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Original article

Targeted albumin infusions in hospitalized patients with cirrhosis receiving terlipressin: A post-hoc analysis of ATTIRE

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ABSTRACT

Introduction and Objectives: The ATTIRE trial showed increased severe adverse events with targeted albumin therapy. Safety concerns exist regarding albumin-terlipressin use for hepatorenal syndrome-acute kidney injury (HRS-AKI), but terlipressin is also used for variceal bleeding and hypotension. We evaluated the safety of terlipressin and albumin for any indication using ATTIRE data.

Materials and Methods: In ATTIRE, hospitalized decompensated cirrhosis patients were randomized to daily 20 % albumin (serum albumin ≥30 g/L) or standard care for up to 14 days post-randomization. Of 777 patients, 42 received terlipressin at randomization in the targeted albumin arm and 41 in standard care. We studied death and fluid-related complications from serious adverse event reporting during the 15-day trial period.

Results: Indications for terlipressin were variceal bleeding (73 %), HRS-AKI (23 %) and sepsis-induced hypotension (3 %). Median albumin dosing was higher with targeted albumin than standard care for variceal bleeding (200 g vs. 0 g) and sepsis-induced hypotension (180 g vs. 0 g), but similar for HRS-AKI (220 g vs. 230 g). A composite of death and fluid-related complications was more common with targeted albumin compared to standard care (log-rank: $p = 0.011$), where the increased risk persisted when adjusting for baseline MELD. This composite outcome occurred more often in variceal bleeding patients treated with targeted albumin ($n = 7$) compared to standard care ($n = 2$), although the difference was not statistically significant ($p = 0.064$).

Conclusions: In hospitalized cirrhosis patients, targeted albumin infusions with terlipressin may increase the risk of death and fluid-related complications, particularly in variceal bleeding. Caution is warranted when using albumin in this subgroup.

Clinical trial number: EudraCT number: 2014–002,300–24 and International Standard RCT Number: 14,174,793 Research Ethics Committee Number: 15/LO/0104

Abbreviations: ACLF, Acute-on-chronic liver failure; AKI, Acute Kidney Injury; ALPS, Albumin to Plasmalyte in Patients with Cirrhosis and Sepsis-Induced Hypotension; aHR, Adjusted Hazard Ratio; ANP, Atrial Natriuretic Peptide; ATTIRE, Albumin To Prevent Infection in Chronic Liver Failure; bpm, Beats Per Minute; CCL8/MCP2, Chemokine (C—C motif) Ligand 8 / Monocyte Chemotactic Protein 2; CI, Confidence Interval; CRP, C-Reactive Protein; EASL, European Association for the Study of the Liver; FiO2, Fraction of Inspired Oxygen; HICF, Health Innovation Challenge Fund; HRS, Hepatorenal Syndrome; HRS-AKI, Hepatorenal Syndrome-Acute Kidney Injury; IL, Interleukin; INR, International Normalized Ratio; IQR, Interquartile Range; LVP, Large-Volume Paracentesis; MAP, Mean Arterial Pressure; MELD, Model for End-Stage Liver Disease; PCT, Procalcitonin; SAE, Serious Adverse Event; SBP, Spontaneous Bacterial Peritonitis; SD, Standard Deviation; SpO2, Saturation of Peripheral Oxygen; TIPS, Transjugular Intrahepatic Portosystemic Shunt; TNF-α, Tumor Necrosis Factor-Alpha; WCC, White Blood Cell Count

Short title: Safety of Albumin and Terlipressin in Cirrhosis

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1. Introduction

Human albumin has been a cornerstone in the management of complications associated with liver cirrhosis for decades. Albumin use spans both evidence-based indications, such as spontaneous bacterial peritonitis, following large-volume paracentesis (LVP), hepatorenal syndrome-acute kidney injury (HRS-AKI) and non-evidence-based indications [1,2]. Terlipressin, a vasopressin analogue, was recently approved in the United States for treating HRS-AKI and is widely used in Europe to treat HRS-AKI and variceal bleeding, but where limited evidence also supports its use in patients with cirrhosis and sepsis-induced hypotension [3,4].

However, two large recent clinical trials have raised concerns about safety for their combined use in hospitalized patients. The ATTIRE trial of daily albumin infusions to target a serum value of ≥30 g/L compared with standard care, found an increased risk of pulmonary edema and fluid overload in patients from the targeted albumin arm [5]. The CONFIRM, phase III trial of terlipressin and albumin compared to albumin alone, had an increased number of respiratory failures in the terlipressin and albumin arm [6]. While CONFIRM protocolized terlipressin use in patients with HRS-AKI, ATTIRE enrolled patients with any acute decompensation of cirrhosis and terlipressin use administered according to the clinician's decision. As the safety of concomitant human albumin and terlipressin outside HRS-AKI is largely unknown, we aimed to evaluate this using ATTIRE trial data.

2. Patients and methods

2.1. Trial population

ATTIRE was a neutral trial of serum targeted albumin infusions versus standard care involving 777 hospitalized patients with decompensated cirrhosis from 35 hospitals across England, Wales and Scotland between 2016 and 2019 [5]. Key inclusion criteria included serum albumin <30 g/L at the time of screening and an expected hospital admission time of ≥5 days at enrollment. Patients were ineligible to participate if they had hepatocellular carcinoma with a life expectancy of <8 weeks, were pregnant, or known to, or had, suspected cardiac dysfunction. All patients signed a written informed consent form prior to any trial-related procedures and the trial adhered to the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript.

2.2. Targeted albumin intervention

Human albumin was given to all patients in the active arm daily according to the pre-defined serum target for albumin. In short, this meant individualized doses of daily 20 % human albumin solution to achieve and maintain a serum albumin ≥30 g/L. Infusions in the targeted albumin group continued for up to 14 days post-randomization, until discharge, or until deemed medically fit for discharge if extended hospitalization was needed for social reasons.

A feasibility study revealed that a target for serum albumin of 35 g/L was needed in order to maintain albumin levels above 30 g/L [7]. For patients in the standard care arm, human albumin was allowed as recommended per clinical practice guidelines, namely spontaneous bacterial peritonitis, HRS-AKI and following a LVP (≥5 L). Albumin infusions outside these indications in the standard arm were considered a protocol deviation. All other clinical treatment decisions, such as non-albumin fluid administration e.g. blood transfusion, were at the attending physician's discretion.

2.3. Terlipressin administration

Terlipressin use was not protocolized, with the treatment regimen at the local physician's discretion. Terlipressin administration was registered at baseline and for the duration of hospitalization. Indications for terlipressin (variceal bleeding, renal impairment HRS-AKI and septic shock) were classified by site investigators. In classifying, more than one indication for use was permissible. We registered the total daily dose of terlipressin in milligrams. All terlipressin was administered as bolus injections.

2.4. Outcomes

The aim of our study was to investigate any potential safety risk of combined terlipressin and albumin use, and so we examined a composite of death and fluid-related complications as the primary outcome for these post hoc analyses. We collected data until day 15 post randomization which constituted the trial treatment period. Mortality data were collected from medical records during hospitalization and discharge if occurring prior to the end of the trial treatment period. We used all-cause instead of fluid-related mortality since patients with cirrhosis often present with multiple contributory causes of death, where the identification of deaths related to fluid administration is difficult [8]. The fluid-related complications and causes of death were identified during the trial treatment period through the serious adverse event (SAE) reporting. For fluid-related complications, we included any SAE mentioning "respiratory failure", "pulmonary edema" or "fluid overload", regardless of the chosen primary Common Terminology Criteria for Adverse Events term. The use of SAE reporting ensured that the primary outcome included only clinically relevant events, as all fluid-related complications had to meet at least one SAE criterion, such as prolonged hospitalization or death. Acute-on-chronic liver failure (ACLF) was defined according to the EASL-CLIF definition [9].

As secondary outcomes, we examined the components of our composite primary outcome, indication for terlipressin use, 180-day mortality, ACLF together with clinical- and biochemical markers associated with the outcomes.

2.5. Statistics

We report numerical data as means and standard deviations (SD) or medians and interquartile ranges (IQR) according to distribution. A Shapiro-Wilk test together with QQ-plots were used to determine the distribution of data. Continuous parametric data between two groups was analysed with Student's *t*-test and the rank sum for testing between groups of non-parametric data. We visualized single variable time-to-event data by Kaplan-Meier curves and tested differences between curves by a log-rank test. We used Cox regression and adjusted hazard ratios (aHR) for multivariable time-to-event data. We tested the proportional hazard assumption of Cox regression by inspection of the Schoenfeld residuals and confirmed no multicollinearity between independent variables of models by testing the variance inflation factor. We performed a competing risk regression where we used fluid-related complications as the outcome of interest and death without a prior fluid-related complication as the competing event. We used STATA 18 (StataCorp TX, US) for all analyses and considered p-values <0.05 as statistically significant results.

2.6. Ethical statement

Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of London–Brent Research Ethics Committee, Approval Number/ID: 15/LO/0104.

3. Results

3.1. Baseline characteristics

Forty-two patients in the targeted albumin group and 41 in the standard care group were prescribed terlipressin at trial randomization (Supplementary Fig. 1). Average time from

Table 1
Baseline characteristics of patients in the targeted albumin and standard care groups.

	Targeted albumin *N* = 42	Standard care *N* = 41
Demographics		
Sex (male), n	31 (74 %)	31 (76 %)
Age, years	54 (±10)	56 (±12)
Clinical characteristics		
Alcohol-related cirrhosis, n	37 (88 %)	34 (83 %)
Admission due to ascites, n	18 (44 %)	24 (57 %)
Heart rate (bpm)	87 (78–97)	80 (71–94)
MAP (mmHg)	80 (73–87)	80 (73–88)
SpO_2/FiO_2	431 (319–507)	390 (338–434)
Mechanical ventilation, n	1 (2 %)	1 (2 %)
Disease severity		
MELD	19 (15–23)	18 (14–24)
ACLF (yes), n	14 (33 %)	10 (24 %)
ACLF grade (1/2/3)	10/2/2	4/3/3
Biochemical parameters		
Albumin (g/L)	24.0 (21.0–25.0)	24.0 (22.0–26.0)
INR	1.6 (1.4–1.9)	1.5 (1.4–1.8)
Creatinine (μmol/L)	77 (60–129)	88 (61–141)
Bilirubin (μmol/L)	62 (44–129)	63 (31–104)
Sodium (mmol/L)	135 (130–137)	135 (132–138)
WCC (10^9/L)	7.0 (5.2–10.3)	7.5 (4.9–11.0)
CRP (mg/L)	24.0 (13.0–70.5)	14.0 (10.0–45.0)

Data are presented as mean (±SD) or median (IQR) for continuous measures, and n (%) for categorical measures. An admission due to ascites was either new overt onset or worsening of known ascites. MELD, creatinine and leucocytes were missing for one patient in the standard care group, while CRP was missing for seven and ten in the targeted albumin and standard care groups, respectively. MAP: mean arterial pressure, SpO_2/FiO_2: saturation to fraction of inspired oxygen ratio, MELD: model for end stage liver disease, ACLF: acute-on-chronic liver failure, INR: international normalized ratio, WCC: white blood cell count, CRP: C-reactive protein.

hospitalization to randomization was one day. Mean age was 54 (SD: ±10) and 56 (SD: ±12) years for the targeted albumin and standard care group, respectively. The dominant etiology of cirrhosis was alcohol-related and median MELD score at baseline was similar between the targeted albumin group (median 19, IQR: 15–23) and standard care (median 18, IQR: 14–24). Baseline characteristics are shown in Table 1.

3.2. Terlipressin and human albumin use during the trial treatment period

Median time of hospitalization from randomization was 8 days (IQR: 5–14) in the targeted albumin arm and 7 days (IQR: 5–15) in standard care arm.

For patients with a single indication for terlipressin use, the majority (74 %) had variceal bleeding. The remaining patients had HRS-AKI (23 %) or sepsis-induced hypotension (3 %) as their terlipressin indication. Nine patients had more than one indication for terlipressin.

At randomization, the median daily dose of terlipressin was 4 mg for variceal bleeding and HRS-AKI, and 8 mg for sepsis-induced hypotension (Supplementary Table 1).

From randomization, the median time on terlipressin was 4 days (IQR: 2–5) in the targeted albumin group and 3 days (IQR: 2–6) with standard care, but with no statistically significant difference in terlipressin administration time between groups ($p = 0.553$).

Patients in the targeted albumin group received a median 20 % human albumin amount of 190 g (IQR 140–260 g), which was significantly more than standard care, who received a median of 0 g (IQR 0–140 g, $p < 0.001$). For the targeted albumin group, the majority of albumin was administered within first few days, as serum albumin levels reached 30 g/L (Figs. 1A and 1B). Separated according to terlipressin indication, patients with variceal bleeding and sepsis-induced hypotension received more albumin with the intervention compared to standard care, whereas patients with HRS-AKI received similar amounts with serum targeted albumin infusions and standard care. Cumulative albumin dosing according to terlipressin indications are shown in Supplementary Table 2 and per day in Supplementary Figure 2.

3.3. Clinical outcomes during the trial treatment period

A total of 19 events occurred during the trial treatment period 15 days post randomization for the 42 patients in the targeted albumin arm. Eleven (26 %) patients died, three (7 %) developed respiratory failure and seven (17 %) developed pulmonary edema or fluid overload. Of the patients who died in the targeted albumin group, four (36 %) had a fluid-related complication prior to death (Supplementary Table 3).

In the standard care group, five patients (12 %) died, while respiratory failure was reported in one patient (2 %) and pulmonary edema or fluid overload in one other (2 %). Here, a fluid-related complication preceded death in two out of the five patients who died (40 %).

No patients in the albumin or standard care arms received liver transplantation during the trial treatment period.

3.4. Targeted albumin infusions, terlipressin use and the risk of death and fluid-related complications

More patients in the targeted albumin group developed a fluid-related complication or died during the 15-day follow-up period compared to standard care (Fig. 2). The difference in the composite of death and fluid-related complications between targeted albumin and the standard care group was statistically significant (log-rank test: $p = 0.011$).

The increased risk of the composite of death and fluid-related complications associated with targeted albumin infusions, persisted when controlling for baseline MELD score or presence of ACLF, as indicators of liver disease severity and organ failure (Table 2). In the targeted albumin group, a separate analysis showed no association between terlipressin dosing and the primary composite outcome of death and fluid-related complications (aHR=0.94; 95 % CI: 0.80–1.10; $p = 0.434$).

Investigating the primary outcome components separately, more patients died in the targeted albumin group during the trial period, compared to standard care (Fig. 3A). This difference was not statistically significant in univariable analysis (log-rank test: $p = 0.107$), nor in multivariable analysis after adjusting for baseline MELD or ACLF presence (Table 2).

In the unadjusted analysis of time to the development of fluid-related complications, more patients receiving terlipressin developed a fluid-related complication in the targeted albumin arm compared to controls (log-rank test: $p = 0.040$) (Fig. 3B). However, this difference was not statistically significant in the multivariable analysis with baseline MELD or ACLF, where death was treated as a competing risk (Table 2).

3.5. Clinical outcomes according to indications for terlipressin use

For patients with a variceal bleeding indication for terlipressin, seven patients met the composite primary outcome of death or developing a fluid-related complication in the targeted albumin group, compared to two with standard care (Table 3). There were no statistically significant differences in the number of patients experiencing the primary outcome for any terlipressin indication.

3.6. Mortality at 180-days follow-up

During a 180 days follow-up after randomization, 40 % ($n = 17$) died in the intervention group and 24 % ($n = 10$) in standard care (Supplementary Figure 3). For time-to-death, the mortality

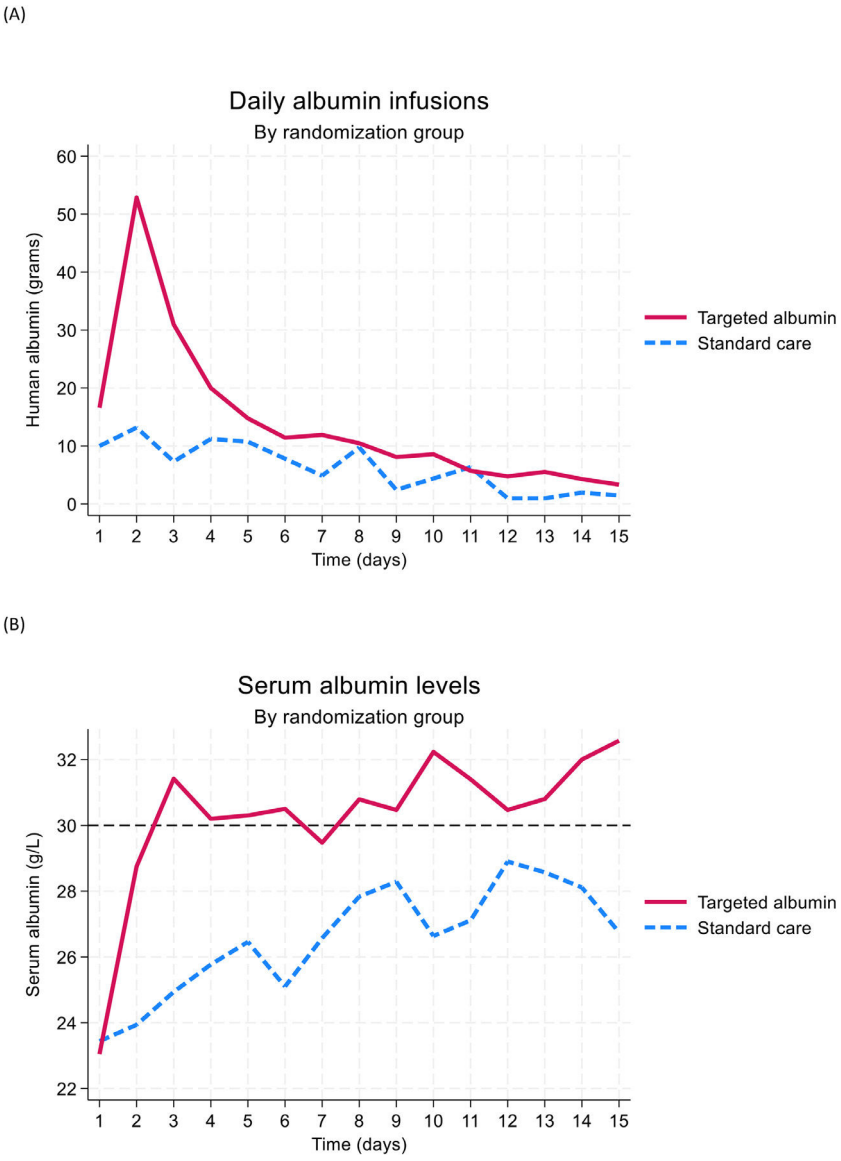


Fig. 1. Human albumin administration and serum albumin levels. A) Mean amount of human albumin administered per day in the targeted albumin and standard care arm. In the targeted albumin group, most albumin was administered within the first few days post randomization. B) Serum albumin levels of patients in targeted albumin and standard care group. With mean serum albumin levels, the target of >30 g/L was achieved on day 3 with targeted albumin infusions and not at any point with standard care during the treatment period.

differences between the targeted albumin infusion group and standard care were not statistically significant (log-rank test: $p = 0.118$) in the unadjusted analysis. In an adjusted analysis controlling for MELD, the difference was still not statistically significant (aHR=1.95, 95 % CI: 0.87–4.35, $p = 0.104$). None of the patients underwent liver transplantation during the 180-day follow-up period.

3.7. Exploratory analyses suggest presence of increased systemic inflammation that predicts the composite of death and fluid-related complications

The development of the composite of fluid-related complications and death was associated with an elevated white blood cell count at randomization (HR=1.094, 95 % CI: 1.022–1.172, $p = 0.010$). Neither baseline levels of INR, oxygen saturation levels, mean arterial pressure or C-reactive protein were statistically significantly correlated with the development of the primary composite outcome (Supplementary Table 4).

In further exploratory analyses, a subset of patients ($n = 8$) from the targeted albumin arm had a panel of inflammatory, cardiac and hemodynamic markers available (Supplementary Figure 4). Patients who died or developed a fluid-related complication were prior to treatment characterized by higher levels of the inflammatory markers procalcitonin, PCT ($p = 0.046$) and tumor necrosis factor-alpha, TNF-α ($p = 0.044$) levels.

4. Discussion

In hospitalized patients with decompensated cirrhosis who were treated with terlipressin at their clinician's discretion, we found concomitant daily human albumin infusions that increased serum albumin to >30 g/L may also have increased the risk of a composite of death and fluid-related complications. Although not statistically significant, this difference in the composite primary outcome seemed to be driven by patients given terlipressin to treat variceal bleeding.

Our findings are consistent with the higher rate of pulmonary edema and fluid overload with targeted albumin infusions from the

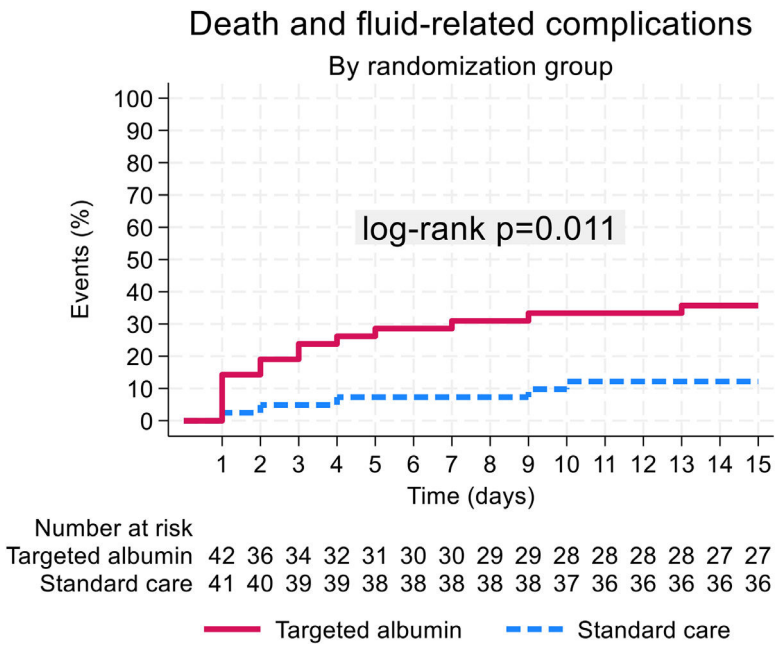


Fig. 2. Primary outcome: composite of death and fluid-related complications. Log-rank test showed higher incidence of the combined outcome with death and fluid-related complications in patients receiving targeted albumin compared to standard care (log-rank test: $p = 0.011$).

complete ATTIRE analyses [5]. Overall, pulmonary edema and fluid overload were rare events in ATTIRE, and therefore it was not possible to make specific recommendations to avoid this complication from the trial. CONFIRM also identified an increased risk of respiratory failure, but did not show a clear relationship with the amount of human albumin given in patients with HRS-AKI [6]. This post hoc analysis identified patients treated with terlipressin and targeted albumin infusions as especially prone to fluid overload events. The potential increased risk of the composite of death and fluid-related complications persisted after adjusting for baseline MELD and the presence of ACLF. This observation indicates that the higher rate of death and fluid-related complications was not necessarily a mere reflection of liver disease severity. Given that patients prescribed terlipressin at randomization in ATTIRE made up only 11 % (42 of 380) of the targeted albumin arm but were involved in 30 % (7 of 23) of the fluid overload events, we strongly advocate exercising caution, when administering albumin and terlipressin concomitantly to decompensated cirrhosis patients.

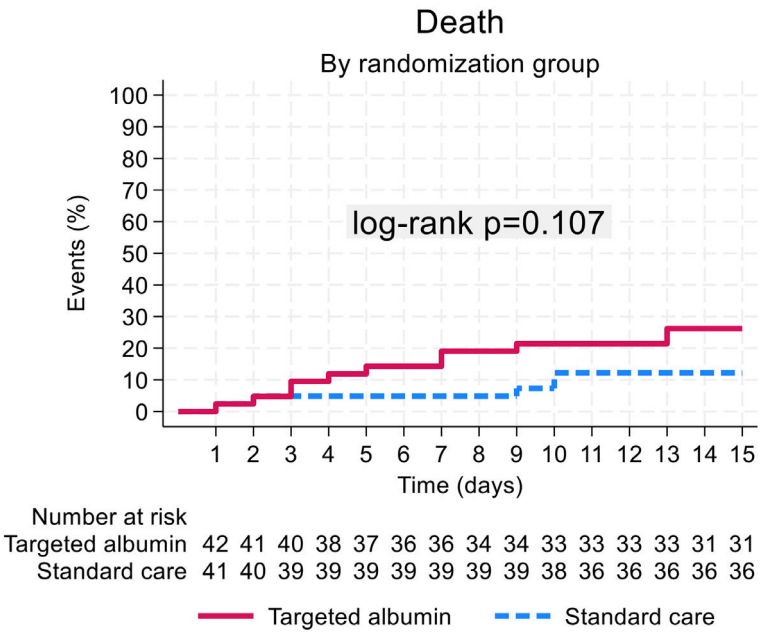
Table 2
Multivariable Cox and competing-risk regression analyses for the composite primary outcome, death, and fluid-related complications during the 15-day treatment period.

	aHR	95 % CI	p-value
Composite primary outcome			
Targeted albumin group	3.74	1.35–10.39	0.011
Baseline MELD	1.07	1.03–1.12	0.001
Targeted albumin group	2.98	1.08–8.25	0.035
ACLF presence, yes	3.98	1.61–9.80	0.003
Death			
Targeted albumin group	2.69	0.92–7.88	0.071
Baseline MELD	1.08	1.03–1.13	0.001
Targeted albumin group	1.98	0.69–5.74	0.207
ACLF presence, yes	4.87	1.76–13.50	0.002
Fluid-related complications			
Targeted albumin group	4.28	0.96–19.18	0.057
Baseline MELD	1.03	0.98–1.08	0.307
Targeted albumin group	4.11	0.90–18.76	0.069
ACLF presence, yes	1.45	0.41–5.15	0.566

Composite primary outcome and death were performed as multivariable Cox regression models and fluid-related complications was performed as a competing risk regression model with death preceding a fluid-related complication as the competing event. Models were adjusted for either baseline MELD or presence of ACLF. aHR: adjusted hazard ratio, CI: confidence interval, MELD: model for end-stage liver disease.

As the indication for terlipressin was not restricted to HRS-AKI, but also included variceal bleed and sepsis-induced hypotension, this study adds important information about the safety of concomitant use of these drugs. Indeed, variceal bleeding was the most common indication for terlipressin. This subgroup of patients was also where we observed the biggest numerical difference in the number of events between the targeted albumin intervention and standard care, although this did not reach statistical significance. As practice guidelines do not recommend use of human albumin as part of fluid resuscitation regimens in patients with cirrhosis and variceal bleed, our findings might be deemed to have limited clinical applicability [10]. However, human albumin use in patients with cirrhosis outside evidence-based indications is common and patients with variceal bleeding frequently develop complications to cirrhosis where albumin is recommended (e.g. spontaneous bacterial peritonitis and renal dysfunction) [2,11] Indeed, in our study the median cumulative amount of albumin administered during hospitalization to patients with variceal bleed was 200 g which is equivalent to 1 L of 20 % human albumin. Importantly, this amount is similar to the guideline recommended dosing for SBP and that given in CONFIRM for patients with HRS-AKI [6,10]. Furthermore, a survey among members of the American Association for the Study of Liver Diseases (AASLD) showed that 9 % would use human albumin in patients with variceal bleeding and 22 % for treating hypoalbuminemia [12]. Though dosing and timing of albumin from the survey was not clear, a retrospective analysis of hospitalized patients with cirrhosis and hyponatremia indeed showed a similar finding where 9 % of patients admitted with variceal bleeding received hypertonic human albumin during admission [13].

(A)



(B)

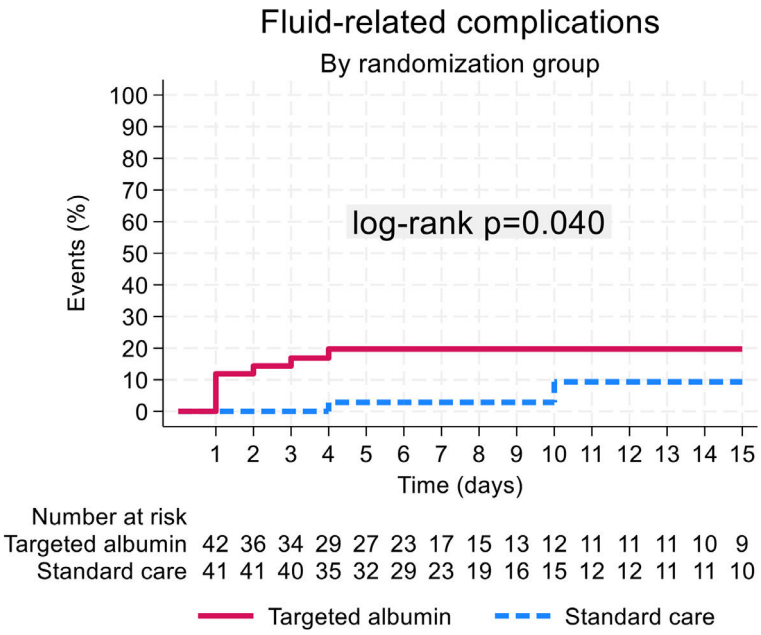


Fig. 3. Separate analyses for components of the composite primary outcome. A) Mortality during 15-day follow-up according to randomization group. In a log-rank test there were no statistical significant difference between the targeted albumin and standard care arm (p = 0.107). B) Development of fluid-related complications (respiratory failure, pulmonary edema and fluid overload) during 15-day follow-up. Incidence of fluid-related complications were statistically significantly higher with targeted albumin compared to standard care (log-rank test: p = 0.040).

Finally, patients with a history of a recent variceal bleed have been excluded from previous albumin trials such as ANSWER [14]. Our study therefore identifies a previously unexplored subgroup where one should exercise caution with the use of albumin.

The fluid overload susceptibility for these patients may be explained by the pharmacodynamics of albumin and terlipressin, together with the hemodynamic changes in patients with decompensated cirrhosis [15]. 20 % human albumin acts as a circulating volume expander by increasing plasma oncotic pressure, while terlipressin is a potent V_1-receptor analogue which causes splanchnic vasoconstriction and increases the effective arterial blood volume [16,17]. Decompensated cirrhosis is characterized by altered hemodynamics and cardiac dysfunction [18] and in patients with cirrhosis, a single bolus dose of terlipressin has been shown to suppress systolic

Table 3
Number of patients with death and/or fluid-related complications within 15 days post-randomization, stratified by terlipressin indication.

	Targeted albumin	Standard care	p-value
Variceal bleeding	7	2	0.064
HRS-AKI	7	4	0.219
Sepsis-induced hypotension	2	1	0.361

HRS-AKI: hepatorenal syndrome-acute kidney injury.

cardiac function [19]. The additive, and maybe even synergistic, effects of combined human albumin and terlipressin may therefore unmask a vulnerable hemodynamic system, in which increased pulmonary hydrostatic pressure cannot be relieved, leading to fluid-related complications [16]. We were unable to explore the contributions from other fluid- and transfusion treatments, such as red blood cell transfusion for patients with variceal bleeding, to the development of fluid-related outcomes since this information was not collected as part of ATTIRE. Nevertheless, most patients were randomized into the trial on the day following admission, and so large systematic differences in fluid resuscitation pre-randomization is unlikely. We found no apparent association between terlipressin dosing and development of the composite of death and fluid-related complications. Neither did we observe a statistically significant effect of targeted albumin on 180-day mortality, which suggests that the potential harmful effects of concomitant targeted albumin and terlipressin are observed only in the immediate period after administration.

In our exploratory analyses of predictors for the composite of death and fluid-related complications, baseline levels of WCC, PCT and TNF-α were all positively correlated associated with the outcome. Notably, all three markers reflect inflammatory processes and could suggest the presence of infection. Infections in patients with cirrhosis are common, especially respiratory tract infections for patients with variceal bleeding [20]. Various studies have shown an association between respiratory tract infections and the development of fluid-related complications with albumin in patients cirrhosis. A trial comparing albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension (ALPS) found pneumonia and 20 % human albumin administration as independent predictors of pulmonary complications [4]. The INFECIR-2 study testing 20 % human albumin to prevent HRS-AKI and death in non-SBP infected patients with cirrhosis found only diabetes mellitus as a predictor for the development of pulmonary edema [21]. Notably, one-third-of patients in the INFECIR-2 had pneumonia at baseline. Unfortunately, we did not collect data on type and site of infections at hospitalization in ATTIRE, and so we could not explore this association any further. Personalized medicine with human albumin may therefore be an important aspect to limit harm and increase treatment efficacy [22].

Besides baseline WCC, we did not identify any routine clinical variables that were associated with the development of the composite primary outcome when treated with targeted albumin infusions. In CONFIRM for patients with HRS-AKI, baseline INR, oxygen saturation and MAP were all associated with the development of respiratory failure in the intervention group [23]. Our contrasting findings may relate to our lower number of events and the severity of disease, where the median MELD was 19 in the current study and 33 in CONFIRM [6].

Our study has a number of strengths. First, our data derives from the largest trial in patients hospitalized with an acute decompensation of cirrhosis. Secondly, we investigated terlipressin use across the clinical indications of variceal bleeding, HRS-AKI and sepsis-induced hypotension. Finally, our primary composite outcome of death and fluid-related complications is highly clinically relevant.

However, there are also limitations. First, this is a post hoc analysis where findings shall be interpreted as exploratory rather than confirmatory. But since our data shows a potential safety risk rather than an efficacy signal, we believe the findings are important for guiding the clinical management of patients receiving terlipressin. All patients from ATTIRE were enrolled between 2016 and 2019 where they were prescribed terlipressin in boluses as part of their routine clinical care. Hence, we do not have the information on the concomitant use of albumin and terlipressin with continuous infusions which appear to have a more favorable safety profile in the HRS-AKI population [24]. The insertion of a transjugular intrahepatic portosystemic shunt (TIPS) is part of the management in patients with variceal bleeding and is currently being tested in a randomized clinical trial for HRS-AKI [25]. As data on TIPS insertion nor fluid treatment regimens were not collected in ATTIRE, we were unable to control for this in our analyses of patients with variceal bleeding. However, current use of TIPS for variceal bleed is very low in the United Kingdom [26].

5. Conclusions

In conclusion, we show that targeted albumin infusions may be associated with a composite of mortality and fluid-related complications in patients with cirrhosis receiving terlipressin. The majority of patients were treated with terlipressin for variceal bleeding and albumin infusions should be used with caution in these patients.

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Data transparency statement

The datasets analyzed during the current study are not publicly available due to data privacy but are available from the corresponding author on reasonable request and subject to approval from the relevant ethical and institutional committees. Any requests for data access will be evaluated on a case-by-case basis to ensure compliance with applicable data protection regulations and ethical standards.

Author contributions

All authors meet the ICMJE criteria for authorship, having each contributed to the conception and design of the study, the acquisition, analysis, or interpretation of data, and the drafting or critical revision of the manuscript; all authors have approved the final version to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT from OpenAI in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of interests

JT has received speaking and/or consulting fees from Versantis, Gore, Boehringer-Ingelheim, Falk, Grifols, Genfit and CSL Behring. AK has served as speaker for Novo Nordisk, Norgine and Siemens and

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2025.101941.

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