Applying Multi-Level Network Meta-Regression (ML-NMR) to a Case Study in Triple-Class Exposed (TCE) Relapsed/Refractory Multiple Myeloma (RRMM)

MSR31

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Introduction

Background

- Indirect treatment comparisons (ITCs), such as network meta-analysis (NMA) of randomized controlled trials (RCTs), are needed to estimate the relative efficacy of competing interventions evaluated across trials
- Differences in effect modifiers between the different direct comparisons may bias NMAs[1-3]
- Network meta-regression (NMR) using aggregate data (AD) has risk of aggregation bias[4,5]
- NMR using individual patient data (IPD) for all RCTs in the network is the gold standard to adjust for differences in effect modifiers[6,7]
- NMR methods to combine IPD with AD in an NMA framework[8,9] that use common regression coefficients for IPD and AD may result in aggregation bias
  - Jansen et al. (2012) proposed a model for IPD and AD that avoids this challenge by integrating over the covariate distribution for the AD studies for binary outcomes and covariates[10]
  - Phillippo et al. (2020)[11] extended this approach to a generalized framework: multi-level network meta-regression (ML-NMR)

Benefits of ML-NMR

- ML-NMR reflects an extension of the standard NMA framework, which addresses challenges with previous ITC methods
- ML-NMR first defines an individual-level regression model, which is then integrated over the aggregate populations to form an aggregate-level model, which can be applied to different types of outcomes (and corresponding likelihoods) and covariates (i.e., dichotomous, continuous, etc.)[11]
- ML-NMR is applicable in networks of various sizes, avoids aggregation bias, and produces estimates in any target population
- ML-NMR may result in less biased estimates compared to NMA without covariates[12] and may improve model fit and lead to more precise estimates as compared to a random-effects NMA model (without covariates) in cases where within- and between-study variation can be explained[13]
- To our knowledge, ML-NMR has only been published and applied to binary outcomes

Objectives

- To highlight the ML-NMR models for time to event outcomes as presented by Phillippo et al. (2019)[14]
- To illustrate their application with a case study evaluating treatments for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) patients in terms of overall survival (OS)

Methods

Case study evidence base

- We included three single-arm clinical trials and two real-world studies:
  - Clinical trials: KarMMa evaluating ide-cel[15]; STORM-2 evaluating selinexor + dexamethasone (Sd)[16]; DREAMM-2 evaluating belantamab mafodotin (BM)[17]
  - Real-world studies: KarMMa-RW evaluating conventional care (CC)[18] and MAMMOTH evaluating CC[19]
- ML-NMR requires a connected network of RCTs; therefore, we generated artificial-RCTs (aRCTs) based on a naïve comparison of (**Figure 1**):
  - KarMMa vs KarMMa-RW (two-arm aRCT based on IPD: ide-cel versus CC)
  - DREAMM-2 intention-to-treat (ITT) vs STORM-2 ITT vs MAMMOTH treated populations (three-arm aRCT based on AD: BM vs. Sd vs. CC)
- Between-study differences were identified based on a rank-ordering of prognostic factors from a systematic literature review, covariates included in published ITCs in TCE RRMM, and predictive models
- The ML-NMR models included number of prior lines, age, and triple-class refractory (TCR) status as covariates (**Figure 1**)

Multi-level Network Meta-Regression for Survival

- Extension of standard NMA framework in which an outcome regression model is defined for the IPD studies and this model is integrated over the aggregate population(s) to create the aggregate-level model for the AD studies[11]

Individual

$$y_{ijk} \sim \pi_{IPD}(\theta_{ijk})$$
$$g(\theta_{ijk}) = \eta_{jk}(x_{ijk}) = \mu_j + \boldsymbol{x}_{ijk}^T(\beta_1 + \beta_{2,k}) + \delta_k$$

Aggregate

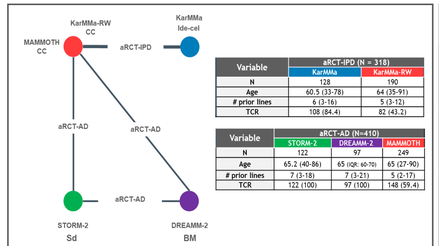
$$y_{.jk} \sim \pi_{AD}(\theta_{.jk})$$
$$g(\theta_{.jk}) = \int_X g^{-1}\, d\left(\eta_{jk}(x)\right) f_{jk}(x)x$$

  - Where, y_{ijk} is an event indicator for patient *i* in study *j* receiving treatment k and $y_{.jk}$ reflects the summary outcome available from AD studies, which are given likelihood distributions π_{IPD} and π_{AD}. The respective conditional and marginal mean outcomes, θ_{ijk} and $\theta_{.jk}$, are linked to the covariates and parameters of the linear predictor, η_{jk}, through the link function $g(\cdot)$
  - Further, μ_j represent study-specific baselines, β_1 and $\beta_{2,k}$ represent the mean effect of covariates and treatment specific effect modifiers, lastly δ_k is the treatment effect of the *k*th treatment relative to the reference
- In the context of survival, the individual likelihood contributions for the proportional hazard models are defined by the survival, S_{jk}, and hazard, λ_{jk}, functions at time, t_{ijk}, as described in **Table 1**

$$L_{ijk|x}(\xi; t_{ijk}, y_{ijk}, \boldsymbol{x}_{ijk}) = S_{jk}(t_{ijk}|\boldsymbol{x}_{ijk})\lambda_{jk}(t_{ijk}|\boldsymbol{x}_{ijk})^{y_{ijk}}$$

- The fixed effect ML-NMR assumed a proportional hazards Weibull, Gompertz, or exponential model, adjusted for number of prior lines, age, and triple-class refractory (TCR) status
- Using a Bayesian framework, parameters were estimated using Markov Chain Monte Carlo method using R (packages: rstan and loo) and Stan[20-22]

Figure 1: Network diagram of artificial randomized controlled trials



Variable	aRCT-IPD (N = 318)	
	KarMMa	KarMMa-RW
N	128	190
Age	60.5 (33-78)	64 (35-91)
# prior lines	6 (3-16)	5 (3-12)
TCR	108 (84.4)	82 (43.2)

Variable	aRCT-AD (N=410)		
	STORM-2	DREAMM-2	MAMMOTH
N	122	97	249
Age	65.2 (40-86)	65 (IQR: 60-70)	65 (27-90)
# prior lines	7 (3-18)	7 (3-21)	5 (2-17)
TCR	122 (100)	97 (100)	148 (59.4)

Abbreviations: AD, aggregate-level data; aRCT, artificial randomized controlled trial; BM, Belantamab mafodotin; CC, Conventional care; Ide-cel, idecabtagene vicleucel; IPD, individual patient data; IQR, interquartile range; Sd, Selinexor + dexamethasone; TCR, triple-class refractory.

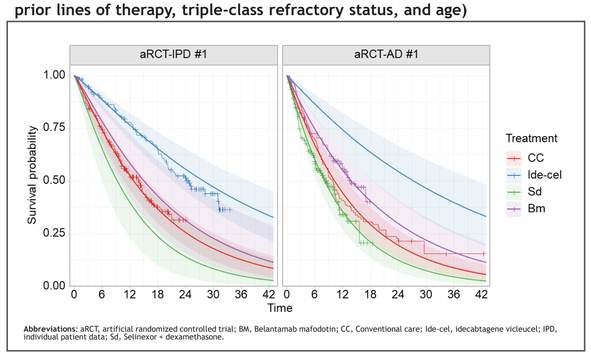
Table 1: Survival and hazard functions for common parametric survival models

Survival Distribution	Parameters	Survival and hazard functions
Exponential	Hazard rate θ_{jk} modelled with $\exp\left(\eta_{jk}(x)\right)$	$S(t)=\exp(-\theta t)$
		$\lambda(t)=\theta$
Weibull	Hazard rate θ_{jk} modelled with $\exp\left(\eta_{jk}(x)\right)$; shape v_j	$S(t) = \exp(-\theta t^v)$
		$\lambda(t) = v\theta t^{v-1}$
Gompertz	Hazard rate θ_{jk} modelled with $\exp\left(\eta_{jk}(x)\right)$; shape v_j	$S(t) = \exp\left(-\frac{\theta}{v}(\exp(tv)-1)\right)$
		$\lambda(t) = \theta\exp(tv)$

Results

- **Figure 2** presents an overlay population-average survival curves estimated using the Weibull distribution relative to the observed Kaplan-Meier curves, which illustrate the fit of the model to the observed data
- Using a Weibull distribution, we estimated hazard ratios (HRs) and 95% credible intervals (CrIs) for the aRCT-IPD (i.e., KarMMa vs KarMMa-RW) target population (**Table 2**), which suggested:
  - Ide-cel was more efficacious than Sd (HR 0.28 [95% CrI: 0.17, 0.47]), BM (HR 0.50 [95% CrI: 0.30, 0.82]), and CC (HR 0.45 [95% CrI: 0.29, 0.69])
  - The CrIs included the null effect for Sd vs CC and BM vs CC
  - Effect modifiers had minimal impact on the model (95% CrIs of the estimates included zero), and only the TCR main effect had an impact on the model
  - The 95% CrIs from adjusted models were wider in comparison to CrIs from models without covariates

Figure 2. Overview of predictions (Weibull model adjusted for number of prior lines of therapy, triple-class refractory status, and age)



Abbreviations: aRCT, artificial randomized controlled trial; BM, Belantamab mafodotin; CC, Conventional care; Ide-cel, idecabtagene vicleucel; IPD, individual patient data; Sd, Selinexor + dexamethasone.

Table 2. Survival and hazard functions for common parametric survival models

HRs predicted for aRCT-IPD population		No covariates	Three covariates
Tx vs. CC	Ide-cel vs. CC	0.50 (0.37, 0.68)	0.45 (0.29, 0.69)
	Sd vs. CC	1.44 (1.06, 1.92)	1.56 (0.98, 2.62)
	BM vs. CC	0.83 (0.61, 1.12)	0.89 (0.54, 1.52)
Ide-cel vs. Tx	Ide-cel vs. Sd	0.35 (0.23, 0.55)	0.28 (0.17, 0.47)
	Ide-cel vs. BM	0.60 (0.39, 0.96)	0.50 (0.30, 0.82)
Model parameters		**No covariates**	**Three covariates**
Main effect	Age	--	0.01 (-0.01, 0.03)
	Triple-class refractory	--	0.59 (0.17, 1.02)
	Number of prior treatments	--	0.02 (-0.10, 0.12)
Effect modifier	Age	--	-0.02 (-0.05, 0.02)
	Triple-class refractory	--	-0.24 (-1.03, 0.65)
	Number of prior treatments	--	-0.02 (-0.17, 0.12)

Abbreviations: aRCT, artificial randomized controlled trial; BM, Belantamab mafodotin; CC, Conventional care; Ide-cel, idecabtagene vicleucel; IPD, individual patient data; Sd, Selinexor + dexamethasone; Tx, treatment.

Conclusion

- This ML-NMR case study demonstrates the feasibility of applying ML-NMR for time-to-event outcomes
- Findings from this analysis suggest that ide-cel is more efficacious than Sd, BM, and CC
- There was little evidence of effect modification, which may have been because of small differences in the covariates
- ML-NMR is designed to indirectly compare treatments based on a connected network of RCTs. Since we generated artificial RCTs based on non-randomized studies (i.e., single-arm clinical trials and real-word studies), results from the illustrative case study may have been biased
- The benefit of using ML-NMR depends to some extent on the reporting of covariate distributions for continuous covariates in AD studies
- Run-time for fitting the model in STAN was approximately 15-30 minutes. Memory usage was more burdensome where 4 MCMC chains with 2000 iterations each required up to 9.6 GB of RAM when saving information for integration checks. Alternatively, fitting the model twice without saving this information and ensuring the same parameter estimates are obtained across runs can be done to reduce RAM usage to 2GB.
- Future research may be beneficial to explore:
  - inclusion of missing covariate values in the ML-NMR model
  - integration of evidence from subgroups
  - additional functional forms
  - more complex network structures with multiple IPD studies
  - time-varying HRs that avoid proportional hazards assumption
- We would expect ML-NMR to have the most value when there are important differences in effect modifiers within the network of evidence that can be adjusted for in the analysis

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