Received: 8 March 2024 | Accepted: 20 March 2024

DOI: 10.1111/aas.14423

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Effects of IV fluid restriction according to site-specific intensity of standard fluid treatment—protocol

Praleene Sivapalan[1,2] | Benjamin Skov Kaas-Hansen[1,2,3] | Tine Sylvest Meyhoff[1,2,4] | Peter Buhl Hjortrup[2,5] | Maj-Brit N. Kjær[1,2] | Jon Henrik Laake[2,6] | Maria Cronhjort[2,7] | Stephan M. Jakob[2,8] | Maurizio Cecconi[9,10] | Marek Nalos[2,11] | Marlies Ostermann[2,12] | Manu L. N. G. Malbrain[2,13] | Morten Hylander Møller[1,2,14] | Anders Perner[1,2,14] | Anders Granholm[1,2]

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

[4]Department of Anaesthesia and Intensive Care, Lillebælt Hospital, Kolding, Denmark

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

[6]Department of Anaesthesiology and Intensive Care Medicine, Division of Emergencies and Critical 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, Pieve Emanuele, Italy

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

[11]Department of Anaesthesiology, Perioperative and Intensive Care Medicine, Masaryk Hospital, J.E. Purkinje University, Usti nad Labem, Czech Republic

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

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

[14]Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark

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

Funding information
Novo Nordisk Fonden, Grant/Award Number: NNF17OC0028608; Læge Sofus Carl Emil Friis og Hustru Olga Doris Friis' legat; Rigshospitalet; Grosserer Jakob Ehrenreich og Hustru Grete Ehrenreichs Fond

Abstract

Background: Variation in usual practice in fluid trials assessing lower versus higher volumes may affect overall comparisons. To address this, we will evaluate the effects of heterogeneity in treatment intensity in the Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care trial. This will reflect the effects of differences in site-specific intensities of standard fluid treatment due to local practice preferences while considering participant characteristics.

Methods: We will assess the effects of heterogeneity in treatment intensity across one primary (all-cause mortality) and three secondary outcomes (serious adverse events or reactions, days alive without life support and days alive out of hospital) after 90 days. We will classify sites based on the site-specific intensity of standard fluid treatment, defined as the mean differences in observed versus predicted

intravenous fluid volumes in the first 24 h in the standard-fluid group while accounting for differences in participant characteristics. Predictions will be made using a machine learning model including 22 baseline predictors using the extreme gradient boosting algorithm. Subsequently, sites will be grouped into fluid treatment intensity subgroups containing at least 100 participants each. Subgroups differences will be assessed using hierarchical Bayesian regression models with weakly informative priors. We will present the full posterior distributions of relative (risk ratios and ratios of means) and absolute differences (risk differences and mean differences) in each subgroup.

Discussion: This study will provide data on the effects of heterogeneity in treatment intensity while accounting for patient characteristics in critically ill adult patients with septic shock.

Registrations: The European Clinical Trials Database (EudraCT): 2018-000404-42, ClinicalTrials. gov: NCT03668236.

KEYWORDS

critical care, fluid therapy, heterogeneity in treatment intensity, machine learning, prediction models, septic shock

1 | INTRODUCTION

Intravenous (IV) fluid therapy is recommended in patients with sepsis, yet the ideal approach is an active area of research. In recent years, several randomised clinical trials have assessed the effects of lower versus higher IV fluid volumes in sepsis.[1] The results indicate that, on average, there is probably little or no difference in mortality between lower and higher IV fluid volumes in these patients.[1]

The recent 'Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care' (CLASSIC) trial, compared a protocol restricting the volumes of IV crystalloids (the restrictive-fluid group) versus a protocol with no upper criteria for the use of IV crystalloids (the standard-fluid group).[2,3] Only adult intensive care unit (ICU) patients with septic shock who had already received at least 1 L of IV fluids were enrolled. The restrictive-fluid group received a median of 1798 mL of IV fluid (interquartile range, 500–4366, full range, 0–31,187) in the ICU within 90 days after randomisation; the standard-fluid group received a median of 3811 mL (interquartile range, 1861–6762, full range, 0–67,180).[2] As no specific volumes were mandated by the protocol in the standard-fluid group,[2,3] practice variation may have affected the overall comparison between the restrictive and standard-fluid groups. While participant characteristics may explain some of this variation, additional local practice variation between sites likely plays a role as well. Such site-specific preferences may have influenced the treatment effects of restricting fluids due to potentially greater differences between the two trial groups on sites with more intense fluid treatment, leading to heterogeneity in treatment intensity. Therefore, we aim to investigate the effects of heterogeneity in treatment intensity in the CLASSIC trial occurred due to variations in treatment intensity in the standard-fluid group, independent of participant characteristics. Understanding the effects and magnitudes of heterogeneity in treatment intensity can refine our interpretation of the effects of IV fluid restriction in septic shock.

In the outlined post hoc analysis of the CLASSIC trial, we will assess the effects of heterogeneity in treatment intensity across different sites while accounting for differences in participant characteristics. We hypothesise that the effects of a restrictive IV fluid therapy will be larger (i.e., increased benefit) in trial sites that routinely administer relatively higher volumes of IV fluid, even after accounting for participant characteristics.

2 | METHODS

The outlined post hoc analyses are inspired by the Protocolized Resuscitation In Sepsis Meta-Analysis of early-goal directed therapy in sepsis[4] and previous heterogeneity of treatment effects analyses.[5–7] The analyses will be conducted once the protocol is accepted for publication in a peer-reviewed journal. The manuscript will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement[8] and the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement[9] (completed checklists are included in Supporting Information S1).

2.1 | POPULATION

In the CLASSIC trial, 1554 adult ICU patients with septic shock, who had already received at least 1 L of IV fluid, were randomised to

restrictive versus standard IV fluid therapy for a maximum duration of 90 days during ICU stay. Participants were enrolled in 31 ICUs in eight countries between November 2018 and November 2021. The exclusion criteria were septic shock for more than 12 h, life-threatening bleeding, severe burns, pregnancy and lack of consent. Additional details on the CLASSIC trial are available elsewhere.[2,3,10] All analyses will be restricted to CLASSIC sites that enrolled at least 15 participants in the standard-fluid group to minimise uncertainties from smaller sites.

2.2 | OUTCOMES

Primary outcome is all-cause mortality within 90 days after randomisation.

Secondary outcomes assessed within 90 days after randomisation are as follows:

1. Number of participants with one or more serious adverse events (SAEs) or serious adverse reactions (SARs) to IV crystalloids. 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 stage of 3).[3,11] SARs were defined as general tonic–clonic seizures, anaphylactic reactions, central pontine myelinolysis, severe hypernatremia, severe hyperchloremic acidosis or severe metabolic alkalosis.[3] Considering the low occurrence of SARs,[2] these were assessed together with SAEs. This will also limit the number of outcomes in this study.
2. Absolute number of days alive without life-support (vasoactive circulatory support, invasive mechanical ventilation, renal replacement therapy).
3. Absolute number of days alive and out of hospital.

3 | STATISTICAL METHODS

3.1 | Descriptive data

We will present descriptive baseline and outcome data for all participants, stratified by treatment allocation and treatment intensity subgroups (defined below). Data will be summarised as medians with interquartile ranges for numerical data, and as counts with percentages for categorical data, consistent with the main publication.[2]

3.2 | Sample size and missing data

We will include 90% (1406 participants) of the fixed CLASSIC population (1554 participants) as we only include CLASSIC sites with at least 15 participants in the standard-fluid group. As the sample size is fixed by this choice, no sample size calculation was performed. We will perform a complete-case analysis as there are limited missing data in the CLASSIC trial: data are missing on at least one variable used in this study in 2.8% of participants from CLASSIC sites with at least 15 participations in the standard-fluid group.

3.3 | Overview

We will classify sites based on treatment intensity using a prediction model trained on participants in the standard-fluid group. Sites will be classified according to the mean absolute differences between observed and predicted standardised total IV fluid volumes, and then grouped into subgroups with increasing fluid treatment intensity. The process is outlined in Figure 1.

3.4 | Standardised fluid volumes

We will estimate standardised total IV fluid volumes accounting for IV fluids administered in the ICU the first 24 h in the CLASSIC trial; here, IV fluids do not comprise fluids given with medication and nutrition or blood products, as per the ESM. The duration of day 1 varied between participants based on their randomisation time; therefore, we will estimate the standardised total IV fluid volumes by extrapolating administered IV fluid volumes on day 1 to 24 h for all participants as detailed in the ESM.

3.5 | Prediction of expected standardised total fluid volumes

We will develop a prediction model specifically designed to predict standardised total IV fluid volumes for participants in the standard-fluid group accounting for baseline predictors (detailed below), see Figure 2. This will correspond to the 'expected' amount of fluid for comparable participants.

The following baseline variables will be included as predictors in the model:

1. Acute surgical admission (yes/no)
2. Age (years)
3. Body weight (kg)
4. Chronic hypertension (yes/no)
5. Country of enrolment
   - Denmark
   - Italy
   - Norway
   - Sweden
   - Switzerland
   - The Czech Republic
   - The United Kingdom
6. Days from hospital admission to randomisation
7. Focus of infection
   - Gastrointestinal

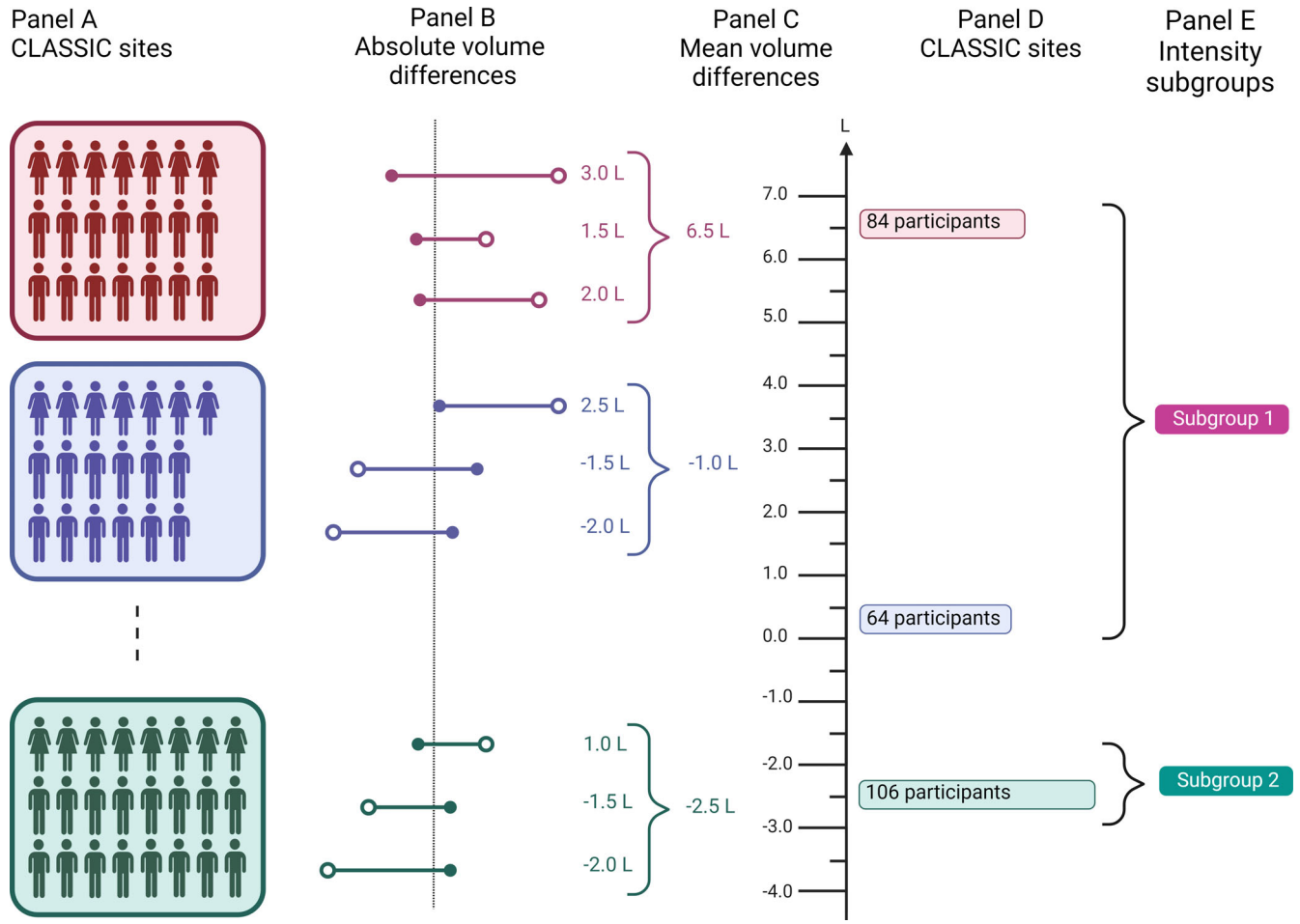

FIGURE 1 Classification of sites. The process of classifying sites into treatment intensity subgroups. Panel A: three examples of (fictive) CLASSIC sites (with at least 15 participants in the standard-fluid group) of various sizes are presented. Panel B: the absolute volume difference between observed (filled circle) and predicted (open circle) standardised total IV fluid volumes are estimated for each participant (only three participants per site are depicted here for illustration purposes). Panels C–E: the mean of the absolute difference in observed versus predicted fluid volumes of all participants in the standard-fluid group in each site is calculated to classify sites into treatment intensity subgroups, each containing at least 100 participants regardless of allocation.

- Pulmonary
- Skin or soft tissue
- Urinary tract
- Other

8. Haematologic or metastatic cancer (yes/no)
9. Highest dose of norepinephrine within 3 h of randomisation (μg/kg/min)
10. Highest plasma creatinine concentration within 24 h prior to randomisation (μmol/L)
11. Highest plasma lactate within 3 h prior to randomisation (mmol/L)
12. Ischaemic heart disease or heart failure (yes/no)
13. Long-term dialysis (yes/no)
14. Lowest systolic blood pressure within 24 h before randomisation (mmHg)
15. Sex (female/male)
16. Source of ICU admission
    - Another ICU
    - Emergency department/prehospital
    - Hospital ward
    - Operating/recovery room
17. Time from ICU admission to randomisation (hours)
18. Use of acute renal replacement therapy (yes/no)
19. Use of circulatory support (yes/no)
20. Use of respiratory support (yes/no)
21. Use of systemic glucocorticoid (yes/no)
22. Volume of IV fluid 24 h before randomisation (mL)

3.6 | Model architecture and evaluation

We will develop a prediction model using extreme gradient boosting in R (R Core Team, R Foundation for Statistical Computing) using the *XGBoost* R package.[12] This is a machine learning algorithm that involves training multiple weak learners (each is a tree-based regression model) that complement each other

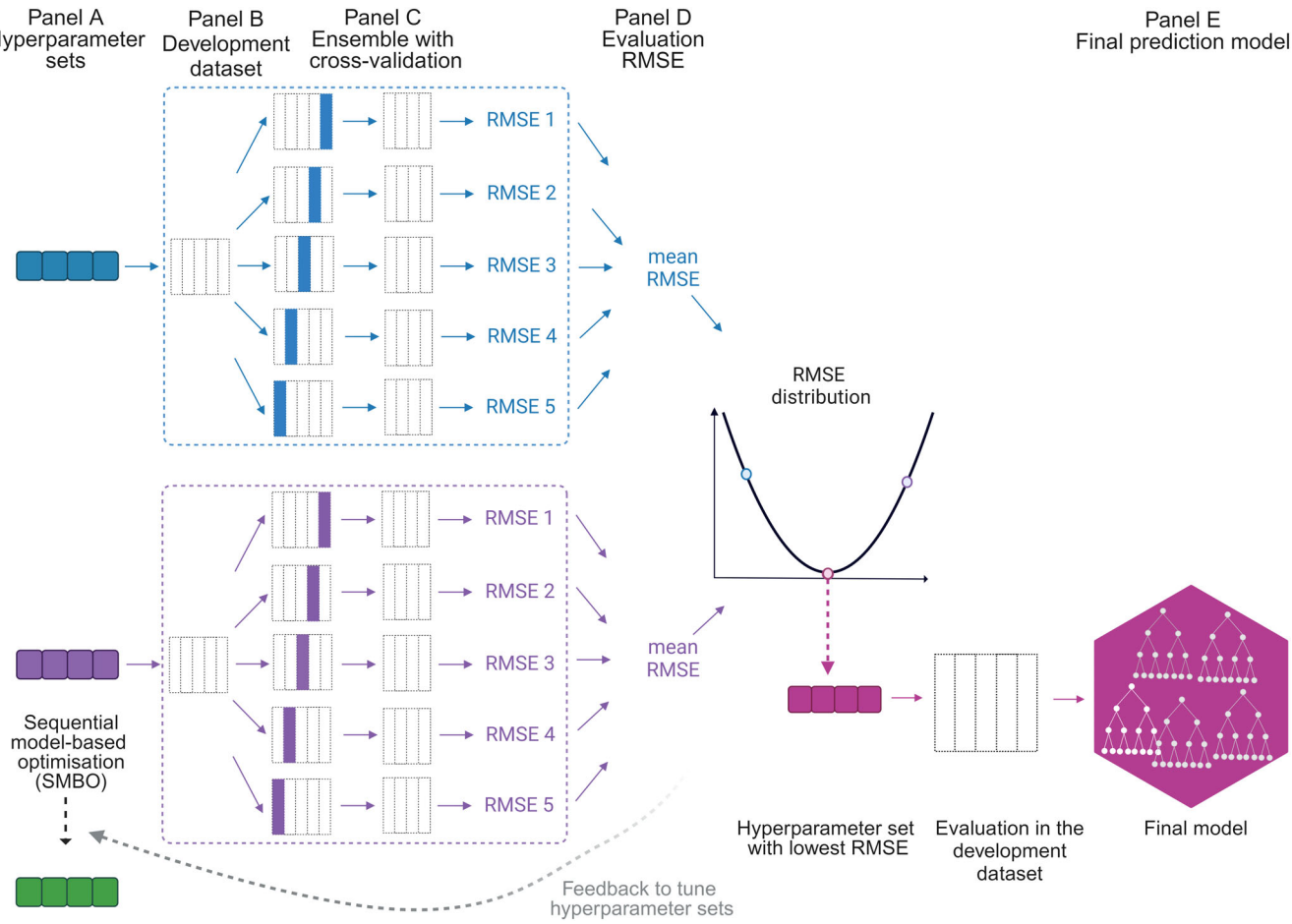

FIGURE 2 Prediction model. The steps in developing the prediction model using machine learning with the extreme gradient algorithm and sequential model-based optimisation (SMBO) with cross-validation. Panel A: three exemplary hyperparameter sets used for hyperparameter tuning with SMBO. Panel B: each hyperparameter set yields 5 root mean squared errors (RMSEs), one for each cross-validation fold, whose sum is used by the SMBO process to suggest new hyperparameter sets. Panel C–E: the final model's hyperparameters will be the set with the lowest sum of RMSE, and the final model is, then, trained on the full development dataset.

to, jointly, achieve superior performance.[12–14] In gradient boosting, trees are learned sequentially and based on the performance of all previous ones.[12–14] Consequently, in the first stage, a decision tree is fitted to the dataset predicting the outcome of interest. Then at each subsequent stage, a new decision tree is trained on the residuals to explain the variation in the outcome not accounted for by the previous trees.

Additionally, we will use sequential model-based optimisation (SMBO) to tune the hyperparameters that control aspects of the algorithm influencing the training of the model,[14,15] with a probabilistic model using five-fold cross-validation, see Figure 2. Each so-called cross-validation fold will use 80% of the full development set for training and 20% for validation.[16] We will use root mean squared errors (RMSEs) to evaluate performance. Each hyperparameter set tried will yield five RMSEs (one for each cross-validation fold), and their average (means) will be fed back to the SMBO procedure, to iteratively help it home in on the best hyperparameter set.[15] After many SMBO iterations, the final hyperparameter set is that with the lowest average RMSE. We will explore a broad hyperparameter space detailed in the ESM.[14] The final selected hyperparameters will be reported.

After identifying the optimal hyperparameters, the model will be trained on the entire development dataset and evaluated using the RMSE and a calibration plot. Using this model, we will predict the standardised total IV fluid volumes for all participants in the standard-fluid group. Additionally, the observed and predicted standardised total IV fluid volumes will be visualised and summarised numerically.

3.7 | Classifying sites and subgrouping

We will classify the sites according to treatment intensity, see Figure 1. Site-specific treatment intensity is defined as the absolute mean difference between the observed and predicted standardised total IV fluid volumes in the standard-fluid group. Sites will then be grouped sequentially into treatment intensity subgroups, ranging from lowest to highest. Starting from both ends of the scale and alternating,

we will create treatment intensity subgroups by grouping sites within 0.5 L absolute mean difference of their standardised total IV fluid volumes until each of the treatment intensity subgroups includes at least 100 participants, incorporating participants from both the standard-fluid and restrictive-fluid groups. This process will result in the classification of several fluid treatment intensity subgroups ranging from lowest to highest treatment intensity.

3.8 | Heterogeneity in treatment intensity

We will assess the effects of heterogeneity in treatment intensity within the defined fluid treatment intensity subgroups using hierarchical Bayesian regression models. Bayesian inference updates previous beliefs, expressed with prior probability distributions (priors), with observed data to produce posterior probability distributions. This method enables a probabilistic interpretation of heterogeneity in treatment intensity allowing us to directly deduce probabilities of different effect sizes from full posterior probability distributions. We will use neutral weakly informative priors (i.e., centred on no difference between the groups) having minimal influence following the approach in previous analyses (detailed provided in the ESM).[5–7] Model diagnostics will be aligned with methods previously described in similar analyses.[5–7]

3.9 | Presentation of results

Standardised total IV fluid volumes extrapolated to the first 24 h and the duration of day 1 will be presented as medians with interquartile range. For each outcome, full posterior distributions of the subgroups will be presented graphically using medians as point estimates with 95% percentile-based credible intervals representing the 95% most plausible effect sizes. Results will be presented as risk ratios and risk differences for binary outcomes and ratios of means and mean difference for count outcomes.

3.10 | Sensitivity analyses

We will conduct similar sensitivity analyses including all CLASSIC sites (with at least 15 participants in the standard-fluid group) as separate groups in hierarchical Bayesian logistic regression models.

4 | ETHICS AND DISSEMINATION

The CLASSIC trial was conducted in accordance with the Declaration of Helsinki with enrolment after informed consent by participants or their legal surrogates; additional details on consent procedures and approvals are available elsewhere.[2,3] No additional data will be collected, and further approvals were not required for this post hoc study. The results will be reported in an international peer-reviewed journal, irrespective of the findings.

5 | DISCUSSION

The outlined post hoc analyses of the CLASSIC trial will provide insight into the effects of heterogeneity in fluid treatment intensity in adult ICU patients with septic shock.

The study has several strengths. First, it will use high-quality data from a large international trial investigating restrictive versus standard IV fluid therapy in ICU patients with septic shock. Although the primary results are published, all analyses in this protocol are prespecified and will be conducted only upon publication of this protocol. Second, Bayesian hierarchical models constitute a partial pooling strategy that shrinks effect estimates of subgroup towards the overall estimate, with more shrinkage in groups with more uncertain results (typically smaller groups) or results farther from the overall estimate.[17] This approach mitigates the impact of extreme subgroup effects to yield a more realistic evaluation of treatment effects across subgroups.[18] Third, the prediction model will leverage the advantages of a machine learning algorithm and SMBO to automate predictor selection and model architecture, thus requiring minimal assumptions about the predictors and their relation to the outcome (standardised fluid volumes). However, this necessitates a large amount of data to achieve stability, which poses a trade-off compared with conventional regressions that rely on reasonable choices of predictors and functional forms. Finally, we will assess the robustness of the study by incorporating sensitivity analyses.

This study also comes with limitations. First, in the CLASSIC trial, clinicians and trial staff were aware of the fluid groups, potentially influencing administered IV fluid volumes. We observed a decrease in the median IV fluid volumes in the standard-fluid group from the first interim analysis to the final analysis, indicating lower IV fluid amounts in this group over time. Second, variations in the duration of day 1 among participants in the CLASSIC trial may introduce uncertainties when estimating standardised total IV fluid volume. For instance, extrapolating these volumes might overestimate standardised IV fluid volumes for participants with shorter day 1, as they might receive higher fluid volumes initially in the ICU. However, based on available data, we chose to only extend the extrapolation to a 24-h period to minimise the duration of overestimation. Third, the approach chosen to classify sites and the grouping of these into treatment intensity subgroups can be debated. However, we have chosen this approach to strike a balance between clinical relevance and practical considerations. By using a 0.5 L fluid volume precision threshold, we ensure that subgroups stay clinically interpretable while preventing them from becoming excessively small or uneven in size. Fourth, we will limit inclusion to CLASSIC sites with at least 15 participants in the standard-fluid group, which is somewhat arbitrary, aiming to strike a balance between excluding smaller sites due to uncertainties while also minimising data loss. Finally, the chosen priors may be challenged, but we deliberately chose weakly informative priors to minimise their

influence consistent with previous analyses.[5,6,19,20] We have not planned sensitivity analyses with alternative priors due to the post hoc nature of the study. Notably, previous Bayesian analyses of the CLASSIC trial were robust to the selection of priors, likely due to the relatively large number of patients.[5]

In conclusion, the outlined study will provide data on the effects of heterogeneity in treatment intensity while considering patient characteristics in critically ill adult patients with septic shock in the CLASSIC trial.

AUTHOR CONTRIBUTIONS

Conceptualisation and study design: Praleene Sivapalan, Benjamin Skov Kaas-Hansen, Tine Sylvest Meyhoff, Morten Hylander Møller, Anders Perner, and Anders Granholm. Writing first draft: Praleene Sivapalan. Critical review and approval of manuscript: all authors.

ACKNOWLEDGMENTS

We sincerely thank everyone involved in the CLASSIC trial for invaluable contributions and collaborations. We wish to extend our heartfelt gratitude to all participants and their families, and we are deeply appreciative of the support from all our dedicated research staff, clinical teams, investigators at the participating intensive care units and funders, who contributed to the success of this trial.

FUNDING INFORMATION

The CLASSIC trial was funded by the Novo Nordisk Foundation (NNF17OC0028608) and Sofus Friis' foundation. PS received funding from the Research Council of Rigshospitalet and Jakob Ehrenreich and his wife Grete Ehrenreich's Foundation. The funders had no influence on the design, conduct or the decision to publish the protocol or results of this secondary study.

CONFLICT OF INTEREST STATEMENT

The Department of Intensive Care, Rigshospitalet receives support for research projects from the Novo Nordisk Foundation, Pfizer, Fresenius Kabi and Sygeforsikringen 'Denmark'. Anders Perner has received honorarium for advisory board work from Novartis.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Praleene Sivapalan https://orcid.org/0000-0002-0442-0032
Benjamin Skov Kaas-Hansen https://orcid.org/0000-0003-1023-0371
Tine Sylvest Meyhoff https://orcid.org/0000-0002-1840-1596
Peter Buhl Hjortrup https://orcid.org/0000-0002-3847-3247
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

REFERENCES

1. Sivapalan P, Ellekjaer KL, Jessen MK, et al. Lower vs higher fluid volumes in adult patients with sepsis: an updated systematic review with meta-analysis and trial sequential analysis. *Chest*. 2023;164:892-912. doi:10.1016/j.chest.2023.04.036
2. Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of intravenous fluid in ICU patients with septic shock. *N Engl J Med*. 2022;387(9):856-857. doi:10.1056/nejmc2210366
3. Meyhoff TS, Hjortrup PB, Møller MH, et al. Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial—protocol and statistical analysis plan. *Acta Anaesthesiol Scand*. 2019;63(9):1262-1271. doi:10.1111/aas.13434
4. Investigators TP. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. *N Engl J Med*. 2017;376(23):2223-2234. doi:10.1056/nejmoa1701380
5. Sivapalan P, Meyhoff TS, Hjortrup PB, et al. Restrictive versus standard IV fluid therapy in adult ICU patients with septic shock-Bayesian analyses of the CLASSIC trial. *Acta Anaesthesiol Scand*. 2024;68(2):236-246. doi:10.1111/aas.14345
6. Klitgaard TL, Schjørring OL, Lange T, et al. Lower versus higher oxygenation targets in critically ill patients with severe hypoxaemia: secondary Bayesian analysis to explore heterogeneous treatment effects in the handling oxygenation targets in the intensive care unit (HOT-ICU) trial. *Br J Anaesth*. 2022;128(1):55-64. doi:10.1016/j.bja.2021.09.010
7. Granholm A, Marker S, Krag M, et al. Heterogeneity of treatment effect of prophylactic pantoprazole in adult ICU patients: a post hoc analysis of the SUP-ICU trial. *Intensive Care Med*. 2020;46(4):717-726. doi:10.1007/s00134-019-05903-8
8. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):1623-1627. doi:10.1371/journal.pmed.0040296
9. TRIPOD Group. TRIPOD checklist: prediction model development. 2015:22.
10. Kjær MBN, Meyhoff TS, Sivapalan P, et al. Long-term effects of restriction of intravenous fluid in adult ICU patients with septic shock. *Intensive Care Med*. 2023;49(7):820-830. doi:10.1007/s00134-023-07114-8
11. Kellum JA, Lameire N, Aspelin P, et al. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care*. 2013;17(1):1-15. doi:10.1186/cc11454
12. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. 2016;785-794. doi:10.1145/2939672.2939785
13. Friedman BJH. 1999 Reitz lecture. *Ann Stat*. 2001;29:1189-1232.
14. Shwartz-ziv R, Armon A. Tabular data: deep learning is not all you need. *Information Fusion*. 2022;81:84-90. doi:10.1016/j.inffus.2021.11.011
15. Jones DR, Schonlau M, William J. Efficient global optimization of expensive black-box functions. 1998;13:455-492.
16. Steyerberg EW. *Statistics for Biology and Health Clinical Prediction Models*. 2nd ed. Chapter 17 Springer NY; 2009.
17. Bürkner PC. Brms: an R package for Bayesian multilevel models using Stan. *J Stat Softw*. 2017;80(1):1-28. doi:10.18637/jss.v080.i01

18. Jones HE, Ohlssen DI, Neuenschwander B, Racine A, Branson M. Bayesian models for subgroup analysis in clinical trials. *Clin Trials*. 2011;8(2):129-143. doi:10.1177/1740774510396933
19. Granholm A, Munch MW, Myatra SN, et al. Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. *Intensive Care Med*. 2022;48(1):45-55. doi:10.1007/s00134-021-06573-1
20. Andersen-Ranberg NC, Poulsen LM, Perner A, et al. Haloperidol vs. placebo for the treatment of delirium in ICU patients: a pre-planned, secondary Bayesian analysis of the AID–ICU trial. *Intensive Care Med*. 2023;49:411-420. doi:10.1007/s00134-023-07024-9

SUPPORTING INFORMATION

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

How to cite this article: Sivapalan P, Kaas-Hansen BS, Meyhoff TS, et al. Effects of IV fluid restriction according to site-specific intensity of standard fluid treatment—protocol. *Acta Anaesthesiol Scand*. 2024;1-8. doi:10.1111/aas.14423