Enhancing Network Meta-Analysis through Predictive Cross-Validation: Assessing Model Performance and Detecting Outliers

MSR134

Akanksha Sharma[1] , Neha Tripathi[1] , Barinder Singh[2] , Shubhram Pandey[1]

[1]Heorlytics, SAS Nagar, Mohali, India, [2]Pharmacoevidence, SAS Nagar, Mohali, India

CONCLUSIONS

- The application of the Predictive Cross-Validation (PCV) in the Network Meta-Analysis (NMA) helps to strengthen comparisons of interventions, particularly in multiple-arm trials
- The method of Bayesian leave-one-out cross-validation (LOO-CV) also helps in the identification of the outliers in the data
- Further, the utilization of the Markov chains, with sufficient burn-in period ensures robust parameter estimation, improving the accuracy of treatment effect estimates

PLAIN LANGUAGE SUMMARY

- In this NMA, a technique called PCV was used to enhance the accuracy of comparing the various treatments.
- The analysis included binomial likelihood functions with a logistic link which permitted a flexible modeling of both trial and treatment differences. Bayesian LOO-CV also allowed identifying outliers or regularization issues within the data set
- By using Markov chains with sufficient length of burn-in phase, better parameter estimation of treatment effects was obtained

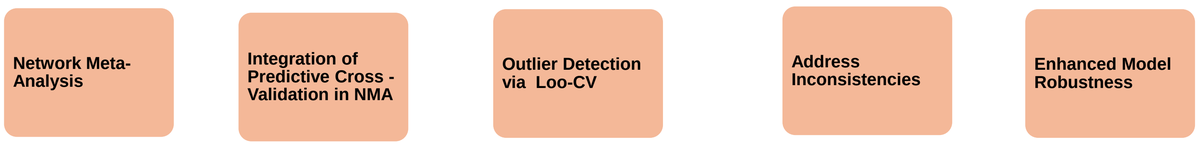
INTRODUCTION

- Network Meta-Analysis (NMA) is an important asset for analyzing clinical trials that include several interventions, which also aids in making direct and indirect comparisons of the treatment outcomes. It can be considered as a primary approach that provides coherent information on the comparative efficacy of the provided treatments
- Predictive Cross-Validation (PCV) is used as an upgrading option for NMA to check its performance, identify unreliable data, and avoid pursuing models with high out-of-sample error rates. It enhances the synthesis of the evidence to increase the accuracy, reliability of the NMA outcome, particularly when simultaneously comparing three or more treatments and helps in identifying treatment effects
- Integrating PCV into the NMA increases the dependability and credibility of results making it a worthy tool

OBJECTIVE

- To demonstrate the enhancement of NMA through the integration of PCV
- To identify potential outliers and heterogeneity in the data, for ensuring the reliability of the results

Figure 1: Flowchart depicting the study methodology



LOO-CV: Leave-one-out cross-validation; NMA: Network meta-analysis

METHODS

- The analysis was implemented in **WinBUGS** software, leveraging its capabilities for Bayesian inference and handling complex models with multiple treatment comparisons
- An NMA was performed, using binomial likelihood model with a logit link function; this model was chosen as the most appropriate for the trials since trial include multiple treatments
- The analysis utilized hypothetical data of 16 trials and 4 treatments, providing a robust evidence base for analysis
- This model incorporated random effects to account for heterogeneity, based on some initial conditions based on the trial circumstances
- To assess the model's accuracy, the Bayesian PCV method was used, where the model was tested on outcomes from new or with held trials, and the predictions were compared to the actual outcomes
- The approach, known as leave-one-out cross-validation (LOO-CV) involved progressively removing each trial and evaluating the model's performance in predicting the omitted trial, allowing for the detection of outliers or irregularities in the dataset
- All the analyses were conducted using three separate Markov chains and 180,000 samples . In this context, the model also needed a burn-in period of 60,000 iterations. This proved to enhance the reliability of parameter estimation and inference of the models

RESULTS

- To account for the effective number of tests that could be performed, the observed p-value was compared to the expected value, calculated as 1/(n+1) = 0.0588, representing the nth uniform order statistic
- The observed p-value of 0.004 is substantially lower than the expected threshold of 0.0588, suggesting that Trial 16 may indeed represent an outlier within the network
- Trial 16 exhibits a trial-specific log-odds ratio that deviates from those of other trials, potentially contributing to the high heterogeneity observed in the network meta-analysis

Figure 2: Network Diagram

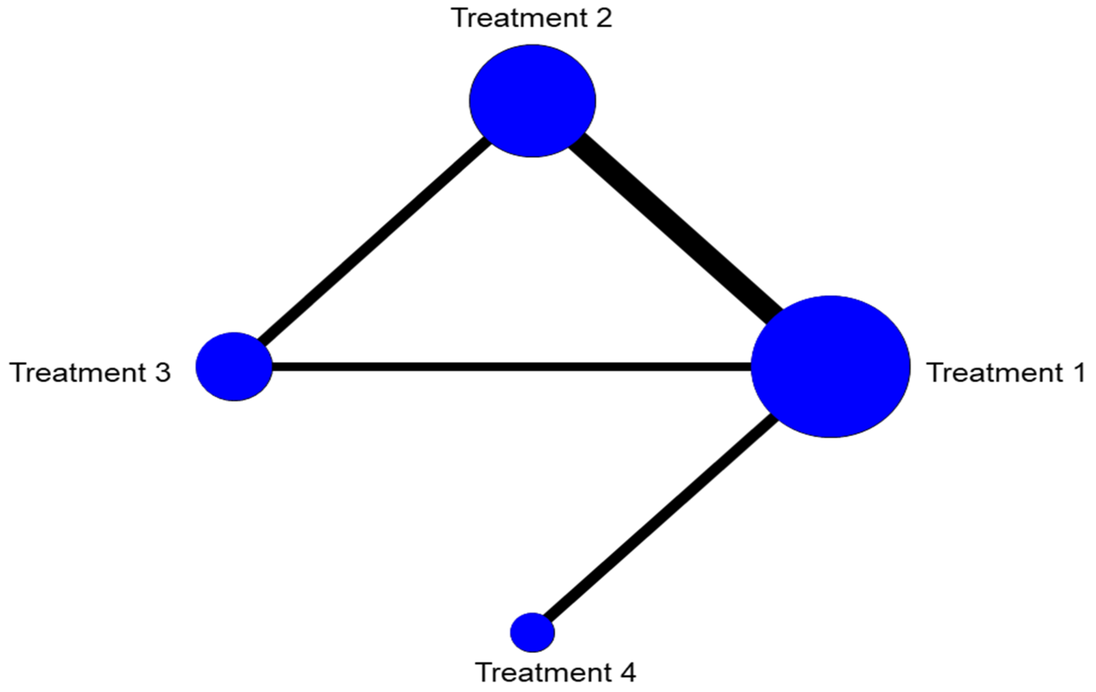
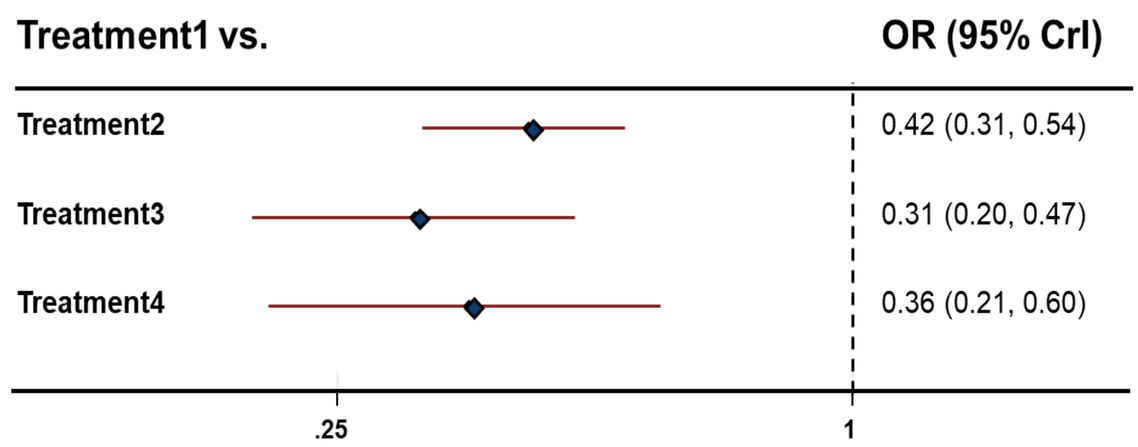
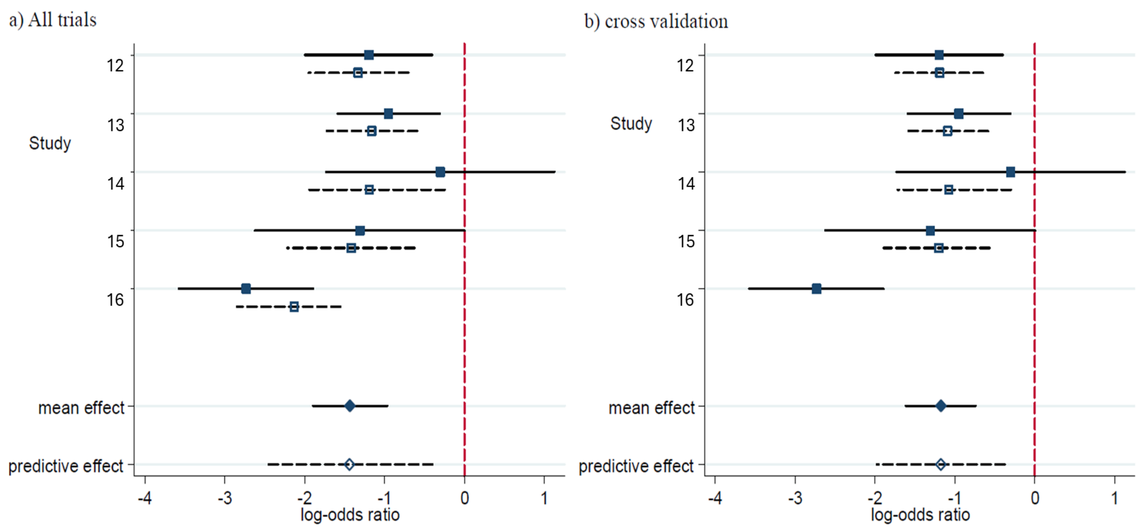


Figure 3 : Forest Plot representing Odds ratio of Treatment1 vs. Others



CI: Confidence interval; OR: Odds ratio

Figure 4: Crude log-odds ratios with 95% CI (filled squares, solid lines); posterior mean with 95% CrI of the trial-specific log-odds ratios, (open squares, dashed lines); posterior mean with 95% CrI of the posterior (filled diamond, solid line) and predictive distribution (open diamond, dashed line) of the pooled treatment effect for a RE model a) including all the trials and b) excluding trial 16 (cross-validation model)



LIMITATIONS

- PCV and Bayesian LOO-CV in NMA provide valuable insights but face limits like high computation, sensitivity to priors, and overfitting
- It also struggles with convergence, generalizability in sparse networks, and complexity in interpretation

References

Dias, S., Sutton, A. J., Welton, N. J., & Ades, A. E. (2011). Evidence synthesis for decision making 3: Heterogeneity, sub-groups, meta-regression, bias and bias-adjustment (NICE DSU Technical Support Document 3). National Institute for Health and Care Excellence (NICE) Decision Support Unit. Available from: https://nicedsu.org.uk/technical-support-documents

Disclosures

AS, NT, BS, and SP, the authors, declare that they have no conflict of interest