ORIGINAL ARTICLE

A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis

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ABSTRACT

BACKGROUND

Infection and increased systemic inflammation cause organ dysfunction and death in patients with decompensated cirrhosis. Preclinical studies provide support for an antiinflammatory role of albumin, but confirmatory large-scale clinical trials are lacking. Whether targeting a serum albumin level of 30 g per liter or greater in these patients with repeated daily infusions of 20% human albumin solution, as compared with standard care, would reduce the incidences of infection, kidney dysfunction, and death is unknown.

METHODS

We conducted a randomized, multicenter, open-label, parallel-group trial involving hospitalized patients with decompensated cirrhosis who had a serum albumin level of less than 30 g per liter at enrollment. Patients were randomly assigned to receive either targeted 20% human albumin solution for up to 14 days or until discharge, whichever came first, or standard care. Treatment commenced within 3 days after admission. The composite primary end point was new infection, kidney dysfunction, or death between days 3 and 15 after the initiation of treatment.

RESULTS

A total of 777 patients underwent randomization, and alcohol was reported to be a cause of cirrhosis in most of these patients. A median total infusion of albumin of 200 g (interquartile range, 140 to 280) per patient was administered to the targeted albumin group (increasing the albumin level to ≥30 g per liter), as compared with a median of 20 g (interquartile range, 0 to 120) per patient administered to the standard-care group (adjusted mean difference, 143 g; 95% confidence interval [CI], 127 to 158.2). The percentage of patients with a primary end-point event did not differ significantly between the targeted albumin group (113 of 380 patients [29.7%]) and the standard-care group (120 of 397 patients [30.2%]) (adjusted odds ratio, 0.98; 95% CI, 0.71 to 1.33; P=0.87). A time-to-event analysis in which data were censored at the time of discharge or at day 15 also showed no significant between-group difference (hazard ratio, 1.04; 95% CI, 0.81 to 1.35). More severe or life-threatening serious adverse events occurred in the albumin group than in the standard-care group.

CONCLUSIONS

In patients hospitalized with decompensated cirrhosis, albumin infusions to increase the albumin level to a target of 30 g per liter or more was not more beneficial than the current standard care in the United Kingdom. (Funded by the Health Innovation Challenge Fund; ATTIRE EudraCT number, 2014-002300-24; ISRCT number, N14174793.)

Liver disease causes 2 million deaths per year worldwide[1] and is the leading cause of death in adults who are 35 to 49 years of age in England, where it accounts for more than 10% of deaths in this age group.[2] Patients with decompensated cirrhosis are highly susceptible to infections leading to kidney failure and death,[3,4] and the risk of infection-related death is increasing among inpatients with cirrhosis in the United States.[5] Furthermore, increased systemic inflammation in patients with cirrhosis contributes to kidney failure and death.[6]

Albumin infusions were first used in patients with cirrhosis more than 70 years ago,[7] and they remain ubiquitously prescribed to restore normovolemia in patients with peripheral arterial vasodilation.[8] International guidelines recommend the use of human albumin solution after large-volume paracentesis in patients with spontaneous bacterial peritonitis and hepatorenal syndrome.[9,10] Infusions have been investigated for hepatic encephalopathy, nonspontaneous bacterial peritonitis infections, hyponatremia, and ascites.[11-13]

Preclinical studies have shown an antiinflammatory effect of albumin in patients with cirrhosis[14-17]; this finding suggests that infusions of albumin might limit systemic inflammation, prevent infections, reduce the risk of kidney dysfunction, and increase survival. A low serum albumin level has been associated with an increased risk of death among hospitalized patients who have cirrhosis and infections,[18] and albumin infusions that increased serum levels to more than 30 g per liter have reduced systemic inflammation among patients with decompensated cirrhosis[17] and have reduced the incidence of nosocomial infection among patients with cirrhosis who were hospitalized with nonspontaneous bacterial peritonitis infections.[19]

However, clinical trials of albumin have shown conflicting results.[20,21] A trial of albumin in patients with spontaneous bacterial peritonitis showed a benefit,[20] but a trial involving patients with other infections did not,[21] and the latter trial was terminated because of lethal pulmonary edema associated with albumin. No fluid was administered as standard care in these trials. A recent meta-analysis did not show that any interventions in patients with the hepatorenal syndrome reduced the incidence of death from any cause,[22] and another recent meta-analysis did not show differences between albumin and other plasma expanders with respect to the incidence of death after large-volume paracentesis.[23]

In a randomized trial involving outpatients with ascites, weekly albumin infusions reduced the incidences of infection and kidney dysfunction and were associated with a lower probability of death than standard care.[24] In contrast, there was no effect in a smaller trial in which albumin was administered less frequently than weekly.[25] Large trials to address the usefulness of albumin in preventing infection, kidney dysfunction, and death in hospitalized patients are lacking. We conducted the ATTIRE (Albumin to Prevent Infection in Chronic Liver Failure) trial to evaluate whether targeting an increase in the serum albumin level to 30 g per liter or more with the use of repeated daily infusions of 20% human albumin solution, as compared with standard care, would reduce the incidences of infection, kidney dysfunction, and death among hospitalized patients with decompensated cirrhosis.

A Quick Take is available at NEJM.org

Methods

Trial Design

The ATTIRE trial was a prospective, interventional, multicenter, randomized, open-label trial involving hospitalized patients with decompensated cirrhosis, acute complications, and an albumin level below 30 g per liter. Our trial management group designed the trial,[26] which was approved by the London–Brent Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency.

Written informed consent was obtained from the patients. For incapacitated patients, a legal representative provided written informed consent until the patient regained capacity. The trial was conducted and reported according to the protocol (available with the full text of this article at NEJM.org). An independent data and safety monitoring committee, whose members were aware of the trial-group assignments, oversaw the conduct of the trial.

The statisticians who analyzed the data are trial authors. The last author wrote the first draft of the manuscript, with contributions from the other authors; all the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

PATIENTS

Evaluated patients were 18 years of age or older, were hospitalized with a clinical diagnosis of acute complications of decompensated cirrhosis, had a serum albumin level of less than 30 g per liter within 72 hours after hospital admission (since early therapy was more likely to be beneficial than later therapy), and had an anticipated length of hospital stay of 5 days or longer at randomization. The investigators used clinical judgment to avoid recruitment of patients for whom only brief hospitalization was warranted and for whom expected short-term survival was good.[27] Patients who were hospitalized with community-onset infection were eligible because they had a high incidence of nosocomial infection.[18] Recruitment occurred between January 15, 2016, and June 28, 2019, at 35 hospitals across England, Scotland, and Wales.

Key exclusion criteria were advanced hepatocellular carcinoma associated with a life expectancy of less than 8 weeks and the receipt of palliative care. Details are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION

Patients were enrolled and randomly assigned to trial groups with the use of a Web-based system (Sealed Envelope). Randomization was performed with a minimization biased coin algorithm that balanced treatment assignments according to center, Model for End-Stage Liver Disease (MELD) score, the number of organ dysfunctions, use or nonuse of antibiotic agents, and serum albumin level (all the patients had an albumin level <30 g per liter at trial commencement).

In the original protocol, subsequent randomizations were permitted more than 30 days after completion of trial treatment, to account for the 21-day half-life of albumin.[25] However, since the trial was not blinded, potential bias may have been introduced because knowledge of the original treatment could have influenced a patient's decision to participate again, and only survivors could do so. Therefore, data on patients who underwent the initial randomization are presented here, and analyses that included data on patients who underwent a subsequent randomization or randomizations are reported in the Additional Statistical Analyses section of the Supplementary Appendix.

INTERVENTION

We previously found that an albumin level of less than 30 g per liter was predictive of immune dysfunction in patients with cirrhosis,[15] and we selected this threshold for our trial. In a previous trial of albumin infusion in patients with sepsis,[28] the targeted albumin level of 30 g per liter or more was not achieved, so we targeted 35 g per liter or more to ensure that 30 g per liter or more would be reached. Patients with a serum albumin level of less than 30 g per liter were assigned to receive either daily 20% human albumin solution (infused at a rate of 100 ml per hour) from day 1 of recruitment, with the aim to maintain an albumin level of 35 g per liter or more, or standard medical care.[26] Infusions in the albumin group continued for a maximum of 14 days after randomization or until discharge (if discharge occurred before 14 days) or until the patient was deemed to be medically fit for discharge if continued hospitalization was warranted for nonmedical reasons such as the arrangement of in-home support (if this determination was made before 14 days). Albumin infusions ended at the time of discharge or when the patient was deemed to be fit for discharge (if this occurred before 14 days). Data were collected until day 15 after randomization, at discharge, or when the patient was deemed to be medically fit for discharge (if this occurred before 15 days) (Fig. S1).

The volume of human albumin solution was determined according to the patient's serum albumin level (or the closest measurement) on the day of administration (see Table S2), and protocol effectiveness was verified in our feasibility study.[27] Infusions in the albumin group continued throughout the trial treatment period, even when patients had a qualifying nonfatal primary event. Clinicians could prescribe differing regimens for patients with large-volume paracentesis, spontaneous bacterial peritonitis, or hepatorenal syndrome, according to guidelines[9]; however, in the albumin group, 20% human albumin solution had to be infused if the patient's serum albumin level was less than 35 g per liter, unless there were safety concerns. Deviations from this plan were recorded in case-report forms.

Since 20% human albumin solution is recommended for patients with large-volume paracentesis, spontaneous bacterial peritonitis, or hepatorenal syndrome,[9,10] it would have been unethical

to withhold its use in patients in the standard-care group who had these conditions. Accordingly, albumin use was permitted for these patients, and the clinicians were responsible for dosing. Administration of albumin infusions for other indications in the standard-care group was considered to be a protocol deviation and was monitored by the independent data and safety monitoring committee. Attending clinicians made all other treatment decisions.

END POINTS

The primary end point was a composite[29] of infection from any cause, kidney dysfunction, or death in hospitalized patients between trial day 3 and day 15, the date of discharge (if before day 15), or the date on which the patient was assessed to be medically fit for discharge (if before day 15). Patients were assessed daily until discharge, death, or the determination that they were medically fit for discharge. Data on infection or kidney dysfunction were not collected after discharge or when the patient was deemed to be fit for discharge. Mortality data were collected after discharge, but only deaths that occurred before the date of discharge or day 15 (whichever was earlier) were included in the evaluation of the primary end point. Deaths between days 3 and 15 in discharged patients were included in the analyses of death at 28 days to 6 months.

Our feasibility study showed that in most patients who received albumin, a serum albumin level of 30 g per liter or more was reached within 3 days,[27] and we reasoned that the assessment of outcomes beginning on day 3 would permit establishment of any biologic effect of albumin. Furthermore, although all the patients who underwent randomization received albumin or standard care on the day of randomization, some died very quickly after admission and were deemed to have been unlikely to benefit from albumin if they had survived. We viewed events that occurred on day 1 or 2 as being unlikely to be related to albumin, and we prospectively excluded these events from the assessment of the primary end point in order to avoid a chance that the between-group difference would affect the trial results.

The diagnosis of infection in patients with cirrhosis can be challenging, with a high incidence of negative cultures.[30] Therefore, we defined infection according to the diagnosis of the attending clinician; such a diagnosis triggered the recording of supportive information for blinded validation by a physician panel.

In the definition of the primary end point, organ dysfunction was changed to solely kidney dysfunction in 2018, after our feasibility study.[27] There was no operational effect, with data collection unchanged, and the analyses followed the database closure in 2019.[26] Kidney dysfunction was defined as a serum creatinine level that was at least 50% higher than the level at randomization, an increase in the serum creatinine level of 0.3 mg per deciliter or more within 48 hours, or the initiation of renal-replacement therapy. Patients who received renal-replacement therapy at baseline could not have this end-point event.

The secondary end points were death at 28 days, 3 months, and 6 months; the composite primary end-point components; the total amount of albumin administered during the trial; the duration of hospital stay; the number of days in the intensive care unit; the incidence of other organ dysfunctions (definitions are provided in Table S3); the incidence of liver transplantation within 6 months after the beginning of the trial; the MELD score at the end of trial; the use of terlipressin for kidney dysfunction, hypotension, or variceal bleeding; and serious adverse events. An analysis of quality of life and a health economic analysis are under way.

STATISTICAL ANALYSIS

We estimated the incidence of a composite primary end-point event to be 30%, given the 20 to 30% incidence of nosocomial infection among patients with cirrhosis and the fact that 30% of these infections cause organ dysfunction.[31,32] We assumed that the targeted albumin level would reduce the incidence of infection by 30%, as in previous studies,[19-21,33-35] and we calculated that 389 patients per group would provide 80% power to detect this between-group difference at a significance level of 0.05. Assuming a 10% loss to follow-up or withdrawal, we estimated a target sample of 433 patients per group; however, because the number of patients who were lost to follow-up or withdrew was lower than expected, we completed enrollment after 828 patients had undergone randomization.

The analysis of the primary end point was performed with a mixed-effects logistic-regression

model that included a binary treatment indicator, stratification variables as fixed effects, and a random intercept for each site. We also performed a time-to-event analysis, with patient data censored at hospital discharge, the day on which the patient was deemed to be fit for discharge, or trial day 15, whichever was earlier. All the patients who underwent randomization were included in the intention-to-treat analyses, but events that occurred on day 1 or 2 (75 events in the albumin group and 94 in the standard-care group) were not classified as primary end-point events, which were prespecified for days 3 through 15. Patients with infection, kidney dysfunction, or both on day 1 or 2 and who also had any component of the primary end point between days 3 and 15 were classified as having a primary end-point event. Supportive analyses included extension of the end-point windows to days 1 through 15 and days 2 through 15.

The secondary end points were the effects of treatment on the individual components of the primary end point.[29] For the secondary end points, point estimates and 95% confidence intervals are reported; these confidence intervals are not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

Over 3 years, 9273 patients were screened and 1563 were considered to be eligible for the trial. A total of 829 patients underwent randomization (although 1 of these patients withdrew consent very early in the trial), of whom 51 underwent a subsequent randomization or randomizations, leaving 777 unique patients who had undergone randomization at least once and who had data that could be evaluated (see Fig. S2). Most of the patients had alcohol-related liver disease, and the groups were matched at baseline (Table 1); 203 of 770 patients (26.4%) were treated for alcohol withdrawal, and 191 of 768 patients (24.9%) were considered to have alcoholic hepatitis. On average, the patients were recruited on the day after hospital admission and had a mean (±SD) albumin level of 23.2±3.7 g per liter. The median number of days of hospitalization during the trial treatment period (planned for ≤14 days) was 8 days (interquartile range, 6 to 15) in the albumin group and 9 (interquartile range, 6 to 15) in the standard-care group, with no significant difference between the two trial groups (Table S8). A total of 40 patients in the albumin group and 47 in the standard-care group were discharged within 5 days after randomization. The minimum duration of follow-up for death was 3 months, and the maximum duration was 6 months after randomization.

With respect to the composite primary end point, the only missing data were for 54 patients whose treatment had been discontinued (35 in the albumin group and 19 in the standard-care group). A threshold analysis that included these missing data ruled out the benefit of albumin therapy (see the Additional Statistical Analyses section in the Supplementary Appendix).

ALBUMIN THERAPY

Throughout the trial, a median of 200 g (interquartile range, 140 to 280) of albumin per patient was administered in the albumin group, as compared with 20 g (interquartile range, 0 to 120) administered in the standard-care group (adjusted mean difference, 143 g; 95% confidence interval [CI], 127 to 158.2). A total of 196 of 397 patients (49.4%) in the standard-care group did not receive any albumin. The daily mean amounts of albumin infused differed substantially between the albumin group and the standard-care group throughout the trial treatment period (Fig. 1A), and the mean albumin level was 30 g per liter or more between days 3 and 15 in the albumin group (Fig. 1B).

PRIMARY END POINT

In the intention-to-treat analysis, a total of 113 of 380 patients (29.7%) in the albumin group and 120 of 397 patients (30.2%) in the standard-care group had a protocol-defined composite primary end-point event (adjusted odds ratio, 0.98; 95% CI, 0.71 to 1.33; P=0.87). When all the reported deaths were included with confirmed dates of death, 116 of 380 patients (30.5%) in the albumin group and 119 of 397 (30.0%) in the standard-care group had a primary end-point event (odds ratio, 1.02; 95% CI, 0.75 to 1.40). The three additional events in the albumin group correspond to patients who died during the qualifying period (days 3 through 15 in the hospital); these deaths were identified by outcome

Table 1. Characteristics of the Patients at Baseline.*

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)
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)

* Plus–minus values are means ±SD. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4. Fio_2 denotes fraction of inspired oxygen, IQR interquartile range, and Spo_2 peripheral-blood oxygen saturation.

† The cause of cirrhosis and reason for admission were reported by the patient or obtained from the clinical notes. Patients could have more than one cause of cirrhosis (e.g., hepatitis C and alcohol-related liver disease) or reason for admission. The three most common causes of cirrhosis and the three most common reasons for admission for decompensated cirrhosis are listed.

‡ Model for End-Stage Liver Disease (MELD) scores range from 9 to 40, with higher scores indicating a higher risk of death at 3 months (www://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/).

verification. The one fewer primary end-point event in the standard-care group was a death that was verified to be outside the primary event window. A time-to-event analysis also showed no significant difference between the groups (hazard ratio for infection, kidney dysfunction, or

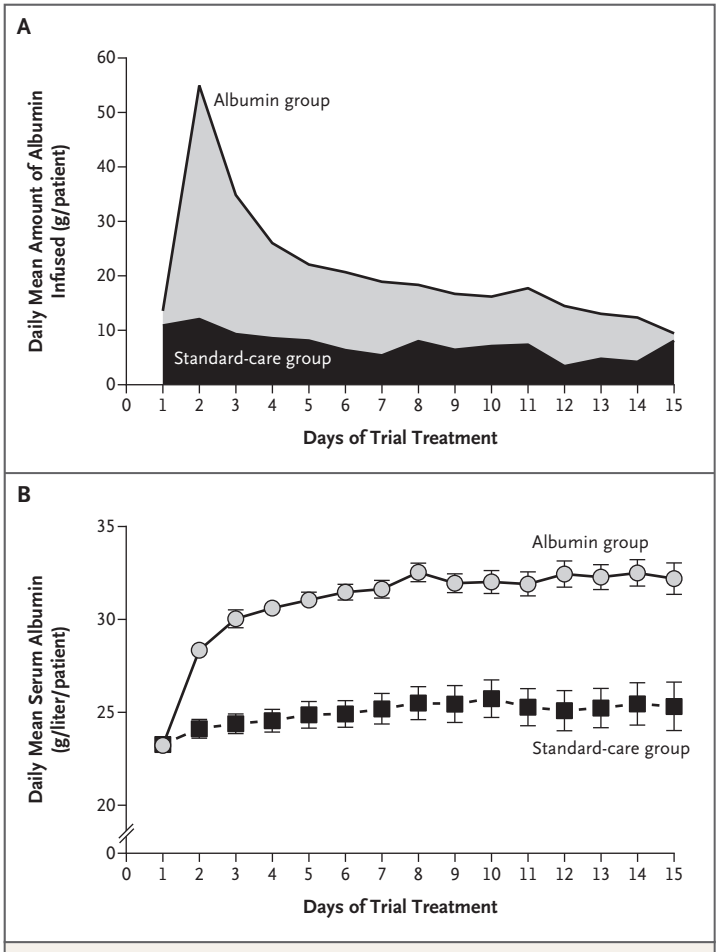

Figure 1. Serum Albumin Infused and Daily Serum Albumin Levels.

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.

death, 1.04; 95% CI, 0.81 to 1.35). Four patients in the albumin group and 6 in the standard-care group died between discharge and day 15, and these deaths were not included as primary composite end-point events but were included in the analyses of death at 28 days and 6 months.

Supportive analyses in which the reporting window was extended to day 1 or 2 showed no significant between-group differences in primary end-point events (see Table S5). Prespecified subgroup analyses did not show evidence of significant differences in primary end-point events according to the baseline MELD score, serum albumin level, use or nonuse of antibiotics, number of organ dysfunctions, reasons for admission, coexisting conditions, and age (see Fig. S4 and Table S6). Figure S4 shows a possible difference according to sex, but confidence intervals crossed 1 for both men and women.

Analyses that included patients who underwent a subsequent randomization or randomizations showed no significant differences between the groups (see Table S7). In an analysis in which the components of the primary end point were examined separately, there was no evidence of a significant between-group difference. New infections occurred in 79 of 380 patients (20.8%) in the albumin group and in 71 of 397 (17.9%) in the standard-care group (adjusted odds ratio, 1.22; 95% CI, 0.85 to 1.75). Infection case-report forms revealed no bias in reporting of infections in the two groups.

Kidney dysfunction occurred in 40 of 380 patients (10.5%) the albumin group and 57 of 397 (14.4%) in the standard-care group (adjusted odds ratio, 0.68; 95% CI, 0.44 to 1.11). Death occurred in 30 of 380 patients (7.9%) in the albumin group and 33 of 397 (8.3%) in the standard-care group (odds ratio, 0.95; 95% CI, 0.56 to 1.59) (Table 2).

SECONDARY END POINTS

There were no significant differences between the groups with respect to death and time to death (see Fig. S3). At 28 days, 53 of 380 patients (14.0%) in the albumin group and 62 of 397 patients (15.6%) in the standard-care group had died (adjusted odds ratio, 0.86; 95% CI, 0.57 to 1.30); at 3 months, 92 patients (24.2%) and 93 patients (23.4%), respectively, had died (adjusted odds ratio, 1.05; 95% CI, 0.74 to 1.48); and at 6 months, 132 patients (34.7%) and 119 patients (30.0%), respectively, had died (adjusted odds ratio, 1.27; 95% CI, 0.93 to 1.73).

There was no evidence of significant between-group differences during treatment with respect to the development of new respiratory, cardiovascular, or cerebral dysfunction or the use of terlipressin. Also, there was no significant between-group difference in the duration of hospitalizations. According to the interquartile range, there may have been more days in the intensive care unit in the albumin group than in the standard-care group, but this number of days was extremely small overall.

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.

ADVERSE EVENTS

There were 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). Additional details are provided in Tables S9 and S10.

DISCUSSION

ATTIRE, a multicenter trial to assess the efficacy of albumin to prevent infection, kidney dysfunction, or death in patients with decompensated cirrhosis, did not show a benefit of targeted albumin therapy over the current standard care in the United Kingdom. There was no effect on the incidence of infection, as shown by no significant between-group differences in the incidence of new infection or end-point events in patients who were admitted with infection or who were receiving antibiotics at enrollment. Despite the targeted regimen to increase the serum albumin level to 30 per liter or more, there were no apparent benefits of the intervention with respect to the primary end point in any of the subgroups analyzed. Finally, there were no significant between-group differences in the incidence of death at 28 days, 3 months, and 6 months.

A limitation of this trial was that it was not blinded. We chose not to use blinding because patients in the standard-care group who were receiving "nonalbumin" fluid may not have had increases in the serum albumin level to a set target level and may have received harmful volumes of fluid in a futile attempt to increase the albumin level, and routine albumin testing would have unblinded the trial. However, patients received substantially different amounts of 20% human albumin solution, especially during the early part of the trial when an increased albumin level might have been expected to have benefit.[33] The median amount of albumin infused in the standard-care group was lower than anticipated, so the between-group differences in the amounts of albumin infused were greater than expected; nevertheless, targeted albumin infusions had no effect on the outcome.

We conclude that targeted albumin therapy had no clinically important effect on preventing infections or reducing the development of kidney dysfunction in hospitalized patients with decompensated cirrhosis. This finding contrasts with those in our laboratory studies,[36] and this difference underscores the importance of appropriately powered confirmatory clinical trials. The infusion of greater quantities of albumin probably would have been unsafe and would have led to more severe or life-threatening serious adverse events in the albumin group.

Although the components of the composite end point were not equivalent in severity, they represent a common disease trajectory and move in line with each other. The use of a composite end point improved statistical efficiency,[29] and a consistent null effect was observed in all compo-

Table 3. Serious Adverse Events.*

Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
		number of events	
Serious adverse event			
Grade 3: severe event	28	11	39
Grade 4: life-threatening event	17	13	30
Grade 5: death	42	48	90
All events	87	72	159
Individual serious adverse events occurring in >1 patient†			
Anemia	1	1	2
Esophageal varices hemorrhage	5	6	11
Gastric hemorrhage	5	4	9
Multiorgan failure	23	31	54
Other infections and infestations: spontaneous bacterial peritonitis	0	5	5
Lung infection	15	8	23
Sepsis	4	3	7
Encephalopathy	4	1	5
Acute kidney injury	2	0	2
Adult respiratory distress syndrome	0	2	2
Hypoxia	1	1	2
Pleural effusion	1	1	2
Pulmonary edema	15	4	19
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

* Patients may have had more than one clinical diagnosis per serious adverse event. A serious adverse event was any new adverse event that was a life-threatening event or resulted in prolongation of an existing hospitalization.
† Serious adverse events are categorized with a single primary event name (graded by two assessors) according to the Common Terminology Criteria for Adverse Events, version 5.0 (2017).
‡ Serious adverse events were labeled by the investigators as involving a primary event but could have involved other contributing events.

nents. We confirmed the severe effect of alcohol-related liver cirrhosis in the United Kingdom, as previously shown in the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial,[37] and results may differ for other causes of cirrhosis.

Our trial did not show a benefit of albumin therapy when used to increase and maintain the serum albumin level to 30 g per liter or more in hospitalized patients with cirrhosis. Given a near tripled difference in the amount of albumin infused between the groups and an absence of benefit across all subgroups and end points examined, these data support the need for a reevaluation of the use of albumin in patients with cirrhosis.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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