Using a Function-Oriented Pipeline Tool to Implement a State-of-the-Art Meta-Analytic Approach in R: Combining `targets` and Multi-Level Network Meta-Regression

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Background and Aims

In recent years, treatment for advanced and unresectable hepatocellular carcinoma (HCC) has advanced, with atezolizumab+bevacizumab (A+B) and durvalumab+tremelimumab (D+T) now approved as first-line treatment.[1] The rapid pace of developments necessitates regular evaluation of treatment efficacy and safety. For instance, camrelizumab+rivoceranib (C+R) shows promise for first-line use, though its safety profile versus A+B raises concerns.[2,3]

Multi-level network meta-regression (ML-NMR) was proposed by Phillippo *et al.* as an extension of standard network meta-analysis (NMA) that allows combining individual-level and aggregate study data.[4,5] The framework improves on existing population adjustment methods and enables prediction into any target population. ML-NMR can handle a range of outcomes and was recently extended to cover time-to-event outcomes.[6]

The implementation of ML-NMR is facilitated with the R package `multinma`. The Bayesian methods underpinning the approach imply a certain computational expense, however, when running analyses. In a typical workflow, complexity may be added by having to run analyses for multiple outcomes and many different output formats, e.g., a report or paper, using different slices of the data while having to incorporate new data when they became available. In such cases, re-running the entire analysis pipeline becomes inefficient and could be improved by re-running only those parts of the analysis affected by a specific change to data, analysis approach, or setting.

Such functionality is provided by pipeline tools such as `Make` in GNU, `Snakemake` in Python, and `targets` in R,[7] which can significantly reduce runtime and computation for data-intensive projects, improving analyses and saving valuable research time. These tools construct a dependency graph of all workflow "steps" (such as reading in, cleaning, and filtering data, running an analysis, or generating a plot). Changes invalidate all dependent steps, and only these are subsequently re-run. For instance, if the resolution of output plots is changed, plots are re-generated, but computationally expensive analyses are left unchanged.

The aim was to develop a proof-of-concept implementation of a `targets` pipeline for an ML-NMR of safety outcomes associated with unresectable HCC treatments, to evaluate the benefits and challenges of setting up a function-oriented pipeline tool for quantitative synthesis.

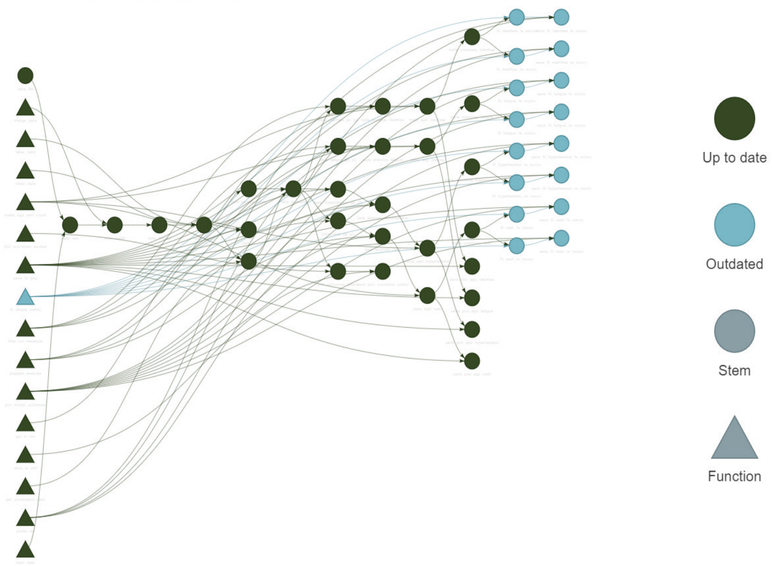
Methods

A targeted literature search was conducted in PubMed up to April 2024, for randomized controlled trials (RCTs) of systemic therapies and selective internal radiation therapy (SIRT) for unresectable HCC. Studies were eligible if they reported target safety outcomes: diarrhea, fatigue, hypertension, and rash.

Data from included RCTs – covering study metadata, baseline data, and outcomes – were extracted into an Open Document Spreadsheet.

A functionally-oriented processing and analysis pipeline was set up in R using targets v1.7.0.[7] Single-purpose functions were developed for data processing, data filtering, analysing, and plotting results, and included as targets in the pipeline (represented by triangles in Figure 1). Data were also read in and processed by the pipeline.

Figure 1: ML-NMR targets pipeline, in a partially invalidated state



For each target safety outcome, fixed-effect and random-effects NMAs were set up, using a probit link and a two-parameter Binomial likelihood for arm-based aggregate data, as suggested by Phillippo *et al.*[4] Sorafenib was used as the reference treatment.

No individual-level data was ultimately included in the present analysis. For this proof-of-concept analysis, meta-regression was also not implemented although the functions programmed are readily extendable to accommodate regression terms. Each model was estimated using four Markov chains with 2,000 iterations each.

Results were shown graphically as relative treatment effects versus sorafenib and based on each treatment's posterior rank.

Results

The analysis included >13,500 data points from fourteen RCTs (Figure 2).

Figure 2: Aggregate data networks across outcomes

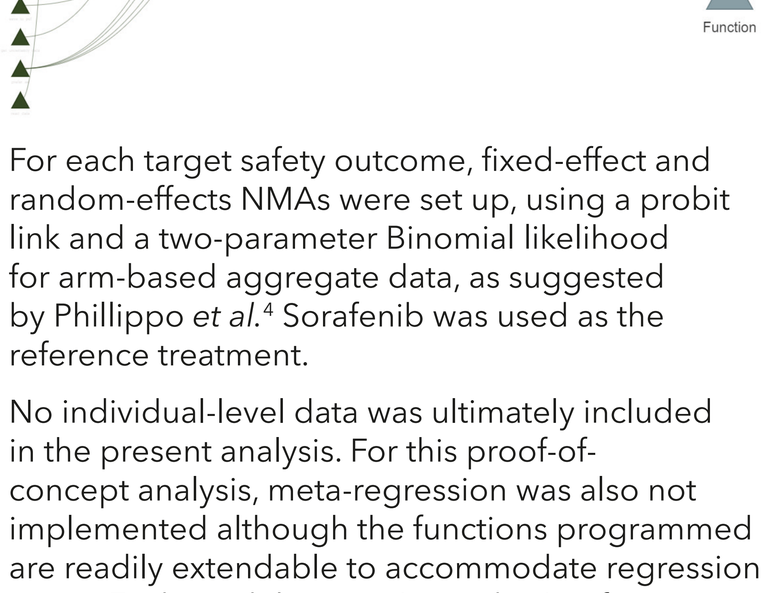
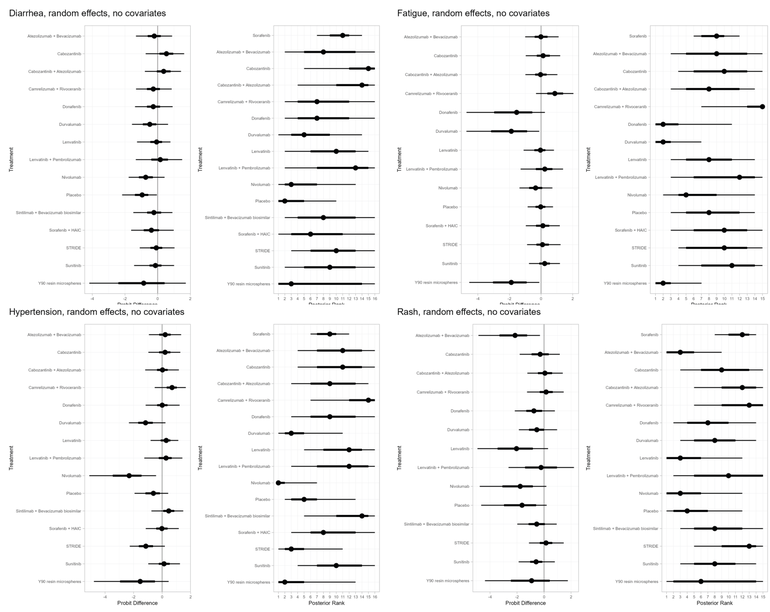


Figure 3: Relative treatment effects and posterior ranks



Initial pipeline execution took 3.6 minutes on a laptop with 16GB RAM and 20 cores. Subsequent modifications to a single model typically required <60 seconds for the entire pipeline to rerun.

Random-effects models suggested the following safety-related findings (Figure 3):

- Among active treatments, SIRT with Y-90 resin microspheres and nivolumab performed best regarding diarrhea, while cabozantinib (alone and with atezolizumab) and lenvatinib+pembrolizumab performed worst.
- Regarding fatigue, SIRT with Y-90 resin microspheres, donafenib, and durvalumab performed best, while C+R ranked last.
- Nivolumab performed best for hypertension, followed by SIRT with Y-90 resin microspheres and durvalumab. C+R ranked last.
- A+B, nivolumab, and lenvatinib ranked best for rash. C+R and STRIDE ranked last.

Discussion

This proof-of-concept study investigated the use of a state-of-the-art meta-analytic tool with a state-of-the-art pipeline framework, to ensure that results could be efficiently generated from a transparent and consistent code base.

The use of `targets` in R was straightforward to set up (with good documentation available online) and implement. Qualitatively, the tool was particularly valuable for indicating all downstream effects of upstream changes to code or data.

Future steps will include extending this proof-of-concept to cover more recent evidence and additional outcomes including survival, and individual-level patient data.

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