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# To Merge Randomized Controlled Trials and Real-world Evidence with Bayesian Network Metaregression: A Case Study in Patients with Myelodysplastic Syndromes

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# Background & Objective

- Randomized controlled trials (RCTs) and realworld evidence (RWE) are often synthesized separately in health technology assessment (HTA).
- One reason is that RCTs and RWE show great heterogeneity in methodology and risk of bias which makes merging the two data sources technically difficult.
- To address this problem, Bayesian Network Meta-regression (BNMR) models have been applied for evidence synthesis in the HTA setting.
- Hence, we aimed to estimate and compare the performance of existing BNMR models in a case study of Myelodysplastic Syndromes (MDS).

#### Method - Meta-analysis

#### Case

- Data source: Song et al. (2021);
- Target population: Patients with acute myeloid leukemia and myelodysplastic syndromes;
- Intervention: Reduced intensity conditioning (RIC);
- Comparator: Myeloablative conditioning
- Outcomes of interest: Overall survival (Binary outcome).

# Identification of BNMR models using the snowballing approach, according to Wohlin (2016)

Website that supports the snowballing
approach:

approach:

Connected Papers;

- Starting from two identified reviews of appraisal tools: Jenkins et al. (2021) & Zhang et al. (2019)
- Eligibility criteria: (1) Bayesian model; (2)
   The model supported binary outcomes; (3)
   Codes for running a model were available.

## Data collection & preparation

- Characteristics of BNMR models;
- Codes used to run the BNMR models;
  - Covariates: age, duration of follow up.

#### Model running

- R package: Crossnma & R2jags;
- Initial value set in the BNMR models: Null;
- Number of iterations of Bayesian meta-
- regression: 50000; Number of burn-in iterations: 20000;
- Number of Markov chains: 4Number of thining of Markov chains: 1.

#### Model comparison

Comparison of mean and confidence interval in a forest plot.

# RESULTS



Figure 1. Flow chart of the BNMR models for comparison

Study		Survival (RIC)		Survival (MAC)		Log Odds Ratio	Forest plot
Pullipp 2830   23   14   31   25   0.12 [-0.25, 0.49]   Pullipp 2830   40   23   44   45   25   24   24   24   24   24	Study	Yes	No	Yes	No	95% CI	
Martino2012   67   59   402   316   -0.05 [-0.21, 0.12]	Shimoni2012	47	59	43	42	-0.11 [-0.36, 0.14]	•
Light 2012   344   697   1269   2462   -0.02 [-0.08, 0.04]	Philipp2010	23	14	31	25	0.12 [-0.25, 0.49]	H <del>H</del> H
Rimonbo   14	Martino2012	67	59	402	316	-0.05 [-0.21, 0.12]	
Minamoto2014   34   47   15   18   -0.09 [-0.44, 0.26]	Luger2012	344	697	1269	2462	-0.02 [-0.08, 0.04]	
Boundary   32   15   80   37   -0.01 [-0.32, 0.31]	Khabori2011	20	19	30	32	0.05 [-0.3, 0.4]	H <del>-</del> H
Sortical	Hiramoto2014	34	47	16	18	-0.09 [-0.44, 0.26]	H <del>H</del> H
Sect1207   93   44   105   30   -0.22 [-0.45, 0.02]	Lioure2012	32	15	80	37	-0.01 [-0.32, 0.31]	H <del>ar</del> t
Ringden2013   14   4   12   7   0.31 [-0.32, 0.94]	Bornhauser2012	57	37	52	38	0.05 [-0.2, 0.31]	·
MC FludT.14/L Trial 12018 98 54 101 67 0.08 [-0.12, 0.28]  Roggar 2017 50 15 40 24 0.3 [-0.0, 0.6]   HB-   Benchmauser 2012 32 67 36 60 -0.1 [-0.16, 0.16]   HB-   Benchmauser 2012 135 105 157 63 0.25 [-0.46, 0.12]   H-   AL Rocecte events as inputs  AL Leopfor a inputs  AL Leopfor a inputs  AL Leopfor a inputs  BL Developed from Schmitz, Adoms, and Wolsh 2013 0.45 [-0.16, 0.03]   H-   BL Logical events as inputs  CL Discrete fevents as in	Scott2017	93	44	105	30	-0.22 [-0.45, 0.02]	•
Registral   So   15   40   24   0.3 [ 0.03 (.61)   Held	Ringden2013	14	4	12	7	0.31 [-0.32, 0.94]	<b>⊢</b> •−
8 mehanuse 2012 32 67 36 60 -0.1 [-0.36, 0.16]	MC-FludT.14/L.Trial I2018	98	54	101	67	0.08 [-0.12, 0.28]	
Beelen 2819   135   105   157   63   -0.29 [-0.46, -0.12]	Kroger2017	50	15	40	24	0.3 [-0.03, 0.63]	H <del>=H</del>
Al. Discrete events as injusts   0.06 [0.05, 0.07]   1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1	Bornhauser2012	32	67	36	60	-0.1 [-0.36, 0.16]	
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C2. Logoda is injust         -0.14 [-0.15, -0.13]         I → □           C3. Developed from Schmitz, Adams, and Walsh 2013         0.3 [-0.5, -2.]         I → □           D. Prior for men only         -0.15 [-0.5, -0.1]         I → □           D2. Prior for both mean and precision         -0.15 [-0.15, -0.1]         I → □           D2. Developed from (Pithnious, Moveldit), Debray, Samara, Belger, Siontis, and et al 2017         0.32 [-0.2, -0.4]         IM           E1. Increasing variance of NRSs through prior distribution of both NRSs and RCTs         -0.12 [-0.14, -0.1]         I → □           E2. Increasing variance of NRSs through prior constraint         -2.17 [-2.77, -2.66]         I → □           E3. Adjusting for probability in internal walifity his via prior prior internal walifity his via brough uniform prior         -0.12 [-0.14, -0.11]         I → □           E4. Adjusting for probability in internal walifity his via brough uniform prior         -0.12 [-0.12, -0.11]         I → □           E5. Developed from New Wellon, Marinho, Salant, Figgins, and Ades 2010         0.42 [-0.3, -0.2]         III           E6. Developed from Verde/2020         0.59 [-0.3, 1.3]         III	B3. Developed from Schmitz, Adams, and Walsh 2013					0.43 [0.31, 0.61]	H
C3. Developed from Schmitz, Adams, and Waish 2013  10. Prior for mean only  10. Developed from Eithimiou, Movridis, Debray, Samara, Belger, Siontis, and et al 2017  10. Developed from Eithimiou, Movridis, Debray, Samara, Belger, Siontis, and et al 2017  10. Developed from Eithimiou, Movridis, Debray, Samara, Belger, Siontis, and et al 2017  10. Surgical for Eithimiou, Movridis, Debray, Samara, Belger, Siontis, and et al 2017  10. Surgical for Eithimiou, Movridis, Debray, Samara, Belger, Siontis, and et al 2017  10. Surgical for Eithimiou, Movridis, Debray, Samara, Belger, Siontis, and et al 2017  10. Surgical for Probability of Internal validity bias through uniform prior  10. Eveloped from Dias, Welton, Marindo, Salanti, Figgins, and Ades 2010  10. Surgical for Probability of Internal validity bias through uniform prior  10. Surgical for Probability Grant Bias, Welton, Marindo, Salanti, Figgins, and Ades 2010  10. Surgical for Probability Grant Bias, Welton, Marindo, Salanti, Figgins, and Ades 2010  10. Surgical for Probability Grant Bias, Welton, Marindo, Salanti, Figgins, and Ades 2010  10. Surgical for Probability Grant Bias, Welton, Marindo, Salanti, Figgins, and Ades 2010  10. Surgical for Probability Grant Bias Probabil	C1. Discrete events as inputs					0.02 [0.01, 0.02]	₩-
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Figure 2 Forest plot	E6. Developed from Verde2020					0.59 [0.33, 1.3]	+
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Figure 2. Forest plot

#### CONCLUSION

- Estimates obtained from the BNMR models are sensitive to model algorithms.
- Further research is needed to confirm our findings by validating these algorithms in other case studies.

## Reference

Song Y, Yin Z, Ding J, Wu T. Reduced Intensity Conditioning Followed by Allogeneic Hematopoietic Stem Cell Transplantation Is a Good Choice for Acute Myeloid Leukemia and Myelodysplastic Syndrome: A Meta-Analysis of Randomized Controlled Trials. Frontiers in oncology. 2021 Oct 7;11:708727.

Jenkins DA, Hussein H, Martina R, Dequen-O'Byrne P, Abrams KR, Bujkiewicz S. Methods for the inclusion of real-world evidence in network meta-analysis. BMC medical research methodology. 2021 Dec;21(1):1-9. Zhang K, Arora P, Sati N, Béliveau A, Troke N, Veroniki AA, Rodrigues M, Rios P, Zarin W, Tricco AC. Characteristics and methods of incorporating randomized and nonrandomized evidence in network meta-analyses: a scoping review. Journal of Clinical Epidemiology. 2019 Sep 1;113:1-0.

Wohlin C. Second-generation systematic literature studies using snowballing. InProceedings of the 20th International Conference on Evaluation and Assessment in Software Engineering 2016 Jun 1 (pp. 1-6).