INSELGRUPPE

A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis

China, Louise, et al., New England Journal of Medicine 384.9 (2021): 808-817.

Hepatology Journal Club, 27 May 2021, presented by Christina Schramm

The ATTIRE★ Trial - Outline

- Research Question and Motivation
- Trial Design
- Results
- Discussion
- Conclusion

★ **A**lbumin **T**o preven**T** **I**nfection in chronic live**R** failur**E**

Research Question / Motivation I

- Liver disease as **leading cause of death** in adults **35 to 49 years** of age in England
- Decompensated cirrhosis associated with high risk of **infections, kidney failure and death**
- **International Guidelines (EASL)** recommend usage of human albumin solution in patients with spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS)
- **Preclinical studies** showed anti-inflammatory effect of albumin in patients with cirrhosis, …
  - … but: **clinical trials** showed **conflicting results** (SBP vs other infections, lethal pulmonary edema),
  - **meta-analyses** did not find increased survival due to albumin in HRS patients/patients after large-volume paracentesis (LVP)
  - Also: **inconsistency** concerning the application interval (weekly vs less often)

Research Question / Motivation II

⇨ **Large** trials to address the usefulness of albumin in **preventing** infection, kidney dysfunction, and death in hospitalized patients are lacking.

⇨ Does **targeting** an increase in the **serum albumin level to ≥30g/l** with the use of repeated daily infusions of 20% human albumin solution, as compared with standard care, **reduce** the incidences of

- **infection,**
- **kidney dysfunction,**
- and **death**



among hospitalized patients with **decompensated cirrhosis**?

ATTIRE – Trial Design I

- Prospective
- Interventional
- Multi-center: 35 hospitals in England, Scotland, and Wales
- Randomized: minimization biased coin algorithm; assignment balanced on center location, MELD score, number of organ dysfunctions, use of antibiotics, serum albumin level
- Open-label

ATTIRE – Trial Design II

Sample:

- ≥18 years
- Hospitalized with acute complications of decompensated liver cirrhosis
- Serum albumin ≤30g/l within 72 hours after hospital admission
- Anticipated length of hospital stay of ≥5 days (clinical judgment)
- Recruitment between 15 January, 2016, and 28 June, 2019
- Exclusion criteria: Advanced HCC with life expectancy ≤8 weeks; palliative care

Descriptives

Characteristic	Albumin Group (N=380)	Standard-Care Group (N=397)
Mean age — yr	53.8±10.6	53.8±10.7
Female sex — no. (%)	123 (32.4)	104 (26.2)
Admitted to ward — no. (%)	370 (97.4)	384 (96.7)
Admitted to intensive care unit — no. (%)	8 (2.1)	10 (2.5)
Cause of cirrhosis — no. (%)†		
Alcohol	347 (91.3)	350 (88.2)
Hepatitis C	24 (6.3)	35 (8.8)
Nonalcoholic fatty liver disease	26 (6.8)	29 (7.3)
Reason for admission — no. (%)†		
Encephalopathy	80 (21.1)	69 (17.4)
Suspected variceal bleed	52 (13.7)	63 (15.9)
New-onset or worsening ascites	236 (62.1)	281 (70.8)
Infection — no. (%)		
Diagnosis of infection at randomization by site medical team	98 (25.8)	113 (28.5)
Use of antibiotics	195 (51.3)	199 (50.1)
Serum albumin level — no. (%)		
<20 g/liter	61 (16.1)	60 (15.1)
20–25 g/liter	207 (54.5)	224 (56.4)
26–29 g/liter	112 (29.5)	113 (28.5)

- 777 unique patients
- Liver disease most often alcohol-related
- 26.4% treated for alcohol withdrawal
- 24.9% with alcoholic hepatitis
- Mean entry albumin level of 23±3.7g/l

Table 1 from China, Louise, et al. "A randomized trial of albumin infusions in hospitalized patients with cirrhosis." New England Journal of Medicine 384.9 (2021): 808-817.

Descriptives

Physiological variable — median (IQR)		
Creatinine level — mg/dl	0.75 (0.58–0.97)	0.78 (0.64–1.06)
Bilirubin level — mg/dl	5.70 (2.75–10.47)	5.56 (2.63–9.68)
International normalized ratio	1.6 (1.4–1.9)	1.6 (1.4–1.9)
MELD score — median (IQR)‡	19.6 (15.4–22.9)	19.5 (15.4–23.4)
Baseline organ dysfunction — no. (%)		
Cerebral: grade III or higher hepatic encephalopathy	10 (2.6)	8 (2.0)
Circulatory: mean arterial pressure <60 mm Hg	10 (2.6)	6 (1.5)
Respiratory: Spo_2:Fio_2 ratio		
Grade 0: >357	345 (90.8)	367 (92.4)
Grade 1: >214 to ≤357	29 (7.6)	23 (5.8)
Grade 2: ≤214 or mechanical ventilation	5 (1.3)	5 (1.3)
Renal: creatinine level ≥1.5 mg/dl	36 (9.5)	46 (11.6)

Table 1 from China, Louise, et al. "A randomized trial of albumin infusions in hospitalized patients with cirrhosis." New England Journal of Medicine 384.9 (2021): 808-817.

ATTIRE – Trial Design III

Intervention:

- **Treatment**: **daily 20% human albumin solution** (infused at a rate of 100 ml/h) from day 1 of recruitment, with a **target level** of ≥30 mg/l
  - Volume determined by initial serum albumin levels
  - Continuation even in case of nonfatal primary event
- **Control**: **Standard medical care**
  - Application of albumin according to guidelines (SBP, HRS, LVP)
- Infusion period: ≤14 days after randomization, or until (possible) discharge
  - No significant difference in the median number of days of hospitalization during the trial between groups: 8 days in the albumin group and 9 days in the standard-care group

Serum Albumin Infused (A) and Daily Serum Albumin Levels (B), Group Means

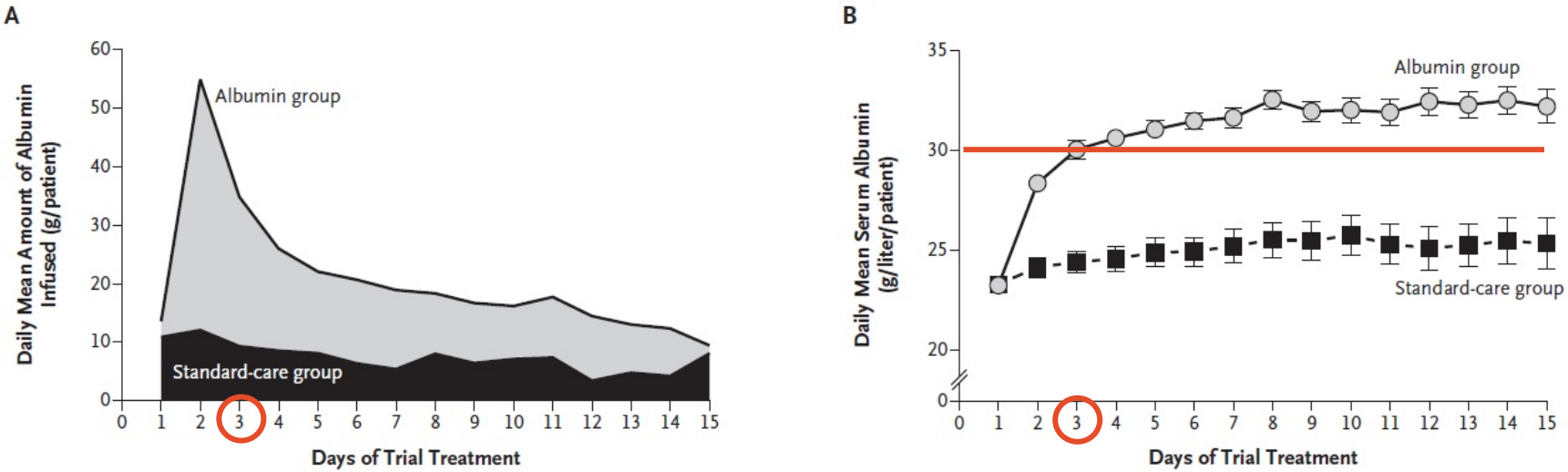
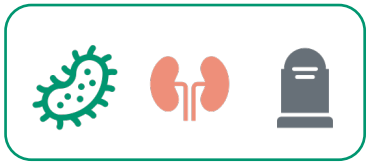


Figure 1 from China, Louise, et al. "A randomized trial of albumin infusions in hospitalized patients with cirrhosis." New England Journal of Medicine 384.9 (2021): 808-817.

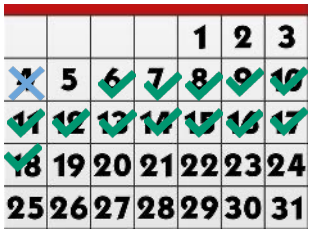
- Albumin group: Median of 200 g (IQR 140-280 g) of albumin per patient
- Standard care: Median of 20 g (IQR 0-120 g)
- 196/397 patients (49.4%) in the standard care group received no albumin
- Target level of ≥30g/l serum albumin reached between day 3 and 15 of trial (mean)

ATTIRE - Trial Design IV

Endpoints:



- **Primary**: composite of infection, kidney dysfunction, or death
  - Kidney dysfunction: serum creatinine level that was ≥50% higher than the level at randomization, **or** an increase in the serum creatinine level of ≥0.3 mg/dl/48h, **or** the initiation of renal-replacement therapy
  - Between trial day 3 and 15, date of discharge, or date of being fit for discharge (if ≤15)
- **Secondary**:
  - Single components:  ,
  - Death at 28 days, 3 months, 6 months;
    duration of hospitalization, number of ICU days,
    other organ dysfunctions, liver transplant within 6 months,
    MELD score, terlipressin use, hypotension, variceal bleeding, serious adverse events



ATTIRE – Trial Design V

Statistical Analysis

- **Logistic regression** ⇨ Odds Ratios

$$Logit(Endpoint_{ic} = 1|X = x_{ic}) = \beta T_{ic} + \delta \boldsymbol{X_{ic}} + \gamma_c$$

Reads as: The probability that the endpoint is reached for patient i treated in hospital c who has covariates x (sex, age,…) … | … as a function of the **binary treatment variable T**, the covariates X, and a fixed effect γ for hospital c.

→ $\beta > 0$ means that a patient in the treatment group has a higher probability of an endpoint event than in the control group.

- **Time-to-Event Analysis** ⇨ Hazard Ratios
- Intention-to-treat analysis

Results I – Primary Endpoint

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)	

- **No significant difference between the groups in the regression analysis**
- **No significant difference between the groups in time-to-event analysis (hazard ratios)**
- Holds in subgroup analyses (e.g., antibiotics, reason for admission)

Table 2 from China, Louise, et al (2021).

Results II – Secondary Endpoint

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)	

- **No significant differences between the groups with respect to death and time to death**
- **No significant differences between the groups for other secondary outcomes**

Table 2 from China, Louise, et al (2021).

Results III – Serious Adverse Events

Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
All serious adverse events that included pulmonary edema or gastrointestinal bleeding‡			
Any pulmonary edema or fluid overload	23	8	31
Any gastrointestinal bleeding	11	13	24

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

Table 3 from China, Louise, et al (2021).

Discussion

- **Limitations**:
  - Not blinded: Feasibility? Bias?
- **Assets:**
  - Big sample size
  - Multi-center
  - Prospective
  - Randomized

Extensions and open questions:

- Threshold of 30 g/l – different target?
- Nature of the relationship between the amount of administered albumin and risk of adverse events? (Linearity vs exponential)
- External validity?
  - Alcohol vs other cases of cirrhosis?
  - Standard care in different countries (UK vs continental Europe)?
- Reasons for conflicting pre-clinical evidence?
- Statistical robustness checks - different statistical models than logit model, covariates
- Cost-benefit analysis? Quality of life?

Conclusion

- The results of the ATTIRE trial **do not favor targeted administration of albumin in patients with decompensated liver cirrhosis to prevent infection, kidney dysfunction, or death**
- There was no evident benefit for patients – in any subgroup and for any endpoint
- This finding differs from pre-clinical evidence and previous clinical studies
- Encourages a critical re-evaluation of the role of albumin infusions in patients with decompensated cirrhosis

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Thank you!

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