

Efficacy and safety of second-generation FLT3 inhibitors in acute myeloid leukemia: A systematic review and meta-analysis of randomized controlled trials

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Abstract. Acute myeloid leukemia (AML) is one of the most frequent forms of acute leukemia and the second most common leukemia subtype in adults. In 2020, the incidence of AML in the United States was estimated to be ~4 cases per 100,000 adults. The FMS-like tyrosine kinase 3 (*FLT3*) internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation are major prognostic indicators of AML. They are more frequently observed in younger AML patients (aged <60 years), likely due to their association with *de novo*. Additionally, these mutations have a stronger negative impact on survival in younger patients. Therefore, quizartinib and gilteritinib are second-generation FLT3 inhibitors that are frequently applied for treating patients with AML. However, to the best of our knowledge, few studies have compared the efficacy of second-generation FLT3 inhibitors for AML

treatment. Therefore, the present study conducted a comprehensive search for studies on the efficacy and safety of FLT3 inhibitors across PubMed, Embase, the Cochrane Library and ClinicalTrials.gov. The search criteria were limited to randomized controlled trials (RCTs). Subsequently, a meta-analysis was performed on a total of five randomized controlled trials, involving 1,543 participants in total, using a random-effects model. In each RCT, compared to the salvage chemotherapy used in the control group, the groups that received second-generation FLT3 inhibitors experienced significant improvements in overall survival (hazard ratio, 0.717; 95% CI, 0.604-0.850; $P < 0.001$). In addition, overall survival was found to be consistent across the different types of second-generation FLT3 inhibitors used and different types of AML. The risks associated with a prolonged heart-rate corrected QT interval (QTc) interval were next evaluated. Compared with the salvage chemotherapy used in the control group, the second-generation FLT3 inhibitor group exhibited a significantly higher risk of having a prolonged QTc interval (odds ratio, 6.311; 95% CI, 3.061-13.013; $P < 0.001$). In conclusion, these findings suggest that second-generation FLT3 inhibitors can improve the overall survival of patients with AML. However, QTc prolongation is a potential adverse effect that should be monitored.

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Introduction

Acute myeloid leukemia (AML) is the most frequent form of acute leukemia and the second most common leukemia subtype in adults (1). In 2020, the incidence of AML in the United States was estimated to be ~4 cases per 100,000 adults (2). Over the past two decades, results from studies has deepened the understanding whilst providing valuable insights into the genomics and pathophysiology of AML. In turn, these insights

have assisted in improvements in prognostic assessment techniques, which have and contributed to the development of novel therapeutic strategies for AML, including the use of second-generation FLT3 inhibitors and venetoclax (targeting Bcl-2) (3,4). In particular, FMS-like tyrosine kinase 3 (*FLT3*) gene mutation has been identified to be a major prognostic indicator for AML (5,6).

Internal tandem duplications (ITDs) in the *FLT3* gene have been detected in ~25% newly diagnosed AML cases, with ~7% *FLT3* mutations manifest as tyrosine kinase domain (TKD) point mutations (7,8). FLT3-ITD mutations are associated with an increased risk of treatment resistance to chemotherapy, particularly in patients receiving chemotherapy without an FLT3 inhibitor. By contrast, individuals with FLT3-TKD mutations may have a lower disease burden at diagnosis and they exhibit a superior response to chemotherapy (4,9). However, this does not necessarily imply that FLT3-TKD mutations will not develop chemotherapy resistance. Previous studies have shown that although FLT3-TKD mutations may respond better to chemotherapy initially, resistance can still develop over time, particularly in the context of clonal evolution or the acquisition of additional mutations during the course of the disease (10,11).

FLT3 inhibitors are a class of tyrosine kinase inhibitors and are categorized as first- and second-generation inhibitors, with the inhibitors categorized on the basis of their specificity and potency against the kinase (9). Midostaurin and sorafenib are examples of first-generation FLT3 inhibitors, whereas quizartinib and gilteritinib are examples second-generation inhibitors. Second-generation inhibitors were designed with structural modifications to improve selectivity and efficacy against mutant FLT3. These inhibitors bind more specifically to the active or inactive conformations of the FLT3 kinase domain, particularly targeting FLT3-ITD and TKD mutations. Specifically, quizartinib is tailored to inhibit mutant FLT3 while minimizing off-target effects on other kinases, whereas gilteritinib is effective against both FLT3-ITD and resistance-conferring D835 mutations, which are common in relapsed/refractory AML (12-15). Quizartinib and gilteritinib are both second-generation FLT3 inhibitors used to treat FLT3-mutated AML, but they target different forms of the mutation. Quizartinib is a type II inhibitor, meaning it primarily targets the FLT3-ITD mutation in the inactive conformation of the FLT3 kinase. By contrast, gilteritinib is a type I inhibitor, which is effective against both FLT3-ITD and FLT3-TKD mutations in their active forms, providing broader activity and potentially reducing the likelihood of resistance due to TKD mutations (16).

To the best of our knowledge, only one study (17) demonstrated improved overall survival in patients with relapsed or refractory AML, highlighting the efficacy of second-generation FLT3 inhibitors for AML treatment. Therefore, the present meta-analysis was performed to compare the clinical efficacy of such second-generation inhibitors in patients with AML in terms of overall survival. Additionally, the safety profiles of second-generation FLT3 inhibitors in relation to cardiac disorders, anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia were compared. For clinical practice, this study suggests that second-generation FLT3

inhibitors are the optimal choice for treating patients with FLT3-mutated AML.

Materials and methods

Study search and selection. A comprehensive search for relevant studies was conducted across multiple databases, including PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://ovidsp-dcl-ovid-com.lib.chimeil.org.tw:8443/ovid-new-a/ovidweb.cgi>), the Cochrane Library (<https://www.cochranelibrary.com/>), Clinicaltril (<https://clinicaltrials.gov/>) and Medline (https://www.nlm.nih.gov/medline/medline_overview.html), from inception until April 28, 2024. To identify relevant studies, the following key words were used: ‘Quizartinib OR AC220’, ‘Gilteritinib OR ASP2215’ and ‘Acute Myeloid Leukemia’. The present study exclusively considered randomized controlled trials (RCTs) assessing the efficacy and safety of second-generation FLT3 inhibitors. Crenolanib was not considered for the present study due to the absence of randomized controlled trial data. The present meta-analysis strictly adhered to including only RCTs to ensure the reliability and validity of the results. Without RCTs, the efficacy and safety of crenolanib in comparison to other second-generation FLT3 inhibitors could not be accurately assessed. Details regarding the search strategy for the present systematic review and meta-analysis are provided in Table SI. In total, two authors (TSW and SYH) conducted a thorough, independent screening and assessment of each study. In cases of discrepancy regarding the inclusion of an article, a third author (CMC) was consulted until a consensus was reached.

Inclusion and exclusion criteria. The population, intervention, comparison and outcome (PICO) framework for the present meta-analysis was as follows: i) P, human participants with AML and FLT3 mutations; ii) I, treatment with second-generation FLT3 inhibitors; iii) C, control group; and iv) O, overall survival time, heart-rate corrected QT interval (QTc) prolongation, cardiovascular disorders, anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia.

In addition, the reference lists of the relevant articles were manually reviewed to identify possible additional eligible papers. No language restrictions were applied. RCTs meeting the following criteria were included: i) Inclusion of patients with a diagnosis of AML; ii) use of a second FLT3 inhibitor as monotherapy or in combination with other chemotherapy as the intervention; iii) reporting study outcomes related to overall survival; and iv) reporting study outcomes related to QTc prolongation or cardiovascular disorders, anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia.

The following studies were excluded from the present review and meta-analysis: i) non-RCTs; ii) studies focusing on pharmacokinetic and pharmacodynamic analyses; iii) *in vitro* or animal experimental studies; iv) studies lacking a control group; and v) studies with participant overlap with previously published trials.

Study quality and outcome assessment. To assess the methodological quality of the included studies, the Cochrane risk of bias tool for randomized trials (version 2, RoB 2, <https://sites>.

google.com/site/riskofbiastool/welcome/rob-2-0-tool) was employed. This tool can be used to evaluate study quality in the following six key domains: Randomization process; adherence to intervention; handling of missing outcome data; outcome measurement; selective reporting; and overall risk of bias (18).

In the present study, the primary outcome was the efficacy of second-generation FLT3 inhibitors in improving overall survival. The exclusion of RFS and DFS from the present primary analysis was primarily due to the lack of available data on these outcomes in the studies included. The secondary outcomes included the risks of cardiovascular events, such as atrial fibrillation, cardiac failure, cardiac arrest, myocardial infarction, acute myocardial infarction and prolonged QT interval on electrocardiogram. Additionally, common adverse events, such as anemia, neutropenia, thrombocytopenia, diarrhea, pneumonia and event-free survival, were also evaluated. Overall survival is defined as the time from the initiation of treatment until death from any cause. It considers only one endpoint-mortality. Event-free survival, on the other hand, is defined as the time from the initiation of treatment until the occurrence of any event that signifies treatment failure, such as relapse, progression of the disease or mortality from any cause (19). It captures a broader range of outcomes, including both death and significant clinical events that indicate the treatment is no longer effective. To account for cells with zero events and to facilitate calculations, 0 was substituted with the value of 0.5. The aforementioned outcomes were quantified using odds ratios (ORs) (20).

Data extraction and general guidelines. In total, two authors (TSW and SYH) independently performed data extraction. The following data were extracted from each study: i) Name of the first author; ii) publication year; and iii) participant demographics, including age, sample size, specific second-generation FLT3 inhibitor used in treatment, outcome measures, efficacy in terms of overall survival and data on the risk of cardiovascular events and QT prolongation on electrocardiogram. The present meta-analysis was performed adhering to the latest version of the PRISMA 2020 guidelines (21). The present study was registered in INPLASY under the registration no. INPLASY202450141. It was not required to obtain ethics review board approval or participant informed consent.

Statistical analysis. Because of the heterogeneity in the types of second-generation FLT3 inhibitors used across the included studies, a random-effects model was used for the present meta-analysis (22). The meta-analysis was conducted using the Comprehensive Meta-Analysis software (version 4; Biostat, Inc.). $P < 0.05$ was considered to indicate a statistically significant difference.

The primary study outcome was quantified by estimating hazard ratios (HRs) with 95% CIs, whereas ORs with their corresponding 95% CIs were calculated to analyze the secondary outcomes. The heterogeneity among the studies was assessed using the I^2 -values. I^2 -values of 25, 50 and 75% were considered to indicate low, moderate and high heterogeneity, respectively (23).

In addition, subgroup analyses according to the type of AML and the specific second-generation FLT3 inhibitor used were performed. Meta-regression analyses were performed to investigate the association between the impact of treatment effects based on age and overall survival outcomes, which were determined by the aforementioned parameters. To ensure the reliability of the meta-analysis, sensitivity analyses were conducted using the one-study removal approach. In this approach, each trial is removed from the analysis to determine whether exclusion of any specific trial leads to a significant change in the summary effect size experienced a statistically significant alteration when any specific trial was excluded. This suggests that the exclusion of individual trials can notably impact the overall results (20). Potential publication bias was assessed using Comprehensive Meta-Analysis software (version 4; Biostat, Inc.) in accordance with the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions (24). Funnel plots were created and visually examined. In this study, bias was assessed using funnel plots. Bias was defined as the asymmetry of the funnel plot, which would suggest that smaller studies with non-significant results were less likely to be published, leading to a potential over-estimation of the treatment effect. A symmetrical funnel plot would indicate the absence of such bias (25).

Results

Study selection. Fig. 1 illustrates the PRISMA flowchart depicting the literature search process (15). After elimination of duplicate articles and exclusion of non-relevant articles through title and abstract screening, 17 articles remained. Among these, 12 were excluded for the following reasons: i) 1 was related to dose analysis (26); ii) 4 focused on pharmacokinetics (27-30); iii) 1 lacked the salvage chemotherapy control group, the commonly used regimens include low-dose cytarabine (LoDAC), mitoxantrone, etoposide and intermediate-dose cytarabine (MEC) or fludarabine, cytarabine and granulocyte colony-stimulating factor (G-CSF) with idarubicin (FLAG-IDA) (31); iv) 1 was a protocol study (32); v) 3 had overlapping participant populations (32-35); and vi) 1 included patients achieving the first complete remission (34). A total of 5 RCTs were included in the final analysis (37-41).

The meta-analysis incorporated five eligible RCTs, involving a collective cohort of 1,543 participants receiving second-generation FLT3 inhibitors. These participants encompassed individuals diagnosed with relapsed or refractory FLT3-ITD AML (37,40) or with *de novo* or secondary AML (38), in addition to those with newly diagnosed FLT3-mutated AML (39,41). The salvage chemotherapy regimens encompassed various treatment protocols, including mitoxantrone, etoposide and cytarabine; fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin; low-dose cytarabine; and azacitidine. Detailed information from the retrieved trials is presented in Table I.

Quality assessment of included studies. Regarding the overall methodological quality of the included studies, the results revealed that 20.0% of the studies exhibited a low risk of bias, whereas 80.0% had some degree of bias but none were

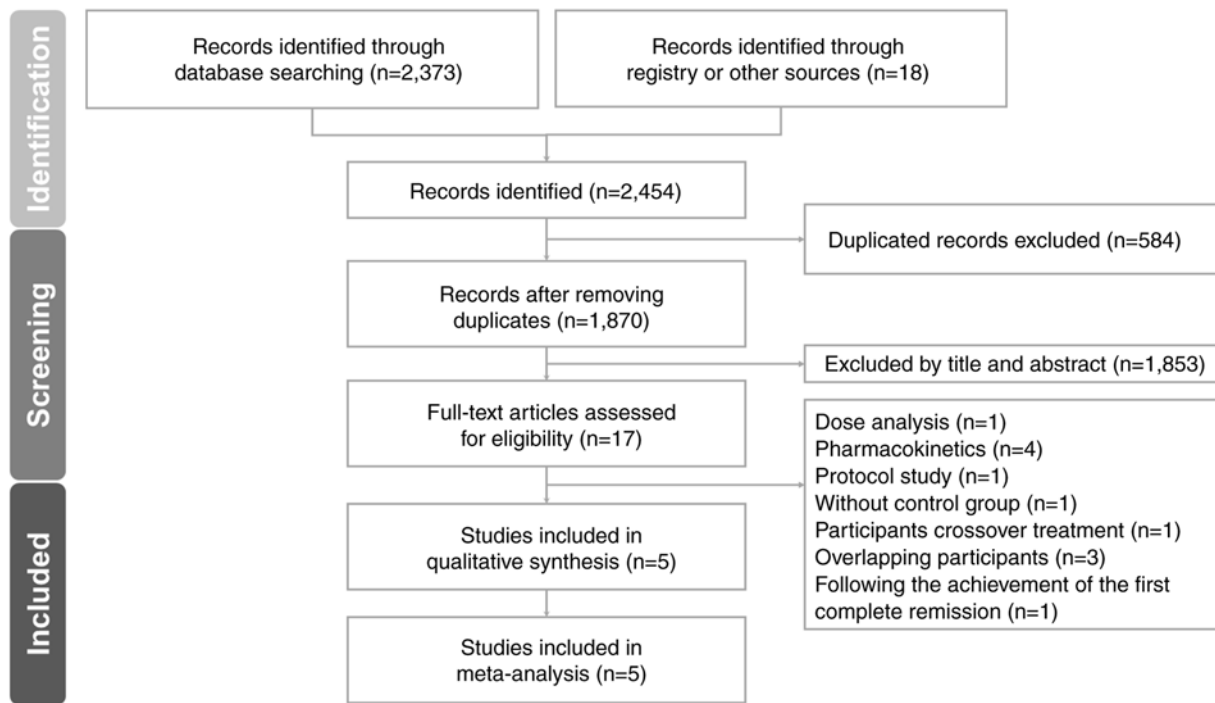


Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of the study selection process.

deemed to have a high risk of bias (Fig. 2). In a comprehensive evaluation, three studies were categorized as having some risk of bias in outcome measurement because of their open-label designs (37,40,41). In addition, one study was classified as having some risk of bias because allocation concealment details were not provided (38). The findings of the risk of bias assessment are summarized in Table II.

Effect of second-generation FLT3 inhibitors on overall survival. In the pooled analysis of the five trials (Fig. 3), second-generation FLT3 inhibitors significantly improved overall survival (HR, 0.717; 95% CI, 0.604-0.850; $P<0.001$). However, low-to-moderate heterogeneity was noted. To address this, a sensitivity analysis was conducted by using the one-study removal method. Second-generation FLT3 inhibitors was revealed to consistently exert a significant effect on overall survival. Notably, the significance of these findings remained unchanged after the exclusion of any of the included studies (Fig. 4).

The included studies were subsequently categorized into two subgroups on the basis of the type of second-generation FLT3 inhibitor used, whereby one group consisted of studies with quizartinib use (30-32), whereas the other consisted of studies with gilteritinib use (40,41). The association between second-generation FLT3 inhibitors and overall survival remained consistent in both subgroups. Specifically, participants receiving quizartinib (HR, 0.707; 95% CI, 0.502-0.987; $P=0.042$) and those treated with gilteritinib (HR, 0.715; 95% CI, 0.551-0.927; $P=0.011$) had consistent HRs with overlapping 95% CIs (Fig. 5).

An additional subgroup analysis associated with the form of AML was subsequently performed. The newly diagnosed group experienced a significant overall survival benefit, indicating that the use of second-generation FLT3 inhibitors

has a favorable effect in both clinically newly diagnosed and relapsed or refractory AML patients (HR, 0.796; 95% CI, 0.642-0.986; $P=0.037$). Similarly, the relapsed or refractory group (HR, 0.696; 95% CI, 0.578-0.837; $P<0.001$) and the other group (HR, 0.330; 95% CI, 0.142-0.769; $P=0.010$) experienced a significant overall survival effect (Fig. 6). A meta-regression analysis was next performed to assess the potential modification of the overall survival effects by age. Age exhibited a statistically significant but clinical trivial correlation with overall survival (coefficient=-0.0058; $P<0.001$; Fig. 7). The funnel plot generated for the five included trials exhibited some asymmetry in the distribution of effect sizes (Fig. S1). However, Egger's regression test yielded $P=0.450$, indicating the absence of publication bias.

Risk of prolongation of QTc interval and cardiovascular disorders. The overall risks associated with a prolonged QTc interval and cardiovascular disorders were next examined. Compared to the salvage chemotherapy control group, in the second-generation FLT3 inhibitor group, the risk of a prolonged QTc interval was found to be significant (OR, 6.311; 95% CI, 3.061-13.013; $P<0.001$; Fig. 8). In addition, the risk of cardiovascular disorders in the second-generation FLT3 inhibitor group was observed to be comparable to that in the salvage chemotherapy control group (OR, 1.451; 95% CI, 0.538-3.911; $P=0.462$; Fig. S2).

Risk of anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia. The risks of anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia were next assessed. Compared to the second-generation FLT3 inhibitor group, the salvage chemotherapy control group showed a significantly higher risk of anemia. (OR, 1.350; 95% CI, 1.021-1.786;

Table I. Summary of the included randomized clinical trials investigating use of second-generation FLT3 inhibitors.

Author, year	Age, years	Population	Number patients	Second generation FLT3	Control	Outcome measurement	(Refs.)
Cortes <i>et al.</i> , 2019	56.0 (18-81) ^a	Relapsed or refractory FLT3-internal tandem duplications AML	Qui, 245; Salvage CT, 122	Qui, 20 OR 30 mg	Salvage CT	OS, EFS, AE and SAE	(37)
Dennis <i>et al.</i> , 2021	77 (60-89) ^a	<i>De novo</i> and secondary AML	Qui, 72; Salvage CT, 71	Qui, 90 mg QD	Salvage CT	OS, AE and response rate	(38)
Erba <i>et al.</i> , 2023	54.0±12.93 ^b	Newly Diagnosed FLT3-mutated AML	Qui, 268; Salvage CT, 271	Qui, 40 mg QD	Salvage CT	OS, EFS, CR rate, AE and SAE	(39)
Perl <i>et al.</i> , 2019	Gil 62 (20.0-84.0) ^a ; Salvage CT 61.5 (19.0-85.0) ^a	Relapsed or Refractory FLT3-mutated AML	Gil, 247; Salvage CT, 124	Gil, 120 mg QD	Salvage CT	OS, EFS and AE	(40)
Wang <i>et al.</i> , 2022	Gil + AZA, 77.4±5.6 ^b ; AZA, 76.7 ± 5.3 ^b	Newly diagnosed FLT3 mutated AML	Gil + Salvage CT, 74; Salvage CT, 49	Gil, 120 mg QD + Salvage CT	Salvage CT	OS, EFS, response rates, AE and SAE	(41)

^aMedian (range); ^bmean ± SD. AML, acute myeloid leukemia; AE, Adverse events; CR, complete remission; CT, chemotherapy; EFS, event-free survival; RFS, relapse-free survival; OS, overall survival; SAE, serious adverse events; Qui, quizartinib; Gil, gilteritinib.

Table II. Comprehensive quality assessment of included studies as conducted using the Cochrane risk of bias 2 tool.

First author, year	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall risk of bias	(Refs.)
Cortes <i>et al</i> , 2019	S ^a	L	L	S ^l	L	S	(37)
Perl <i>et al</i> , 2019	S ^a	L	L	S ^l	L	S	(40)
Dennis <i>et al</i> , 2021	S ^b	L	L	L	L	S	(38)
Wang <i>et al</i> , 2022	S ^a	L	L	L	L	S	(41)
Erba <i>et al</i> , 2023	L	L	L	L	L	L	(39)

^aOpen-label study, where the participants were aware of the intervention allocated to them; ^bAllocation concealment details were not provided in the study. L, Low risk; S, Some concern.

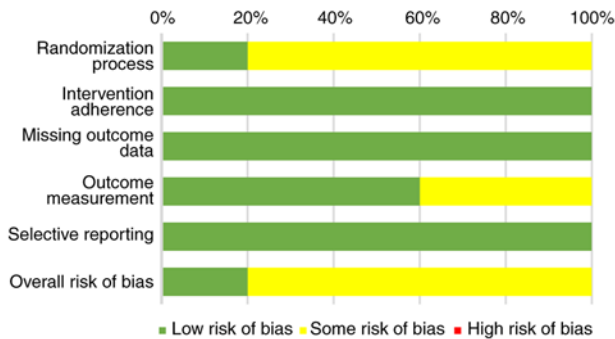


Figure 2. Overview of the quality assessment of included studies, conducted using the Cochrane risk of bias tool for randomized trials, version 2.

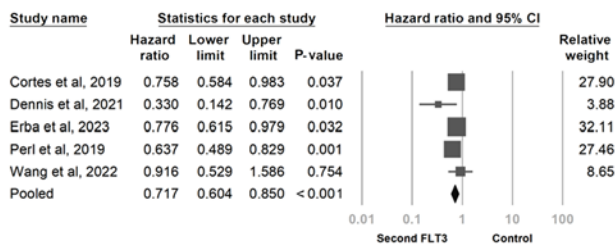


Figure 3. Summary of overall survival effect of second-generation FLT3 inhibitors. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

$P=0.035$; Fig. S3). Additionally, the risk of neutropenia observed in the second-generation FLT3 inhibitor group was found to be similar to that in the salvage chemotherapy control group (OR, 1.380; 95% CI, 0.808-2.359; $P=0.238$; Fig. S4). The risk of thrombocytopenia was also comparable between the second-generation FLT3 inhibitor group and the salvage chemotherapy control group (OR, 1.321; 95% CI, 0.974-1.791; $P=0.073$; Fig. S5), whereas the incidence of diarrhea was comparable between the second-generation FLT3 inhibitor group and the salvage chemotherapy control group (OR, 1.315;

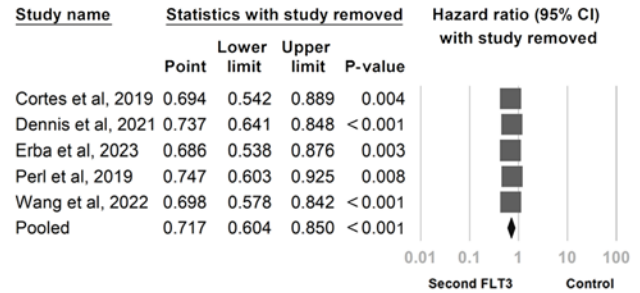


Figure 4. Sensitivity analysis of second-generation FLT3 inhibitors for the treatment of acute myeloid leukemia. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

95% CI, 0.684-2.527; $P=0.412$; Fig. S6). No significant difference could be observed in the incidence of pneumonia between the second-generation FLT3 inhibitor group and the salvage chemotherapy control group (OR, 1.271; 95% CI, 0.725-2.227; $P=0.403$; Fig. S7).

Event free survival. Event-free survival was next assessed, which found that second-generation FLT3 inhibitors significantly improved event-free survival compared with that in the salvage chemotherapy control group (HR, 0.755; 95% CI, 0.582-0.980; $P<0.05$; Fig. S8).

Discussion

In the present meta-analysis, second-generation FLT3 inhibitors was found to significantly improve overall survival. In addition, the observed significant difference persisted in the sensitivity analyses. Various second-generation FLT3 inhibitors, such as Gilteritinib and Quizartinib, have been associated with improved overall survival. This improvement was consistent across different types of AML. Additionally, increasing age was correlated with improvements in overall survival. Although Hedges (42) addressed

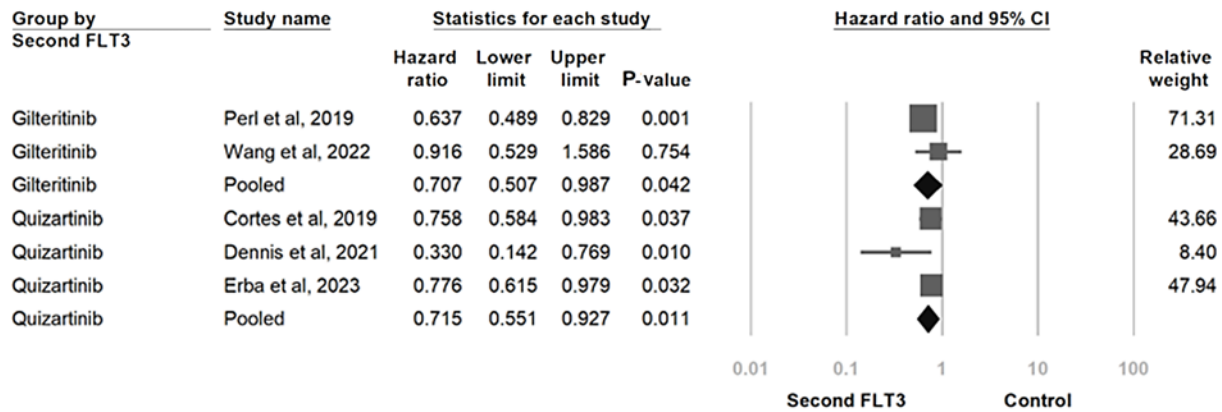


Figure 5. Subgroup analysis of overall survival effects following sorting by second-generation FLT3 Inhibitor. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

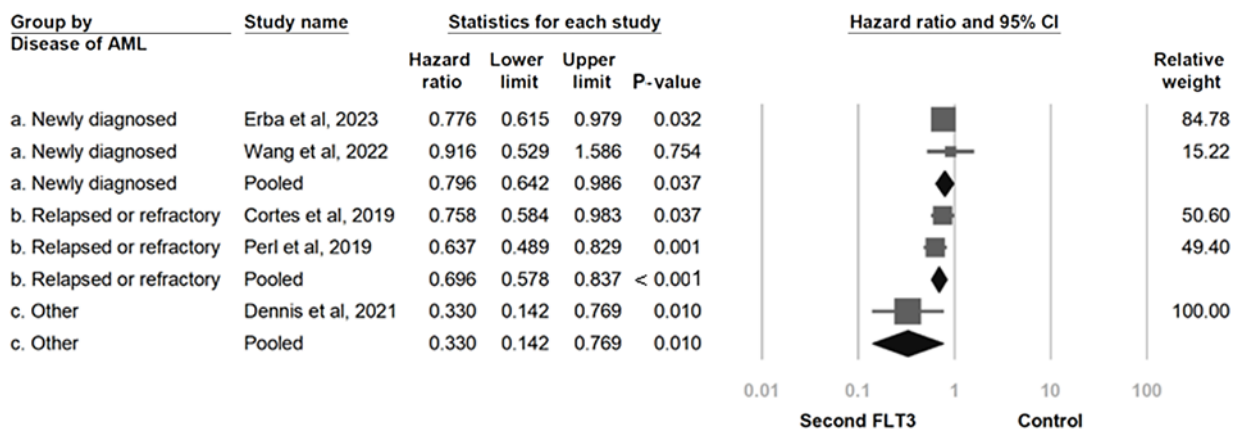


Figure 6. Subgroup analysis of overall survival effects stratified by the form of AML. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. AML, acute myeloid leukemia.

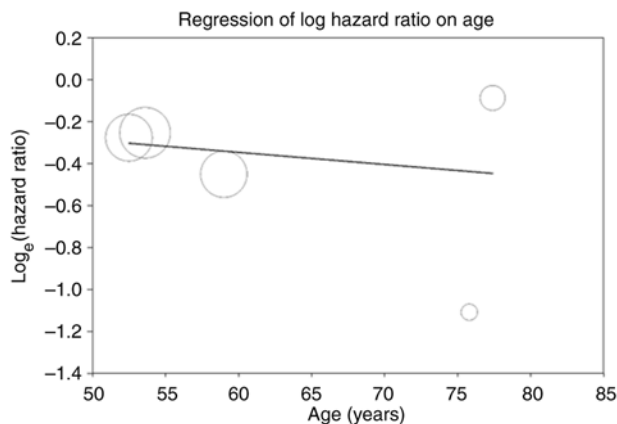


Figure 7. Meta-regression analysis of association between log HR and age. The sizes of each circle represent the relative weight of each study, and the base of the logarithm used was e.

the effect size and Deeks *et al* (20) explained the concept of low-to-moderate heterogeneity, to the best of our knowledge, the present study is the first to synthesize these insights in a systematic review and meta-analysis specifically focused on second-generation FLT3 inhibitors. By quantifying the heterogeneity observed across the included studies, the

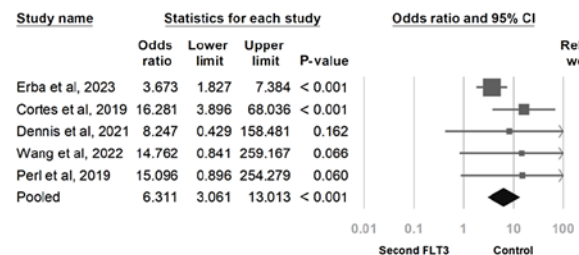


Figure 8. Comparison of the risk of prolonged QTc interval between second-generation FLT3 inhibitor group and control group. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

present analysis further supports the consistency of the therapeutic benefits of these inhibitors on overall survival across diverse patient populations and settings.

Previous meta-analyses have demonstrated improvements in overall survival to be associated with both first-generation inhibitors (such as sorafenib, lestaurtinib and midostaurin) and second-generation inhibitors (such as gilteritinib and quizartinib) (37-39,43). Mohebbi *et al* (17) previously reported that second-generation FLT3 inhibitors can improve overall survival in patients with relapsed or refractory AML (17). These findings are consistent with results from the

present study. However, the study by Mohebbi *et al* (17) on second-generation FLT3 inhibitors was limited by the early publication dates and two RCT studies by Cortes *et al* (37) and Perl *et al* (40). It is hoped that the present meta-analysis can bridge this gap in the literature by providing an updated evaluation of the efficacy and safety of second-generation FLT3 inhibitors.

FLT3, belonging to the receptor tyrosine kinase family, exhibits a broad expression pattern in hematopoietic progenitor cells and is commonly overexpressed in AML blasts (44). Mutations in FLT3 are some of the most prevalent genomic aberrations in AML, being detected in ~33.3% of newly diagnosed adults (45). FLT3 mutations can occur in the juxtamembrane domain, with such mutations commonly referred to as ITD mutations (FLT3-ITD) (46) or in the TKD (FLT3-TKD) (47,48). Second-generation FLT3 inhibitors, such as quizartinib, selectively inhibit FLT3 kinase activity, thereby preventing receptor autophosphorylation. This inhibition leads to the suppression of downstream FLT3 receptor signaling and arrest of the cell proliferation process that is dependent on FLT3-ITD (13). Gilteritinib, another second-generation FLT3 inhibitor, can also inhibit FLT3 receptor signaling and subsequently proliferation using a mechanism similar to that of quizartinib (49). Orally administered gilteritinib was reported to induce apoptosis in leukemic cells with FLT3-ITD mutations (50) and gilteritinib has been demonstrated to effectively target both FLT3 mutation subtypes (ITD and TKD) while both subtypes exhibit only weak activity against c-Kit (51,52). Although both gilteritinib and quizartinib are second-generation FLT3 inhibitors, they exhibit different levels of activity against the c-Kit receptor. Gilteritinib demonstrates relatively weak inhibition of c-Kit, with an IC_{50} of ~100 nM, meaning its impact on c-Kit is minimal, reducing the likelihood of marrow suppression. By contrast, quizartinib has stronger inhibitory activity against c-Kit, which may contribute to a higher risk of myelosuppression in clinical use (50).

In the separate subgroup analyses by use of gilteritinib or quizartinib in patients with different forms of AML, significant summary effect sizes were observed in both subgroups. This observation may be attributable to the efficacy of both treatments in improving overall survival in AML. Additionally, subgroup analyses were conducted for different forms of AML, including newly diagnosed, relapsed or refractory and other (referring to *de novo* or secondary) AML. Regardless of the AML subtype, second-generation FLT3 inhibitors were found to significantly improve overall survival. These findings suggest that second-generation FLT3 inhibitors led to a significant improvement in overall survival across multiple different AML subtypes. Furthermore, a statistically significant, though clinically trivial, correlation between patient age and overall survival in response to treatment was observed. These findings suggest that second-generation FLT3 inhibitors have greater effectiveness in improving overall survival in younger patients with AML with FLT3 mutations (coefficient=-0.0058 $P<0.001$).

Relapsed or refractory solid tumors in patients with advanced-stage cancer can potentially influence the physiological condition of the host. A possible reason is the disruption of the blood-brain barrier (52), allowing tumor cells to invade

the brain. A previous study has reported that melanoma, skin, ovarian, and lung tumor cells may secrete hypothalamic hormones, pituitary hormones, steroids, catecholamines, serotonin, N-acetylserotonin, melatonin and leptin. The secretion of such neurohormonal modulators can ultimately disrupt the body's homeostasis (53). For instance, in AML, FLT3 mutations, particularly FLT3-ITD, result in the constitutive activation of downstream signaling pathways, such as the PI3K/Akt and STAT5 pathways, which are crucial for cell survival and proliferation (54,55). This activation can lead to the dysregulation of various cellular processes, much like how solid tumors disrupt homeostasis through the secretion of neurohormonal modulators.

QTc prolongation is the most frequent adverse event associated with the use of second-generation FLT3 inhibitors (26,56). The present study revealed the occurrence of QTc prolongation with the use of second-generation FLT3 inhibitors, to suggest that administration of second-generation FLT3 inhibitors may induce QTc prolongation due to elevated concentrations in patients with FLT3 mutations (57). Elevated concentrations of second-generation FLT3 inhibitors, such as quizartinib, can occur due to co-administration with cytochrome P450 3A4 inhibitors, which impede the drug's metabolism, leading to reduced clearance. This results in the accumulation of the drug in plasma, increasing its concentration over time. Such interactions are common, especially when patients are on multiple medications metabolized by the same pathway (58,59). At higher concentrations, FLT3 inhibitors (such as quizartinib) may block the human ether-a-go-go-related gene potassium channels, which are critical for cardiac repolarization. Inhibition of these channels disrupts the heart's electrical activity, leading to QTc prolongation. The risk of this effect is dose-dependent, meaning the higher the concentration of the drug, the more pronounced the QTc prolongation. This has been demonstrated in clinical studies of quizartinib, where elevated levels were directly associated with QTc interval changes. Therefore, greater attention should be given to such patients receiving these inhibitors (59,60). Additionally, an analysis of drug-related cardiovascular adverse events was conducted, but could not yield any significance. An analysis of common adverse events, such as anemia, neutropenia, thrombocytopenia, diarrhea, and pneumonia was also performed. A significant difference was found in only the incidence of anemia among patients treated with second-generation FLT3 inhibitors, likely due to the impact of these inhibitors on reducing platelet function (61). This finding highlights the importance of monitoring anemia in patients receiving second-generation FLT3 inhibitors. Additionally, the effect of second-generation FLT3 inhibitors on event-free survival compared with the control group was assessed. The results show that the use of second-generation FLT3 inhibitors significantly improved event-free survival, suggesting that second-generation FLT3 inhibitors can enhance event-free survival due to their activity against both FLT3 mutation subtypes (ITD and TKD).

The present study has several limitations. The second-generation FLT3 inhibitors used among the included trials differed, potentially contributing to heterogeneity. Therefore, the measurements were standardized using HRs, before applying

a random-effects model to combine the studies and perform subgroup analyses to address heterogeneity in accordance with the standard approach as recommended by the Cochrane Handbook (62,63). In addition, variability was observed in the age distribution among the trials, which may have influenced the estimated effects. Therefore, a meta-regression analysis was performed to investigate the presence of a linear relationship between age and overall survival. The present study also did not include the second-generation FLT3 inhibitor crenolanib due to the lack of randomized controlled trials. Future research should include RCTs involving crenolanib if data on such trials become available.

In summary, in the present study, second-generation FLT3 inhibitors, such as gilteritinib and quizartinib, were found to significantly improve overall survival, whereby age was statistically significant, though clinically trivial, correlation between patient age and overall survival in response to treatment. However, clinicians should remain aware of potential QTc prolongation when prescribing second-generation FLT3 inhibitors. Further investigations are warranted to explore the combined effect of crenolanib and second-generation FLT3 inhibitors, such as gilteritinib and quizartinib, on overall survival.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SYH and YTH were responsible for designing the research and extracting the data. CMC, WTL and CYL conducted the statistical analysis and handled data visualization and interpretation. SYH and TSW prepared the initial draft of the manuscript. Both SYH and TSW performed critical revisions to the manuscript, focusing on essential intellectual content, and reviewed the data analysis. SYH and TSW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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