BACKGROUND

- Because individual patient-level data (IPD) are rarely available for all trials when doing indirect treatment comparisons, aggregate patient data (APD) are typically used.
- In special cases, however, when IPD are available for one trial and APD are available for another trial, alternative methods can provide an additional level of control (through the adjustment of patient characteristics between trials).
- Methods that combine IPD and APD to make indirect treatment comparisons include covariate centering with multivariable modeling (CCMM), matching-adjusted indirect comparison (MAIC), and simulated treatment comparison (STC).

OBJECTIVE

- To use simulated data sets for two oncology clinical trials to compare the CCMM, MAIC, and STC methods in the estimation of a progression-free survival (PFS) HR in the scenario where IPD are available for one trial and APD are available for another trial.

METHODS

**Data**

- Patient-level data sets were generated to simulate two oncology clinical trials, each with 1,000 patients (500 in each arm) who met identical assumed entry criteria (Figure 1):
  - Trial 1: Treatment A versus placebo with accessible IPD
  - Trial 2: Treatment B versus placebo with accessible APD

**Figure 1. Schematic of Simulated Oncology Trial Network**

![Figure 1. Schematic of Simulated Oncology Trial Network](image)

- Variables included in both data sets were time to PFS, its corresponding censoring indicator, and the following patient characteristic variables of interest: age, sex, disease stage, laboratory test positivity, and brain metastases history.
- APD assumed to be available for Trial 2 included cross-tabulations by treatment (i.e., counts and percentages) of patient characteristic variables, and the HR and 95% CLs of treatment A versus placebo.
- PFS times in each trial followed the Weibull distribution.

**Statistical Methods**

- Descriptive statistics of patient characteristics were generated for Trial 1 and compared to the APD from Trial 2 to assess differences between trials.
- A Cox regression on PFS time was performed on Trial 1 data to generate a predictive model for the outcome as a function of the following characteristics: treatment group, age, sex, disease stage, laboratory test positivity, brain metastases history, and the interaction between treatment group and laboratory test positivity.
- To avoid nonlinearly bias as described in Ishak et al., a patient profile data set was simulated based on the mean values of patient characteristic variables reported in the APD for Trial 2 under the multicollinearity-normal distribution.
- The coefficients of the predictive model were applied to each simulated patient profile to compute individual log hazards and the adjusted HR of treatment A versus placebo. AIC was performed to estimate the adjusted HR of treatment A versus treatment B.

**RESULTS**

- The age and sex distribution of patients was similar between trials. Patients in Trial 1 were less likely to have late-stage disease and more likely to have positive laboratory tests and a history of brain metastases than patients in Trial 2 (Table 1).
- The unadjusted HR of treatment A versus placebo observed in Trial 1 was 0.24 (95% CL, 0.20, 0.30), and the HR of treatment B versus placebo available in the APD of Trial 2 was 0.45 (95% CL, 0.37, 0.54). These results yielded a naive HR of treatment A versus treatment B of 0.55 (95% CL, 0.42, 0.72).
- The adjusted HR derived from the CCMM method of treatment A versus placebo was 0.28 (95% CL, 0.22, 0.35) (Table 2).
- After applying MAIC, patient characteristics from Trial 1 and Trial 2 were adequately balanced (Table 3). The adjusted HR of treatment A to placebo patients was 0.31 (95% CL, 0.26, 0.37).
- Upon implementation of the STC method, the adjusted HR of treatment A versus placebo was 0.31 (95% CL, 0.29, 0.33) (Table 4).

**DISCUSSION**

- As with all treatment comparisons of this nature, these statistical methods rely on many important assumptions that cannot be tested directly.
- These methods cannot adjust for the potential effects of unmeasured confounders on the treatment comparison. Potential effect modification and subgroup effects are difficult to assess.

**CONCLUSIONS**

- Based on our simulation, the naive (unadjusted) comparison demonstrated a protective effect of treatment A compared to treatment B for PFS.
- All three methods of adjustment yielded HR values that approached the value of the fully adjusted reference point, with MAIC and STC performing slightly better than CCMM.

### Table 1. Patient Characteristic Variables Pre- and Postmatching Using MAIC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prematch</th>
<th>Postmatch</th>
<th>Reported</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td>66.6</td>
<td>66.6</td>
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<tr>
<td>Sex (male)</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>Disease stage (stage 3)</td>
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<td>60%</td>
<td>60%</td>
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<tr>
<td>Laboratory positive</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**REFERENCES**


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