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Meta-analysis on the effectiveness and safety of venetoclax-based combination therapy with hypomethylation in acute myeloid leukemia

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Abstract

The combined therapy strategy of venetoclax with hypomethylating agents (HMAs) has demonstrated encouraging efficacy in the treatment of acute myeloid leukemia (AML), particularly in elderly patients or those deemed unfit for standard treatments. However, due to differences in the research focuses of various research centers, the results have not yet comprehensively and systematically demonstrated the clinical significance of this treatment approach. Therefore, in this meta-analysis, we aimed to assess the effectiveness and safety of venetoclax in combination with HMAs for the treatment of AML. We included a total of 20 clinical studies that met the search criteria, including research focused on AML patients carrying FLT-3 and IDH mutations. Results revealed an overall response (OR) rate of 0.57 and a complete remission (CR)/complete remission with incomplete marrow recovery (CRi) rate of 0.52. Subgroup analyses indicated varying CR/CRi rates among patients with different genetic mutations, with the highest rate observed in IDH mutation carriers at 0.71, FLT-3 mutation carriers at 0.64, and TP53 mutation carriers at 0.44. Simultaneously, we observed adverse events such as anemia, neutropenia, and thrombocytopenia, underscoring the importance of careful management during venetoclax and HMAs treatment. This study emphasizes the potential of venetoclax and HMAs as a promising therapeutic approach for AML while highlighting the critical need for monitoring and managing adverse events in such treatment regimens.

Keywords Venetoclax, HMAs, AML, Adverse events, Meta-analysis

Introduction

Acute myeloid leukemia (AML) is a malignancy characterized by clonal hematopoietic stem cell expansion, resulting in the accumulation of immature progenitor cells and hematopoietic suppression [1]. AML can affect individuals of all age groups, with a higher incidence observed in those aged 65 years or older [2]. AML exhibits significant heterogeneity, manifesting in variations in morphology, immunophenotype, genetic and epigenetic characteristics, and responses to treatment, this heterogeneity is often assessed by genetic abnormalities, which play a crucial role in stratifying patients based

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on prognostic risk [3–7]. Notably, the NCCN Oncology Clinical Practice Guidelines classify AML patients with specific genetic mutations, such as FMS-like tyrosine kinase 3 (FLT3) or TP53 mutations in normal cytogenetics, as poor risk [8]. Furthermore, FLT3 gene mutations, found in approximately 30% of newly diagnosed AML patients, are considered genetic drivers that activate FLT3 kinase through constitutive activation, promoting leukemia cell proliferation and survival [9–13]. Similarly, mutations in isocitrate dehydrogenase 1 and 2 (IDH1 and ID2), accounting for about 30% of AML cases, are also prevalent in AML patients [14].

The discovery of the efficacy of cytarabine and anthracycline in AML, along with their incorporation into the "3+7 regimen" (comprising 3 days of daunorubicin and 7 days of cytarabine) in 1973, has long been regarded as a standard treatment [15–18]. This approach has yielded a long-term cure rate of 30% to 40% in young AML patients [1, 15–18]. Despite these advancements, the cure rate remains notably low, with a 5-year survival rate ranging from 40 to 50% for young patients and less than 10% for elderly individuals [19–21]. Interestingly, as our understanding of the molecular landscape of AML has advanced, especially via extensive genomic analysis,

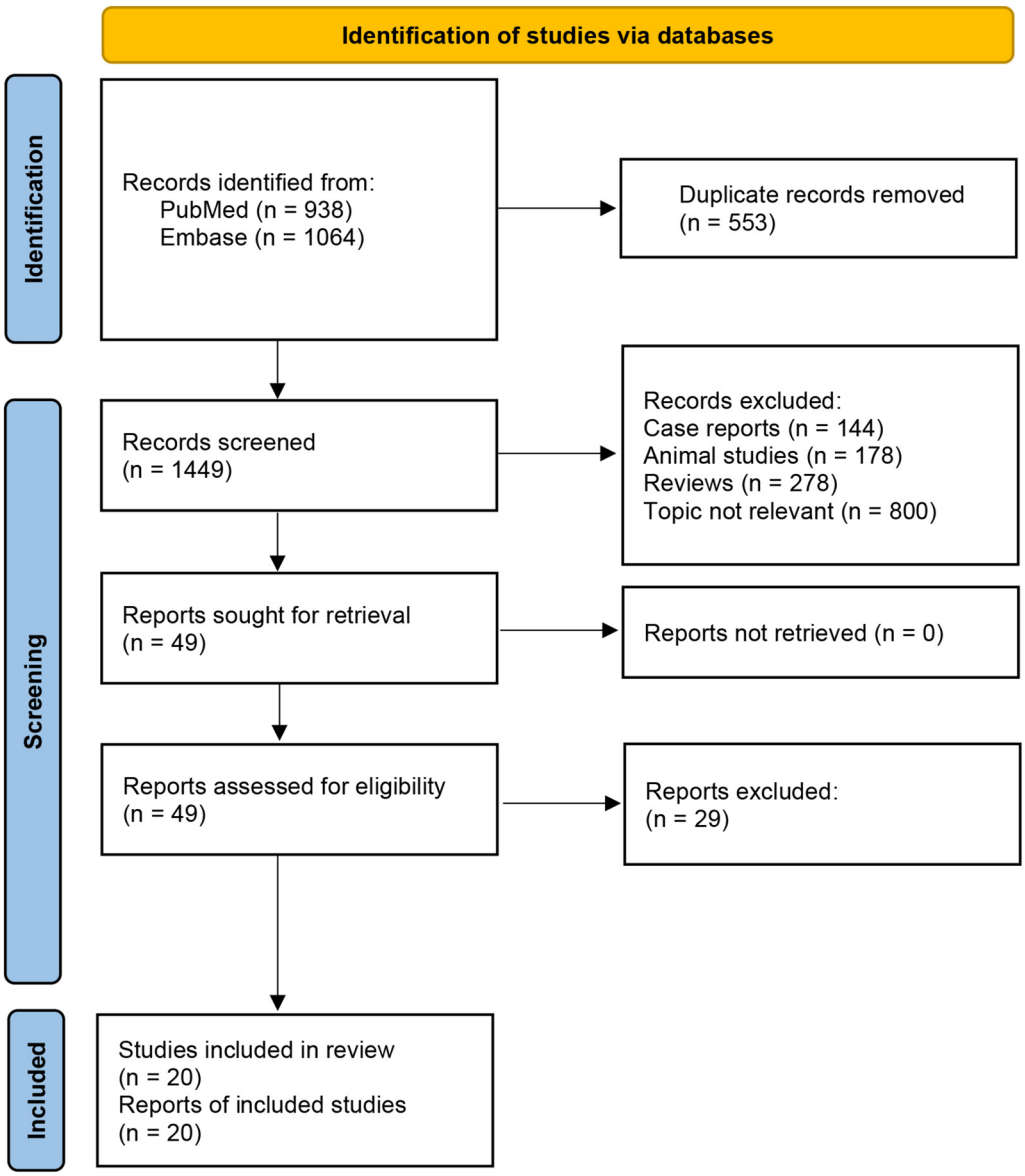

Fig. 1 Search results and flowchart of the meta-analysis of venetoclax and HMAs in AML

Table 1 Study characteristics of venetoclax and HMAs in AML

Author	Year	Study design	Number of patients	Age, y	Female, %	Type of patients	FLT3, %	IDH1/2, %	TP53, %	ECOG PS, %		
										0–1	2	3–4
DiNardo	2018	Non-randomized, open-label, phase 1b study	45	74 (71–80)	56	Untreated	16	31	13	82	18	0
Winters	2019	Retrospective	30	72	NS	Untreated	20	16.7	16.7	NS	NS	NS
Byrne	2020	Retrospective	16	61 ± 13	NS	Untreated	12.5	6.3	18.8	NS	NS	NS
DiNardo	2020	This phase 3, multicenter, randomized, double-blind, placebo-controlled trial	286	76 (49–91)	40	Untreated	14	25	23	NS	NS	NS
Lou	2020	Retrospective	48	61 (19–73)	42	R/R AML	27.1	25	16.7	NS	NS	NS
Cherry	2021	Retrospective	143	69.5 (22–91)	49.6	Untreated	14	27.3	17.4	NS	NS	NS
Mirgh	2021	Retrospective	24	60 (30–79)	54.1	16-newly diagnosed, 8-relapsed/refractory	50	16.6	8.3	50	37.5	12.5
Pollyea	2021	Open-label, non-randomized, multicenter phase 1b	115	> 60	42.6	Untreated	13.9	26.1	21.7	73.9	24.3	1.7
Ucar	2021	Retrospective	62	65 (19–85)	45.2	R/R AML	NS	NS	NS	NS	NS	NS
Garciaz	2022	Retrospective	77	72 (22–86)	42	38-newly diagnosed, 39-relapsed/refractory	12	24	22	NS	NS	NS
Matthews	2022	Retrospective	439	75 (36–88)	44	NS	7	16	13	14	NS	NS
Salhotra	2022	Retrospective	51	63.5 (27–73)	50	NS	7	NS	31	NS	NS	NS
Wang	2022	RCT	10	70 (60–83)	50	R/R AML	NS	NS	NS	NS	NS	NS
Aiba	2023	Retrospective	13	79 (72–86)	23.1	Untreated	NS	NS	NS	NS	NS	NS
Freeman	2023	Retrospective	39	68	NS	NS	13.2	NS	NS	71.8	25.6	2.6
Göker	2023	Retrospective	14	50.5 (28.2–60.5)	42.9	Relapsed AML	NS	NS	NS	NS	NS	NS
Hoff	2023	Retrospective	106	77 (70–81)	52	NS	16.4	22.6	39.6	34	NS	NS
Hu	2023	Retrospective	10	71 (65–82)	30	R/R AML	10	40	30	0	60	40
Laloi	2023	Retrospective	91	63 (20–89)	45.1	NS	NS	NS	NS	66.7	ns	ns
Xia	2023	RCT	21	63 (24–77)	33.3	Untreated	28.6	NS	9.5	9.5	52.4	38.1

NS, not specified

Table 2 Risk-of-bias assessment of single-armed studies using the Methodological Index for Non-Randomized Studies (MINORS) tool

Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	Total
DiNardo2018	2	2	2	2	2	2	2	2	16
Winters2019	2	2	2	2	2	2	2	1	15
Byrne2020	2	2	2	2	2	2	2	1	15
DiNardo2020	2	2	2	2	2	2	2	2	16
Lou2020	2	2	2	2	2	2	2	1	15
Cherry2021	2	2	2	2	2	2	2	1	15
Mirgh2021	2	2	2	2	2	2	2	1	15
Pollyea2021	2	2	2	2	2	2	2	2	16
Ucar2021	2	2	2	2	2	2	2	1	15
Garciaz2022	2	2	2	2	2	2	2	1	15
Matthews2022	2	2	2	2	2	2	2	1	15
Salhotra2022	2	2	2	2	2	2	2	1	15
Wang2022	2	2	2	2	2	2	2	2	16
Aiba2023	2	2	2	2	2	2	2	1	15
Freeman2023	2	2	2	2	2	2	2	1	15
Göker2023	2	2	2	2	2	2	2	1	15
Hoff2023	2	2	2	2	2	2	2	1	15
Hu2023	2	2	2	2	2	2	2	1	15
Laloi2023	2	2	2	2	2	2	2	1	15
Xia2023	2	2	2	2	2	2	2	2	16

and with the development of targeted therapies such as anti-FLT3 and anti-IDH, the insight of AML treatment strategy has undergone significant transformations [22]. Especially, the selective inhibition of BCL-2 (venetoclax) has successfully restored the apoptotic pathway in malignant cells [23, 24]. The anti-tumor activity of venetoclax was observed across various hematological malignancies [25–27]. The synergistic potential of venetoclax in combination with hypomethylating agents (HMAs) such as decitabine and azacytidine, as suggested by preclinical models, presents a promising treatment strategy for AML [28].

Currently, clinical research on venetoclax-based strategies is thriving in various centers. However, due to the differing emphases in the design of these clinical trials, redundant clinical data have been reported. Therefore, it has become essential to systematically comprehend the current clinical practice of venetoclax in combination with hypomethylating agents in AML patients. This meta-analysis focuses on evaluating the efficacy and adverse reactions of venetoclax in combination with HMAs in AML treatment, especially in subgroups of patients harboring FLT-3 or IDH mutations.

Methods

We performed this meta-analysis following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [29]. The review was not registered.

Search strategy and study selection

We conducted a comprehensive computerized search of the electronic databases PubMed and Embase up to April 30, 2024, limited to English language publications. The search terms utilized included: venetoclax, RG7601, ABT-199, acute myeloblastic leukemia, acute myeloid leukemia, and AML. Additionally, we manually examined the references of relevant reviews and meta-analyses to identify any potentially additional studies. The inclusion criteria for this meta-analysis were as follows: (1) clinical trials focusing on the evaluation of venetoclax in combination with HMAs concerning their efficacy and adverse events in AML patients; (2) treatment responses and adverse events were reported; (3) studies published in English. Exclusion criteria encompassed case reports, reviews, news articles, and conference abstracts.

Two independent investigators conducted the initial database searches. In cases of disagreement, consensus was reached through discussion with a third reviewer.

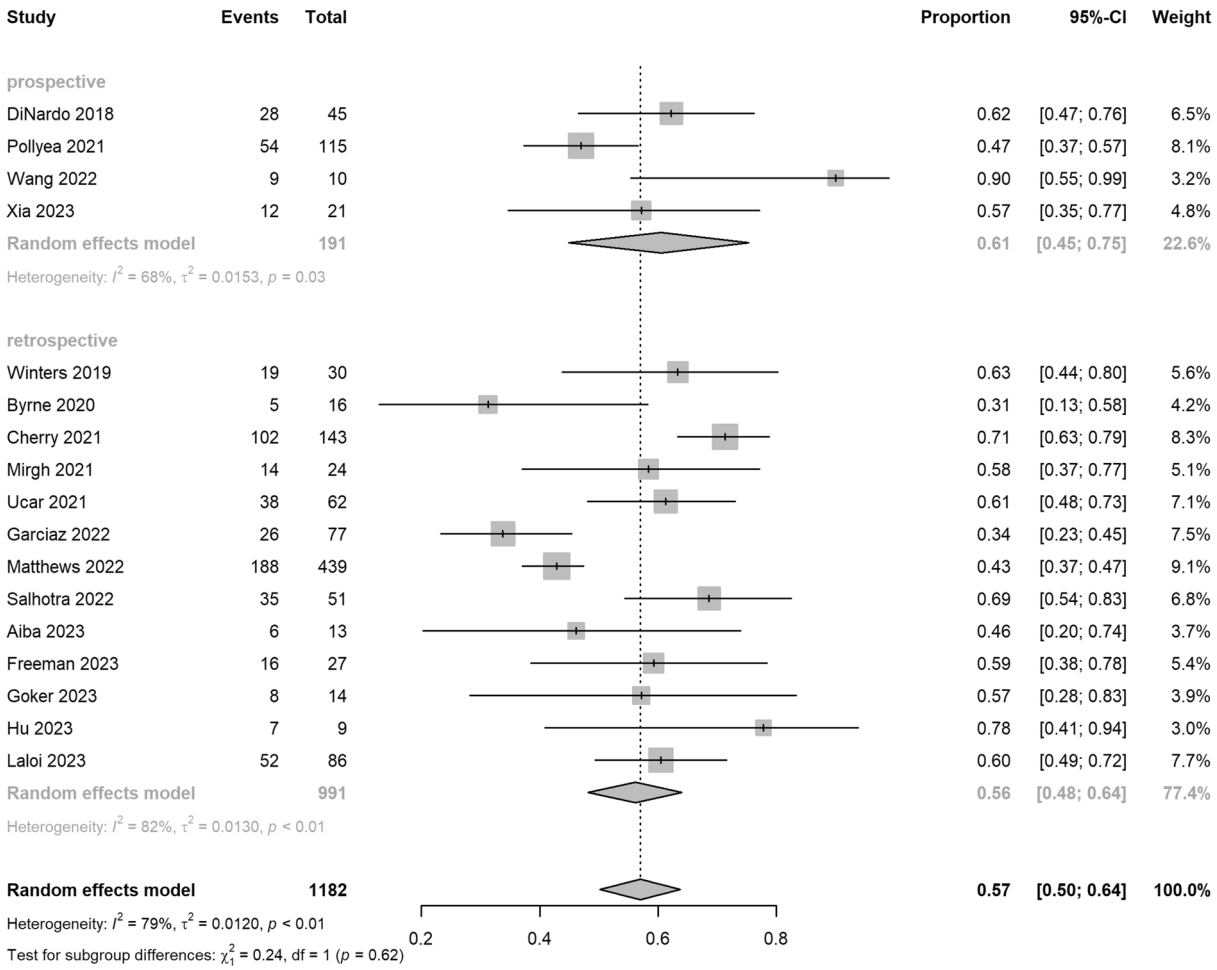

Fig. 2 Forest plot of pooled OR for venetoclax and HMAs

Initially, the two authors screened the titles and abstracts of the articles identified in the literature search. Subsequently, a full-text evaluation of the remaining citations was performed to make the final inclusion assessments.

Data extraction and quality assessments

Information extracted from each study included the first author's name, publication year, study design, number of patients, patient age, percentage of the female participants, patient classification, mutation status, ECOG scores, treatment outcomes, and occurrence of adverse events. Treatment outcomes included overall response (OR), complete remission (CR), complete remission with incomplete marrow recovery (CRi), partial remission (PR), stable disease (SD), progressive disease (PD). For randomized controlled trials (RCTs), the Cochrane Collaboration's tool for assessing the risk of bias [30] was employed. Non-randomized controlled studies were assessed for bias using the Newcastle–Ottawa scale (NOS) [31]. Risk-of-bias assessment for single-arm studies was conducted using the methodological index for non-randomized studies (MINORS) [32].

Statistical analysis

All statistical analyses were conducted using R (Version 4.1.2, Vienna, Austria). We calculated the OR, CR, CRi, PR, SD, PD, and adverse events rates with their corresponding 95% confidence intervals (CIs) employing a random-effects model. To assess heterogeneity among the included studies, we utilized the Cochran Q test and the I^2 statistic. Significance in heterogeneity was determined with a p-value < 0.05 in the Cochran Q test and an I^2 statistic > 50%. Subgroup analysis was performed based on FLT-3 or IDH mutations, untreated or relapsed/refractory AML (R/R AML), and study design. Sensitivity analysis was conducted to evaluate the robustness of the results. Furthermore, we conducted Egger's tests to appraise the presence of

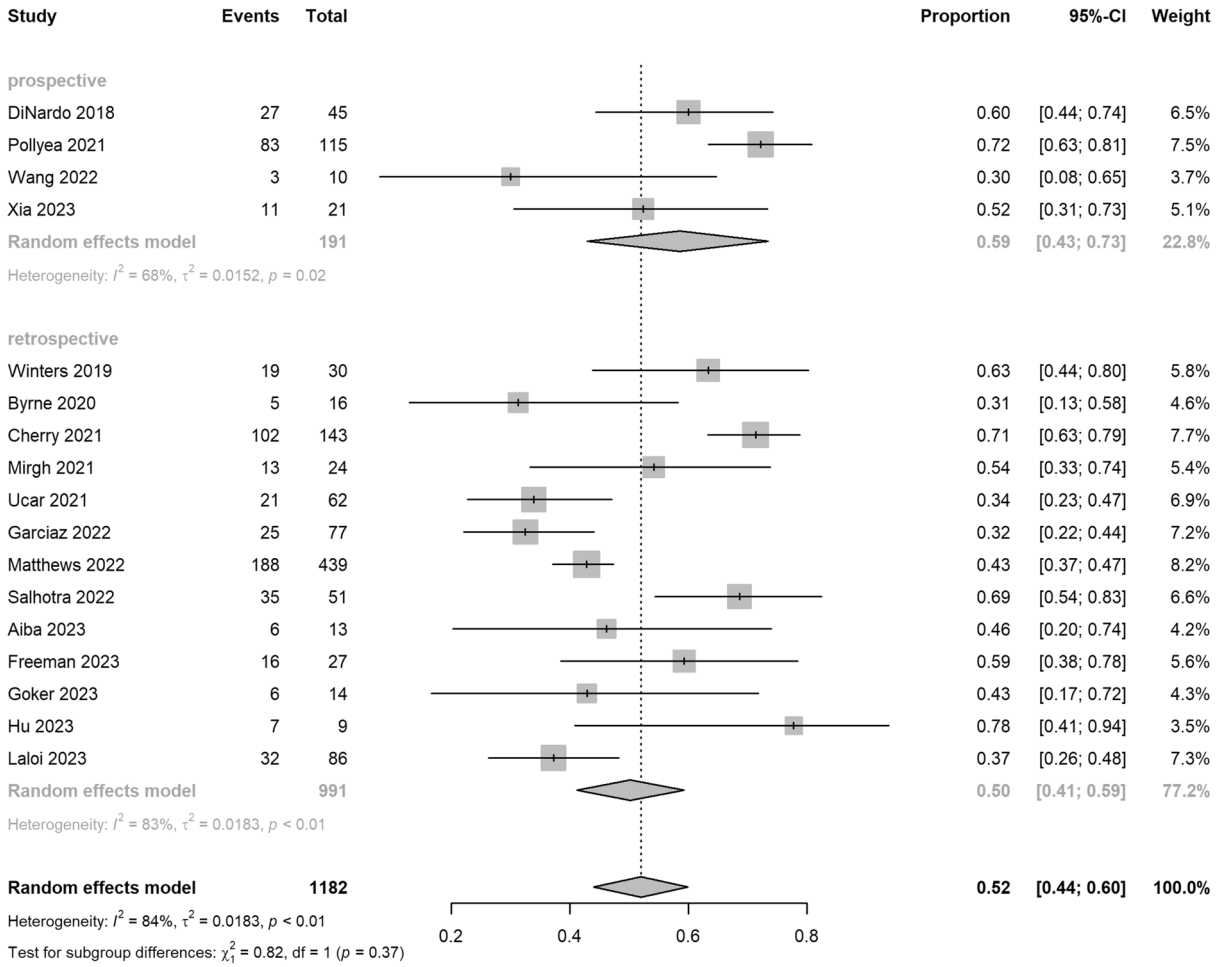

Fig. 3 Forest plot of pooled CR/CRi for venetoclax and HMAs

publication bias in the included studies, with statistical significance set at a p-value < 0.05.

Results

Study selection and characteristics

We initially identified 2002 citations through the literature search. After removing 553 duplicate citations and conducting title and abstract screening, we excluded 1400 studies. Finally, after a thorough full-text review of the remaining 49 articles, we included 20 studies in our analysis [33–52]. Figure 1 provides an overview of the literature search process and study selection. The included studies containing a total of 1640 patients with diagnosed AML. Among them, eight studies focused on previously untreated AML patients [33–36, 38, 40, 46, 52], while five studies reported treatment outcomes for R/R AML cases [37, 41, 45, 48, 50]. Two trials included both newly diagnosed and R/R AML patients [39, 42]. For detailed information about the included studies, please refer to Table 1. The quality assessment of these studies was rated as high based on the MINORS tool, as indicated in Table 2.

Efficacy

The overall OR rate was 0.57 (95% CIs: 0.50, 0.64; $I^2 = 79\%$, $p < 0.01$), results of subgroup analyses showed that the OR rate for prospective studies was 0.61 (95% CIs: 0.45, 0.75; $I^2 = 68\%$, $p = 0.03$), for retrospective studies, the OR rate was 0.56 (95% CIs: 0.48, 0.64; $I^2 = 82\%$, $p < 0.01$) (Fig. 2); for untreated AML, the OR rate was 0.56 (95% CIs: 0.46, 0.67; $I^2 = 73\%$, $p < 0.01$), for R/R AML, the OR rate was 0.68 (95% CIs: 0.54, 0.80; $I^2 = 27\%$, $p = 0.25$) (Figure S1). The pooled CR/CRi rate was 0.52 (95% CIs: 0.44, 0.60; $I^2 = 84\%$, $p < 0.01$), results of subgroup analyses showed that the CR/CRi rate for prospective studies

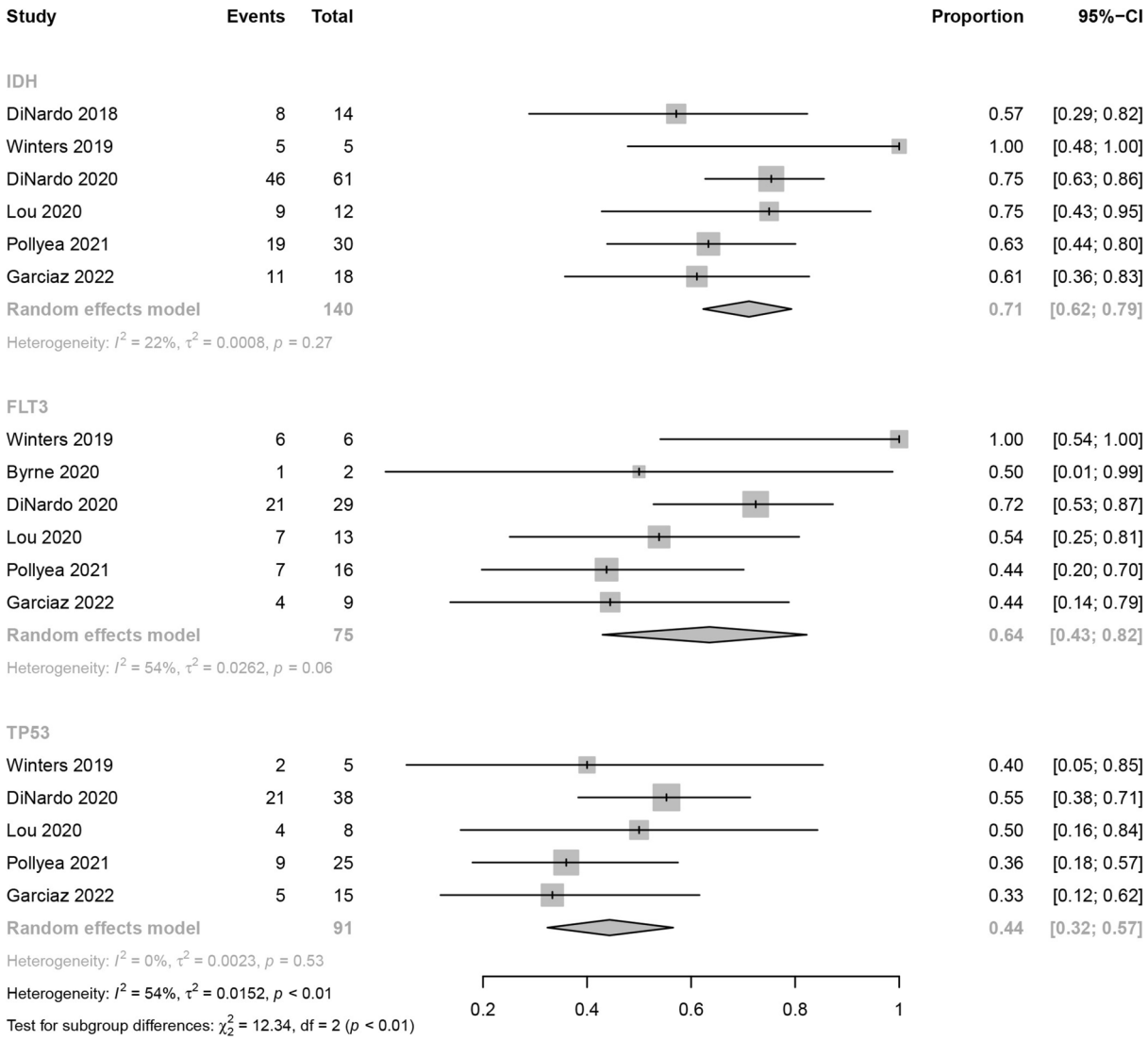

Fig. 4 Forest plots of pooled CR/CRi rates for patients with IDH, FLT-3, and TP53 mutations

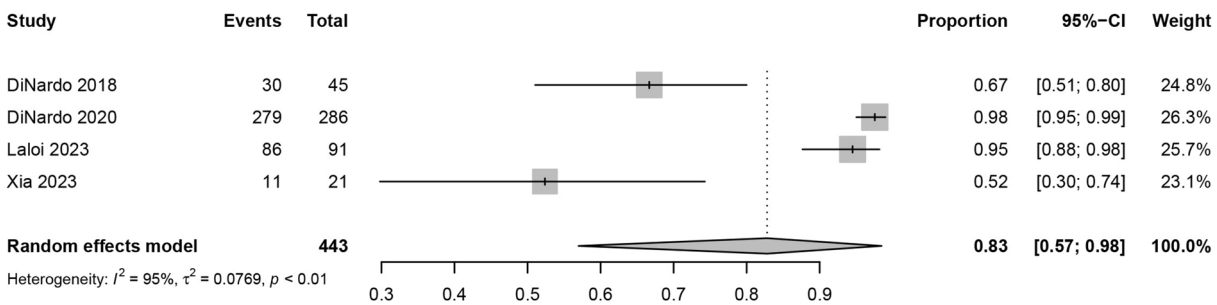

Fig. 5 Forest plot of pooled rate of adverse events ≥ Grade 3

was 0.59 (95% CIs: 0.43, 0.73; I^2 = 68%, p = 0.02), for retrospective studies, the CR/CRi rate was 0.50 (95% CIs: 0.41, 0.59; I^2 = 84%, p < 0.01) (Fig. 3); for untreated AML, the pooled CR/CRi rate was 0.61 (95% CIs: 0.50, 0.71; I^2 = 63%, p = 0.01), for R/R AML, the pooled CR/CRi rate was 0.43 (95% CIs: 0.25, 0.61; I^2 = 53%, p = 0.10)

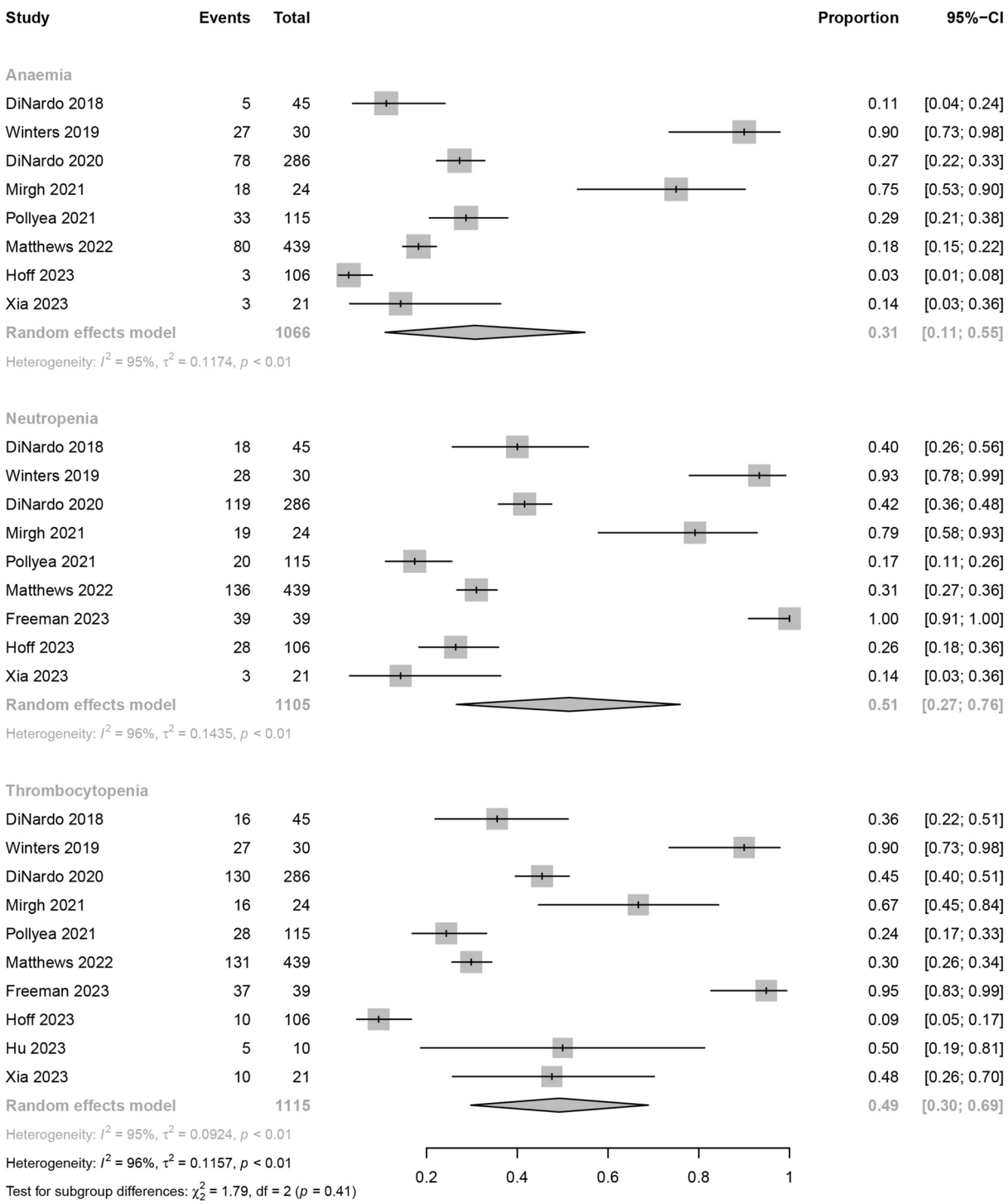

Fig. 6 Forest plot of hematological adverse events

(Figure S2). When examining specific genetic mutations, the pooled CR/CRi rates for patients with IDH, FLT-3, and TP53 mutations were 0.71 (95% CIs: 0.62, 0.79; $I^2 = 22\%$, $p = 0.27$ 0.01), 0.64 (95% CIs: 0.43, 0.82; $I^2 = 54\%$, $p = 0.06$), and 0.44 (95% CIs: 0.32, 0.57; $I^2 = 0\%$, $p = 0.53$), respectively (Fig. 4).

Adverse events

The pooled rate of adverse events ≥ Grade 3 was 0.83 (95% CIs: 0.57, 0.98; $I^2 = 95\%$, $p < 0.01$) as illustrated in Fig. 5. In terms of hematological adverse events, the overall rates of anemia, neutropenia, and thrombocytopenia were 0.31 (95% CIs: 0.11, 0.55; $I^2 = 95\%$, $p < 0.01$), 0.51 (95% CIs: 0.27, 0.76; $I^2 = 96\%$, $p < 0.01$), and 0.49 (95% CIs: 0.30, 0.69; $I^2 = 95\%$, $p < 0.01$), respectively, as demonstrated in Fig. 6.

Publication bias and sensitivity analysis

The results of Egger's tests indicated that there was no significant publication bias detected in the meta-analyses of OR, CR/CRi, adverse events ≥ Grade 3, and hematological adverse events. Furthermore, after systematically excluding each included study one by one, the pooled outcomes were robust.

Discussion

Venetoclax, a highly selective and potent inhibitor of BCL-2, has the potential to restore the apoptotic capabilities of cancer cells [23, 24]. While its functionality is yet to be fully elucidated, it has significantly reshaped the therapeutic landscape for hematological malignancies, especially AML [53]. The combination of venetoclax and HMAs agents disrupts amino acid uptake and catabolism in leukemia stem cells, introducing a novel molecular mechanism for synergistically induces cell death [54, 55]. In this context, we performed a comprehensive meta-analysis to explore the efficacy and safety of venetoclax and HMAs in the treatment of AML patients, with a particular focus on those harboring FLT-3 and IDH mutations.

Our study revealed a pooled OR rate of 0.57, and CR/CRi rate of 0.52. Of note, the OR rate was higher in patients with R/R AML than untreated patients. These findings align with previous studies involving patients with either newly diagnosed or R/R AML [39, 40, 44, 48]. It is important to consider that the majority of patients in the enrolled studies had an average or median age exceeding 60 years. Existing research has indicated the role of DNA methylation and other epigenetic changes in the pathogenesis of elderly AML [56]. As such, HMAs agents represent a favorable treatment choice for newly diagnosed elderly AML patients who may not be suitable candidates for high-intensity chemotherapy or hematopoietic stem cell transplantation, as well as those with R/R AML [57].

A retrospective study by Lachowiez et al. demonstrated that the CR/CRi rate in the group receiving venetoclax and HMAs was higher than that in the group receiving HMAs alone (56% vs. 28%) [58]. When it comes to adverse effects, our study's pooled results, including anemia, neutropenia, and thrombocytopenia, were consistent with previous research findings [33, 34, 36, 39]. These hematological adverse events cannot be underestimated and underscore the importance of close monitoring and management during treatment. The observed association between venetoclax and increased hematological toxicities warrants further investigation. Prospective studies and well-designed randomized controlled trials (RCTs) are needed to assess venetoclax's role in AML treatment and identify optimal strategies for minimizing toxicities.

Furthermore, our study delved into the treatment effects of venetoclax + HMAs in subgroups of AML patients with common mutations such as FLT-3, IDH, and TP53. The results indicated favorable CR/CRi rates among patients with FLT-3 or IDH1/2 mutations, suggesting that FLT-3 and IDH1/2 mutations may serve as remarkable prognostic factor for the treatment of AML patients with venetoclax + HMA regimens and additional targeting drugs. Nevertheless, further investigation is required to substantiate this hypothesis and elucidate the underlying mechanisms. Additionally, we explored the effects of FLT-3 inhibitors and IDH1/2 inhibitors, with or without other agents, in the therapy for FLT-3-mutated and IDH1/2-mutated AML patients based on pooled results from controlled studies in the current analysis. The results manifested that, compared to control groups, both FLT-3 inhibitors and IDH inhibitors exhibited significant better treatment response with non-significant differences on hematological adverse events. These results, consistent with previous studies [59–62], suggest that FLT-3 inhibitors and IDH1/2 inhibitors are generally well-tolerated, and possess anti-leukemic activity in AML patients with FLT-3-mutated and IDH1/2-mutated.

It's important to note that our meta-analysis was based on data extracted from published articles, relying on a comprehensive literature search. The process of data extraction, analysis, and quality assessment was conducted independently by multiple authors to minimize errors and bias. Sensitivity analyses indicated the robustness of our pooled outcomes, and no significant publication bias was detected in the enrolled studies. However, like any other meta-analysis, our study has certain limitations. Firstly, significant heterogeneity was observed between included studies in several meta-analyses, which may be attributed to variations in baseline patient characteristics: studies used different venetoclax administration schedules (e.g., 14-day vs. 28-day cycles) and HMA dosing frequencies. For instance, Aiba et al. (2023) reported shorter venetoclax durations with comparable efficacy but reduced toxicity; subgroup analyses stratified untreated vs. relapsed/refractory (R/R) AML patients showed differing response rates (OR: 0.56 vs.

0.68), indicating prior treatment history as a confounder; dose reductions or interruptions due to cytopenia were inconsistently reported, potentially affecting response rates and toxicity profiles; in addition, co-treatments such as G-CSF (for neutropenia management) and antibiotics (for infection prophylaxis/treatment) were inconsistently reported across studies. For example, Mirgh et al. (2021) noted baseline infections influencing treatment duration, while others omitted such details. These variables could confound hematological adverse event rates (e.g., neutropenia) and response durability. Secondly, the included studies in the meta-analysis of venetoclax + HMA were predominantly single-armed studies or data extracted from one arm of a single RCT, which may introduce selection bias and baseline variability of the results due to the absence of randomized designs and direct cross-study comparisons as controlled trials often had stricter inclusion criteria than retrospective single-arm studies. Thirdly, survival data (e.g., OS, EFS) were not extractable because most included studies did not report survival outcomes at uniform timepoints or provided insufficient follow-up durations. Lastly, adverse events among patients with mutations were not assessed due to the lack of available relevant data. Additional studies are warranted to investigate the toxicity profile of venetoclax + HMA in the treatment of AML.

Conclusion

Our study provides comprehensive insights into the efficacy and safety of venetoclax and HMAs in AML treatment, particularly in patients with FLT-3 and IDH mutations. The findings underscore the potential benefits of this therapeutic approach while emphasizing the need for further research, including prospective studies and well-designed RCTs, to optimize the clinical use of venetoclax and minimize associated toxicities.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02571-x.

Additional file 1: Figure S1. Forest plots of pooled OR for different types of AML.

Additional file 2: Figure S2. Forest plots of pooled CR/CRi for different types of AML.

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Not applicable.

Author contributions
Yi Wang, Yingying Chen, and Dongdong Ji conceived and designed this study. Yi Wang, Yingying Chen, and Dongdong Ji were responsible for the collection, extraction, and analysis of the data. Yi Wang, Yingying Chen, and Dongdong Ji were responsible for writing the paper. Ling Ge, Yu Zhang, Lixia Liu, Lei Jiang, and Leiming Xia performed the quality evaluation and completed data analysis. Yi Wang, Fengbo Jin and Leiming Xia polished the English language. All authors and participants reviewed the paper and reached an agreement to approve the final manuscript.

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Availability of data and materials
The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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