A Literature Review to Identify Prognostic Factors and Treatment Effect Modifiers in Population-adjusted Indirect Comparisons for Multiple Myeloma

MSR152

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INTRODUCTION

- Rapid technological advances have introduced numerous novel therapeutic classes (e.g., chimeric antigen T-cell therapies, bispecific antibodies, etc.) within the last decade into the multiple myeloma (MM) treatment landscape.[1,2,3,4]
- Head-to-head randomized controlled trials (RCTs) are considered the highest quality of evidence to inform updates of MM treatment guidelines. However, it is not feasible to conduct head-to-head comparisons for all relevant therapies.
- In the absence of such RCTs, indirect treatment comparisons (ITCs) can serve as a valuable resource to provide insights into clinical-effectiveness.[5]
- Validity of traditional unadjusted ITC estimates rely on the assumption that populations for comparison have homogenous distributions of outcome-influencing covariates.[6] Such covariates can be either prognostic factors (PFs) that affect outcomes regardless of intervention, or treatment effect modifiers (TEMs) that affect the effectiveness of a treatment on an outcome.[7] When individual patient data are available, population-adjusted indirect comparisons (PAICs), such as matching-adjusted indirect comparisons (MAICs) etc. can be leveraged.[8]
- To date, limited details on the process for selecting appropriate TEMs or PFs in MM have been reported.[9]

OBJECTIVE

- To examine how PFs and TEMs were determined in published PAICs of MM populations.

METHOD

- Embase, Ovid MEDLINE® (including Epub Ahead of Print and In-Process & Other Non-Index Citations), Ovid MEDLINE® Daily, and Cochrane Database of Systematic Reviews were searched for English-language articles of PAICs published between 1 January 2013 and 19 October 2023.
- A supplementary search of health technology assessment (HTA) submissions were also conducted for the following authorities:
  - Canada's Drug Agency (CDA, formerly known as Canadian Agency for Drugs and Technologies in Health [CADTH])
  - National Institute for Health and Care Excellence (NICE)
  - Federal Joint Committee (GBA)
- Eligible records were selected based on pre-specified Population, Intervention, Comparator, Outcome, Study Design (PICOS) criteria (**Table 1**) and reviews aligned with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement.[10,11]
- Data were summarized descriptively by the following factors:
  - MM subgroups
  - Trials and treatments compared
  - Method of PAICs (e.g., propensity score matching models [PSMs], inverse probability weighting [IPTW], MAIC, etc.)
  - Anchored or unanchored comparison
  - Covariates used for population-adjustment in either the base-case or sensitivity analysis
  - Method(s) leveraged to select covariates
  - Cut-off values for covariate stratifications
  - Survival outcomes analyzed (i.e., overall survival [OS], progression-free survival [PFS], or both).
- Rankings of covariates based on expected clinical importance for adjustment informed by clinical expert consultations were extracted from published PAICs.

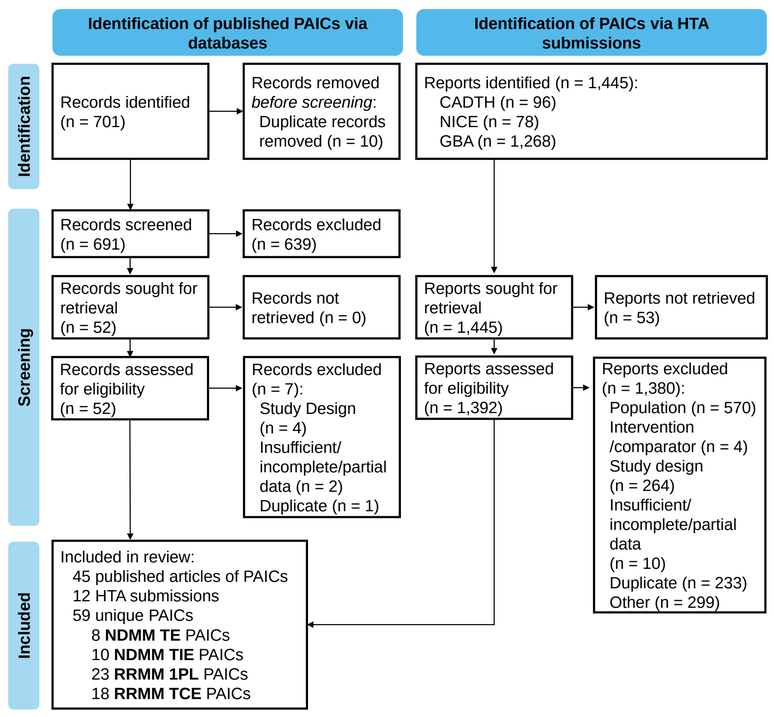
Table 1. PICOS Criteria

	Inclusion Criteria
Population	• Study populations or subgroups of adult patients (≥18 years) with ○ Newly-diagnosed MM (NDMM) AND ➢ are transplant eligible (TE) OR ➢ are transplant ineligible (TIE) ○ Relapsed or refractory MM (RRMM) AND ➢ have ≥1 prior treatment line (1PL) OR ➢ have been exposed to ≥1 proteasome inhibitor (PI) AND ≥1 immunomodulatory drug (IMiD) AND ≥1 anti-CD38 monoclonal antibody (mAb), also known as triple class exposed (TCE)
Interventions / Comparators	• Any pharmaceutical therapies approved or under investigation for multiple myeloma
Outcomes	• Overall survival (OS) and/or progression-free survival (PFS)
Study Design	• Population-adjusted indirect comparisons, including ○ Propensity score matching models (PSMs) ○ Inverse probability weighting (IPTWs) ○ Matching-adjusted indirect comparisons (MAICs) ○ Simulated treatment comparisons (STCs) ○ Multilevel network meta-regression (ML-NMR) ○ Mixed treatment comparisons (MTCs)/network meta-analyses (NMAs) with population-adjustments
Location	• All geographic regions
Language	• English only
Date Limit	• Publications from the past ten years (2013 to present) • HTA submissions from the past five full years (2018 to present)

RESULTS

- Of the 2,146 records identified through the database and supplementary searches, a total of 59 unique PAICs reported in 45 peer-reviewed publications and 12 HTA submission documents were included (**Figure 1**).
- 18 PAICs were in NDMM, including 8 in TE and 10 in TIE, while 41 were in RRMM, including 23 with 1PL and 18 with TCE. Only 2 PAICs were anchored comparisons. MAICs was the most commonly identified population-adjustment method, compared to PSMs or IPTWs (**Table 2**).
- No statistical analyses assessing prognostic strength or treatment effect modification were reported. 59% and 20% of PAICs reported clinical expert informed variable selection and ranking, respectively.
- Results for commonly adjusted variables varied by MM population:
  - **NDMM TE**: cytogenetic risk, International Staging System (ISS)/Revised-ISS (R-ISS) stage, age, sex, type of MM, creatinine clearance, and hemoglobulin levels.
  - **NDMM TIE**: ISS/R-ISS stage, age, sex, creatinine clearance, cytogenetics risk and type of MM.
  - **RRMM 1PL**: number of prior lines of therapies (LOTs), Eastern Cooperative Oncology Group performance score (ECOG PS), age, time since diagnosis, ISS/R-ISS stage, prior stem cell transplant (SCT), sex, IMiD refractory status, prior PI, creatinine clearance, prior IMiD, PI refractory status, and cytogenetic risk.
    - ❖ Three PAICs in RRMM 1PL reported covariate rankings based on clinical importance. Refractory status and number of LOT ranked the highest (**Figure 3**).
  - **RRMM TCE**: number of prior LOTs, age, sex, ISS/R-ISS stage, ECOG PS, time since diagnosis, cytogenetic risk, refractory status, prior SCT, extramedullary disease (EMD)/plasmacytoma, race, type of MM, creatinine clearance, time since progression, refractory to PI, refractory to IMiD, and hemoglobulin levels.
    - ❖ Nine PAICs in RRMM TCE reported covariate rankings based on clinical importance, Refractory status, number of prior LOTs, cytogenetic risk, EMD/plasmacytoma, ISS/R-ISS ranking the highest (**Figure 4**).
- Among PAICs submitted to HTAs, feedback from HTA authorities on appropriateness of PFs and TEMs selected is lacking.

Figure 1. PRISMA Flow Diagram



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 2. Summary of Included PAIC Methods by Population

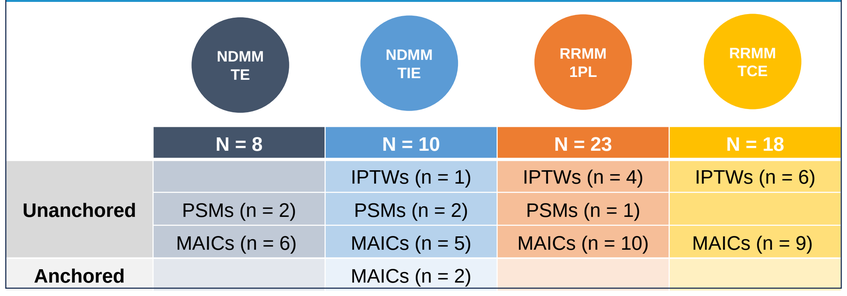


Figure 3. Covariate Rankings of Clinical Importance in Published PAICs of RRMM 1PL

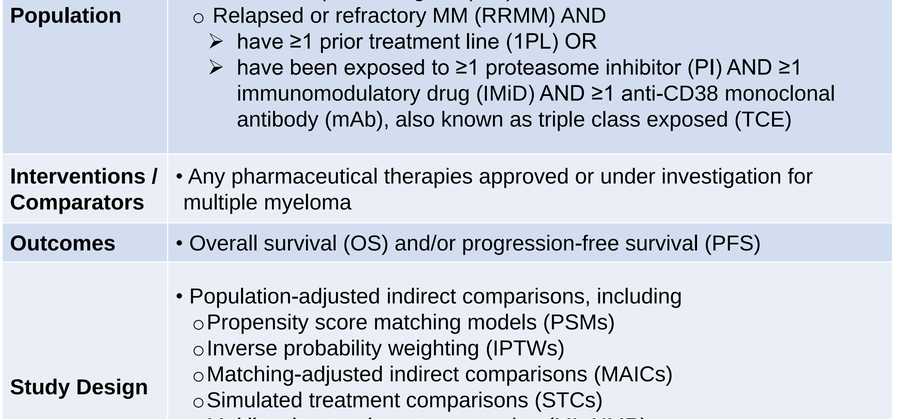
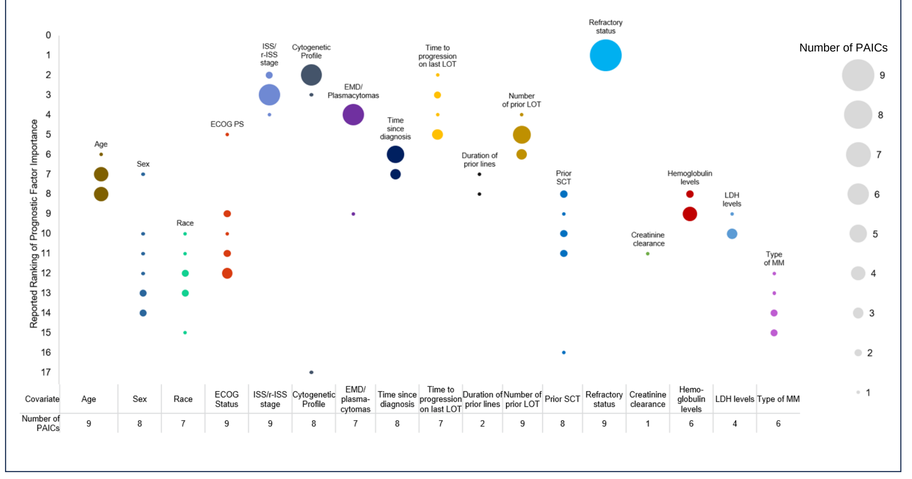


Figure 4. Covariate Rankings of Clinical Importance in Published PAICs of RRMM TCE



CONCLUSIONS

- This literature review identified variables that were commonly adjusted for in published PAICs.
- Limited information on the method of variable selection was reported in published PAICs, with most variables selected based on clinical expert opinion only.
- Recent HTA guidelines require a systematic search of prognosis variables, confounders and effect modifiers be conducted and documented to reduce risk of bias. Further validation of variables identified in this review is warranted to improve robustness of future PAICs.

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Abbreviations: 1PL = at least 1 prior treatment line, CADTH = Canadian Agency for Drugs and Technologies in Health, CDA= Canada's Drug Agency, ECOG PS = Eastern Cooperative Oncology Group performance score, EMD = extramedullary disease, GBA = Federal Joint Committee, HTA = health technology assessment, IMiD = immunomodulatory drug, IPTW = inverse probability weighting, ISS = International Staging System, ITC = indirect treatment comparison, LOT = line of therapy, mAb = monoclonal antibody, MAIC = matching-adjusted indirect comparison, ML-NMR = multilevel network meta-regression, MM = multiple myeloma, MTC = mixed treatment comparison, NDMM = newly-diagnosed multiple myeloma, NICE = National Institute for Health and Care Excellence, NMA = network meta-analysis, OS = overall survival, PAIC = population-adjusted indirect comparison, PF = prognostic factor, PFS = progression-free survival, PI = proteasome inhibitor, PICOS = Population, Intervention, Comparator, and Study Design, PRISMA = Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses, PSM = propensity score matching, R-ISS= Revised Multiple Myeloma International Staging System, RCT = randomized controlled trial, RRMM = relapsed or refractory MM, SCT = stem cell transplant, STC =simulated treatment comparison, TCE = triple class exposed, TE = transplant eligible, TEM = treatment effect modifier, TIE = transplant ineligible,

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