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RESEARCH ARTICLE

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Restrictive versus standard IV fluid therapy in adult ICU patients with septic shock—Bayesian analyses of the CLASSIC trial

Praleene Sivapalan[1,2,3] | Tine Sylvest Meyhoff[1,3] | Peter Buhl Hjortrup[3,4] | Theis Lange[3,5] | Benjamin Skov Kaas-Hansen[1,3,5] | Maj-Brit N. Kjær[1,2,3] | Jon Henrik Laake[3,6] | Maria Cronhjort[3,7] | Stephan M. Jakob[8] | Maurizio Cecconi[9,10] | Marek Nalos[11] | Marlies Ostermann[3,12] | Manu L. N. G. Malbrain[13] | Morten Hylander Møller[1,2,3] | Anders Perner[1,2,3] | Anders Granholm[1,2,3]

[1]Department of Intensive Care, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark

[2]Deptartment of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark

[3]Collaboration for Research in Intensive Care (CRIC), Copenhagen, Denmark

[4]Department of Cardiothoracic Anaesthesia and Intensive Care, The Heart Center, Copenhagen University Hospital—Rigshospitalet Copenhagen, Copenhagen, Denmark

[5]Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark

[6]Department of Intensive Care, Oslo University Hospital, Oslo, Norway

[7]Department of Clinical sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

[8]University of Bern, Bern, Switzerland

[9]Biomedical Sciences Department, Humanitas University, Milan, Italy

[10]Department of Anaesthesia and Intensive Care, IRCCS-Humanitas Research Hospital, Milan, Italy

[11]Department of Intensive Care, University Hospital Pilsen, Pilsen, Czech Republic

[12]Department of Intensive Care, Guy's and St Thomas' Hospital, London, UK

Abstract

Background: The CLASSIC trial assessed the effects of restrictive versus standard intravenous (IV) fluid therapy in adult intensive care unit (ICU) patients with septic shock. This pre-planned study provides a probabilistic interpretation and evaluates heterogeneity in treatment effects (HTE).

Methods: We analysed mortality, serious adverse events (SAEs), serious adverse reactions (SARs) and days alive without life-support within 90 days using Bayesian models with weakly informative priors. HTE on mortality was assessed according to five baseline variables: disease severity, vasopressor dose, lactate levels, creatinine values and IV fluid volumes given before randomisation.

Results: The absolute difference in mortality was 0.2%-points (95% credible interval: −5.0 to 5.4; 47% posterior probability of benefit [risk difference <0.0%-points]) with restrictive IV fluid. The posterior probabilities of benefits with restrictive IV fluid were 72% for SAEs, 52% for SARs and 61% for days alive without life-support. The posterior probabilities of no clinically important differences (absolute risk difference ≤2%-points) between the groups were 56% for mortality, 49% for SAEs, 90% for SARs and 38% for days alive without life-support. There was 97% probability of HTE for previous IV fluid volumes analysed continuously, that is, potentially relatively lower mortality of restrictive IV fluids with higher previous IV fluids. No substantial evidence of HTE was found in the other analyses.

Conclusion: We could not rule out clinically important effects of restrictive IV fluid therapy on mortality, SAEs or days alive without life-support, but substantial

[13]First Department of Anaesthesiology and Intensive Therapy, Medical University of Lublin, Lublin, Poland

Correspondence
Praleene Sivapalan, Department of Intensive Care, Copenhagen University Hospital—Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Email: praleene.sivapalan.01@regionh.dk

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effects on SARs were unlikely. IV fluids given before randomisation might interact with IV fluid strategy.

KEYWORDS
Bayesian analysis, fluid therapy, heterogeneity of treatment effects, intensive care unit, septic shock

Editorial Comment

This planned secondary analysis of the CLASSIC study, the trial which assessed benefit of two different fluid therapy approaches in ICU septic shock patients, presents a detailed Bayesean analysis of the different outcomes. In this analysis, pre-study likelihood estimates are included in re-analysis to generate estimates or models of probability distributions for each outcome which are also guided by the study observations. Presenting results in this way allows a more detailed view of the likelihood that the findings could have fallen on either side of the treatment effect estimates which again are based on both prior knowledge and the trial findings.

1 | INTRODUCTION

Sepsis and septic shock cause millions of deaths globally each year.[1,2] The Surviving Sepsis Campaign guidelines consider intravenous (IV) fluid therapy a cornerstone in the management of sepsis and septic shock.[1] However, no recommendations currently exist to guide the use of a restrictive or liberal fluid strategy due to insufficient evidence.[1]

The 'Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care' (CLASSIC) trial assessed the effects of restricted versus standard IV fluid therapy in adult intensive care unit (ICU) patients with septic shock.[3,4] The primary analysis showed an absolute difference of 0.1%-points (95% confidence interval—4.7 to 4.9) in 90-day all-cause mortality in the restrictive-fluid group compared with the standard-fluid group.

Herein, we present a pre-planned secondary analysis of the CLASSIC trial using Bayesian inference.[5] We aim to provide probabilistic interpretations of the CLASSIC results to aid researchers and clinicians with decision-making. The Bayesian analysis provides direct probabilities and allows a more straightforward way to quantify uncertainties using credible intervals (CrI) representing a range within which the true parameter value falls with a certain probability.[6–12] This is often clearer and more intuitive to interpretate compared to the frequentist confidence intervals. Additionally, we sought to nuance the interpretation as the Bayesian framework enables integration of pre-existing knowledge such as findings from recent meta-analyses.[6,12] This enhances sequential updating as new evidence emerges, making it suitable for addressing evolving research questions. As the sepsis definition covers a broad spectrum of heterogenous patients, we also assessed potential heterogeneity of treatment effects (HTE) according to baseline markers of illness severity and circulatory and renal impairment on 90-day all-cause mortality. Here, the Bayesian framework allows flexible modelling with complex hierarchical structures even with small sample sizes, which can be advantageous when data are limited.[11,13,14]

In the CLASSIC trial, the hypothesis was that IV fluid restriction would improve patient-important outcomes.[4] Therefore, we hypothesised that restricted IV fluid would reduce 90-day mortality and the effects might be larger in patients with greater severity of illness and more pronounced circulatory or renal impairment.[5]

2 | METHODS

This paper reports the results of pre-planned secondary Bayesian analyses of the CLASSIC trial.[5] The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[15] (see the Electronic Supplementary Material, ESM) and the analyses were conducted and reported according to the Reporting Of Bayes Used in clinical Studies (ROBUST) guideline.[16]

2.1 | CLASSIC trial

The European Clinical Trials Database (2018-000404-42), ClinicalTrials.gov: NCT03668236. The CLASSIC trial was an European, stratified, parallel-group, open-label randomised clinical trial.[3,4] Participants were enrolled in 31 ICUs in Denmark, Norway, Sweden, Switzerland, Italy, the Czech Republic, the United Kingdom and Belgium between November 2018 and November 2021. Adult ICU patients with septic shock according to the Sepsis-3 criteria[17] were eligible if onset was within 12 h and 1 L of IV fluids had been administered within 24 h prior to screening.[4] The participants were randomly assigned 1:1 to restricted IV fluid or standard IV fluid therapy. In the restrictive-fluid group, IV fluid could only be given in four prespecified conditions: (1) severe hypoperfusion, (2) replacing documented fluid losses, (3) correcting dehydration or electrolyte deficiencies or (4) ensuring a daily intake of 1 L of fluids.[3,4] In the standard-fluid group, no upper limits were set, and IV fluid should be administered under three conditions: (1) if the patient's haemodynamic factors improved,[18] (2) to replace expected or observed losses or correct dehydration or electrolyte derangements or

(3) maintenance fluid as recommendations at the ICU.[3,4] Additional details on the CLASSIC trial are available elsewhere.[3–5,19]

2.2 | Outcomes

2.2.1 | Primary outcome

All-cause mortality within 90 days after randomisation.

2.2.2 | Secondary outcomes

1. Number of patients with one or more serious adverse events (SAEs) in the ICU within 90 days after randomisation. SAEs were defined as ischaemic events (cerebral, cardiac, intestinal or limb ischaemia) or a new episode of severe acute kidney injury (modified Kidney Disease: Improving Global Outcomes [KDIGO] stage of 3).[20]
2. Number of patients with one or more serious adverse reactions (SARs) ascribed to IV crystalloids in the ICU within 90 days after randomisation.
3. Days alive without life-support within 90 days after randomisation (vasoactive circulatory support, invasive mechanical ventilation and renal replacement therapy).

2.3 | Statistical analyses

All statistical analyses were conducted using R version 4.1.2 (R Core Team, R Foundation for Statistical Computing) and Stan[21] (*RStan* version 2.21.0) through the *brms* R package.[13] All analyses were conducted in the intention-to-treat population as defined in the primary publications,[4,19] that is, after excluding five participants who did not consent to use of any data. Additionally, the primary outcome data were missing in four (0.3%) participants. Secondary outcome data were missing in eight (0.5%) participants. All analyses were adjusted for the stratification variables (trial site and absence or presence of haematologic/metastatic cancer).[4,5]

2.3.1 | Descriptive data

Descriptive data for the full trial cohort and all HTE-subgroups (defined below) stratified by treatment group are summarised as medians (interquartile ranges, IQRs) for numerical data, and as counts (percentages) for categorical data.

2.3.2 | Bayesian analyses

We used Bayesian inference to combine prior probability distributions and the observed CLASSIC trial data to estimate the posterior probability distributions of the treatment effect by way of Markov chain Monte Carlo sampling,[22] done in line with secondary analyses of previous trials.[8–11,23,24] We present the full posterior distributions graphically and summarise them by their medians (point estimates) and 95% percentile-based credible intervals (CrIs).[22] To leverage the probabilistic nature of Bayesian inference, we also present probabilities of any benefit/harm, clinically important benefit/harm, and no clinically important difference according to pre-defined thresholds (specified below).[5] Model specifications and diagnostics are presented in the ESM.

2.3.3 | Priors

The primary analyses of all outcomes used weakly informative priors covering all plausible effect sizes and centered at no difference, while having minimal influence on the posteriors. The sensitivity analyses used two additional sets of priors for the treatment effect to challenge the robustness of the primary analysis.[5] First, evidence-based priors based on the results from 12 other trials included in the latest systematic review (i.e., meta-analyses from the systematic review were re-run excluding CLASSIC, see the ESM).[25] Second, neutral sceptical priors (priors sceptical of large effect sizes but centered around no effect) were used as small or uncertain effects are found in many interventional trials in critically ill patients.[26]

2.3.4 | Primary and secondary outcomes

We used Bayesian logistic regression models adjusted for stratification variables to analyse binary outcomes (90-day mortality, SAEs and SARs) with results presented as conditional risk ratios (RRs) and risk differences (RDs), and secondarily as conditional odds ratios (ORs), in each group. We considered an absolute RD ≥2.0%-points as the minimally clinically important difference as protocolised and consistent with thresholds used in similar studies.[8,9] Days alive without life-support were analysed using a Bayesian linear regression model adjusted for the stratification variables with absolute difference as a conditional mean difference (MD) and the relative differences as conditional ratios of means (RoMs). We considered an absolute MD ≥1 day as clinically important in adherence with the predefined a prior thresholds.[5] Conditional effect estimates were derived by predicting expected outcomes for patients in each treatment group while keeping the adjustment variables at their most common values.

2.3.5 | Heterogeneity of treatment effects

We assessed potential HTE on 90-day all-cause mortality according to five pre-defined baseline characteristics reflecting the overall severity of illness and the degree of circulatory and renal impairment, using both four quartile-based subgroups and continuous scales[5]:

1. Simplified Mortality Score for the Intensive Care Unit (SMS-ICU, a severity score).[27]

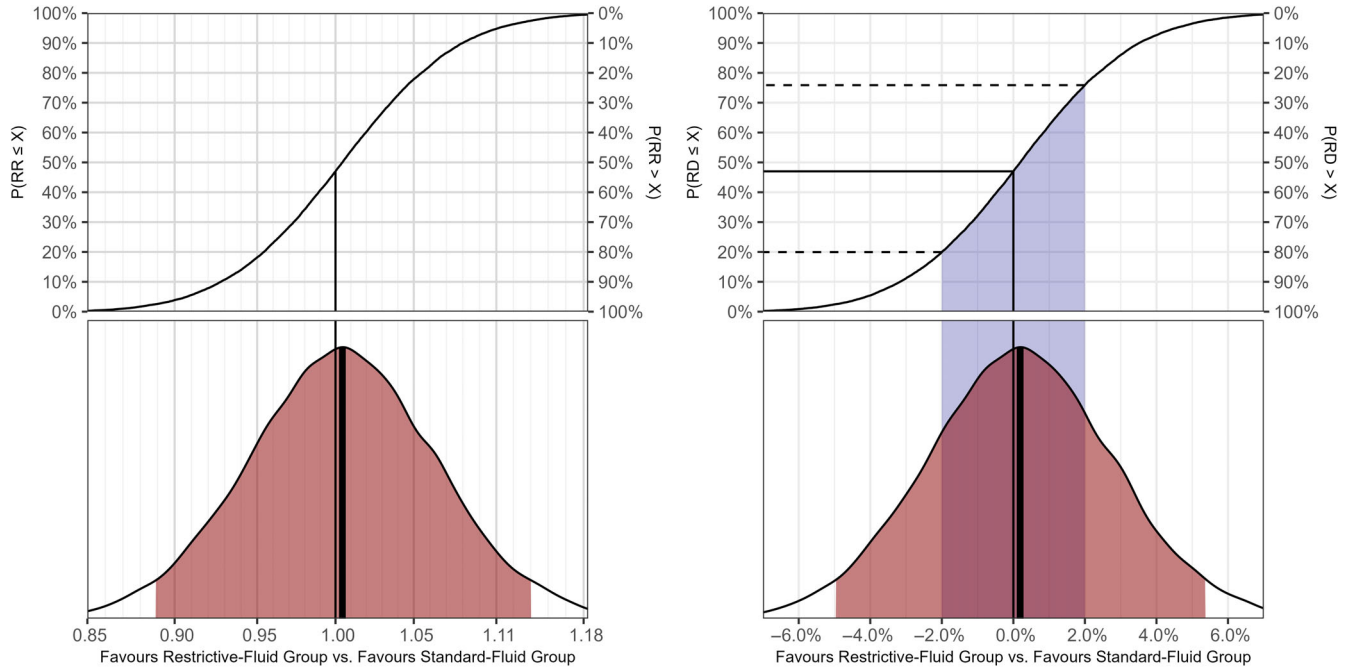

FIGURE 1 Posterior probability distributions for 90-day mortality using weakly informative priors. Posterior probability distributions for the conditional risk ratio and risk difference for 90-day all-cause mortality in the primary analysis using weakly informative priors, adjusted for trial site and the presence or absence of hematologic or metastatic cancer (stratification variables). The thin vertical lines represent exactly no difference. Top panels: cumulative posterior distributions of effect sizes. Bottom panels: corresponding posterior density plots with medians (thick vertical lines) and percentile-based 95% credible intervals (CrI, red areas). Left: risk ratio (RR) with a median of 1.00 (95% CrI 0.89 to 1.14) rounded to two decimals. Right: risk difference (RD) with a median of 0.2%-points (95% CrI −5.0 to 5.4). The blue area demarks effect sizes smaller than the pre-defined minimally clinically important effect. X denotes various treatment effect sizes on the horizontal axis with the corresponding probabilities of RR ≤ X or RD ≤ X values on the left Y-axis and RR > X or RD > X on the right Y-axis. For example, a probability of any benefit (RR <1.00 or RD <0.0%-points) with restrictive fluid is 47% (thin horizontal line), whereas the probability of no clinically important difference is 56% (dashed horizontal lines 76%–20%).

2. Highest dose of noradrenaline (within 3 h prior to randomisation).
3. Highest plasma lactate value (within 3 h prior to randomisation).
4. Highest plasma creatinine concentration (within 24 h prior to randomisation).
5. IV fluid volume in the 24 h prior to randomisation.

The full definitions of the baseline variables are available in the original trial protocol.[3] We used adjusted hierarchical Bayesian logistic regression models in each set of subgroups and present conditional RRs, RDs and ORs with adjustment variables set to their most frequent value. On the continuous scale, the models included interactions between the baseline variable of interest and the treatment effect. Conditional effects plots were used to visualise changes in probability of 90-day all-cause mortality in each group as the continuous baseline variable of interest increases whilst keeping all adjustment variables at their most frequent value. The probabilities for interaction ORs <1.00 (negative interaction, i.e., relatively lower mortality with restrictive IV fluids according to higher values of the baseline variable of interest) and interaction ORs >1.00 (positive interaction, i.e., relatively higher mortality risk with restrictive IV fluids according to higher values of the baseline variable of interest) are also presented in the plots.

2.3.6 | Missing data

As missingness was <5% for all variables of interest in each analysis, all analyses used complete cases only.[5]

3 | RESULTS

A total of 1545 patients (99.4%) were included, of whom 764 were assigned to the restrictive-fluid group and 781 to the standard-fluid group. Baseline characteristics were similar across the two treatment groups (ESM Table S1). All model diagnostics were considered acceptable (details in the ESM).

3.1 | Primary outcome

For 90-day all-cause mortality the RD was 0.2%-points (95% CrI: −5.0 to 5.4) corresponding to a RR of 1.00 (95% CrI 0.89 to 1.14). The probability of any benefit (i.e., a RD <0.0%-points) with restrictive IV fluid therapy was 47%, and the probability of clinically important benefit (i.e., a RD ≤−2.0%-points) was 20%. The probability of no

TABLE 1 Conditional treatment effect estimates and probabilities of effects.

Outcome	Effect estimates				Probability of effects with restrictive IV fluid therapy				
	Restrictive-fluid group Prob. (95% CrI)	Standard-fluid group Prob. (95% CrI)	Relative difference RR (95% CrI)[a]	Absolute difference RD (95% CrI)[a]	Any benefit (%)	Any harm (%)	Clinically important benefit (%)	Clinically important harm (%)	No clinically important difference (%)
Primary analyses using weakly informative priors									
All-cause 90-day mortality	42.5% (36.6 to 48.7)	42.3% (36.4 to 48.4)	1.00 (0.89 to 1.14)	0.2%-points (−5.0 to 5.4)	47%	53%	20%	24%	56%
Serious adverse events	33.7% (28.2 to 39.8)	35.2% (29.6 to 41.2)	0.96 (0.83 to 1.11)	−1.5%-points (−6.5 to 3.6)	72%	28%	42%	8.8%	49%
Serious adverse reactions	4.9% (3.0 to 7.4)	4.9% (3.1 to 7.5)	0.99 (0.61 to 1.59)	0.0%-points (−2.5 to 2.3)	52%	49%	5.2%	4.3%	90%
Days alive without life-support[a]	49.4 days (45.1 to 53.9)	50.0 days (45.7 to 54.4)	ROM 0.99 (0.92 to 1.07)	MD −0.54 days (−4.4 to 3.3)	61%	39%	41%	22%	38%
Sensitivity analyses using evidence-based priors									
All-cause 90-day mortality	42.1% (36.5 to 48.0)	42.8% (37.2 to 48.6)	0.98 (0.90 to 1.07)	−0.7%-points (−4.2 to 2.7)	66%	34%	23%	6.3%	71%
Serious adverse events	33.5% (28.1 to 39.3)	35.5% (30.0 to 41.3)	0.94 (0.83 to 1.07)	−2.0%-points (−6.4 to 2.3)	82%	18%	50%	3.5%	46%
Serious adverse reactions	4.5% (2.8 to 7.0)	5.2% (3.3 to 7.8)	0.88 (0.55 to 1.37)	−0.6%-points (−2.9 to 1.6)	71%	29%	11%	1.2%	87%
Days alive without life-support[a]	49.8 days (45.8 to 53.9)	49.7 days (45.6 to 53.7)	ROM 1.00 (0.98 to 1.03)	MD 0.15 days (−1.0 to 1.3)	40%	60%	2.4%	7.4%	90%
Sensitivity analyses using neutral sceptical priors									
All-cause 90-day mortality	42.5% (36.8 to 48.4)	42.4% (36.6 to 48.2)	1.00 (0.91 to 1.11)	0.1%-points (−4.0 to 4.3)	47%	53%	16%	19%	66%
Serious adverse events	34.1% (28.6 to 39.8)	35.0% (29.6 to 40.8)	0.97 (0.86 to 1.09)	−1.0%-points (−5.0 to 3.0)	68%	32%	31%	7.2%	62%
Serious adverse reactions	4.9% (3.3 to 7.2)	4.9% (3.3 to 7.2)	1.00 (0.78 to 1.28)	0.0%-points (−1.2 to 1.3)	52%	49%	0.1%	0.1%	99.7%
Days alive without life-support[a]	49.6 days (45.4 to 53.9)	49.9 days (45.6 to 54.2)	ROM 0.99 (0.93 to 1.06)	MD −0.3 days (−3.4 to 2.8)	58%	42%	33%	20%	47%

Note: All analyses were conducted in the intention-to-treat population after exclusion of five participants who did not consent to use of any data; four participants were not included in the analyses due to missing primary outcome data ($n = 1545$). Secondary outcomes were missing in eight participants, and further eight participants were missing number of serious adverse events as baseline creatinine was not available. All analyses were adjusted for stratification variables being trial site and the presence or absence of hematologic or metastatic cancer. The effect estimates are reported as conditional treatment effects with median posterior values as point estimates and percentile-based 95% credible intervals (CrIs). All definitions of thresholds for clinically important differences were pre-specified in the protocol[5] and are listed in the methods section. For all binary outcomes, any benefit is the probability of an RD <0.0% (RR <1.00) and for count outcome MD >0 day (RoM >1). Similarly, any harm is the probability of an RD >0.0%-points (RR >1.00) or an MD <0 day (RoM <1). Clinically important benefit is defined as the probability of an RD ≤−2.0%-points (for binary outcomes) or MD ≤ −1 day (for count outcomes). Correspondingly, clinically important harm is the probability of an RD ≥2.0%-points (for binary outcomes) and an MD ≥1 day (for count outcomes). No clinically important difference is the probability of a RD >−2.0% and a RD <2.0% or an MD >−1 day and an MD <1 day.

[a]The relative difference is reported as ratios of means (RoMs) and the absolute differences as mean differences (MDs) for the secondary count outcome (days alive without life-support).

Abbreviations: CrI, credible interval; MD, mean difference; RD, risk difference; RoM, ratio of means; RR, risk ratio.

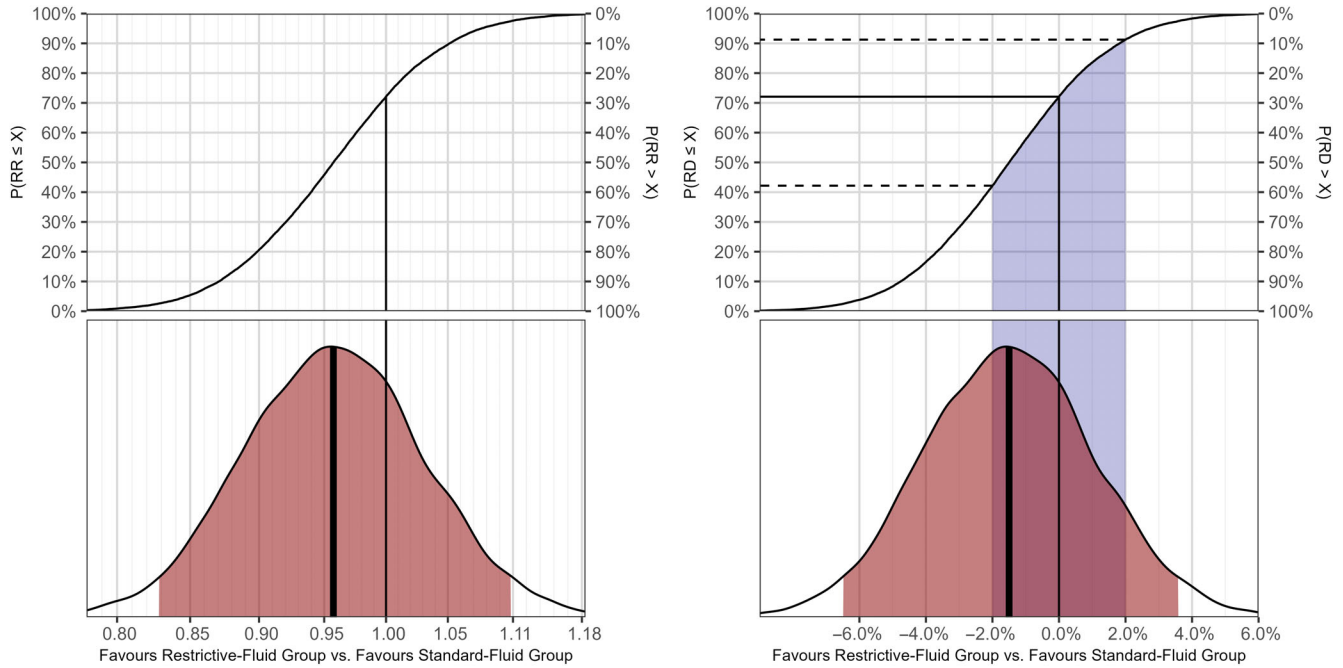

FIGURE 2 Posterior probability distribution for serious adverse events using weakly informative priors. Posterior probability distributions for the conditional risk ratio and risk difference for serious adverse events in the primary analysis using weakly informative priors, adjusted for trial site and the presence or absence of hematologic or metastatic cancer (stratification variables). The thin vertical lines represent exactly no difference. Top panels: cumulative posterior distributions of effect sizes. Bottom panels: corresponding posterior density plots with medians (thick vertical lines) and percentile-based 95% credible intervals (CrI, red areas). Left: risk ratio (RR) with a median of 0.96 (95% CrI 0.83 to 1.11). Right: risk difference (RD) with a median of −1.5%-points (95% CrI—6.5 to 3.6). The blue area demarking effect sizes smaller than pre-defined minimally clinically important effect. X denotes various treatment effect sizes on the horizontal axis with the corresponding probabilities of RR ≤ X or RD ≤ X values on the left Y-axis and the RR > X or RD > X on the right Y-axis. For example, a probability of any benefit (RR <1.00 or RD <0.0%-point) with restrictive fluid is 72% (thin horizontal line), whereas the probability of no clinically important difference is 49% (dashed horizontal lines 91%–42%).

clinically important difference (i.e., a RD >−2.0%-point and RD <2.0%-point) was 56%. The full posterior probability distributions are illustrated in Figure 1 and Figure S1. In the sensitivity analyses using an evidence-based prior, the probability of any benefits of restrictive IV fluid was 66% (47% with a neutral sceptical prior) and 23% for clinically important benefits (16% with a neutral sceptical prior). The estimated treatment effects and probabilities of select effect sizes for all sets of priors are presented in Table 1. The full posterior probability distributions of the sensitivity analyses are presented in the ESM (Figures S2 and S3).

3.2 | Secondary outcomes

We found a RD of −1.5%-points (95% CrI: −6.5 to 3.6) with 72% probability of any benefit (i.e., RD <0.0%-points) with restrictive IV fluid therapy for SAEs (Figure 2). For SARs the RD was 0.0%-points (95% CrI: −2.5 to 2.3) with 90% probability of no clinically important difference (i.e., a RD > −2.0%-point and RD <2.0%-point) with restrictive versus standard IV fluid therapy. The MD was −0.5 days (95% CrI −4.4 to 3.3) for days without life support with 38% probability of no clinically important difference between the groups. In sensitivity analysis using an evidence-based prior, the probability of any beneficial effects (i.e., a RD <0.0%-points) of restrictive IV fluid therapy was 82% for SAEs, while it was 68% using a neutral sceptical prior. The probabilities of no clinically important differences between the groups with evidence-based and neutral sceptical priors were 87% and 99.7%, respectively, for SARs, and 90% and 47%, respectively, for days alive without life-support. Table 1 shows the conditional treatment effect estimates and probabilities of pre-defined effect sizes for all secondary outcomes. The full posterior probabilities are presented for all secondary outcomes in the ESM (Figures S4–S12).

3.3 | Heterogeneity of treatment effects

Baseline characteristics according to the quintiles of HTE subgroups are presented in the ESM (Tables S2–S6). There was a 97% probability of negative interaction between the restrictive IV fluid strategy and IV fluid volumes given before randomisation in the continuous HTE analysis on mortality (i.e., a decreased mortality of restrictive IV fluid therapy with higher IV fluid volumes given before randomisation and conversely a reduced mortality of

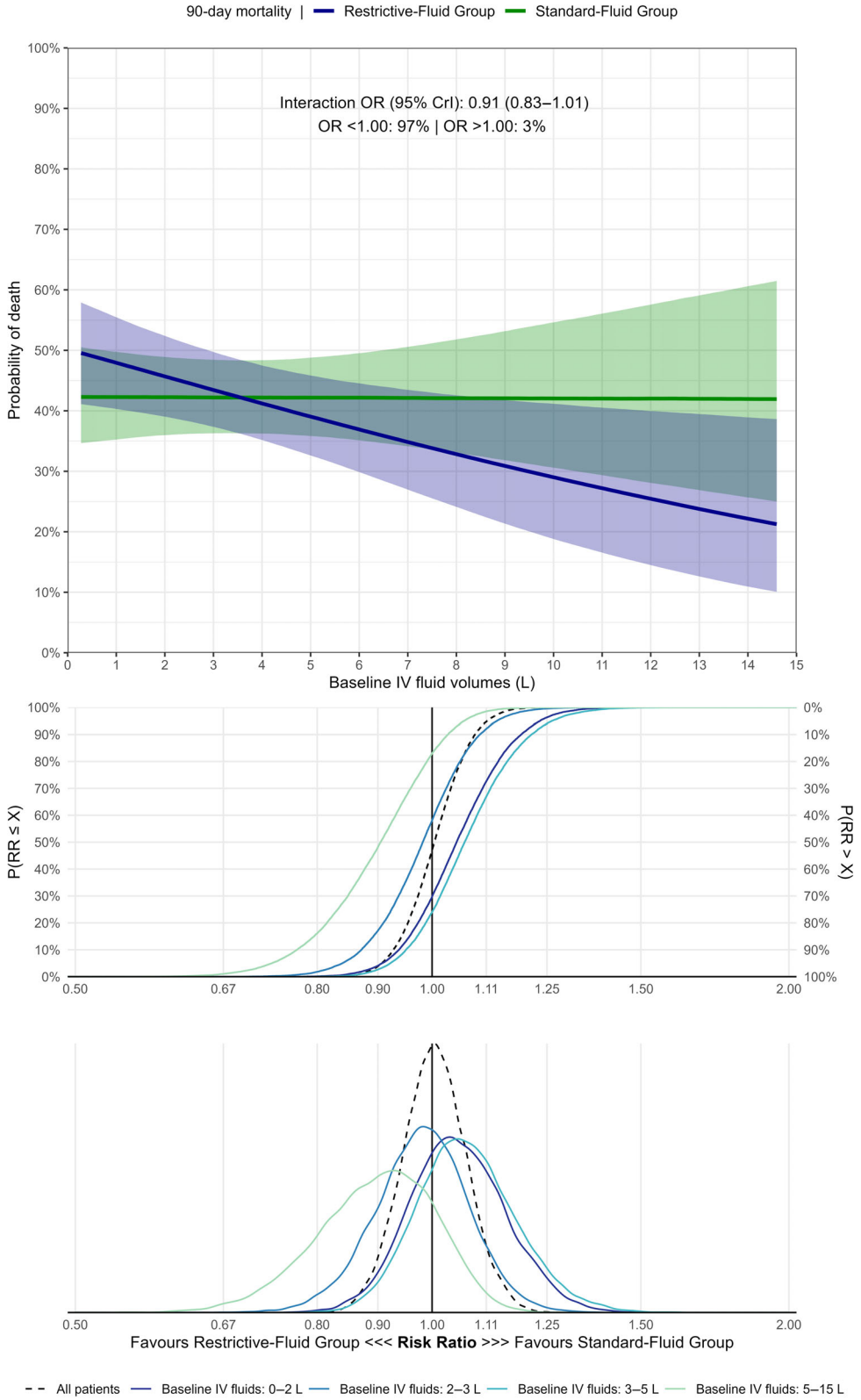

FIGURE 3 HTE analyses according to baseline IV fluid volumes using weakly informative priors. Analysis of heterogeneity of treatment effects for 90-day all-cause mortality using weakly informative priors. Upper panel: conditional effects of the interaction between treatment allocation and baseline IV fluid use (IV fluid volume received in the 24 h prior to randomisation). The plot displays the estimated mortality risk on the vertical axis and IV fluid volumes given before randomisation on the horizontal axis. The conditional odds ratio of the interaction is 0.91 (95% credible interval: 0.81 to 1.01), and there is a 97% probability that mortality in the restrictive fluid group decreases with increased IV fluid volumes given before randomisation. Lower panel: the cumulative posterior probability distributions with corresponding posterior density plots of the conditional risk ratios of 90-day all-cause mortality in the full sample and by quartile-based subgroups.

TABLE 2 Summarised effect measures for 90-day all-cause mortality—using weakly informative priors.

Group	*n*	Restrictive-fluid group Prob. (95% CrI)	Standard-fluid group Prob. (95% CrI)	Relative difference RR (95% CrI)	Absolute difference RD (95% CrI)
All patients	1545	42.5% (36.6 to 48.7%)	42.3% (36.4 to 48.4%)	1.00 (0.89 to 1.14)	0.2% (−5.0 to 5.4%)
Baseline SMS-ICU	1537				
7–19	365	30.0% (23.3% to 37.5%)	28.6% (21.8% to 36.4%)	0.96 (0.73 to 1.21)	−1.3% (−9.1% to 5.7%)
20–21	229	36.3% (27.2% to 45.6%)	37.8% (28.7% to 48.1%)	1.03 (0.83 to 1.42)	1.0% (−6.6% to 12.9%)
22–24	418	44.3% (36.4% to 52.3%)	44.8% (37.0% to 52.9%)	1.01 (0.85 to 1.22)	0.3% (−7.0% to 8.8%)
25–38	525	62.0% (53.8% to 69.8%)	59.4% (51.1% to 67.0%	0.96 (0.84 to 1.07)	−2.5% (−10.4% to 4.0%)
Baseline vasopressor dose—mg/kg/min	1537				
0–0.11	356	30.3% (23.0% to 38.4%)	32.4% (25.3% to 40.9%)	0.94 (0.70 to 1.16)	−1.8% (−11.0% to 4.7%)
0.12–0.23	407	38.7% (31.2% to 46.6%)	39.1% (31.8% to 47.0%)	0.99 (0.82 to 1.19)	0.98 (0.72% to 1.33%)
0.24–0.42	289	45.9% (38.1% to 54.0%)	45.2% (37.3% to 53.1%)	1.01 (0.86 to 1.22)	1.02 (0.77% to 1.44%)
0.43–3.4	385	50.8% (42.8% to 58.9%)	50.0% (41.8% to 58.0%)	1.01 (0.88 to 1.21)	1.03 (0.77% to 1.46%)
Baseline lactate—mmol/L	1537				
1.1–2.6	357	36.5% (28.8% to 44.5%)	37.3% (29.9% to 45.4%)	0.98 (0.78 to 1.18)	−0.7% (−9.2% to 6.2%)
2.7–3.7	396	35.9% (28.6% to 43.8%)	34.9% (27.7% to 42.6%)	1.03 (0.85 to 1.28)	0.9% (−5.8% to 8.6%)
3.8–6	394	39.6% (31.8% to 47.8%)	38.0% (30.5% to 45.8%)	1.04 (0.87 to 1.29)	1.3% (−5.4% to 9.9%)
6.1–29	390	57.8% (49.5% to 65.7%)	58.8% (50.9% to 66.6%)	0.99 (0.85 to 1.11)	−0.8% (−9.3% to 6.2%)
Baseline creatinine—mmol/L	1528				
21–95	377	37.6% (30.0% to 45.7%)	36.9% (29.0% to 45.0%)	1.02 (0.82 to 1.28)	0.7% (−7.1% to 8.9%)
96–143	387	35.6% (27.5% to 44.0%)	39.4% (31.6% to 47.5%)	0.91 (0.69 to 1.12)	−3.5% (−13.6% to 4.4%)
144–222	381	48.1% (39.6% to 56.7%)	48.1% (39.8% to 56.4%)	1.00 (0.84 to 1.19)	0.0% (−8.5% to 8.5%)
223–2000	383	49.7% (41.5% to 58.4%)	45.8% (38.0% to 53.9%)	1.08 (0.91 to 1.33)	3.5% (−4.4% to 13.6%)
Baseline IV fluids—L	1537				
0–2	347	45.7% (37.8% to 54.4%)	43.3% (36.6% to 50.9%)	1.05 (0.88 to 1.27)	2.1% (−5.5% to 11.0%)
2–3	421	40.9% (33.0% to 48.8%)	41.7% (34.7% to 48.6%)	0.98 (0.81 to 1.17)	−0.7% (−8.3% to 6.5%)
3–5	384	44.5% (36.7% to 53.0%)	41.7% (34.3% to 48.8%)	1.07 (0.90 to 1.31)	2.7% (−4.5% to 11.8%)
5–15	385	38.1% (29.5% to 46.8%)	42.4% (35.5% to 49.6%)	0.90 (0.70 to 1.09)	−4.0% (−13.5% to 3.7%)

Note: All analyses were conducted in the intention-to-treat population after exclusion of five participants who did not consent to use of any data; four participants were not included in the analyses due to missing primary outcome data ($n = 1545$). All baseline variables were missing in eight participants, and further nine participants were missing baseline creatinine.

Abbreviations: CrI, credible interval; IV, intravenous; Prob., probability; RD, risk difference (<0.0%-points favours the restrictive-fluid group); RR, risk ratio (<1.00 favours the restrictive-fluid group); SMS-ICU, Simplified Mortality Score for the Intensive Care Unit.[27]

standard IV fluid therapy with lower volumes before randomisation, Figure 3). In the subgroup-based HTE analyses of IV fluid volumes given before randomisation, the posterior distribution for the highest subset (5–15 L) favoured the restrictive group corresponding to an RD of −4.0%-points (95% CrI: −13.5 to 3.7) in 90-day all-cause mortality (Table 2). In the lowest IV fluid subset (0–2 L), we found a RD in the other direction of 2.1%-points (95% CrI: −5.5 to 11.0). However, no dose-dependent relationship across all four subsets was present (Figure 3, Table 2). There were no strong suggestions of HTE in the subgroup-based analyses of other baseline variables as the posterior distributions generally covered both benefit and harm. The summarised effect measures of 90-day all-cause mortality with corresponding estimates in the four sets of subgroups using weakly informative priors are reported in Table 2 (estimates from the sensitivity analyses are reported in the ESM Tables S7 and S8). The full posterior probability distributions of the subgroup-based HTE analyses are available in the ESM (Figures S13–S21).

The probabilities of negative interactions between restrictive IV fluid strategy and the remaining baseline variables were 82% with higher baseline lactate concentrations, 68% with higher plasma creatinine concentrations, 57% with higher severity of illness (SMS-ICU) and 44% with higher vasopressor doses. Results were generally consistent across sensitivity analyses using other priors. The conditional effects plots for all five baseline variables of interest with estimated interactions are presented in the ESM (Figures S22–S24).

4 | DISCUSSION

In this pre-planned secondary Bayesian analysis of the CLASSIC trial, we could not rule out clinically important effects of restrictive IV fluid therapy on mortality, SAEs or days alive without life support, but substantial effects on SARs were unlikely. Furthermore, IV fluid volumes given before randomisation may interact with IV fluid strategy.

The Bayesian framework provides a unique opportunity to nuance the interpretation of the trial and enables integration of all available evidence including knowledge from previous studies (here incorporated in the sensitivity analyses evidence-based priors) even if the results are conflicting.[6] Applying the evidence-based priors yielded fairly high posterior probabilities for no clinically important difference with restrictive versus standard IV fluid therapy for SARs and days alive without life-support; for mortality, it yielded a moderate probability of no clinically important difference between the groups; for SAEs, it yielded a moderate probability of benefit with restrictive fluid therapy. So when taking previous finding into account, even though IV fluid strategy in the CLASSIC trial may not have exerted any clinically important effects on SARs and days alive without live support, some uncertainty remains as to the effects on all-cause mortality and SAEs.

A recent systematic review with meta-analysis including 13 randomised clinical trials (including CLASSIC) concluded that lower as compared with higher IV fluid volumes probably result in little to no difference in all-cause mortality, but the result was limited by imprecision, as the estimate did not exclude potential benefit or harm.[4,25] Although the trial sequential analysis assessing imprecision of the effect estimate had reached futility based on a priori 15% relative risk reduction of a 45% mortality rate, the evidence was downgraded as smaller clinically relevant risk reduction could still exist.[25] Given the nature of the widely practiced intervention in sepsis management, uncovering even smaller difference in mortality could be of relevance for patients, clinicians, researchers and policymakers. However, this would require larger sample sizes than conventionally used within this field.

Our results emphasise the potential impact of initial IV fluids as our analyses of potential HTEs suggest that a restrictive approach may be favourable in patients who have received higher IV volumes before randomisation, whereas the opposite may have been the case for those who received lower IV volumes before randomisation. However, a dose–response relationship, if any, was not clear in the subgroup-based HTE analysis, and thus, these observations should be interpreted cautiously. Nevertheless, it is important to follow and thoroughly register initial fluid volumes to assess clinical implications. Evidence from ongoing trials will provide data on the potential effects of initial fluid volumes.[28–35]

This study has strengths, including those of the CLASSIC trial, that is, international recruitment, large sample size and high levels of data completeness.[4] This was a pre-planned secondary study where the protocol and statistical analysis plan were submitted for publication before closing the CLASSIC trial database. Lastly, our results were relatively robust to different priors.

There are also limitations to our study. First, limitations related to the CLASSIC trial, for example, its open-label nature equally apply here. The trial protocol was violated in 162 participants (21.5%) in the restrictive-fluid group and 101 participants (13.0%) in the standard-fluid group, which may have affected the estimated intervention effects. Second, the categorisation of participants in the subgroup-based HTE analyses was data-driven, and cut-offs may not reflect the most clinically relevant ones. However, this limitation was counterbalanced by the analyses of HTE on a continuous scale. Third, the assumption of linearity (on the log-odds scale) in the HTE analyses may have been restrictive but was chosen to avoid potential overfitting and increased complexity of models without this limitation. However, the results in the subgroups agreed reasonably well with those using the continuous data directly in most instances. Fifth, our protocolised definitions of clinically important effect sizes can be challenged, and other reasonable thresholds could be considered. However, as the full posteriors are available, the estimation of probabilities of alternative effect sizes of interest is straightforward.

In conclusion, we could not rule out clinically important effects of restrictive IV fluid therapy on mortality, SAEs and days alive without life-support among ICU patients with septic shock, but clinically important effects on SARs were unlikely. We found no clear evidence of HTE, but our results suggest an interaction between IV fluid volumes given before randomisation and IV fluid strategy.

AUTHOR CONTRIBUTIONS

Conceptualisation and study design: PS, TM, MHM, AP and AG. *Data analysis*: PS, BSKH and AG. *Writing first draft*: PS. *Critical review and approval of manuscript*: all authors. *Guarantor*: AP.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Praleene Sivapalan https://orcid.org/0000-0002-0442-0032
Tine Sylvest Meyhoff https://orcid.org/0000-0002-1840-1596
Peter Buhl Hjortrup https://orcid.org/0000-0002-3847-3247
Theis Lange https://orcid.org/0000-0001-6807-8347
Benjamin Skov Kaas-Hansen https://orcid.org/0000-0003-1023-0371
Maj-Brit N. Kjær https://orcid.org/0000-0002-6536-0504
Jon Henrik Laake https://orcid.org/0000-0001-6157-5359
Maria Cronhjort https://orcid.org/0000-0002-0444-8553
Stephan M. Jakob https://orcid.org/0000-0002-2195-0473
Maurizio Cecconi https://orcid.org/0000-0002-4376-6538
Marek Nalos https://orcid.org/0000-0002-7977-9410
Marlies Ostermann https://orcid.org/0000-0001-9500-9080
Manu L. N. G. Malbrain https://orcid.org/0000-0002-1816-5255
Morten Hylander Møller https://orcid.org/0000-0002-6378-9673
Anders Perner https://orcid.org/0000-0002-4668-0123
Anders Granholm https://orcid.org/0000-0001-5799-7655

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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