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RESEARCH ARTICLE

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Albumin administration in septic shock—Protocol for post-hoc analyses of data from a multicentre RCT

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Abstract

Background: Intravenous (IV) albumin is suggested for patients with septic shock who have received large amounts of IV crystalloids; a conditional recommendation based on moderate certainty of evidence. Clinical variation in the administration of IV albumin in septic shock may exist according to patient characteristics and location.

Methods: This is a protocol and statistical analysis plan for a post-hoc secondary study of the Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) RCT of 1554 adult ICU patients with septic shock. We will assess if specific baseline characteristics or trial site are associated with the administration of IV albumin during ICU stay using Cox models with competing events. All models will be adjusted for the treatment allocation in CLASSIC (restrictive vs. standard IV fluid), and all analyses will consider competing events (death, ICU discharge and loss-to-follow-up). We will present results as hazard ratios with

95% confidence intervals and *p*-values for the associations of baseline characteristics or site with IV albumin administration. Between-group differences (interactions) will be assessed using *p*-values from likelihood ratio tests. All results will be considered exploratory only.

Discussion: This secondary study of the CLASSIC RCT may yield important insight into potential practice variation in the administration of albumin in septic shock.

1 | BACKGROUND

The choice of intravenous (IV) fluid for patients with sepsis and septic shock is a topical question in critical care.[1,2] Albumin has been suggested as a resuscitation fluid due to its oncotic properties.[1,3,4] Additionally, hypoalbuminemia occurs frequently during sepsis, and may be associated with worse outcomes.[5] Therefore, another potential indication for albumin administration is to correct hypoalbuminaemia. In the latest iteration of the Surviving Sepsis Campaign guideline, it is suggested to give albumin to patients who have already received large volumes of crystalloids.[1] This is a conditional recommendation based on moderate certainty of evidence. The guideline rationale describes that the conditional recommendation is largely informed by higher blood pressures and lower fluid balances in patients randomised to albumin in the Albumin Italian Outcome Sepsis (ALBIOS) randomised clinical trial (RCT) from 2014[1,6]; measures which may not be directly important for patients.

In the ALBIOS RCT, 1818 Intensive Care Unit (ICU) patients with sepsis were randomised to albumin and crystalloids versus crystalloids alone.[6] The primary outcome, 28-day mortality, was similar between the groups. In a post-hoc subgroup analysis of the secondary outcome, 90-day mortality, heterogeneity of treatment effect in patients with sepsis versus septic shock was suggested. The effect estimate and 95% confidence interval (CI) for the sepsis subgroup was mostly compatible with harm but could not rule out important benefit, whereas that for septic shock showed lower 90-day mortality with the administration of albumin (*p*-value for interaction: .03).[6] In the Saline versus Albumin Fluid Evaluation (SAFE) RCT from 2004, 6997 adult ICU patients were randomised to albumin versus saline, which resulted in similar rates of death at Day 28 (the primary outcome).[7] A potential differential treatment effect in the subgroup of patients with or without severe sepsis was subsequently debated.[8] A systematic review of critically ill patients found moderate certainty of evidence for little to no difference in mortality with the administration of albumin or fresh frozen plasma versus crystalloids.[9] Additionally, albumin is more costly than crystalloids and most commercially available albumin solutions are derived from human blood.[10,11] Taken together, uncertainties remain regarding the value and appropriateness of albumin administration in septic shock.

In the Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) RCT from 2022, 1554 adult ICU patients with septic shock were randomised to restrictive IV fluid versus standard IV fluid therapy.[12] The RCT was designed to intervene on volumes of crystalloid, but the protocol additionally suggested that IV albumin should only be administered in case of large ascites drainage.[13] Nevertheless, approximately 45% of the randomised patients received IV albumin during their ICU stay. The administration appeared to differ between treatment allocations, as albumin was given to 37% in the restrictive IV-fluid group, and 53% in the standard IV-fluid group.[12]

This protocol outlines a post-hoc secondary analysis of the CLASSIC RCT. We aim to describe the administration of albumin and assess if the observed variation in the administration may be explained by variations in patient characteristics and/or site. We hypothesise that the administration of IV albumin will be associated with markers for increased disease severity and will differ between trial sites beyond what can be explained by these patient factors.

2 | METHODS

The present manuscript is a protocol and statistical analysis plan for a post-hoc analysis of a multicentre RCT. The outlined analyses will be conducted after this protocol is accepted for publication in a peer-reviewed journal, or after online registration at a publicly available registry. The final manuscript will be reported according to the STROBE statement.[14]

2.1 | Study design and data sources

We will perform a post-hoc analysis of data from the CLASSIC RCT.[12] The trial protocol, analysis plan and 90-day outcomes have been published elsewhere.[12,13]

2.2 | Study setting and population

In CLASSIC, 1554 adult ICU patients with septic shock, who had received at least 1 L IV fluid, were randomised 1:1 to IV fluid restriction versus standard IV fluid during ICU stay to a maximum of 90 days. Exclusion criteria were septic shock for more than 12 h, life-threatening bleeding, severe burns, pregnancy and lack of consent.[13] Patients were included from November 2018 to November 2021 across 31 ICUs in 8 countries, and the trial was completed on 16 November 2022, when the last patient reached

1-year follow-up. The results of the 1-year follow-up are pending.[15] We will include all patients from the CLASSIC RCT in this study, except five patients who did not consent to the use of their data.[12]

2.3 | Research questions

In adult patients with septic shock …

1. … are specific patient baseline characteristics separately associated with IV albumin administration during ICU stay, when accounting for the allocated IV fluid strategy in the CLASSIC trial?
2. … are specific patient baseline characteristics associated with IV albumin administration during ICU stay, when accounting for other baseline characteristics and the allocated IV fluid strategy in the CLASSIC trial?
3. … is trial site associated with IV albumin administration during ICU stay, when accounting for selected baseline characteristics, and the allocated IV fluid strategy in the CLASSIC trial?

2.4 | Data, outcomes and variables assessed

2.4.1 | Baseline variables

The complete baseline characteristics of the CLASSIC cohort are described elsewhere.[12]

We will assess the following baseline variables in this secondary study:

1. Allocation group (restrictive or standard IV fluid).
2. Trial site (only assessed in the analyses focused on site. Sites with less than 25 included patients will be combined according to country).
3. Disease severity as per the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)[16] (categorised as minimum value–19, 20–22, 23–25 or 26–maximum value).
4. Focus of infection (gastrointestinal, pulmonary, urinary tract, skin or soft tissue, or other focus).
5. Volume of IV fluid 24 h before randomisation (categorised as 0–2000, 2001–3000, 3001–4800 or 4801–maximum value [mL]).
6. Age (categorised as 18–60, 61–70, 71–80 or 81–maximum value [years]).
7. Highest dose of norepinephrine within 3 h before randomisation (categorised as 0.00–0.10, 0.11–0.20, 0.21–0.40 or 0.41–maximum value [μg/kg/min]).
8. Highest plasma lactate value within 3 h before randomisation (categorised as min value–2.6, 2.7–3,6, 3.7–5.6 or 5.7–maximum value [mmol/L]).
9. Source of ICU admission (emergency department or prehospital; hospital ward; operating or recovery room; or another ICU).

2.4.2 | Daily variables

In CLASSIC, daily administration of all types of IV and oral fluids were registered for all patients while in the ICU for a maximum of 90 days. Daily fluid data included IV albumin, which was defined as the total volume of all albumin solutions (4%, 5% and 20% solutions combined). For patients who were transferred to a non-trial ICU, daily data collection ceased at transfer.

2.4.3 | Outcomes

Primary outcome: time to first administration of IV albumin (all solutions combined as registered in the original database) in the ICU within 90 days.

We will include the following descriptive data regarding albumin administration in the two intervention groups:

TABLE 1 Fluid input in study cohort (mock table).

	Restrictive group and albumin administered (*N* = XXX)	**Restrictive group and albumin not administered (*N* = XXX)**	**Standard group and albumin administered (*N* = XXX)**	**Standard group and albumin not administered (*N* = XXX)**
	Median (IQR) [mean]	Median (IQR) [mean]	Median (IQR) [mean]	Median (IQR) [mean]
Fluid volumes (ml) after 90 days				
Intravenous fluid	*X,XXX (YYY to Z,ZZZ) [X,XXX]*	*X,XXX (YYY to Z,ZZZ) [X,XXX]*	*X,XXX (YYY to Z,ZZZ) [X,XXX]*	*X,XXX (YYY to Z,ZZZ) [X,XXX]*
Total fluid	*XX,XXX (Y,YYY to ZZ,ZZZ) [XX,XXX]*	*XX,XXX (Y,YYY to ZZ,ZZZ) [XX,XXX]*	*XX,XXX (Y,YYY to ZZ,ZZZ) [XX,XXX]*	*XX,XXX (Y,YYY to ZZ,ZZZ) [XX,XXX]*
Albumin[a]	*X (Y to ZZZ) [XXX]*	–	*X (Y to ZZZ) [XXX]*	–
Details on albumin administration				
Number of days with albumin	*XX (Y–ZZ) [XX]*	–	*XX (Y–ZZ) [XX]*	–

Note: Due to expected skewness on all fluid data means will be reported without standard deviations as in the original CLASSIC publication.[12]

[a]Total volume of albumin (4%, 5% and 20% solutions combined).

TABLE 2 Baseline data for the study cohort (mock table).

Characteristic	Restrictive group and albumin administered (*N* = XXX)	Restrictive group and albumin not administered (*N* = XXX)	Standard group and albumin administered (*N* = XXX)	Standard group and albumin not administered (*N* = XXX)
Median age (IQR), years	XX (YY–ZZ)	XX (YY–ZZ)	XX (YY–ZZ)	XX (YY–ZZ)
No. (%) of patients in sub-categories of age				
18–60	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
61–70	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
71–80	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
81-max value	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Male sex, no. (%)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)
Coexisting condition, no. (%)				
Haematological or metastatic cancer	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Ischaemic heart disease or heart failure	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Chronic hypertension	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Long-term dialysis[a]	X (Y.Y)	X (Y.Y)	X (Y.Y)	X (Y.Y)
Median time from ICU admission to randomisation (IQR), h	X (Y–Z)	X (Y–Z)	X (Y–Z)	X (Y–Z)
Median SMS-ICU score (IQR)[b]	XX (YY–ZZ)	XX (YY–ZZ)	XX (YY–ZZ)	XX (YY–ZZ)
No. (%) of patients in sub-categories of SMS-ICU score				
Min-19	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
20–22	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
23–25	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
26-max value	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Source of ICU admission, no. (%)				
Emergency department or pre-hospital	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Hospital ward	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Operating or recovery room	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Another ICU	X (Y.Y)	X (Y.Y)	X (Y.Y)	X (Y.Y)
Focus of infection, no. (%)[c]				
Gastrointestinal	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)
Pulmonary	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)
Urinary tract	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Skin or soft tissue	X (Y.Y)	X (Y.Y)	X (Y.Y)	X (Y.Y)
Other	X (Y.Y)	X (Y.Y)	X (Y.Y)	X (Y.Y)
Body weight, blood values and interventions				
Median body weight (IQR). kg	XX (YY–ZZ)	XX (YY–ZZ)	XX (YY–ZZ)	XX (YY–ZZ)
Median highest plasma lactate (IQR), mmol per litre[d]	X.X (Y.Y–Z.Z)	X.X (Y.Y–Z.Z)	X.X (Y.Y–Z.Z)	X.X (Y.Y–Z.Z)
No. (%) of patients in sub-categories of plasma lactate				
Min–2.6	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
2.7–3.6	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
3.7–5.6	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
5.6–max value	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Median highest dose of norepinephrine (IQR), μg/kg/min[e]	X.XX (Y.YY–Z.ZZ)	X.XX (Y.YY–Z.ZZ)	X.XX (Y.YY–Z.ZZ)	X.XX (Y.YY–Z.ZZ)
No. (%) of patients in sub-categories of norepinephrine				
0.00–0.10	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
0.11–0.20	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
0.21–0.40	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
0.41–max value	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)

TABLE 2 (Continued)

Characteristic	Restrictive group and albumin administered (*N* = XXX)	Restrictive group and albumin not administered (*N* = XXX)	Standard group and albumin administered (*N* = XXX)	Standard group and albumin not administered (*N* = XXX)
Median volume of intravenous fluid 24 h before randomisation (IQR), mL[f]	X,XXX (Y–Z,ZZZ)	X,XXX (Y–Z,ZZZ)	X,XXX (Y–Z,ZZZ)	X,XXX (Y–Z,ZZZ)
No. (%) of patients in sub-categories of volume of intravenous fluid				
0–2000	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
2001–3000	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
3001–4800	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
4800–max value	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)	XX (YY.Y)
Use of systemic glucocorticoid, no. (%)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)
Median highest plasma creatinine (IQR), mg/dL[g]	X.X (Y.Y–Z.Z)	X.X (Y.Y–Z.Z)	X.X (Y.Y–Z.Z)	X.X (Y.Y–Z.Z)
Use of respiratory support, no. (%)[h]	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)	XXX (YY.Y)

[a]Long-term dialysis was defined as the use of haemodialysis (or haemofiltration) or peritoneal dialysis at least once a week before hospital admission.
[b]The Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)[16] is a mortality prediction score, with scores ranging from 0 to 42 points and corresponding predicted 90-day mortality of 3.3%–91.0%.
[c]The listed location was the documented or suspected focus of infection at the time of randomisation.
[d]Shown are the highest plasma lactate levels within the 3 h before randomisation.
[e]The infusion rate of norepinephrine reflects the highest rate within the 3 h before randomisation.
[f]Volumes of intravenous fluid within the 24 h before randomisation were defined as all crystalloid fluids (any saline, sodium bicarbonate, Ringer's solutions or Plasma-Lyte solution), colloid fluids (albumin 4%, 5% or 20%; or gelatine, hydroxyethyl starch or dextran solutions) and blood products (units of red cells, plasma or platelets) the patient had received within the 24 hours before undergoing randomisation, independent of location (in-hospital or prehospital) and including intravenous fluids that contained medication or nutrition.
[g]Values reflect the highest plasma creatinine level within the 24 h before randomisation.
[h]Respiratory support includes the continuous use of invasive or non-invasive mechanical ventilation or continuous positive airway pressure at baseline.

1. Median (IQR) and mean volume of fluid intake (IV fluids, total fluids and albumin) among patients exposed versus not exposed to albumin (Table 1).
2. Median (IQR) number of days in ICU with IV albumin infusion among patients exposed to albumin (Table 1).
3. Number of patients with IV albumin infusions according to days from randomisation (presented visually as previously[17]). For each day, we will differentiate between patients who had their first infusion on that day, and patients who had already received albumin.

2.4.4 | Sample size

The CLASSIC trial has a fixed sample size of 1554. This post-hoc analysis will include all patients with consent for the use of their data, and thus no formal sample size calculation has been performed. As the primary outcome of this secondary study (administration of IV albumin) occurred in around 45% of the patients in the full trial cohort, we expect the study to have reasonable power.

2.4.5 | Statistical analyses

Baseline data will be presented stratified by treatment allocation and administration of albumin during ICU stay, with numerical data presented as medians with interquartile ranges (IQRs) and categorical data presented as numbers with percentages (Table 2). The baseline data that we plan to categorise in the analyses (as outlined above) will be presented both categorised and using raw, numeric data.

To assess if baseline patient characteristics were associated with administration of IV albumin, we will use Cox proportional hazards models with days since randomisation as underlying time-axis and competing events.[18,19] Two sets of analyses will be conducted: first, we will assess the baseline factors in separate models adjusted for allocation only, second, we will assess all the above-mentioned baseline factors and allocation together in a single model.

All models will be adjusted for treatment allocation (with the standard IV fluid group as reference) as the administration of albumin was distinctly different between the groups as previously outlined. Furthermore, an additional set of analyses will include interaction term(s) between baseline risk factors (separately and simultaneously) and allocation.

For all analyses, the following competing events will be considered with observations censored at the first competing event:

1. Death.
2. ICU discharge (including discharge to non-trial ICUs, as daily data was only registered while the patients were in the ICU).
3. Loss to follow-up for any of the events considered.

TABLE 3 Associations between baseline characteristics and IV albumin administration (mock table).

	Analyses adjusted for allocation only				Analyses adjusted for allocation and other baseline factors			
	HR (95% CI and *p* value) for albumin versus no albumin				HR (95% CI and *p* value) for albumin versus no albumin			
	All patients.	Restrictive group	Standard group	*p*-value[a]	All patients.	Restrictive group	Standard group	*p*-value[a]
Age				$p = \#$				$p = \#$
18–60	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
61–70	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
71–80	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
81–max value	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
SMS-ICU				$p = \#$				$p = \#$
Min value-19	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
20–22	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
23–25	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
26–max value	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
Focus of infection				$p = \#$				$p = \#$
Gastrointestinal	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
Pulmonary	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
Urinary tract	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
Skin or soft tissue	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
Other	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
Highest dose of norepinephrine				$p = \#$				$p = \#$
0.00–0.10	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
0.11–0.20	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
0.21–0.40	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
0.40–max value	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
IV fluid volume prior to randomisation				$p = \#$				$p = \#$
0–2000	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
2001–3500	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
3501–4800	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
4801-max value	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	
Highest plasma lactate				$p = \#$				$p = \#$
Min–2.6	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
2.7–3.6	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)		x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	x.xx (y.yy to z.zz, $p = \#$)	

TABLE 3 (Continued)

	Analyses adjusted for allocation only				Analyses adjusted for allocation and other baseline factors			
	HR (95% CI and *p* value) for albumin versus no albumin				HR (95% CI and *p* value) for albumin versus no albumin			
	All patients.	Restrictive group	Standard group	*p*-value[a]	All patients.	Restrictive group	Standard group	*p*-value[a]
3.7–5.6	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)		x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	
5.7–max value	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)		x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	
Source of ICU admission				*p* = #				*p* = #
p = #								
ED/pre-hospital	1.0 (reference)	1.0 (reference)	1.0 (reference)		1.0 (reference)	1.0 (reference)	1.0 (reference)	
Hospital ward	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)		x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	
Operating/ recovery room	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)		x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	
Another ICU	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)		x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	x.xx (y.yy to z.zz, *p* = #)	

[a]*p*-value for the test of interaction.

Results will be presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and *p*-values for the associations of baseline factors with IV albumin administration; between-group differences (interactions) will be assessed using *p*-values from likelihood ratio tests (Table 3).

To assess if site is associated with administration of IV albumin when adjusting for the above baseline patient characteristics, we will conduct an analysis including trial site (with the largest site as reference), treatment allocation and all baseline factors considered in a similar Cox model with the same competing events as outlined above.

Results for the adjusted association of trial site with IV albumin administration will be presented graphically and numerically by adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) and a *p*-value from a likelihood ratio test assessing the overall effect of trial site.

2.4.6 | Assessment of model accuracy

We will assess the model assumption of proportional hazards (that the hazards for the included variables are proportional and do not cross at any time point) by using scaled Schoenfeld residuals[20] and handle model violations, if required, using time-varying effects; if this is not sufficient, we will consider using alternative models or other adaptations as necessary. In case of alternative models or adaptations, we will specify these as deviations including their rationales in the final manuscript.

We will present two-tailed *p*-values with no specific cut-off for statistical significance and no corrections for multiple testing. Evidence will be interpreted as a continuous measure, and the results will be considered exploratory only with the intent to inform future trials.

2.4.7 | Missing data

The proportions of missing data for all variables will be presented. Patients with missing daily albumin data will be censored in the analyses at the time of first missing value. We will perform complete case analyses if less than 5% of patients have missing data for variables included in any analysis, which we expect, as missingness for individual baseline variables in the CLASSIC trial was limited and below 1.5% for all variables. If 5% or more of patients have missing data for one or more covariates in any analysis, we will use multiple imputation with chained equations for that analysis.[21,22] All baseline variables mentioned above, administration of albumin at any time (yes/no), 90-day mortality and treatment allocation will be included in the imputation models. We will create 25 imputed datasets separately for each allocation group.[23] Imputations will be performed using chained equations via the *mice* R package,[24] using predictive mean matching for continuous variables and logistic regression for binary/categorical variables, with results combined as appropriate.[21]

3 | DISCUSSION

In this post-hoc secondary study of the multicentre CLASSIC RCT, we will describe the administration of albumin in patients with septic

shock and assess if the already observed variation may be explained by patient characteristics and site.

Our study has several strengths: it will use and explore high-quality data from a contemporary, international trial of IV fluid volumes in ICU patients with septic shock. The CLASSIC trial randomised patients across 31 ICUs in both university and non-university hospitals in Europe, thus the external validity will likely be high for this setting. Additionally, the proportion of patients receiving IV albumin was high, which should ensure adequate power for these secondary analyses. All analyses are pre-specified and will not be conducted until the present protocol is either accepted for publication or registered in a publicly available online registry.

The proposed study also comes with limitations. The protocolised criteria for IV fluid volumes in both groups may have affected clinicians' decision to administer IV albumin, and thus we cannot be sure that the administration of IV albumin within the trial setting reflects clinical practice. Additionally, the protocol recommended that albumin was only used in case of large ascites drainage, but the administration in approximately 45% of the full trial population suggests some degree of non-adherence with this recommendation. In CLASSIC, registration of daily albumin was collected as a combined volume of all types of albumin solutions. Therefore, differentiations into less and more concentrated solutions is not possible. As the fluid intervention in CLASSIC was unblinded for clinicians and trial staff, there was a risk of performance bias due to inequity of care, for example in the administration of albumin, between the groups. The original trial protocol therefore contained suggestions for the use of concomitant interventions such as vasopressors and colloids, but the open-label intervention may still have affected the administration of albumin. Furthermore, the planned models are complex, and violations of the model assumptions or non-convergence may occur, which may require changes to the planned analysis strategy. Finally, the CLASSIC RCT was not designed to intervene on the administration of albumin or not, and thus this secondary study will only assess associations with patient and geographical factors, and not causal relations between the administration of albumin and outcomes.

In conclusion, this secondary study of the CLASSIC RCT will assess if patient characteristics and site are associated with the administration of IV albumin in a contemporary cohort of ICU patients with septic shock. This may inform and motivate future trials of albumin in these patients.

AUTHOR CONTRIBUTIONS

TSM, AG, MHM and AP conceived and designed the project. TSM wrote the first draft of the manuscript and submitted the manuscript for publication. All authors contributed to development of the protocol and critically reviewed the manuscript prior to submission.

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CONFLICT OF INTEREST STATEMENT

All authors were involved in the conduct of the CLASSIC trial. Tine Sylvest Meyhoff, Anders Granholm, Praleene Sivapalan, Morten Hylander Møller and Anders Perner are affiliated with the Department of Intensive Care at Rigshospitalet, which has received funding for other projects from The Novo Nordisk Foundation, Pfizer and Fresenius Kabi, Sygeforsikringen 'danmark', and has conducted contract research for AM-Pharma (the REVIVAL trial). Anders Perner has received an honorarium from Novartis for participation in an advisory board. Manu L.N.G. Malbrain is member of the medical advisory Board of Pulsion Medical Systems (part of Getinge group), Serenno Medical, Potrero Medical, Sentinel Medical and Baxter. He consults for B. Braun, Becton Dickinson, ConvaTec, Spiegelberg and Holtech Medical, and received speaker's fees from PeerVoice. He holds stock options for Serenno Medical and Potrero Medical. He is co-founder and President of the International Fluid Academy (IFA). The IFA (http://www.fluidacademy.org) is integrated within the not-for-profit charitable organisation iMERiT, International Medical Education and Research Initiative, under Belgian law.The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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