Prognostic implications of myelodysplasia-related gene mutations in *NPM1*-mutated acute myeloid leukemia: a systematic review and meta-analysis

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Abstract

NPM1-mutated (*NPM1*^{mut}) acute myeloid leukemia (AML) is generally classified as favorable-risk under the 2022 European LeukemiaNet (ELN-2022) guidelines, except in the presence of *FLT3*-internal tandem duplication or adverse-risk cytogenetics. However, the prognostic significance of co-occurring myelodysplasia-related gene (MRG) mutations remains unclear, with prior studies yielding inconsistent results. To clarify this issue, we conducted a systematic review and meta-analysis in accordance with PRISMA guidelines, searching PubMed, Embase, and MEDLINE through March 2025. MRG mutations were defined as pathogenic variants in *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2* and *RUNX1*, and the primary analysis incorporated studies regardless of *RUNX1* inclusion. Data from ten cohorts across nine studies (1 of which included an independent validation cohort), encompassing a total of 4,363 patients, were analyzed. Of these, 655 patients (15.0%) harbored co-occurring MRG mutations. Among the patients with ELN-2022 intermediate risk (N=1,294), 108 (8.3%) had MRG mutations. The presence of MRG mutations was significantly associated with inferior overall survival (pooled hazard ratio [HR]=1.30; 95% confidence interval [CI]: 1.11-1.51; P<0.001; I^2=39.2%), shorter event-free survival (HR=1.43; 95% CI: 1.11-1.85; P=0.006; I^2=18.2%), and lower complete remission rates (risk ratio=0.94; 95% CI: 0.90-0.99; P=0.01; I^2=0.0%). Subgroup analyses confirmed the adverse prognostic impact in patients receiving intensive therapy and those classified as ELN-2022 favorable risk. These findings suggest that MRG mutations confer an adverse prognostic effect in *NPM1*^{mut} AML and support the integration of MRG status into future risk stratification frameworks for *NPM1*^{mut} AML.

Introduction

Acute myeloid leukemia (AML) is a heterogenous hematologic malignancy characterized by distinct genetic and molecular alterations that influence disease prognosis and therapeutic response. *Nucleophosmin* (*NPM1*)-mutat-

ed (*NPM1*^{mut}) AML accounts for approximately 30% of AML cases[1] and is recognized as a distinct disease entity in the contemporary World Health Organization (WHO) Classification of Hematolymphoid Tumours[2] and International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias.[3] According to the European LeukemiaNet 2022 (ELN-2022) recommendations, *NPM1*^{mut} AML is categorized as favorable risk in intensively treated patients unless accompanied by a *FLT3*-internal tandem duplication (*FLT3*-ITD) or adverse-risk cytogenetics, which modify its prognostic classification.[4]

On the other hand, mutations in *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1,* and *ZRSR2*, are strongly associated with secondary AML arising from myelodysplastic neoplasms/syndromes (MDS).[5] These eight genes, along with *RUNX1*, are categorized as myelodysplasia-related gene (MRG) mutations in the 2022 ICC,[3] and the adverse-risk group in the ELN-2022 risk classification. Their presence has been linked to adverse outcomes in *de novo* AML.[5-7] However, the prognostic relevance of MRG mutations in the context of *NPM1*^{mut} AML remains uncertain. While some studies suggest that the presence of MRG abrogate the favorable prognosis of *NPM1*^{mut} AML,[8,9] others indicate that their effect may be dependent on additional co-mutations, treatment regimens, or measurable residual disease (MRD) status.[10,11] The inconsistency across studies highlights the need for a comprehensive synthesis of available evidence to determine whether the presence of MRG mutations would influence risk stratification and treatment decisions in patients with *NPM1*^{mut} AML. To address these uncertainties, this systematic review and meta-analysis aims to quantify the prognostic impact of MRG mutations in *NPM1*^{mut} AML, aiding clinicians in decision making and refining current AML risk classifications.

Methods

Systemic literature review

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The study was registered on INPLASY (registration number: INPLASY202530128; https://inplasy.com/inplasy-2025-3-0128/). A comprehensive literature search was performed across PubMed, Embase, and MEDLINE databases to identify relevant studies published up to March 2025 (*Online Supplementary Table S1*). The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords, specifically targeting “Acute Myeloid Leukemia”, “NPM1”, and “Myelodysplasia-related”, along with their relevant synonyms. Boolean operators were applied to refine the search. Additionally, conference abstracts from the American Society of Clinical Oncology, American Society of Hematology and European Hematology Association were manually reviewed to capture the latest findings in the field.

Eligibility criteria

Both prospective and retrospective studies were included in the meta-analysis. Studies were eligible if they met the following criteria: (i) enrolled patients diagnosed with *NPM1*^{mut} AML and assessed the prognostic impact of co-occurring MRG mutations; (ii) provide detailed survival data, including hazard ratios (HR), 95% confidence interval (CI), and *P* values. Studies were excluded if they lacked sufficient survival data, reported only median survival without an accompanying survival curve or HR, focused on *NPM1*^{mut} AML with MDS-related cytogenetic abnormalities, or were review articles, animal studies, or case reports.

Study selection

After removing duplicates, two independent reviewers (YSC and YWL) screened the titles and abstracts to identify studies meeting the predefined eligibility criteria. Full-text articles of potentially relevant studies were then reviewed in detail to confirm inclusion. Discrepancies between reviewers were resolved through discussion, and if necessary, a third reviewer (HAH) was consulted. Finally, nine studies (1 study with an independent validation cohort) were included in the meta-analysis, as shown in Figure 1.

Data extraction, quality assessment, data synthesis and statistical analysis

Full details of data extraction procedures, risk of bias assessment and statistical methodology are provided in the Online Supplementary Appendix.

Ethics statement

This study is a systematic review and meta-analysis of previously published data and did not involve any direct contact with patients or access to individual-level data. As such, institutional review board approval was not required. However, the study was conducted in accordance with the ethical standards and regulations of the country in which it was performed.

Results

Literature search

A systematic search of Embase, MEDLINE, and PubMed identified 955 records (Embase, N=578; MEDLINE, N=300; PubMed, N=77). After removing 142 duplicates, 813 unique records underwent screening, with 777 excluded due to irrelevance (N=664), article type (N=104), or non-English language (N=9). The full texts of 36 articles were reviewed, resulting in the exclusion of 27 studies due to the absence of relevant outcome data (N=15), an ineligible patient population (N=7), or overlapping cohorts (N=5). Ultimately, nine studies met the inclusion criteria, with one study

contributing an additional independent validation cohort (Figure 1).[8-11, 13-17]

Characteristics of studies

The baseline characteristics of the nine primary studies and one validation cohort are summarized in *Online Supplementary Table S2*. All studies were retrospective in design and published between 2022 and 2025. Collectively, these studies included 4,363 patients with *NPM1*^{mut} AML, of whom 655 (15.0%) harbored co-occurring MRG mutations. Three studies defined MRG mutations according to WHO-2022 classification criteria[2] and therefore did not include *RUNX1* mutations. The most frequently co-occurring MRG were *SRSF2* (range, 3.3-10.5%), *ASXL1* (range, 0.8-16.5%), and *STAG2* (range, 0-5%) (*Online Supplementary Table S3*). Seven of the nine studies reported median age comparisons between MRG and non-MRG groups, all showing significantly older age in the MRG group (all $P<0.01$). Among the ten cohorts, three included only patients with ELN-2022 favorable risk, while the remaining seven cohorts (N=3,656) included all three ELN-2022 risk categories. The majority were classified as favorable risk (N=2,203; 60.3%), followed by intermediate (N=1,294; 35.4%) and adverse risk (N=109; 3.0%). The distribution of MRG mutations differed significantly across ELN-2022 risk groups, with 516 (23.4%) in favorable, 108 (8.3%) in intermediate, and 31 (28.4%) in adverse-risk patients ($P<0.001$). Additionally, among the seven studies that included both *FLT3*-ITD-positive and -negative patients, MRG mutations were associated with a lower frequency in concomitant *FLT3*-ITD (MRG^{mut} 20% *vs*. MRG^{WT} 38%; $P<0.001$).

Risk of bias was assessed using the QUIPS tool. All studies were judged to have an overall low risk of bias (*Online Supplementary Figure S1A*). Domains related to outcome measurement and prognostic factor ascertainment were consistently rated as low risk. Moderate risk was noted in select domains, including participation, attrition, confounding, and statistical reporting; however, these were limited in number and did not compromise overall study quality (*Online Supplementary Figure S1B*).

Pooled analysis

Meta-analysis of ten cohorts (9 studies and 1 with additional validation cohort) demonstrated that MRG mutations were significantly associated with inferior overall survival (OS) in *NPM1*^{mut} AML, with a pooled HR of 1.30 (95% CI: 1.11-1.51; $P<0.001$; Figure 2A). Between-study heterogeneity was moderate (I^2=39.2%, τ^2=0.0062; P=0.10). To evaluate the stability of the overall estimate, leave-one-out sensitivity analyses were performed (Figure 2B). Sequential exclusion of individual studies yielded consistent results (HR range, 1.27-1.37), all of which remained statistically significant ($P<0.01$). Heterogeneity estimates remained within an acceptable range (I^2=0.0-45.8%), and no single study exert-

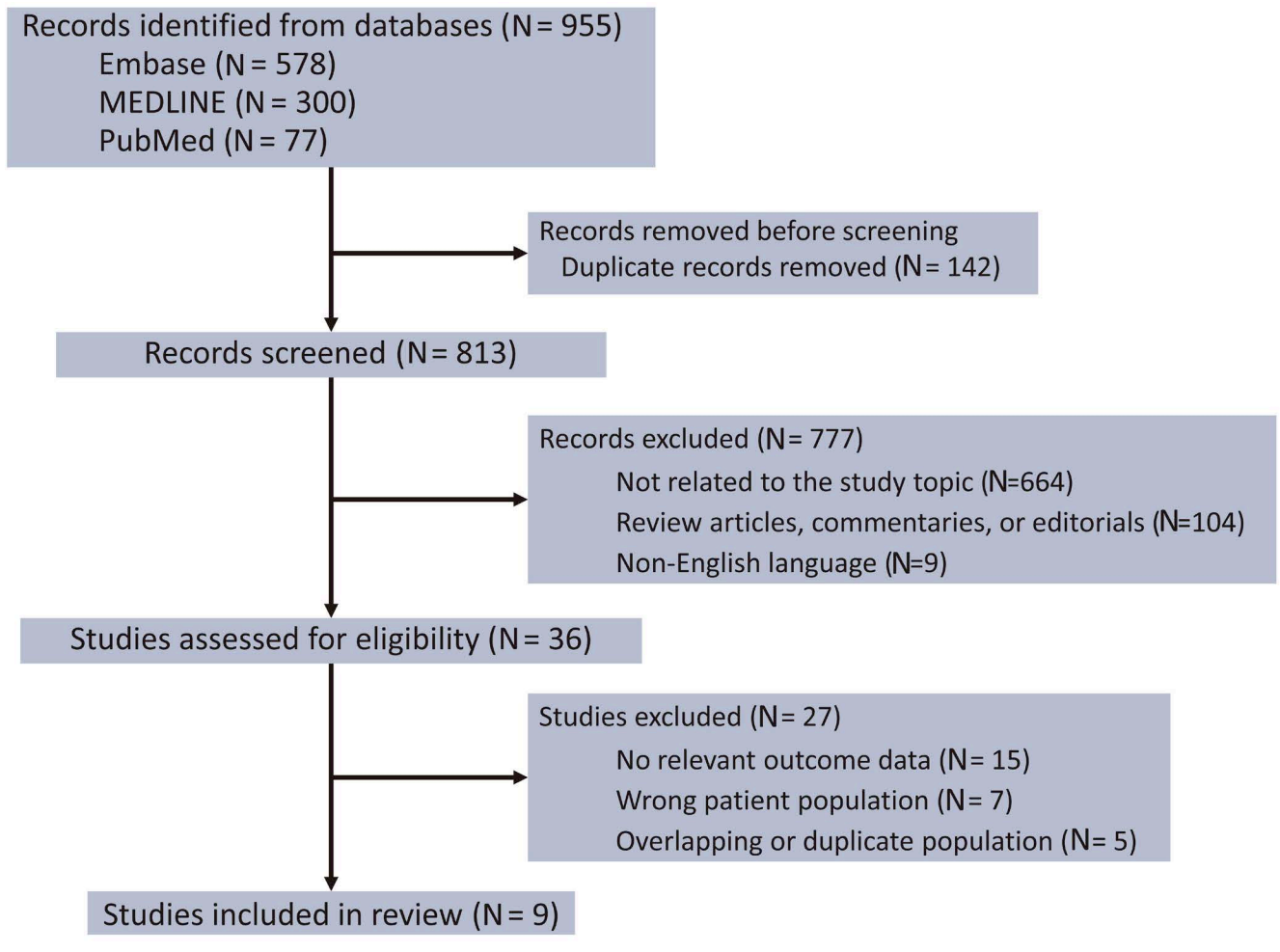
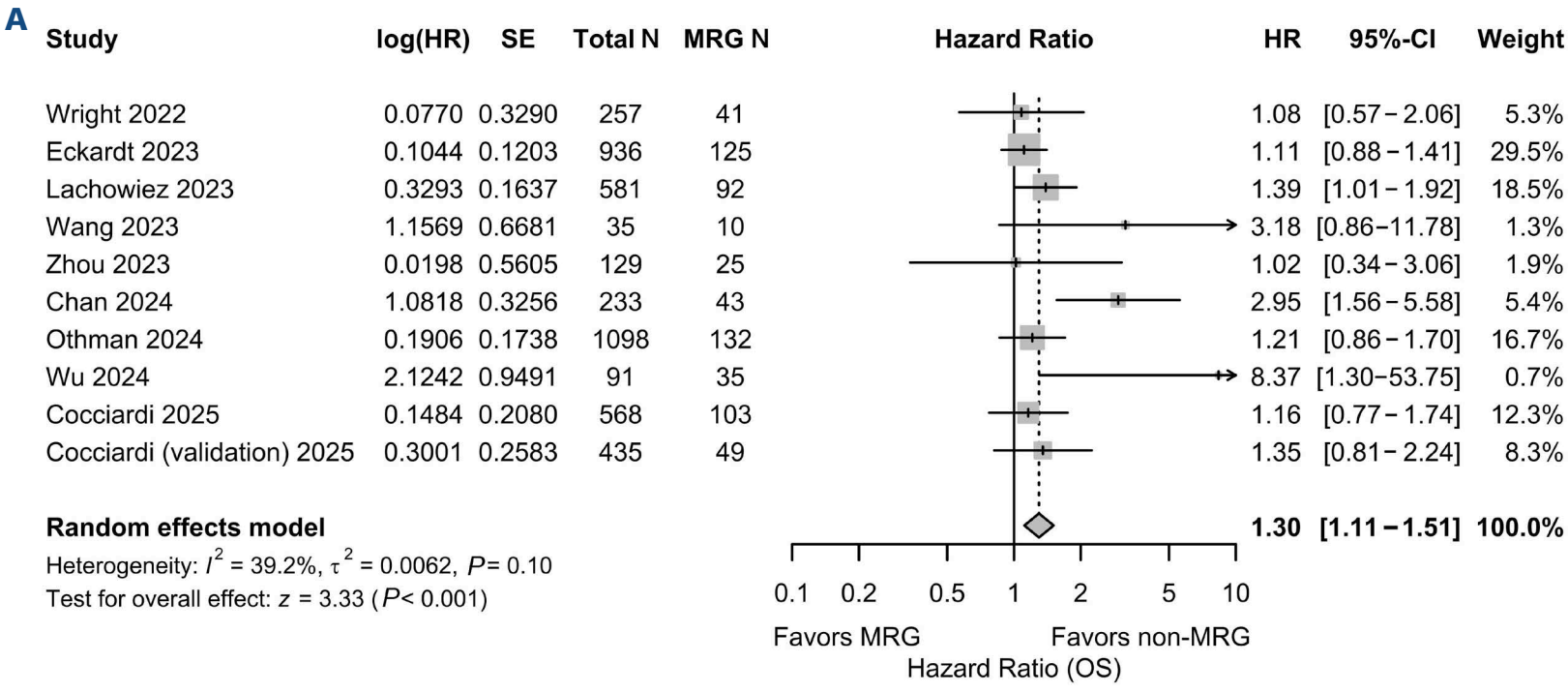


Figure 1. PRISMA flow diagram of study selection. Study selection process for the systematic review and meta-analysis, following PRISMA guidelines. A total of 955 records were identified; after removing duplicates and screening, 36 full-text articles were assessed for eligibility. Nine studies met the inclusion criteria and were included in the final analysis.

ed disproportionate influence. Potential publication bias was assessed via funnel plot, which demonstrated visible asymmetry suggestive of small-study effects (*Online Supplementary Figure S2A*). Egger's regression test supported the presence of bias (t=2.34; *P*=0.047), with a bias estimate of 1.59 (SE=0.68). To adjust for potential publication bias, the trim-and-fill method was applied. One imputed study was added, resulting in a total of 11 cohorts included in the adjusted analysis. After adjustment, the association between MRG mutations and OS remained statistically significant (pooled HR=1.28; 95% CI: 1.10-1.48; *P*=0.001; *Online Supplementary Figure S2B, C*).

Subgroup and meta-regression analyses

To evaluate the prognostic relevance of MRG mutations in intensively treated *NPM1*^{mut} AML, six cohorts[9-11,14,16] along with the intensively treated subgroup from Zhou *et al.*[17] were included in a predefined subgroup analysis. The presence of MRG mutations remained significantly associated with inferior OS (pooled HR=1.20; 95% CI: 1.02-1.41; *P*=0.027), and low between-study heterogeneity (I^2=14.1%; *P*=0.32; Figure 3A). A further subgroup analysis assessed the prognostic impact of MRG mutations according to the ELN-2022 risk classification. Due to the small number of patients in the ELN-adverse risk category (N= 109, 2.5%), the model for this subgroup in some individual studies did not converge,[10,11] and its prognostic effect was therefore not evaluated. Three cohorts[9,15,16] and the ELN-favorable subgroups from five additional cohorts[10,11,14,17] contributed data for the ELN-favorable category, while three cohorts[10,14,17] provided data for the ELN-intermediate category. In the ELN-favorable subgroup, MRG mutations were significantly associated with inferior OS (pooled HR=1.34; 95% CI: 1.14-1.59; I^2=0.0%; Figure 3B). In contrast, no significant association was observed in



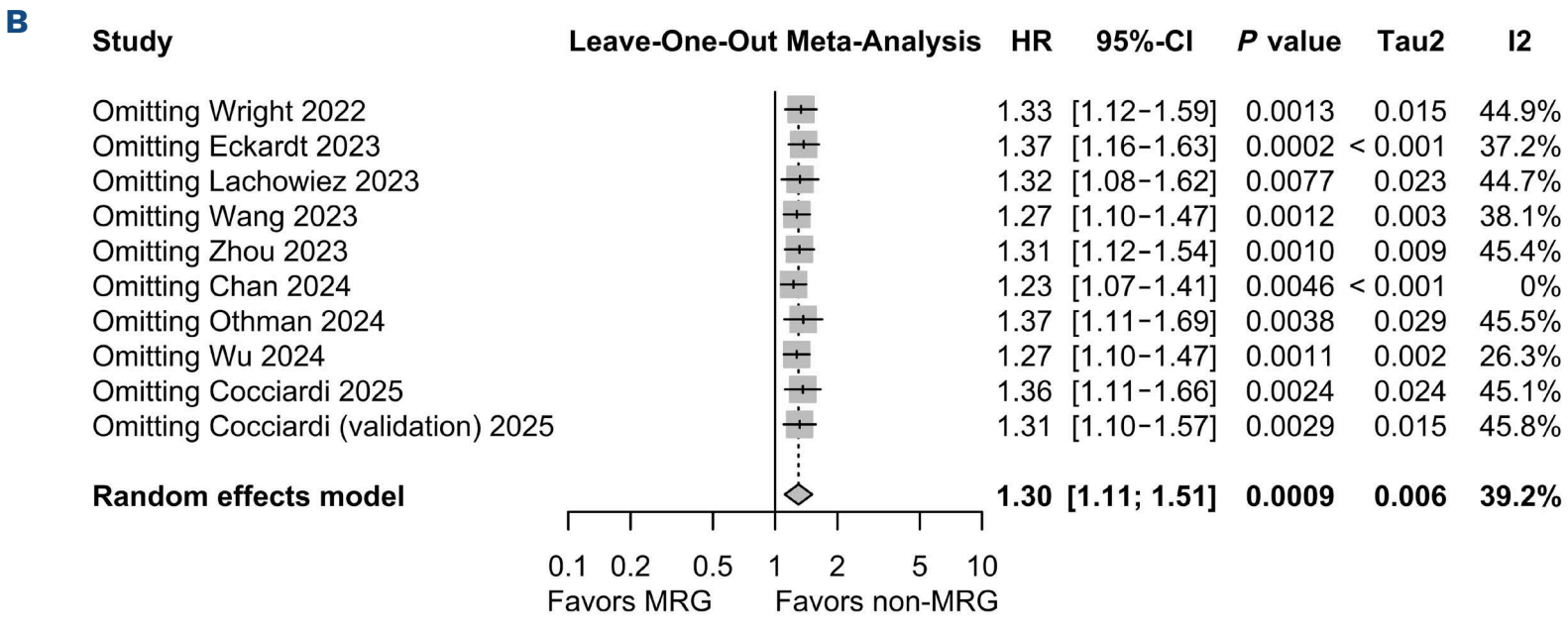


Figure 2. Association between myelodysplasia-related gene mutations and overall survival in *NPM1*-mutated acute myeloid leukemia. (A) Forest plot displaying hazard ratios for overall survival (OS) in patients with *NPM1*-mutated acute myeloid leukemia stratified by presence of myelodysplasia-related gene (MRG) mutations. (B) Leave-one-out sensitivity analysis assessing the influence of individual studies on the overall association between MRG mutations and OS. CI: confidence interval; HR: hazard ratio.

the ELN-intermediate subgroup (pooled HR=0.85; 95% CI: 0.57-1.27; I^2=0.0%). The difference between subgroups was statistically significant (*P*=0.04).

In the age-stratified subgroup analysis, three cohorts[10,15,17] provided data for patients aged ≥60 years and <60 years. MRG mutations were not significantly associated with OS in either subgroup (age ≥60: pooled HR=1.04; 95% CI: 0.72-1.49; I^2=54.5%, and age <60: pooled HR=1.24; 95% CI: 0.84-1.81; I^2=46.5%), and the difference between age groups was not significant (*P*=0.52; Figure 4A). When the analysis was restricted to patients with ELN-favorable risk, age <60 years was associated with inferior outcomes (pooled HR=1.50; 95% CI: 1.12–2.02; I^2=0.0%), whereas age ≥60 years was not (pooled HR=0.85; 95% CI: 0.46-1.57; I^2=59.2%); the age-group difference remained non-significant (*P*=0.10; Figure 4B). However, the absence of a statistically significant interaction between age subgroups may be noteworthy, given the modest number of elderly patients with *NPM1*

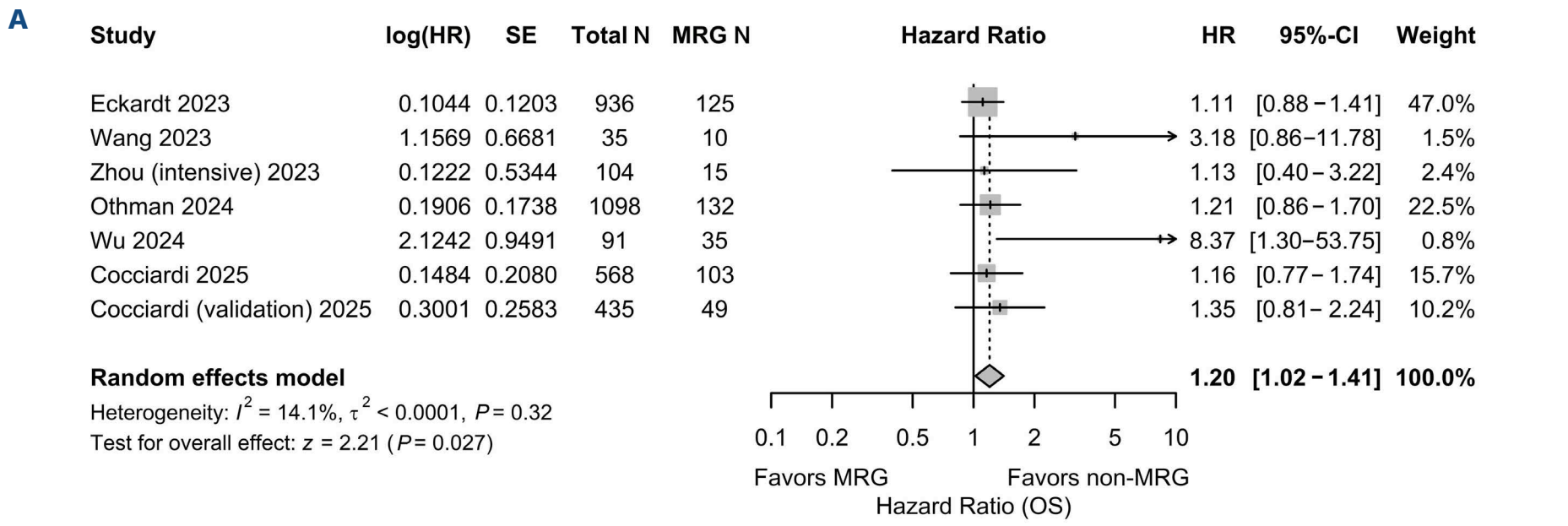


Figure 3. Subgroup analysis of overall survival in *NPM1*-mutated acute myeloid leukemia with myelodysplasia-related gene mutations by treatment and European LeukemiaNet risk. (A) Forest plot of hazard ratios (HR) for overall survival (OS) in patients who received intensive chemotherapy. (B) Forest plot of HR for OS among patients classified as favorable or intermediate risk according to the 2022 European LeukemiaNet (ELN) criteria. MRG: myelodysplasia-related gene; CI: confidence interval.

mutation in the pooled cohort and should therefore be interpreted with caution.

For the hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1) subgroup analysis, four cohorts[10,14,15,17] contributed data for patients who underwent HSCT in CR1 and for those who did not. In the HSCT group,

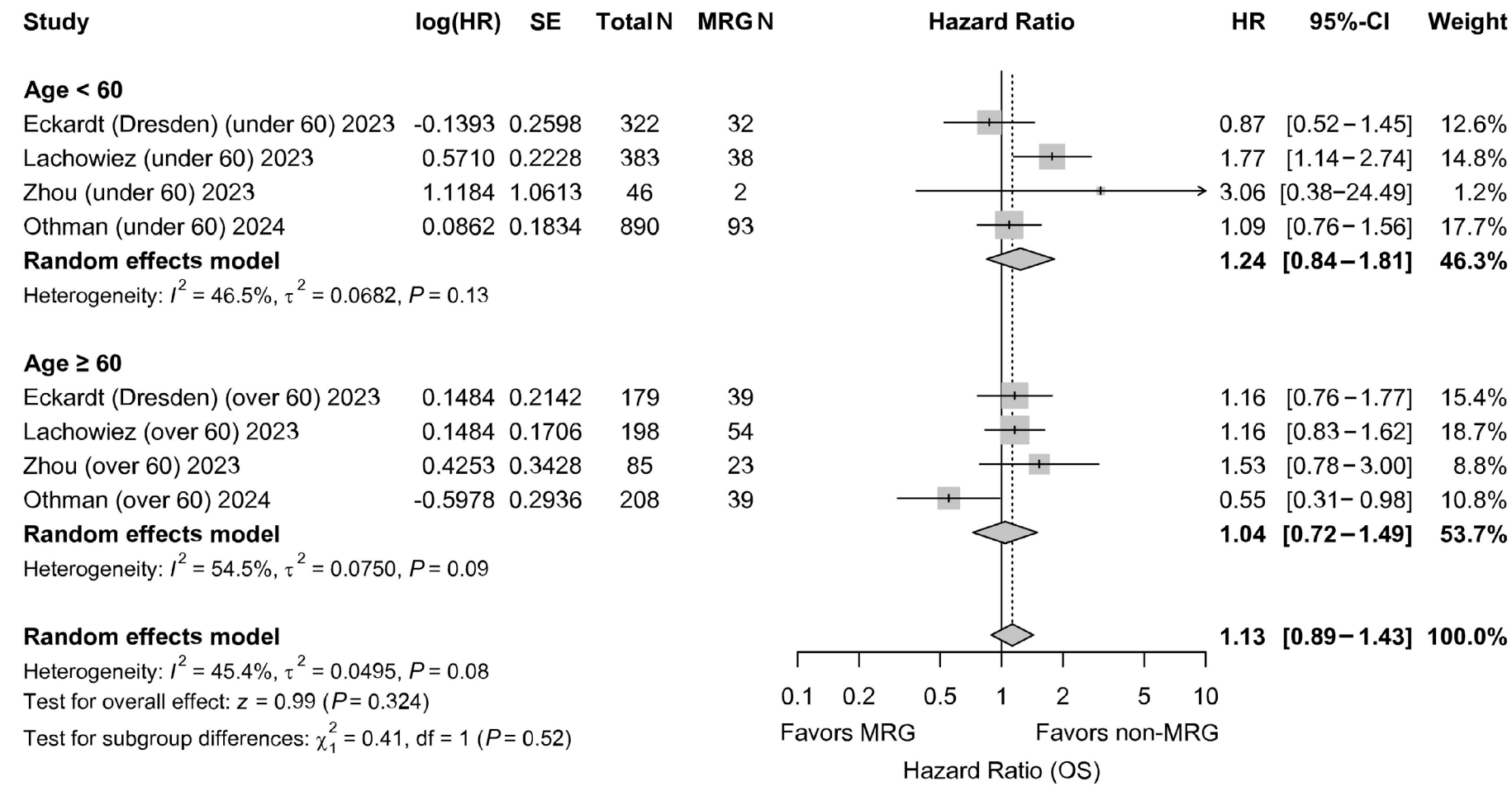


Figure 4. Subgroup analysis of overall survival in *NPM1*-mutated acute myeloid leukemia with myelodysplasia-related gene mutations by age. (A) Forest plot of hazard ratios (HR) for overall survival (OS) among patients aged <60 years *versus* those ≥ 60 years. (B) Forest plot of HR for OS by age subgroup (<60 *vs.* ≥60 years) restricted to patients in the European LeukemiaNet (ELN) favorable-risk category. MRG: myelodysplasia-related gene; CI: confidence interval.

MRG mutations were not significantly associated with OS (pooled HR=1.46; 95% CI: 0.72-2.95; I^2=45.8%), and no significant association was observed in the no-HSCT group (pooled HR=1.09; 95% CI: 0.89-1.33; I^2 0.0%). The difference between HSCT and no-HSCT subgroups was not statistically significant (*P*=0.43; Figure 5). These findings may be confounded by the fact that patients with *NPM1*^{mut} AML typically do not undergo transplantation in CR1; those who did receive HSCT in CR1 were often ELN intermediate-risk due to co-occurring *FLT3*-ITD, representing a population with inherently higher baseline risk. Across all subgroup analyses, the absence of statistical significance outside the ELN-favorable subgroup should be interpreted with caution. These analyses were based on a limited number of studies and relatively small sample sizes, which may have reduced statistical power to detect modest effects. We performed study-level meta-regression to examine whether key cohort characteristics influenced the prognostic effect of MRG mutations on OS (Table 1). In univariable analyses, median age (coefficient β=0.009; 95% CI: -0.033 to 0.051; *P*=0.668), proportion of patients receiving intensive treatment (β= -1.165; 95% CI: -2.939 to 0.609; *P*=0.198) or HSCT (β=4.831; 95% CI: -0.232 to -2.604; *P*=0.101), and frequency of *FLT3* co-mutation (β=0.223; 95% CI: -0.661 to 1.108; *P*=0.621) were not significantly associated with the HR for OS. In multivariable analysis adjusting for these factors, none reached statistical significance (all *P*>0.05). These findings indicate that the prognostic effect of MRG mutations was consistent across studies, with no evidence of modification by median age, *FLT3* co-mutation prevalence, or the

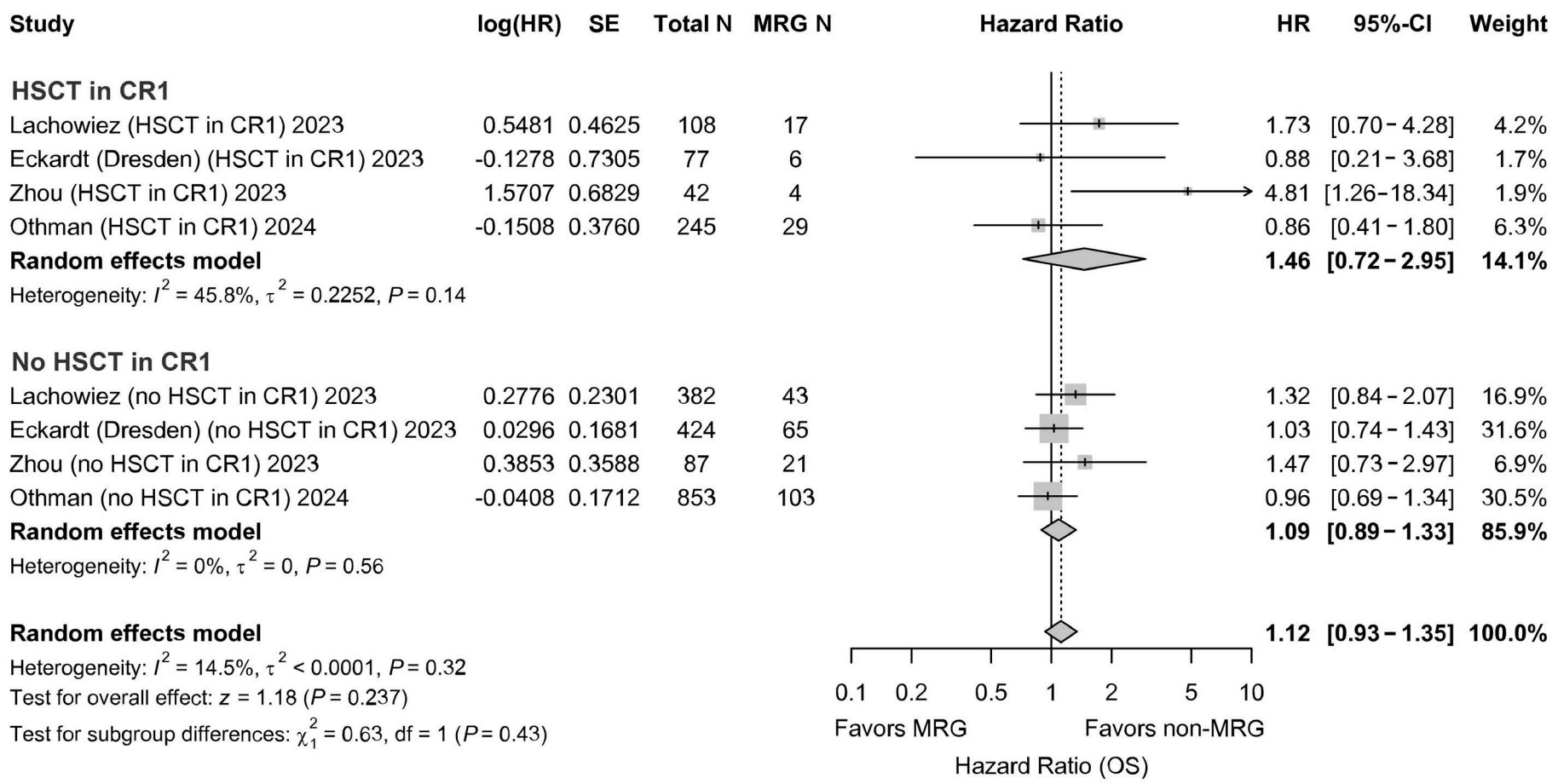


Figure 5. Subgroup analysis of overall survival in *NPM1*-mutated acute myeloid leukemia with myelodysplasia-related gene mutations by transplantation status. Forest plot of hazard ratios (HR) for overall survival (OS) among patients who underwent hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1) *versus* those who did not. MRG: myelodysplasia-related gene; CI: confidence interval.

Table 1. Meta-regression analysis using study-level characteristics.

Characteristics	Univariable analysis			Multivariable analysis		
	Coefficient (β)	95% CI	*P*	Coefficient (β)	95% CI	*P*
Median age, years	0.009	-0.033 to 0.051	0.668	-0.052	-0.333 to 0.230	0.720
Intensive treatment, %	-1.165	-2.939 to 0.609	0.198	-1.963	-13.909 to 9.984	0.748
FLT3 co-mutation, %	0.223	-0.661 to 1.108	0.621	-1.334	-5.404 to 2.737	0.521
HSCT, %	4.831	-0.232 to 2.604	0.101	8.049	-6.637 to 22.735	0.283

CI: confidence interval; HSCT: hematopoietic stem cell transplantation

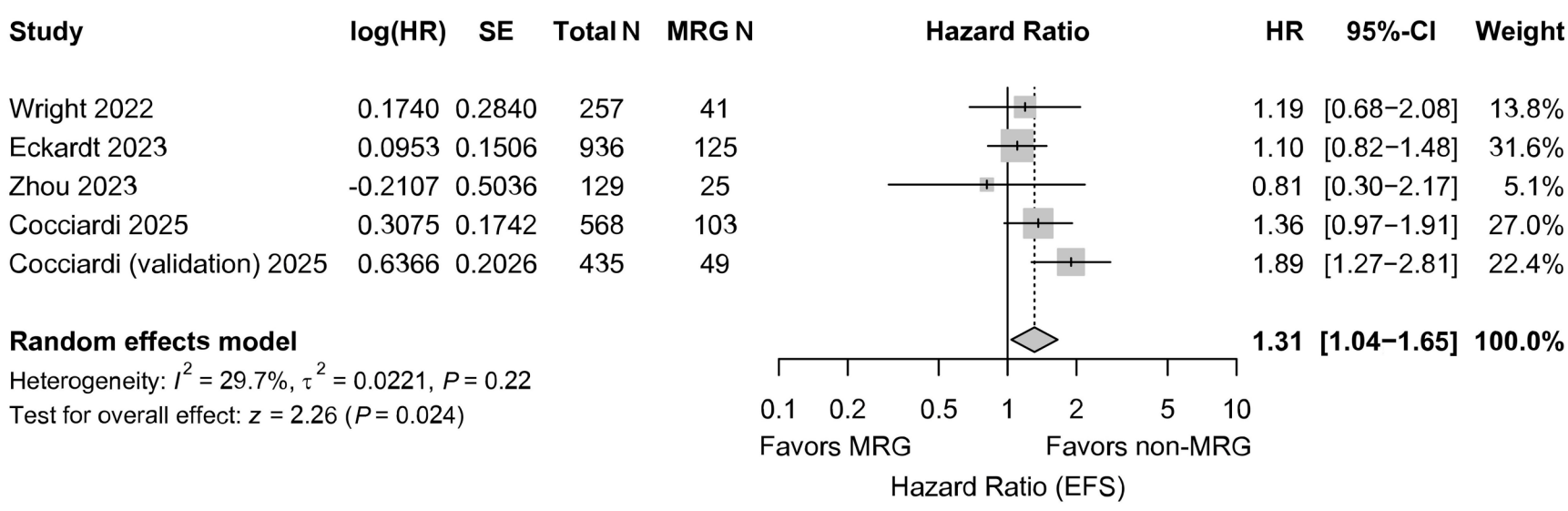
proportion of patients receiving intensive therapy or HSCT.

RUNX1 inclusion and the prognostic significance of MRG mutations

To assess whether the inclusion of *RUNX1* in the definition of MRG mutations impacts their prognostic association with OS, we conducted a network meta-analysis (NMA) using non-MRG as the common comparator (*Online Supplementary Figure S3A*). In this analysis, MRG defined with *RUNX1* was associated with significantly inferior OS compared to the non-MRG group (pooled HR=1.48; 95% CI: 1.16-1.89; *Online Supplementary Figure S3B*). In contrast, MRG defined with *RUNX1* demonstrated a trend toward worse outcomes relative to MRG without *RUNX1*, but the association did not reach statistical significance (pooled HR=1.35; 95% CI: 0.88-2.08). These findings suggest that inclusion of *RUNX1* may enhance the prognostic discrimination of MRG mutations in identifying patients at higher risk for adverse outcomes.

Prognostic impact of individual MRG mutations

To assess the prognostic contribution of individual MRG mutations, we conducted subgroup analyses of the most frequent co-occurring mutations among four cohorts[10,14,15,17] with available data: ASXL1 (N=28, 1.5%), SRSF2 (N=98, 7.6%), and STAG2 (N=73, 4.1%). Compared with patients without MRG mutations, only *ASXL1* was associated with inferior survival (pooled HR=2.27; 95% CI: 1.44-3.59; I^2=0.0%; *Online Supplementary Figure S4*), whereas *SRSF2* (pooled HR=1.14; 95% CI: 0.85-1.54; I^2=0.0%) and *STAG2* (pooled HR=0.86; 95% CI: 0.36-2.10; I^2=71.5%) were not. The difference between subgroups was statistically significant (*P*=0.03). We further performed univariable meta-regression using the frequency of each gene mutation among MRG-positive patients as study-level covariates. A higher frequency of *ASXL1* mutations was significantly associated with increased hazard of death (β=5.45; P=0.004; *Online Supplementary Table S4*), corresponding to a 1.73-fold increase in HR per 10% increase in *ASXL1* prevalence. *ASXL1, RUNX1, SF3B1* and *STAG2* explained over 99% of between-study heterogeneity (R^2>99%), while other mutations did not show statistically significant associations.



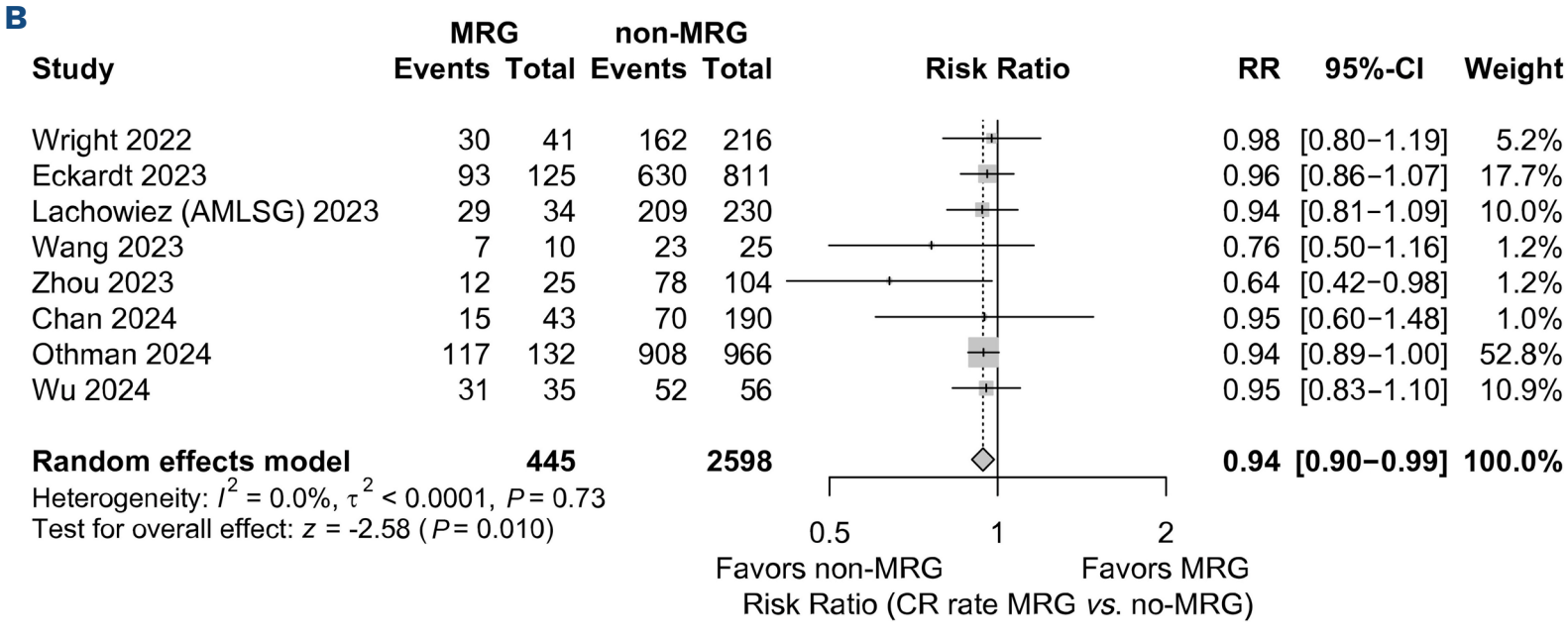


Figure 6. Event-free survival and complete remission rates in *NPM1*-mutated acute myeloid leukemia with or without myelodysplasia-related gene mutations. (A) Forest plot of hazard ratios (HR) for event-free survival (EFS) comparing patients with *versus* without myelodysplasia-related gene (MRG) mutations. (B) Forest plot of risk ratios (RR) for complete remission (CR) rates comparing patients with *versus* without MRG mutations. CI: confidence interval; HR: hazard ratio.

Event-free survival and complete remission

Four studies[11,13,14,17] and one additional validation cohort reported event-free survival (EFS) data stratified by MRG mutation status in patients with *NPM1*^{mut} AML. Pooled analysis demonstrated a significant association between MRG mutations and inferior EFS (pooled HR=1.31; 95% CI: 1.04-1.65; *P*=0.024), and a moderate between-study heterogeneity (I^2=29.7%; *P*=0.22; Figure 6A). On the other hand, eight studies[8-10,13-17] reported CR rates. MRG mutations were associated with a modestly lower likelihood of achieving CR, with a pooled risk ratio of 0.94 (95% CI: 0.90-0.99; *P*=0.010), with minimal heterogeneity (I^2=0.0%; *P*=0.73; Figure 6B). Among the four studies[9,10,14,15] reporting time to CR data in patients who achieved CR1, no significant difference was observed between those with and without MRG mutations (*Online Supplementary Table S2*).

Discussion

This meta-analysis demonstrates that MRG mutations confer adverse prognostic significance in patients with *NPM1*^{mut} AML. Among 4,363 patients included across nine studies (10 cohorts), the presence of MRG mutations was significantly correlated with inferior OS, EFS, and lower CR rates. These findings challenge the current risk stratification paradigm, which classifies *NPM1*^{mut} AML with MRG mutations as favorable-risk subgroup under the ELN-2022 guidelines,[4] and highlight the importance of incorporating co-occurring high-risk molecular alterations into future prognostic models.

Although prior studies have explored the prognostic impact of MRG mutations in *NPM1*^{mut} AML, their findings have been inconsistent. Some reports suggest that MRG mutations attenuate the favorable prognosis typically associated with *NPM1*^{mut} AML,[8,9,15,18] while others have not demonstrated a significant effect.[10,11,13,14,16,17] Notably, despite clinical and biological heterogeneity across the included studies, the adverse impact of MRG mutations remained statistically significant in pre-specified subgroup analyses, including intensively treated patients and those classified as ELN-2022 favorable risk. Although potential patient overlap existed between the studies by Lachowiez *et al.*[15] and Othman *et al.*,[10] a leave-one-out sensitivity analysis that sequentially excluded each study yielded similar results, and the prognostic association remained robust after adjustment for potential publication bias and across multiple sensitivity analyses, reinforcing the consistency of the pooled estimates. Furthermore, meta-regression demonstrated that treatment intensity did not account for the observed heterogeneity in outcomes, suggesting that the adverse prognostic effect is likely attributable to the intrinsic biology of MRG mutations rather than therapeutic context alone. While MRG mutations were significantly associated with worse outcomes in *NPM1*^{mut} AML, the magnitude of risk (pooled HR=1.30 in the overall cohort and HR=1.34 in the ELN favorable-risk subgroup) seemed less pronounced than the prognostic differential typically observed between ELN intermediate- and favorable-risk categories (HR=~1.5-2.27).[19,20] This suggests that MRG mutations may function as moderate risk-modifying factors within an otherwise favorable subset of AML.

In most studies (7/9), patients with *NPM1*^{mut} AML harboring co-occurring MRG mutations were older at diagnosis. In the study by Chan *et al.*,[8] the adverse prognostic impact of MRG mutations was confined to patients aged ≥60 years; however, another study demonstrated that this association remained significant after adjusting for age, indicating that the effect of MRG mutations on prognosis is not solely age-dependent.[15] In the age-stratified subgroup analysis (N=1,810), MRG mutations were not significantly associated with poor OS and no differences among age groups were found. However, when the age-stratified subgroup was confined to ELN-2022 favorable group patients, younger patients with MRG mutations was associated with poorer outcomes, suggesting potential age-dependent effect.

Moreover, Tazi *et al.*[21] reported that the presence of ≥2 MRG mutations is associated with inferior survival, and a similar trend toward worse outcomes was observed in a study specifically evaluating *NPM1*^{mut} AML.[10] These findings raise the possibility that the total number of MRG mutations may further refine risk stratification beyond their mere presence or absence. However, due to limited reporting in this subset, a pooled analysis of mutation burden could not be performed. Future investigations incorporating individual-level genomic data will be essential to determine whether the number of MRG mutations carries incremental prognostic value within the *NPM1*^{mut} AML population.

This study has several inherent limitations. First, as a study-level meta-analysis, it lacks access to individual participant data, precluding adjustment for patient-level confounders that could refine effect estimates. Specifically, factors such as MRD negativity, microclones with low variant allele frequency, and HSCT could potentially mitigate the adverse outcomes associated with MRG mutations in *NPM1*^{mut} AML but could not be comprehensively evaluated in this analysis. Second, all included studies were retrospective in design, potentially introducing selection and publication biases; however, this limitation is largely unavoidable in genetic prognostic research, and our findings remained robust across multiple sensitivity analyses. Finally, the interpretation of the adverse prognostic impact of MRG mutations in specific subgroups of *NPM1*^{mut} AML - such as those with co-occurring ELN-2022 adverse risk cytogenetics, *FLT3*-ITD, or those receiving non-intensive therapy - should be approached with caution due to the relatively small sample sizes in the total cohort. Recent advances in menin inhibitors have shown clinical meaningful responses in relapsed or refractory *NPM1*^{mut} AML[22] and are

now being evaluated in combination with intensive chemotherapy for newly diagnosed cases.[23] Given the adverse impact of co-occurring MRG mutations, evaluating whether menin inhibitor-based regimens can overcome this high-risk genomic feature and improve outcomes represents an important area for future investigation.

In conclusion, MRG mutations are associated with significantly worse survival and lower remission rates in patients with *NPM1*^{mut} AML, challenging the assumption that this genetic subtype uniformly portends a favorable prognosis. These findings advocate for the incorporation of MRG mutation status into contemporary AML risk models and underscore the need for prospective studies to elucidate the biological and therapeutic implications of this high-risk molecular subgroup.

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Contributions

Conceptualization, methodology, formal analysis, investigation, data curation, writing of the original draft, and visualization by YSC. Methodology, formal analysis, investigation, data curation, validation, writing - review and editing by YWL. Investigation, data curation, supervision, validation, writing - review and editing by CYL. Data curation by JO, J-NE and QZ. Investigation, resources, writing - review and editing by FMT, XC-HT, TWL, and CCL. Validation, resources, writing - review and editing by BSK and WCC. Data curation and supervision by HC, CR, NR and RD. Conceptualization, methodology, supervision, validation, writing - review and editing, project administration, funding acquisition by HAH. All authors have reviewed and approved the final manuscript.

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Data-sharing statement

This meta-analysis utilized data extracted from publicly available, previously published studies. All relevant data analyzed in this study are included in the main article and its supplementary materials. Additional information can be requested by contacting the corresponding author.

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