ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

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ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

During the first 7 days, patients in the albumin group, as compared with those in the crystalloid group, had a higher mean arterial pressure ($P=0.03$) and lower net fluid balance ($P<0.001$). The total daily amount of administered fluid did not differ significantly between the two groups ($P=0.10$). At 28 days, 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; $P=0.94$). At 90 days, 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; $P=0.29$). No significant differences in other secondary outcomes were observed between the two groups.

CONCLUSIONS

In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days. (Funded by the Italian Medicines Agency; ALBIOS ClinicalTrials.gov number, NCT00707122.)

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For decades, human albumin has been administered to patients to provide adequate oncotic pressure and intravascular volume.[1] In 1998, however, a report from the Cochrane Injuries Group Albumin Reviewers indicated that the administration of albumin may be potentially harmful in critically ill patients, as compared with the administration of crystalloid solutions.[2] Subsequent meta-analyses reported contradictory findings.[3,4]

To clarify this issue, a large, double-blind, randomized trial (the Saline versus Albumin Fluid Evaluation [SAFE] study)[5] was conducted, in which 4% albumin solution was compared with normal saline as fluid replacement in critically ill patients, with results indicating that albumin administration was safe. A predefined subgroup analysis showed that patients with severe sepsis receiving albumin were at a lower, although not significantly lower, risk for death than those receiving normal saline. In addition, a subsequent study pointed out a potential benefit of maintaining serum albumin at a level of more than 30 g per liter in critically ill patients.[6]

There is a convincing rationale for the potential advantages of albumin administration during severe sepsis.[7] Albumin is the main protein responsible for plasma colloid osmotic pressure[8]; it acts as a carrier for several endogenous and exogenous compounds,[9] with antioxidant and anti-inflammatory properties, and as a scavenger of reactive oxygen[10,11] and nitrogen[12] species and operates as a buffer molecule for acid–base equilibrium.[13] We therefore conducted a randomized, controlled trial to investigate the effects of the administration of albumin and crystalloids, as compared with crystalloids alone, targeting a serum albumin level of 30 g per liter or more in a population of patients with severe sepsis.

METHODS

STUDY OVERSIGHT AND DESIGN

We conducted the Albumin Italian Outcome Sepsis (ALBIOS) study — an investigator-initiated, multicenter, open-label, randomized, controlled trial — in 100 intensive care units (ICUs) in Italy. The members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study, were responsible for its execution and for the data analysis, made the decision to submit the manuscript for publication, and assume responsibility for the fidelity of the study to the protocol (available at NEJM.org).

The trial was funded by the Italian Medicines Agency, which had no role in the conduct of the study, the reporting of the data, or the supply of

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Albumin Group (N=903)	Crystalloid Group (N=907)
Age — yr		
Median	70	69
Interquartile range	57–77	59–77
Female sex — no. (%)	360 (39.9)	357 (39.4)
Body-mass index†	27±6	27±6
Reason for ICU admission — no. (%)		
Medical	511 (56.6)	518 (57.1)
Elective surgery	69 (7.6)	58 (6.4)
Emergency surgery	323 (35.8)	331 (36.5)
Preexisting condition — no. (%)‡		
Liver disease	13 (1.4)	14 (1.5)
COPD	113 (12.5)	108 (11.9)
Chronic renal failure	44 (4.9)	32 (3.5)
Immunodeficiency	115 (12.7)	128 (14.1)
Congestive or ischemic heart disease	149 (16.5)	165 (18.2)
SAPS II score§		
Median	48	48
Interquartile range	37–59	37–60

Table 1. (Continued.)

Characteristic	Albumin Group (N=903)	Crystalloid Group (N=907)
Physiological variable¶		
Heart rate — beats/min	105±22	106±20
Mean arterial pressure — mm Hg	74±16	73±15
Central venous pressure — mm Hg	10.0±4.9	9.8±4.7
Urine output — ml/hr		
Median	50	50
Interquartile range	20–100	25–100
Lactate — mmol/liter		
Median	2.3	2.5
Interquartile range	1.4–4.2	1.6–4.3
Serum albumin — g/liter	24.1±6.3	24.2±6.2
Hemoglobin — g/dl	10.9±2.1	11.0±2.0
Central venous oxygen saturation — %		
Median	73	73
Interquartile range	65–79	68–80
SOFA score‖		
Median	8	8
Interquartile range	6–10	5–10
Organ dysfunction — no. (%)**		
1 organ	188 (20.8)	208 (22.9)
2 organs	361 (40.0)	303 (33.4)
3 organs	236 (26.1)	248 (27.3)
4 organs	89 (9.9)	115 (12.7)
5 organs	29 (3.2)	33 (3.6)
Shock — no. (%)††	565 (62.6)	570 (62.8)
Mechanical ventilation — no. (%)	709 (78.5)	737 (81.3)
Fluid administration in previous 24 hr — no. (%)		
Albumin	153 (16.9)	176 (19.4)
Synthetic colloids	452 (50.1)	479 (52.8)

* Plus–minus values are means ±SD. There were no significant differences between the two groups except with respect to central venous oxygen saturation (P=0.02) and number of patients with organ dysfunction (P=0.04). COPD denotes chronic obstructive pulmonary disease, and ICU intensive care unit.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Among preexisting conditions, liver disease was defined as the presence of cirrhosis, portal hypertension, or previous episodes of liver insufficiency; immunodeficiency as the concurrent presence of immunosuppressive diseases or receipt of immunosuppressive therapies; and congestive or ischemic heart disease as New York Heart Association class II.

§ The Simplified Acute Physiology Score (SAPS II)[16] was used to assess the severity of systemic illness at baseline. Scores range from 0 to 163, with higher scores indicating more severe illness.

¶ Data on central venous pressure were available for 841 patients in the albumin group and 858 in the crystalloid group; data on lactate level, for 874 and 867, respectively; data on serum albumin level, for 821 and 813, respectively; data on hemoglobin level, for 893 and 894, respectively; and data on central venous oxygen saturation, for 798 and 802, respectively.

‖ The Sequential Organ Failure Assessment (SOFA) score[17] includes subscores ranging from 0 to 4 for each of five components (respiratory, coagulation, liver, cardiovascular, and renal components), with higher scores indicating more severe organ dysfunction. The scoring was modified by excluding the assessment of cerebral failure (the Glasgow Coma Scale), which was not performed in these patients, and by decreasing to 65 mm Hg the mean arterial pressure threshold for a cardiovascular subscore of 1, for consistency with the hemodynamic targets as defined according to the early goal-directed therapy.[15]

** Organ dysfunctions were defined as a SOFA score of 2 or more on the respiratory component; 2 or more on the coagulation component; 2 or more on the liver component; 1, 3, or 4 on the cardiovascular component; and 2 or more on the renal component.[5] A score of 2 on the cardiovascular component was not included because that score is assigned for the use of vasopressor drugs at low doses (a condition not considered to be strictly related to cardiovascular dysfunction).

†† Shock at the time of randomization was defined as a score of 3 or 4 on the cardiovascular component of the SOFA.[5]

study fluids. Albumin administered during the study was provided by each participating institution as part of the clinical treatment of critically ill patients. The study protocol and the informed-consent process were approved by the ethics committee at each participating institution. Written informed consent or deferred consent was obtained from each patient.

Randomization was performed centrally, with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to the participating ICU and the interval between the time that the patient met the clinical criteria for severe sepsis and randomization. The conduct of the trial was overseen by the data and safety monitoring board, which performed an interim analysis after the enrollment of 700 patients.

PATIENTS

Patients 18 years of age or older who met the clinical criteria for severe sepsis[14] within the previous 24 hours at any time during their stay in the ICU were enrolled in the study after being screened for eligibility criteria. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

STUDY TREATMENTS

Patients were randomly assigned to receive either 20% albumin and crystalloid solution (albumin group) or crystalloid solution alone (crystalloid group) from randomization until day 28 or discharge from the ICU, whichever came first. During the early phase of volume resuscitation, fluids were administered in both groups according to early goal-directed therapy.[15]

After randomization, patients in the albumin group received 300 ml of 20% albumin solution. From day 1 until day 28 or ICU discharge (whichever came first), 20% albumin was administered on a daily basis, to maintain a serum albumin level of 30 g per liter or more. In both groups, crystalloids were administered whenever it was clinically indicated by the attending physician. The administration of synthetic colloids was not allowed. All other treatments were at the discretion of the attending physician.

OUTCOMES

The primary outcome measure was death from any cause at 28 days after randomization. The principal secondary outcome measure was death from any cause at 90 days after randomization. Additional secondary outcomes were the number of patients with organ dysfunction and the degree of dysfunction and the length of stay in the ICU and the hospital. The severity of systemic illness was assessed with the use of the Simplified Acute Physiology Score, with scores ranging from 0 to 163 and higher scores indicating more severe illness.[16] Organ function was assessed daily with the use of the Sequential Organ Failure Assessment (SOFA) score,[17] which ranges from 0 to 4 for each of five components (respiratory, coagulation, liver, cardiovascular, and renal components), with higher scores indicating more severe organ dysfunction (Table S1 in the Supplementary Appendix). New organ failures were defined as a change in a component score during the study from a baseline score of 0, 1, or 2 to a score of 3 or 4.[5,18,19] Tertiary outcomes, which were assessed in post hoc analyses, included the use of renal-replacement therapy, the incidence of acute kidney injury, the duration of mechanical ventilation, and the time to suspension of the administration of vasopressor or inotropic agents.

STATISTICAL ANALYSIS

We originally determined that a sample of 1350 patients would provide the study with 80% power to detect an absolute between-group difference of 7.5 percentage points in mortality at 28 days, on the basis of an estimated baseline mortality of 45%, with a two-sided P value of less than 0.05 indicating statistical significance. The study protocol specified the possibility of increasing the sample to 1800 patients on the basis of a recommendation by the data and safety monitoring board during an interim analysis.

All the analyses were conducted on an intention-to-treat basis. Binary outcomes were compared with the use of the chi-square test, and continuous outcomes with the use of the Wilcoxon rank-sum test. Comparisons of fluid volumes and physiological data over time were performed with the use of a two-factor analysis of variance for repeated measurements. We calculated survival estimates according to the Kaplan–Meier method and compared them using a log-rank test. We performed an adjusted analysis using robust Poisson regression for binary outcomes. In a post hoc analysis, the primary and principal

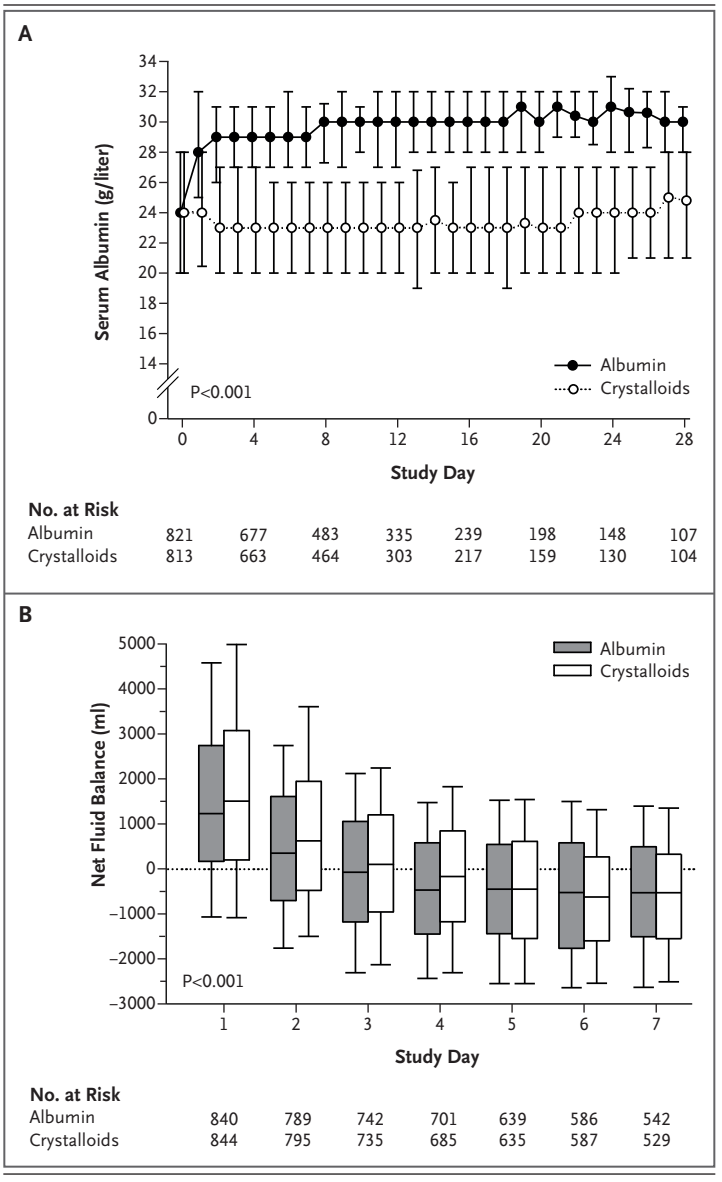


Figure 1. Serum Albumin Levels through Day 28 and Net Fluid Balance through Day 7.

Panel A shows the serum albumin concentration through day 28 in patients receiving albumin and crystalloids or crystalloids alone. Day 0 was defined as the time of randomization. Data are medians, with I bars indicating interquartile ranges. The P value is for the between-group comparison performed with the use of a two-factor analysis of variance for repeated measurements to test time (29 days for serum albumin, including day 0) and group effects. Panel B shows the net fluid balance through day 7 for patients receiving albumin and crystalloids or crystalloids alone. The daily net fluid balance was calculated as the difference between the total amount of administered fluid (including 20% albumin; crystalloids; other blood products, such as packed red cells, fresh-frozen plasma, or platelets; and other fluids) and the total amount of excreted fluid each day (including urinary output and other fluid losses, such as fluids potentially removed with continuous renal-replacement therapy, fluids lost as feces, aspirated gastric content, drainage fluids, and insensible perspiration). For day 1, the net fluid balance was computed from the time of randomization to day 1, which averaged 16 hours in the two study groups. The horizontal line in the boxes indicates the median, the top and bottom of the box the interquartile range, and I bars the 5th and 95th percentile range. The P value is for the between-group comparison performed with the use of the two-factor analysis of variance for repeated measurements to test time (7 days) and group effects.

secondary outcomes were assessed in patients who had septic shock and those who did not have septic shock at the time of enrollment. Heterogeneity of treatment effects among subgroups was assessed with the use of the test for a common relative risk. SAS software, version 9.2 (SAS Institute), was used for all the analyses.

RESULTS

STUDY POPULATION

From August 2008 through February 2012, a total of 1818 patients with severe sepsis were randomly assigned to receive 20% albumin and crystalloid solution (910 patients) or crystalloid solution alone (908) for fluid replacement. Per protocol, patient enrollment was stratified according to the interval between the time the patient met the clinical criteria for severe sepsis and randomization: 6 hours or less (579 patients [31.8%]) versus more than 6 hours (1239 [68.2%]). A total of 8 patients were excluded from the analysis (2 patients in the albumin group owing to withdrawal of consent, and 5 in the albumin group and 1 in the crystalloid group owing to a randomization error) (Fig. S1 in the Supplementary Appendix).

After follow-up, data regarding death at 90 days were available for 888 of 903 patients (98.3%) in the albumin group and for 893 of 907 (98.5%) in the crystalloid group. Baseline characteristics were similar between the two study groups, except for a slight imbalance in the number of patients with organ dysfunction and values of central venous oxygen saturation (Table 1). The primary site of

infection, the type of identified microorganism, and the proportion of patients receiving antibiotics were similar in the two groups (Table S2 in the Supplementary Appendix).

FLUID THERAPY AND TREATMENT EFFECTS

During the first 7 days, the albumin group, as compared with the crystalloid group, received a significantly larger volume of 20% albumin solution (P<0.001) and less crystalloid solution (P<0.001). In the albumin group, the administration of 20% albumin solution accounted for a median daily average of 4.3% (interquartile range, 2.9 to 5.8) of the total administered fluids. The total daily amount of administered fluids in the first 7 days did not differ significantly between the albumin group and the crystalloid group (3738 ml [interquartile range, 3174 to 4437] and 3825 ml [interquartile range, 3205 to 4533], respectively; P=0.10) (Table S3 in the Supplementary Appendix).

The serum albumin level was significantly

Table 2. Outcomes.

Outcome	Albumin Group	Crystalloid Group	Relative Risk (95% CI)	P Value
Primary outcome: death at 28 days — no./total no. (%)	285/895 (31.8)	288/900 (32.0)	1.00 (0.87–1.14)	0.94
Secondary outcomes				
Death at 90 days — no./total no. (%)	365/888 (41.1)	389/893 (43.6)	0.94 (0.85–1.05)	0.29
New organ failures — no./total no. (%)*				0.99
None	372/836 (44.5)	383/841 (45.5)		
1 organ	283/836 (33.9)	287/841 (34.1)		
2 organs	130/836 (15.6)	123/841 (14.6)		
3 organs	40/836 (4.8)	36/841 (4.3)		
4 organs	10/836 (1.2)	11/841 (1.3)		
5 organs	1/836 (0.1)	1/841 (0.1)		
SOFA score†			—	0.23
Median	6.00	5.62		
Interquartile range	4.00–8.50	3.92–8.28		
SOFA subscore†				
Cardiovascular			—	0.03
Median	1.20	1.42		
Interquartile range	0.46–2.31	0.60–2.50		
Respiratory			—	0.63
Median	2.00	2.00		
Interquartile range	1.56–2.48	1.57–2.50		
Renal			—	0.15
Median	0.83	0.75		
Interquartile range	0.14–2.14	0.07–2.00		
Coagulation			—	0.04
Median	0.64	0.50		
Interquartile range	0.00–1.62	0.00–1.59		
Liver			—	0.02
Median	0.28	0.20		
Interquartile range	0.00–1.00	0.00–0.92		
Length of stay — days				
In ICU			—	0.42
Median	9	9		
Interquartile range	4–18	4–17		
In hospital‡			—	0.65
Median	20	20		
Interquartile range	10–36	9–38		

Table 2. (Continued.)

Outcome	Albumin Group	Crystalloid Group	Relative Risk (95% CI)	P Value
Tertiary outcomes§				
Renal-replacement therapy — no./total no. (%)¶	222/903 (24.6)	194/907 (21.4)		0.11
Acute kidney injury — no./total no. (%)‖	183/834 (21.9)	190/837 (22.7)		0.71
Duration of mechanical ventilation — days**			—	0.50
Median	6	6		
Interquartile range	2–14	2–13		
Time to suspension of vasopressor or inotropic agents — days††			—	0.007
Median	3	4		
Interquartile range	1–6	2–7		

* New organ failures were defined by a change in a specific component of the SOFA[17] from a score of 0, 1, or 2 at baseline to a score of 3 or 4 during the study period.[5,17,18]

† The values are the median and interquartile range of the SOFA score, representing the average of the daily SOFA scores for each individual patient during his or her study period (including the SOFA score at baseline). No imputation was performed for missing data.

‡ The length of stay in the hospital included the length of stay in the ICU.

§ Tertiary outcomes were analyzed in post hoc analyses.

¶ Included are patients with any form of renal-replacement therapy prescribed by the attending physician during the study period, including patients with chronic renal failure at baseline.

‖ Acute kidney injury was defined according to the risk, injury, failure, loss, and end-stage kidney injury (RIFLE) criteria[20] for acute kidney injury on the basis of daily incremental increases in serum creatinine levels from baseline during the study period.

** The duration of ventilatory support includes only the time during the study period, which was not necessarily the total duration of ventilatory support.

†† The time to the suspension of vasopressor or inotropic agents was assessed as the number of days of administration of vasopressor or inotropic agents in patients for whom such treatment was ongoing at baseline. Data were available for 582 patients in the albumin group and 576 in the crystalloid group.

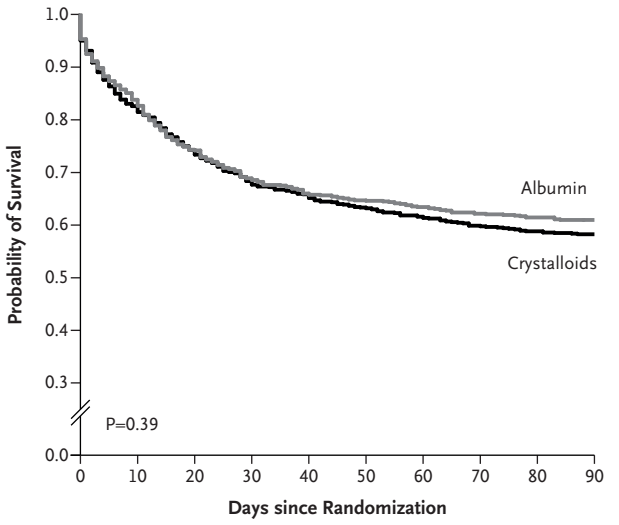
higher in the albumin group than in the crystalloid group from day 1 to day 28 (P<0.001) (Fig. 1A). During the first 7 days, patients in the albumin group had a significantly lower heart rate than those in the crystalloid group (P=0.002), as well as a significantly higher mean arterial pressure (P=0.03) (Table S4 and Fig. S2 in the Supplementary Appendix). Daily net fluid balances were lower in the albumin group than in the crystalloid group (P<0.001) (Fig. 1B). The median cumulative net fluid balance was also significantly lower in the albumin group than in the crystalloid group (347 ml [interquartile range, −3266 to 4042] vs. 1220 ml [interquartile range, −2767 to 5034], P=0.004) (Table S5 in the Supplementary Appendix).

OUTCOMES

At 28 days after randomization, 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; P=0.94) (Table 2). At 90 days of follow-up, 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; P=0.29). No significant difference in the probability of survival was observed between the albumin group and the crystalloid group during the 90 days after randomization (P=0.39) (Fig. 2).

No significant difference was observed between the two study groups with respect to either the number of newly developed organ failures or the median SOFA score (Table 2). Analysis of the SOFA score for each organ system revealed that, as compared with the crystalloid group, the albumin group had a lower cardiovascular score (P=0.03), a higher coagulation score (P=0.04), and a higher liver score (P=0.02). No significant differences were observed in other secondary and tertiary outcomes, with the exception of the time to suspension of the administration of vasopressor or inotropic agents, which was shorter in the albumin group than in the crystalloid group (P=0.007) (Table 2).

In subgroup analyses, no significant difference was observed in the prespecified subgroups that were stratified according to the interval between the time the patient met the clinical crite-



No. at Risk										
Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

Figure 2. Probability of Survival from Randomization through Day 90.
The graph shows the Kaplan–Meier estimates for the probability of survival among patients receiving albumin and crystalloids and among those receiving crystalloids alone. The P value was calculated with the use of the log-rank test.

ria for severe sepsis and randomization (Fig. S3 in the Supplementary Appendix). Conversely, a significant difference was observed in a post hoc subgroup analysis that included 1121 patients with septic shock, as compared with 660 without septic shock, at the time of enrollment (relative risk with septic shock, 0.87; 95% CI, 0.77 to 0.99; relative risk without septic shock, 1.13; 95% CI, 0.92 to 1.39; P=0.03 for heterogeneity) (Fig. S3 in the Supplementary Appendix). Adjustment for baseline covariates did not significantly modify these results (Table S6 in the Supplementary Appendix).

DISCUSSION

The main results of this large-scale trial provide evidence regarding both the efficacy and the safety of the use of human albumin during severe sepsis — an interventional strategy that has long been debated.[21,22] The addition of albumin to crystalloids during the first 28 days of treatment to maintain a serum albumin level of 30 g per liter or more is safe but does not provide a survival advantage over crystalloids alone, over a follow-up period of 90 days. Similar findings were observed in the subgroup stratified according to the interval between the time the patient met the clinical criteria for severe sepsis and treatment application.

The findings in our trial may appear to contradict those of the predefined subgroup analysis from the SAFE study,[5] which suggested a survival advantage with an albumin-based strategy during severe sepsis. The plausibility of this hypothesis was supported by the significant hemodynamic advantages observed[23] and by further investigations showing that the correction of hypoalbuminemia reduced the severity of organ dysfunction.[4,6] Similar beneficial effects were also suggested by a large meta-analysis, which concluded that the use of albumin-containing solutions could be associated with lower mortality than that seen with other fluid regimens.[24]

Our results confirm that administration of albumin produces small but significant hemodynamic advantages. A significantly greater proportion of patients in the albumin group than in the crystalloid group reached the targeted mean arterial pressure within 6 hours after randomization (Table S7 in the Supplementary Appendix). During the first 7 days, the mean arterial pressure was higher, whereas the heart rate and net fluid balance were lower, in the albumin group than in the crystalloid group. Moreover, the average cardiovascular SOFA subscore over the course of the study period was lower in the albumin group, and the time to the suspension of inotropic or vasopressor agents was shorter, indicating a decreased use of vasopressors. These effects were obtained with similar amounts of administered fluids in the two study groups. These findings confirm a physiological advantage of albumin administration during severe sepsis, including a larger fluid distribution within the intravascular compartment and, in addition, possible effects of albumin as a scavenger of nitric oxide,[12] mediating peripheral vasodilatation during sepsis.[25,26]

The secondary outcomes also provide a detailed profile of the safety of albumin administration during severe sepsis. The incidence of new organ failures during the study was similar in the two groups. We observed slightly higher average SOFA subscores for liver and coagulation in the albumin group, indicating a higher serum bilirubin and a lower platelet

count, respectively, than were observed in the crystalloid group. Nonetheless, the absolute excess in the serum bilirubin concentration in the albumin group was marginal (median, 1.0 mg per deciliter [interquartile range, 0.6 to 1.7] vs. 0.9 mg per deciliter [interquartile range, 0.5 to 1.5], P<0.001) and was probably related to the methods used to prepare albumin solutions, which may be inefficient in clearing bilirubin content from plasma.[21,27] The slight reduction in platelet counts in the albumin group may be a further marker of a larger expansion of the intravascular compartment in this group than in the crystalloid group, with a consequent dilution of the hemoglobin content (Table S4 in the Supplementary Appendix).

Post hoc univariate and multivariate analyses of data from the 1121 patients with septic shock showed significantly lower mortality at 90 days in the albumin group than in the crystalloid group. Conversely, in the subgroup of patients with severe sepsis without shock, mortality appeared to be higher among those who were treated with albumin than among those treated with crystalloids alone, although the difference was far from significant. This analysis was not prespecified, and therefore it may be characterized by well-known biases. Nonetheless, a state of shock associated with severe sepsis represents a well-defined clinical entity. Moreover, if the oncotic, anti-inflammatory, and nitric oxide–scavenging properties of albumin are of clinical importance, these may be maximally exploited in the conditions that are the most severe, such as cardiovascular dysfunction.

Our trial has certain limitations. First, we included the use of albumin solutions with a greater concentration than those used in the SAFE study (20% vs. 4%). Consequently, the volume of albumin solution that was administered was markedly lower than that administered in the SAFE study, since our goal was to correct hypoalbuminemia and not to directly replace intravascular volume. Second, the observed mortality at 28 days was lower than originally expected, thereby increasing the likelihood that the study was underpowered. Finally, only approximately one third of the patients were enrolled during the early phase of severe sepsis.

In conclusion, the use of albumin in addition to crystalloids to correct hypoalbuminemia, as compared with the use of crystalloids alone, in patients with severe sepsis during their stay in the ICU did not provide a survival benefit at 28 or 90 days, despite improvements in hemodynamic variables. The clinical benefit of albumin that was seen in the post hoc analysis of the subgroup of patients with septic shock warrants further confirmation.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Albumin Replacement in Severe Sepsis or Septic Shock

TO THE EDITOR: The Albumin Italian Outcome Sepsis study conducted by Caironi et al. (April 10 issue)[1] is the third large-scale, randomized trial to compare albumin with crystalloids in adult patients with severe sepsis. The first such trial was the Saline versus Albumin Fluid Evaluation study.[2] In addition, the Early Albumin Resuscitation during Septic Shock study has been completed and its mortality results published.[3]

In all three trials, mortality was lower among patients receiving albumin, and the respective relative risks coincided closely, ranging from 0.87 to 0.94 (Fig. 1). Although the effect did not attain statistical significance in any of the individual trials, the pooled relative risk in all three trials is 0.92 (95% confidence interval [CI], 0.84 to 1.00; P=0.046), indicating a significant reduction in mortality associated with albumin use among adults with severe sepsis. This result supports the conclusion of a previous meta-analysis involving predominantly small trials with different control fluids and patient populations.[4] The result is also consistent with the observed reduction in mortality associated with albumin use among patients with spontaneous bacterial peritonitis, a disease that shares important pathophysiological features with severe sepsis.[5]

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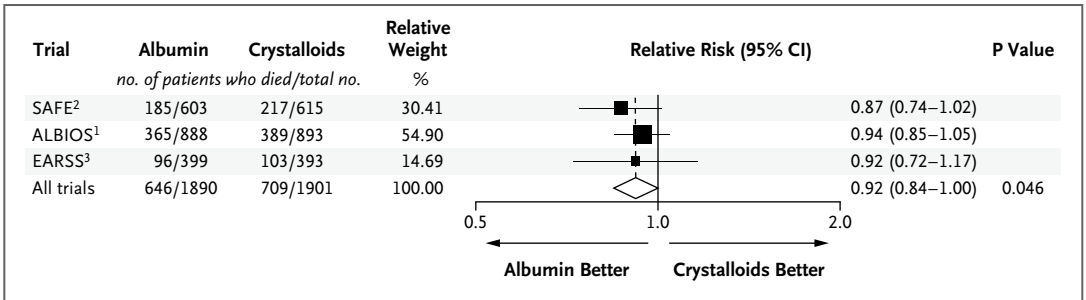

Figure 1. Meta-Analysis of Mortality in Large-Scale Randomized Trials Comparing Albumin with Crystalloids in Adult Patients with Severe Sepsis.

A fixed-effect model was used in the analysis. The size of the squares indicates the data points from the individual trials scaled according to the percentage of total weight (with individual trial weight equaling the proportion of total patients receiving albumin multiplied by the number of deaths in the crystalloids group), and the diamond indicates the pooled findings. The dashed line indicates the pooled relative risk. The proportion of variation attributable to heterogeneity (I^2) was 0% (P=0.71). ALBIOS denotes Albumin Italian Outcome Sepsis, CI confidence interval, EARSS Early Albumin Resuscitation during Septic Shock, and SAFE Saline versus Albumin Fluid Evaluation.

THE AUTHORS REPLY: Wiedermann and Joannidis suggest that there is a survival advantage associated with albumin use in patients with severe sepsis. Formal meta-analyses will confirm or refute their findings. Our study was not limited to the resuscitation phase but included albumin supplementation for 28 days after enrollment. The improvement in survival associated with albumin use was concentrated among patients with septic shock (1121 patients; 90-day mortality, 43.6% in the albumin group vs. 49.9% in the crystalloid group; relative risk, 0.87; 95% CI, 0.77 to 0.99; P=0.03). These data, together with the lack of effects in patients enrolled with early sepsis, suggest that there are beneficial effects associated with albumin use in relation to its ancillary functions, rather than only to its primary oncotic properties.[1] We may speculate that the benefits of albumin administration manifest mainly when endogenous albumin is functionally exhausted owing to the severity of the injury, leading to insufficient pharmacologic activity, as nitric oxide modulation,[2] antioxidant action,[3] and anti-immunosuppressive action.[4] Although this mechanism is speculative, the available data suggest that in patients with the most severe expression of sepsis albumin supplementation may represent an option.

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Thyroid Hormone Inactivation in Gastrointestinal Stromal Tumors

TO THE EDITOR: Maynard and collaborators (April 3 issue)[1] report the overexpression of type 3 iodothyronine deiodinase (D3) in gastrointestinal stromal tumors (GISTs), resulting in consumptive hypothyroidism. D3 overexpression is suggested as an inherent property of these tumors, but the authors also acknowledge the possibility of its secondary induction by kinase inhibitors. Indeed, the index patient was treated with sorafenib before the diagnosis of consumptive hypothyroidism, and it is not stated whether any of the additional four patients with hypothyroidism had previously received kinase inhibitors.

In a translational protocol of a randomized trial of sunitinib in breast cancer,[2] supported by a grant from Pfizer to Karolinska University Hospital, we obtained sequential metastatic biopsy specimens for gene-expression profiling at baseline and 2 weeks after the start of treatment. Expression of messenger RNA (mRNA) encoded by the D3 gene (*DIO3*) was significantly up-regulated in patients treated with sunitinib

Figure 1 (facing page). Effect of Treatment with Sunitinib on *DIO3* mRNA Levels in Tumor Specimens.

Panel A shows levels of messenger RNA (mRNA) encoded by the type 3 iodothyronine deiodinase (D3) gene (*DIO3*), as determined by gene-expression microarray analysis, in sequential metastatic-tumor-biopsy specimens obtained from patients treated with sunitinib and docetaxel (combination therapy) or docetaxel alone. A significant increase in expression of *DIO3* mRNA was observed in the combination-therapy group (P=0.047 by Wilcoxon signed-rank test) but not in the docetaxel group (P=0.94). Panel B shows the percentage change in serum thyrotropin levels from baseline to the first assessment during the treatment period (around day 20) versus the percentage change in *DIO3* mRNA levels from baseline to day 14. A linear relationship between relative changes in thyrotropin levels and *DIO3* mRNA levels was observed, with two distinct groups indicating the contribution of another, currently unknown factor. Patients 10 and 14, who had the highest percentage increase in *DIO3* mRNA level in the combination-therapy group, had a pathologic elevation of thyrotropin levels that returned to normal after sunitinib therapy was terminated.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. DOI: 10.1056/NEJMoa1305727

SUPPLEMENTARY APPENDIX

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

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Protocol violations

Analysis of adherence to the study protocol revealed that 377 patients (41.8%) in the Albumin group did not comply with the study rules for albumin administration at least once, for a total of 789 of 10101 patient-days (7.8%) of protocol violations. Of these, 451 of 10101 patient-days (4.5%) concerned omitted administration when albumin administration was expected, while 338 of 10101 patient-days (3.3%) concerned a dosage of administered albumin greater than expected. In the Crystalloid group, 336 patients (37.1%) received albumin at least once over the study period, for a total of 958 of 9697 patient-days (9.9%) of protocol violations.

Finally, 205 patients (22.7%) in the Albumin group received synthetic colloids at least once, over the study period, for a total of 310 of 10101 patient-days (3.1%) of protocol violations, as compared to 214 patients (23.6%) in the Crystalloid group, for a total of 388 of 9697 patient-days (4.0%) of protocol violations.

Inclusion criteria

Patients with severe sepsis or septic shock[1], if each one of the following criteria is satisfied:

1. Proved or suspected infection in at least one site:
   a) lung
   b) abdomen
   c) genito-urinary tract
   d) other (*blood, skin and soft tissue, central nervous system, bones and joints, cardiac system, catheter-related infection, other*)

2. Two or more of the following:
   a) a core temperature ≥ 38° C o ≤ 36° C;
   b) a heart rate ≥ 90 beats/min;
   c) a respiratory rate ≥ 20 breaths/min or $PaCO_2$ ≤ 32 mmHg or use of mechanical ventilation for an acute process;
   d) a white blood cell count ≥ 12000/ml or ≤ 4000/ml or immature neutrophils > 10%.

3. Presence of at least a severe and acute sepsis-related organ dysfunction, as measured by the modified Sequential Organ Failure Assessment (SOFA) score (see Table S8)[2]:
   a) respiratory score > 1;
   b) hematologic score > 1;
   c) hepatic score > 1;
   d) cardiovascular score equal to 1, 3 or 4;
   e) renal score > 1.

Exclusion criteria

1. Age below 18 years
2. Terminal state
3. Known adverse reaction to albumin administration
4. Severe sepsis or septic shock in patients after proved or suspected head injury, clinically active
5. Congestive heart failure (New York Heart Association class of 3 or 4)
6. Pathological conditions in which albumin administration is clinically indicated (hepatic cirrhosis with ascites, intestinal malabsorption syndrome, nephrotic syndrome, burns)
7. More than 24 hours since inclusion criteria were met
8. Religious objection to the administration of human blood products
9. Inclusion in other experimental studies

Study fluids management

Patients were assigned to receive either 20% albumin and crystalloids (Albumin group), or crystalloids alone (Crystalloid group) for volume replacement from randomization until day 28 or until ICU discharge, whichever came first. In both treatment assignments, fluids were administered according to the "early-goal directed therapy"[3] protocol.

In the Albumin group, immediately after randomization, patients received 300 ml of 20% albumin solution. Subsequently, from day 1 until the end of the study, 20% albumin was administered on a daily basis, to maintain serum albumin equal or greater than 30 g/L, based upon serum albumin determination, according to the following schema:

1) administration of 300 ml of 20% albumin solution (for a total of 60 grams of albumin), if serum albumin concentration was lower than 25 g/L;
2) administration of 200 ml of 20% albumin solution (for a total of 40 grams of albumin), if serum albumin concentration was equal or higher than 25 g/L and below 30 g/L;
3) no infusion of albumin, if serum albumin concentration was equal to or higher than 30 g/L.

Further administration of crystalloids was allowed, when clinically judged as necessary by the attending physician.

In the Crystalloid group, crystalloids were administered whenever necessary on clinical bases. Administration of 20% albumin was restricted, as protocol violation, to emergency use, based on standard criteria of each participating unit.

Additional methods for statistical analysis

Survival estimates were calculated with the use of Kaplan-Meier method, and comparison between groups was performed by log-rank test. Patients with unknown survival status at 90 days (n = 29, Figure 1 of the main text) were censored on the last day they were known to be alive. For 90-day follow-up, outcome measures were obtained from national registries by investigators who were blinded as for the treatment assignment.

No imputation was performed for missing data.

Adjusted analysis of 90-day mortality was performed with the use of robust Poisson regression for binary outcomes (Table S4). Adjustments were performed either for unbalanced covariates at baseline (including covariates which were statistically different between groups at baseline, with $P<0.05$), and for covariates at baseline which were considered clinically relevant, including age, SOFA score, serum lactate, and central venous oxygen saturation. For the overall population, unbalanced covariates included the number of organ dysfunction, and central venous oxygen saturation. For patients enrolled within 6 hours, unbalanced covariates included central venous oxygen saturation, while for patients enrolled after 6 to 24 hours unbalanced covariates included heart rate and the presence of ventilatory support. Finally, for patients with septic shock, unbalanced covariates included serum lactate, central venous oxygen saturation, and the presence of chronic renal failure, while for patients without septic shock no unbalanced covariates were observed.

Figure S1

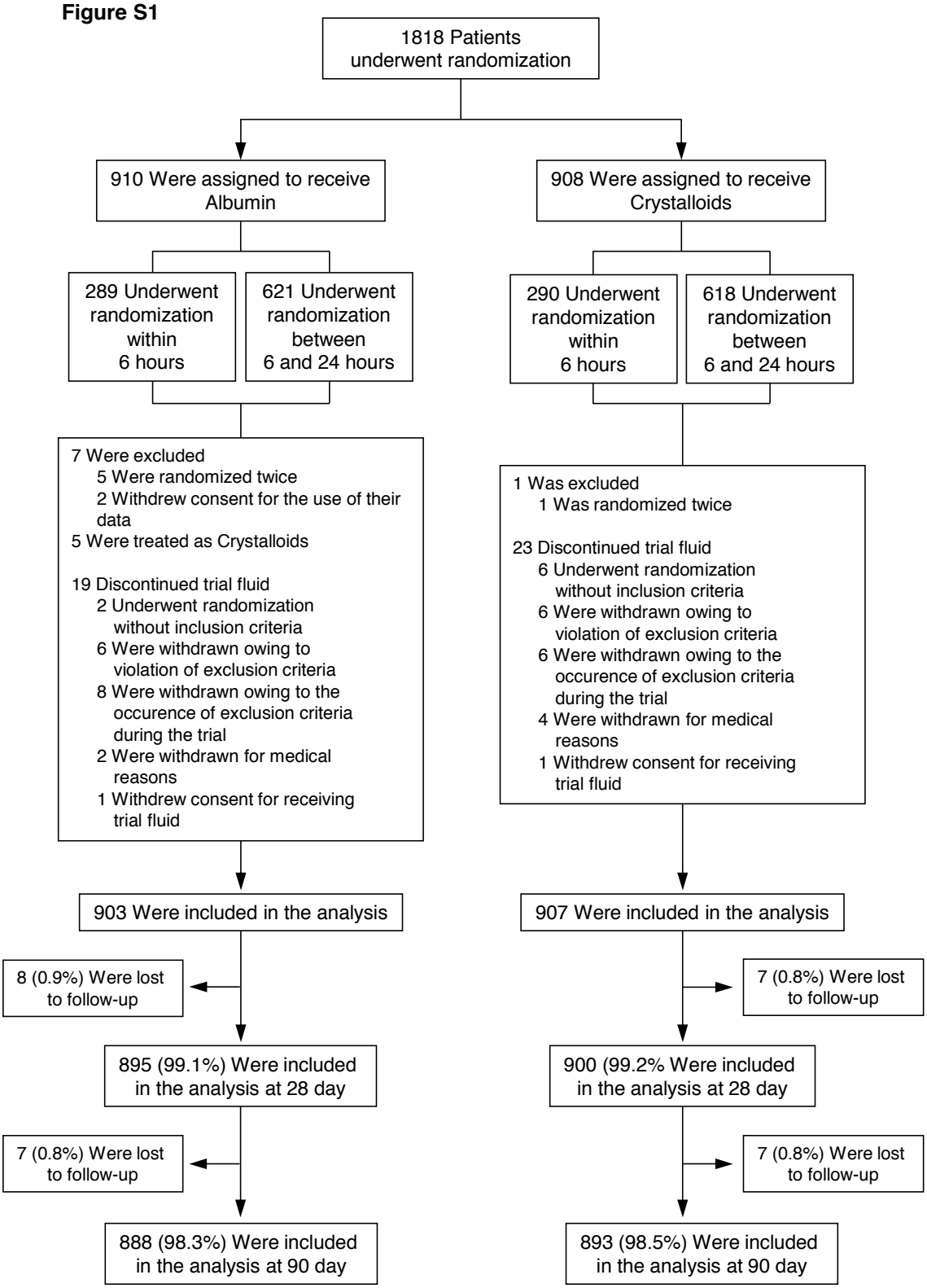

Figure S1. Randomization, Stratification, and Follow-up of Study Patients.
Six patients were excluded after the end of the study as they had been already and previously randomized in the trial. Two patients withdrew consent for the use of their data after the end of the study. Due to the high number of participating centers (100 ICUs), and the potential heterogeneity between their organizational structures, no data on screened patients were collected.

Figure S2

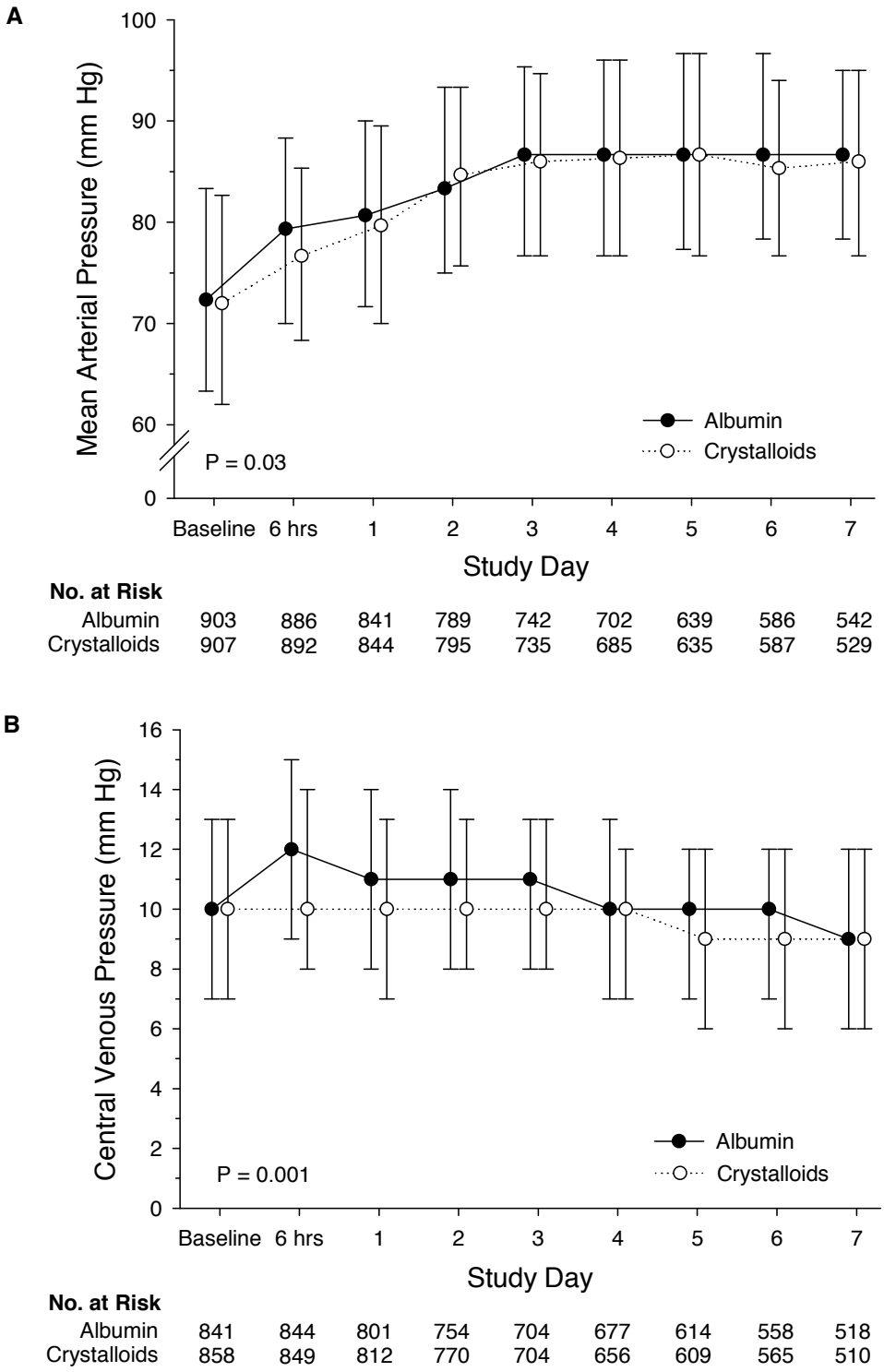

Figure S2. Mean Arterial and Central Venous Pressure through Day 7
Albumin denotes the Albumin group (receiving albumin and crystalloids), while Crystalloids the Crystalloid group (receiving crystalloids alone). Data are expressed as median value and interquartile range. P values are for between-group comparisons performed by using 2-factor analysis of variance for repeated measurements to test time and group effects.

Figure S3

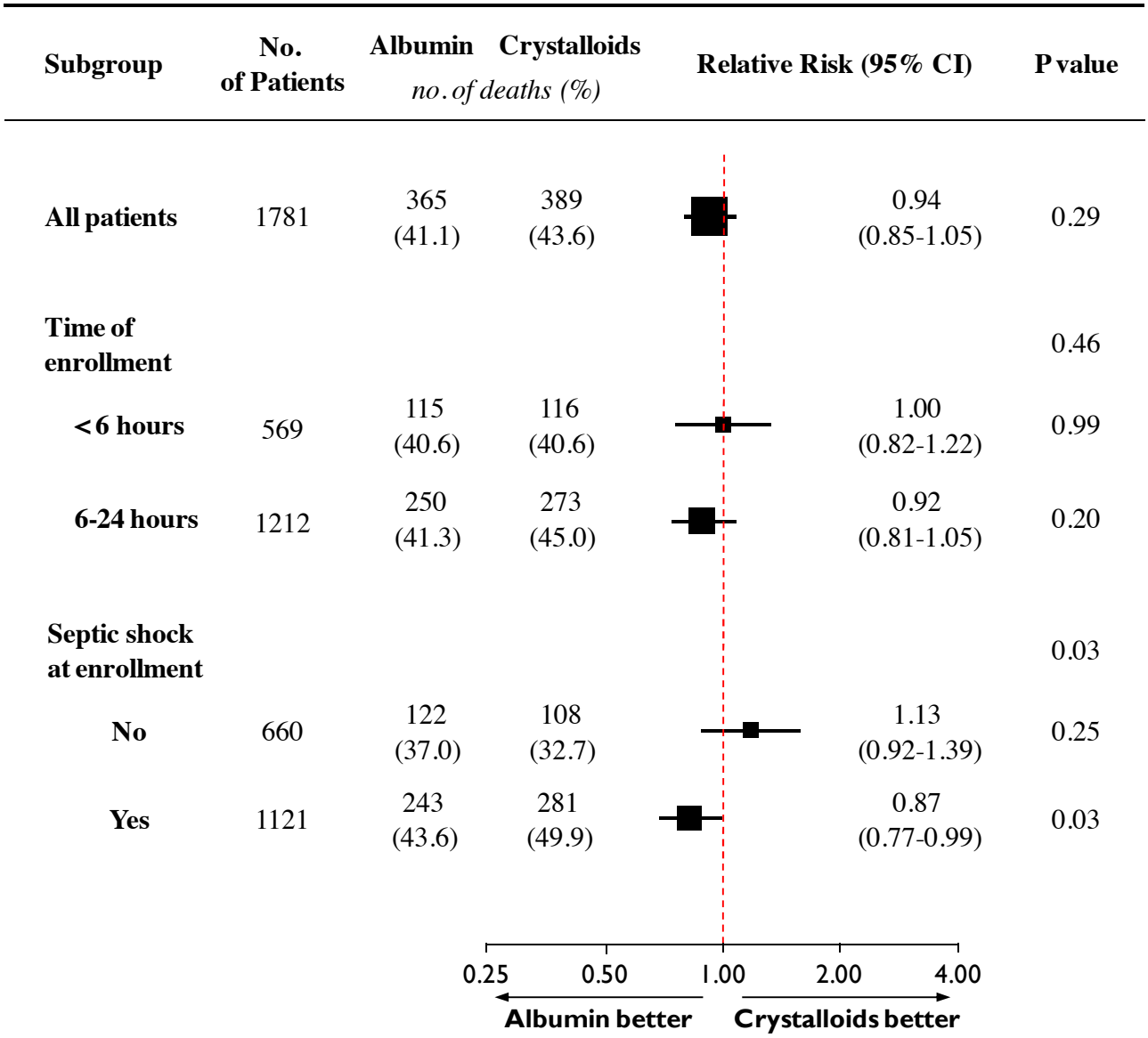

Figure S3. Risk of Death at 90 Days, according to Subgroup Analysis
Figure shows the relative risk and 95% confidence interval for death at 90 days for patients stratified at randomization based upon the time at which inclusion criteria were present, and for patients with or without septic shock at the time of randomization, as post-hoc analysis. The size of the symbols indicates the relative number of deaths. P values are for heterogeneity for each group. Septic shock at enrollment was defined as a baseline SOFA score of the cardiovascular component of 3 or 4[2].

Table S1. Sequential Organ Failure Assessment Scoring System[4] in the ALBIOS study

Organ System	0	1	2	3	4
Respiration					
PaO_2/FiO_2	> 400	301 – 400	< 301	101 – 200 (*with MV*)	≤ 100 (*with MV*)
Coagulation					
Platelets (x $10^3/mm^3$)	> 150	101 – 150	51 – 100	21 – 50	≤ 20
Liver					
Bilirubin (mg/dl)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12.0
(µmol/L)	< 20	20 – 32	33 – 101	102 – 204	> 204
Cardiovascular					
Hypotension*	No	MAP < 65 mmHg	Dopamine ≤5.0 or Dobutamine (any dose)	Dopamine >5.0 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15.0 or Epinephrine >0.1 or Nonepinephrine >0.1
Kidney†					
Creatinine (mg/dl)	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	≥ 5.0
(µmol/L)	< 110	110 – 170	171 – 299	300 – 440	> 440
or Urinary Output				or < 500 ml/day (or < 20 ml/hr)‡	or < 200 ml/day (or < 10 ml/hr) ‡

PaO_2/FiO_2 denotes the arterial to inspired oxygen concentration ratio, MV mechanical ventilation, MAP mean arterial pressure. Doses of dopamine, epinephrine and norepinephrine are expressed as µg/kg/min. SOFA score was modified by excluding the Glasgow Coma Scale, which was not assessed, and by decreasing to 65 mmHg the mean arterial pressure threshold of the cardiovascular sub-score of 1, for consistency with the hemodynamic targets as defined according to the early-goal directed therapy[3].

* Administration of vasoactive drugs for at least 1 hour.

† Patients receiving renal replacement therapy were assigned a renal SOFA sub-score of 4.

‡ During screening for eligibility criteria at baseline

Table S2. Site and Cause of Infection.

Variable	Albumin (N = 903)	Crystalloids (N = 907)	P value
Primary site of infection – no. (%)			
Lung	350 (38.8)	378 (41.7)	0.21
Abdomen	353 (39.1)	363 (40.0)	0.69
Urinary tract	126 (14.0)	112 (12.4)	0.31
Other site†	167 (18.5)	172 (19.0)	0.80
Positive site culture – no./total no. (%)	527/816 (64.6)	512/827 (61.9)	0.26
Type of infection according to site culture – no. (%)			0.63
Purely gram-negative bacteria	207 (22.9)	174 (19.2)	
Purely gram-positive bacteria	120 (13.3)	132 (14.6)	
Mixed bacteria	58 (6.4)	62 (6.8)	
Virus	11 (1.2)	11 (1.2)	
Fungus	26 (2.9)	30 (3.3)	
Mixed	105 (11.6)	103 (11.4)	
Culture negative	289 (32.0)	315 (34.7)	
Culture not obtained	87 (9.6)	80 (8.8)	
Positive blood culture – no./total no. (%)	269/806 (33.4)	258/784 (32.9)	0.84
Antibiotics at the time of randomization – no. (%)	837 (92.7)	836 (92.2)	0.68
Antibiotics at 6 hours after randomization – no./total no. (%)	882/886 (99.6)	885/892 (99.2)	0.37

† Other site includes blood, skin and soft tissues, central nervous system, bone, cardiovascular system, intravascular catheter-related infections, and others.

Table S3. Fluid Therapy during Study Treatment.

Variable	Albumin		Crystalloids		P value
	No. of Patients	Value	No. of Patients	Value	
20% Albumin (ml)					
After 6 hours	886	300 [300-300]	892	0 [0-0]	<0.001
Day 1*	841	300 [300-300]	844	0 [0-0]	<0.001
Day 2	789	200 [0-200]	795	0 [0-0]	<0.001
Day 3	742	200 [0-200]	735	0 [0-0]	<0.001
Day 4	702	200 [0-200]	685	0 [0-0]	<0.001
Day 5	639	200 [0-200]	635	0 [0-0]	<0.001
Day 6	586	200 [0-200]	587	0 [0-0]	<0.001
Day 7	542	100 [0-200]	529	0 [0-0]	<0.001
Total†	903	1100 [500-2000]	907	0 [0-250]	<0.001
Crystalloids (ml)					
After 6 hours	886	1000 [600-1800]	892	1281 [758-2091]	<0.001
Day 1*	841	2500 [1500-3550]	844	2829 [1800-4098]	<0.001
Day 2	789	2100 [1316-3000]	795	2400 [1500-3450]	<0.001
Day 3	742	1796 [1050-2532]	735	1980 [1200-2789]	0.02
Day 4	702	1500 [940-2400]	685	1710 [1000-2518]	0.003
Day 5	639	1500 [930-2228]	635	1585 [1000-2400]	0.04
Day 6	586	1397 [678-2050]	587	1545 [1000-2215]	0.003
Day 7	542	1320 [770-2100]	529	1400 [870-2200]	0.18
Total†	903	14150 [7370-27610]	907	16160 [8638-28000]	0.07
Total administered fluids (ml)‡					
After 6 hours	886	1802 [1280-2703]	892	1800 [1200-2700]	0.54
Day 1*	841	4300 [3100-5600]	844	4250 [3100-5767]	0.67
Day 2	789	3800 [3100-4850]	795	4000 [3200-5135]	0.02
Day 3	742	3551 [2900-4500]	735	3685 [2990-4500]	0.18
Day 4	702	3443 [2800-4200]	685	3500 [2850-4370]	0.21
Day 5	639	3468 [2800-4190]	635	3500 [2730-4250]	0.74
Day 6	586	3330 [2700-4130]	587	3437 [2740-4083]	0.78

Day 7	542	3346 [2700-4170]	529	3350 [2740-4141]	0.77
Total†	903	31867 [15692-63000]	907	31970 [15750-59630]	0.51
20% Albumin as percentage of Total administered fluids (%)					
After 6 hours	886	13.5 [8.8-20.3]	892	0.0 [0.0-0.0]	<0.001
Day 1*	841	7.0 [5.1-9.3]	844	0.0 [0.0-0.0]	<0.001
Day 2	789	4.1 [0.0-6.2]	795	0.0 [0.0-0.0]	<0.001
Day 3	742	4.0 [0.0-6.2]	735	0.0 [0.0-0.0]	<0.001
Day 4	702	3.9 [0.0-6.3]	685	0.0 [0.0-0.0]	<0.001
Day 5	639	4.2 [0.0-6.3]	635	0.0 [0.0-0.0]	<0.001
Day 6	586	3.0 [0.0-6.0]	587	0.0 [0.0-0.0]	<0.001
Day 7	542	2.7 [0.0-5.7]	529	0.0 [0.0-0.0]	<0.001
Total†	903	3.7 [2.5-5.0]	907	0.0 [0.0-0.6]	<0.001

Values are mean ±standard deviation or medians [interquartile ranges].
* Values at day 1 include fluids administered from randomization to day 1, which averaged 16 hours in the two study groups, including also fluids administered after 6 hours from randomization.
† Total values represent cumulative data for the entire study period (from randomization until ICU discharge or day 28, whichever came first).
‡ Total administered fluids represent the sum of 20% albumin, crystalloids, other blood products, and other administered fluids.

Table S4. Physiological Effects of Treatment.

Variable	Albumin		Crystalloids		P value
	No. of Patients	Value	No. of Patients	Value	
Heart rate (beats/min)					
After 6 hrs	886	97 ±21	892	101 ±20	<0.001
Day 1	841	94 ±21	844	99 ±22	<0.001
Day 2	789	89 ±20	795	92 ±20	<0.001
Day 3	742	86 ±20	735	89 ±19	0.01
Day 4	702	86 ±18	685	87 ±18	0.49
Day 5	639	86 ±18	635	86 ±18	0.96
Day 6	586	86 ±18	587	86 ±17	0.95
Day 7	542	85 ±17	529	87 ±16	0.04
Mean arterial pressure (mm Hg)					
After 6 hrs	886	79 ±14	892	77 ±13	<0.001
Day 1	841	81 ±14	844	80 ±14	0.02
Day 2	789	84 ±14	795	84 ±14	0.52
Day 3	742	87 ±14	735	86 ±14	0.43
Day 4	702	87 ±13	685	87 ±14	0.82
Day 5	639	87 ±14	635	87 ±14	0.97
Day 6	586	87 ±14	587	86 ±14	0.07
Day 7	542	87 ±13	529	86 ±13	0.24
Central venous pressure (mm Hg)					
After 6 hrs	844	11.4 ±4.7	849	10.3 ±4.3	<0.001
Day 1	801	10.9 ±4.3	812	10.0 ±4.3	<0.001
Day 2	754	10.8 ±4.3	770	10.3 ±4.1	0.02
Day 3	704	10.4 ±4.2	704	10.1 ±4.2	0.33
Day 4	677	9.8 ±4.3	656	9.6 ±4.3	0.34
Day 5	614	9.5 ±4.2	609	9.2 ±4.2	0.15
Day 6	558	9.2 ±3.9	565	8.8 ±4.3	0.08
Day 7	518	8.9 ±4.1	510	8.7 ±4.1	0.47
Central venous oxygen saturation (%)					
After 6 hrs	774	75 [69-80]	768	75 [69-81]	0.64

Day 1	753	75 [69-80]	765	75 [69-80]	0.34
Day 2	707	74 [68-79]	708	74 [68-80]	0.27
Day 3	654	73 [68-78]	645	72 [67-78]	0.61
Day 4	615	73 [68-78]	598	73 [68-77]	0.62
Day 5	554	73 [67-78]	558	73 [68-77]	0.68
Day 6	507	72 [67-78]	507	72 [67-77]	0.96
Day 7	472	72 [67-78]	464	72 [66-77]	0.60
Lactate (mmol/liter)					
Day 1	825	1.7 [1.1-2.8]	826	1.8 [1.2-3.0]	0.05
Day 2	774	1.5 [1.0-2.1]	774	1.6 [1.1-2.2]	0.10
Day 3	727	1.4 [1.0-2.0]	716	1.5 [1.1-2.1]	0.06
Day 4	686	1.3 [1.0-1.9]	672	1.4 [1.0-2.1]	0.04
Day 5	620	1.4 [1.0-2.0]	620	1.4 [1.0-2.0]	0.34
Day 6	572	1.3 [1.0-1.8]	577	1.4 [1.0-1.9]	0.16
Day 7	534	1.3 [1.0-1.8]	515	1.4 [1.0-1.9]	0.05
Serum albumin (g/liter)					
Day 1	829	28.6 ±5.4	816	24.0 ±5.2	<0.001
Day 2	771	28.7 ±4.1	754	23.5 ±5.0	<0.001
Day 3	719	29.0 ±3.5	705	23.2 ±4.9	<0.001
Day 4	677	29.0 ±3.5	663	23.2 ±5.0	<0.001
Day 5	619	29.3 ±3.5	606	23.2 ±5.0	<0.001
Day 6	578	29.4 ±3.5	562	23.1 ±5.0	<0.001
Day 7	531	29.4 ±3.3	510	23.1 ±4.7	<0.001
Hemoglobin (g/dl)					
After 6 hrs	869	10.3 ±1.7	880	11.0 ±1.7	<0.001
Day 1	828	10.4 ±1.6	834	10.9 ±1.7	<0.001
Day 2	773	10.4 ±1.5	784	10.6 ±1.5	0.01
Day 3	731	10.3 ±1.4	726	10.5 ±1.4	0.03
Day 4	681	10.4 ±1.5	672	10.5 ±1.5	0.30
Day 5	617	10.3 ±1.4	619	10.5 ±1.5	0.03
Day 6	562	10.2 ±1.4	572	10.5 ±1.5	0.02
Day 7	517	10.1 ±1.5	512	10.3 ±1.4	0.05

Values are mean ±standard deviation or medians [interquartile ranges].

Table S5. Additional Data on Fluid Therapy, Urinary Output and Fluid Balance during Study Treatment.

Variable	Albumin		Crystalloids		P value
	No. of Patients	Value	No. of Patients	Value	
Other blood products (ml)*					
After 6 hours	886	0 [0-300]	892	0 [0-230]	0.34
Day 1†	841	0 [0-600]	844	0 [0-600]	0.04
Day 2	789	0 [0-300]	795	0 [0-100]	0.25
Day 3	742	0 [0-0]	735	0 [0-0]	0.61
Day 4	702	0 [0-0]	685	0 [0-0]	0.79
Day 5	639	0 [0-0]	635	0 [0-0]	0.56
Day 6	586	0 [0-0]	587	0 [0-0]	0.32
Day 7	542	0 [0-0]	529	0 [0-0]	0.19
Total‡	903	900 [0-2300]	907	600 [0-2000]	0.007
Other administered fluids (ml)§					
After 6 hours	886	180 [0-500]	892	200 [0-500]	0.79
Day 1†	841	1000 [400-1740]	844	1000 [320-1707]	0.56
Day 2	789	1344 [784-2000]	795	1400 [700-2000]	0.82
Day 3	742	1500 [965-2100]	735	1500 [970-2089]	0.51
Day 4	702	1500 [1000-2200]	685	1600 [1000-2175]	0.82
Day 5	639	1600 [1000-2200]	635	1700 [1100-2275]	0.44
Day 6	586	1700 [1100-2250]	587	1700 [1100-2250]	0.89
Day 7	542	1616 [1050-2300]	529	1700 [1200-2300]	0.50
Total‡	903	13250 [4450-30058]	907	12525 [4000-28050]	0.40
Urinary output (ml)					
After 6 hours	886	540 [280-950]	892	530 [270-945]	0.59
Day 1¶	840	1800 [905-2802]	844	1660 [890-2730]	0.26
Day 2	789	2360 [1500-3470]	795	2300 [1500-3280]	0.24
Day 3	742	2730 [1730-3560]	735	2500 [1720-3580]	0.23
Day 4	701	2800 [1900-3790]	685	2650 [1790-3550]	0.05
Day 5	639	2770 [1840-3680]	635	2770 [1990-3600]	0.87
Day 6	586	2865 [1850-3820]	587	2850 [1950-3800]	0.72

Day 7	542	2810 [1810-3785]	529	2700 [1940-3700]	0.66
Total‡	903	23282 [8470-47080]	907	22261 [8010-45150]	0.40
Other excreted fluids (ml)‖					
After 6 hours	886	240 [144-400]	892	246 [146-400]	0.79
Day 1¶	840	800 [485-1230]	844	800 [500-1200]	0.74
Day 2	789	848 [561-1345]	795	810 [572-1290]	0.64
Day 3	742	860 [600-1330]	735	875 [550-1280]	0.50
Day 4	701	922 [600-1360]	685	900 [600-1400]	0.87
Day 5	639	934 [600-1500]	635	912 [600-1450]	0.54
Day 6	586	950 [600-1488]	587	970 [608-1426]	0.69
Day 7	542	950 [600-1481]	529	930 [600-1420]	0.76
Net fluid balance (ml)**					
Day 1	840	1229 [168 / 2379]	844	1504 [201 / 3073]	0.09
Day 2	789	350 [-705 / 1607]	795	620 [-480 / 1945]	0.002
Day 3	742	-72 [-1180 / 1055]	735	100 [-960 / 1200]	0.04
Day 4	701	-470 [-1450 / 575]	685	-170 [-1165 / 841]	0.003
Day 5	639	-452 [-1440 / 545]	635	-450 [-1550 / 610]	0.85
Day 6	586	-525 [-1763 / 580]	587	-625 [-1600 / 265]	0.60
Day 7	542	-530 [-1508 / 490]	529	-530 [-1550 / 316]	0.72
Total‡	903	-1618 [-7917 / 3160]	906	-858 [-7750 / 3732]	0.13

Values are medians [interquartile ranges].
* Other blood products include packed red blood cells, fresh frozen plasma and platelets.
† Values at day 1 include fluids administered from randomization to day 1, which averaged 16 hours in the two study groups, including also fluids administered after 6 hours from randomization.
‡ Total values represent cumulative data for the entire study period (from randomization until ICU discharge or day 28, whichever came first).
§ Other administered fluids include fluids other than crystalloids or albumin, i.e., glucose and water, as administered for either enteral or parenteral nutrition (as well as for maintenance), mannitol, any protein or lipid solutions, and colloids administered as violation to the study protocol.
¶ Values at day 1 include urinary output or other excreted fluids from randomization to day 1, which averaged 16 hours in the two study groups, including also urinary output or other excreted fluids after 6 hours from randomization.
‖ Other excreted fluids included fluid losses other than urinary output, such as fluids potentially removed with continuous renal replacement therapy, fluids lost as feces, aspirated gastric content, drainage fluids, and insensible perspiration.
** Daily net fluid balance was calculated as the difference between the total amount of administered fluid and the total amount of excreted fluid each day, which included urinary output,

and other fluid losses, such as fluids potentially removed with continuous renal replacement therapy, fluids lost as feces, aspirated gastric content, drainage fluids, and insensible perspiration. For day 1, net fluid balance was computed from the time of randomization to day 1, which averaged 16 hours in the two study groups.

Table S6. Results of the Unadjusted and Adjusted Analyses of the 90-Day Mortality

Subgroup	Albumin	Crystalloids	RR (95% CI), P Value Un-adjusted	RR (95% CI), P Value Adjusted For unbalances*	RR (95% CI), P Value Adjusted for clinically relevant variables†
	no. of deaths/total (%)				
All patients	365/888 (41.1)	389/893 (43.6)	0.94 (0.85-1.05), P = 0.29	0.93 (0.82-1.04), P = 0.19	0.94 (0.84-1.05), P = 0.26
Time of enrollment‡					
< 6 hours	115/283 (40.6)	116/286 (40.6)	1.00 (0.82-1.22), P = 0.99	0.92 (0.75-1.14), P = 0.44	1.05 (0.86-1.29), P = 0.62
6-24 hours	250/605 (41.3)	273/607 (45.0)	0.92 (0.81-1.05), P = 0.20	0.95 (0.83-1.08), P = 0.42	0.89 (0.78-1.02), P = 0.09
Septic shock at enrollment§					
No	122/330 (37.0)	108/330 (32.7)	1.13 (0.92-1.39), P = 0.25	1.13 (0.92-1.39), P = 0.25	1.05 (0.84-1.31), (P = 0.68)
Yes	243/558 (43.6)	281/563 (49.9)	0.87 (0.77-0.99), P = 0.03	0.85 (0.74-0.98), P = 0.02	0.88 (0.77-1.01), P = 0.07

RR denotes relative risk and CI confidence interval.
* Adjustments were performed for unbalances at baseline (variables significantly different, P<0.05) between the Albumin group and the Crystalloid group in the entire population and in each specific sub-group.
† Adjustments were performed for variables clinically considered as relevant, including age, Sequential Organ Failure Assessment (SOFA)[5] score at baseline, serum lactate at baseline, central venous oxygen saturation at baseline.
‡ Randomization was stratified according to the time of enrollment after inclusion criteria were present.
§ Septic shock at enrollment was defined as a baseline SOFA score of the cardiovascular component of 3 or 4[2].

Table S7. Hemodynamic Goals during the First 6-24 Hours.

Variable	Albumin (N = 903)	Crystalloids (N = 907)	P value
Central venous pressure after 6 hours – no./total no. (%)			<0.001
< 8 mm Hg	158/844 (18.7)	234/849 (27.6)	
8 to 12 mm Hg	356/844 (42.2)	377/849 (44.4)	
>12 mm Hg	330/844 (39.1)	238/849 (28.0)	
Mean arterial pressure after 6 hours ≥ 65 mm Hg – no./total no. (%)	762/886 (86.0)	736/892 (82.5)	0.04
Central venous oxygen saturation after 6 hours ≥ 70% - no./total no. (%)	568/774 (73.4)	557/768 (72.5)	0.70
Lactate at day 1 < 2 mmol/liter – no./total no. (%)	478/825 (57.9)	446/826 (54.0)	0.11
Vasoactive drugs at day 1 – no./total. (%)			
Dopamine	209/841 (24.9)	231/844 (27.4)	0.24
Norepinephrine	473/841 (56.2)	499/844 (59.1)	0.23
Epinephrine	52/841 (6.2)	61/844 (7.2)	0.39
Dobutamine	123/841 (14.6)	117/844 (13.9)	0.65
Vasopressin	6/841 (0.7)	10/844 (1.2)	0.32
Two or more vasoactive drugs at day 1 – no./total (%)	239/841 (28.4)	271/844 (32.1)	0.10
Doses of vasoactive drugs at day 1 – µg/kg/min			
Dopamine	7.0 ±3.5	7.3 ±3.8	0.38
Norepinephrine	0.29 ±0.35	0.33 ±0.36	0.003
Epinephrine	0.16 ±0.16	0.16 ±0.15	0.86
Mean arterial pressure at day1 ≥ 65 mm Hg – no./total no. (%)	748/841 (88.9)	735/844 (87.1)	0.24

Values are mean ±standard deviation.

Table S8. Details on SOFA scores at Baseline and during the Study

Variable	Albumin		Crystalloids		P value
	No. of Patients	Value	No. of Patients	Value	
SOFA score					
Baseline	868	8 [6-10]	872	8 [5-10]	0.61
Day 1	814	8 [5-10]	826	7 [5-10]	0.25
Day 2	759	7 [4-10]	766	7 [5-10]	0.62
Day 3	712	6 [4-9]	705	6 [4-9]	0.46
Day 4	661	6 [3-9]	658	6 [3-9]	0.73
Day 5	605	5 [3-8]	599	5 [3-8]	0.37
Day 6	548	5 [3-8]	552	5 [3-7]	0.03
Day 7	504	5 [3-8]	499	4 [2-7]	0.03
SOFA Cardiovascular subscore					
Baseline	903	3 [1-4]	907	3 [1-4]	0.70
Day 1	841	3 [0-4]	844	3 [0-4]	0.02
Day 2	789	2 [0-4]	795	3 [0-4]	<0.001
Day 3	742	0 [0-3]	735	2 [0-3]	0.001
Day 4	702	0 [0-3]	685	0 [0-3]	0.04
Day 5	639	0 [0-2]	635	0 [0-3]	0.23
Day 6	586	0 [0-2]	587	0 [0-2]	0.15
Day 7	542	0 [0-2]	529	0 [0-2]	0.73
SOFA Respiratory subscore					
Baseline	895	2 [2-3]	897	2 [2-3]	0.84
Day 1	831	2 [2-3]	835	2 [2-3]	0.68
Day 2	772	2 [2-3]	782	2 [2-3]	0.62
Day 3	730	2 [2-3]	726	2 [2-3]	0.41
Day 4	683	2 [2-3]	672	2 [2-3]	0.20
Day 5	620	2 [2-3]	620	2 [1-3]	0.58
Day 6	561	2 [1-3]	569	2 [1-3]	0.37
Day 7	519	2 [1-3]	510	2 [1-3]	0.77

SOFA Renal subscore					
Baseline	899	1 [0-3]	902	1 [0-3]	0.19
Day 1	837	1 [0-2]	842	1 [0-2]	0.33
Day 2	785	1 [0-2]	787	1 [0-2]	0.88
Day 3	737	1 [0-2]	725	1 [0-2]	0.87
Day 4	696	0 [0-2]	678	0 [0-2]	0.86
Day 5	633	0 [0-2]	629	0 [0-2]	0.39
Day 6	577	0 [0-2]	581	0 [0-2]	0.20
Day 7	537	0 [0-2]	524	0 [0-2]	0.15
SOFA Coagulation subscore					
Baseline	898	0 [0-2]	904	0 [0-2]	0.82
Day 1	838	1 [0-2]	841	0 [0-2]	0.07
Day 2	787	1 [0-2]	790	1 [0-2]	0.08
Day 3	737	1 [0-2]	729	1 [0-2]	0.12
Day 4	698	1 [0-2]	681	1 [0-2]	0.35
Day 5	635	1 [0-2]	631	1 [0-2]	0.15
Day 6	582	0 [0-2]	584	0 [0-2]	0.03
Day 7	537	0 [0-2]	525	0 [0-1]	0.005
SOFA Liver subscore					
Baseline	874	0 [0-1]	882	0 [0-1]	0.31
Day 1	827	0 [0-1]	836	0 [0-1]	0.05
Day 2	776	0 [0-1]	779	0 [0-1]	0.06
Day 3	725	0 [0-1]	714	0 [0-1]	0.08
Day 4	681	0 [0-1]	672	0 [0-1]	0.07
Day 5	624	0 [0-1]	613	0 [0-1]	0.008
Day 6	570	0 [0-1]	570	0 [0-1]	<0.001
Day 7	528	0 [0-1]	515	0 [0-1]	0.003

Values are medians [interquartile ranges].

Table S9. Details on Cumulative Administration of Blood Products

Variable	Albumin		Crystalloids		P value
	No. of Patients	Value	No. of Patients	Value	
Other blood products (ml)					
Total*	903	900 [0-2300]	907	600 [0-2000]	0.007
Packed red blood cells (ml)					
Total*	903	600 [0-1500]	907	300 [0-1200]	<0.001
Fresh Frozen Plasma (ml)					
Total*	903	0 [0-600]	907	0 [0-600]	0.78
Platelets (ml)					
Total*	903	0 [0-0]	907	0 [0-0]	0.47

Values are medians [interquartile ranges].
* Total values represent cumulative data for the entire study period (from randomization until ICU discharge or day 28, whichever came first).

Table S10. Clinical Treatments Applied during the Study.

Variable	Albumin (N = 903)	Crystalloids (N = 907)	P value
Administration of activated protein C			
For at least 2 days – no./total no. (%)*	28/841 (3.3)	21/844 (2.5)	0.30
Total patient-days – no./total no. (%)	124/10101 (1.2)	98/9697 (1.0)	0.15
Tight glycemic control			
For at least 5 days – no./total no (%)*	456/841 (54.2)	481/844 (57.0)	0.25
Total patient-days – no./total no. (%)	6913/10101 (68.4)	7067/9697 (72.9)	<0.001
Administration of corticosteroids			
For at least 5 days – no./total no (%)*	224/841 (26.6)	236/844 (28.0)	0.54
Total patient-days – no./total no. (%)	2410/10101 (23.9)	2663/9697 (27.5)	<0.001
Use of extra-corporeal hemofiltration techniques for the treatment of sepsis			
For at least 2 days – no./total no (%)*	38/841 (4.5)	32/844 (3.8)	0.45
Total patient-days – no./total no. (%)	178/10101 (1.8)	184/9697 (1.9)	0.48

* Number of days includes the minimum number of days of the specific treatment applied during the study period regardless whether they were consecutive or not.

Table S11. Details on Hydroxyethyl Starches Administration before and during the Study

Variable	Albumin (N = 903)	Crystalloids (N = 907)	P value
Hydroxyethyl Starches in previous 24 hr before randomization			
No ./Total (%)	288/903 (31.9)	305/907 (33.6)	0.43
Total* – ml	500 [500-1000]	500 [500-1000]	0.52
Death at 90 Days according to the administration of Hydroxyethyl starches before randomization – no./total (%)			0.79
No	239/607 (39.4)	249/591 (42.1)	0.33
Yes	126/281 (44.8)	140/302 (46.4)	0.71
Hydroxyethyl Starches during the Study			
For at least 1 day – no./total (%)	158/903 (17.5)	154/907 (17.0)	0.77
Total† – ml	750 [500-1000]	1000 [500-1300]	0.81
Death at 90 Days according to the administration of Hydroxyethyl Starches during the study – no./total (%)			0.66
No	290/731 (39.7)	309/741 (41.7)	0.43
Yes	75/157 (47.8)	80/152 (52.6)	0.39
Acute Kidney Injury according to the administration of Hydroxyethyl Starches during the study – no./total (%)‡			0.88
No	142/685 (20.7)	149/689 (21.6)	0.68
Yes	41/149 (27.5)	41/148 (27.7)	0.97

Values are medians [interquartile ranges].
* Total values represent cumulative data within the 24-hours period before randomization.
† Total values represent cumulative data for the entire study period (from randomization until ICU discharge or day 28, whichever came first) for patients who have received hydroxyethyl starches during the study
‡ Acute kidney injury was defined according to the risk, injury and failure RIFLE criteria for acute kidney injury on the basis of daily incremental increases in serum creatinine levels from baseline during the study period[6].

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