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REVIEW ARTICLE

Conservative vs. liberal fluid therapy in septic shock – Protocol for secondary Bayesian analyses of the CLASSIC trial

Praleene Sivapalan[1,2] | Tine S. Meyhoff[1,2] | Peter B. Hjortrup[1,2] | Theis Lange[2,3] | Morten Hylander Møller[1,2] | Anders Perner[1,2] | Anders Granholm[1,2]

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

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

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

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

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Abstract

Background: Clinical equipoise exists regarding intravenous (IV) fluid volumes in sepsis. The Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) trial investigates the effect of restricted vs. standard IV fluid therapy in 1554 adult intensive care unit patients with septic shock.

Methods: This protocol describes secondary Bayesian analyses of the primary outcome (90-day all-cause mortality) and three secondary outcomes at day 90. We will analyse all binary outcomes with adjusted Bayesian logistic regressions and present results as conditional relative risks and risk differences with 95% credibility intervals (CrIs). The secondary count outcome will be analysed using adjusted Bayesian linear regression with results summarised as conditional mean differences and ratios of means with 95% CrIs. We will use weakly informative priors for the primary analyses, and sceptical and evidence-based priors in the sensitivity analyses. Exact probabilities will be presented for any benefit/harm, clinically important benefit/harm and no clinically important difference. We will assess whether heterogeneity of treatment effects on mortality is present using Bayesian hierarchical models in subgroups and on the continuous scale using models with interactions according to five baseline variables assessing the overall severity of illness and the degree of circulatory and renal impairment.

Discussion: The outlined analyses will supplement the primary analysis of the CLASSIC trial by describing probabilities of beneficial and harmful effects and evaluating heterogeneity of treatment effects in a framework that may be easier to interpret for researchers and clinicians.

1 | INTRODUCTION

Intravenous (IV) fluids are considered essential in the management of sepsis, and the Surviving Sepsis Campaign guideline suggests at least 30 ml/kg IV fluid volumes should be given initially to adult patients based on low quality evidence.[1] The guideline committee found that there was insufficient evidence to make recommendation on the use of restrictive versus liberal fluid strategy after initial

Trial registration: The European Clinical Trials Database (2018-000404-42) and www.clinicaltrials.gov: NCT03668236.

resuscitation.[1] On the other hand, concerns have been raised regarding potential harm from higher IV fluid volumes, as recent systematic reviews have indicated that restrictive fluid therapy may be associated with reduced mortality,[2,3] length of stay in intensive care unit (ICU),[3] and occurrence of serious adverse events[3] in critically ill patients. However, the certainty of evidence was very low.[2] Likewise, the evidence is uncertain about whether a restrictive approach may increase the number of ventilator-free days.[2,3]

The Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) trial randomised 1554 adult ICU patients with septic shock to restricted IV fluid versus standard fluid therapy.[4]

In this outlined secondary analysis of the CLASSIC trial, we will conduct Bayesian analyses of the primary outcome and three secondary outcomes and analyses of heterogeneity of treatment effects (HTE) according to different baseline characteristics on the primary outcome. This will complement the primary analysis by describing probabilities of beneficial and harmful effects of various magnitudes.

We hypothesise that restricted IV fluid will reduce 90-day mortality, an effect which may be larger in patients with greater severity of illness and more pronounced circulatory or renal impairment.

2 | METHODS

2.1 | Study design

This is a protocol and statistical analysis plan for a predefined secondary Bayesian analysis including HTE analysis of the CLASSIC trial. We prepared the manuscript according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[5] (see checklist in the supplement) and the Bayesian analyses in accordance with the Reporting of Bayes Used in clinical STudies (ROBUST) guidelines.[6]

2.2 | CLASSIC trial

The CLASSIC trial is an international, randomised, stratified, parallel-group, open-label clinical trial.[4] The trial included 1554 adult ICU patients (≥18 years) with septic shock, according to the Sepsis-3 criteria.[7] Complete enrolment criteria are available in the primary trial protocol[4] and in the supplement. The patients were randomly assigned 1:1 to restricted IV fluid or standard fluid therapy. The first patient was enrolled November 27, 2018, the last patient on November 16, 2021 with complete 90-day follow-up on February 14, 2022. The trial database is expected to be closed on March 7, 2022.

2.2.1 | Approvals

The CLASSIC trial is registered at the European Clinical Trials Database (2018-000404-42) and ClinicalTrials.gov (NCT03668236); approved by the Danish Medicines Agency (2018020596), the Danish National Committee on Health Research Ethics (H-18006255) and the Danish Data Protection Agency. Additional details about the trial is available in the primary protocol[4] and the trial website.[8]

2.3 | Statistical analyses

2.3.1 | General principles

This study will use data from all patients in the intention-to-treat population of the CLASSIC trial (all randomised patients except those without consent for use of their data). All statistical analyses will be conducted using R (R Core Team, R Foundation for Statistical Computing) and Stan[9] through the *brms* R package.[10] This statistical analysis plan has been prepared according to recent recommendations,[11,12] and follows the principles outlined in recent secondary Bayesian analyses including HTE analyses.[13–15]

2.3.2 | Descriptive data

We will present descriptive baseline and outcome data as medians with interquartile ranges for numerical data, and as numbers with percentages for categorical data as in the main publication.[4] A table stratified by treatment allocation will be presented including the baseline variables age, sex, stratification variables, variables used in the HTE analyses specified below and the four outcomes assessed in this study. Moreover, baseline data for each subgroup including stratification by treatment allocation will be presented in the supplement.

2.3.3 | Bayesian statistical methods

We will use Bayesian analyses to assess probabilities of different effect sizes of interest. This approach incorporates previous belief with a prior probability distribution, which is updated with the collected data from the trial to inform and reallocate probabilities to form a posterior probability distribution.[16]

2.3.4 | Bayesian analysis of primary and secondary outcomes

We will conduct secondary Bayesian analyses of the primary outcome, 90-day all-cause mortality and three secondary outcomes: (1) number of patients with one or more serious adverse events; (2) number of patients with one or more serious adverse reactions; (3) and days alive without life support at day 90, defined as the absolute number of days alive without circulatory support, invasive mechanical or renal replacement therapy received up to day 90.[4] Binary outcomes will be analysed using Bayesian logistic regression models adjusted for stratification

variables, i.e. site and metastatic or hematologic cancer. Adjusted relative risks (RRs) will be estimated using conditional predicted probabilities for a reference in each treatment group with adjustment variables set to their most frequent category. Adjusted risk differences (RDs) will similarly be calculated from conditional predicted probabilities. Exact probabilities will be presented for any benefit/harm (defined as RD < 0 or RD > 0 percentage points, respectively), clinically important benefit/harm (defined as a RD > 2 or RD<−2 percentage points, respectively) and no clinically important difference.

We expect the continuous secondary outcome, days alive without life support, to be skewed (non-normally distributed) and zero-inflated. Despite the skewed distribution, this outcome will be analysed using a Bayesian linear regression model, which is robust and adequately allows estimation of the effect measures of interest.[17] We will present adjusted conditional mean differences (MD) and ratios of means. Exact probabilities will be presented for any benefit/harm (defined as MD > 0 or MD < 0), and clinically important benefit/harm (defined as a MD ≥ 1 and MD ≤ 1), and no clinically important difference.

2.3.5 | Subgroup-based HTE analysis of the primary outcome

We will assess the presence and magnitude of HTE for the primary outcome according to five sets of four quartile-based subgroups based on the following baseline variables:

1. Overall severity of illness: baseline Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).[18]
2. Vasopressor requirement: highest dose of noradrenaline within 3 h prior to randomisation.
3. Lactate concentration: highest plasma lactate value within 3 h prior to randomisation.
4. Creatinine concentration: highest plasma creatinine value within 24 h prior to randomisation.
5. IV fluid volumes: volume of IV fluid 24 h prior to randomisation.

Severity of illness measured with SMS-ICU considers multiple independent risk factors, which together predicts 90-day mortality.[18] Noradrenaline dose and plasma lactate concentrations are both proxy markers for severity of shock, which has been associated with increased mortality in these patients.[7] Patients with higher creatine levels might receive more IV fluid as acute kidney injury is a common indication for use of fluid[19] and is also a common indication for renal replacement therapy (RRT).[20] Fluid overload with initiation of RRT has been associated with increased mortality.[20]

The presence of HTE will be assessed separately in each set of subgroups using hierarchical Bayesian logistic regression models adjusted for the stratification variables with results presented as conditional RRs and RDs, calculated as specified above. Hierarchical models partially pool data and shrink effect estimates in each subgroup towards the overall estimate to protect again exaggerated subgroup effects.[10] Thus, more shrinkage will be applied with more extreme or uncertain subgroup estimates to produce more reliable subgroups effect.

2.3.6 | Continuous HTE analyses

Additionally, we will conduct analyses of HTE on the primary outcome, 90-day all-cause mortality, according to the five selected baseline variables on the continuous scale using adjusted Bayesian logistic regression models with interactions. We will assess the effects between each variable of interest on the continuous scale, the treatment effects, and their interaction on all-cause mortality at day 90 in separate models. The results will be presented graphically as conditional effects plots (on the natural outcome scale) with all adjustment variables set to their most common value. When all other variables are kept constant, the conditional effects show how the probabilities of an outcome change with changes in the baseline variable of interest in the two treatment groups.

2.3.7 | Priors

We will use three different types of prior distributions in separate analyses to check the robustness of our findings according to different prior assumptions. We will use weakly informative priors including all plausible effect sizes for the primary analyses, which means our prior beliefs will have minimal influence on the results. Furthermore, two sensitivity analyses will be conducted using sceptical priors centred on no difference for the treatment effects, and evidence-based priors based on a recent systematic review and meta-analysis of RCTs comparing higher vs. lower fluid volumes in adult patients with sepsis.[2] There are currently not adequate data to specify an evidence-based prior for one of the secondary outcomes, serious adverse reactions. Consequently, this outcome will only be analysed using weakly informative and sceptical priors unless an evidence-based prior becomes available. Exact priors and detailed reasoning are presented in the supplement.

2.3.8 | Summarisation and presentation of results

Full posterior distributions for the parameters of interest (treatment) will be graphically presented and summarised using median values as point estimates with 95% percentile-based credible intervals (CrIs) representing the 95% most plausible effect sizes according to the prior data and model.[16]

2.3.9 | Missing data handling

We expect limited missing data for all included outcomes and stratification variables in the CLASSIC trial. We will present the amount

of missing data. Complete case analysis will be performed if <5% of patients in total have missing data for each analysis. Otherwise, 25 datasets that will be multiply imputed separately in each intervention group using the *mice* R package[21] under the assumption data are missing at random. We will use the predictive mean matching method for continuous variables and logistic regression for missing categorical variables.[21] If multiple imputation is used, models will be fit separately in each imputed dataset, followed by stacking the posterior draws from all models and using the stacked posteriors for all subsequent calculations.

Multiple imputation will be performed using all outcomes described in this protocol, the variables used in the HTE analyses described above, the stratification variables, site of infection at baseline, comorbidities at baseline (i.e. ischemic heart disease or heart failure, chronic hypertension or chronic RRT), participant weight at baseline, mechanical ventilation at baseline, use of corticosteroids at baseline and habitual p-creatinine.[4]

In case of multiple imputation, model fit will be assessed separately in each dataset before pooling the posterior draws, with the required number of post-warm-up samples and bulk/tail effective sample sizes applying to the pooled posteriors. Descriptive baseline data and the percentiles used to subgroup patients will be calculated using data from all the imputed stacked datasets.

2.3.10 | Model diagnostics

We will use Stan's default dynamic Hamiltonian Monte–Carlo sampler with fours chains with at least 10,000 post-warm-up samples in total, and at least 1000 bulk/tail effective sample sizes for all parameters. Model adequacy will be assessed as previously described.[17,22–24]

2.3.11 | Dissemination

The results of the outlined secondary analysis will be submitted to an international peer-reviewed journal regardless of their direction. The results will be reported according to the STROBE statement[5] and ROBUST guidelines.[6]

3 | DISCUSSION

The outlined secondary Bayesian analyses will supplement the primary conventional frequentist analyses of the CLASSIC trial. The analyses will provide important data on the probable effects of the two different IV fluid strategies, and whether these differ according to overall severity of illness, and that of circulatory or renal impairment. The results from the outlined Bayesian analyses may aid researchers and clinicians in the interpretation of the effects of fluid volume in patients with septic shock.

Frequentist p-values provide no information on the effect size. Moreover, frequentist confidence intervals are commonly misinterpreted as a Bayesian CrI, i.e. as the 95% most likely values (given the prior data and model).[25,26] The Bayesian approach has the advantage of allowing calculation of probabilities of *all* effect sizes and incorporation of data from previous studies into the analysis using evidence-based priors.

Bayesian hierarchical models limit extreme subgroup effects in groups with few events as it uses information across groups through shrinkage to reduce parameters' sensitivity to noise. Additionally, trials are generally only powered for the primary analysis and not subgroup analyses. Thus, true differences are unlikely to obtain statistical significance in subgroup analyses (high risk of type 2 error).[12,27] On the other hand, the risk of type 1 errors is increased due to multiple testing, which may exaggerate and overestimate false discoveries.[12,27]

3.1 | Limitations

The outlined secondary analyses have some limitations. The Bayesian approach does not salvage general limitations related to the CLASSIC trial including bias due to the open-label nature of the trial.[4] Subgroup and HTE analyses must always be interpreted with care due the risk of chance findings. Firstly, few events in each subgroup can result in imprecision even with the use of shrinkage in the hierarchical models. Secondly, categorisation, which is often easier to interpret, leads to loss of information. Therefore, we will also assess the five baseline variables of interest on a continuous scale in addition to the subgroup-based analyses. Thirdly, the chosen priors may be challenged as one's results can be influenced by these. Our reasoning to use a weakly informative prior was to nuance the CLASSIC results with minimal influence of the priors chosen. This will be challenged by the sensitivity analyses using both sceptical priors and evidence-based priors. Finally, our definition of clinically important effect sizes can be questioned, and other reasonable thresholds could be considered.

4 | CONCLUSIONS

The outlined secondary Bayesian analyses will supplement the primary analysis of the CLASSIC trial by describing probabilities of beneficial and harmful effects and evaluating heterogeneity of treatment effects in a framework that may be easier to interpret for researchers and clinicians.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

The idea for this project was conceived by Morten Hylander Møller, Anders Perner and Anders Granholm. Praleene Sivapalan, Tine S. Meyhoff and Anders Granholm wrote the first draft of this protocol, which was critically revised by all authors. All authors are involved in the CLASSIC trial.

ORCID

Praleene Sivapalan https://orcid.org/0000-0002-0442-0032
Tine S. Meyhoff https://orcid.org/0000-0002-1840-1596
Peter B. Hjortrup https://orcid.org/0000-0002-3847-3247
Theis Lange https://orcid.org/0000-0001-6807-8347
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 may be found in the online version of the article at the publisher's website.

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