Role of albumin in treatment of cirrhosis

Management of acute-on-chronic liver failure

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MICROB-PREDICT and DECISION symposium

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- No disclosures

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Outline

- Background and presumed beneficial effects of albumin
- Widely accepted indications for albumin in cirrhosis
- Exploratory indications for albumin in cirrhosis
- Conclusions

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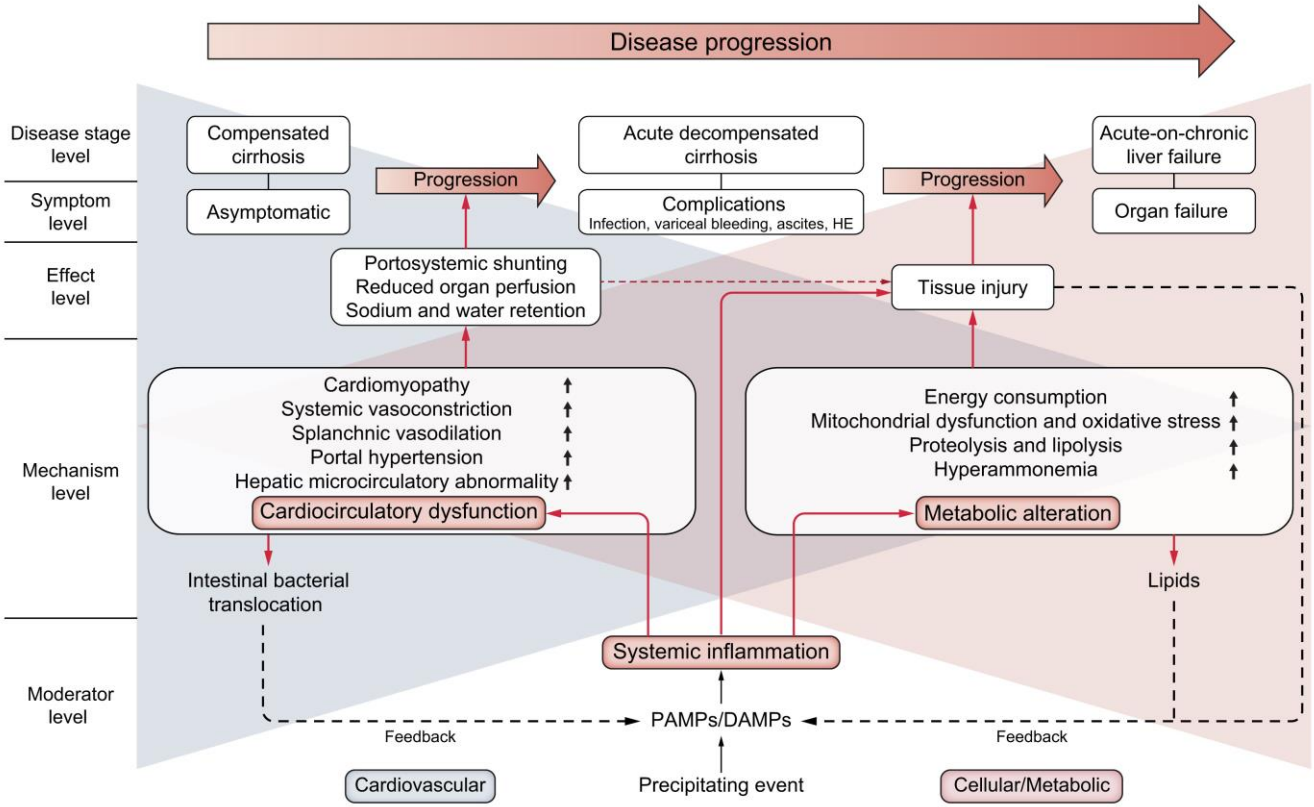
Pathophysiology of cirrhosis complications



J Hepatol 2021 Jul;75 Suppl 1:S49-S66.

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Systemic Inflammation and circulatory dysfunction in DC and ACLF

TABLE 1. Plasma Concentrations of Renin (PRC), Copeptin (PCC), and Cytokines and Albumin Oxidation Fractions in Healthy Subjects and in Patients With and Without ACLF

	Healthy Controls N = 40	No ACLF N = 285	ACLF N = 237	*P* Value*
Markers of SCD				
PRC (microIU/mL)	8 (6-17)	65 (17-242)	134 (36-378)	<0.001
PCC (pmol/L)	0 (0-10)	9 (3-23)	31 (13-61)	<0.0001
Proinflammatory cytokines				
TNFα (pg/mL)	9 (7-12)	20 (14-27)	29 (17-41)	<0.001
IL-6 (pg/mL)	0.3 (0.3-0.3)	21 (11-41)	39 (17-115)	<0.001
IL-8 (pg/mL)	1.6 (0.6-3.3)	37 (20-76)	84 (41-169)	<0.001
MCP-1 (pg/mL)	337 (218-413)	318 (228-436)	410 (288-713)	<0.001
IP-10 (pg/mL)	328 (234-428)	965 (558-1,676)	1,184 (665-2,157)	0.004
MIP-1β (pg/mL)	13 (6-17)	20 (13-34)	28 (19-50)	<0.001
G-CSF (pg/mL)	2.1 (1.8-11)	23 (11-50)	32 (14-83)	0.001
GM-CSF (pg/mL)	7.5 (7.5-7.5)	4.7 (2.0-9.5)	7.3 (3.5-16.8)	<0.001
Anti-inflammatory cytokines				
IL-10 (pg/mL)	1.1 (0.4-1.1)	3.4 (1.1-9.2)	8.1 (2.1-29.9)	<0.001
IL-1ra (pg/mL)	7 (3-9)	10 (5-22)	23 (9-63)	<0.001
Other cytokines				
IFNγ (pg/mL)	0.8 (0.8-4.9)	6 (2-18)	7 (3-24)	0.044
IFNα2 (pg/mL)	3 (3-3)	22 (8-56)	27 (11-63)	0.113
Eotaxin (pg/mL)	94 (55-122)	110 (81-155)	124 (89-179)	0.018
IL-17a (pg/mL)	0.7 (0.7-2.7)	3.7 (1.6-10.3)	4.5 (1.6-15.6)	0.128
IL-7 (pg/mL)	1.4 (0.1-3.9)	2.6 (1.0-8.5)	3.5 (1.6-11.1)	0.012
EGF (pg/mL)	17 (4-29)	26 (9-66)	19 (8-41)	0.046
VEGF (pg/mL)	26 (26-28)	85 (28-226)	91 (29-252)	0.745
Albumin oxidation fractions†				
HMA (%)	71 (68-74)	53 (42-62)	45 (33-56)	<0.001
HNA1+HNA2 (%)	28 (25-30)	46.4 (37.5-56.9)	51.8 (42.2-65.6)	<0.001
HNA2 (%)	1.3 (0.3-1.9)	4.5 (2.5-8.8)	9.8 (5.6-14.8)	<0.001

Claria et al, Hepatology 2016

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Presumed beneficial effects of albumin in cirrosis

- Oncotic properties (accounts for 75% of plasma oncotic pressure)
- Antioxidant and scavenging activities
- Binding and transport of drugs, biolipids, metabolites, inflammatory mediators
- Endothelial protective functions
- Immune modulating effects: e.g. modulates innate immune responses, PGE2-mediated immune dysfunction

(Costs in NL € 91-109,87 per vial 100 ml (200 mg/ml))

Gut 2020;**69**:1127–1138

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Well-established indications for albumin in cirrhosis

EASL CPG for management of decompensated cirrhosis

Acute or short-term albumin administration in decompensated cirrhosis aimed at maintaining or improving effective circulating volume

- Spontaneous bacterial peritonitis to prevent acute kidney injury (AKI) (I;1)
- Prevention of post-paracentesis circulatory dysfunction after large-volume paracentesis (I;1)
- AKI> 1A or infection-induced AKI: 1 g of albumin/kg body weight for 2 days (III;1)
- Vasoconstrictors and albumin 20-40 g/day in all patients with AKI-HRS stage >1A (III;1).
- Hypervolemic hyponatremia, although limited data to support its use (II-3;2)

Journal of Hepatology 2018; 69: 406–460

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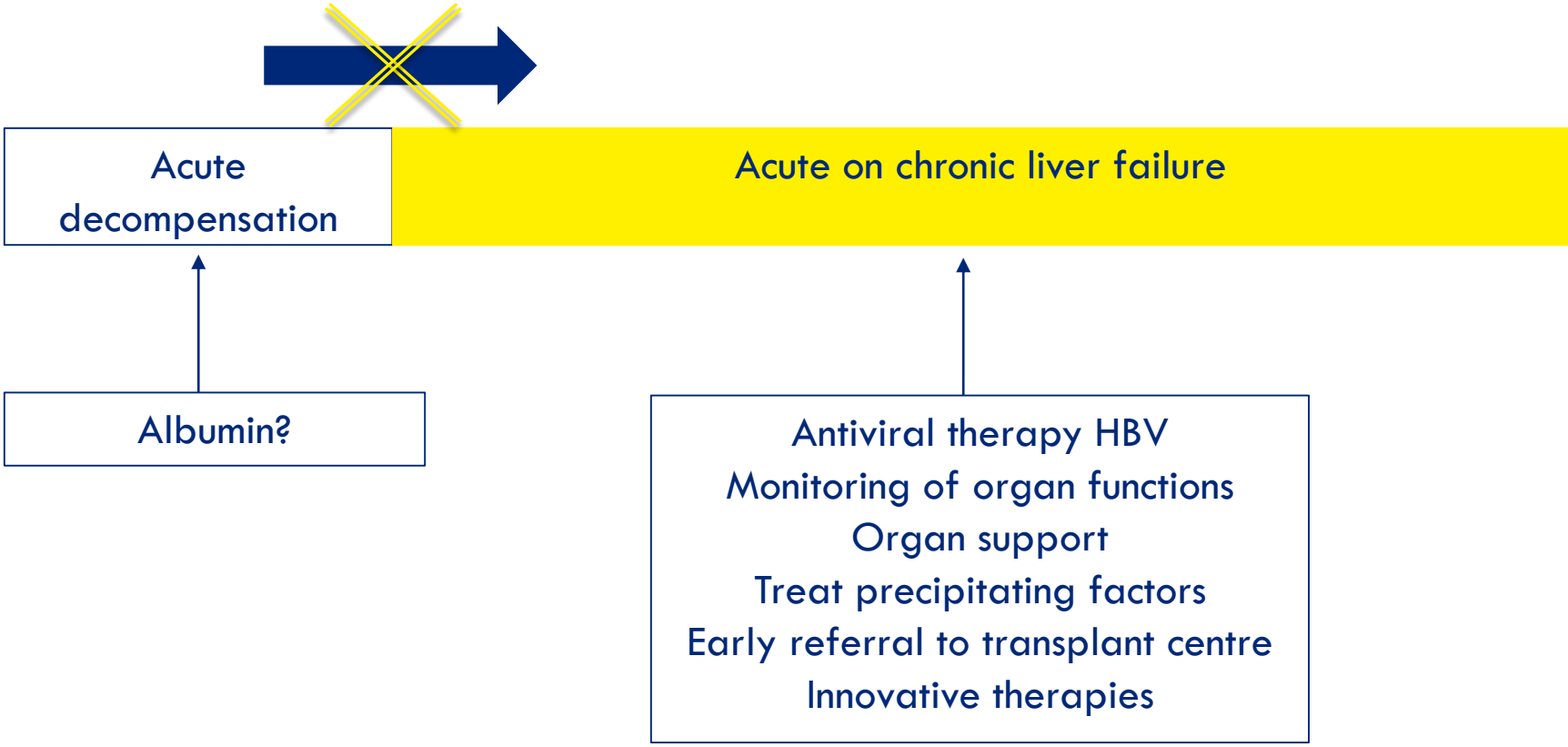
Can the natural history of cirrhosis be modified?



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Long-term albumin administration

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

Aim

Assess effect of long-term albumin administration on overall mortality, management of ascites and incidence of complications in patients with DC

Methods

- Multicentre randomised, parallel, open-label, pragmatic trial in 33 academic and non-academic Italian hospitals
- Patients with cirrhosis and uncomplicated ascites on anti-aldosteronic drugs (≥200 mg/day) and furosemide (≥25 mg/day)
- Standard medical treatment (SMT) or SMT plus albumin (40 g twice weekly for 2 weeks, and then 40 g weekly) for up to 18 months
- Primary endpoint: 18-month mortality

Caraceni et al, Lancet 2018

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

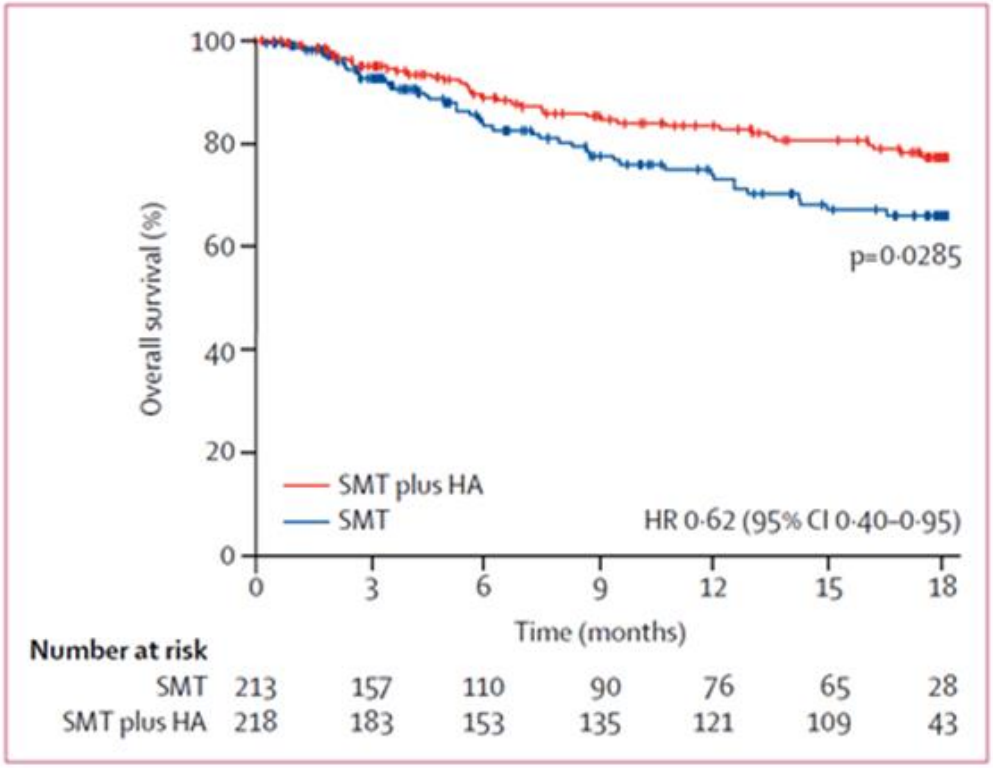
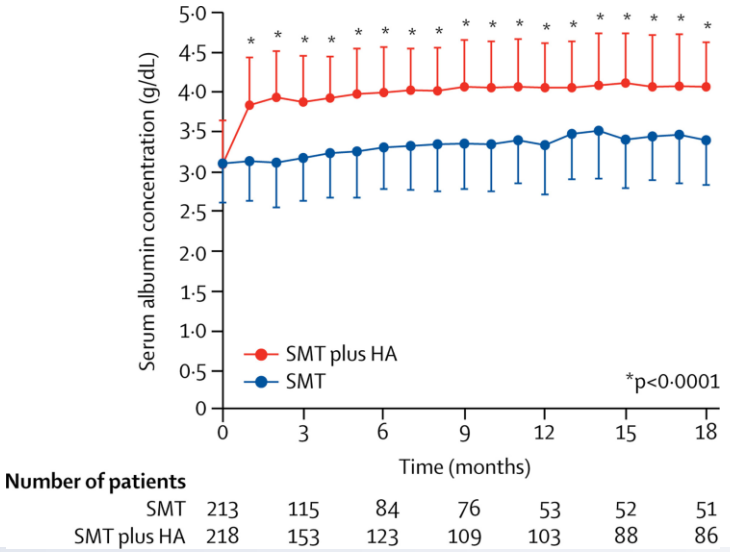


Figure 3: Overall survival



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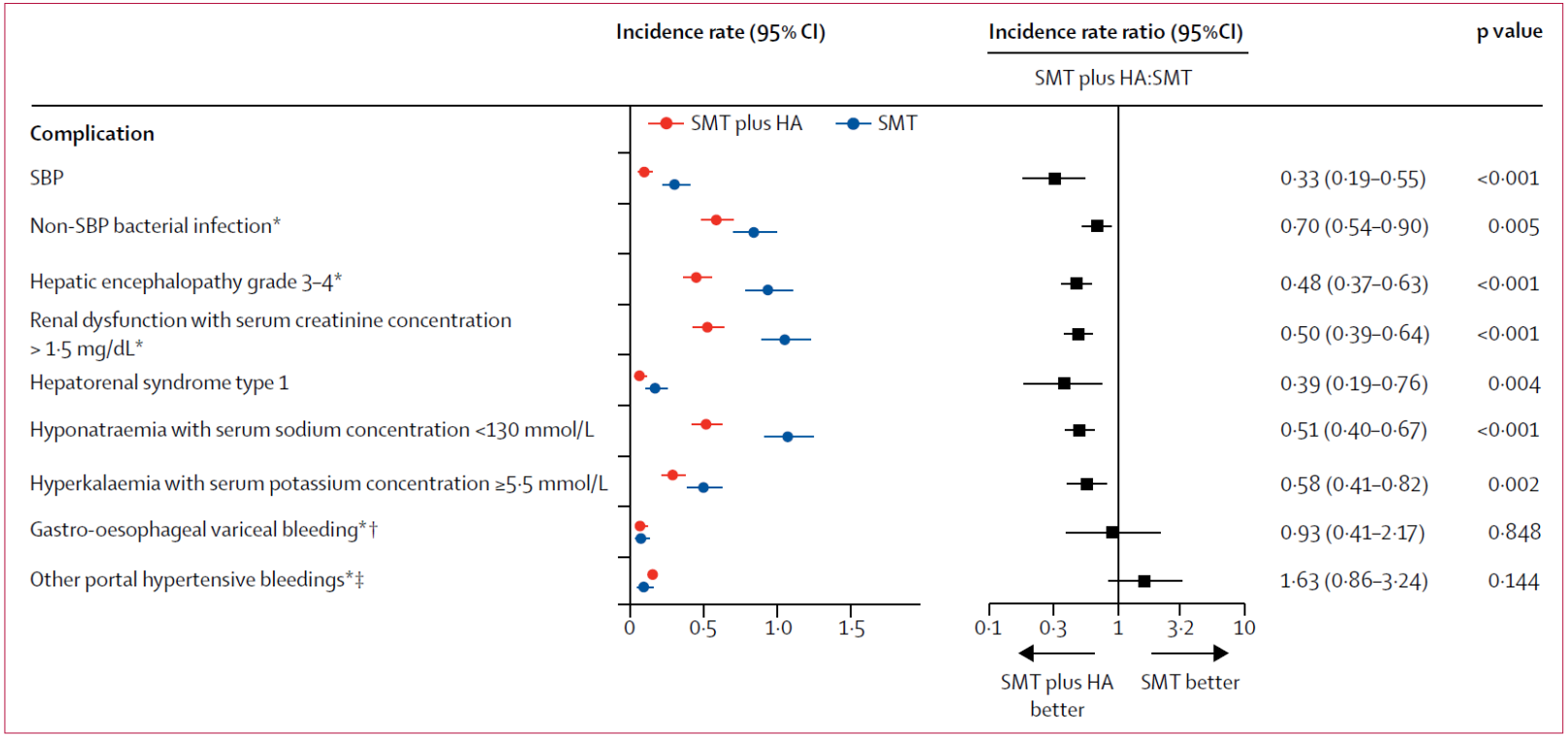

Figure 7: Complications of cirrhosis

Caraceni et al, Lancet 2018

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Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation

Aim

Investigate whether administration of midodrine and albumin improves circulatory dysfunction and prevents complications of cirrhosis in patients awaiting LT

Methods

- Patients with cirrhosis and ascites included on the waiting list for LT in 3 LT centers in Spain (n=173)
- Midodrine 15-30 gr daily & albumin 40 gr every 2 wks for 1 year
- Primary endpoint: incidence of complications (renal failure, hyponatremia, infections, HE, gastrointestinal bleeding)

J Hep 2018; 69: 1250-1259

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Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation

Serum albumin concentration:	Albumin/midodrine	Placebo
Baseline	30 ± 0.6 g/L	30 ± 0.6 g/L
Week 4	32 ± 0.4	30 ± 0.5
Week 12	34 ± 3.3	32 ± 0.5
Week 24	34 ± 0.4	33 ± 0.6
Week 48	35 ± 0.4	39 ± 2,2

Not significantly different between the two groups ($p = 0.684$).

J Hep 2018; 69: 1250-1259

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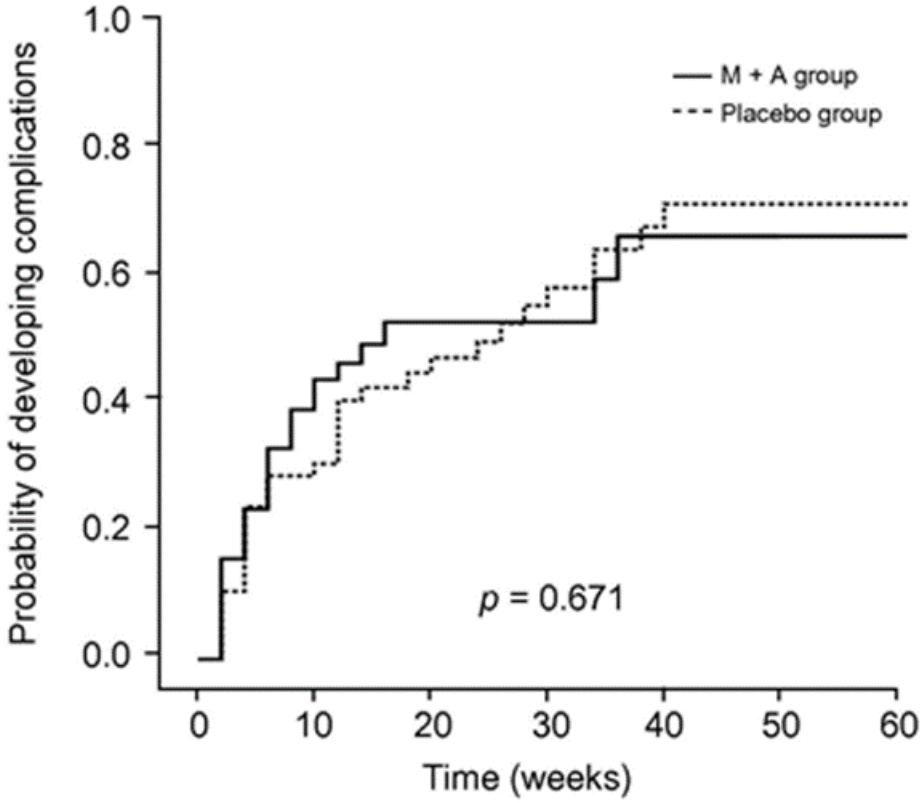

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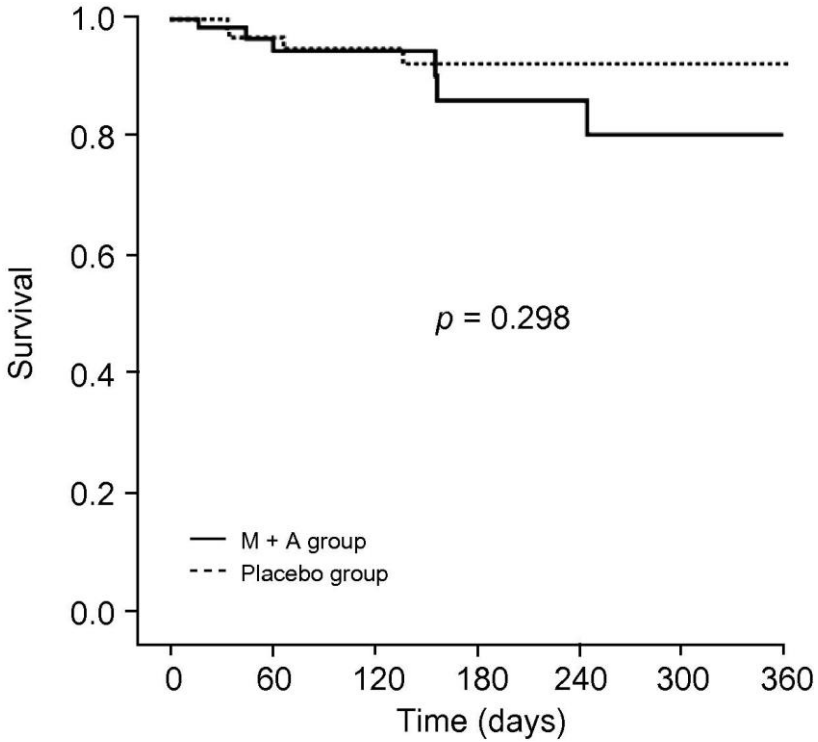

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Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites

Aim

Assess effectiveness of prolonged albumin administration on survival, occurrence of hospitalization due to complications and recurrence of ascites

Methods

- Non-randomized prospective study (University Hospital of Padova)
- Patients with cirrhosis and refractory ascites, followed for LVP
- Albumin 20g twice per week (n=45) vs SOC (n=25)

Results

- Mean total weekly dose of albumin administered 60.7 ± 15.2 g vs 22 ± 14.1 g in the SOC group ($P < 0.001$).

Liv Int 2019;39:98-105

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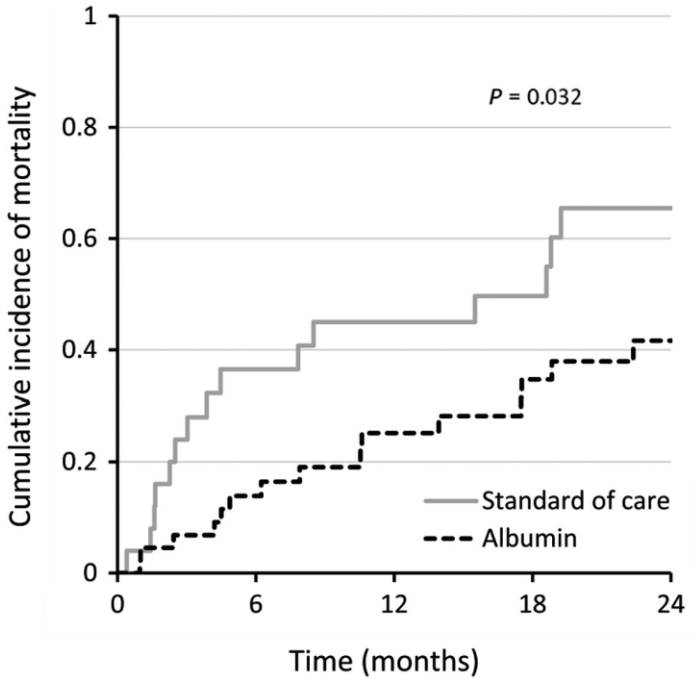
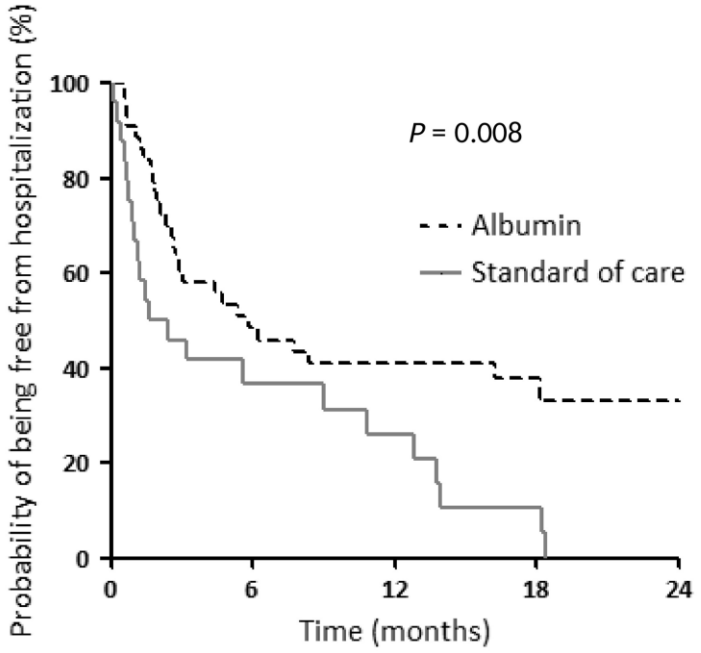
Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites



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



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

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Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites

Table 3. Probability of emergent hospitalization due to complications of cirrhosis during the 24-mo follow-up

Complication	Albumin (%)	Standard of care (%)	*P*
HRS	22.5%	57.7%	0.084
HE	26.9%	64.5%	0.016
Ascites	37.1%	71.0%	0.002
SBP	7.9%	50.6%	0.004
Non-SBP infection	27.2%	88.6%	0.001
Variceal bleeding	2.4%	4.5%	0.603

HE, hepatic encephalopathy; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

Liv Int 2019;39:98-105

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Short-term albumin administration

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Albumin infusions in hospitalized patients with decompensated cirrhosis: ATTIRE study

Aim

evaluate whether targeting an increase in the serum albumin level to 30 g/l by repeated daily infusions of albumin would reduce the incidences of infection, kidney dysfunction, and death among hospitalized patients with decompensated cirrhosis

Methods

- Patients admitted with decompensated cirrhosis and serum albumin < 30 g/l
- Randomly assigned to targeted 20% human albumin solution for up to 14 days or until discharge, whichever came first, or standard care
- Composite primary end point: new infection, kidney dysfunction, or death between days 3 and 15 after the initiation of treatment

N Engl J Med 2021; 384:808-817

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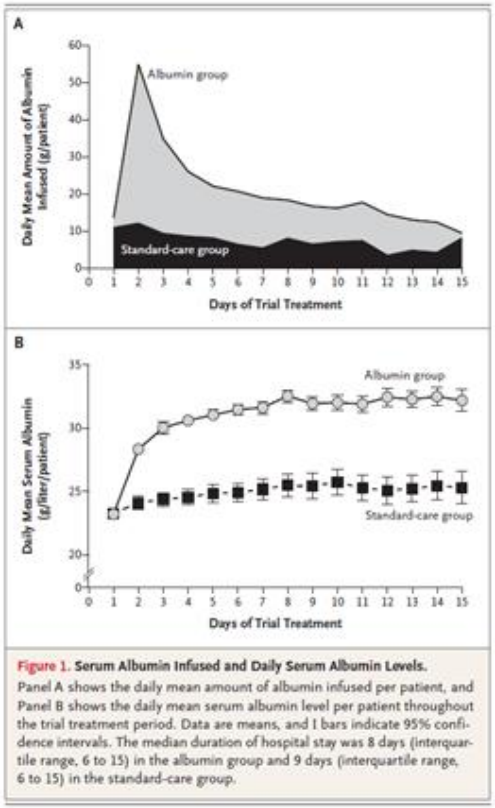

Figure 1. **Serum Albumin Infused and Daily Serum Albumin Levels.** Panel A shows the daily mean amount of albumin infused per patient, and Panel B shows the daily mean serum albumin level per patient throughout the trial treatment period. Data are means, and I bars indicate 95% confidence intervals. The median duration of hospital stay was 8 days (interquartile range, 6 to 15) in the albumin group and 9 days (interquartile range, 6 to 15) in the standard-care group.

N Engl J Med 2021; 384:808-817

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Albumin infusions in hospitalized patients with decompensated cirrhosis: ATTIRE study

Table 2. End Points.*

Variable	Albumin Group (N=380)	Standard-Care Group (N=397)	Adjusted Odds Ratio (95% CI)†	P Value
Composite primary end point — no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71–1.33)	0.87
Components of composite primary end point — no. (%)‡				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85–1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44–1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56–1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57–1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74–1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93–1.73)	
Total median albumin infused per patient (IQR) — g	200 (140–280)	20 (0–120)	143 (127–158)§	

* Unless stated, the time of the end point is during the trial treatment period (15 days after randomization).
† Odds ratios are adjusted for stratification variables, with sites as random intercept terms.
‡ The end points are defined in the original trial protocol.[26]
§ This is the adjusted mean difference between the groups.

More severe or life-threatening serious adverse events, especially pulmonary edema or fluid overload, in the albumin group than in the standard-care group

China et al. NEJM 2021

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Role of albumin in infections other than SBP?

EASL CPG management of decompensated cirrhosis 2018:

- Routine use of albumin is not recommended in infections other than SBP (I;1)
- Albumin may protect against deterioration in renal and circulatory function, but albumin did not improve survival and thus it cannot be recommended

J Hepatol. 2015 Apr;62(4):822-30, J Hepatol. 2012 Oct;57(4):759-65.

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Efficacy of Albumin Treatment for Patients with Cirrhosis and Infections Unrelated to SBP

Aim

Assess if albumin treatment impacted hospital survival among patients with cirrhosis with non-SBP infections at high risk of hospital mortality

Methods

Patients with cirrhosis and non-SBP infections (UTI, pneumonia, bacteremia, cellulitis, acute cholangitis, or suspected bacterial infection); and advanced liver disease (serum creatinine ≥ 1.2 mg/dL, serum sodium ≤ 130 mEq/L, and/or serum bilirubin ≥ 4 mg/dL)

Randomization between antibiotics alone or antibiotics plus albumin (1.5 g/kg BW at day 1 and 1 g/kg BW at day 3)

Primary outcome: in-hospital mortality

Clinical Gastroenterology and Hepatology 2020;18:963–973

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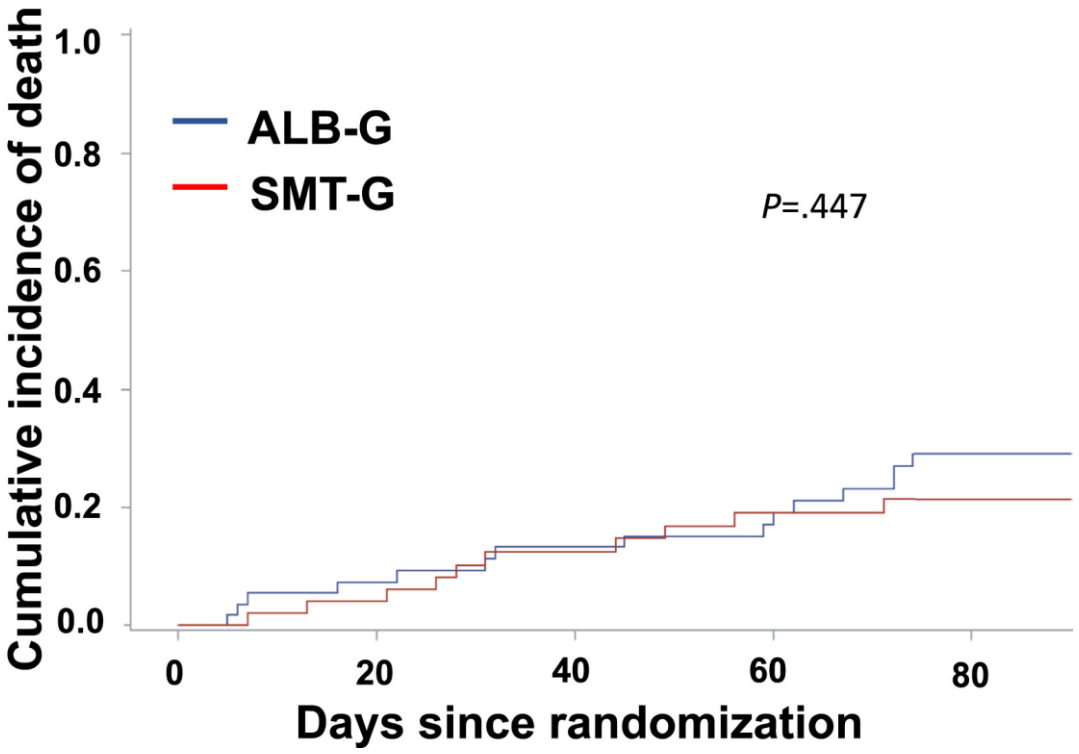
Efficacy of Albumin Treatment for Patients with Cirrhosis and Infections Unrelated to SBP

Per protocol patients



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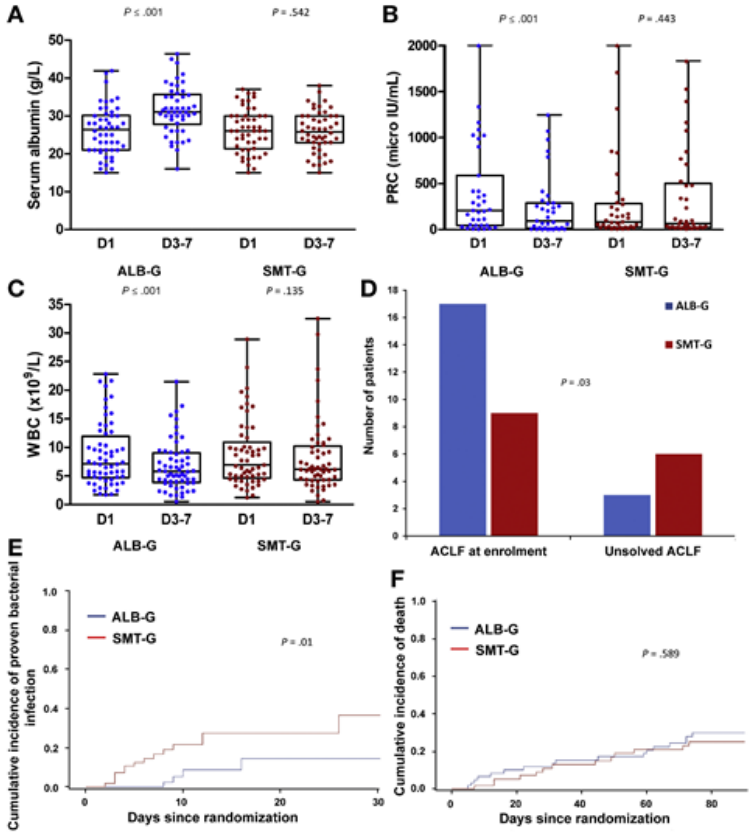

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ALB trial in MICROB-PREDICT

Aims to provide a clinical tool for personalized treatment with albumin that can detect high-risk patients who are likely to benefit from treatment, and those who are unlikely to benefit from treatment

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Conclusions

- Pleiotropic non-oncotic properties of albumin: potential multitarget agent for treatment of decompensated cirrhosis
- Accepted indications for albumin administration: SBP, AKI and AKI-HRS, LVP
- Long-term albumin administration to patients with decompensated cirrhosis improves survival, prevents cirrhosis complications, facilitates the management of ascites and reduces hospitalisations
- Further investigations required for personalized use of albumin: which patients benefit most of long-term albumin administration, optimal dosage scheme
- Short-term albumin administration in hospitalized patients with decompensated cirrhosis does not reduce mortality, new infections and kidney dysfunction
- Routine use of albumin is not recommended in infections other than SBP

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