Exploratory application of bivariate network meta-analysis to predict missing hazard ratios in mCRPC using simulated correlation data

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Background and Objective

- Conventional network meta-analysis (NMA) analyzes one outcome at a time, which is appropriate when outcomes are independent. However, in many clinical settings, particularly for time-to-event endpoints such as radiographic progression-free survival (rPFS) and overall survival (OS), treatments tend to move both endpoints in the same direction. Ignoring this dependency leaves precision on the table, widens uncertainty, and may yield treatment rankings that differ across outcomes.[1,2]
- In bivariate (or multivariate) NMA models, two outcomes are analyzed jointly, using within-study and between-study correlations to link treatment effects across trials. This approach offers two immediate benefits:
  - **Borrowing of strength:** Information flows from outcomes that are better reported to those that are sparser, typically tightening credible intervals relative to separate univariate NMA[1]
  - **Prediction of missing outcomes:** If a study reports the log HR (Hazard ratio) for OS but omits rPFS (or vice versa), the bivariate model can impute the missing effect coherently from the observed one[1]
- Bivariate NMA requires access to patient-level data to recover the within-study correlation between the two log HRs. Because stronger correlations induce more borrowing and hence narrower intervals. [1,3]
- The objective was to demonstrate, using a realistic oncology evidence base, that bivariate NMA yields more precise and more complete treatment comparisons than conventional outcome-by-outcome NMA.

Methods

- A systematic literature review identified RCTs (Randomized clinical trials) in metastatic castration resistant prostate cancer (mCRPC). Publications rarely report within-study correlations or share individual patient data and, thus, patient-level data for OS and rPFS were simulated to calculate within-study correlation between log HR(OS) and log HR(rPFS) using two approaches[4,5]:
- **Bootstrap (primary):** We used bootstrap resampling of patients, refit Cox models to obtain paired hazard ratios, and computed their correlation across bootstrap replicates to obtain correlation estimate.
- **Gaussian copula (sensitivity):** Simulated paired log HR were drawn from marginal distributions, followed by fitting of a Gaussian copula to recover correlation.
- Correlation was used as a prior with uniform distribution in BUGS for studies with both outcomes and switched off when only one outcome was available. The within-study covariance matrix was built from standard errors and correlation, then inverted to obtain within-study precision.
- Bivariate random-effects NMA was implemented which was consistent with multivariate evidence synthesis principles using BUGS program as follows[2]:
- **Study-level likelihood**: Bivariate log HR vector $y_i = (\log HR_{rPFS}, \log HR_{OS})$ followed bivariate normal with mean equal to study-specific treatment contrast and precision equal to inverse of within-study covariance.
- We accounted for between-study differences using a shared 2×2 covariance matrix with outcome-specific standard deviations and a cross-outcome correlation, reflecting that treatment effects on the two outcomes tend to move together.
- **Consistency:** Standard NMA equations linked observed contrasts to basic treatment effects. Cross-outcome shrinkage was applied at the basic parameter level ($meanD[m,k] \leftarrow \alpha[k] + \gamma[m]$) with non-informative priors enabling modest borrowing across outcomes.
- **Missing outcomes**: If a trial reports only one outcome, the likelihood reduces to the observed margin while the joint model predicts the missing effect using the estimated within-study and between-study correlations.
- **Computation:** Diffuse priors and multiple dispersed chains were used, standard Markov chain Monte Carlo simulation diagnostics were monitored, and residual deviance was assessed for model fit and coherence.

Results

1. Evidence based on the SLR

A total of 13,537 records were identified through database and conference searches. After removing duplicates and screening titles, abstracts, and full texts, 80 publications were included. Following data extraction and application of eligibility criteria (excluding dose-ranging studies, disconnected networks, and treatments not approved by National Comprehensive Cancer Network), 18 relevant studies were included in the NMA.

2. Network Meta-Analysis

Bivariate NMA, which jointly models rPFS and OS through correlated likelihoods, reduced credible interval widths by approximately 86–97% (Figures 2 and 3) compared to separate univariate analyses. The approach recovered estimates for five interventions where univariate models failed, transforming the same evidence into decision-grade precision while maintaining consistent point estimates.

Figure 1 PRISMA Flow

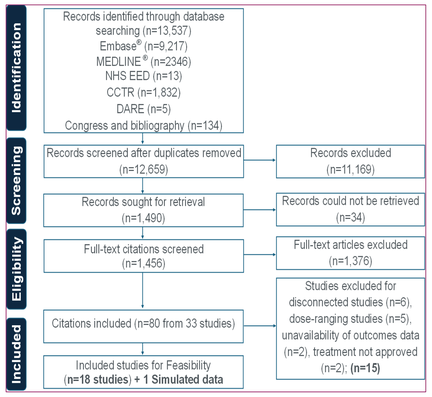


Figure 2 Comparison plot OS

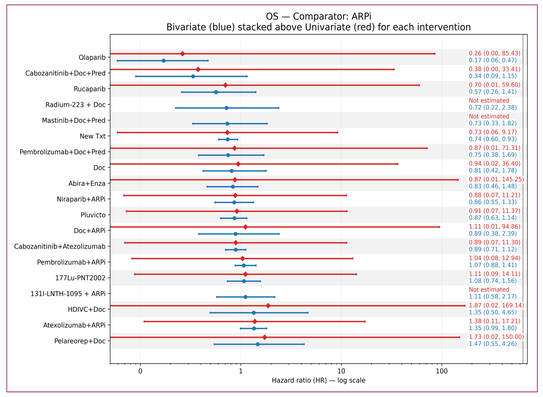
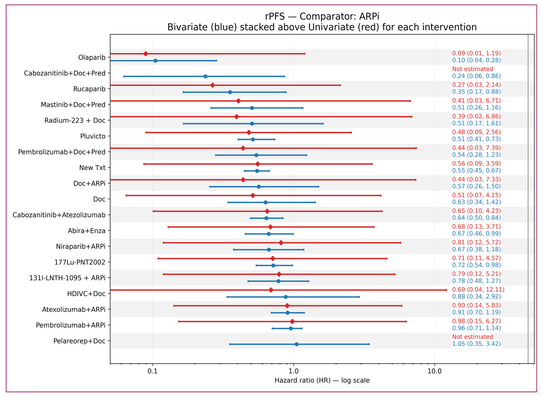


Figure 3 Comparison plot rPFS



Conclusions and Limitations

- Bivariate NMA transformed incomplete and imprecise univariate NMA results into complete, decision-ready synthesis using the same trials. By borrowing strength across correlated endpoints, the joint model stabilized sparse data and tightened credible intervals while preserving treatment effect estimates. This was especially critical for OS, where univariate analysis often failed to produce usable intervals.
- Given that within-study correlations were derived from simulated data and that some effects were predicted, all findings should be regarded as exploratory and primarily intended to illustrate the methodological advantages of bivariate NMA rather than to guide clinical decisions without further validation.

References

[1] Multivariate & network meta-analysis rationale, borrowing of strength, and prediction of missing outcomes Riley RD, Jackson D, Salanti G, et al. BMJ. 2017;358:j3932.
[2] Framework for multiple outcomes & explicit modeling of within /between study correlations; predicting unreported outcomes Achana FA, Cooper NJ, Bujkiewicz S, et al. BMC Med Res Methodol. 2014;14:92
[3] Multivariate NMA with optional class effects (not used here, but cited to position scope) Owen RK, Bujkiewicz S, Tincello DG, Abrams KR. BMC Med Res Methodol. 2020;20:184
[4] Nelsen RB. An Introduction to Copulas. 2nd ed. Springer; 2006.
[5] Burzykowski T, Molenberghs G, Buyse M. The Evaluation of Surrogate Endpoints. Springer; 2005