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SYSTEMATIC REVIEW & META-ANALYSIS

Clinical and Hematological Profile of Nucleophosmin 1-Mutated Acute Myeloid Leukemia Compared with NPM1 Wild-Type Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Nucleophosmin 1 (NPM1) mutation, the commonest genetic lesion in adult acute myeloid leukemia (AML), defines a distinct entity, but its presenting profile has been described only in single cohorts.

Objective: To quantify how the presenting features of NPM1-mutated AML differ from those of NPM1 wild-type AML.

Methods: PubMed/MEDLINE, Europe PMC, OpenAlex and Scopus were searched for cohorts reporting presenting features by NPM1 status. Standardized mean differences (SMD) and odds ratios (OR) were pooled with random-effects models, and certainty was rated with GRADE. The primary outcome was white blood cell (WBC) count.

Results: Twenty-eight studies (7,126 patients; 1,747 NPM1-mutated) from nineteen countries were included. The WBC count difference was small and compatible with none (SMD 0.15 (95% CI −0.02 to 0.33); 11 studies; I^2 27.6%; low certainty). NPM1-mutated AML had higher marrow blast percentages (SMD 0.50 (0.15 to 0.84)) and higher odds of female sex (OR 1.56 (1.39 to 1.77)), FAB M4/M5 morphology (2.21 (1.27 to 3.84)), FLT3-ITD (2.78 (1.89 to 4.08)) and normal karyotype (7.14 (3.97 to 12.83)), and lower odds of CD34 positivity (0.24 (0.13 to 0.46)). Certainty was moderate for sex and karyotype and low or very low otherwise. Complete remission, a treatment-dependent outcome, was more frequent (OR 2.36 (1.40 to 3.98)).

Conclusion: NPM1-mutated AML presents more often in women, with monocytic morphology, CD34-negative blasts, normal karyotype and FLT3-ITD; any excess in WBC count is small and uncertain. These features may help prioritize NPM1 testing where molecular diagnostics are limited, but cannot replace it.

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1. Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia of adults. Over three decades, Global Burden of Disease analyses estimated, incident cases worldwide rose by 82% and deaths by 74%.[1] Most of this burden fell on adults aged 60 years and older, whose outcomes remained poor.[2] Cooperative-group cohorts stratified by age showed that the frequencies of driver mutations changed across age groups.[3] In Indonesia, bone marrow examinations over a decade at a national referral hospital showed that myeloid-lineage malignancies predominated among primary hematological malignancies of the marrow.[4] Adults with AML who presented with hyperleukocytosis had a high early mortality.[5] Molecular characterization was available in few centers. There it nonetheless linked genotype to presenting white blood cell counts and to survival,[6] and in neighboring Malaysia genetic profiles and risk groups differed by age, sex and ethnicity.[7]

Mutations in exon 12 of the nucleophosmin 1 (NPM1) gene relocate the nucleolar chaperone nucleophosmin to the cytoplasm. They occur in roughly one-third of adult AML.[8–10] Both the fifth edition of the World Health Organization classification and the International Consensus Classification recognized AML with mutated NPM1 as a distinct entity; the former set no blast threshold and the latter a reduced threshold of 10%.[8,9] The current European LeukemiaNet (ELN) recommendations assigned favorable risk to NPM1-mutated AML without FLT3 internal tandem duplication (FLT3-ITD).[10] Several lines of work characterized the lesion. It was an early, founding event, detectable in blood months before diagnosis.[11] It produced a characteristic transcriptional program with biologically distinct subtypes.[12,13] Occasionally it arose outside exon 12 and gave the same cytoplasmic phenotype.[14] Outcome after intensive therapy depended on co-mutations, particularly FLT3-ITD, rather than on secondary-type mutations.[15–17] New treatments were aimed specifically at this genotype: gemtuzumab ozogamicin, venetoclax-based regimens and menin inhibitors, with molecular monitoring of mutant transcripts to guide therapy.[18–22]

Treatment increasingly depends on NPM1 status, so the genotype should be recognized early. Where sequencing is unavailable or slow, clinicians have to rely on the presenting picture. Individual cohorts associated NPM1 mutation with higher white blood cell counts, female sex, myelomonocytic or monocytic morphology, CD34 negativity, normal karyotype and FLT3-ITD.[23–25] Immunophenotypic, morphological and image-based tools that use these features were proposed as surrogates for molecular testing.[26–29] The associations were nevertheless inconsistent. Several cohorts found no difference in white blood cell count, platelet count, hemoglobin or sex,[30–32] and most cohorts were small. Recent meta-analyses examined the prognostic impact of co-mutations in NPM1-mutated AML and regional mutation

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frequencies.[33,34] They did not examine the presenting phenotype. The size and consistency of these differences across populations therefore remained unquantified.

This gap matters in practice in Indonesia. Molecular characterization of AML has been reported from few centers,[6] and the diagnostic work-up in most hospitals rests on morphology, flow cytometry and conventional cytogenetics. Knowing which routinely available features are associated with NPM1 mutation, and how strongly, would help clinicians choose patients to prioritize for molecular testing and know what to expect at presentation.

To our knowledge, this is the first systematic review and meta-analysis to quantify the presenting clinical and hematological profile of NPM1-mutated AML against NPM1 wild-type disease from the same cohorts. It draws on Asian, Middle Eastern, African, European and North American populations and uses effect sizes that allow features measured on different scales to be compared. The aim was to estimate the differences between NPM1-mutated and NPM1 wild-type AML in white blood cell count (the primary outcome), other hematological parameters, age, sex, morphology, CD34 expression, karyotype, FLT3-ITD co-mutation and complete remission, and to summarize narratively the physical signs reported by the same cohorts (not a prespecified outcome).

2. Methods

2.1 Study design

This systematic review and meta-analysis followed the PRISMA 2020 statement.[35] The review question, eligibility criteria, outcomes, subgroup analyses and analysis plan were defined before the searches were run, together with the completed PRISMA 2020 checklist. Ethical approval was not required because only published aggregate data were analyzed.

2.2 Search strategy

PubMed/MEDLINE, Europe PMC (which also indexes Agricola and Chinese Biological Abstracts), OpenAlex and Scopus were searched. OpenAlex was included as a multidisciplinary index that aggregates Crossref, repository and journal metadata and therefore captures regional journals that are not indexed in MEDLINE; Embase and Web of Science were not searched. No date or language limits were applied in the searches; the language criterion was applied at screening. Two concept blocks were combined with AND: nucleophosmin or NPM1 (Medical Subject Heading and free-text terms) and acute myeloid leukemia (Medical Subject Heading and free-text synonyms). The PubMed string was:

```
("Nucleophosmin"[Mesh] OR nucleophosmin*[tiab] OR
NPM1[tiab] OR "NPM 1"[tiab] OR "NPM-1"[tiab] OR
NPMc[tiab] OR "NPMc+"[tiab] OR "cytoplasmic
NPM"[tiab]) AND ("Leukemia, Myeloid, Acute"[Mesh] OR
"acute myeloid leukemia*"[tiab] OR "acute myeloid
leukemia*"[tiab] OR "acute myelogenous
leukemia*"[tiab] OR "acute myelogenous
leukemia*"[tiab] OR "acute myeloblastic
leukemia*"[tiab] OR "acute non-lymphocytic
leukemia*"[tiab] OR "acute nonlymphocytic
leukemia*"[tiab] OR AML[tiab]) NOT ("Animals"[Mesh]
NOT "Humans"[Mesh]) NOT ("Review"[pt] OR "Case
Reports"[pt] OR "Comment"[pt] OR "Editorial"[pt] OR
"News"[pt])
```

Equivalent strings were adapted to the other databases, as listed in Supplementary Table S1. Reference lists of the included studies were searched backwards for additional reports.

2.3 Eligibility criteria

Studies were eligible if they enrolled patients with newly diagnosed AML tested for NPM1 mutation and reported at least one presenting feature or complete remission separately for NPM1-mutated and NPM1 wild-type patients from the same cohort. Adult and predominantly adult cohorts were included; pediatric-only series were excluded. Accepted methods of NPM1 assessment included polymerase chain reaction (PCR) fragment analysis, allele-specific PCR, Sanger or next-generation sequencing, denaturing high-performance liquid chromatography (DHPLC) and conformation-sensitive gel electrophoresis (CSGE) screening, and immunohistochemistry for cytoplasmic nucleophosmin. Only full reports in English, published in journals indexed in MEDLINE, Scopus or Web of Science, were eligible, because the extraction of numerical data from tables required reliable reading of the full text. The eligibility criteria are detailed in Table 1.

Table 1. Eligibility criteria.

Element	Inclusion	Exclusion
Population	Patients with newly diagnosed AML (de novo or unselected; any karyotype or normal karyotype only) tested for NPM1 mutation at diagnosis; adult or predominantly adult cohorts	Pediatric-only cohorts; relapsed or refractory disease; cohorts selected on another mutation (e.g. FLT3-mutated only) or on outcome
Exposure	NPM1 exon 12 mutation detected by PCR fragment analysis, allele-specific PCR, Sanger or next-generation sequencing, DHPLC or CSGE screening; cytoplasmic nucleophosmin by immunohistochemistry	NPM1 status inferred from transcript expression levels
Comparator	NPM1 wild-type AML from the same cohort and diagnostic work-up	External or historical comparators
Outcomes	Presenting WBC count (primary); platelet count, hemoglobin, bone marrow and peripheral blood blasts, LDH, age; female sex, FAB M4/M5 morphology, CD34 positivity, FLT3-ITD, normal karyotype, complete remission after induction	Survival-only outcomes; measurable residual disease; post-transplant outcomes
Design and report	Cohort, cross-sectional and treatment-trial cohorts reporting data by NPM1 status; full English-language reports in journals indexed in MEDLINE, Scopus or Web of Science	Reviews, case reports and series without a wild-type comparator, conference abstracts, letters, laboratory or animal studies; overlapping reports of the same cohort (most informative report retained)

Notes: AML, acute myeloid leukemia; CSGE, conformation-sensitive gel electrophoresis; DHPLC, denaturing high-performance liquid chromatography; FAB, French-American-British; FLT3-ITD, FLT3 internal tandem duplication; LDH, lactate dehydrogenase; NPM1, nucleophosmin 1; PCR, polymerase chain reaction; WBC, white blood cell.

The primary outcome was the white blood cell (WBC) count in peripheral blood at diagnosis ($\times 10^9$/L). Secondary continuous outcomes were the platelet count ($\times 10^9$/L), hemoglobin concentration (g/dL; values reported in g/L were divided by 10), bone marrow and peripheral blood blast percentages, lactate dehydrogenase and age. Secondary binary outcomes were female sex; French-American-British (FAB) M4 or M5 morphology, with the number of patients with an assigned FAB subtype as the denominator; CD34 positivity as defined by each study's flow cytometry threshold; FLT3-ITD co-mutation; normal karyotype on conventional cytogenetics, analyzed only in cohorts not restricted to normal karyotype; and complete remission after induction chemotherapy as defined by each study, counting

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remissions after one or two induction courses where both were reported. Complete remission was analyzed separately from the presenting features because it depends on treatment. Physical signs (hepatomegaly, splenomegaly, lymphadenopathy, gum hypertrophy and other extramedullary involvement) were not among the prespecified outcomes; where included studies tabulated them by NPM1 status, they were summarized narratively without pooling.

2.4 Study selection and data extraction

Records were merged and de-duplicated on PubMed identifier, digital object identifier and normalized title. A rule-based triage marked records that were clearly ineligible (conference abstracts, reviews, letters, case reports, laboratory or animal studies, pediatric-only cohorts and records on other questions). All remaining records were screened on title and abstract, and potentially eligible reports were assessed in full text. Screening, full-text assessment and data extraction were performed by one reviewer; every inclusion decision and every extracted value was verified in a second, complete pass against the source reports, and uncertain values were resolved against the study totals. Independent duplicate screening and extraction were not performed.

Data were recorded in a standardized workbook. The following items were extracted: first author, year, country, institution, recruitment period, design, population (karyotype restriction, age range, inclusion of acute promyelocytic or secondary AML), method of NPM1 assessment, numbers of NPM1-mutated and wild-type patients, all outcome data and any physical signs reported by NPM1 status. Continuous variables were recorded in the format reported (mean and standard deviation [SD] or median with range). When characteristics were tabulated by NPM1/FLT3-ITD genotype, the mutually exclusive genotype groups were summed to obtain NPM1-mutated and wild-type totals, with double-mutated patients counted once; medians reported separately for genotype subgroups could not be combined and were not pooled. Counts reported only as percentages were back-calculated from the group sizes; group means and SDs were computed from individual patient listings when a study tabulated every patient. Internal inconsistencies were resolved in favor of the figures consistent with the study totals. Values that were missing were recorded as not reported, and no data were imputed.

Overlap between cohorts was assessed from the institution, recruitment period, sample size and authorship of each report. When two reports described the same patients, the report with the most usable data was retained; reports from the same institution with non-overlapping recruitment periods were both retained.

2.5 Risk of bias and certainty of evidence

Because the included studies were comparative cross-sectional analyses of presenting features within cohorts, the Newcastle-Ottawa Scale adapted for cross-sectional studies was used (maximum 10 stars). In the selection domain (5 stars), one star each was given for a representative cohort (consecutive or unselected patients, or an entire trial population, rather than a selected biopsy or convenience series), for a sample of at least 100 patients and for NPM1 status available in at least 90% of the cohort, and two stars for mutation analysis covering all exon 12 variants (one star for a type A-specific assay or immunohistochemistry). In the comparability domain (2 stars), one star was given for comparison within the same cohort and diagnostic work-up and a second for restriction to normal karyotype, which removes the strongest compositional difference between the groups. In the outcome domain (3 stars), two stars were given for laboratory data reported directly (one when counts had to be back-calculated or were internally inconsistent) and one for a reported statistical comparison. Studies with at least 8 stars were rated at low, 6–7 at moderate and 5 or fewer at high risk of bias. Item-level ratings are given in Supplementary Table S2. Tools designed for prognostic-factor studies were not used because the review question concerned associations at presentation rather than prediction of outcome.

Certainty of evidence for each outcome was rated with the GRADE approach for association questions. Certainty started at high because the comparisons were made within representative cohorts, which is the design best suited to describing associated features, and was rated down one level for risk of bias (unadjusted comparisons, converted or back-calculated data), one level for inconsistency when I^2 was 50–74% and two levels when I^2 was 75% or more with a prediction interval spanning no difference, one level for imprecision when the 95% confidence interval included no difference or fewer than 400 patients contributed (a pragmatic optimal information size), and one level for possible small-study effects when the Egger or Harbord test gave $p<0.10$.

2.6 Statistical analysis

For continuous outcomes, the standardized mean difference (SMD) was calculated as Hedges' g with its small-sample correction (Equation 1); positive values indicate higher values in NPM1-mutated AML.

The SMD was chosen because white blood cell and platelet counts are strongly right-skewed and reported on different scales and units, and because it allows features measured in different ways to be compared on one scale; values of 0.2, 0.5 and 0.8 were read as small, moderate and large differences.

$$
\begin{aligned}
g &= J \times \frac{\overline{x}_{\mathrm{M}} - \overline{x}_{\mathrm{W}}}{S_{\mathrm{p}}}, \\
S_{\mathrm{p}} &= \sqrt{\frac{(n_{\mathrm{M}}-1)s_{\mathrm{M}}^2 + (n_{\mathrm{W}}-1)s_{\mathrm{W}}^2}{n_{\mathrm{M}}+n_{\mathrm{W}}-2}}, \\
J &= 1 - \frac{3}{4(n_{\mathrm{M}}+n_{\mathrm{W}})-9}, \\
v_g &= \frac{n_{\mathrm{M}}+n_{\mathrm{W}}}{n_{\mathrm{M}}n_{\mathrm{W}}} + \frac{g^2}{2(n_{\mathrm{M}}+n_{\mathrm{W}})}
\end{aligned}
\qquad (1)
$$

When only the median and range were reported, the mean was estimated with the Luo method and the SD with the Wan method (Equation 2). These estimators were prespecified for the primary analysis because they are the most widely used and allow comparison with other syntheses, although they assume approximate symmetry and can attenuate differences when distributions are highly skewed. Two approaches that do not rely on this assumption were prespecified as sensitivity analyses: Box-Cox estimation of means and SDs from medians, and the ratio of means on the log scale.[36–38]

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$$\bar{x} \approx w\frac{a+b}{2} + (1-w)m, \quad w = \frac{4}{4n^{0.75}}, \quad s \approx \frac{b-a}{2\Phi^{-1}\left(\frac{n-0.375}{n+0.25}\right)} \tag{2}$$

For binary outcomes, the log odds ratio and its variance were computed from the 2x2 table, adding 0.5 to all cells of tables with a zero count (Equation 3).

$$y_i = \ln\left(\frac{a_i d_i}{b_i c_i}\right), \quad v_i = \frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i} \tag{3}$$

Study estimates were pooled by inverse-variance random-effects models. The between-study variance τ^2 was estimated by the DerSimonian–Laird method (Equation 4), the pooled estimate was the weighted mean of study estimates (Equation 5) and its 95% confidence interval (CI) was calculated with the Hartung–Knapp method (Equation 6).

$$\tau^2 = \max\left\{0, \frac{Q-(k-1)}{\sum_i w_i - \frac{\sum_i w_i^2}{\sum_i w_i}}\right\}, \quad w_i = \frac{1}{v_i} \tag{4}$$

$$\hat{\mu} = \frac{\sum_i w_i^* y_i}{\sum_i w_i^*}, \quad w_i^* = \frac{1}{v_i + \tau^2} \tag{5}$$

$$\hat{\mu} \pm t_{k-1,0.975}\sqrt{\frac{\sum_i w_i^*(y_i-\hat{\mu})^2}{(k-1)\sum_i w_i^*}} \tag{6}$$

Heterogeneity was quantified with Cochran's Q and I^2 (Equation 7), with I^2 of 25%, 50% and 75% read as low, moderate and substantial, and the 95% prediction interval (PI) described the range of effects expected in a new cohort (Equation 8).

$$Q = \sum_i w_i(y_i - \hat{\mu}_{\mathrm{FE}})^2, \quad I^2 = \max\left\{0, \frac{Q-(k-1)}{Q}\right\} \times 100\% \tag{7}$$

$$\hat{\mu} \pm t_{k-2,0.975}\sqrt{\tau^2 + \mathrm{SE}^2(\hat{\mu})} \tag{8}$$

Random-effects models were used throughout because the cohorts differed in population, period, NPM1 assay and treatment, so that a single common effect was implausible; the Hartung–Knapp adjustment was preferred to Wald-type intervals because it maintains coverage when the number of studies is small, at the cost of wide intervals when very few studies contribute. Single-study subgroups were reported with Wald-type intervals.

Prespecified subgroup analyses for the primary outcome compared region, restriction to normal karyotype, age group, data form (reported means versus estimated from medians) and risk of bias. Sensitivity analyses used restricted maximum likelihood, Wald-type intervals, a common-effect model, Box-Cox estimation of means and SDs from medians, restriction to studies reporting means, exclusion of moderate or high risk of bias, exclusion of mixed-age cohorts and of the largest study, the ratio of means, and leave-one-out analysis; meta-regression examined publication year and sample size. Small-study effects were assessed with a funnel plot and Egger's test for the primary outcome and with Harbord's test for binary outcomes when at least 10 studies contributed. Twelve outcomes were analyzed without adjustment for multiplicity; estimates and their intervals, rather than p values, were therefore emphasized in interpretation. Analyses used R 4.5.3 with the meta (version 8.2.1), metafor (version 4.8.0) and estmeansd (version 1.0.1) packages; two-sided p<0.05 was considered significant.

3. Results

3.1 Study selection

The searches identified 12,978 records (PubMed/MEDLINE 2,270, Europe PMC 2,317, OpenAlex 5,239 and Scopus 3,152). After removal of 6,780 duplicates and 4,312 records marked ineligible by the rule-based triage, 1,886 records were screened and 101 reports were sought in full text. Of these, 58 could not be retrieved and 43 were assessed; 15 were excluded and 28 studies were included, as illustrated in Figure 1. Backward citation searching identified no additional eligible reports.

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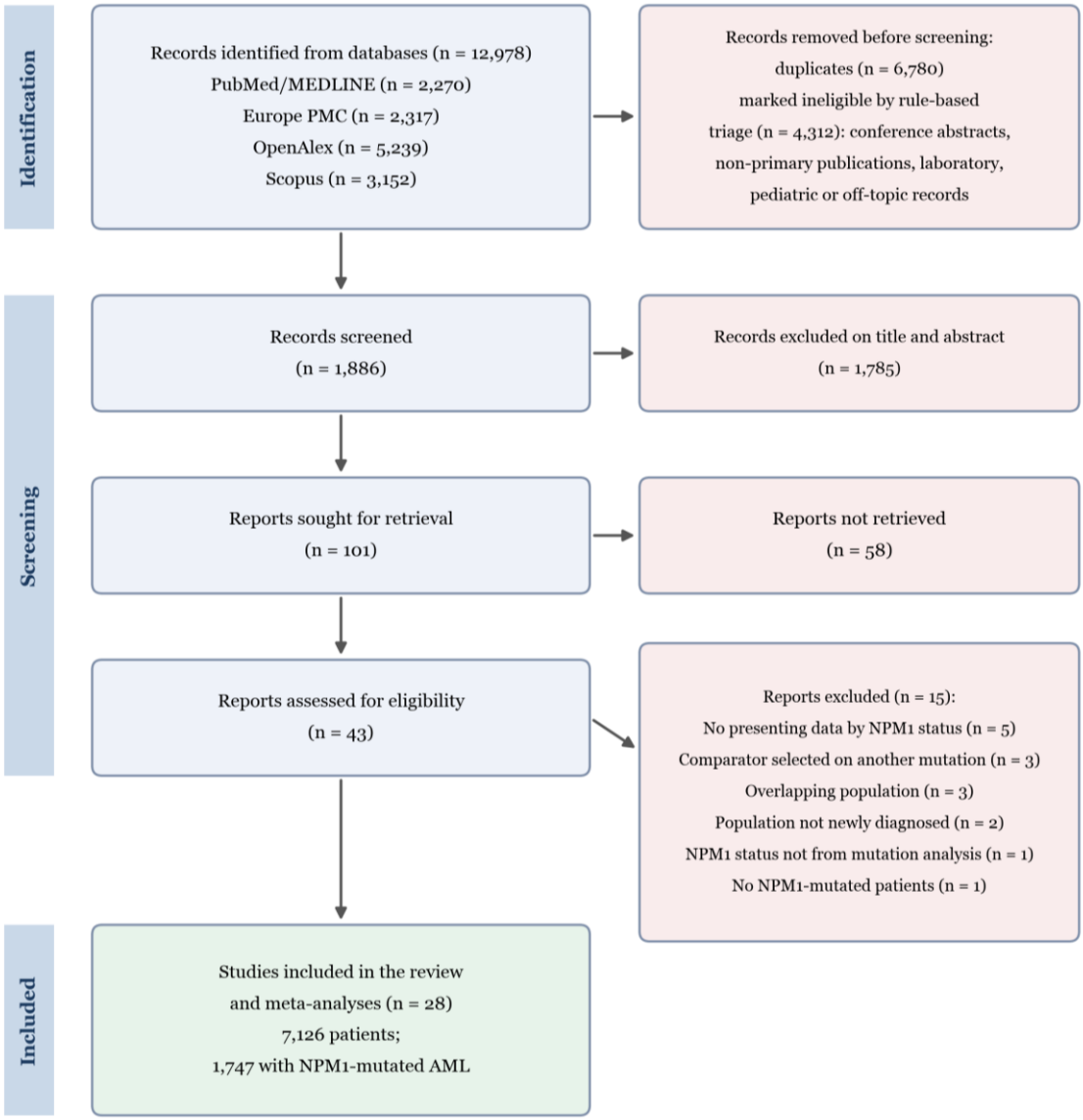


Figure 1. PRISMA 2020 flow diagram of the identification, screening and inclusion of studies.

The 58 reports that could not be retrieved included several large European and East Asian cooperative-group and single-center cohorts of up to 1,485 patients and cohorts from Egypt, China, Iraq, Lebanon, Malaysia and Indonesia, among others. Their abstracts indicated that most reported the same features as the included studies, chiefly white blood cell count, FLT3-ITD, karyotype and complete remission, and that the largest of them described associations in the same directions as those found here. These reports are listed in Supplementary Table S3, and the full-text exclusions with reasons in Supplementary Table S4.

3.2 Characteristics of the included studies

The twenty-eight included studies[23–25,30–32,39–60] enrolled 7,126 patients, of whom 1,747 (24.5%) had NPM1-mutated AML. They came from nineteen countries: twelve from Asia, five from the Middle East and North Africa, seven from Europe (including one from Turkey, which was counted with the European cohorts throughout), three from North America and one from sub-Saharan Africa. Eight cohorts were restricted to cytogenetically normal AML, two to patients aged 60 or 65 years and older, and seven included a minority of children or adolescents. NPM1 status was determined by mutation analysis in most studies, by a type A-specific assay in two and by cytoplasmic nucleophosmin immunohistochemistry in two. The characteristics of each study are summarized in Table 2.

Table 2. Characteristics of the included studies (ordered by year of publication).

Study	Country	Design	Population	NPM1 assessment	NPM1-mutated / wild-type (n)	Outcomes contributed	NOS (risk of bias)
Boonthimat 2008[23]	Thailand	Cross-sectional	Consecutive de novo AML, all ages and karyotypes	DHPLC screening and sequencing	105 / 295	Sex, FLT3-ITD, NK	9 (Low)
Lo-Coco 2008[39]	Italy	Prospective trial cohort (GIMEMA LAM99P)	Newly diagnosed adult AML (APL excluded)	Immunohistochemistry (cytoplasmic NPM), confirmed by DHPLC/CE in 65	86 / 184	FLT3-ITD, CR	6 (Moderate)
Becker 2010[40]	USA	Trial cohort (CALGB)	De novo CN-AML aged ≥60 years	PCR and sequencing	83 / 65	WBC, PLT, Hb, BMB, PBB, Age, Sex, FAB, FLT3-ITD, CR	10 (Low)

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Study	Country	Design	Population	NPM1 assessment	NPM1-mutated / wild-type (n)	Outcomes contributed	NOS (risk of bias)
Kim 2010[24]	South Korea	Retrospective cohort	CN-AML aged ≤60 years	GeneScan fragment analysis	65 / 56	WBC, PLT, Hb, BMB, Age, Sex, FAB, FLT3-ITD, CR	10 (Low)
Wang 2010[41]	China	Retrospective cohort	Newly diagnosed CN-AML (APL excluded)	Multiplex PCR	20 / 56	FLT3-ITD, CR	9 (Low)
Pazhakh 2011[42]	Iran	Cross-sectional	AML, all karyotypes incl. APL	CSGE screening and sequencing	23 / 108	FAB, FLT3-ITD	8 (Low)
de Jonge 2011[43]	Netherlands, Belgium	Trial cohort (HOVON/SAKK)	Newly diagnosed AML aged 15–77 years	Sequencing (NPMc+ by mutation)	94 / 366	FLT3-ITD	8 (Low)
Chauhan 2013[44]	India	Cross-sectional	De novo AML, all karyotypes, adults and children	PCR and sequencing	34 / 127	Sex, FAB, CD34, FLT3-ITD, CR	8 (Low)
Daver 2013[45]	USA	Retrospective cohort	AML aged ≥65 years given intensive chemotherapy	PCR	23 / 123	CR	6 (Moderate)
Zidan 2013[46]	Egypt	Cohort	De novo AML, all karyotypes	PCR and sequencing	12 / 43	WBC, BMB, Age, Sex, FAB, NK, CR	8 (Low)
Balatzenko 2014[47]	Bulgaria	Cohort	Adult AML, all karyotypes incl. APL	Allele-specific RT-PCR and RQ-PCR (type A only)	26 / 79	WBC, PLT, Hb, BMB, Age, Sex, CD34, FLT3-ITD, NK, CR	8 (Low)
Helbig 2014[31]	Poland	Cohort	De novo AML aged ≤60 years, all karyotypes	PCR	21 / 39	WBC, PLT, Hb, BMB, PBB, Age, Sex, FLT3-ITD, NK, CR	8 (Low)
Marshall 2014[48]	South Africa	Retrospective cross-sectional	Adult de novo AML, all karyotypes	PCR fragment analysis	21 / 139	Sex, FLT3-ITD, NK	8 (Low)
Chopra 2016[49]	India	Cross-sectional (diagnostic)	Primary AML with marrow biopsy, all ages	Allele-specific PCR (with immunohistochemistry)	21 / 14	WBC, PLT, Hb, BMB, PBB, Age, Sex, FAB	6 (Moderate)
Koczkodaj 2016[50]	Poland	Cross-sectional	Adult AML, all karyotypes incl. APL	PCR and direct sequencing	3 / 47	WBC, Age, Sex, FAB, FLT3-ITD, NK	8 (Low)
Mevatee 2017[51]	Thailand	Cross-sectional	CN-AML	PCR and sequencing	7 / 33	Sex, FLT3-ITD	9 (Low)
Rezaei 2017[30]	Iran	Cross-sectional	Adult de novo CN-AML	PCR and direct sequencing	11 / 42	WBC, PLT, Hb, BMB, FLT3-ITD	9 (Low)
Mahmood 2019[52]	Pakistan	Cross-sectional with induction follow-up	AML, all ages and karyotypes incl. APL	ARMS PCR, PAGE	37 / 71	Sex, FAB, FLT3-ITD	7 (Moderate)
Mat Yusoff 2019[53]	Malaysia	Cross-sectional	CN-AML	Conventional PCR, fragment sizing	54 / 145	Sex, FLT3-ITD	10 (Low)
Juliusson 2020[54]	Sweden	Population-based registry cohort	AML aged <75 years with NPM1 and FLT3 data	PCR (national routine diagnostics)	448 / 1013	Sex, FLT3-ITD	7 (Moderate)
Alarbeed 2021[55]	Syria	Cross-sectional	Adult de novo CN-AML	PCR and sequencing	10 / 34	WBC, PLT, Hb, BMB, Age, Sex, FAB	9 (Low)
Naseem 2021[56]	India	Cross-sectional	De novo AML, all karyotypes incl. APL	Allele-specific PCR, PAGE	21 / 71	Sex, FAB, CD34, FLT3-ITD	8 (Low)
Oravakandy 2022[57]	India	Cross-sectional (diagnostic)	AML with marrow biopsy, all ages	Immunohistochemistry (NPMc), validated by RT-PCR and sequencing in 50	12 / 59	Sex, FAB, CD34	4 (High)
Alserihi 2023[58]	Saudi Arabia	Cross-sectional (pilot)	AML, all ages and karyotypes	Multiplex PCR fragment analysis	7 / 26	Sex, FLT3-ITD	6 (Moderate)
Ningombam 2023[32]	India	Prospective cohort	Adult de novo CN-AML	PCR-based screening (published protocols)	50 / 101	WBC, PLT, Hb, BMB, PBB, Age, Sex, FLT3-ITD	9 (Low)
Chantrathammachart 2025[59]	Thailand	Retrospective cohort	Adult AML (de novo and secondary)	Targeted NGS (25 genes)	46 / 178	NK, CR	8 (Low)
Catma 2026[60]	Turkey	Retrospective cohort	Adult AML, all karyotypes incl. APL	PCR (NPM1 type A)	11 / 46	CR	7 (Moderate)
Farhat 2026[25]	USA	Retrospective cohort	Newly diagnosed AML, all karyotypes (therapy-related included)	Next-generation sequencing / PCR	396 / 1819	WBC, PLT, BMB, PBB, Age, Sex, FAB, FLT3-ITD, NK, CR	9 (Low)

Notes: Outcomes listed are those contributing to at least one meta-analysis (continuous outcomes only when reported as mean (SD) or median with range). NOS, adapted Newcastle–Ottawa Scale score out of 10 (risk of bias). APL, acute promyelocytic leukemia; BMB, bone marrow blasts; CN-AML, cytogenetically normal AML; CR, complete remission; FAB, FAB M4/M5 morphology; Hb, hemoglobin; NGS, next-generation sequencing; NK, normal karyotype; PBB, peripheral blood blasts; PLT, platelet count; WBC, white blood cell count. Other abbreviations as in Table 1.

Study size ranged from 33 to 2,215 patients (median 114.5). Two pairs of reports came from the same institutions, one in the United States and one in India; their recruitment periods did not overlap, and the other reports from the same country came from different institutions. In cohorts not restricted to normal karyotype, the crude proportion of NPM1-mutated cases was 28.0% in European, 25.3% in Asian, 19.2% in Middle Eastern and North African, 17.7% in North American and 13.1% in the sub-Saharan African cohort; these proportions reflect differences in case mix (inclusion of therapy-related, secondary and promyelocytic leukemia, and age) as well as true population differences. Continuous outcomes were reported as mean (SD) in 5 studies, as median with range in six and only as medians or means without dispersion in four, so that not every study could contribute to every analysis. No included study reported quartiles.

3.3 Risk of bias

Using the adapted Newcastle–Ottawa Scale, 20 studies were at low, seven at moderate and one at high risk of bias. The commonest limitations were small samples, incomplete NPM1 testing of the cohort, selected biopsy series and outcome data that had to be back-calculated from percentages, as shown in Figure 2. Because every study compared groups from the same cohort, the comparability domain distinguished studies mainly by restriction to normal karyotype.

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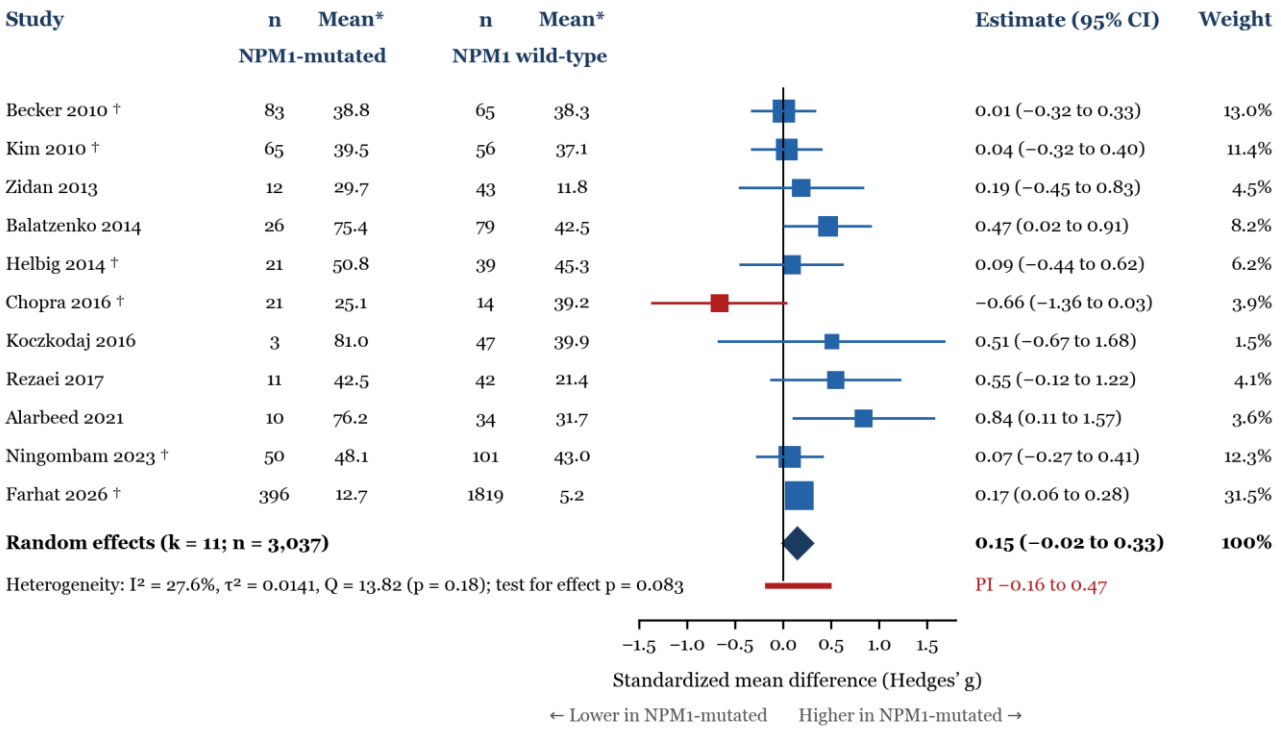
Figure 2. Adapted Newcastle–Ottawa Scale ratings of the included studies by domain. Numbers are stars awarded; colors indicate the proportion of available stars (green ≥75%, amber 50–74%, red <50%) and, for the total score, low (≥8), moderate (6–7) or high (≤5) risk of bias.

3.4 Primary outcome: white blood cell count

Eleven studies (3,037 patients; 698 NPM1-mutated, 2,339 wild-type) contributed to the primary analysis. The pooled estimate showed a small difference that was compatible with no difference (SMD 0.15 (95% CI −0.02 to 0.33); p=0.08). Heterogeneity was low to moderate (I^2 27.6%; τ^2 0.0141; Q 13.82, p=0.18) and the 95% PI ranged from −0.16 to 0.47, as illustrated in Figure 3. The two prespecified approaches that do not assume symmetric distributions gave estimates in the same direction: Box-Cox estimation yielded an SMD of 0.26 (95% CI 0.04 to 0.47) and the ratio of means was 1.33 (95% CI 0.98 to 1.81), corresponding to a mean count about one-third higher in NPM1-mutated AML with an interval that included no difference.

Five studies reported means and SDs and six reported medians with ranges that were converted. Ten of the eleven study estimates pointed towards a higher count in NPM1-mutated AML. The largest study[25] contributed 31.5% of the weight and showed a small but statistically significant difference, whereas a selected biopsy series of 35 patients[49] pointed in the opposite direction. All 5 studies that reported means and SDs showed higher counts in NPM1-mutated AML, two of them significantly. The certainty of evidence for the primary outcome was low. The pooled results for all outcomes, with their certainty of evidence, are summarized in Table 3.

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*Mean white blood cell count (×10⁹/L), as reported or, for studies marked †, estimated from the median and range.

Figure 3. Forest plot of the standardized mean difference (Hedges' g) in white blood cell count at diagnosis between NPM1-mutated and NPM1 wild-type AML. Squares are study estimates (size proportional to random-effects weight) with 95% confidence intervals; the diamond is the random-effects pooled estimate (DerSimonian–Laird, Hartung–Knapp) and the red bar the 95% prediction interval. *Means (×10⁹/L) as reported or, for studies marked †, estimated from the median and range.

Table 3. Pooled differences in presenting features between NPM1-mutated and NPM1 wild-type AML, with certainty of evidence.

Outcome	*k*	Patients	Crude % (mutated vs wild-type)	Effect (95% CI)	I^2 (%)	95% PI	GRADE certainty
Continuous presenting features (SMD, Hedges' g)							
White blood cell count	11	3,037	—	0.15 (−0.02 to 0.33)	27.6	−0.16 to 0.47	Low
Platelet count	9	2,932	—	0.26 (−0.06 to 0.59)	78.1	−0.58 to 1.11	Very low
Hemoglobin	8	717	—	0.11 (−0.20 to 0.42)	61.9	−0.66 to 0.88	Very low
Bone marrow blasts	10	2,987	—	0.50 (0.15 to 0.84)	94.3	−1.32 to 2.32	Very low
Peripheral blood blasts	5	2,609	—	0.60 (0.16 to 1.05)	83.1	−0.52 to 1.73	Very low
Age	10	2,984	—	−0.04 (−0.32 to 0.23)	68.7	−0.73 to 0.64	Very low
Categorical presenting features (OR)							
Female sex	20	5,708	53.7 vs 43.1	1.56 (1.39 to 1.77)	0.0	1.37 to 1.79	Moderate
FAB M4/M5 morphology	12	3,141	40.9 vs 19.7	2.21 (1.27 to 3.84)	68.8	0.47 to 10.44	Low
CD34 positivity	4	385	38.6 vs 72.7	0.24 (0.13 to 0.46)	0.0	0.10 to 0.57	Low
FLT3-ITD co-mutation	21	5,763	40.8 vs 16.6	2.78 (1.89 to 4.08)	69.7	0.88 to 8.76	Very low
Normal karyotype*	8	3,146	78.8 vs 29.6	7.14 (3.97 to 12.83)	40.8	2.39 to 21.27	Moderate
Response to induction (OR)							
Complete remission after induction	12	3,436	76.9 vs 57.2	2.36 (1.40 to 3.98)	60.8	0.72 to 7.69	Low

Notes: Random-effects models (DerSimonian–Laird τ^2, Hartung–Knapp 95% CI). Positive SMD or OR >1 indicates a higher value or a higher frequency in NPM1-mutated AML. Crude percentages are unweighted pooled raw proportions (NPM1-mutated vs wild-type), shown for orientation only; they are not pooled estimates and should not be compared directly with the odds ratios. Reasons for rating down certainty are listed in Supplementary Table S5. *Cohorts not restricted to normal karyotype only. CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; PI, 95% prediction interval; SMD, standardized mean difference.

3.5 Secondary continuous outcomes

Bone marrow blast percentage was higher in NPM1-mutated AML (SMD 0.50 (0.15 to 0.84); 10 studies), as was the peripheral blood blast percentage (SMD 0.60 (0.16 to 1.05); 5 studies), although both analyses were highly heterogeneous (I^2 94.3% and 83.1%). The platelet count (SMD 0.26 (−0.06 to 0.59); 9 studies) pointed towards higher values in NPM1-mutated AML, but the interval included no difference and the prediction interval (−0.58 to 1.11) was wide. Hemoglobin (SMD 0.11 (−0.20 to 0.42); 8 studies) and age (SMD −0.04 (−0.32 to 0.23); 10 studies) did not differ significantly. These estimates are illustrated in Figure 4, and the study-level forest plots are shown in Supplementary Figures S1-S5. Lactate dehydrogenase was reported with dispersion by a single study and was not pooled.

The heterogeneity of the blast analyses arose mainly from the size of the difference rather than its direction: the largest registry cohort[25] reported a median marrow blast percentage of 61% in NPM1-mutated and 37% in wild-type AML, whereas most cohorts restricted to normal karyotype, in which wild-type cases are themselves blast-rich, showed smaller differences.

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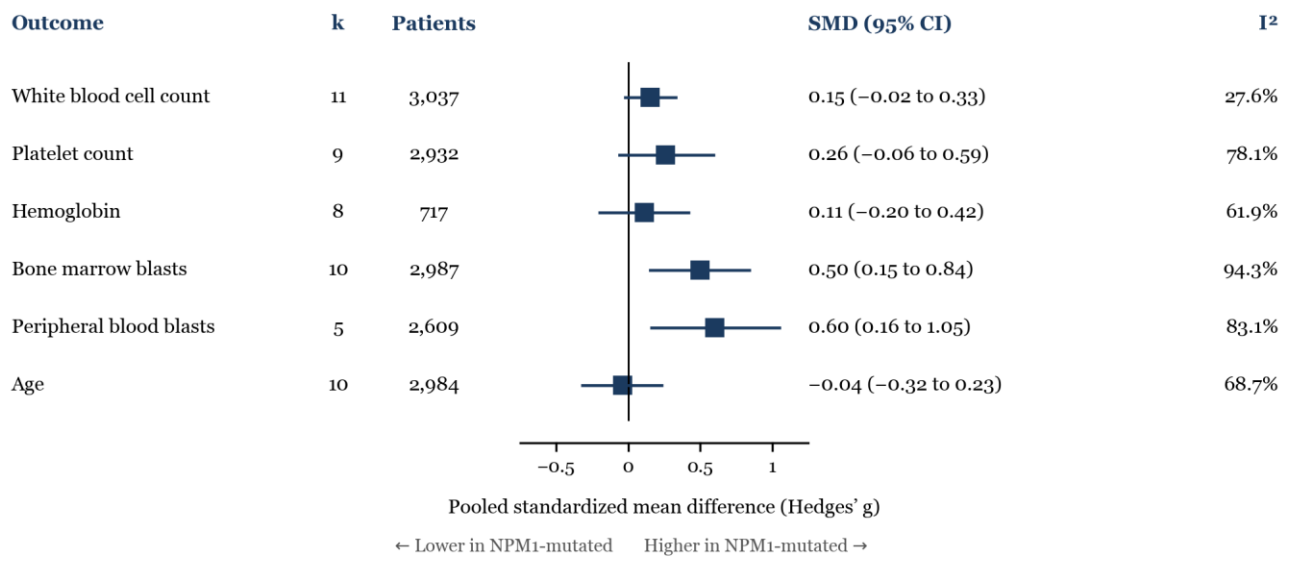


Figure 4. Pooled standardized mean differences (Hedges' g, 95% confidence interval) for the continuous presenting features; positive values indicate higher values in NPM1-mutated AML. I^2, between-study heterogeneity.

3.6 Categorical presenting features and complete remission

NPM1-mutated AML was more often female (53.7% versus 43.1%; OR 1.56 (1.39 to 1.77); 20 studies, I^2 0.0%) and more often of FAB M4 or M5 morphology (40.9% versus 19.7%; OR 2.21 (1.27 to 3.84); 12 studies), and less often CD34-positive (38.6% versus 72.7%; OR 0.24 (0.13 to 0.46); 4 studies). FLT3-ITD co-occurred more frequently (40.8% versus 16.6%; OR 2.78 (1.89 to 4.08); 21 studies), and in cohorts not restricted by karyotype a normal karyotype was much more common (78.8% versus 29.6%; OR 7.14 (3.97 to 12.83); 8 studies). Because these outcomes were common, the odds ratios exceed the corresponding ratios of proportions; for example, the odds of a normal karyotype were about seven times higher, while the crude proportions were 78.8% and 29.6%. The pooled odds ratios are illustrated in Figure 5, and the study-level forest plots in Supplementary Figures S6-S11.

A higher proportion of women among NPM1-mutated patients was seen in 15 of 20 studies, and the pooled estimate was homogeneous; the opposite direction occurred only in small cohorts. CD34 positivity was reported by 4 studies using different thresholds, all of which showed lower positivity in NPM1-mutated AML; with 385 patients, however, this estimate was imprecise.

The heterogeneity of FAB morphology and FLT3-ITD was examined post hoc at study level. For FAB M4/M5 morphology, two South Asian cohorts that included children or acute promyelocytic leukemia showed no association,[44,52] whereas another showed a very strong one[56] and the largest cohort a clear association. For FLT3-ITD, two small cohorts showed inverse estimates, one of them with no co-mutated patient,[31,56] and a trial cohort showed no association,[43] whereas the two population-based or registry cohorts[25,54] showed odds ratios above four.

Complete remission after induction was more frequent in NPM1-mutated AML (76.9% versus 57.2%; OR 2.36 (1.40 to 3.98); 12 studies; I^2 60.8%). Three cohorts showed no advantage, one of which included acute promyelocytic leukemia among the wild-type patients.[24,41,60] Most of the weight came from cohorts treated with intensive induction; the largest cohort also included patients given lower-intensity regimens.[25]

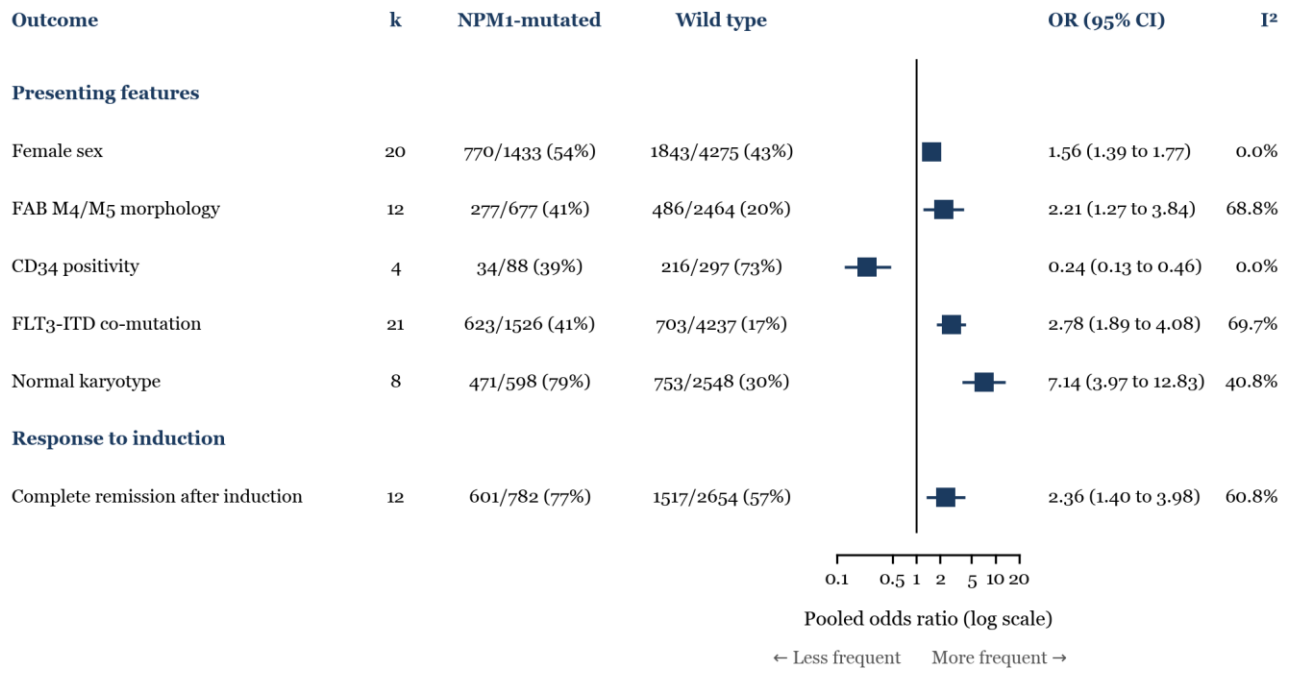


Figure 5. Pooled odds ratios (95% confidence interval, log scale) for the categorical presenting features and for complete remission; values above 1 indicate a higher frequency in NPM1-mutated AML. Raw pooled counts and percentages are shown for each group.

3.7 Physical signs at presentation

Seven included studies tabulated physical signs by NPM1 status, as summarized in Supplementary Table S6.[25,31,40,44,46,47,56] Their definitions and comparators differed, and the data were not pooled. Hepatomegaly, splenomegaly and lymphadenopathy showed no consistent pattern: 4 studies found no significant difference,[31,40,46,47] one cohort that included children found hepatosplenomegaly less often in NPM1-mutated patients (38% versus 64% of patients without NPM1 or FLT3 mutation),[44] and another found splenomegaly (48% versus 21%) and hepatomegaly (52% versus 21%) more often, although the authors' comparison across five genotype groups was not significant.[56] Extramedullary involvement was similar in the 2 cohorts that reported it (25% versus 23% in older adults with normal karyotype and 3% versus 2% in a large unselected cohort).[25,40] Gum hypertrophy, recorded in one cohort, was more frequent in NPM1-mutated AML (15% versus 3%).[40]

3.8 Subgroup and sensitivity analyses

The difference in white blood cell count was larger and statistically significant in studies that reported means and SDs (0.49 (95% CI 0.22 to 0.75); 5 studies) than in studies whose medians were converted (0.08 (95% CI −0.11 to 0.27); p for difference <0.001). This comparison was confounded by study size: the studies reporting means enrolled 44 to 105 patients, whereas the converted studies included the four largest cohorts. The difference did not vary by karyotype restriction (p=0.95) or region (p=0.10). Restricted maximum likelihood (0.16 (95% CI 0.04 to 0.28)) and the common-effect model (0.16 (95% CI 0.07 to 0.25)) yielded significant estimates, as did Box-Cox estimation, whereas the ratio of means and exclusion of the largest study (0.16 (95% CI −0.09 to 0.40)) did not. Leave-one-out estimates ranged from 0.13 to 0.18. Subgroup and sensitivity results are detailed in Table 4 and illustrated in Figure 6. Meta-regression showed no association with publication year or sample size.

Table 4. Subgroup and sensitivity analyses of the primary outcome (white blood cell count).

Analysis	*k*	SMD (95% CI)	I^2 (%)	*p* for difference
Subgroup analyses				
Region: Europe and North America	5	0.17 (0.05 to 0.29)	0.0	0.10
Region: Asia	3	−0.07 (−0.90 to 0.76)	45.0	
Region: Middle East and North Africa	3	0.50 (−0.31 to 1.30)	0.0	
Karyotype restriction: Normal karyotype only	5	0.16 (−0.20 to 0.53)	33.9	0.95
Karyotype restriction: All karyotypes	6	0.15 (−0.18 to 0.48)	34.1	
Age group: Older adults (≥60 years)	1	0.01 (−0.32 to 0.33)	—	—
Age group: Adults	9	0.19 (0.08 to 0.29)	0.0	
Age group: Mixed-age cohorts	1	−0.66 (−1.36 to 0.03)	—	
Data form: Estimated from median	6	0.08 (−0.11 to 0.27)	23.3	<0.001
Data form: Reported mean (SD)	5	0.49 (0.22 to 0.75)	0.0	
Risk of bias: Low risk of bias	10	0.17 (0.07 to 0.27)	0.0	—
Risk of bias: Moderate or high risk of bias	1	−0.66 (−1.36 to 0.03)	—	
Sensitivity analyses				
Primary analysis (DL, Hartung–Knapp)	11	0.15 (−0.02 to 0.33)	27.6	
REML, Hartung–Knapp	11	0.16 (0.04 to 0.28)	27.6	
DL, Wald-type confidence interval	11	0.15 (0.01 to 0.30)	27.6	

Analysis	*k*	SMD (95% CI)	I^2 (%)	*p* for difference
Common-effect model	11	0.16 (0.07 to 0.25)	—	
Box-Cox estimation of means and SDs from medians	11	0.26 (0.04 to 0.47)	44.7	
Studies reporting means and SDs only	5	0.49 (0.22 to 0.75)	0.0	
Studies reporting medians only (converted)	6	0.08 (−0.11 to 0.27)	23.3	
Excluding moderate or high risk of bias	10	0.17 (0.07 to 0.27)	0.0	
Excluding mixed-age cohorts	10	0.17 (0.07 to 0.27)	0.0	
Normal-karyotype cohorts only	5	0.16 (−0.20 to 0.53)	33.9	
Excluding Farhat 2026 (largest study)	10	0.16 (−0.09 to 0.40)	34.0	
Ratio of means (DL, Hartung–Knapp)†	11	1.33 (0.98 to 1.81)	49.7	

Notes: All subgroup analyses were prespecified. Estimates are SMDs (Hedges' g) unless stated otherwise; p values test the difference between subgroups (random effects). Single-study subgroups (age group and risk of bias) use Wald-type intervals and do not allow a meaningful test of subgroup difference. DL, DerSimonian–Laird; REML, restricted maximum likelihood. †Ratio of means, not an SMD. The p value for difference is not shown for age group and risk of bias because each contrast rests on one study.

Studies that assessed NPM1 with a type A-specific assay or by immunohistochemistry contributed 8.2% of the weight to the primary analysis and at most 33.9% to any secondary analysis (CD34 positivity), and exclusion of mixed-age cohorts gave an estimate of 0.17 (95% CI 0.07 to 0.27) for the primary outcome.

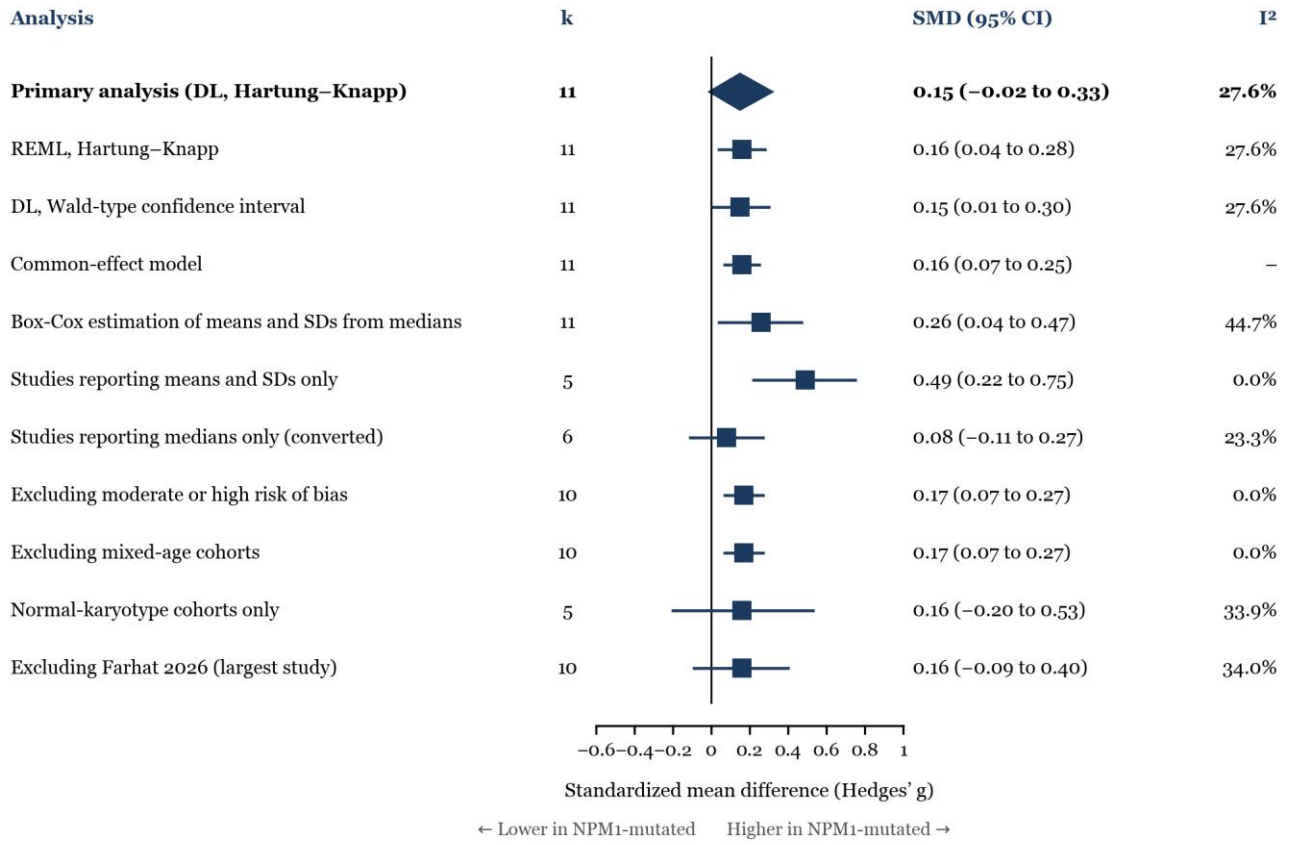


Figure 6. Sensitivity analyses of the primary outcome: pooled standardized mean differences under alternative estimators, conversions of medians and study sets. The dark diamond is the primary analysis. DL, DerSimonian–Laird; REML, restricted maximum likelihood.

3.9 Small-study effects

The funnel plot for white blood cell count was symmetrical (Egger intercept 0.12, *p*=0.84), as illustrated in Figure 7; trim-and-fill imputed one study and gave an adjusted SMD of 0.13 (95% CI −0.07 to 0.33). Harbord's test gave *p*=0.06 for FLT3-ITD, below the 0.10 threshold used for rating down certainty, and showed no evidence of small-study effects for female sex (*p*=0.17), FAB M4/M5 morphology (*p*=0.16) or complete remission (*p*=0.97). For FLT3-ITD, the asymmetry reflected weaker or inverse associations in several smaller cohorts and among the strongest associations in the large registry cohorts, which is the opposite of the pattern expected from selective publication of small positive studies.

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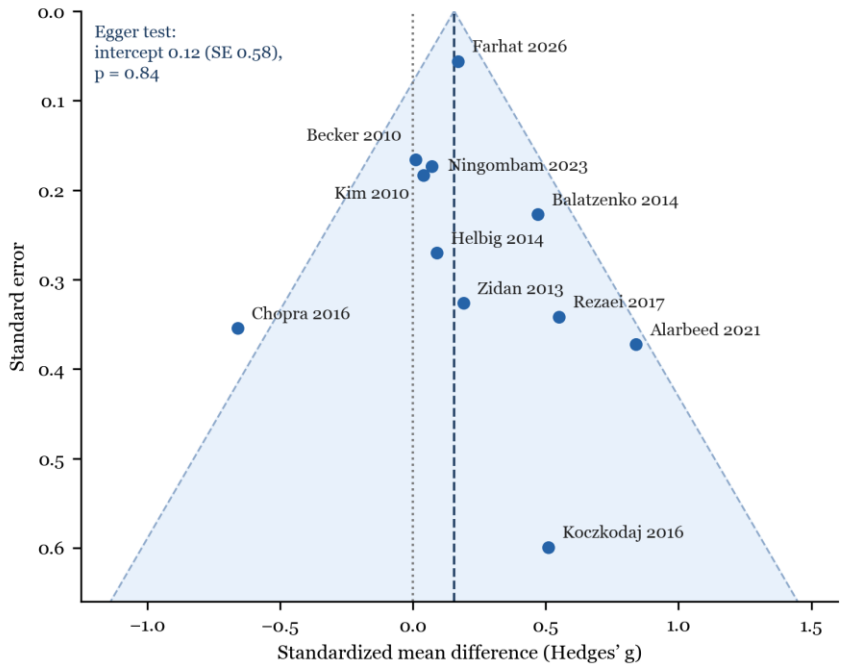


Figure 7. Funnel plot of study standardized mean differences in white blood cell count against their standard errors. The dashed line marks the pooled estimate, the dotted line no difference and the shaded region the pseudo 95% confidence limits.

4. Discussion

4.1 Principal findings

This meta-analysis of 28 studies and 7,126 patients showed that NPM1-mutated AML differed from wild-type disease in several presenting features. The odds of female sex were about one and a half times higher, and the odds of FAB M4/M5 morphology about two times higher. The odds of FLT3-ITD were nearly three times higher and the odds of a normal karyotype about seven times higher, while the odds of CD34 positivity were about one quarter as high. As crude proportions, these differences were 53.7% versus 43.1% for female sex, 40.9% versus 19.7% for monocytic morphology, 40.8% versus 16.6% for FLT3-ITD, 78.8% versus 29.6% for a normal karyotype and 38.6% versus 72.7% for CD34 positivity. Marrow and blood blast percentages were also higher. The white blood cell count, by contrast, showed only a small difference that was compatible with none in the primary analysis.

The certainty of evidence was moderate for female sex and normal karyotype. It was low for the white blood cell count, FAB M4/M5 morphology, CD34 positivity and complete remission, and very low for platelet count, hemoglobin, bone marrow blasts, peripheral blood blasts, age and FLT3-ITD. The findings therefore describe tendencies that make NPM1 mutation more or less likely; they are not features that define it. Complete remission was more frequent in NPM1-mutated AML. It reflects response to treatment rather than the presenting phenotype and is discussed separately.

4.2 Comparison with previous evidence

Large cooperative-group and registry cohorts had described similar associations,[25,40,54] and the pooled estimates were consistent with them in populations not represented in the original reports. The excess of women agreed with a sex-stratified analysis of 1,726 adults treated on Alliance protocols, validated in 954 patients of the German AML Cooperative Group. In that analysis, women more often had NPM1 mutations, FLT3-ITD and a normal karyotype.[61] Driver-mutation frequencies changed with age.[3] Asian, African and Middle Eastern cohorts in this review also reported lower crude proportions of NPM1-mutated cases than European series,[42,48,59] in line with a recent synthesis that estimated an NPM1 frequency of 19% among Iranian patients with AML.[34] Whether the phenotype itself differs by region could not be tested for the categorical outcomes. The strong association with a normal karyotype reflects the near mutual exclusivity of NPM1 mutations with recurrent translocations.[8] Previous syntheses of NPM1-mutated AML concentrated on the prognostic weight of co-mutations,[33] and the present review complements them by describing what distinguishes the genotype before treatment.

4.3 Biological plausibility and physical signs

Single-cell and multi-omic studies showed that NPM1-mutated leukemic cells span committed myeloid maturation states instead of a stem-like arrest. Their transcriptional subtypes differ in stem-cell signature and in the stage of maturational skewing.[12,13] This fits the monocytic morphology and CD34 negativity observed here. The same program appears in a characteristic immunophenotype, CD34 and HLA-DR double negativity, which resembles acute promyelocytic leukemia and carries a risk of early vascular complications.[26,62–64] Monocytic differentiation was also linked to tissue tropism, including leukemia cutis and extramedullary disease.[65,66] The excess of gum hypertrophy in one cohort agrees with this tropism. The physical signs reported by the included studies, however, did not show a consistent difference in organomegaly, lymphadenopathy or extramedullary involvement. In the included studies the examination findings of NPM1-mutated AML were therefore not distinctive, and the laboratory, morphological and cytogenetic features carry most of the information.

4.4 Age

The absence of an age difference deserves comment. One included cohort enrolled both children and adults; NPM1 mutation was found in 25.8% of adults but in 8.8% of children.[44] Age-stratified cooperative-group analyses likewise showed that driver-mutation frequencies change across age groups.[3] Most included cohorts, however, enrolled adults within a restricted age band (for example 60 years or younger, or 60 years and older), and mean age differed little within these bands. The age distribution of the genotype is

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therefore better described by age-specific frequencies than by a difference in mean age.

4.5 White blood cell count, FLT3-ITD and confounding

The small overall difference in white blood cell count should be read together with the strong association with FLT3-ITD. FLT3-ITD itself raises the white blood cell count. It was present in 40.8% of NPM1-mutated cases but in only 16.6% of wild-type cases, so part of any excess in white blood cell count may be explained by co-occurring FLT3-ITD. Studies of hyperleukocytosis consistently found NPM1 and FLT3-ITD enriched among patients with the highest counts.[67–69] Few studies tabulated white blood cell counts by the four NPM1/FLT3-ITD genotypes with dispersion, and this mediation could not be tested formally.

The same reasoning applies to the other outcomes, with different consequences. Mediation by FLT3-ITD would inflate the blast differences attributed to NPM1, so the blast estimates are more likely to overstate than to understate the effect of NPM1 mutation alone. For the karyotype-related outcomes, the comparator differed between study types. In cohorts with all karyotypes, wild-type AML included patients with recurrent translocations and complex karyotypes. In normal-karyotype cohorts the comparison was between genotypes with similar cytogenetics. FAB subtype and CD34 expression differ between cytogenetic groups, so part of the morphological and immunophenotypic differences in unrestricted cohorts reflects the composition of the comparator and not NPM1 mutation itself. All comparisons were unadjusted, and none of these effects could be removed with the published data.

Clinically, the higher blast burden and the concentration of hyperleukocytosis in NPM1/FLT3-ITD co-mutated disease mean that leukostasis, tumor lysis and coagulopathy should be anticipated in these patients.[68] FLT3-ITD testing should also accompany NPM1 testing, because the combination determines ELN risk and eligibility for FLT3 inhibitors.[10,17]

4.6 Platelet count and hemoglobin

The platelet estimate (SMD 0.26 (−0.06 to 0.59)) pointed towards higher counts in NPM1-mutated AML, in line with an included cohort that reported a higher median platelet count with NPM1 mutation.[44] The confidence interval, however, included no difference, heterogeneity was high (I^2 78.1%) and the prediction interval spanned both directions. The lack of a statistically significant difference is therefore not evidence that platelet count is unrelated to NPM1 status, and a modest association may exist in some populations. Hemoglobin showed a smaller and equally uncertain difference. Neither index can be used to infer NPM1 status in an individual patient.

4.7 Complete remission as a treatment-dependent outcome

The higher remission rate agreed with the chemosensitivity of the genotype, although response to venetoclax-based therapy differed with monocytic phenotype and co-mutations.[19,70] Remission depends on induction intensity and supportive care. It also depends on the composition of the comparator, which in unrestricted cohorts included adverse-risk karyotypes and, in some cohorts, acute promyelocytic leukemia treated with differentiation therapy. The pooled odds ratio should therefore be read as a description of outcome in the treated cohorts and not as a feature of the phenotype. Its interpretation depends on FLT3-ITD status, which separates favorable from intermediate ELN risk in NPM1-mutated AML.[10,15]

4.8 Heterogeneity and the conversion of medians

Heterogeneity was low for the primary outcome and for female sex, but high for blast percentages, FAB morphology, FLT3-ITD and remission. Several explanations are likely: differences in case mix (inclusion of acute promyelocytic leukemia, therapy-related or secondary AML and children), in FAB classification practice, in FLT3-ITD assay sensitivity and in induction regimens. The study-level patterns described in the Results fit these explanations. They were identified post hoc, however, and could not be tested formally with so few studies per outcome.

White blood cell counts are extremely skewed, so the conversion of medians deserves particular attention. In the largest older-adult cohort of the primary analysis, the median white blood cell count was almost four times higher in NPM1-mutated AML, yet the converted means were nearly identical, because the conversion was driven by the extreme maximum of the wild-type range. Estimators that assume approximate symmetry thus tend to shrink differences towards zero when a few very high counts dominate the range; the bias runs towards no difference. Box-Cox estimation, which accommodates skewness, and the analysis restricted to reported means both gave larger estimates. The ratio of means, which compares groups on the log scale, pointed the same way. The primary estimate may therefore underestimate the true difference in white blood cell count. The larger effect in studies reporting means must still be read with caution, because those studies were all small and small studies may overstate differences.

4.9 Applicability to Indonesian practice

In Indonesia, conventional cytogenetics, flow cytometry and immunohistochemistry are more widely available than sequencing, and molecular characterization has been reported from few centers.[6] The present findings suggest a practical sequence for such settings. Patients with FAB M4/M5 morphology, CD34-negative blasts and a normal karyotype, particularly women, are more likely to carry NPM1 mutation. They can be prioritized for molecular testing when capacity is limited. Immunohistochemistry for cytoplasmic nucleophosmin on trephine biopsies offers an inexpensive surrogate where molecular testing is delayed.[49,57] The CD34-negative, HLA-DR-negative variant of NPM1-mutated AML mimics acute promyelocytic leukemia and is associated with coagulopathy, so PML-RARA must be excluded rapidly before such a phenotype is attributed to NPM1 mutation.[62,63]

Two inexpensive refinements could strengthen this prioritization. Flow cytometry panels that already include CD34 and HLA-DR identify the double-negative immunophenotype, which was associated with NPM1 and FLT3-ITD mutations in non-promyelocytic AML.[26] Review of blast morphology for cup-like nuclei helped to predict NPM1 mutation in a cohort with normal karyotype.[27] Neither replaces genotyping. Both can be recorded routinely and audited against molecular results as testing capacity grows.

The absence of these features does not exclude NPM1 mutation, and the combination has not been validated as a decision rule; molecular testing therefore remains the standard wherever it is available. Patients presenting with hyperleukocytosis carry a high early mortality in Indonesian practice.[5] They should be tested for both NPM1 and FLT3-ITD, because the co-mutated genotype is concentrated in this group. Indonesian data could not be included in this review, so generalization rests on neighboring Southeast Asian and South Asian cohorts with similar case mix. To support future local studies, clinicians and laboratories should record the white blood cell count, platelet count, hemoglobin, marrow and blood blast percentages, FAB subtype, CD34 and HLA-DR expression, karyotype, FLT3-ITD status, organomegaly and extramedullary disease for every patient tested for NPM1. They should report these by genotype, with means and SDs.

4.10 Strengths and limitations

Strengths include a search of four databases that covers regional journals, a large multinational sample with considerable representation from Asia and the Middle East, and prespecified effect measures that allow features measured on different scales to be compared. Extensive prespecified sensitivity analyses addressed the data-conversion step, certainty of evidence was graded transparently, and the analyses are fully reproducible.

Several limitations apply. First, 58 reports that may have been eligible, including several large cohorts and one report from Indonesia, could not be retrieved in full. Their abstracts described associations in the same directions, so their absence more probably reduced precision than created the associations, but it may have altered the magnitude of the pooled estimates. Second, one reviewer performed screening and extraction, with complete verification of every decision and value, instead of two independent reviewers; this raises the risk of undetected errors. Third, only English-language reports were eligible, and cohorts published in national-language journals may have been missed. Fourth, many studies reported medians that had to be converted to means. The direction of the primary result was stable, but its magnitude depended on the estimator. Fifth, all comparisons were unadjusted, and confounding by co-mutations (particularly FLT3-ITD) and by karyotype cannot be excluded. Sixth, several small studies included children, acute promyelocytic leukemia or exposure defined by a type A-specific assay or immunohistochemistry, which tends to bias comparisons towards no difference, and some counts were back-calculated from percentages.

Seventh, the adapted Newcastle–Ottawa Scale does not capture confounding by co-mutations, and its comparability domain distinguished studies mainly by karyotype restriction. Eighth, certainty started at high; had observational evidence started at low, every outcome would have been rated very low. Ninth, twelve outcomes were analyzed without adjustment for multiplicity, so isolated significant findings among the secondary outcomes should be interpreted cautiously. Tenth, outcome definitions varied between studies, particularly for CD34 positivity and complete remission. Physical signs were summarized only narratively, because they were not prespecified and few studies reported them.

4.11 Implications for practice and research

For practice, the combination of female sex, monocytic morphology, CD34 negativity and a normal karyotype increases the likelihood of NPM1 mutation. It can be used to prioritize NPM1 and FLT3-ITD testing where molecular capacity is scarce,[71] in line with recent work on image-based and morphological prediction.[27–29] Pooled odds ratios from different studies cannot be combined into a probability for an individual patient. The white blood cell count alone is not a reliable pointer. For research, presenting features should be reported by NPM1 and FLT3-ITD genotype, with means and SDs or individual patient data. They should be adjusted for co-mutations and karyotype and combined in multivariable prediction models validated in Indonesian and other underrepresented populations.

5. Conclusion

NPM1-mutated AML differed from wild-type disease at presentation. It was more often seen in women, with monocytic morphology, CD34-negative blasts, a normal karyotype, frequent FLT3-ITD co-mutation and higher marrow and blood blast percentages. The difference in white blood cell count was small and uncertain. Platelet count, hemoglobin, age and physical signs did not clearly distinguish the genotypes. Complete remission after induction was more frequent, but this reflects treatment response and not the presenting phenotype. Certainty of evidence was moderate for female sex and normal karyotype and low or very low for the other outcomes. These features can guide prioritization of NPM1 testing in resource-limited settings. They cannot replace molecular diagnosis. Prospective cohorts that report presenting features by NPM1 and FLT3-ITD genotype, including Indonesian patients, are needed to refine these estimates.

Declarations

Ethics approval and consent to participate

Not applicable. This review analyzed published aggregate data only.

Consent for publication

Not applicable.

Use of artificial intelligence

None declared.

Author contributions

D.P.: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. R.A.: Conceptualization, Supervision, Validation, Writing – review & editing. Both authors approved the final manuscript.

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Conflict of interest

The authors declare no competing interests.

Data availability

All data are available from corresponding author on reasonable request.

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