MSR85

Comparison of Methods for Estimating Therapy Effects in Unanchored Indirect Comparison: A Simulation Study

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OBJECTIVE

Various unanchored indirect comparison methods have been developed in the absence of head-to-head RCTs. This study aims to compare the performance between matching-adjusted indirect comparison (MAIC) and naïve treatment indirect comparison (NIC) on survival outcomes.

METHODS

The simulation study was reported following the ADEMP (Aims, Data-generating mechanisms, Estimands, Methods, Performance measures) structure.

- **Aims**
  - To compare the performance of MAIC and NIC across a wide range of scenarios that may be encountered in practice.
- **Data-generating mechanisms**
  - A simulation study was conducted based on a large number of simulated trial data sets generated by Monte Carlo approach.
  - A total of 729 (3^6) simulated scenarios were created by performing a full factorial arrangement of six factors with three levels for each, including the sample size of individual patient data, the sample size of aggregate data, the correlation between covariates and outcomes, the correlation of covariates, the overlap of covariates and the true relative treatment effect.

Table 1 Parameters used in the simulation of the A and B arms

Fixed parameters	
Baseline characteristic variables	Covariates X_1 to X_4 are all binary variables
Survival time	Follow a Weibull distribution with shape parameter 1.3 and scale parameter 8.5
Censoring time	Follow an Exponential distribution with 30% probability
Situational factors	
The sample size of IPD	{50, 150, 300}
The sample size of AgD	{50, 150, 300}
The correlation between covariates and outcomes	{ln (1.1), ln (1.5), ln (2)}
The correlation of covariates	{0,0.2,0.4}
The overlap of covariates	Follow a Binomial distribution with probability of X_A~{0.4, 0.65, 0.8} and probability of X_B=0.9
The true relative treatment effect	{0.3, 0.6, 1}

- **Estimands**
  - In health technology assessment, the marginal treatment effect is typically of interest when decision-making is conducted at the population level. Therefore, the estimands is to evaluate the impact of a new intervention on the target population for the decision problem, that is, we are interested in the average effect of moving from treatment A to B for each person in the target population.
- **Methods**
  - MAIC utilized the inverse probability of treatment weighting approach to adjust for the differences between the patient populations characteristics of the drug A and drug B trial. The calculated patient weights were used in a weighted Cox regression with the pseudo-IPDs from comparator to calculate the relative efficacy between drug A and drug B after matching.
  - NIC reconstructed the pseudo-IPD data merely based on AgD and performed Cox regression to compare the efficacy of the two interventions without any adjustment for unbalanced differences between trials..
- **Performance measures**
  - For each indirect comparison method, we selected certain performance measures to assess the following properties: (1) trueness; (2) precision and (3) accuracy.

Trueness	Precision	Accuracy
To quantify the impact of systematic error **Bias**	To quantify the impact of random error **Empirical standard error, ESE**	To quantify the overall impact of both systematic and random errors **Coverage; Mean square error, MSE**

Fiugure 1 Performance Measurement Indicators

- **Implementation**
  - All simulation study and data analyses were performed in the software R software version 3.6.3. Each of the 729 scenarios performed 1000 iterations.

RESULTS

This section was split according to the evaluated performance. The performance measures across all 729 simulation scenarios are illustrated in Figures 2~5 using nested loop plots.

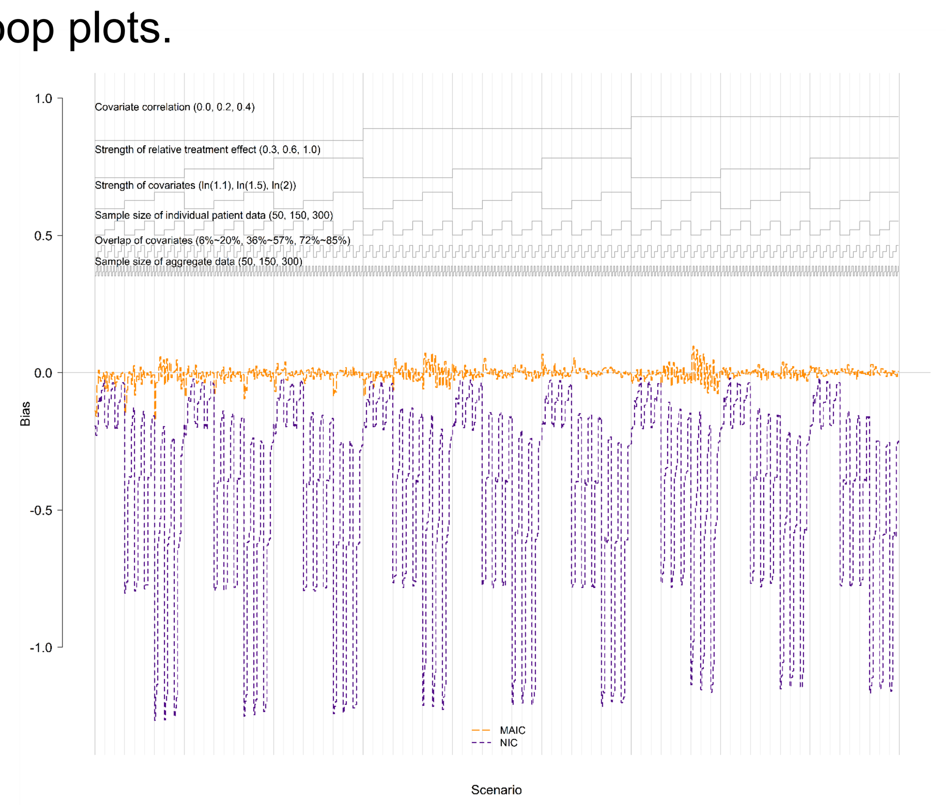

Figure 2 Biases for MAIC and NIC across all scenarios

- In 99% (728/729) scenarios, MAIC yielded less biased estimates than NIC, and therefore a more unbiased method. As covariate strength increases, covariate overlap increases and relative efficacy decreases, MAIC is more likely to yield biased results than NIC.

- In 77% (560/729) scenarios, MAIC achieved an ESE greater than NIC, indicating a low precision. As the correlation between covariates and outcomes, the overlap of covariates decreases and the correlation of covariates decreases, MAIC is more likely to have a larger ESE than NIC, indicating poorer precision of the estimates at this point.

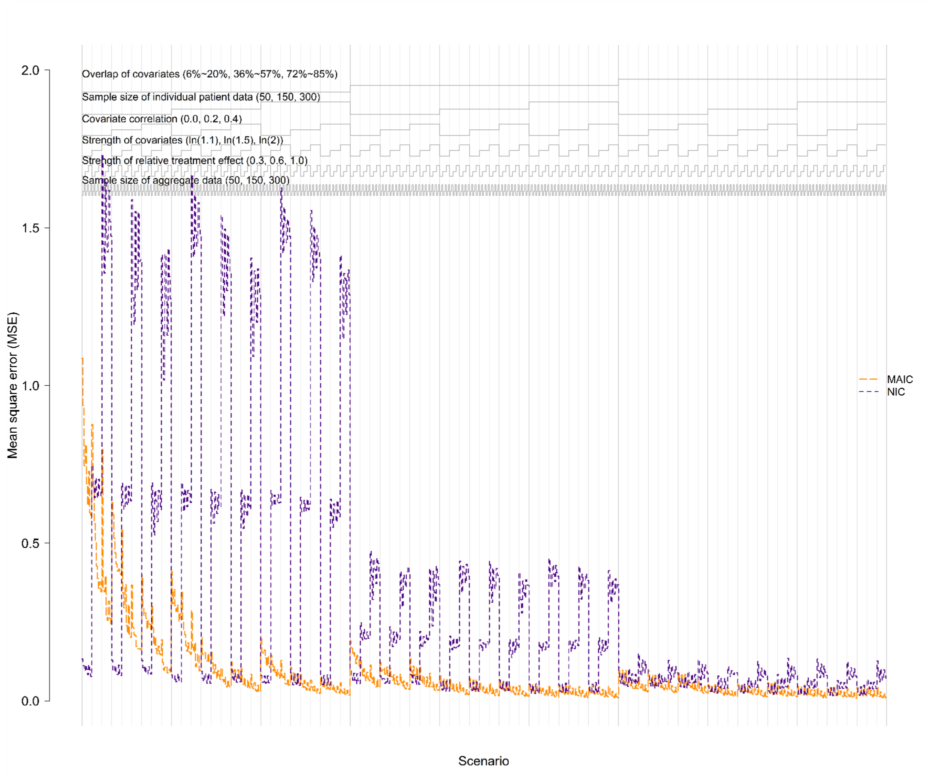

Figure 3 Empirical standard error for MAIC and NIC across all scenarios

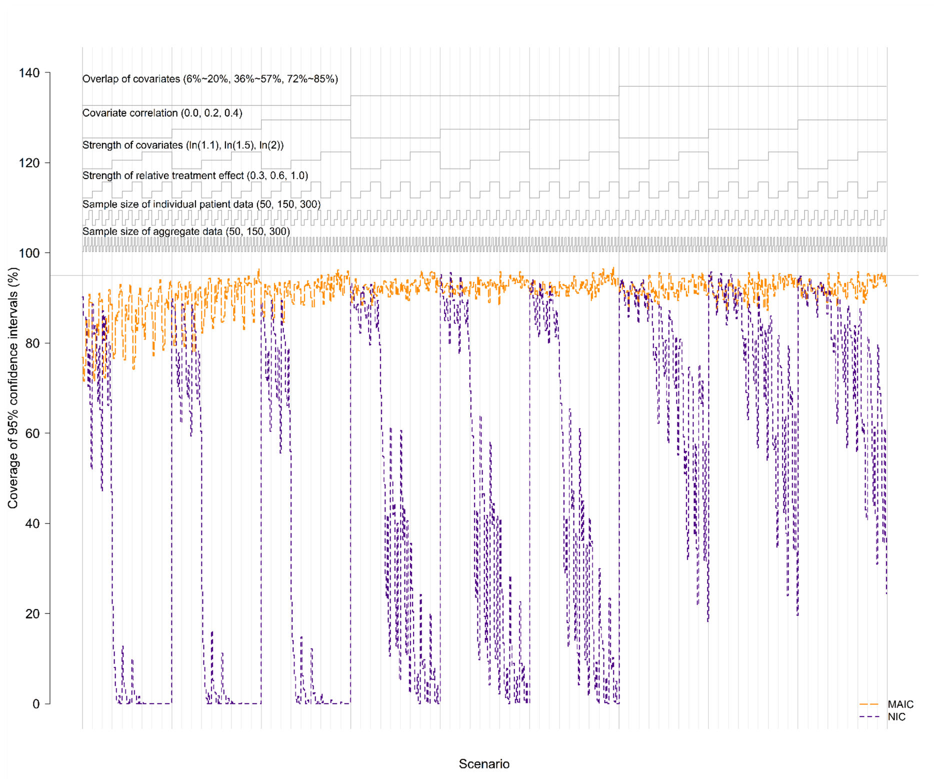

Figure 4 Coverage for MAIC and NIC across all scenarios

- In 90% (657/729) scenarios, MAIC obtained a wider confidence interval coverage than NIC. As the sample size of IPD, the correlation between covariates and outcomes increases, MAIC is more likely to have lower confidence interval coverage than NIC, indicating that the estimates are less accuracy at this point.

- In 76% (551/729) scenarios, MAIC showed a smaller MSE than NIC, indicating greater accuracy. As covariate strength decreases, relative efficacy decreases and IPD sample size decreases, MAIC is more likely to have a larger MSE than NIC, indicating that the estimates are less accurate at this point.

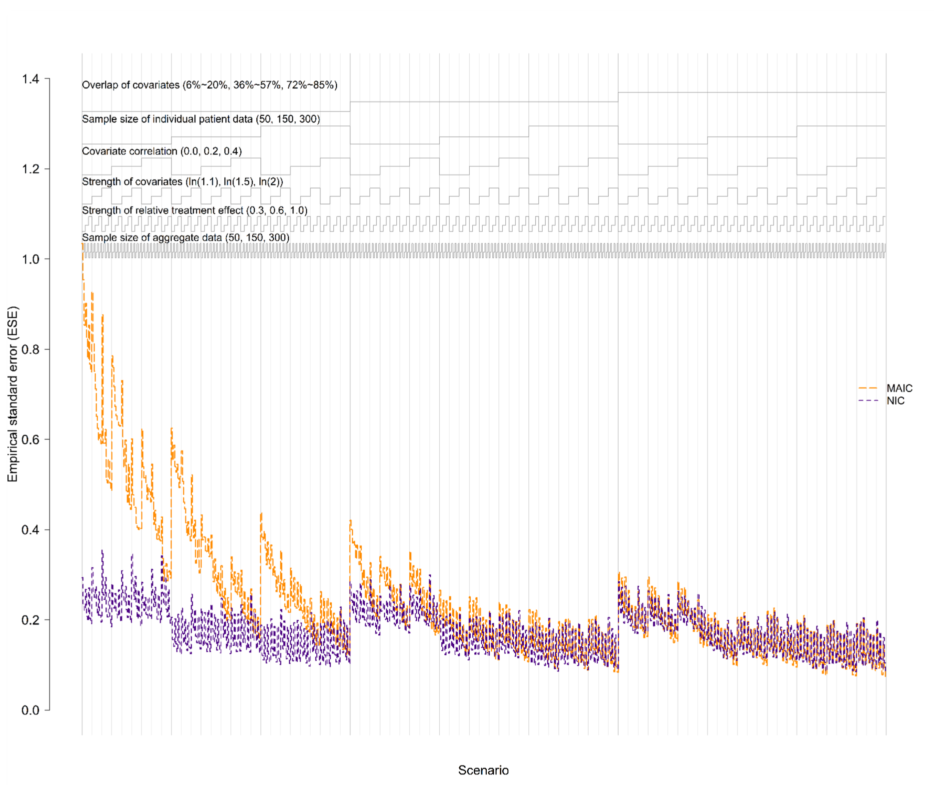

Figure 5 Mean square error for MAIC and NIC across all scenarios

CONCLUSION

MAIC has a higher degree of trueness and accuracy than NIC in the vast majority of scenarios, but has slightly less precision, indicating that there may be greater uncertainty in the results. In addition, because of the large number of underlying assumptions in the MAIC approach, caution is needed in interpreting the results of indirect comparisons so that the propagation of uncertainty does not lead to poor decision-making in health technology assessment.