Review of paper "Combination of direct and indirect evidence in mixed treatment comparisons" written by G Lu and A. E. Ades

Abstract

mixed treatment comparison, or network meta-analysis is a generalization of standard pairwise meta-analysis includes 2+ treatments within a trial. The strength of this study is that it could integrate more information in the study and provide strengthened inference. On the other hand, it may test whether inconsistency exists between results from direct comparison and indirect comparison. In this paper, we would apply Bayesian hierarchical models using Markov chain Monte Carlo to get posterior distribution of the results based on public data and use simulation to replicate the methods provided in this paper.

Introduction

Compared to the traditional two-arms clinical trials, three arms or more are increasingly popular in recent trials. However, the MTC problem is often encountered in the following situations: for a large proportion of health interventions, there is no direct evidence that relates the interventions to the health outcome. Also, direct information exists on a specific treatment comparison, but does not provide enough information of a substantial statistical analysis. we then need to "borrow strength" from indirect comparisons which is the focus of this paper. Previous paper such as Lumley[1] raised the interesting concept of comparison networks for indirect treatment comparisons but limited to two-arm trials. In this paper, we will discuss K-comparisons under a Bayesian framework.

Even though direct comparison could provide better estimates than indirect comparison when possible since indirect comparisons may be subject to greater bias than direct comparisons. [2,3] it has been claimed that the assumptions being made in MTC are no different from those made in standard pairwise meta-analysis[4]. However, this depends on the methods we use to pool studies. We will apply a simple pairwise meta-analysis the parameters of primary interest should be the differences between treatments such as log odds ratio rather than single arms. Here, a fundamental assumption in all meta-analysis is that the true treatment effect is constant across trials (fixed effects) or that the trial-specific treatment differences are from a common distribution (random effects). MTC further requires that if treatment B had been observed in the A vs C trials and if A had been observed in the B vs C trials, then the true AB differences in these studies would be identical to the true AB difference in direct A vs B trials, or at least from the same common distribution.

Data description

In total there are 26 randomized trials of non-surgical treatment of first bleeding in cirrhosis, making MTC between three treatments beta-blocker (A), sclerotherapy (B) and control (C), where 2 trials compare all three treatments, 7 trials compare A and C, and 17 B and C. The data are given in full in Table I. All data are publicly available from Pagliaro et al[6]

Table I. Randomized trials of non-surgical treatment of first bleeding in cirrhosis.

Study number	Number of patients		
	Beta-blockers (A) Bled/total	Sclerotherapy (B) Bled/total	Control (C) Bled/total
1	2/43	9/42	13/41
2	12/68	13/73	13/72
3	4/20	—	4/16
4	20/116	—	30/111
5	1/30	—	11/49
6	7/53	—	10/53
7	18/85	—	31/89
8	2/51	—	11/51
9	8/23	—	2/25
10	—	4/18	0/19
11	—	3/35	22/36
12	—	5/56	30/53
13	—	5/16	6/18
14	—	3/23	9/22
15	—	11/49	31/46
16	—	19/53	9/60
17	—	17/53	26/60
18	—	10/71	29/69
19	—	12/41	14/41
20	—	0/21	3/20
21	—	13/33	14/35
22	—	31/143	23/138
23	—	20/55	19/51
24	—	3/13	12/16
25	—	3/21	5/28
26	—	6/22	2/24

Proposed Approach-model specification

By choosing treatment 1 as the baseline, we have

$$r_{ik} \sim bin(p_{ik}, n_{ik})$$

$$logit(p_{i1}) = \mu_i - \frac{\delta_{i2}}{K} - \cdots - \frac{\delta_{iK}}{K}$$

$$logit(p_{ik}) = \mu_i - \frac{\delta_{i2}}{K} - \cdots + \frac{\delta_{iK}}{K} * (K-1)$$

$$(\delta_{i2} \ldots \delta_{iK})^T \sim N(\delta, \Sigma)$$

And the interests of research:

$$\delta_{iK} = logit(p_{ik}) - logit(p_{i1}), k = 2,3, \ldots, K$$

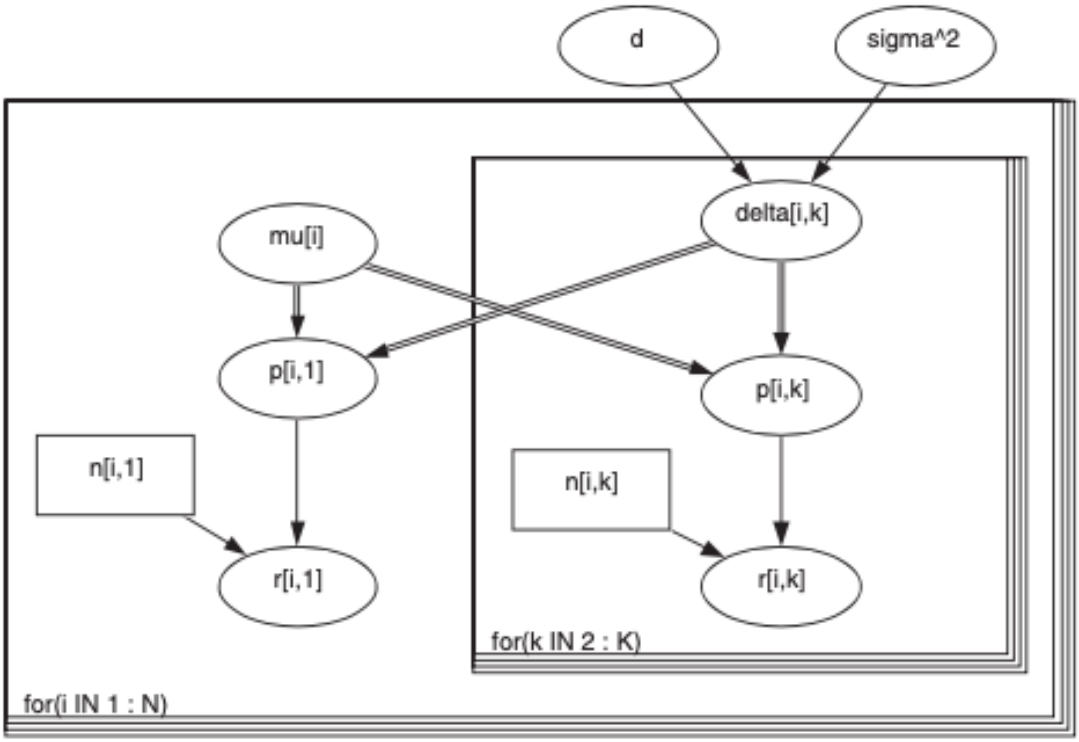


Figure 1. DAG for K-comparison SST-model.

From the model above, we could have

$$logit(p_{ik}) = X_k^T\theta_i \; where \; \theta_i = (\theta_{i1}, \theta_{i2}, \theta_{i3}, \dots \theta_{iK})^T = (\mu_i, \delta_{i2}, \dots, \delta_{iK})$$

Then the available data are $\{(r_{ik}, n_{ik}), i = 1, \dots, N, k \in T_i\}$
So the likelihood function is given by

$$\prod_{i=1}^{N} \prod_{k \in T_i}^{N} \frac{e^{r_{ik} X_k^T \theta_i}}{(1 + e^{X_k^T \theta_i})^{n_{ik}}}$$

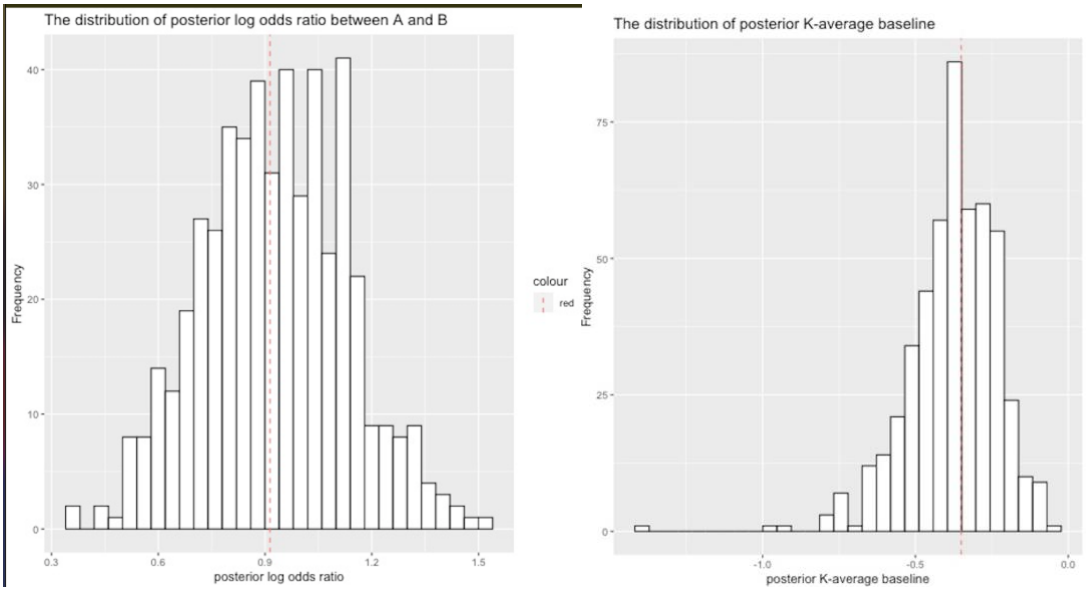
For the Σ, we assume homogeneity of the variances of $logit(p_{ik})$ which suppose a common Gamma distribution from which σ_k^2 are drawn and estimated from the data given weak priors:

$$\sigma_k^2 \sim Gamma(a, b), a \sim Exp(0.01), b \sim Gamma(10^{-3}, 10^{-3}), k = 1,2$$

we will test the fixed effect model where μ_i are unrelated and unconstrained with priors $\mu_i \sim N(0, 10^{-3})$

Simulation Study

Using the given methods, suppose we have the true value and simulate the process for 3000 times.



In the simulation process, we suppose three arms are being compared and each of them have 10 studies and each of them have 30 participants. The prior of the log odds ratio of treatment B and A is 2.06 while the log odds ratio of treatment C and A is 4.97. all other settings such as design matrix X is similar to the paper and the results would be recorded once one iteration finishes. Given the prior settings, after 3000 times simulation, the true value of log odds of ratio between treatment A and B could be estimated and the distribution of log odds ratio show an approximately normal distribution, which is based on the nature of log odds ratio when sample is large. Also, the parameter M, which is the K-average baseline, could also be estimated well using the posterior mode or mean.

Data analysis

Figure 2 is the Bayesian credible interval for A vs B comparison in the first bleeding data using different priors using different priors. All of the results could be replicated using simulation attached code and the summary of posterior distribution of models can be explored.

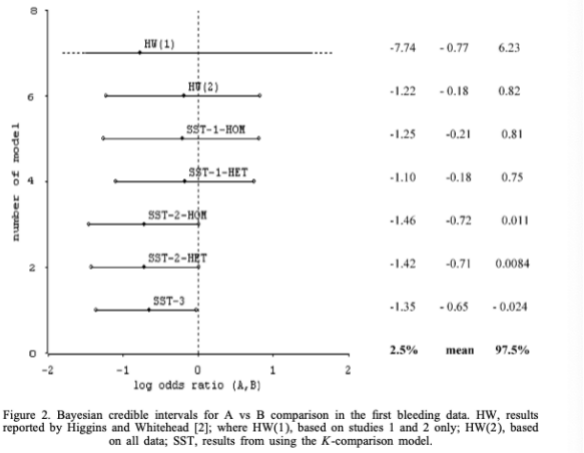


Figure 2. Bayesian credible intervals for A vs B comparison in the first bleeding data. HW, results reported by Higgins and Whitehead [2]; where HW(1), based on studies 1 and 2 only; HW(2), based on all data; SST, results from using the *K*-comparison model.

While the mean of the baseline remains around −1.4, representing a 20 per cent K-average event rate, in SST-2 and SST-3 models the variance of the distribution of baselines severely decreased, illustrating the extent of 'shrinkage' of baselines toward their mean. At the same time the SST-2-HOM, SST-2-HET and the SST-3 models all produce posterior mean in the region of −0:7, and a greater posterior precision that the SST-1 and HW-2 models, as evidenced by the narrower credible intervals.

Conclusions

This approach can well estimate the treatment effect among multiple arms from the simulation results. However, some limitations still exist for example the prior settings, even though the paper mentioned that the results are not sensitive to the prior. We still could improve this approach through a better prior setting. Also, further approach could be considered if the results are not binary.

References

1. Eddy DM, Hasselblad V, Shachter R. Meta-analysis by the Confidence Profile Method. Academic Press: London, 1992.
2. Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. Statistics in Medicine 1996; 15:2733–2749.
3. Hasselblad V. Meta-analysis of multi-treatment studies. Medical Decision Making 1998; 18:37–43.
4. Domenici F, Parmigiani G, Wolpert RL, Hasselblad V. Meta-analysis of migraine headache treatments: combining information from heterogenous designs. Journal of the American Statistical Association 1999; 94:

16 –28.

5. Parmigiani G. Modeling in Medical Decision Making: a Bayesian Approach. Wiley: New York, 2002.
6. Sche□e H. The Analysis of Variance. Wiley: New York, 1959.
7. Hasselblad V, McCrory DC. Meta-analytic tools for medical decision making: a practical guide. Medical

Decision Making 1995; 15:81–96.

8. Whitehead A. Meta-analysis of Controlled Clinical Trials. Chichester, UK, 2002.