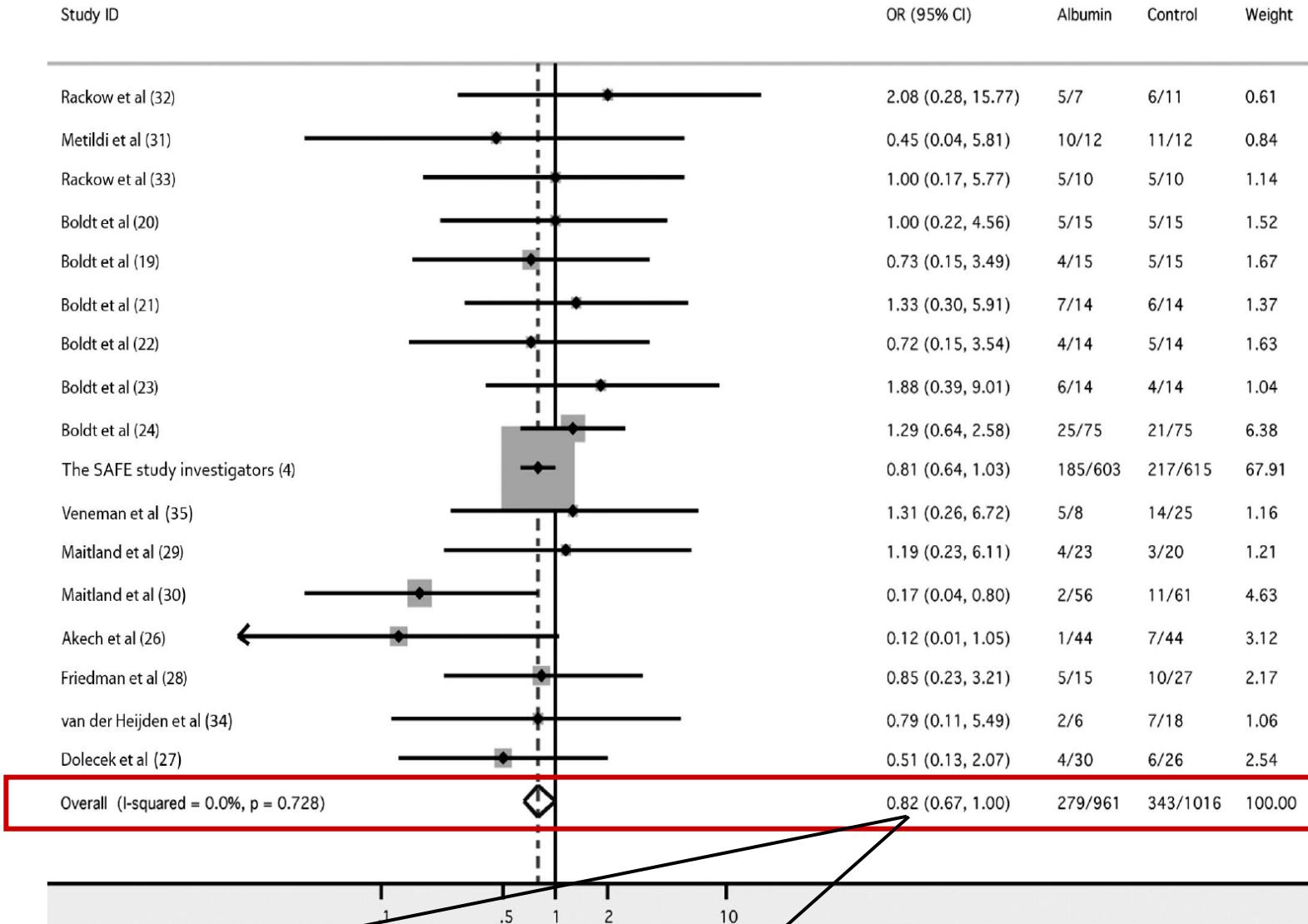
Higher mortality in traumatic brain injury

SAFE Investigators, *N Engl J Med* 2004

SAFE Investigators, *BMJ* 2006

SAFE Investigators, *N Engl J Med* 2007

EFFECTS OF ALBUMIN IN PATIENTS WITH SEPSIS

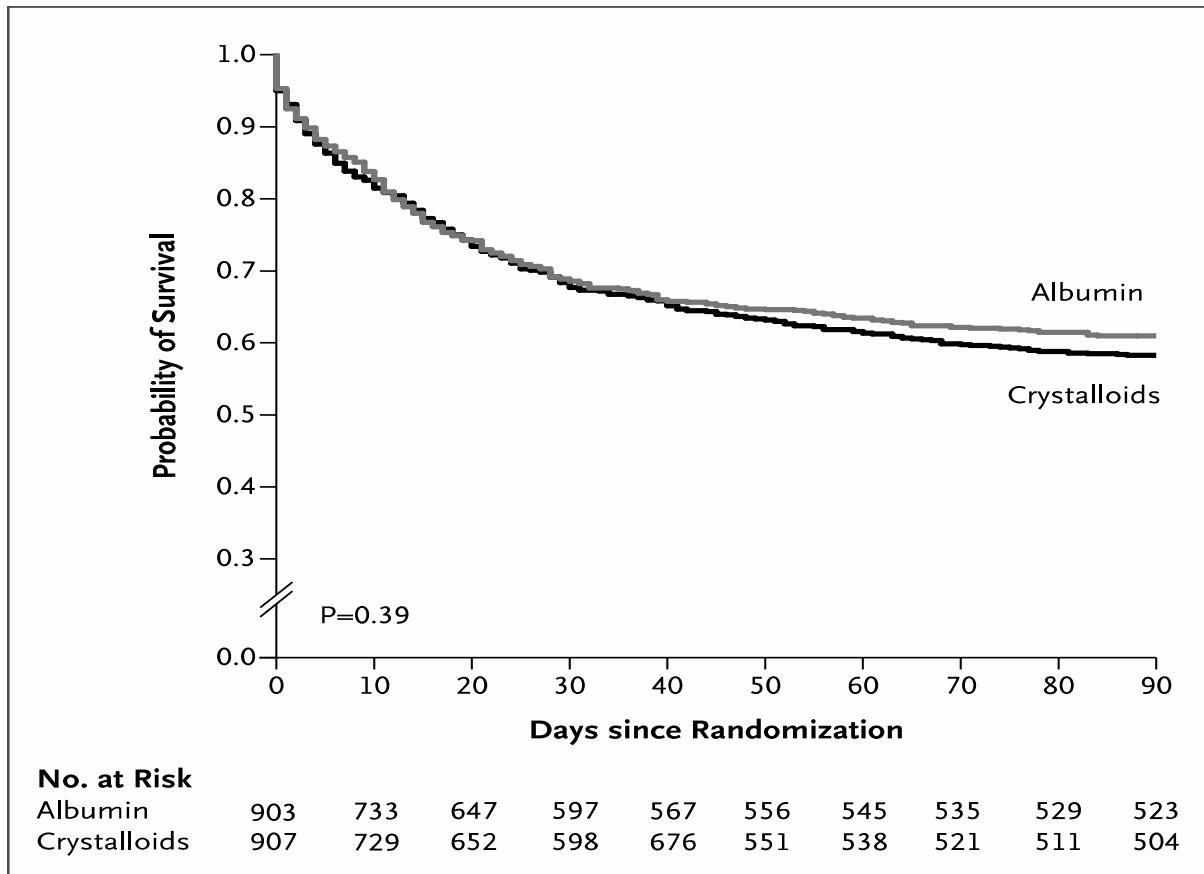


0.82 (0.67-1.00) – P = 0.047

Delaney et al, Crit Care Med 2011

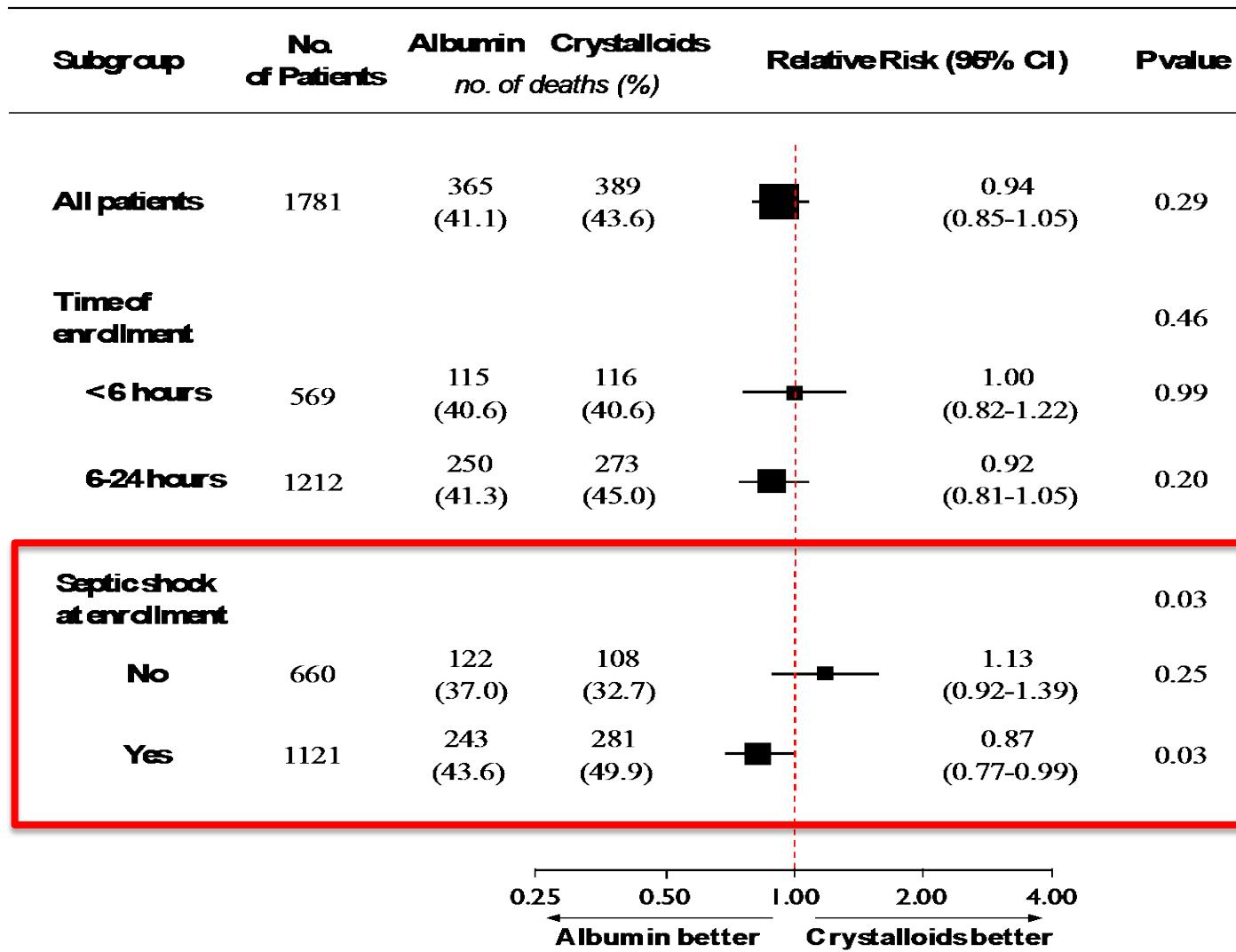
THE ALBIOS STUDY

PROBABILITY OF 90-DAY SURVIVAL IN PATIENTS WITH SEVERE SEPSIS



THE ALBIOS STUDY

RISK OF DEATH AT 90-DAY



SURVIVING SEPSIS CAMPAIGN

International guidelines for management of severe sepsis and septic shock (2012)

L'**uso dei cristalloidi** è raccomandato come prima scelta nel supporto intensivo della sepsi grave e dello shock settico.

L'**uso dell'albumina** è consigliato nella terapia infusionale della sepsi grave e dello shock settico quando i pazienti richiedono notevoli quantità di liquidi.



AMIDO IDROSSIETILICO (HES)

Raccomandazioni AIFA

- I prodotti contenenti HES **devono essere utilizzati solo** per il trattamento dell'ipovolemia causata da emorragia acuta quando i cristalloidi da soli non sono considerati sufficienti.
- I prodotti contenenti HES devono essere utilizzati alla più bassa dose efficace per il più breve periodo di tempo. Il trattamento deve essere guidato da un monitoraggio emodinamico continuo, in modo da poter interrompere l'infusione non appena siano stati raggiunti adeguati valori emodinamici.
- I prodotti contenenti HES sono ora **controindicati** nelle seguenti condizioni:
 - *Sepsi*
 - *Ustioni*
 - *Insufficienza renale o terapia renale sostitutiva*
 - *Emorragia intracranica o cerebrale*
 - *Pazienti critici (tipicamente ricoverati in Terapia Intensiva)*
 - *Pazienti iperidratati, inclusi i pazienti con edema polmonare*
 - *Pazienti disidratati*
 - *Iperkaliemia (applicabile solo ai prodotti contenenti potassio)*
 - *Grave iponatriemia o grave ipercloremia*
 - *Coagulopatia grave*
 - *Funzionalità epatica gravemente compromessa*
 - *Insufficienza cardiaca congestizia*
 - *Pazienti sottoposti a trapianto d'organo*

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- Paziente critico
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INAPPROPRIATE USE OF ALBUMIN

- **Use of albumin in 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

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

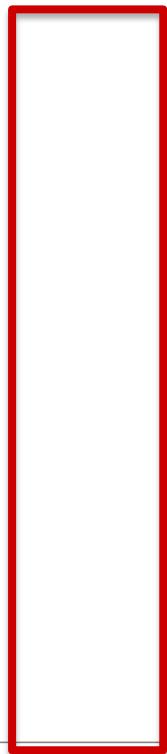
Main reasons for inappropriate use:

- nutritional intervention
- hypoalbuminemia *per se*
- abdominal and general surgery
- nephrotic syndrome

USO INAPPROPRIATO DELL'ALBUMINA



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Bologna



si

o

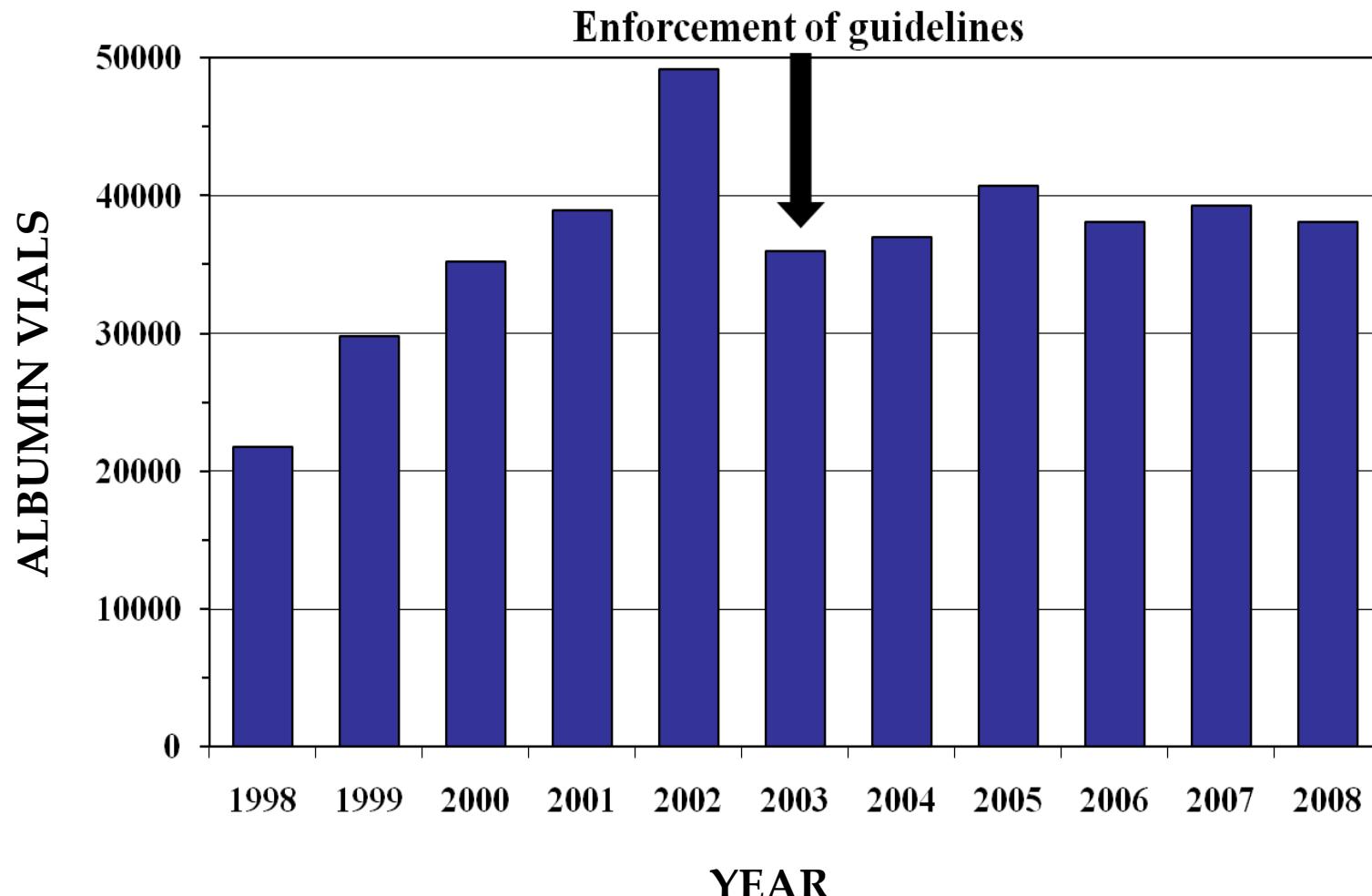
POLICLINICO S. ORSOLA-MALPIGHI

IN-HOSPITAL GUIDELINES FOR THE USE OF ALBUMIN

Acute diseases	First-line treatment	Second-line treatment
Hypovolemic shock [1,A]	Colloid/crystalloid solutions	Human albumin if: Sodium intake restriction Hypersensitivity to colloids or crystalloids Lack of response to combined use of colloids and crystalloids
Major surgery [6,C] (1) Cardiovascular surgery	Colloid/crystalloid solutions	Human albumin if: Lack of response to combined use of colloids and crystalloids As for hypovolemic shock
(2) Other surgery	As for hypovolemic shock	
Burns [6,C]	Colloid/crystalloid solutions	Human albumin plus cristalloid solutions if: Lack of response to colloid or crystalloid solutions alone Severe burns (> 50% body surface)
Chronic diseases	First-line treatment	Second-line treatment
Cirrhosis	Human albumin	
(1) Paracentesis [1,A]	8 g/L of removed ascites if paracentesis > 4 L	
(2) Spontaneous bacterial peritonitis [1,A]	1.5 g/kg at diagnosis and 1 g/kg on third day + antibiotic therapy	
(3) Hepatorenal syndrome [1,A]	1 g/kg at diagnosis followed by 20-40 g/day + vasoconstrictors	
(4) Ascites [1,A]	Diuretic treatment	Human albumin if: Ascites resistant to diuretics
Plasmapheresis [6,C]	Human albumin if plasma changes > 20 mL/kg per week	
Protein wasting enteropathy/ malnutrition	Enteral or parenteral nutrition	Human albumin only if: severe diarrhea (> 2 L/d) albuminemia < 2 g/dL clinical hypovolemia

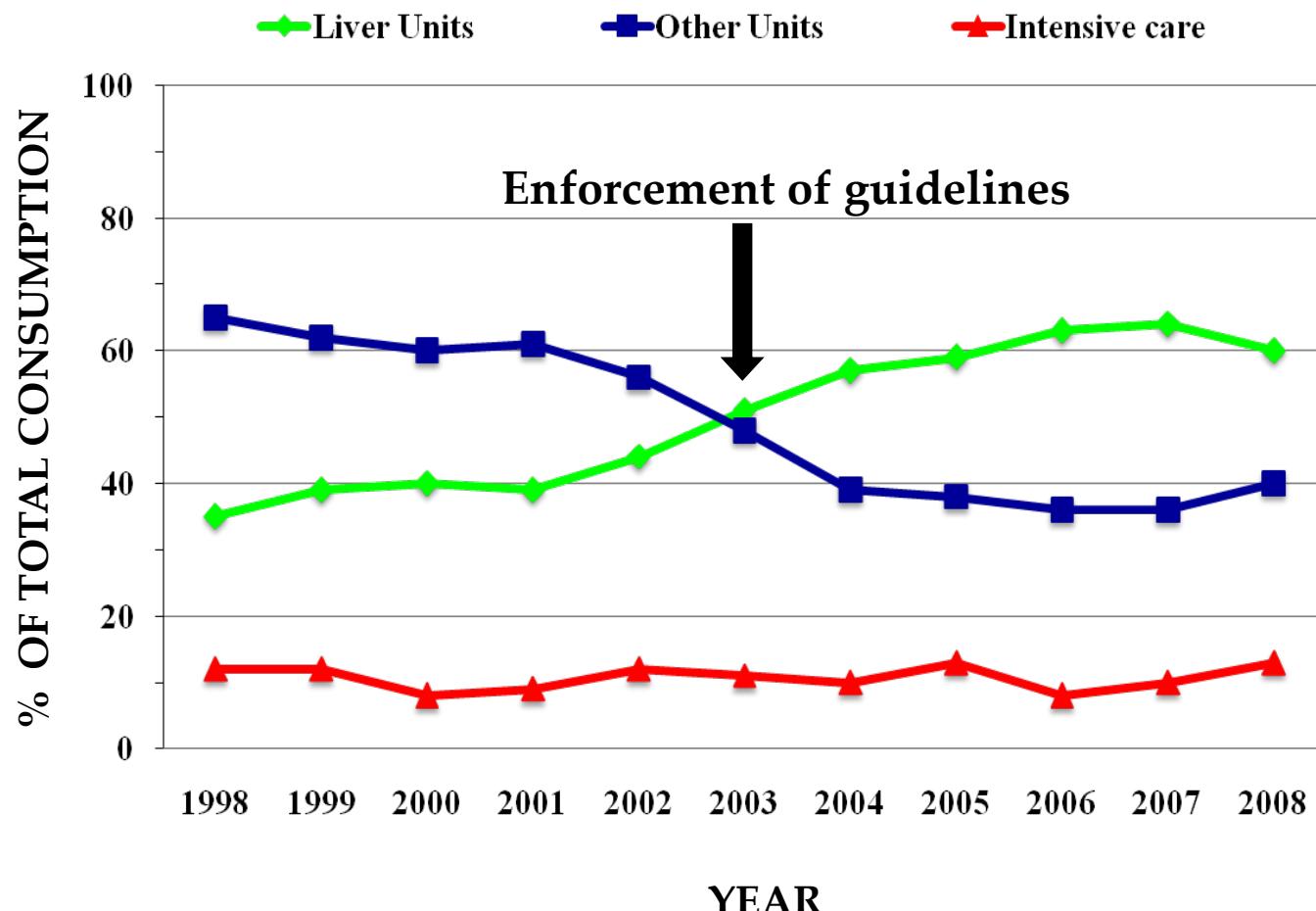
POLICLINICO S. ORSOLA-MALPIIGHI

IMPACT OF GUIDELINES ON ALBUMIN CONSUMPTION



POLICLINICO S. ORSOLA-MALPIGHI

DISTRIBUTION OF CONSUMPTION AMONG UNITS





Medico/Decisore



Appropriatezza terapeutica

Solide evidenze scientifiche di efficacia

Studi di farmacoeconomia

Raccomandazioni/linee guida condivise



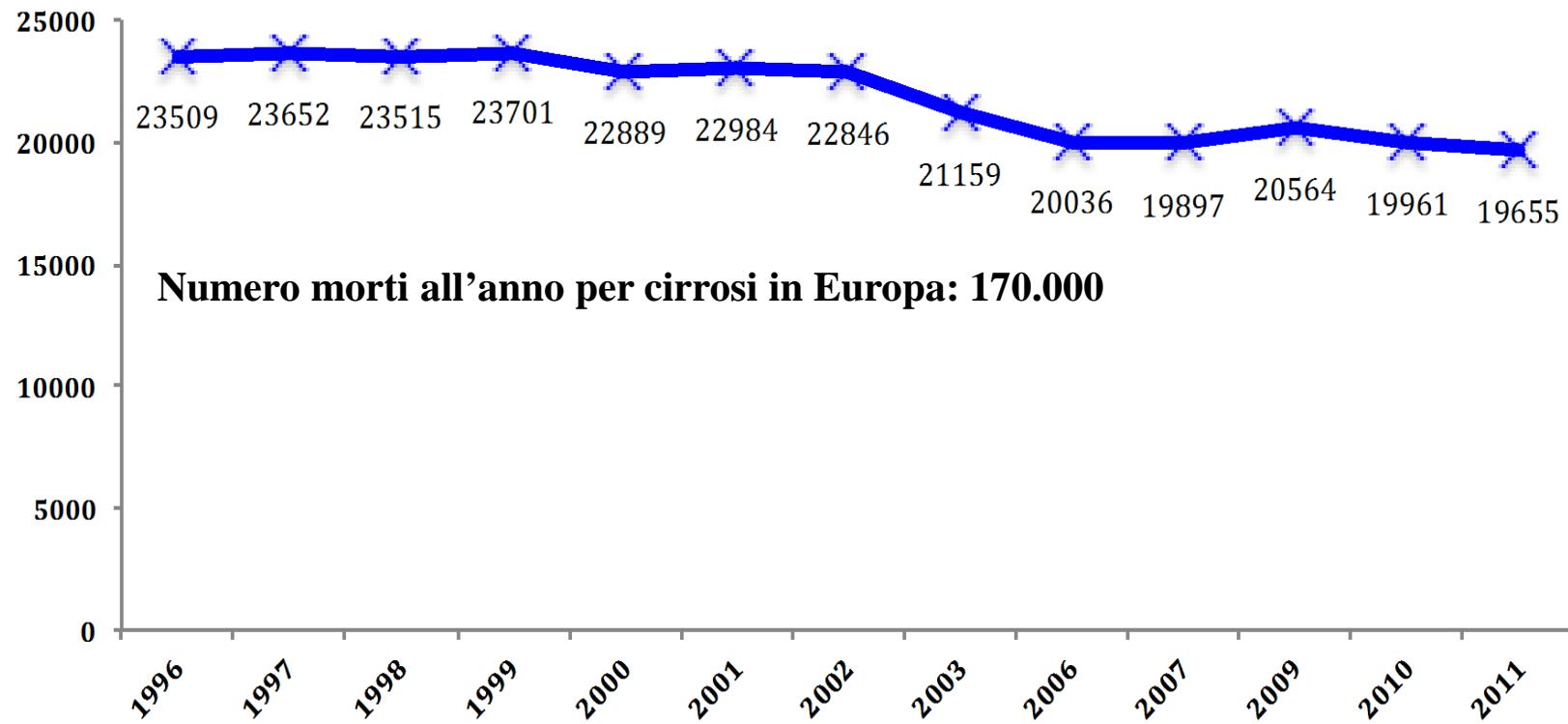
GRAZIE

PER

L'ATTENZIONE!

NUMERO DI MORTI PER CAUSE CORRELATE ALLA CIRROSI

ITALIA



Europa: 1.8% del numero totale di decessi

Italia: 3.2% del numero totale dei decessi

Dati ISTAT, 2013

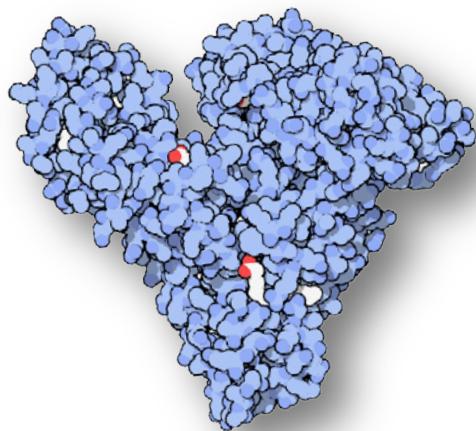
COMPLICANZE DELLA CIRROSI EPATICA

USO DELL'ALBUMINA

- Elevata prevalenza della cirrosi in Italia
- Solido presupposto fisiopatologico
- Disponibilità di molti studi clinici

HUMAN ALBUMIN

A drug for decompensated cirrhosis?



ONCOTIC PROPERTIES

Plasma volume expansion

NON-ONCOTIC PROPERTIES

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

ASCITES

RENAL FAILURE

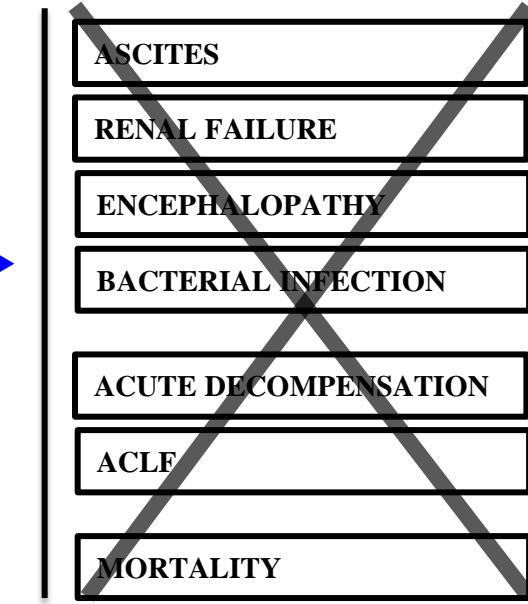
ENCEPHALOPATHY

BACTERIAL INFECTION

ACUTE DECOMPENSATION

ACLF

MORTALITY



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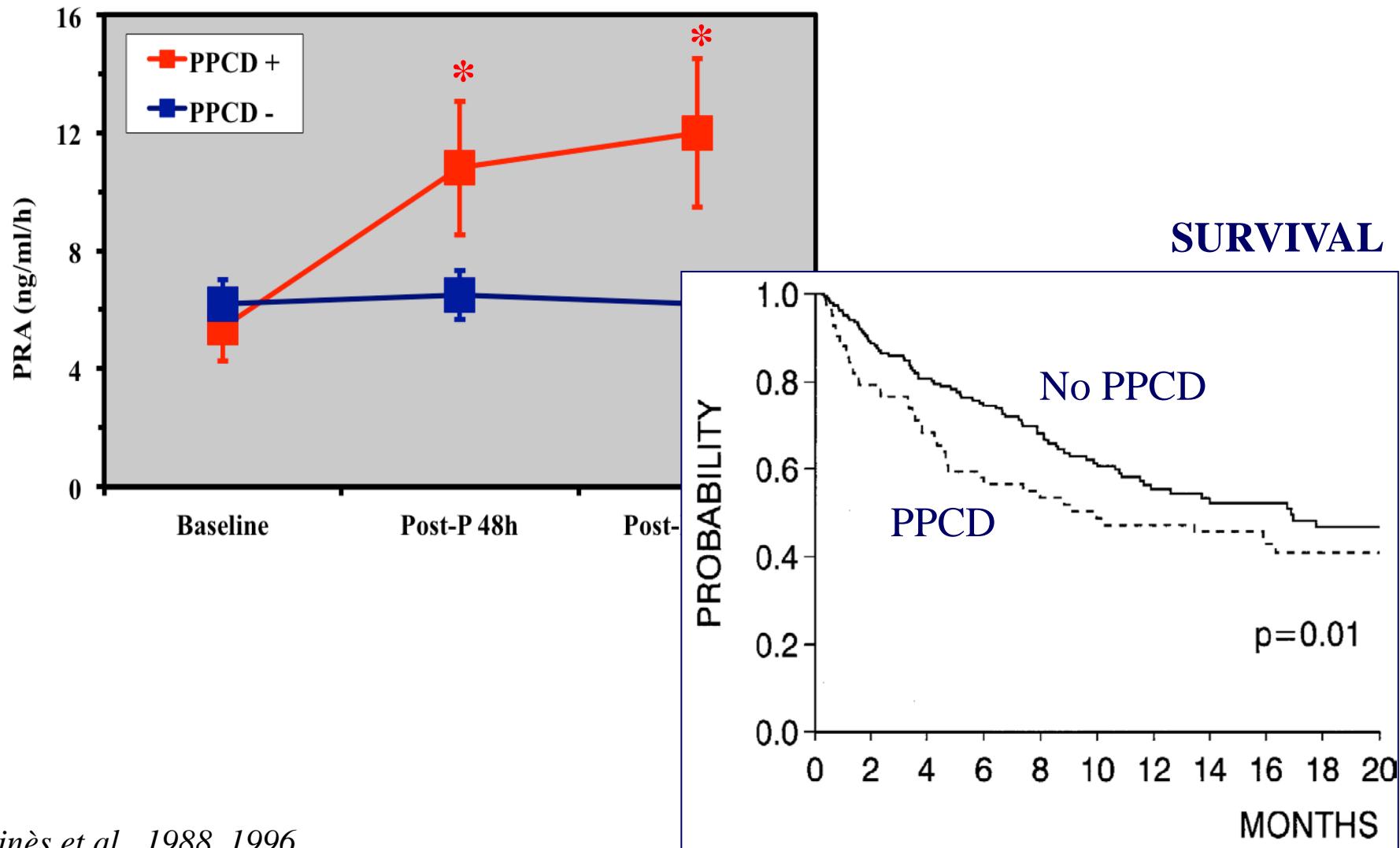
DISFUNZIONE CIRCOLATORIA POST-PARACENTESI

PREVENZIONE

ESPANSIONE PLASMATICA MEDIANTE INFUSIONE DI:

- Albumina umana: 6-8 g/L
- Poligelina: 150 ml/L
- Destrano 70: 8 g/L
- Soluzione salina: 170 ml/L

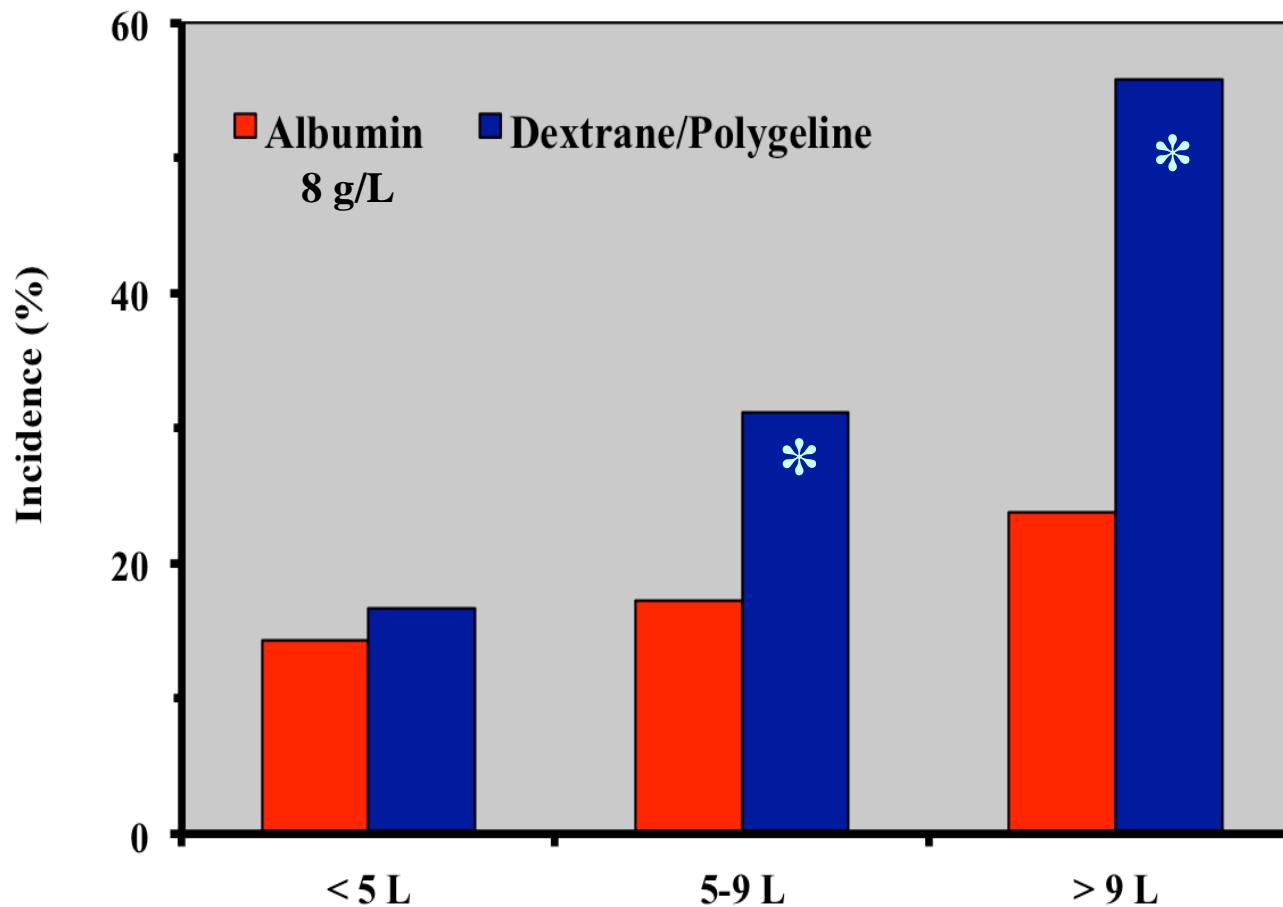
POST-PARACENTESIS CIRCULATORY DYSFUNCTION



Ginès et al., 1988, 1996

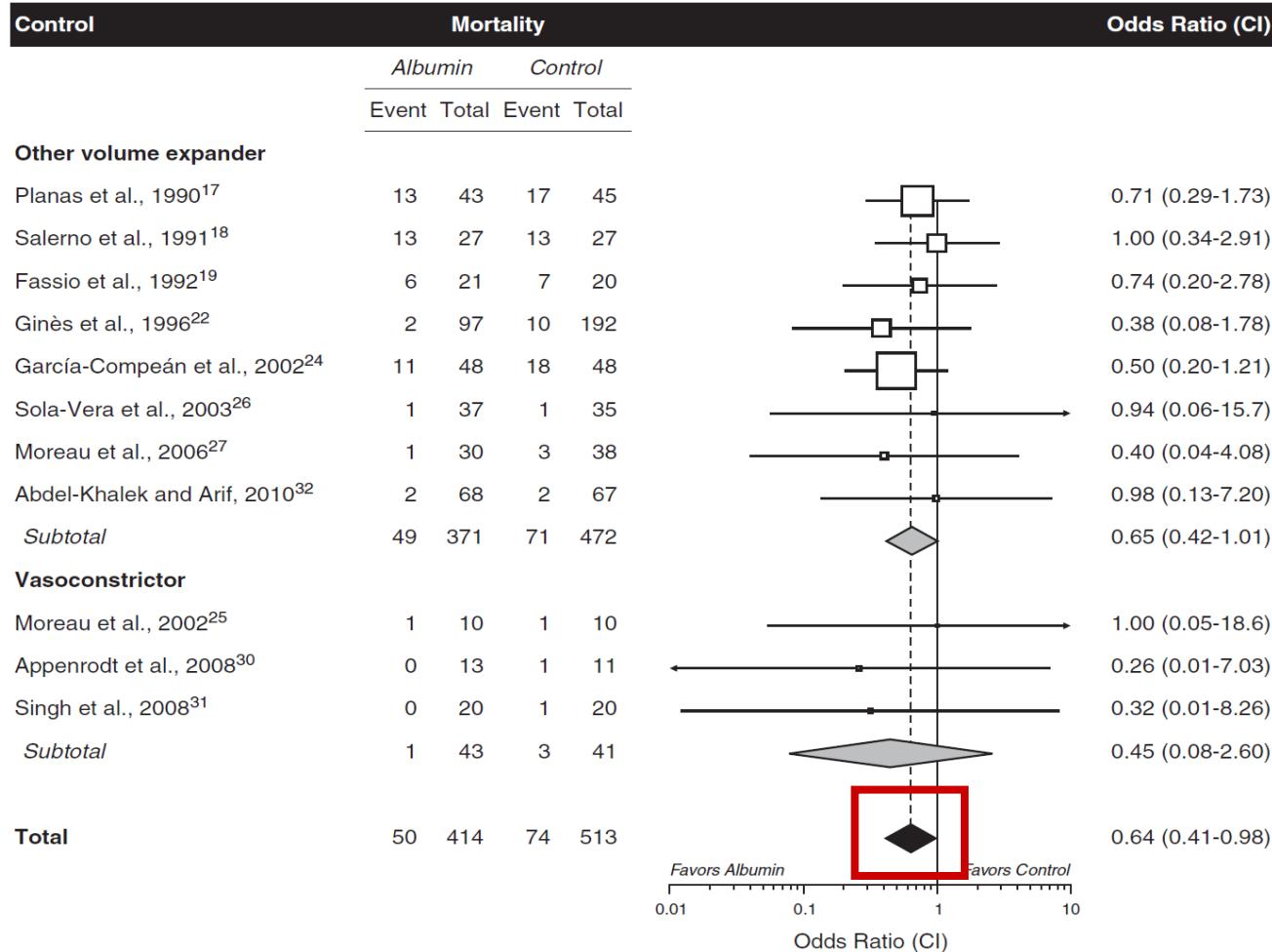
PREVENTION OF PPCD

Albumin vs Dextrane/Polygeline



MORTALITY AFTER PARACENTESIS

Albumin vs other Plasma-expanders and/or Vasoconstrictors



ALBUMIN vs POLYGELINE IN CIRRHOSIS

Efficacy & cost analysis

Cirrhosis with ascites:

- 30 albumin group
- 38 polygeline group

Inclusion criteria:

- therapeutic paracentesis
- renal impairment
- severe hyponatremia

Follow-up:

- 6 months

RISK FOR DEVELOPING LIVER RELATED COMPLICATIONS*

Polygeline vs Albumin: HR 1.95; 95% CI [1.323.37], P < 0.016

**adjustment for baseline: history of portal hypertensive bleeding, creatinine clearance, serum albumin*

MEDIAN COST ADJUSTED TO A 30-DAY PERIOD

Polygeline: €4,612 vs Albumin: €1,915; P < 0.004

RACCOMANDAZIONI AISF-SIMTI

CLINICAL CONDITION		DOSES AND SCHEDULES OF ADMINISTRATION	INDICATION FOR THE USE OF HA	QUALITY OF EVIDENCE STRENGTH OF RECOMMENDATION
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Diagnosis of HRS		1 g/kg/die for 2 consecutive days	To be used regularly	D1
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Treatment of septic shock		To be defined	Consider in all patients	C1
Treatment of hepatic encephalopathy		-----	Not indicated at present	B1