Assessing the impact of the prior distribution for the within-study correlation in bivariate network meta-analysis

A case study in relapsed/refractory multiple myeloma

MSR47

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Background

- Bivariate network meta-analysis (bvNMA) offers a powerful framework for measuring the study-level correlation of treatment effect on a pair of outcomes[1-3].
- The *within-study* correlation is typically a fixed input in bvNMA, which could be problematic since individual patient data from which to estimate this parameter may only be available for a small number of studies. Otherwise, vague priors are usually employed, which may also be undesirable since bvNMA estimates often have high uncertainty.
- Here, we investigate the impact of employing alternative prior distributions for the within-study correlation on bvNMA model predictions, to ascertain the level of rigor with which this required input should be regarded by the modeler and scrutinized by health authorities.

Methods

- We analyzed a network of 15 trials in relapsed/refractory multiple myeloma (RRMM) using Bayesian bivariate random effects meta-analysis to estimate the study-level correlation between complete response rate (CRR) odds ratios (ORs) and progression-free survival (PFS) hazard ratios (HRs).
  - The included studies were those that were the subject of previous NMAs[4] for which both outcomes were reported.
  - The network is relatively small and so prior distributions are liable to make an appreciable contribution to the posterior density, providing a challenging case study.
- We considered three alternative prior distributions for the within-study correlation parameter, which was assumed to be homogeneous across treatment contrasts:
  - (1) a weakly informative transformed beta prior centered at zero correlation (mean 0.00, 90% credible interval (CrI): -0.62,+0.62).
  - (2) a weakly informative uniform prior bounded by independence and perfect negative correlation.
  - (3) a strongly informative logit-normal prior characterizing moderately negative correlation (mean -0.55, 90% CrI: -0.65,-0.45).
- We specified a weakly informative asymmetric prior distribution, $(\rho + 1)/2 \sim \text{Beta}(1.5,4.5)$, favoring moderately negative correlation (mean -0.50, 90% CrI: -0.93,+0.13), for the study-level correlation parameter, ρ. We compared posterior estimates for this quantity and for correlation measures from derived linear models across the alternative bvNMA models.
- bvNMA models were implemented in Stan[5].

Results and Discussion

- CRR and PFS outcomes were found to be moderately correlated at the study level (Fig. 1). Posterior mean estimates and 90% CrIs for the between-study correlation parameter were highly similar across the three scenarios, thereby demonstrating that bvNMA models are very strongly robust to the prior distribution for the within-study correlation (Table 1, Fig. 2).
- The basic parameters were also highly insensitive to the prior distribution for the within-study correlation.
  - e.g., the mean absolute difference across estimates for all basic parameters between bvNMA models (1) and (3) was <0.01.
  - Treatment rankings for both the CRR and PFS outcomes did not change between the three bvNMA models.
- bvNMA model (3), which used the least uncertain prior for the within-study correlation, yielded the narrowest CrIs for the gradient of the equivalent linear model (Table 1).

Table 1: Summary of bvNMA model estimates [and 90% CrIs] for measures of correlation under alternative prior distributions for the within-study correlation, for the network of CRR and PFS outcomes in RRMM.

Prior on within-study correlation	Within-study correlation	Between-study correlation	Linear intercept	Linear gradient
Beta (weak)	-0.08 [-0.67,+0.55]	-0.66 [-0.94,-0.21]	-0.17 [-0.49,+0.22]	-0.33 [-0.70,-0.06]
Uniform (weak)	-0.52 [-0.96,-0.07]	-0.66 [-0.96,-0.19]	-0.18 [-0.49,+0.12]	-0.33 [-0.79,-0.06]
Logit-normal (strong)	-0.55 [-0.65,-0.45]	-0.65 [-0.94,-0.19]	-0.19 [-0.48,+0.13]	-0.30 [-0.60,-0.06]

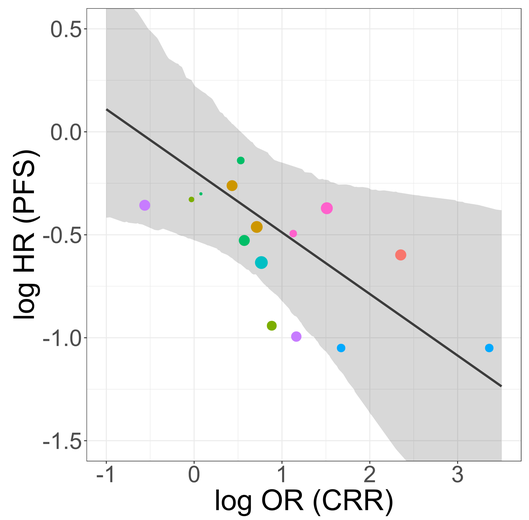

Figure 1: Relationship between treatment effect on CRR and PFS for the RRMM network, and predictions from a linear estimator (posterior mean and 90% CrIs) corresponding to bvNMA model (3). Trial-reported outcomes are colored by treatment contrast and sized in proportion to the number of patients in the study.

- Using a prior distribution for the within-study correlation that has small but nonzero variance, based on an estimate from a single study, provides an appealingly simple method to allow some heterogeneity in this parameter across alternative studies and treatment contrasts.

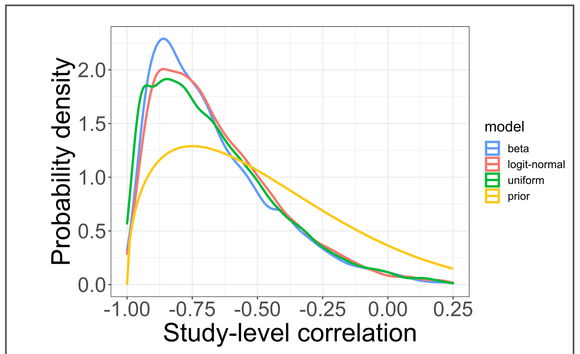

Figure 2: Posterior distributions for the study-level correlation under alternative prior distributions for the within-study correlation, compared to the prior distribution, for the network of CRR and PFS outcomes in RRMM.

Conclusions

- Estimates of study-level correlation from bvNMA are very strongly robust to the prior distribution for the within-study correlation.
- Modellers and health authorities should instead pay closer attention to the prior distribution for the study-level correlation parameter, to which bvNMA estimates can be highly sensitive, especially for smaller networks.

REFERENCES

[1] Bujkiewicz S, et al. *Stat Med*. 2019; 38(18):3322-41.
[2] Riley RD, et al. *BMJ*. 2017; 358:j3932].
[3] Bujkiewicz S, et al. NICE DSU TSD 20. DSU. 2019.
[4] Botta C, et al. *Blood Adv.* 2017; 1(7): 455-466.
[5] Carpenter B, et al. *J Stat Softw*. 2017; 76(1):1-32.

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