CENTRO NAZIONALE SANGUE

Uso appropriato dell'Albumina
nella Cirrosi Epatica:
le raccomandazioni AISF-SIMTI
Istituto Superiore di Sanità, Roma
Martedì 29 Marzo, 2016

L'uso appropriato dell'albumina nel trattamento del paziente settico

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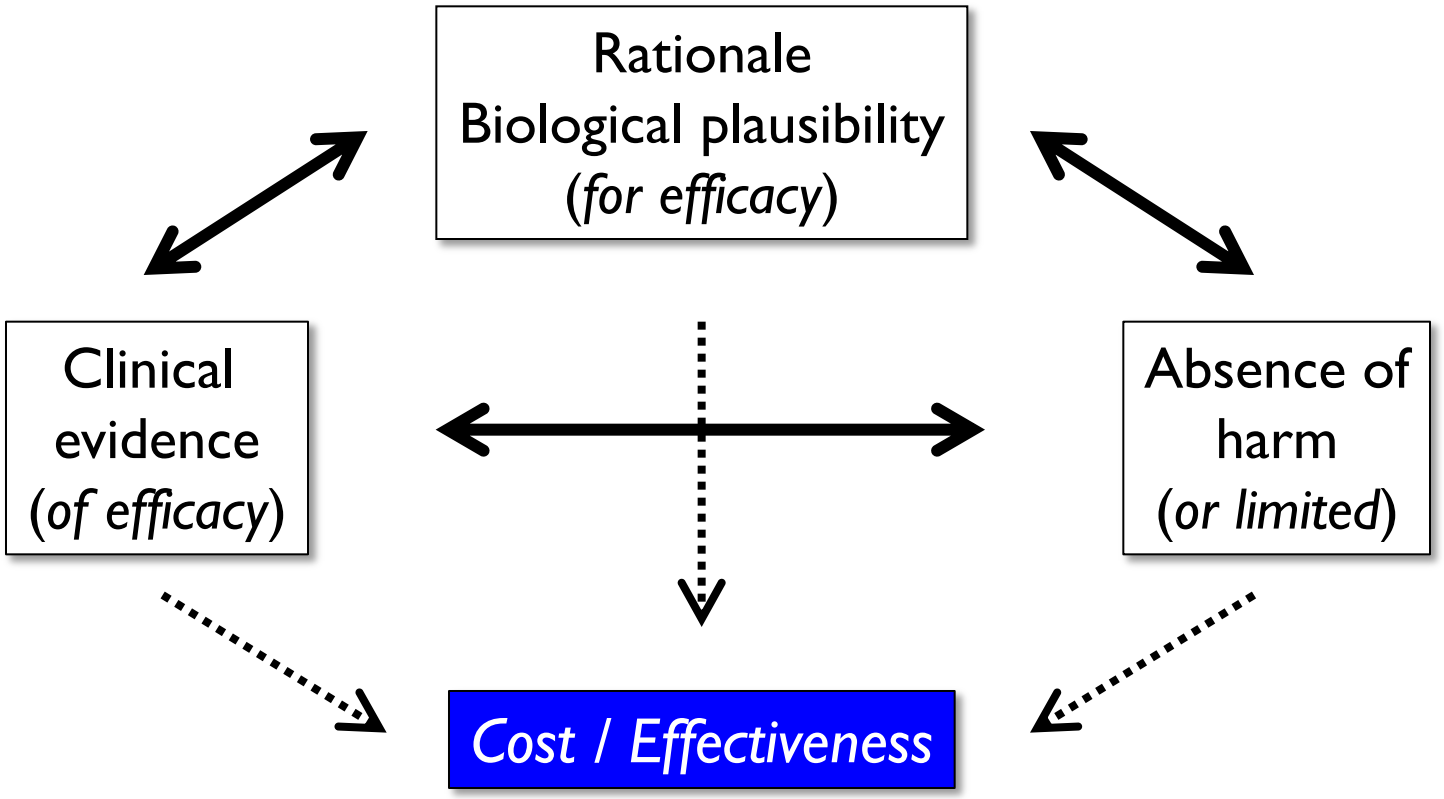
Appropriate use of Human Albumin in Septic Patients



The RIGHT patients for the RIGHT treatment
[*Sepsis is widely heterogeneous…*]

2009 SIMTI Recommendations

Recommendations for the use of albumin and immunoglobulins

Giancarlo Liumbruno[1], Francesco Bennardello[2], Angela Lattanzio[3], Pierluigi Piccoli[4], Gina Rossetti[5] as Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) Working Party

Indications

On the basis of clinical evidence, the use of albumin can be indicated in acute conditions[31], in which it is necessary to expand the volume and maintain the circulation, and in some chronic states of low serum albumin; there are some widely shared and fully agreed indications for the appropriate use of human albumin and indications that are occasionally appropriate, that is, when other criteria are fulfilled (table I)[32,33]. Albumin is also used in all cases in which there is a contraindication to the use of non-protein colloids.

- Appropriate indications (3)
- Occasionally appropriate indications (9)
- Inappropriate indications (13)

Blood Transfus 2009;7:216-34

2016 AISF-SIMTI Recommendations in Cirrhosis

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

Paolo Caraceni[1], Paolo Angeli[2], Daniele Prati[3], Mauro Bernardi[1], on behalf of the Italian Association for the Study of the Liver (AISF); Giancarlo M. Liumbruno[4], Francesco Bennardello[5], Pierluigi Piccoli[6], Claudio Velati[7], on behalf of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

7. Clinical indications under investigations

7.2 Treatment of septic shock

AISF-SIMTI recommendations on the use of albumin in the treatment of septic shock in patients with cirrhosis

- *HA solutions might be effective and safe in cirrhotic patients with septic shock (C1).*

Blood Transfus 2016;14:8-22

- Why albumin in sepsis patients ?
  (*current guidelines and rationale)*
- Clinical evidence in Severe Sepsis / Septic Shock
- Possible future developments
  and area of research
  (*efficacy, appropriate use, precision medicine*)

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

Hemodynamic Support and Adjunctive Therapy (Table 6)

G. Fluid Therapy of Severe Sepsis

Type

Dose, Velocity

1. We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B). (This recommendation is based on the results of the VISEP [128], CRYSTMAS [122], 6S [123], and CHEST [124] trials. The results of the recently completed CRYSTAL trial were not considered.)
3. We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. We recommend an initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (see Initial Resuscitation recommendations) (grade 1C).
5. We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

Crit Care Med 2013;41:580-637

History of SSC guidelines (from 2004 to 2013)

2004

E. Fluid Therapy

1. Fluid resuscitation may consist of natural or artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another.

As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema.

2008

E. Fluid Therapy

1. We recommend fluid resuscitation with either natural/artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another (grade 1B).

As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema. Crystalloids are less expensive.

2013

G. Fluid Therapy of Severe Sepsis

"We recommend CRYSTALLOIDS be used as the initial fluid of choice…"

Rationale. The absence of any clear benefit following the administration of colloid solutions compared to crystalloid solutions, together with the expense associated with colloid solutions, supports a high-grade recommendation for the use of crystalloid solutions in the initial resuscitation of patients with severe sepsis and septic shock.

?

Reasons from "superiority" of *Crystalloids vs. Colloids*

Choice of fluid in acute illness: what should be given? An international consensus‡

Raghunathan K et al, BJA, 2014;113:772-83

1. Limited evidence on superiority (*clinically* and *physiologically*)
2. Evidence of potential toxicity

All resuscitation fluids can contribute to the formation of interstitial oedema and fluid balance may be more important than fluid type.[18] Hence, the selection of specific fluids should be based on the understanding that differences in efficacy are modest, while differences in safety are significant (Table 1).

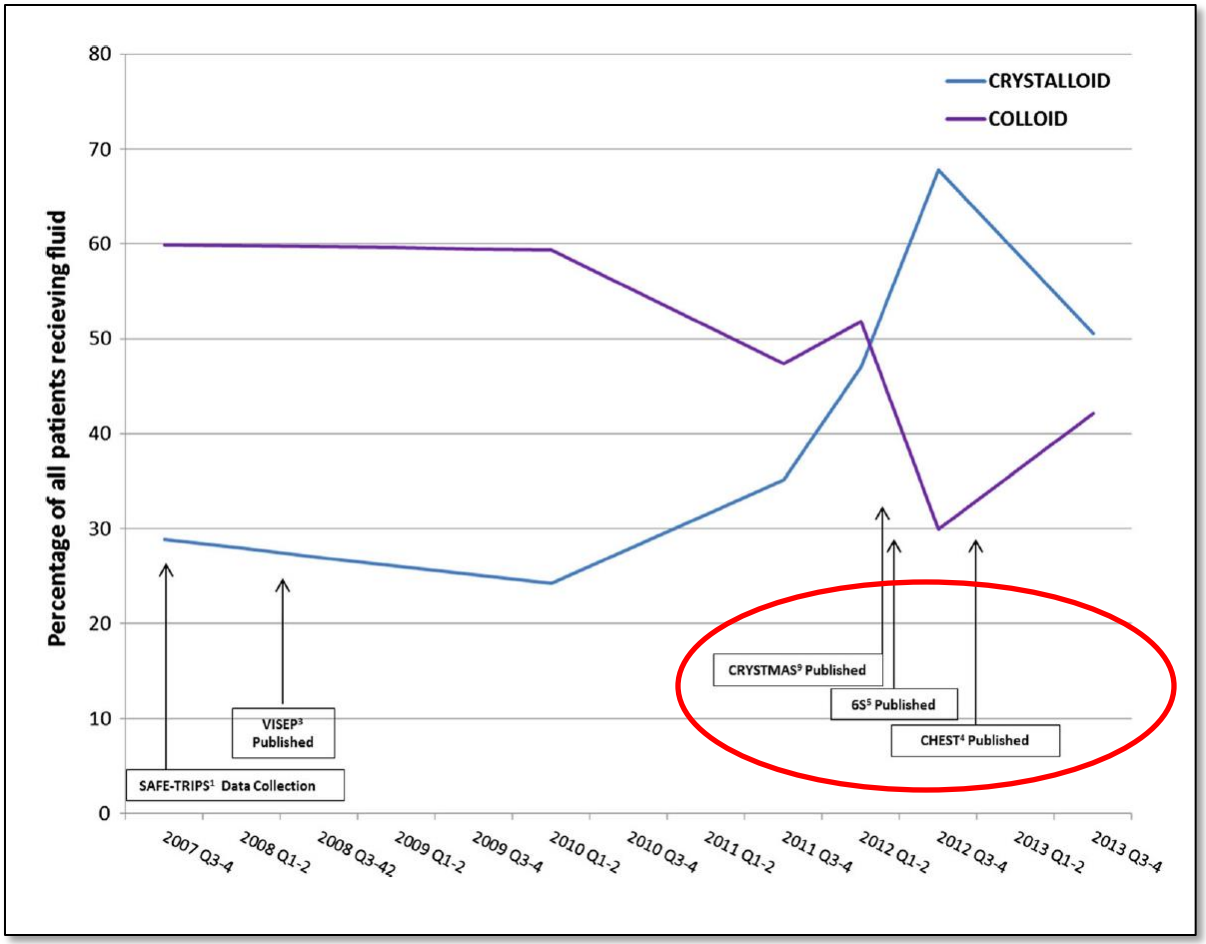
2008	VISEP trial	HES *vs.* RL	HES harmful
2012	CRYSTMAS trial	HES *vs.* RA	No difference
2012	6S trial	HES *vs.* RA	HES harmful
2012	CHEST trial	HES *vs.* RA	No diff./HES harmful
2012	EARSS trial	Albumin *vs.* NS	No difference
2013	CRYSTAL trial	Coll. *vs.* Crys	No diff./Coll. better

N. E. Hammond
C. Taylor
M. Saxena
B. Liu
S. Finfer
P. Glass
I. Seppelt
L. Willenberg
J. Myburgh

Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013

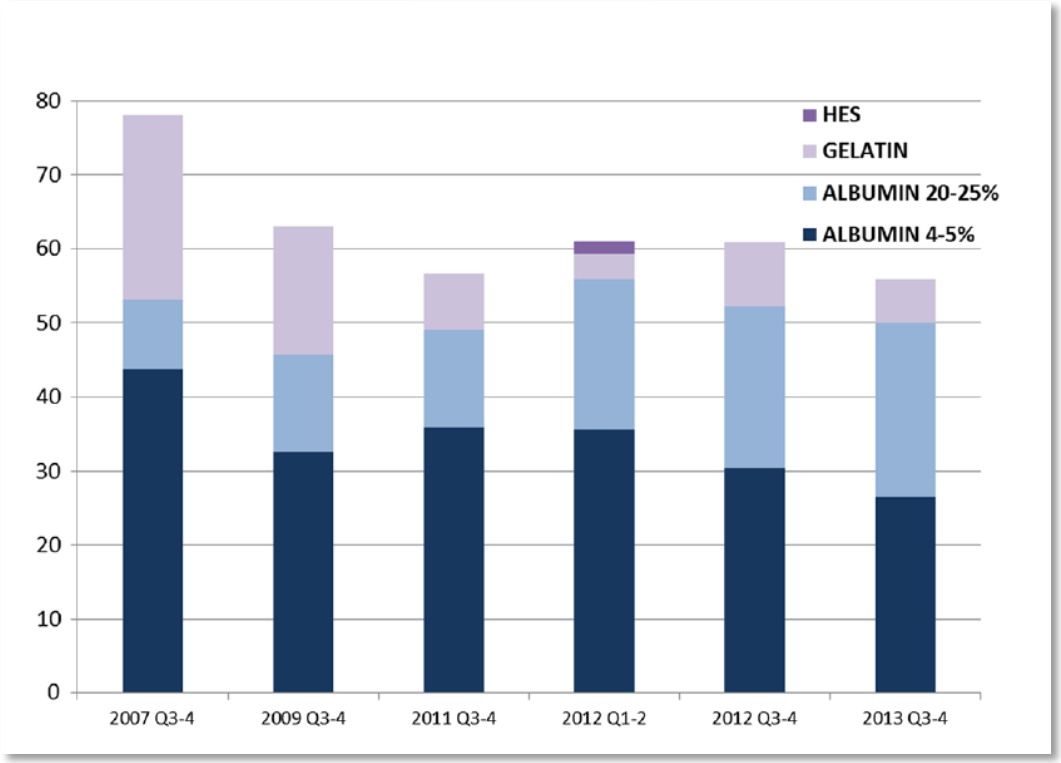
Intensive Care Med 2015;41:1611-9

- Cross-sectional prevalent study (*6 study days, 2007-2013*)
- 2825 ICU pts screened (*754 resuscitated, 254 with sepsis*)
- Change in patterns of fluid use



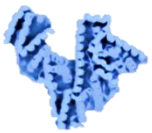
Albumin in Critically Ill Patients in 2016…

COLLOIDS



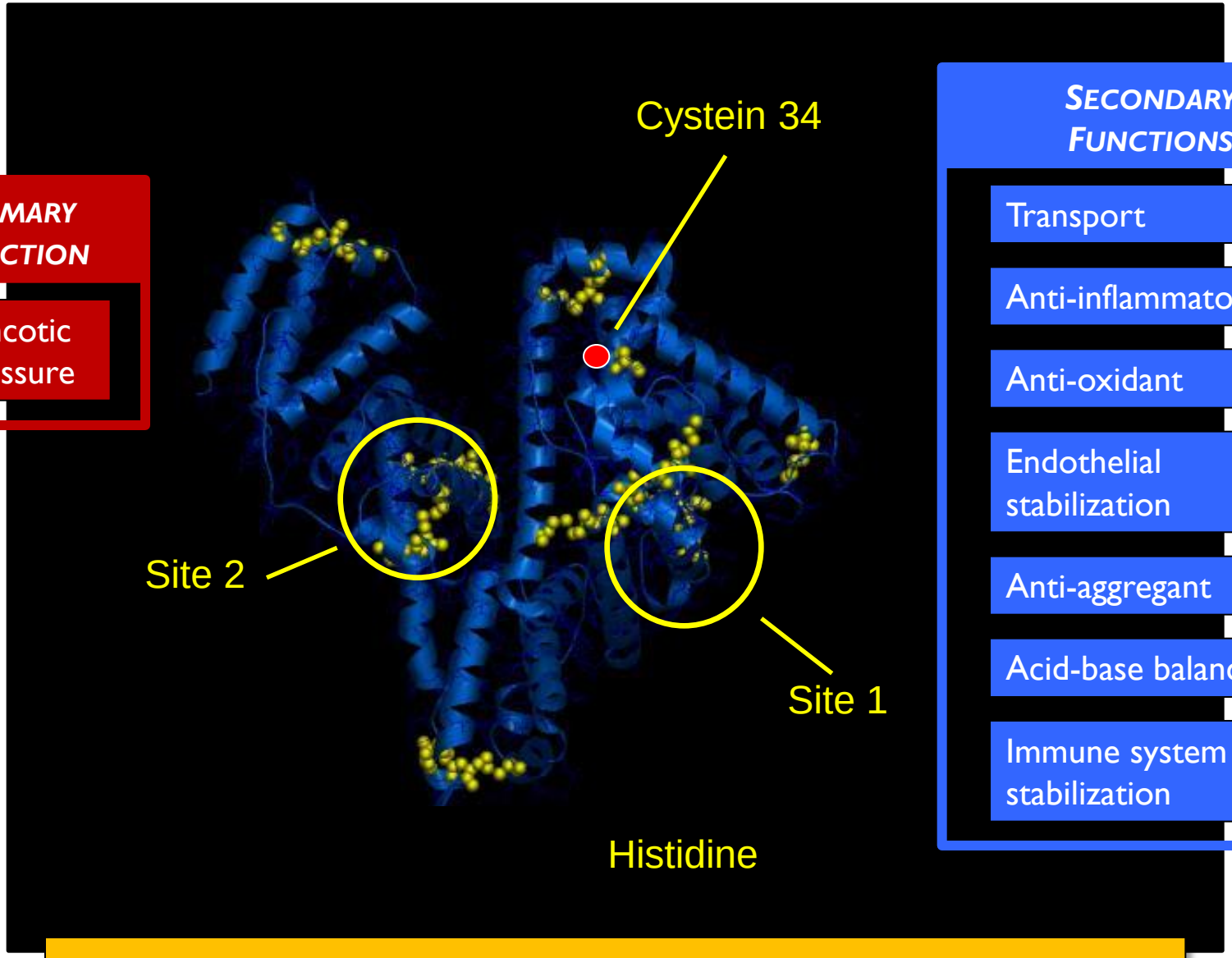
Albumin (4/5% - 20-25%)

Hammond NE et al., Intensive Care Med 2015;41:1611-9



PRIMARY FUNCTION

Oncotic Pressure



SECONDARY FUNCTIONS

- Transport
- Anti-inflammatory
- Anti-oxidant
- Endothelial stabilization
- Anti-aggregant
- Acid-base balance
- Immune system stabilization

Both functions as potentially important in critically ill patients

ALBUMIN AS A DRUG

- Why albumin in sepsis patients ?
  (*current guidelines and rationale)*
- Clinical evidence in Severe Sepsis / Septic Shock
- Possible future developments
  and area of research
  (*efficacy, appropriate use, precision medicine*)

The SAFE trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

ABSTRACT

BACKGROUND

It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

- Prospective, randomized, double-blinded trial
- 6997 patients
- 16 ICU (*Australia, New Zeland*)
- 4% albumin *vs.* 0.9% NaCl
- Death at 28-days

N Engl J Med 2004, 350:2247-56

SAFE study – 2004 – *predefined* subgroup analysis

Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)

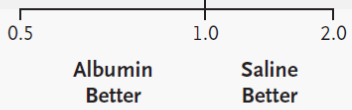


Figure 2. Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.

The size of each symbol indicates the relative number of events in the given group. The horizontal bars represent the confidence intervals (CI). ARDS denotes the acute respiratory distress syndrome.

	Treated %	Control %	P
Trauma patients	13.6	10.0	0.06
Severe sepsis patients	30.7	35.3	0.09
ARDS patients	39.3	42.4	0.72

- 1800 patients with severe sepsis or septic shock
- Albumin + Crystalloids *vs.* Crystalloids
- 28-day and 90-day mortality
- Funded by AIFA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

ABSTRACT

BACKGROUND

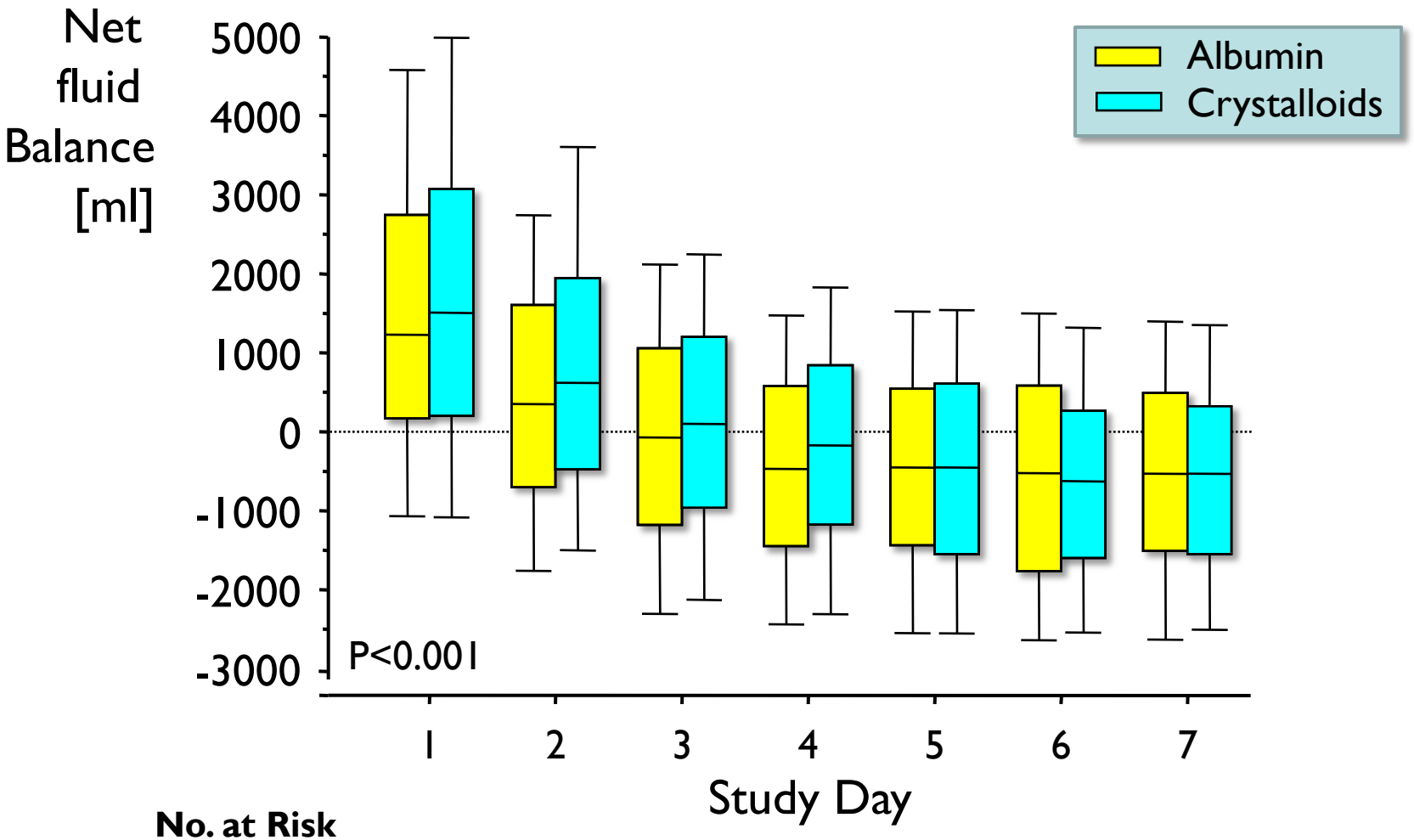
Although previous studies have suggested the potential advantages of albumin administration in patients with severe sepsis, its efficacy has not been fully established.

METHODS

In this multicenter, open-label trial, we randomly assigned 1818 patients with severe sepsis, in 100 intensive care units (ICUs), to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g per liter or more until discharge from the ICU or 28 days after randomization. The primary outcome was death from any cause at 28 days. Secondary outcomes were death from any cause at 90 days, the number of patients with organ dysfunction and the degree of dysfunction, and length of stay in the ICU and the hospital.

N Engl J Med 2014;370:1412-21

From ALBIOS trial: net daily fluid balance

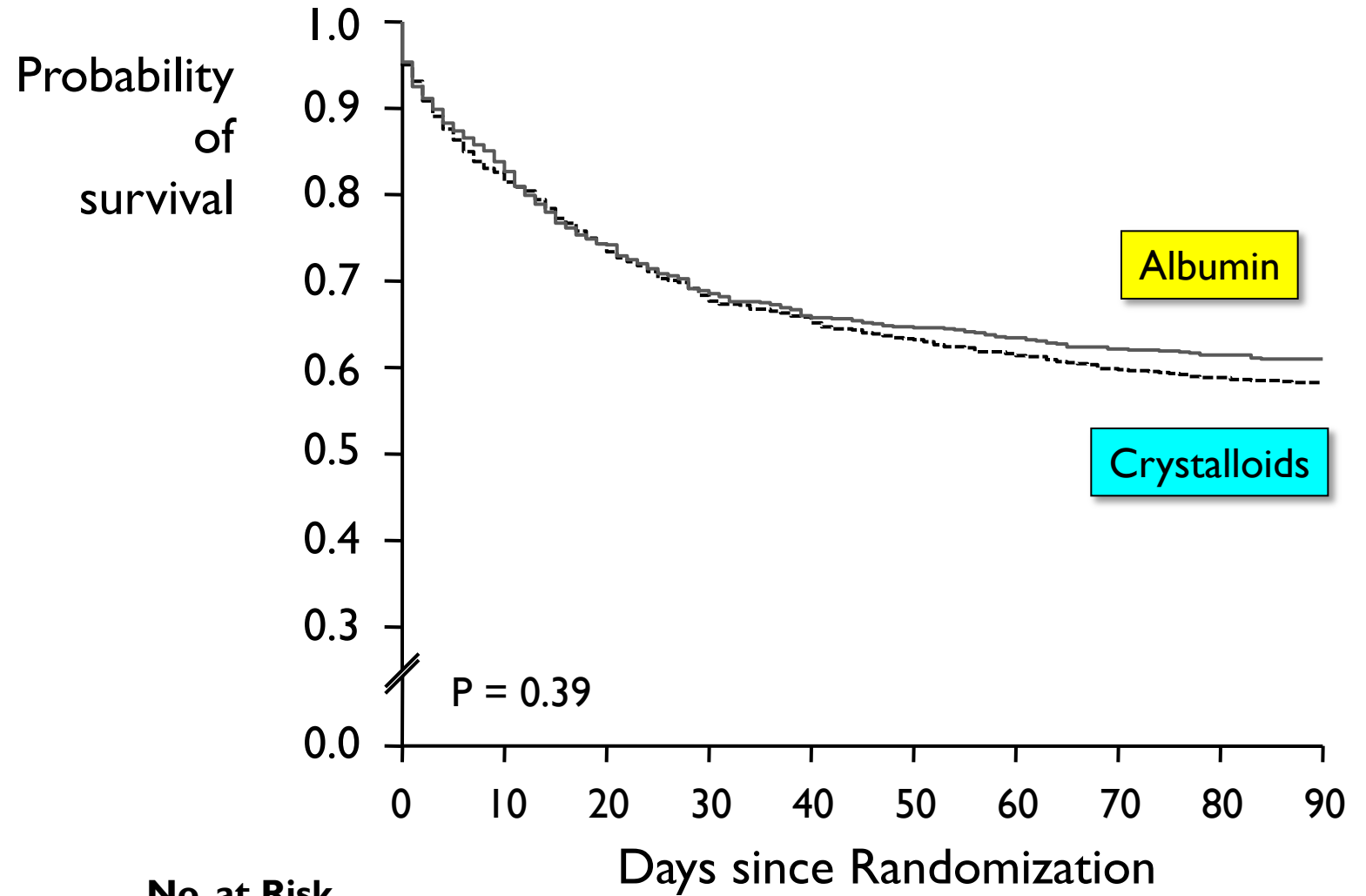


No. at Risk

Albumin	840	789	742	701	639	586	542
Crystalloids	844	795	735	685	635	587	529

Caironi P et al., N Engl J Med 2014;370:1412-21

Results – Primary Outcome

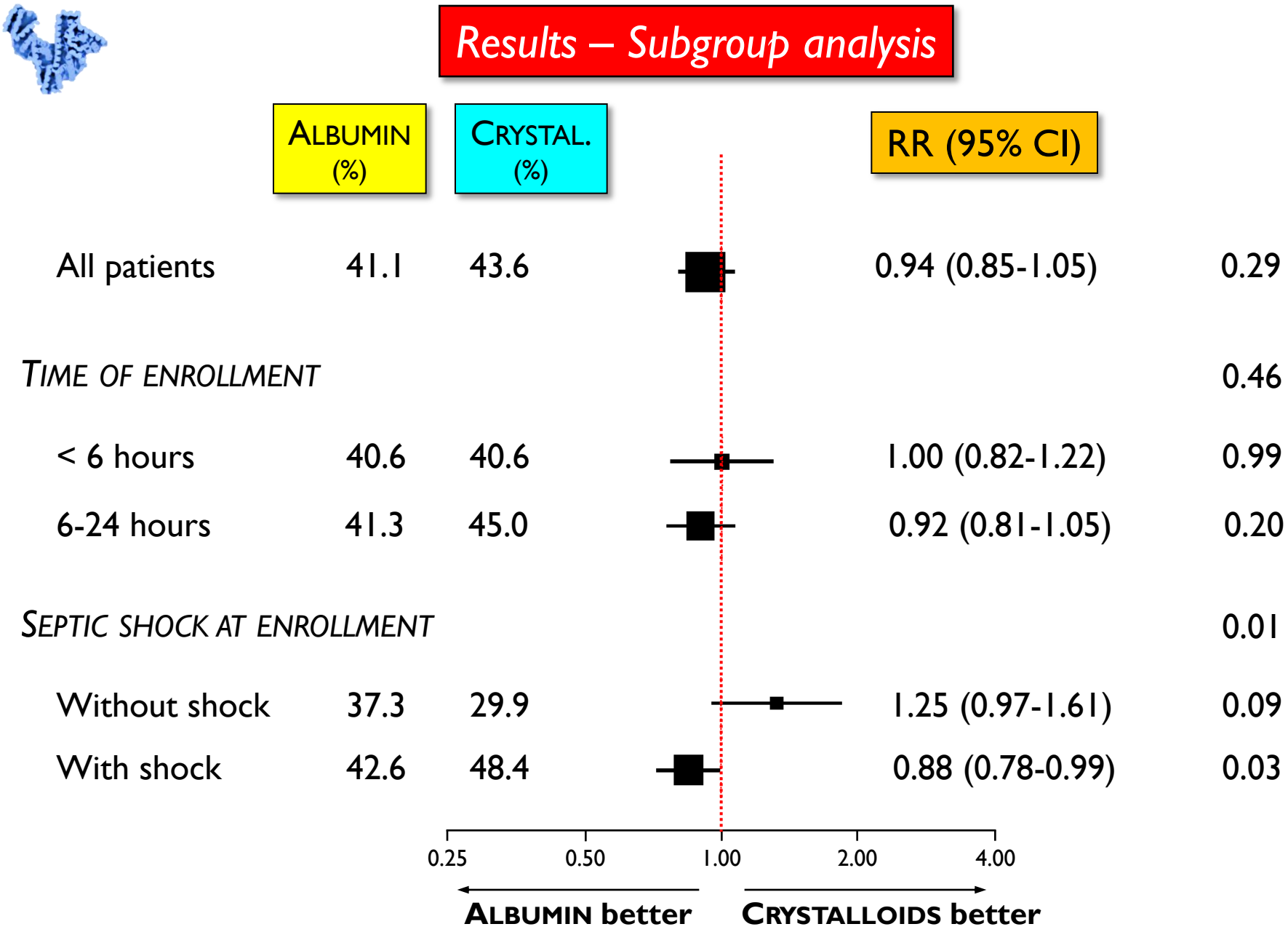


No. at Risk

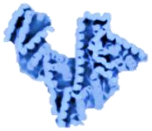
Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

Caironi P et al., N Engl J Med 2014;370:1412-21

Results – Subgroup analysis



Caironi P et al., N Engl J Med 2014;370:1412-21



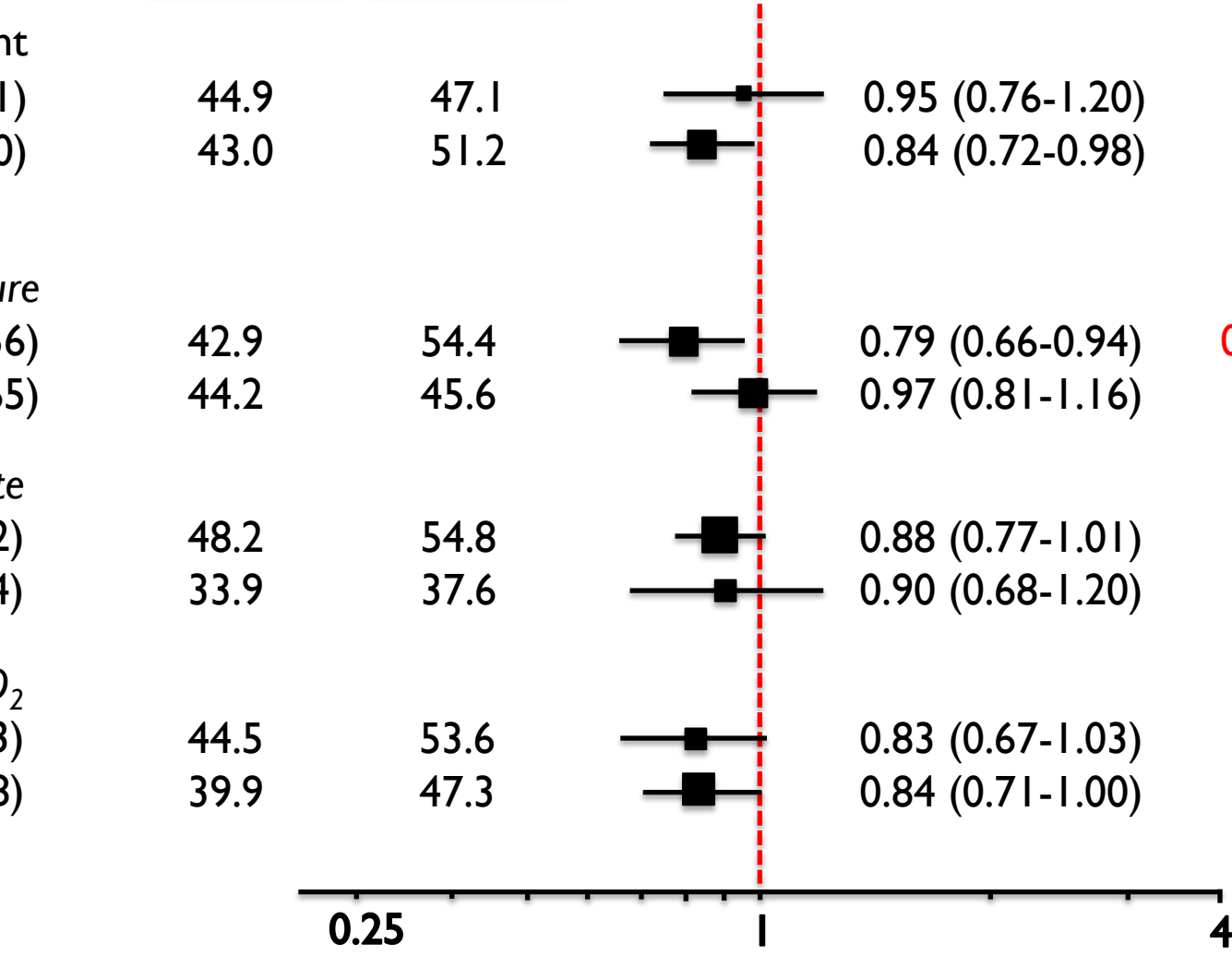
Albumin in SEPTIC SHOCK: rationale for a novel large RCT…

Authors	Year of publication	Inclusion criteria	Number of studies included (sample size)	Comparison	Types of studies included	Primary outcomes	Results (OR or RR, 95% CI)
Delenay et al.	2011 [45]	Sepsis of any severity (Adults and Pediatrics) Predefined subgroups	17 (N=1977)	Albumin vs. Crystalloid or Colloid	RCTs	All-cause mortality at the longest follow-up available	*Sepsis* OR 0.82 (0.67-1.00), P=0.047
Cui JY et al.	2012 [46]	Sepsis of any severity (Adults)	14 (N=1729)	Albumin vs. Crystalloid or Colloid	RCTs	All-cause mortality	*Sepsis* OR 0.87 (0.71-1.07), P=0.18
Leitch A et al.	2013 [47]	Severe sepsis	9 (N=1435)	Albumin vs. Crystalloid or Colloid	RCTs	All-cause mortality at the longest follow-up available	*Severe sepsis* RR 0.90 (0.79-1.02), P=0.11
Wiedermann et al.	2014 [48]	Severe sepsis (Adults)	3 (N=3791)	Albumin vs. Crystalloid	Large scale RCTs	All-cause mortality at the longest follow-up available	*Severe sepsis* RR 0.92 (0.84-1.00), P=0.046
Rochwerg B et al.	2014 [49]	Severe sepsis (Adults) Predefined subgroup and network meta-analysis	14 (N=18916)	Any fluid strategy compared to a different fluid strategy	RCTs	All-cause mortality at the longest follow-up available	*Severe sepsis* Albumin vs. Crystalloids OR 0.83 (0.65-1.04)
Patel A et al.	2014 [50]	Sepsis of any severity (Adults) Predefined subgroups	16 (N=4190)	Albumin vs. Crystalloid or Colloid	RCTs	All-cause mortality at the longest follow-up available	*Sepsis* RR 0.94 (0.87-1.01), P=0.11 *Severe sepsis without shock* RR 0.95 (0.85-1.06), P=0.35 [N=2070] *Septic shock* RR 0.92 (0.83-1.02), P=0.10 [N=1962]
Jiang L et al.	2014 [51]	Sepsis of any severity (Adults and Pediatrics) Predefined subgroups	15 (N=6998)	Albumin vs. Crystalloid or Colloid	RCTs	All-cause mortality at the longest follow-up available	*Sepsis* RR 0.94 (0.87-1.02), P=0.15 *Severe sepsis without shock* RR 0.95 (0.85-1.07), P=n.s. *Septic shock* RR 0.89 (0.80-0.99), P=0.04
Xu JY et al.	2014 [52]	Severe sepsis (Adults) Predefined subgroup	6 (N=3658)	Albumin vs. Crystalloid	RCTs and parallel trials	All-cause mortality (including 28-, 90-day mortality, or at other time points)	*Severe sepsis* OR 0.88 (0.76-1.01), P=0.08 *Shock* OR 0.81 (0.67-0.97), P=0.03

Caironi P et al., Curr Opin Crit Care 2015;21:302-308

- Why albumin in sepsis patients ?
  (*current guidelines and rationale)*
- Clinical evidence in Severe Sepsis / Septic Shock
- Possible future developments
  and area of research
  (*efficacy, appropriate use, precision medicine*)

90-DAY SURVIVAL according to baseline characteristics



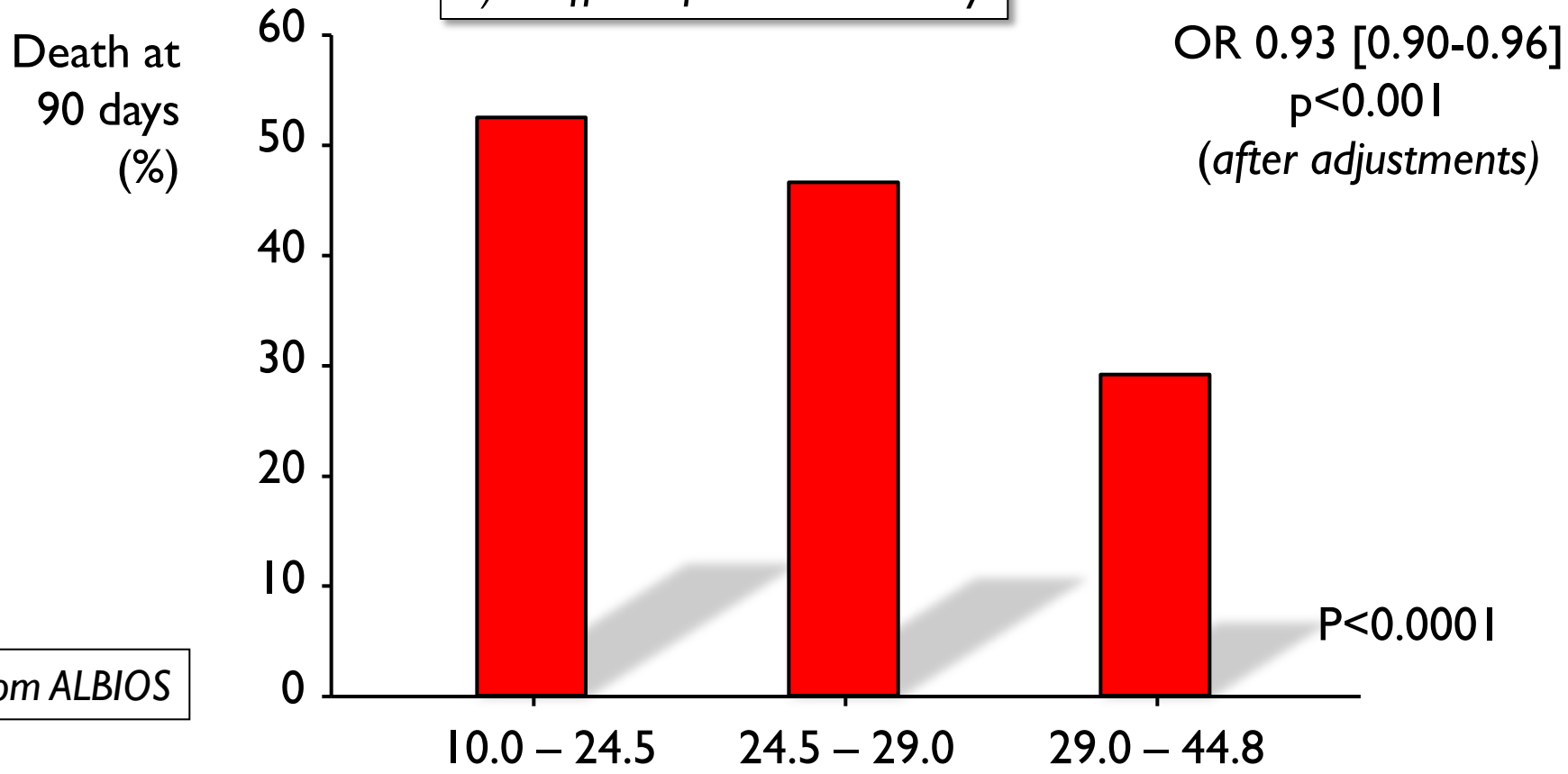
Death at 90 days (%)	ALBUMIN (%)	CRYSTAL. (%)	RR (95% CI)	P
Time of enrollment				
< 6 hours (341)	44.9	47.1	0.95 (0.76-1.20)	0.68
6-24 hours (780)	43.0	51.2	0.84 (0.72-0.98)	0.02
Mean arterial pressure				*0.09*
< 70 mmHg (556)	42.9	54.4	0.79 (0.66-0.94)	0.007
≥ 70 mmHg (565)	44.2	45.6	0.97 (0.81-1.16)	0.74
Lactate				0.70
> 2 mmol/L (752)	48.2	54.8	0.88 (0.77-1.01)	0.07
≤ 2 mmol/L (334)	33.9	37.6	0.90 (0.68-1.20)	0.48
Central SvO_2				0.81
< 70% (333)	44.5	53.6	0.83 (0.67-1.03)	0.10
≥ 70% (668)	39.9	47.3	0.84 (0.71-1.00)	0.05

In preparation

2 Average albumin during the study vs. 90-day mortality

1) *Effect of treatment*
2) *Effect of disease severity*

Pts with SHOCK



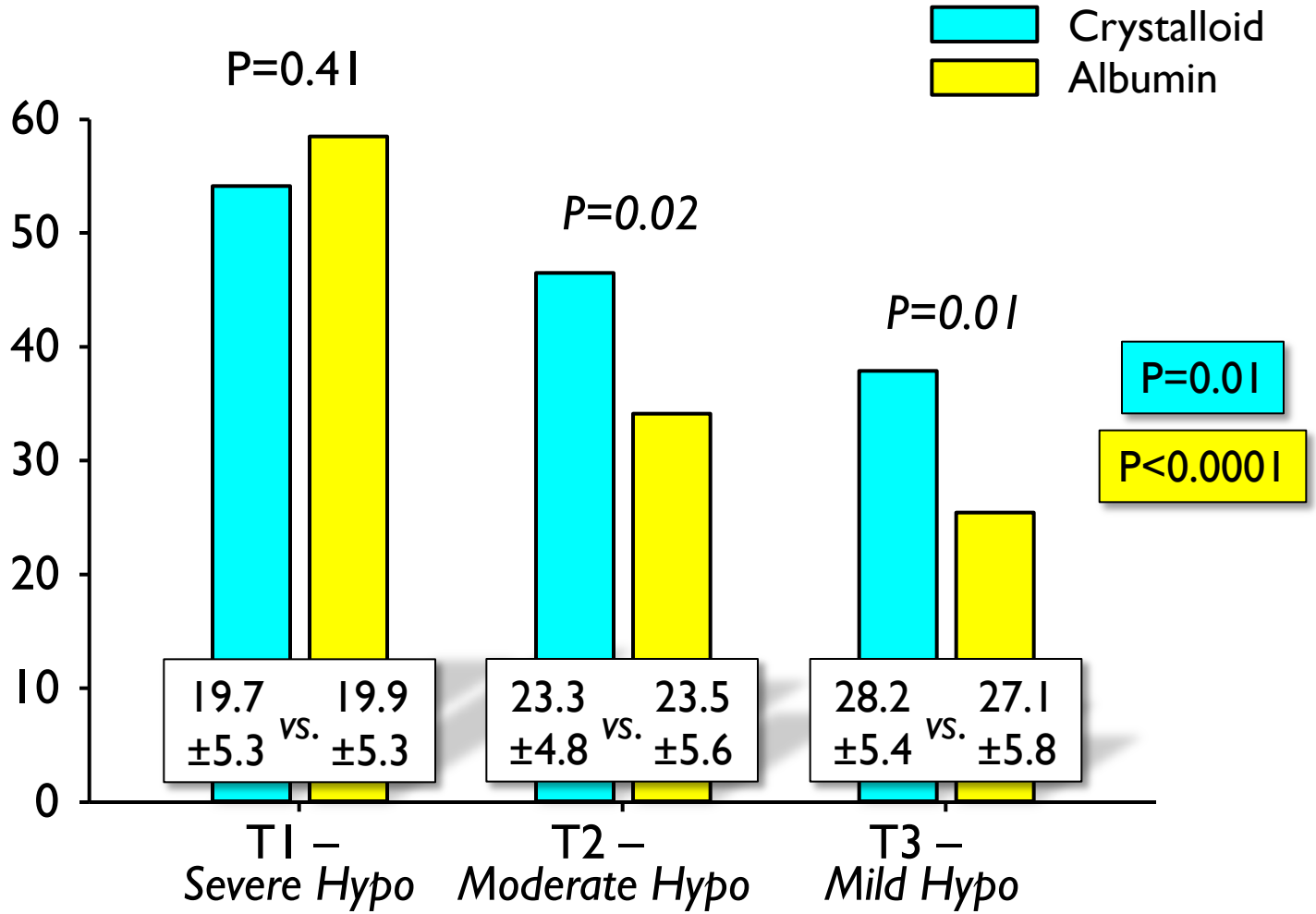
From ALBIOS

N=1135
Pts with Septic Shock

In preparation

Average albumin level during the study by treatment groups

Death at 90 days (%)



Average serum albumin level of the Crystalloid group as marker of disease severity

Tertiles of average serum albumin level during the study for each study group (g/L)

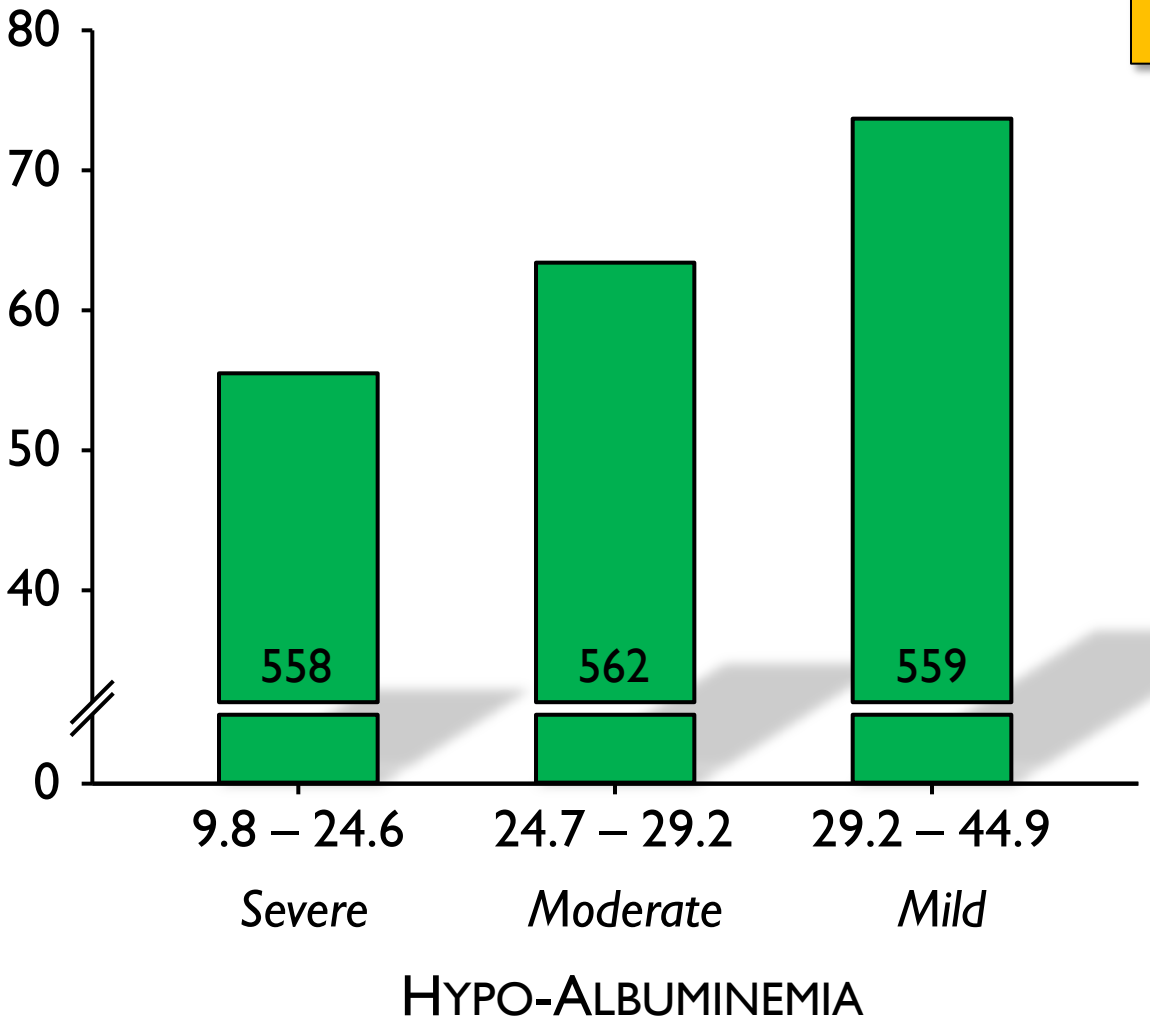
In preparation

3

Serum Albumin vs. Resolution of the Primary Infection

Clinical resolution of the Primary Infection (%)

Overall population

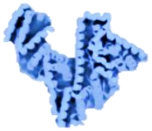


P<0.0001

N=1679

Overall study population

Unpublished



Independent role of Serum Albumin Level

Serum albumin level as independently associated with the clinical resolution of the Primary Infection

Overall population (*n=1401*)

Average serum albumin level during the study (for each g/L increase)

OR 1.06 (1.04-1.09) P<0.0001

Septic shock (*n=866*)

Average serum albumin level during the study (*for each g/L increase*)

OR 1.06 (1.03-1.10) P=0.0002

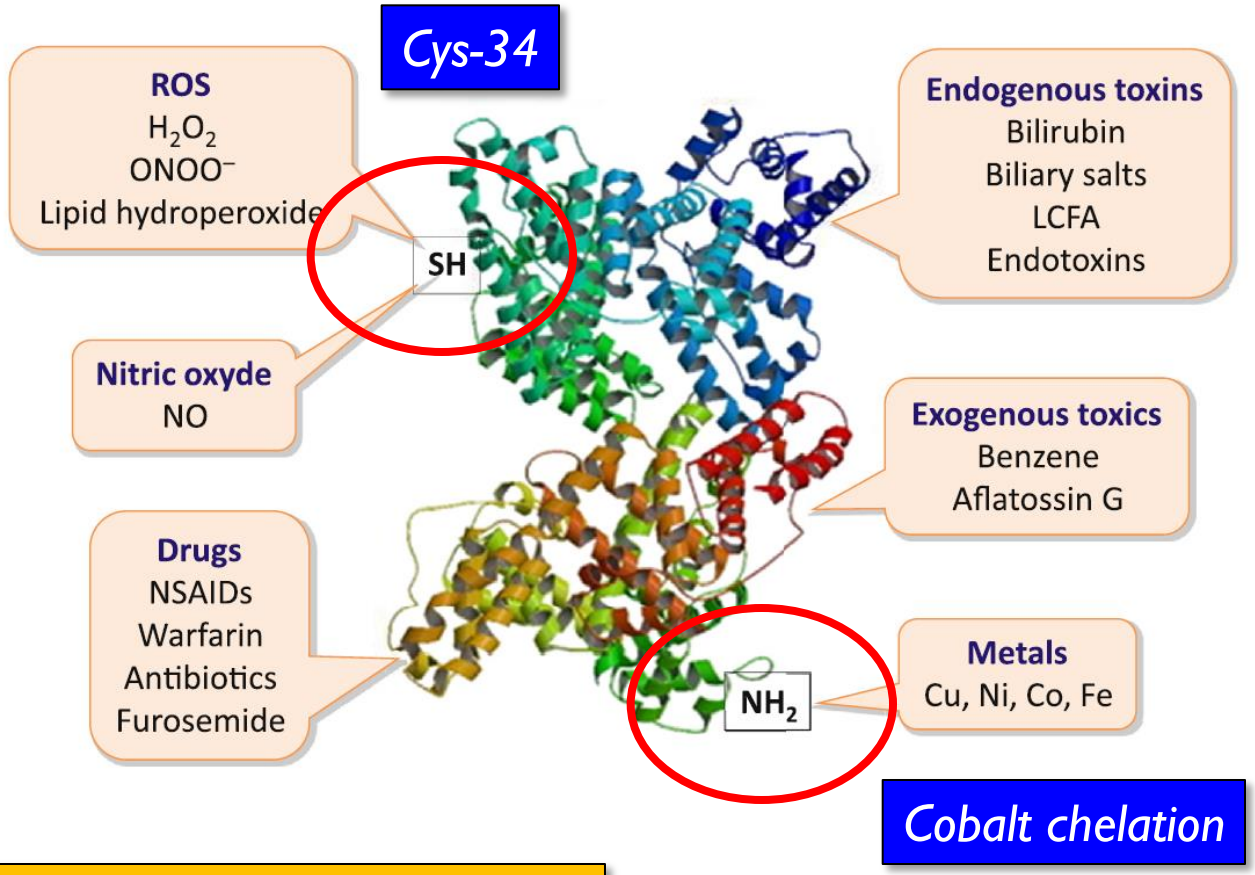
After adjustments for overall severity (SAPS II score), SOFA at baseline, age, ICU stay during the study

Unpublished

4 Endogenous HA alterations during inflammation

1 *Interaction with immuno-system*

2 *Alteration of endogenous albumin*



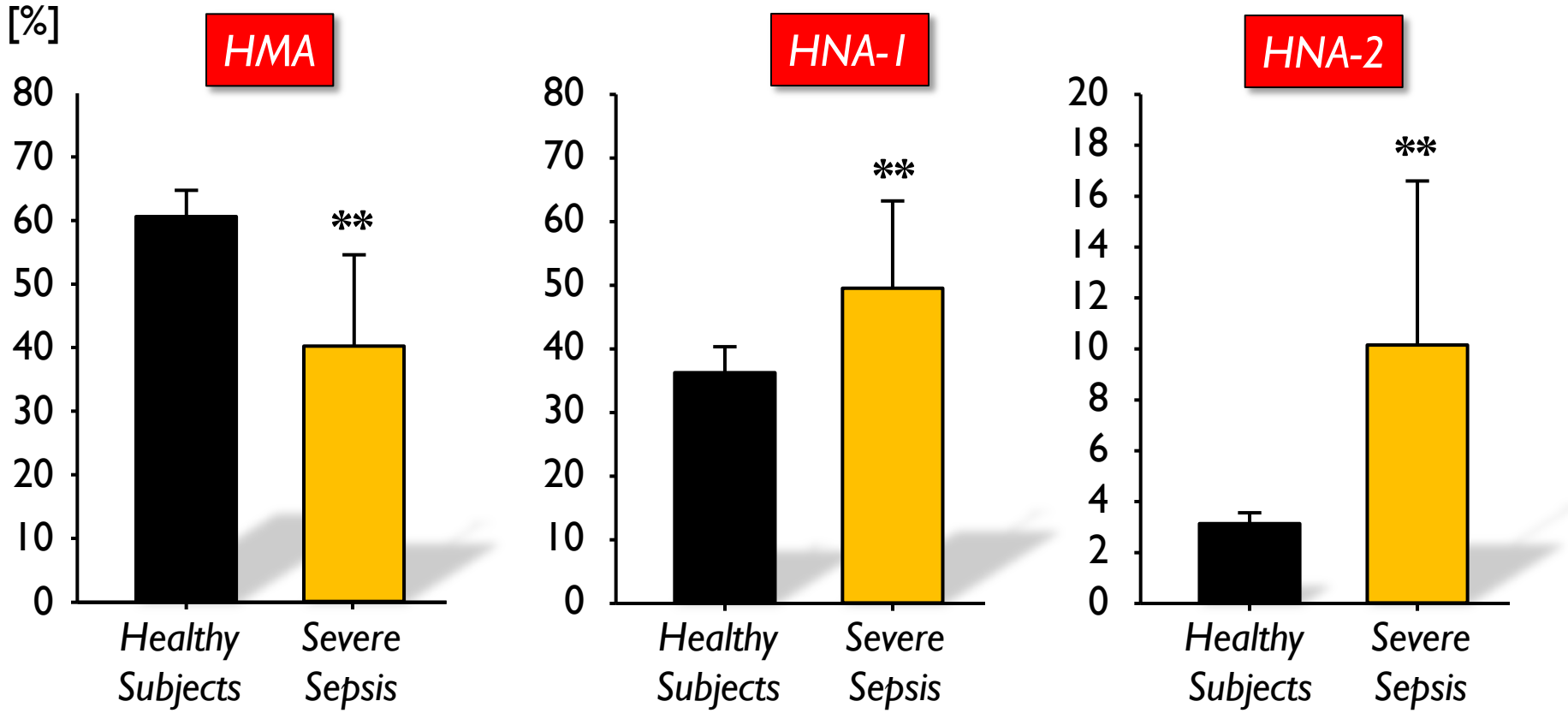
Ischemia-Modified Albumin (IMA)

Bernardi M. et al, J Clin Exp Hepatol 2014;3:302-311

Oxidized Albumin on Cys-34: HMA, HNA-1 and HNA-2

Human Mercaptalbumin (HMA): *reduced*
Human Non-Mercaptalbumin-1 (HNA-1): *rev. oxidized*
Human Non-Mercaptalbumin-2 (HNA-2): *irrev. oxidized*

60 pts with severe sepsis
30 healthy subjects
by HPLC-fluorescence

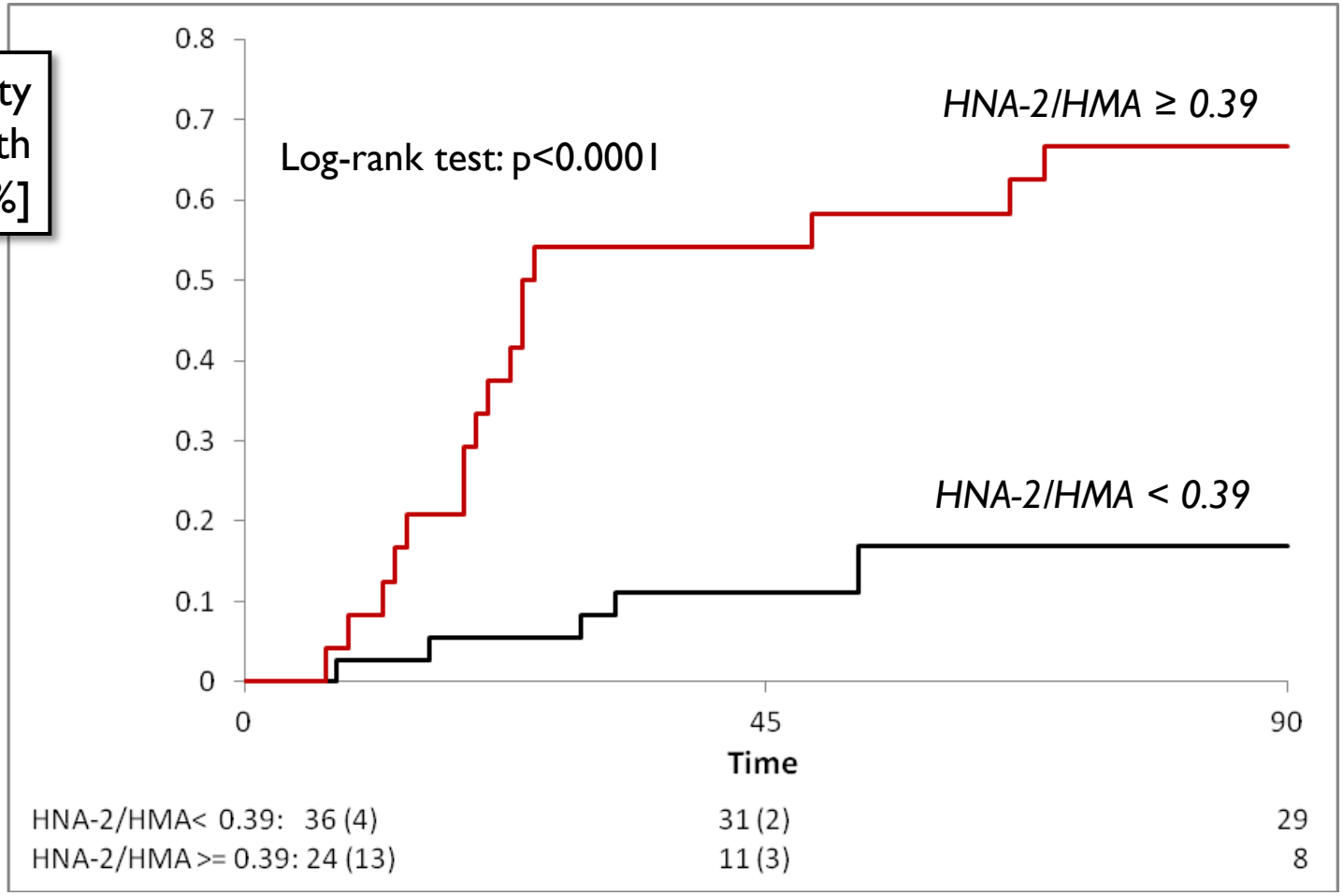


From ALBIOS biobank

P<0.001 *for all*

Unpublished

HNA-2 / HMA ratio and 90-Day Mortality



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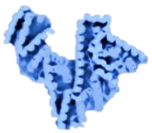

CONCLUSIONS

- Albumin is not just a colloid solution, but is a "physiologic" drug which has many crucial properties (*secondary functions*).

- In critically ill patients with severe sepsis albumin administration is SAFE, but its not associated with an improved survival, despite hemodynamic advantages. The beneficial effect of albumin replacement in septic shock needs further confirmations (the *ALBIOSS-BALANCED* trial).

- The efficacy (and the appropriate use) of albumin in septic patients may depend on specific, yet unproven, clinical characteristics, and specific effects (hemodynamic status, serum concentration, anti-infective / immuno-modulating effect, red-ox state, etc.).