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Venetoclax and hypomethylating agents versus induction chemotherapy for newly diagnosed acute myeloid leukemia patients: a systematic review and meta-analysis

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Abstract

Background Venetoclax with hypomethylating agents (VEN-HMAs) has shown inconsistent efficacy versus induction chemotherapy (IC) in newly diagnosed AML (ND-AML). Whether or not VEN-HMAs are of clinical benefit remains uncertain. We conducted this meta-analysis to evaluate the clinical benefit of VEN-HMAs versus IC in various subtypes of ND-AML.

Methods We searched PubMed, Embase, Cochrane Library, and Web of Science databases up to 17 June 2024. The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS). Data were extracted to perform meta-analysis or descriptive analysis. The random-effects model was used to calculate the effect sizes and 95% confidence interval (CI). Relative risk (RR) was used to estimate complete response (CR), CR/ complete response with incomplete blood count recovery (CRi), overall response rate (ORR), and 30-day mortality. Hazard ratio (HR) was used to evaluate overall survival (OS) data.

Results Fifteen retrospective cohort studies with 3809 participants were identified. Compared to the IC group, the pooled RR estimates for VEN-HMAs were 1.05 (95% CI 0.88–1.26, $P=0.591$) for CR, 1.09 (95% CI 0.96–1.23, $P=0.195$) for CR/ CRi, 0.84 (95% CI 0.60–1.18, $P=0.318$) for ORR, and 0.86 (95% CI 0.50–1.49; $P=0.596$) for 30-day mortality. VEN-HMAs prolonged the OS advantage in the ND-AML population (HR = 0.80, 95% CI 0.66–0.97, $P=0.025$), and was demonstrated in patients with nucleophosmin 1 (NPM1) mutation (HR = 0.64, 95% CI 0.44–0.92, $P=0.017$). In AML patients with RUNX1::RUNX1T1 cytogenetic abnormalities, the pooled ORR was lower in the VEN-HMAs group (RR = 0.44, 95% CI 0.28–0.69, $P<0.001$), but OS was of no significantly different (HR = 1.30, 95% CI 0.52–3.26,$P=0.58$). However, only 2 studies were available and the results should be taken with caution. OS benefit was similar in other subgroup analyses based on cytogenetic risk, age, and AML type (de novo, secondary, treatment-related or prior therapy for myeloid disease cohort).

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Conclusion Compared with the IC group, VEN-HMAs improved OS in ND-AML, especially in the NPM1 mutation subgroup (HR = 0.64), ensured the efficacy of CR, CR/CRi and ORR, without increasing 30-day mortality, necessitating further head-to-head randomized controlled trials (RCTs).

Trial registration This trial was registered with PROSPERO (www.crd.york.ac.uk/prospero/) on 13 July 2024, the registration number is CRD42024560585.

Keywords Meta-analysis, Acute myeloid leukemia, Venetoclax, Hypomethylating agents, Intensive chemotherapy, Survival

Introduction

There are many unmet clinical needs in the treatment of newly diagnosed acute myeloid leukemia (ND-AML). Intensive chemotherapy (IC) has been the backbone of treatment for medically fit AML for decades, but patients in the adverse-risk category have a significantly lower complete response (CR) rate and a poor prognosis according to the European LeukemiaNet (ELN) genetic risk stratification [1]. The median age at diagnosis of AML is 68 years, and more than two-thirds of diagnosed patients are over the age of 60 [2]. Elderly patients have more comorbidities and complications, and the efficacy of IC is limited.

Over the past five years, new therapeutic options have increased choices for patients with AML. The BCL2 inhibitor venetoclax (VEN) in combination with hypomethylating agents (VEN-HMAs) improves overall survival (OS), providing a giant leap forward for elderly unfit AML patients, and is increasingly being used in medically fit patients [3]. A meta-analysis conducted by Dinesh Keerty indicated that the use of VEN and Azacitidine (VEN-AZA) has a better relative risk (RR) of death than IC in elderly unfit intermediate to high-risk patients [4]. In a multi-center phase 2 study (NCT04752527), VEN and Decitabine (VEN-DEC) achieved a composite complete remission (CRc) of 93% in younger fit ELN adverse-risk AML patients [5]. While fitness criteria remain subjective and inconsistently defined, VEN-HMAs offer a potentially less toxic and more widely accessible treatment alternative.

Several retrospective studies have suggested that medically fit populations with ND-AML may benefit from VEN-HMAs over IC, while others haven't [6–9]. The question of whether less intensive VEN-HMAs would be more beneficial than IC is important but remains controversial. Subgroup analyses based on karyotypes, mutations, age, and AML type are imperative to comprehending the heterogeneity of ND-AML, and to develop personalized treatment strategies for individual patients. These analyses have established prognostic significance in both the 2022 ELN risk stratification and prior studies [10–14]. By stratifying patients according to these characteristics, clinicians can optimize therapeutic approaches and improve outcomes in ND-AML. Currently no published study has comprehensively evaluated the therapeutic efficacy of VEN-HMAs versus IC in ND-AML and in all subgroups mentioned above. We performed this meta-analysis to evaluate the benefit of VEN-HMAs versus IC in diverse ND-AML populations.

Materials and methods

This study rigorously adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [15], and was registered in PROSPERO (CRD42024560585) on 13 July 2024. As all analyses were based on existing published studies, ethical approval or patient consent was considered unnecessary.

Data sources and literature search strategy

Two researchers Yun Liu and Jinhong Gao independently performed a comprehensive literature search of PubMed, Embase, Web of Science, and the Cochrane Library databases up to 17 June 2024. Any discrepancies in the included literature were resolved by consensus or by consultation with another senior investigator. The primary search terms consisted of"Leukemia, Myeloid, Acute","acute myeloid leukemia"or"AML","Venetoclax"or"Venclexta","Azacitidine"or"Vidaza","Decitabine "or"Dacogen","hypomethyl*"or"HMA", combined with the phrase"randomized controlled trial","cohort studies", with no time or language restrictions. The references of all identified studies were screened to identify eligible studies. The full search strategy is shown in Table S1.

Literature inclusion and exclusion criteria

Inclusion criteria: (1)Participants: Adult ND-AML patients; (2) Intervention: VEN-HMAs regimens; (3) Comparison: IC defined as a multi-day cytarabine (≥ 100 mg/m^2 per day) based regimens or cladribine/fludarabine based regimens; (4) Outcome: The study provided the primary outcomes on CR/complete response with incomplete blood count recovery (CRi) rate and OS data; secondary outcomes of CR, overall response rate (ORR) and 30-day mortality; (5) Study design: Cohort studies, randomized controlled trials (RCTs); (6) More than 10 participants in each study group.

Exclusion criteria: (1) Low-intensity chemotherapy; (2) Reviews, meta-analysis, case reports, conference abstracts without full-text availability, and non-human studies; (3) Studies didn't include one of the primary measurable outcomes; (4) Incomplete raw data; (5) Duplicate publications.

Data extraction

Data collected for each study included authors, year of publication, country of study population, study period, study design, entry criteria, sample size, participant gender, age, AML type, Eastern Cooperative Oncology Group (ECOG) performance status, cytogenetic risk, outcome variables (CR, CR/CRi, ORR, 30-day mortality), median OS, median follow-up time. Data extraction was performed independently by 2 authors (Yun Liu and Jinhong Gao), with disagreements resolved by discussion or by consulting a third author, Fang Xie.

Quality assessment

Finally, 15 retrospective cohort studies and none of the RCTs were included. Two independent authors (Yun Liu and Jinhong Gao) assessed the quality studies according to the 9-star Newcastle–Ottawa Scale (NOS) [16]. The NOS is divided into three columns: selection, comparability and outcome, with 6 out of 9 stars or more being considered high quality literature. Any discrepancies were resolved by discussion.

Statistical analysis

Data analysis was performed with STATA version 16. Results were presented as forest plots for the individual studies and calculated as RR or hazard ratio (HR). A 95% confidence interval (CI) was reported for each outcome. We analyzed the outcome measures in an intention-to-treat population. The random-effects model was used to pool study results and obtain heterogeneity between studies. The heterogeneity of study results was assessed using the chi-squared statistic, with significance being set at P value <0.1. The I^2 was used to estimate the total variation. $I^2 < 30\%$, 30%−50%, 50%−75%, and $>75\%$ were considered as low, moderate, substantial, and considerable levels of heterogeneity, respectively. Sensitivity analyses were used to assess the stability of the results. Publication bias of the studies was assessed using funnel plots and Egger's test.

Results

Literature search

The detailed steps of the literature screening are shown in Fig. 1. The search returned 1801 potentially relevant articles, of which 532 duplicates were excluded, 1269 records were screened by title and abstract. 35 were considered for further investigation. After excluding 20 for various reasons, 15 retrospective cohort studies met our inclusion criteria and were comprehensively analyzed [6–9, 17–27].

Study characteristics

A total of 15 studies with 3809 patients were contained. 6 of the studies were multi-center [8, 9, 20, 21, 23, 25], and 2 queried the University of Pennsylvania Health System (UPHS) electronic medical record database and the Flatiron Health database, which is a nationwide electronic health record (EHR) database [8, 9]. Data from the Flatiron Health database were also analyzed in 2 other single-center studies [17, 22]. Propensity-score matching (PSM) can reduce selection bias by balancing confounding factors in non-randomized studies. A total of 5 studies using PSM methods were included in this meta-analysis [7, 17, 19–21]. If other studies included reported multiple corrected HRs, data were extracted from multivariate models of propensity scores [6, 8, 9, 18].

Among all of the included ND-AML studies, 1 study involved patients without cytogenetic abnormalities of core binding factor [6], 2 studies involved cytogenetic abnormalities of RUNX1::RUNX1 T1 [19, 20], 2 studies were patients with tumor protein p53 (TP53) mutation or del17p [22, 26], 1 study was patients with nucleophosmin 1 (NPM1) mutation [27], and 1 study was patients with isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations [23]. 1 study included patients with secondary AML [24], 1 included patients with treated secondary AML [18], and 1 with molecularly defined secondary AML [25]. These studies differed in terms of demographic, baseline disease and treatment characteristics. Overall, they were considered to be of good quality in the analysis, and were published in refereed journals. The characteristics of publication are listed in Table 1.

Quality assessment

The bias of each included study was assessed using the NOS scores of the retrospective cohort studies, as detailed in Table S2. The NOS scores were greater than or equal to 7 for all the studies.

Pooled prognosis of overall study

Comparable pooled efficacy was achieved between the VEN-HMAs and IC groups (CR: RR = 1.05, 95% CI 0.88–1.26, P = 0.591, 10 studies; CR/CRi: RR = 1.09, 95% CI 0.96–1.23, P = 0.195,10 studies; ORR: RR = 0.84, 95% CI 0.60–1.18, P = 0.318, 6 studies) with substantial heterogeneity (CR: I^2 = 62.9%, P = 0.004; CR/CRi: I^2 = 68.2%; P = 0.001; ORR:I^2 = 86.6%; P < 0.001) using random-effects models (Fig. 2A-C). 14 studies were available for the analysis of OS, VEN-HMAs prolonged OS (HR = 0.80, 95%

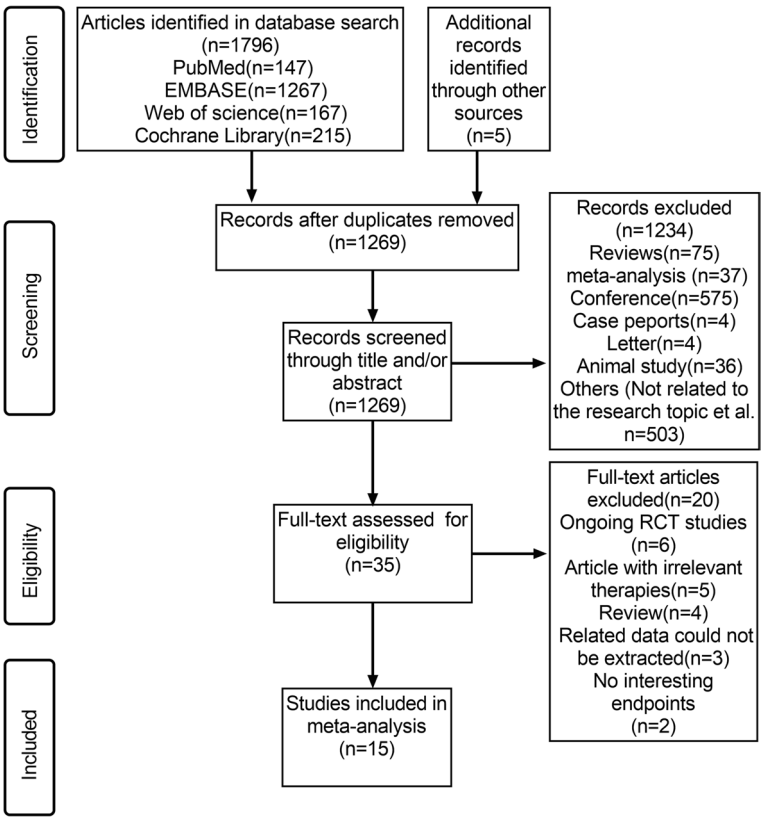

Fig. 1 Flow chart of study identification and selection procedure

CI 0.66–0.97, P= 0.025) with moderate heterogeneity (I^2= 47.5%, P= 0.025, random-effects models, Fig. 2D). Sensitivity analysis confirmed that the overall RR of CR, CR/CRi, ORR and HR of OS were stable and not affected by any single study (Fig.S1 A-D). Both the funnel plot (Fig.S2 A-D) and Egger's test (CR: P= 0.999; CR/CRi: P= 0.942; ORR: P= 0.331; HR: P= 0.441) showed no significant publication bias.

Subgroup analysis regarding karyotypes

Among AML patients with cytogenetic abnormalities of RUNX1::RUNX1 T1 (only 2 studies available), the ORR was worse in the VEN-HMAs group than in the IC group (RR =0.44, 95% CI 0.28–0.69, P< 0.001; I^2= 0; Fig. 3A), but OS was of no different (HR =1.30, 95% CI 0.52–3.26,P= 0.58; I^2= 0; Fig. 3B). These findings should be interpreted cautiously due to the limited data and require validation in larger cohorts or randomized studies.

In terms of favorable risk cytogenetics, OS results in the VEN-HMAs group were similar to those in the IC group (HR =1.23, 95% CI 0.78–1.94, P= 0.373; 3 studies) without heterogeneity (Fig. 4). In addition, the VEN-HMAs group had no statistically significant advantage over IC in either intermediate-risk karyotypes (HR =1.23, 95% CI 0.65–2.32, P= 0.519; I^2= 81.5%, P< 0.001; 5 studies) or adverse-risk cytogenetics (HR =1.14, 95% CI 0.73–1.77, P= 0.558; 6 studies), and considerable heterogeneity was observed in both subgroups. For intermediate-risk karyotypes, sensitivity analysis demonstrated that heterogeneity was overcome by removing the study from Maiti et al. [7], showing a pooled HR of 1.44 (95% CI 1.01–2.05, P= 0.042; 4 studies; Fig.S3 A). For adverse-risk cytogenetics, the considerable heterogeneity was not eliminated by sensitivity analysis, showing a stable randomized model (Fig.S4 A).

Subgroup analysis regarding mutations

Regarding mutations, VEN-HMAs consistently favored better OS in the NPM1 mutation cohort (HR =0.64, 95% CI 0.44–0.92, P= 0.017; I^2= 19.1%, P= 0.279; 7 studies; Fig. 5). OS was of no statistical significance between the two groups in additional sex combs-like 1 (ASXL1) (HR =1.31, 95% CI 0.96–1.78, P= 0.161; I^2= 0, P= 0.716; 5 studies), rat sarcoma (RAS) (HR =1.26, 95% CI 0.83–1.89, P= 0.276; I^2= 0, P= 0.884;3 studies), IDH1/2 (HR =0.63, 95% CI 0.25–1.60, P= 0.335; I^2= 86.1%, P< 0.001; 5 studies), TP53 (HR =0.84, 95% CI 0.61–1.16, P= 0.284; I^2= 50.6%, P= 0.072; 6 studies), fms-like tyrosine kinase

Table 1 Characteristics of the included studies

Author /Year	Country/ Period	Entry criteria	Study design	Treatment protocol	Patients (male)	Median age (years)	AML type	ECOG PS	Cytogenetics risk category	CR	CR/ CRi	ORR (CR/CRi + MLFS)	30-day mortality	Median OS (months)	Median follow-up time (months)
Cherry 2021 [6]	United States/2007–2020	ND-AML without CBF-AML	retro-spective	VEN- AZA	143 (72)	69.5 (22–91)	De novo:57 Second-ary:59 Treat-ment-related:27 Prior HMAs:17	NA	Favorable: 24; Inter-mediate:24; adverse: 93; unknown: 2	89	102	110	7	16.1	26.9
				IC (7 + 3 ± other agent; Ara-C ± clo-farabine; FLAG ± ida-rubicin; CPX-351)	149 (78)	52.7 (19–81)	De novo:92 Second-ary:42 Treat-ment-related:15 Prior HMAs:15	NA	Favorable: 23; Inter-mediate:24; adverse:60; unknown:42	98	100	105	8	29.5	56.5
Maiti 2021 [7]	United States/ 2000–2019	ND-AML	Retro-spective (PSM)	VEN- DEC	85 (45)	72 (69–78)	De novo:55 Second-ary:15 Treat-ment-related:16	0–1: 55; 2: 30	Favorable:0; Intermedi-ate:44; adverse:40	52	69	NA	1	12.4	12.4
				IC (regimens containing Ara-C 1 g/m2/d)	85 (48)	73 (67–76)	De novo:59 Second-ary:9 Treat-ment-related:19	0–1: 58; 2: 27	Favorable:0; Intermedi-ate:33; adverse:52	36	44	NA	20	5	81.2

Table 1 (continued)

Author /Year	Country/ Period	Entry criteria	Study design	Treatment protocol	Patients (male)	Median age (years)	AML type	ECOG PS	Cytogenetics risk category	CR	CR/ CRi	ORR (CR/CRi + MLFS)	30-day mortality	Median OS (months)	Median follow-up time (months)
Matthews 2023 [8]	United States/ 2017–2021/ UPHS; EHR	ND-AML	retro-spective	VEN- HMAs	488 (284)	71 (60–75)	De novo:104 Second-ary: 312 Therapy-related: 72	0: 112; 1–2:269; Missing: 107	Favorable:45; Intermedi-ate 62 Adverse:258; Missing: 123	NA	NA	NA	24	10	13
				IC (7 + 3)	312 (175)	67 (60–70)	De novo: 159 Second-ary: 140 Therapy-related:13	0: 71; 1–2: 146; Missing: 95	Favorable:59; Intermediate: 89; Adverse:99; Missing: 65	NA	NA	NA	10	22	13
Matthews 2022 [9]	United States/ 2017–2021 UPHS; EHR	ND-AML	retro-spective	VEN- AZA	439 (248)	75 (36–88)	De novo:226 Second-ary:150 Therapy-related:63	0–1: 62; 2–4: 197; Missing: 181	Favorable:34; Intermediate: 117 Adverse: 172; Missing:116	75	188	NA	22	11	8.8
				IC (CPX-351)	217 (105)	67 (21–82)	De novo:63 Second-ary:104 Therapy-related:50	0–1: 31; 2–4: 72; Missing: 116	Favorable:15; Intermedi-ate:64 Adverse:92; Missing: 46	27	108	NA	11	13	13.4
Zeidan 2023 [17]	United States/2018–2021/ EHR	ND-AML	retro-spective (PSM)	VEN- AZA	138 (85)	71 (59–83)	De novo:84 Second-ary:44 Therapy-related:10	0–1: 74; ≥ 2: 18; Unknown: 46	Favorable:6; Interme-diate15; adverse:30; unknown87	NA	NA	61(44.2)	NA	11.3	NA
				IC (Ara-C + anthra-cycline; cladribine/ fludarabine -based regimens;)	138 (78)	69 (59–79)	De novo:84 Second-ary:44 Therapy-related:10	0–1: 65; ≥ 2: 22; Unknown: 51	Favorable:9; Intermediate:7; adverse:41; unknown:81	NA	NA	84(60.9)	NA	17.7	NA

Table 1 (continued)

Author /Year	Country/ Period	Entry criteria	Study design	Treatment protocol	Patients (male)	Median age (years)	AML type	ECOG PS	Cytogenetics risk category	CR	CR/ CRi	ORR (CR/CRi + MLFS)	30-day mortality	Median OS (months)	Median follow-up time (months)
Short 2022 [18]	United States/ 2004–2021	ts-AML	retro-spective	VEN- HMAs	54	71 (42–84)	Prior therapies: 54	NA	Diploid:16; Non-diploid, non-adverse:7; Adverse:25; unknown: 6	14	21	29	4	5.8	47
				IC (7 + 3/ cladribine/ fludara-bine- based regimens ± other agent)	271	65 (21–91)	Prior therapies: 271	NA	Diploid:82 Non-diploid; non-adverse:56 Adverse:111; unknown:22	43	64	82	27	4.5	47
Wang 2023 [19]	China/ 2015–2023	ND-AML with RUNX1:: RUNX1 T1	retro-spective (PSM)	VEN- HMAs	18 (12)	39.5 (17–69)	NA	0–1: 13; ≥ 2: 5	NA	2	5	5	NA	NR	14.8
				IC (7 + 3)	34 (18)	41.5 (16–59)	NA	0–1: 23; ≥ 2: 11	NA	18	21	22	NA	NR	28.6
Jin 2024 [20]	China/ 2020–2023	ND-AML with RUNX1:: RUNX1 T1	retro-spective (PSM)	VEN -HMAs	20 (7)	< 65 (13) ≥ 65 (7)	De novo:19 Second-ary 1	≤ 2:10; > 2:10	Favorable:20; Intermedi-ate:0; adverse:0	NA	NA	8	NA	NR	NA
				IC (Ara-C + anthracy-cline; HAG; cladrib-ine- based regimens)	20 (10)	< 65 (13) ≥ 65 (7)	De novo:19 Second-ary: 1	≤ 2:11; > 2:9	Favorable:18; Intermedi-ate:0; adverse:0; missing:2	NA	NA	18	NA	NR	NA
LIU 2024 [21]	China/ 2021–2022	ND-AML	retro-spective (PSM)	VEN- AZA	25 (18)	70 (60–75)	NA	< 2: 0; ≥ 2: 25	Favorable0; Intermedi-ate:18 Adverse:7	15	16	17	3	NR	8
				IC (7 + 3)	25 (16)	63 (60–75)	NA	< 2: 0; ≥ 2: 25	Favorable0; Intermedi-ate:18 Adverse:7	17	18	21	1	NR	12

Table 1 (continued)

Author /Year	Country/ Period	Entry criteria	Study design	Treatment protocol	Patients (male)	Median age (years)	AML type	ECOG PS	Cytogenetics risk category	CR	CR/ CRi	ORR (CR/CRi + MLFS)	30-day mortality	Median OS (months)	Median follow-up time (months)
Daver 2023 [22]	United States/ 2014–2021/ EHR	ND-AML with TP53 Mutation or del17p	retro-spective	VEN -HMAs	94 (56)	75 (69–80)	Second-ary: 32 therapy-related:15 Prior HMAs:10	0–1: 48; ≥ 2: 21 Missing: 25	Adverse: 75	NA	NA	NA	NA	7.4	6
				IC (Ara-C + anthra-cycline; cladribine/ fludarabine -based regimens; MEC)	135 (75)	62 (56–68)	Second-ary: 37 therapy-related:11 Prior HMAs:7	0–1:43; ≥ 2: 9 Missing: 83	Adverse:62	NA	NA	NA	NA	9.4	7
Bewers-dorf 2024 [23]	United States/ NA	ND-AML with IDH1/2 mutation	retro-spective	VEN -HMAs	70 (38)	75 (60–88)	Second-ary: 22 Therapy-related:11 Prior HMAs:5	NA	Favorable: 16; Intermedi-ate: 9 Adverse: 39	32	47	NA	NA	13.8	NA
				IC (conven-tional or CPX-351 ± third agent)	81 (48)	67 (60–76)	Second-ary: 16 Therapy-related:13 Prior HMAs:12	NA	Favorable:20; Intermediate: 11 Adverse: 39	53	54	NA	NA	25.3	NA
Salhotra 2021 [24]	United States/ 2018–2020	Secondary AML	retro-spective	VEN- DEC	30 (14)	63 (35–72)	Second-ary16: Therapy-related:10 Prior HMAs:4	NA	Favorable:0: Intermedi-ate:6; Adverse: 24	14	21	NA	NA	10.1	9.9
				IC (CPX-351)	20 (13)	63 (43–73)	Second-ary:7 Therapy-related:6 Prior HMAs:7	NA	Favorable:0; Intermedi-ate:10; Advers:10	6	10	NA	NA	11.3	11.3

Table 1 (continued)

Author /Year	Country/ Period	Entry criteria	Study design	Treatment protocol	Patients (male)	Median age (years)	AML type	ECOG PS	Cytogenetics risk category	CR	CR/ CRi	ORR (CR/CRi + MLFS)	30-day mortality	Median OS (months)	Median follow-up time (months)
Shimony 2024 [25]	United States/ /	molecularly defined s- AML	retro-spective	VEN- HMAs	162 (105)	74 (25–89)	Second-ary: 72 Therapy-related:30 Prior thera-pies:46	NA	Adverse:162	NA	91	NA	4	15	NA
				IC (7 + 3)	167 (120)	63 (22–78)	Second-ary: 45 Therapy-related:24 Prior thera-pies:33	NA	Adverse:167	NA	94	NA	5	22	NA
				IC (CPX-351)	66 (42)	66 (44–76)	Second-ary: 52 Therapy-related:12 Prior thera-pies:33	NA	Adverse:66	NA	29	NA	3	12	NA
Zhao 2023 [26]	Canada/ 2015–2021	ND-AML With TP53 mutation	retro-spective	VEN- AZA	10 (6)	72.0 (55.2–83.1)	De novo: 7 Second-ary: 1 Therapy-related: 2	NA	Adverse:10	5	NA	NA	NA	12	NA
				IC (FLAG -IDA; 3 + 7; CPX-351)	57 (32)	63.7 (34.3–76.7)	De novo: 46 Second-ary: 7 Therapy-related:4	NA	Adverse: 57	29	NA	NA	NA	10.8	NA

Table 1 (continued)

Author /Year	Country/ Period	Entry criteria	Study design	Treatment protocol	Patients (male)	Median age (years)	AML type	ECOG PS	Cytogenetics risk category	CR	CR/ CRi	ORR (CR/CRi + MLFS)	30-day mortality	Median OS (months)	Median follow-up time (months)
Lachowiez 2020 [27]	United States/ 2007–2019	ND-AML with NPM1 mutation	retrospective	VEN- HMAs	28	71 (NA)	De novo: 25 Secondary: 1 Therapy-related: 2	0–1: 15; 2–3: 9;	Favorable: 24; Intermediate:0 Adverse: 4	25	27	NA	1	NR	NA
				IC (Ara-C + anthracycline ± other agents)	228	55 (NA)	De novo: 213 Secondary:4 Therapy-related: 11	0–1: 180; 2–3: 27;	Favorable: 183; Intermediate: 4 Adverse: 11	193	204	NA	9	44	NA

Abbreviations: *ND- AML* Newly diagnosed- acute myeloid leukemia, *ts-AML* Treated secondary- AML, *CBF* Core binding factor, *PSM* Propensity-score matching, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CR* Complete remission, *Cri* Complete remission with incomplete hematological recovery, *ORR* Overall response rate, *MLFS* Morphological leukemia-free state, *OS* Overall survival, *VEN* Venetoclax, *AZA* Azacitidine, *DEC* Decitabine, *HMAs* Hypomethylating agents, *IC* Intensive chemotherapy, *UPHS* The University of Pennsylvania Health System, *EHR* Electronic health record, *LIT* Low-intensity therapy, *Ara-C* Cytarabine, *FLAG* Fludarabine + Ara-C + colony stimulating factor, *MEC* Mitoxantrone + etoposide + Ara-C, *7 + 3* 7 days of Ara-C + 3 days of anthracycline, *CPX-351* Liposomal cytarabine/daunorubicin, *NA* Not available, *NR* Not reached

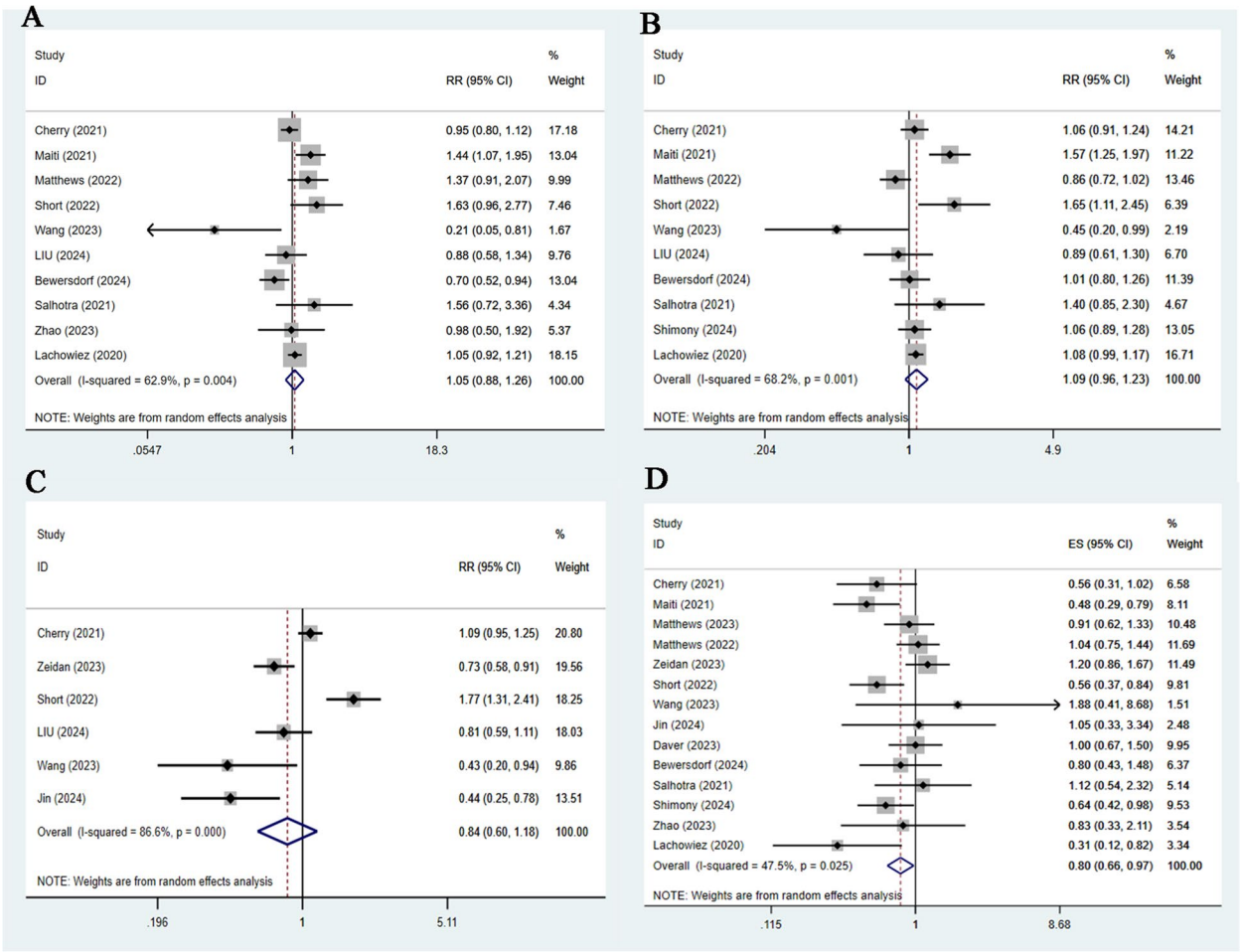

Fig. 2 Forest plot of pooled prognosis. **A** CR. **B** CR/CRi. **C** ORR. **D** OS. The diamonds represent the overall summary RR and HR estimates with 95% CI. HR < 1 indicates a reduced risk of death and increased survival in the VEN-HMAs group

3 (FLT3) (HR = 0.83, 95% CI 0.38–1.80, P = 0.632; I^2 = 75.5%, P < 0.001; 6 studies) and runt-related transcription factor 1 (RUNX1) mutation cohorts (HR = 0.92, 95% CI 0.36–2.36, P = 0.861; I^2 = 67.6%, P < 0.001;4 studies) (Fig. 5). For the TP53 mutation cohort, substantial heterogeneity disappeared when the study of Zeidan et al. [17] was excluded after sensitivity analysis (HR = 0.90, 95% CI 0.87–0.93, P < 0.001;I^2 = 0; 5 studies) (Fig.S3B). For the IDH1/2, FLT3 and RUNX1 mutation cohorts, sensitivity analysis indicated a stable randomized model (Fig.S4 B-D).

Subgroup analysis regarding age

With respect to age, no change was seen in adult ND-AML populations aged < 60 years (HR = 0.92, 95% CI 0.76–1.11, P = 0.384; I^2 = 0, P = 0.424;4 studies) or 60–75 years (HR = 1.05, 95% CI 0.89–1.24, P = 0.569; I^2 = 0, P = 0.483; 5 studies). For patients older than 75 years, VEN-HMAs also offered little superiority (HR = 0.66, 95% CI 0.44–1.00, P = 0.052; I^2 = 0, P = 0.483; 3 studies) (Fig. 6).

Subgroup analysis regarding AML type

In a subgroup analysis based on AML type, there was no significant difference in de novo AML when comparing the VEN-HMAs with the IC group (HR = 1.11, 95% CI 0.59–2.08, P = 0.745), but considerable heterogeneity was observed (I^2 = 89.9%; P < 0.001) (Fig. 7). Removal of Maiti's study significantly reduced heterogeneity (I^2 = 0; P = 0.481), and the direction of the new pooled HR changed (HR = 1.49, 95% CI 1.18–1.89, P = 0.001) (Fig.S3 C). In addition, no differences were found in the secondary AML (HR = 1.02, 95% CI 0.75–1.40, P = 0.896; I^2 = 68.5%, P = 0.002;), treatment-related AML (HR = 1.2, 95% CI 0.9–1.61, P = 0.219; I^2 = 0, P = 0.555;) or prior therapy for myeloid disease

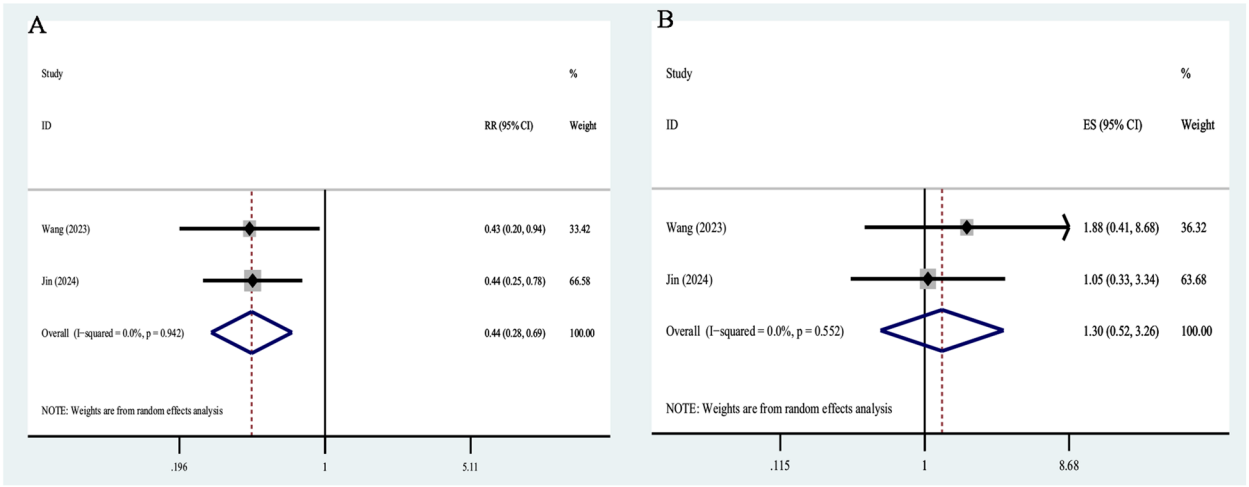

Fig. 3 Forest plot of (**A**) ORR and (**B**) OS in AML patients with cytogenetic abnormalities of RUNX1::RUNX1 T1. The diamonds represent the overall summary RR and HR estimates with 95% CI. RR < 1 indicates a reduced ORR in the VEN-HMAs group. Only 2 studies were available and the results should be taken with caution

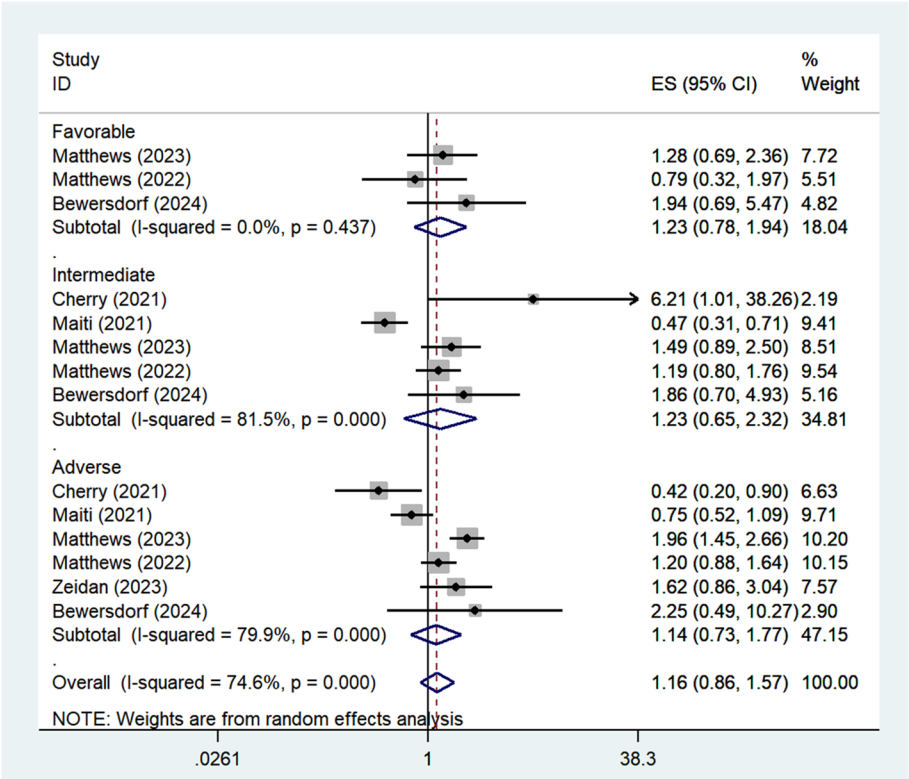

Fig. 4 Forest plot of OS subgroup analysis regarding karyotypes. The diamonds represent the overall summary HR estimates with 95% CI

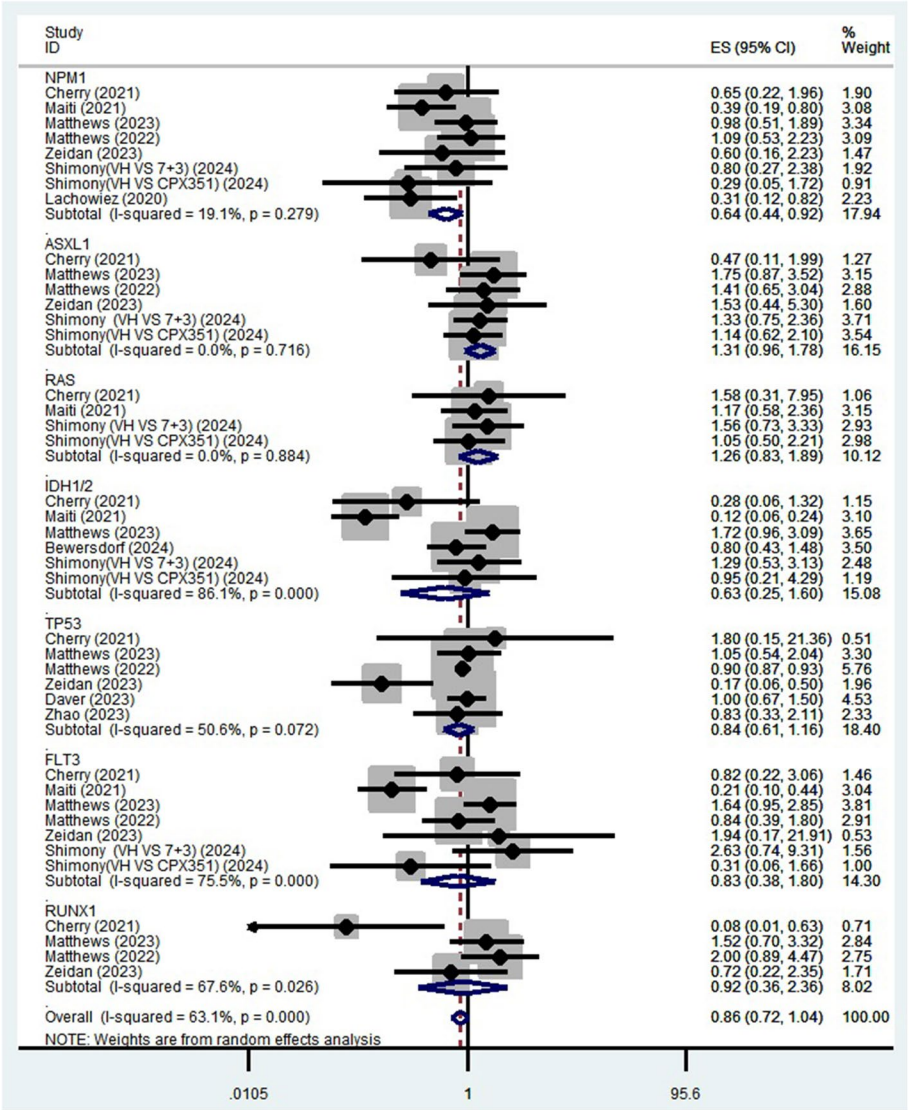

Fig. 5 Forest plot of OS subgroup analysis regarding mutations. The diamonds represent the overall summary HR estimates with 95% CI

cohort (HR = 0.67, 95% CI 0.43–1.04, P = 0.073; I^2 = 32.4%, P = 0.218) (Fig. 7). Further sensitivity analysis confirmed that the overall HR for secondary AML was stable. (Fig.S4E).

30-day mortality

Figure 8 shows that when comparing VEN-HMAs with IC, no change in 30-day mortality (RR = 0.86; 95% CI 0.50–1.49; P = 0.596) was observed with moderate heterogeneity (I = 44.7%; P = 0.081). Sensitivity analysis indicated a stable randomized model (Fig.S1E). Both the funnel plot (Fig.S2E) and Egger's test (P = 0.302) showed no significant publication bias.

Discussion

This meta-analysis synthesizes data from 15 retrospective cohort studies (n = 3809) comparing VEN-HMAs with IC in ND-AML. To our knowledge, this is the first comprehensive evaluation of VEN-HMAs versus IC across molecular, cytogenetic, and clinical subgroups. Our findings demonstrate that VEN-HMAs significantly improve OS compared to IC (HR = 0.80, 95% CI 0.66–0.97), particularly in patients with NPM1 mutations (HR = 0.64, 95% CI 0.44–0.92), while maintaining comparable CR, CR/CRi, ORR and 30-day mortality. Beyond survival benefits, the use of VEN-HMAs combination therapy may improve quality of life for patients

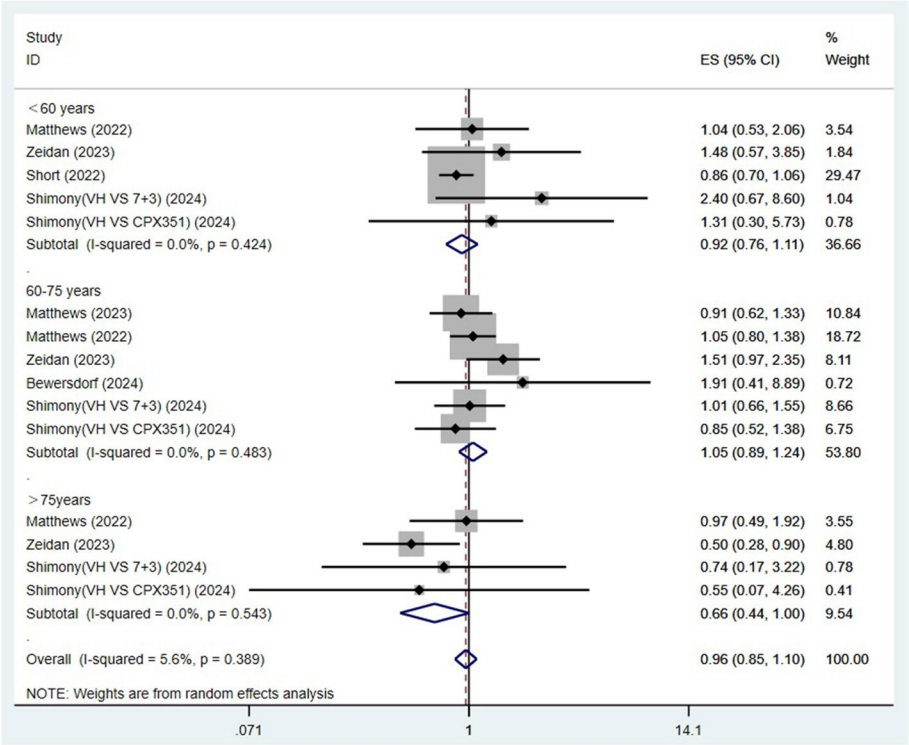

Fig. 6 Forest plot of OS subgroup analysis regarding age. The diamonds represent the overall summary HR estimates with 95% CI

by reducing hospitalization needs and treatment-related toxicity, as suggested by prior studies [3]. Additionally, its oral administration and manageable toxicity profile allow broader application in rural or community hospitals, potentially addressing disparities in AML care access [28]. These advantages position VEN-HMAs as a viable frontline option, especially for elderly patients or those with limited access to tertiary centers. OS benefits were similar in other subgroup analyses based on cytogenetic risk, age, and AML type. Given the limited data (2 studies), the lower ORR and similar OS benefit of VEN-HMAs in RUNX1::RUNX1 T1 AML should be interpreted with caution.

Sensitivity analyses confirmed the robustness of our findings despite heterogeneity in response rates (CR: $I^2 = 62.9\%$; CR/CRi: $I^2 = 68.2\%$; ORR: $I^2 = 86.6\%$) and OS ($I^2 = 47.5\%$). These results are consistent with interim data from NCT05177731 showing comparable CR/CRi rates between VEN-DEC (86%) and 7 + 3 (79%) in younger ND-AML patients [29]. Achievement of CR/CRi remains the strongest predictor of long-term survival regardless of treatment approach [30, 31].

Cytogenetic risk analysis revealed comparable survival outcomes across favorable, intermediate, and adverse-risk groups. However, sensitivity analysis identified the Maiti study [7] as the primary source of heterogeneity in intermediate-risk patients. This study used a high-dose cytarabine regimen (1 g/m2/d) in the IC group, contrasting with standard-dose regimens (≥ 100 mg/m2/d) in other studies, and reported increased treatment-related mortality. Excluding this study reversed the direction of survival benefit, favoring IC in intermediate-risk patients. These findings are supported by a recent Markov analysis, which confirms the advantage of VEN-AZA in adverse-risk patients, while IC remains preferred in intermediate-risk cases [32].

Mutations in NPM1 AML have been reported to be highly sensitive to VEN-based treatment regimens [28, 33, 34], and our findings confirmed with this. As the beneficial impact of NPM1 decreases with increasing age in patients treated with IC, based on our findings, we suggest VEN-HMAs as the optimal treatment for patients with this molecular subgroup, especially for elderly patients. Our review showed similar survival benefits in the ASXL1, RAS, IDH1/2, TP53, FLT3, and RUNX1 mutation cohorts. Notably, the exclusion of Zeidan et al. [17] (with nearly 60% of patients missing TP53 data) revealed a VEN-HMA survival benefit while eliminating heterogeneity (I^2 from 50% to 0). Studies have shown that TP53 and FLT3-ITD mutations are associated with adaptive resistance and poor survival in VEN, demonstrating a significant need for improved treatment [34,

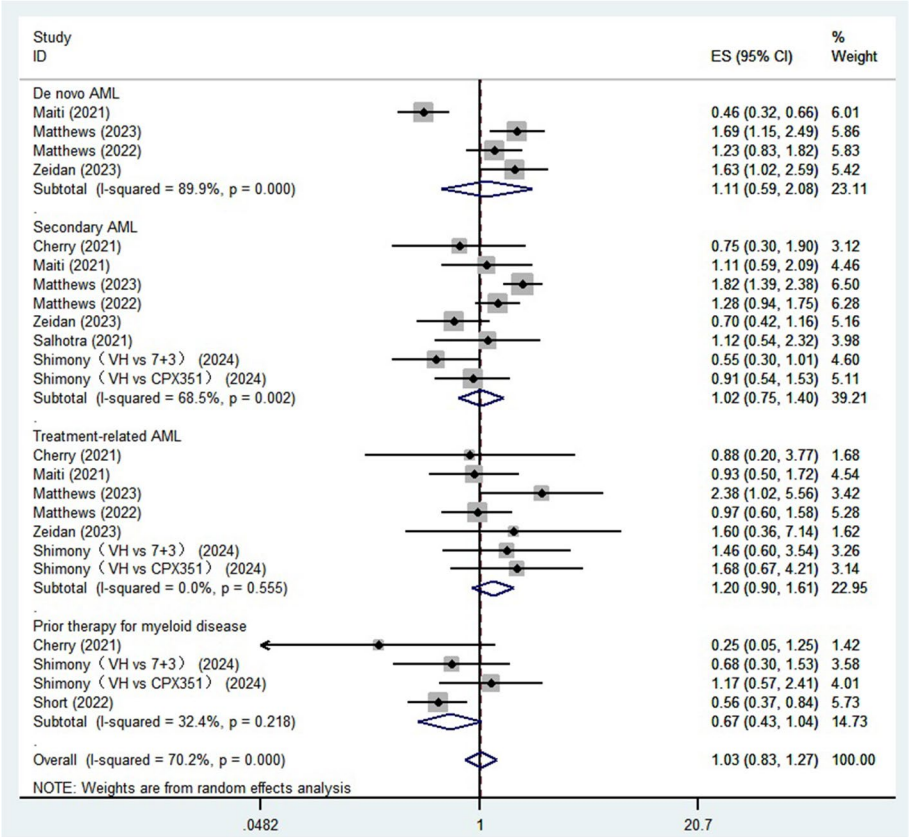

Fig. 7 Forest plot of OS subgroup analysis regarding AML type. The diamonds represent the overall summary HR estimates with 95% CI

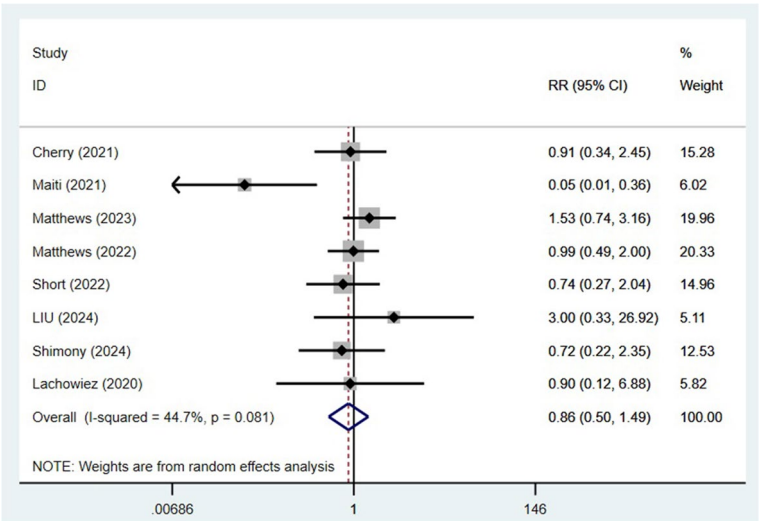

Fig. 8 Forest plot of 30-day mortality. The diamonds represent the overall summary RR estimates with 95% CI

35]. Recent data reported that patients with FLT3-mutations benefited from triplet therapy (VEN-HMAs + FLT3 inhibitors) [36]. Venugopal's study showed no difference in 2-year OS rates between patients with RUNX1 mutations who received IC or VEN-low intensity chemotherapy (2-year OS: 50% versus 53%, $P = 0.47$) [37]. This study

also found that the presence of RUNX1 mutations may not affect clinical outcomes when using VEN-based regimens. In addition, ASXL1 mutations are associated with an initial favorable response to VEN-HMAs, but have a high relapse rate and a negative impact on survival due to the persistence of measurable residual disease [38]. For RAS-mutated AML, a study showed that VEN-HMAs were lack of OS benefit and only high-dose cytarabine regimens were associated with improved survival [39]. Although VEN-HMAs were associated with high rates of durable responses in IDH1/2-mutated AML [40, 41], our study confirms that VEN-HMAs provide a similar survival benefit compared to IC.

In elderly AML patients (> 75 years), VEN-HMAs showed a non-significant survival trend versus IC (HR = 0.66, 95% CI 0.44–1.00), which may be limited by the small sample size (3 studies). Age-stratified analyses showed comparable results between the younger cohort (< 60 years) and the middle-aged cohort (60–75 years), as well as between different AML subtypes (de novo, secondary, treatment-related, prior therapy for myeloid disease). Sensitivity analysis confirmed that Maiti's study [7] again contributed to the heterogeneity in de novo AML, after removing this study, the results were more in favor of IC. This finding emphasizes the influence of regimen intensity on meta-analysis results. The large real-world study from the United Kingdom noted that NPM1, RUNX1, and IDH2 mutations were associated with improved survival, whereas age, secondary and treatment-related mutations in AML, complex karyotypes, and ASXL1 were associated with poorer survival [28]. Our results are partially at variance with these studies and require further RCTs.

Although this study provides the most comprehensive comparative data to date, it has some important limitations. It relied heavily on the included retrospective cohort studies (despite high-quality NOS scores ≥7), which may introduce selection bias. The 15 retrospective cohort studies were heterogeneous in many aspects, such as populations of patients, baseline diseases, treatment characteristics, statistical methods of PSM etc. Several included studies reported hazard ratios (HRs) and confidence intervals (CIs), but did not report the exact number of patients in each group. Raw data were not available. Although funnel plots and Egger's test showed no significant publication bias (Figure S2), retrospective meta-analyses are still at risk of publication bias, especially for emerging therapies such as VEN-HMAs, where negative studies may be under-reported, and heterogeneity in study design (e.g. different IC protocols) may also confound asymmetry tests. For patients with RUNX1::RUNX1 T1 cytogenetic abnormalities, only 2 studies were available, so the conclusion that IC is recommended because of the response benefit should be taken with caution and needs to be validated in larger cohorts or randomized studies. The National Institutes of Health Clinical Trials Registry has 6 registered trials, of which 1 is a completed trial with final results not yet published (NCT05177731) [42] and 5 are ongoing trials (NCT04801797, NCT05628623, NCT05554393, NCT05554406, NCT05939180) [43–47]. We will follow them closely.

Conclusion

This meta-analysis suggests that VEN-HMAs improved OS in untreated AML compared to the IC group, especially for those with NPM1 mutation, ensured the efficacy of remission rate, without increasing 30-day mortality. It suggests that more populations may benefit from VEN-HMAs over IC and makes VEN-HMAs an attractive option for induction therapy in ND-AML patients. In the future, more well-designed head-to-head RCTs with long-term follow-up aiming at remission, overall survival and mortality are required.

Abbreviations

ND-AML	Newly diagnosed acute myeloid leukemia
VEN	Venetoclax
HMAs	Hypomethylating agents
IC	Induction chemotherapy
NOS	The Newcastle–Ottawa Scale
CI	Confidence interval
RR	Relative risk
CR	Complete response
CRi	Complete response with incomplete blood count recovery
ORR	Overall response rate
HR	Hazard ratio
OS	Overall survival
TP53	Tumor protein p53
NPM1	Nucleophosmin 1
IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase 2
RCTs	Randomized controlled trials
ELN	The European LeukemiaNet
AZA	Azacitidine
DEC	Decitabine
ECOG	Eastern Cooperative Oncology Group
UPHS	The University of Pennsylvania Health System
HER	Electronic health record
PSM	Propensity-score matching
IDH	Isocitrate dehydrogenase
ASXL1	Additional sex combs-like 1
RAS	Rat sarcoma
FLT3	Fms-like tyrosine kinase 3
RUNX1	Runt-related transcription factor 1

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14311-9.

Supplementary Material 1: Table S1 The strategy of the literature search from inception to 17 June 2024.

Supplementary Material 2: Table S2 The quality of the 15 included studies was assessed using the NOS scores

Supplementary Material 3: Fig.S1 Sensitivity analysis of pooled prognosis and 30-day mortality. (A) CR. (B) CR/CRi. (C) ORR. (D) OS. (E) 30-day mortality. White circles and white vertical bars represent composite effect sizes (e.g. HR, RR) and 95% confidence intervals (CIs) recalculated after excluding individual studies on an item-by-item basis

Supplementary Material 4: Fig.S2 Funnel plot of pooled prognosis and 30-day mortality. (A) CR. (B) CR/CRi. (C) ORR. (D) OS. (E) 30-day mortality

Supplementary Material 5: Fig.S3 Forest plot of OS subgroup analysis for intermediate-risk karyotypes (A) TP53 mutation (B) and de novo AML (C) after sensitivity analysis

Supplementary Material 6: Fig.S4 Sensitivity analysis of OS in various subgroups. (A) Karyotypes. (B) IDH1/2 mutation. (C) FLT3 mutation. (D) RUNX1 mutation. (E) Secondary AML. White circles and white vertical bars represent composite effect sizes (e.g. HR, RR) and 95% confidence intervals (CIs) recalculated after excluding individual studies on an item-by-item basis

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Authors' contributions
Conception and design: Yun Liu, Lijuan Wang, and Jinsong Yan. Data extraction and analysis: Yun Liu, Jinhong Gao, and Fang Xie. Manuscript writing: Yun Liu, Jinhong Gao and Chengtao Zhang. Revision of the manuscript: Ying Zhang, Peimin Mao, Jinsong Yan. All authors contributed to the preparation of this article and approved the version submitted.

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All data generated or analyzed during this study are included in this article and its supplementary materials.

Declarations

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Consent for publication
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Competing interests
The authors declare no competing interests.

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