INPLASY

Prognostic Implications of Myelodysplasia-Related Gene Mutations in NPM1-Mutated Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Nil.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202530128

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 March 2025 and was last updated on 30 March 2025.

INTRODUCTION

Review question / Objective To evaluate the prognostic impact of myelodysplasia-related gene (MRG) mutations on survival outcomes in patients with NPM1-mutated acute myeloid leukemia (AML), with specific focus on overall survival (OS), event-free survival (EFS), and complete remission (CR) rate.

Rationale NPM1-mutated AML is classified as favorable-risk under the ELN 2022 guidelines unless accompanied by FLT3-ITD or adverse-risk cytogenetics. MRG mutations, however, are associated with adverse risk and secondary AML phenotypes. Despite this, the current ELN 2022 framework still considers NPM1-mutated AML with co-occurring MRG mutations as favorable risk. Given conflicting evidence regarding the prognostic significance of MRG mutations in this setting, a systematic review and meta-analysis is warranted to clarify their clinical impact and inform future risk stratification models.

Condition being studied Acute myeloid leukemia (AML) with NPM1 mutations, with or without co-occurring myelodysplasia-related gene (MRG) mutations.

METHODS

Search strategy A comprehensive literature search will be performed in PubMed, MEDLINE, and Embase for studies published up to March 2025. The search will use a combination of Medical Subject Headings (MeSH) and free-text terms, including:
"Acute Myeloid Leukemia", "NPM1", "Myelodysplasia-related". Conference abstracts from ASH, ASCO, and EHA will be manually reviewed. Boolean operators will be used to refine the search.

Participant or population Patients diagnosed with NPM1-mutated AML, regardless of age, sex, or geographic region.

Intervention Presence of MRG mutations, defined by WHO 5th edition or ICC 2022 criteria (ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 with or without RUNX1).

Comparator Patients with NPM1-mutated AML who do not harbor MRG mutations.

Study designs to be included Retrospective and prospective cohort studies reporting hazard ratios (HRs), survival curves, or sufficient data to estimate HRs comparing outcomes between MRG-mutated and MRG-wildtype NPM1-mutated AML.

Eligibility criteria
Inclusion Criteria:
Studies enrolling patients with NPM1-mutated AML
Studies assessing the prognostic impact of MRG mutations
Reporting HRs, 95% confidence intervals, or extractable survival curves for OS, EFS, or CR
Published in English

Exclusion Criteria:
Review articles, case reports, animal studies
Studies lacking survival data or reporting only median survival without curves or HRs
Studies focusing exclusively on patients with adverse cytogenetics or lacking defined NPM1-mutated subgroup.

Information sources PubMed, MEDLINE, Embase, Conference abstracts (ASH, ASCO, EHA).

Main outcome(s) Overall survival (OS), defined as time from diagnosis to death from any cause.

Additional outcome(s) Event-free survival (EFS), defined as time to relapse, treatment failure, or death.
Complete remission (CR) rate, based on morphological criteria.

Data management Data will be extracted by two independent reviewers using a standardized form.
Discrepancies will be resolved by consensus or third author adjudication.

Quality assessment / Risk of bias analysis The Quality in Prognostic Studies (QUIPS) tool will be used to assess risk of bias across six domains.
Risk-of-bias visualizations will be generated using the robvis package in R.

Strategy of data synthesis Random-effects meta-analysis will be performed.
Pooled HRs and risk ratios will be calculated with 95% confidence intervals.
Heterogeneity will be assessed using I^2, τ^2, and Cochran's Q test.
Statistical analyses will be conducted in R (version 4.4.1).

Subgroup analysis
Intensively treated patients
ELN 2022 favorable-risk subgroup
FLT3-ITD wild-type patients.

Sensitivity analysis Leave-one-out analysis
Trim-and-fill method to adjust for publication bias
Funnel plot asymmetry and Egger's test.

Language restriction Only studies published in English will be included.

Country(ies) involved Taiwan.

Other relevant information Nil

Keywords Acute myeloid leukemia, NPM1, myelodysplasia-related.

Dissemination plans Findings will be submitted for publication in a peer-reviewed hematology journal.

Contributions of each author
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