International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

# Prognostic Impact of c-KIT and FLT3 Mutations in Core-Binding Factor AML: Evidence of Inferior Outcomes in t(8;21) – An Updated Systematic Review and Meta-Analysis

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## ADMINISTRATIVE INFORMATION

**Support -** None.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202610076

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 January 2026 and was last updated on 22 January 2026.

## INTRODUCTION

**Review question / Objective** Among patients with CBF-AML, what is the prognostic impact of c-KIT and FLT3 mutations on survival and relapse-related outcomes?

**Rationale** Core-binding factor acute myeloid leukemia (CBF-AML) is a distinct AML subtype defined by the t(8;21) and inv(16)/t(16;16) cytogenetic abnormalities, accounting for about 15–20% of adult cases. Although traditionally considered a favorable-risk leukemia due to good responses to cytarabine-based therapy, outcomes vary, and many patients still relapse. This heterogeneity has led to interest in co-occurring mutations; particularly c-KIT and FLT3, which may influence prognosis. Some studies suggest these mutations increase relapse risk, while others do not show a consistent adverse effect, leaving their true prognostic significance uncertain. Given the lack of consensus and the growing emphasis on molecularly informed risk stratification in AML, a systematic review and meta-analysis is needed to synthesize the available evidence. Clarifying the true prognostic impact of c-KIT and FLT3 mutations in CBF-AML is crucial, as these lesions occur within a group historically regarded as favorable risk but still marked by non-negligible relapse rates. A better understanding of these mutations could refine current risk classification systems, inform post-remission therapy choices, and shape the design of future clinical trials.

**Condition being studied** CBF-AML based on the presence of c-KIT or FLT3 mutations.

## METHODS

**Search strategy** PubMed, EMBASE and Cochrane Library were searched for all relevant articles published from inception to 31 December 2024 using search terms related to CBF-AML, c-KIT, and FLT3 mutations. No language or date restriction was applied. In addition, a manual search of

references to relevant literature was conducted to avoid the omission of any potential articles.

Database MeSH terms
1. PubMed:
("Leukemia, Myeloid, Acute"[MeSH] OR "acute myeloid leukemia"[tiab] OR AML[tiab])
AND ("core binding factor"[tiab] OR "core-binding factor"[tiab] OR CBF[tiab]
OR "t(8;21)"[tiab] OR RUNX1-RUNX1T1[tiab] OR AML1-ETO[tiab]
OR "inv(16)"[tiab] OR "t(16;16)"[tiab] OR CBFB-MYH11[tiab])
AND (KIT[tiab] OR c-KIT[tiab] OR FLT3[tiab] OR "FLT3-ITD"[tiab] OR "FLT3-TKD"[tiab]
OR NPM1[tiab] OR DNMT3A[tiab] OR ASXL1[tiab] OR NRAS[tiab]
OR cytogenetic*[tiab] OR karyotyp*[tiab] OR "chromosomal abnormal*"[tiab])

2. Embase:
('acute myeloid leukaemia'/exp OR 'acute myeloid leukaemia':ab,ti OR AML:ab,ti)
AND ('core binding factor':ab,ti OR 'core-binding factor':ab,ti OR CBF:ab,ti
OR 't(8;21)':ab,ti OR 'RUNX1-RUNX1T1':ab,ti OR 'AML1-ETO':ab,ti
OR 'inv(16)':ab,ti OR 't(16;16)':ab,ti OR 'CBFB-MYH11':ab,ti)
AND ('kit'/exp OR kit:ab,ti OR 'c-kit':ab,ti
OR 'flt3'/exp OR flt3:ab,ti OR 'flt3-itd':ab,ti OR 'flt3-tkd':ab,ti
OR npm1:ab,ti OR dnmt3a:ab,ti OR asxl1:ab,ti OR nras:ab,ti
OR cytogenetic*:ab,ti OR karyotyp*:ab,ti OR 'chromosomal abnormal*':ab,ti)

3. Cochrane Library:
S1 – Acute myeloid leukemia
"Acute myeloid leukaemia" OR "acute myeloid leukemia" OR AML
S2 – Core-binding factor / CBF AML
"Core binding factor" OR "core-binding factor" OR CBF
S3 – CBF-defining cytogenetics
"t(8;21)" OR RUNX1-RUNX1T1 OR AML1-ETO
OR "inv(16)" OR "t(16;16)" OR CBFB-MYH11
S4 – Gene mutations
KIT OR "c-KIT" OR FLT3 OR "FLT3-ITD" OR "FLT3-TKD"
OR NPM1 OR DNMT3A OR ASXL1 OR NRAS
S5 – Cytogenetics
cytogenetic OR cytogenetics OR karyotype OR karyotypic
OR chromosomal abnormalities OR chromosomal abnormalities
Final combination
S1 AND (S2 OR S3) AND (S4 OR S5).

**Participant or population** The study must focus on adult patients of 18 years or older at diagnosis and report any of the following outcomes: overall survival (OS), disease-free survival (DFS), event-free survival (EFS), leukemia-free survival (LFS), relapse-free survival (RFS), or cumulative incidence of relapse (CIR). Studies that reported hazard ratios (HR) and associated 95% confidence intervals (CI) of these outcomes would be included in the meta-analysis.

**Intervention** NA.

**Comparator** NA.

**Study designs to be included** Retrospective and Prospective cohort studies.

**Eligibility criteria** Included studies must be observational studies that evaluated the survival outcomes of patients with CBF-AML based on the presence of c-KIT or FLT3 mutations. The study must focus on adult patients of 18 years or older at diagnosis and report any of the following outcomes: overall survival (OS), disease-free survival (DFS), event-free survival (EFS), leukemia-free survival (LFS), relapse-free survival (RFS), or cumulative incidence of relapse (CIR). Studies that reported hazard ratios (HR) and associated 95% confidence intervals (CI) of these outcomes would be included in the meta-analysis. Case series, case reports, letters, opinions, narrative reviews, conference abstracts, dissertations, and other non-original articles were excluded.

**Information sources** PubMed, EMBASE and Cochrane Library were searched for all relevant articles published from inception to 31 December 2024 using search terms related to CBF-AML, c-KIT, and FLT3 mutations. No language or date restriction was applied. In addition, a manual search of references to relevant literature was conducted to avoid the omission of any potential articles. The complete list of search terms, including database-specific MeSH terms, is provided in Supplementary Table 1. Two reviewers (R.M., R.H.) independently screened each study using the Rayyan systematic review management website (https://www.rayyan.ai/). Disagreements between the two reviewers were resolved through discussion with the senior author (S.M.).

**Main outcome(s)** Outcomes of interest include OS, DFS, EFS, LFS, RFS, and CIR. OS is defined as the time from diagnosis to death from any cause, while EFS is defined as the time from diagnosis to relapse, treatment failure, or death, whichever happens first. RFS, LFS, and DFS are

defined as the time from diagnosis to leukemic relapse or death. CIR is defined as the proportion of patients who developed leukemic relapses within a specific time period, per the study.

**Additional outcome(s)** NA.

**Data management** A standardized data collection form was utilized to aggregate the data as follows: first author's last name, year of publication, the country where the study was conducted, age, sex, number of patients with secondary AML, chromosomal aberration subtype (t(8;21) or inv(16)), mutational subtype (c-KIT, FLT3-ITD, FLT3-TKD), study design, and the number of patients with and without each chromosomal aberration and mutational subtype.

**Quality assessment / Risk of bias analysis** The quality of the studies included was independently assessed by two authors (H.K. and Y.E.) using the Methodological Standard for Epidemiological Research (MASTER) scale V1.01, which comprised 36 safeguards under seven methodological standards. These domains were 1) equal recruitment, 2) equal retention, 3) equal ascertainment, 4) equal implementation, 5) equal prognosis, 6) sufficient analysis, and 7) temporal precedence. Any disagreements were resolved by discussion with the senior author (S.M.).

**Strategy of data synthesis** We performed all statistical analyses using R version 4.3.2 software (Vienna, Austria) and "meta" version 7.0-0. The generic inverse variance method was utilized to combine point estimates and 95% CI to calculate the pooled HR for OS, RFS, and CIR. DFS, EFS, and LFS were used as an estimate for RFS if the study did not report RFS (9). The random-effects model was implemented instead of the fixed-effects model, as interstudy heterogeneity is likely to occur among the included studies. Cochran's Q test and I^2^ statistic were implemented for statistical heterogeneity (10). I^2^ values of 0–25%, 26–50%, 51–75%, and 76–100% signify insignificant, low, moderate, and high heterogeneity, respectively.

**Subgroup analysis** Subgroup analyses were conducted based on the chromosomal abnormality (t(8;21) vs. inv(16)) and concomitant gene mutation (FLT3-ITD and FLT3-TKD). A sensitivity analysis was also performed for c-KIT exon 17 mutational status. The presence of publication bias was determined via direct visualization of the funnel plots.

**Sensitivity analysis** A sensitivity analysis was also performed for c-KIT exon 17 mutational status. The presence of publication bias was determined via direct visualization of the funnel plots.

**Language restriction** No language restriction.

**Country(ies) involved** United States, Qatar, Canada.

**Other relevant information** NA

**Keywords** CBF acute myeloid leukemia, c-kit mutation, FLT3 mutation, prognosis.

**Dissemination plans** Publication in open-access peer-reviewed journals and presentation of findings at major clinical and scientific conferences.

**Contributions of each author**

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