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Comparative efficacy and safety in low-intensity treatment for acute myeloid leukemia in older patients: a systematic review and network meta-analysis

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Abstract

Background Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with a median age at diagnosis of 68 years. The outcomes in older or unfit AML patients on intensive chemotherapy are poor, and thus, it is necessary to explore alternative strategies. In recent years, non-intensive therapies have transformed the standard of care for this population. Despite the increasing number of randomized clinical trials (RCTs) and cohort studies in this area, the optimal treatment approach remains unclear.

Methods We sourced four databases, PubMed, Embase, Cochrane, and Web of Science, until July 07, 2024, to identify all Phase II/III randomized controlled trials (RCTs) and cohort studies evaluating low-intensity treatments for older AML patients. Overall survival (OS), recurrence-free survival (RFS), complete remission (CR), complete remission with incomplete hematologic recovery (CRi), overall response rate (ORR), and adverse events (AEs) graded ≥ 3 were analyzed using a Bayesian fixed-effects network meta-analysis (NMA).

Results A total of 4920 patients across 26 trials were included. In terms of improving OS, AZA + VEN, LDAC + glasdegib, and LDAC + VEN (SUCRA = 0.936, 0.898, and 0.718, respectively) were the most effective treatments. For CR, ORR, and CRi, AZA + VEN ranked highest among all therapies (SUCRA = 0.836, 0.911, and 0.829, respectively).

Conclusion This systematic review and network meta-analysis suggest that AZA + VEN is superior to the current standard of care, particularly in improving OS, CR, ORR, and CRi. LDAC + glasdegib also demonstrated promising efficacy and warrants further investigation.

Keywords Acute myeloid leukemia, Hypomethylating agents, Venetoclax, Network meta-analysis, Elderly

Introduction

Acute myeloid leukemia (AML) is a malignant infiltrative disease of the myeloid lineage, characterized by the accumulation of myeloid precursor cells in bone marrow, blood, and other tissues, resulting in reduced production of mature blood cells [1]. Currently, the median age of patients at diagnosis is 68 years, with 54% of patients aged over 65 years and 33% aged over 75 years [2]. Advanced age is considered an unfavorable prognostic factor in AML, as it is associated with lower complete remission (CR) rates, shorter recurrence-free survival (RFS), and worse overall survival (OS) outcomes [3]. Historical studies using intensive chemotherapy in older AML patients reported CR rates of 40–50%, 4- to 8 week mortality rates of 26–36%,

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median survival of 4–6 months, and 1 year survival rates below 30% [4, 5]. While the intensive "7 + 3" chemotherapy regimen offers a potential cure for some old AML patients, it carries substantial risks, primarily due to treatment-related morbidity and mortality from bone marrow suppression and cardiotoxicity. A retrospective study of 998 AML patients aged ≥ 65 years found that the high early mortality rates suggest that intensive therapy remains excessively risky for many older patients [6]. Given these poor outcomes, it is imperative to explore lower-intensity therapies, such as low-dose cytarabine (LDAC) and hypomethylating agents (HMAs), so as to reduce treatment-related mortality rates and enhance long-term prognosis [7–9]. In recent years, novel drugs, such as venetoclax and targeted therapies like isocitrate dehydrogenase (IDH) and FMS-like tyrosine kinase 3 (FLT3) inhibitors, have been actively developed. Various low-intensity monotherapies and combination therapies have been introduced, transforming the treatment outlook for old AML patients [10].

Despite these advancements, old AML patients remain underrepresented in clinical trials, and their treatment methods are often determined by individual physicians' preferences rather than standardized protocols. Additionally, direct head-to-head clinical trials comparing different low-intensity treatments are lacking, leaving no established consensus on the optimal treatment strategy for this population [11]. A summary of the medications evaluated in the included RCTs is shown in Supplementary Table S1.

Network meta-analysis (NMA) is an advanced analytical method that allows the simultaneous comparison of multiple interventions by integrating direct and indirect evidence within a single analysis [12]. Additionally, NMA ranks interventions based on specified outcomes and estimates their relative efficacy, thereby assisting in clinical decision-making. Therefore, we conducted a network meta-analysis using data from prior randomized controlled trials (RCTs) and cohort studies to evaluate the relative efficacy and safety of different types of low-intensity treatments. Our objective was to determine the optimal low-intensity treatment approach and provide stronger evidence-based guidance for the clinical management of old AML patients.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) guidelines [13]. The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023403568).

Search strategy

Four databases, PubMed, Embase, Cochrane, and Web of Science, were comprehensively searched, until July 07, 2024, to identify all English-language Phase II/III RCTs, as well as prospective and retrospective studies evaluating low-intensity treatments for old AML patients. Additionally, reference lists were manually reviewed to ensure that no relevant studies were omitted. The search keywords included as follows: Leukemia, Myeloid, Acute, Age, Randomized Controlled Trial, Cohort Analysis, and Case–Control Studies. No restrictions were applied regarding treatment strategies to ensure comprehensiveness and accuracy. Detailed search terms are provided in Supplementary Table S2.

Selection criteria

Inclusion criteria

Studies were included if they met the following criteria:

(1) Enrolled old patients diagnosed with AML, regardless of treatment-naïve or relapsed/refractory status. (2) Compared low-intensity treatments, including hypomethylating agents (HMA: azacitidine/decitabine) and low-dose cytarabine (LDAC, also known as low-dose Ara-C), either as monotherapies or combination therapies. (3) Study design: Phase II/III RCTs (blinded or unblinded), prospective, or retrospective studies. (4) Reported at least one of the following clinical outcomes: OS, RFS, CR, complete remission with incomplete hematologic recovery (CRi), overall response rate (ORR), and adverse events (AEs) graded ≥ 3.

Exclusion criteria

Studies were excluded if they met any of the following criteria:

(1) Meta-analyses, reviews, pathology reports, guidelines, animal studies, and conference abstracts. (2) Studies involving elderly patients with acute promyelocytic leukemia (APL). (3) Studies including standard intensive chemotherapy in either the intervention or control group. (4) Studies focusing exclusively on supportive therapy. (5) Studies solely compared dosage differences. (6) Studies from which statistical data cannot be extracted.

Data extraction

Two independent reviewers extracted data, with excluded studies and the reasons for exclusion documented and checked by a third reviewer. The extracted information included author, publication year, study type, treatment measures, sample size, patients' age, gender ratio, and the

number of de novo and secondary AML cases. For binary data such as CR, ORR, and CRi, the number of randomized patients and events per group was recorded. For OS and RFS, the hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted, along with the number of randomized patients. In some studies, when HRs and 95% CIs were not explicitly reported, Engauge Digitizer software was used to extract survival data from Kaplan–Meier curves.

Risk-of-bias assessment

The selected retrospective and prospective studies were independently assessed by two researchers according to the Newcastle Ottawa Scale (NOS). The evaluation was based on three aspects: (1) Cohort selection (representativeness, ascertainment of exposure, and absence of the outcome at baseline). (2) Comparability of the exposed and non-exposed cohorts. (3) Outcome measurement (outcome assessment methods, adequacy of follow-up duration, completeness of follow-up). The maximum NOS score was 10, and studies scoring above five were classified as high-quality studies. The quality assessment results are presented in Supplementary Table S3. For RCTs, the risk of bias was independently assessed by using the RoB2.0 tool in the 2019 Cochrane Collaboration Handbook. The results are displayed in Supplementary Figure S1. Disagreements in the assessment process were resolved through group discussion. Among the included studies, four enrolled both treatment-naïve and relapsed/refractory patients, which could limit the interpretation of the results. Treatment-naïve patients generally respond better because they have not yet been exposed to any agents that could induce drug resistance. In contrast, relapsed/refractory patients may exhibit pre-existing drug resistance, potentially influencing the effectiveness of new therapeutic approaches. This difference could partially limit the generalizability or comparability of the results.

Statistical analysis

Relative treatment effects of different treatment regimens for OS and RFS were assessed using HRs with 95% credible intervals (CrIs). CR, ORR, and CRi were analyzed using relative risk (RRs) with 95% CrIs. In view of the heterogeneity between trials, a Bayesian hierarchical random-effects model was initially fitted for multiple treatment comparisons [14, 15]. All statistical analyses and graphs were generated using the (R 4.2.2) and (Stata 15.1). Based on the theory of likelihood function and some prior assumptions, Markov chain Monte Carlo (MCMC) simulation was performed using Bayesian inference in (R 4.2.2). 500,000 iterations were run with a 20,000-step annealing process to investigate the posterior distributions of examined treatments [16–18]. On the other hand, the relationships among different treatment regimens were visualized using a network graph, and a comparison-adjusted funnel plot was used to test potential publication bias [19, 20]. Moreover, surface under the cumulative ranking curve (SUCRA) values were used to rank the examined treatments. SUCRA values range from 0 to 1, with higher values indicating better treatment rankings [21, 22]. A league table was generated to present pairwise comparisons for each outcome. Furthermore, sensitivity analyses were conducted to assess the robustness of the results and explore the source of heterogeneity.

Results

Trial selection

A total of 18,453 records were retrieved (6195 from PubMed, 8989 from Embase, 2271 from Cochrane, and 998 from Web of Science). After removing duplicates and articles published before 1990, the titles and abstracts of 14,522 studies were screened, and 210 potentially relevant studies were identified. Based on the inclusion and exclusion criteria, 26 RCTs and prospective or retrospective cohort studies were included in the analysis, involving 4920 patients [23–48]. The flowchart outlining the study selection process is shown in Fig. 1. The characteristics of the included studies are listed in Table 1. Out of the 26 studies, 21 were RCTs, and 5 were cohort studies. Eleven studies compared the efficacy of low-dose cytarabine (LDAC) alone or in combination with other drugs [23, 32, 34, 35, 37–39, 41, 45, 47, 48]. Three studies compared hypomethylating agents (HMA) with LDAC [25, 26, 28]. Eleven studies compared the efficacy of HMA alone or in combination with other drugs [27, 29–31, 36, 40, 42–44, 46, 49]. One study compared the difference between decitabine and azacitidine (AZA) [33]. The network plots for each outcome of interest are shown in Fig. 2, where the size of each circle represents the number of patients, the connecting lines indicate direct comparisons, and the thickness of the lines corresponds to the number of studies. Specifically, there were 17 interventions included for OS, 7 interventions for RFS, 16 interventions for CR, 14 interventions for CRi, and 16 interventions for ORR.

Overall survival (OS) and recurrence-free survival (RFS)

Twenty-one studies with 4311 patients reported OS, while 5 studies with 1091 patients reported RFS. The results showed that AZA plus venetoclax significantly improved OS compared to AZA monotherapy (HR = 1.66, 95% CrI = 1.23–2.36). LDAC plus glasdegib

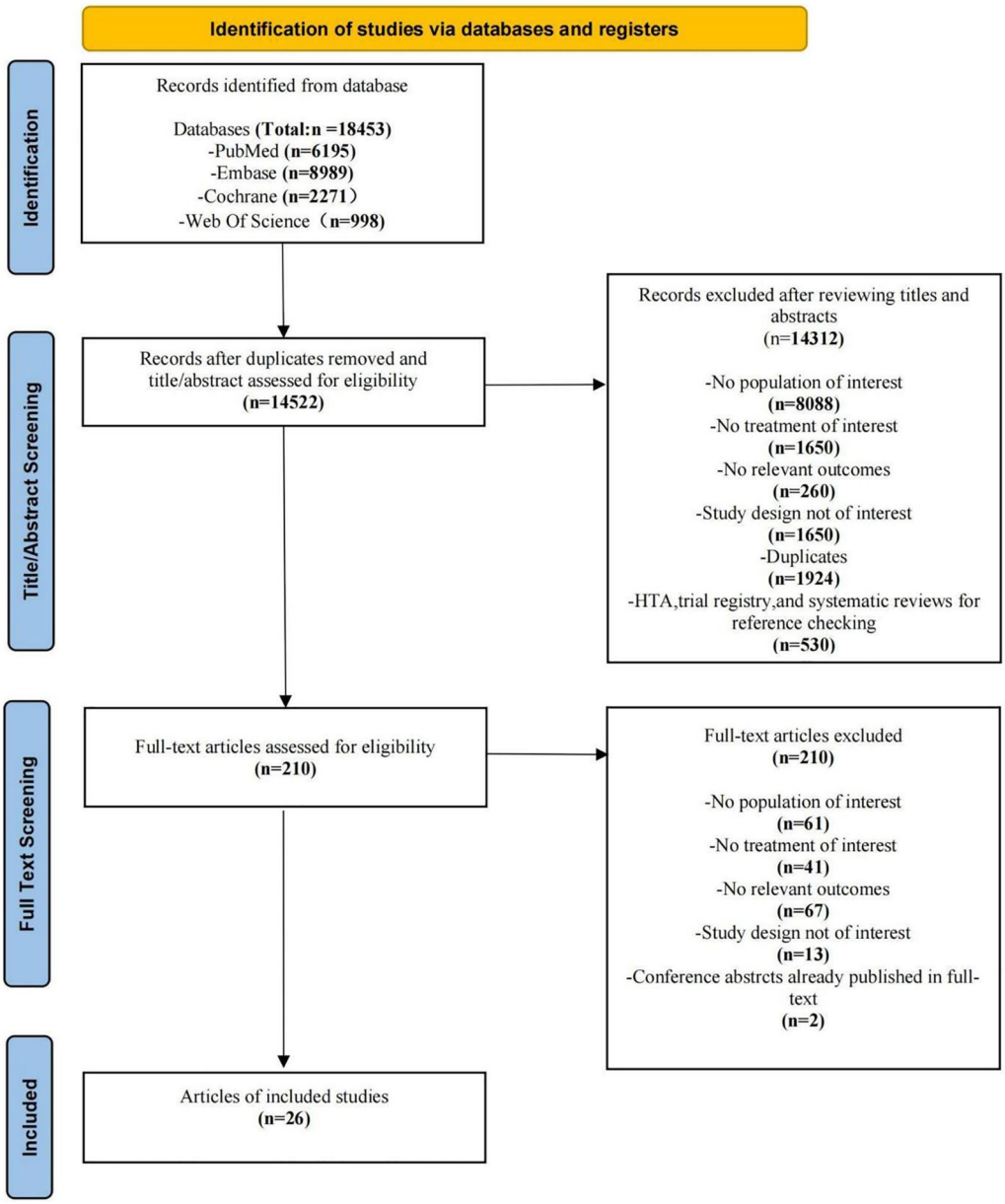

Fig. 1 Search strings and flow charts for filtering and research selection

demonstrated significant survival advantages over LDAC plus gemtuzumab ozogamicin (GO) (HR = 0.5, 95%CrI = 0.27–0.93), LDAC plus vosaroxin (HR = 0.39, 95%CrI = 0.19–0.82), and vosaroxin monotherapy (HR = 0.26, 95%CrI = 0.13–0.53). Additionally, AZA plus venetoclax was also superior to decitabine monotherapy (HR = 0.49, 95%CrI = 0.24–0.94), decitabine plus bortezomib (HR = 0.42, 95%CrI = 0.18–0.92), and LDAC monotherapy (HR = 0.43, 95%CrI = 0.2–0.97). However, for RFS, all 95% CIs included the null value, and thus, the results were not statistically significant. Other significant results are specifically highlighted in Table 2A. The ranking of interventions for OS was as follows: AZA plus venetoclax (SUCRA = 0.936), LDAC plus glasdegib (SUCRA = 0.898), and LDAC plus venetoclax (SUCRA = 0.718). The top three treatments for RFS were LDAC plus vosaroxin (SUCRA = 0.859), sapacitabine (SUCRA = 0.631, and LDAC plus tosedostat (SUCRA = 0.576). The specific rankings for those low-intensity treatments are shown in Table 3 and Fig. 3.

Table 1 Characteristics of the studies

Author	Year	Type	Sample size	Age, median (range)	Gender (male/female)	Tx 1	Tx 2	De novo,n	Secondary, n
Burnett, A. K	2013	RCT	495	75 (54–90)	300/195	LDAC	LDAC + GO	325	106
Kantarjian, H. M	2013	RCT	77	76 (61–85)	45/32	LDAC	Barasertib	35	42
Döhner, H	2014	RCT	87	75.5 (57–87)	48/39	LDAC	LDAC + Volasertib	60	27
Thomas, X. G	2014	RCT	485	73 (64–91)	288/197	LDAC	Dec	314	171
Burnett, A. K	2015	RCT	143	75 (54–88)	94/49	LDAC	Sapacitabine	85	37
Dennis, M	2015	RCT	104	75 (60–89)	67/37	LDAC	Vosaroxin	65	31
Dennis, M.2	2015	RCT	104	75 (60–91)	69/35	LDAC	LDAC + Vosaroxin	65	27
Jacob, L. A	2015	Cohort study	30	63.5	24/6	Decitabine	LDAC	28	2
Roboz, G. J	2018	RCT	165	72.4 (60.5–92.3)	113/50	Decitabine	Dec + Bortezomib	110	18
Cortes, J. E	2019	RCT	132	76 (58–92)	95/37	LDAC	LDAC + Glasdegib	*	*
DiNardo, C. D	2020	RCT	431	76 (49–91)	259/172	Azacitidine	Aza + Venetoclax	324	107
Huls, G	2020	RCT	144	75.5 (66–89)	89/55	Decitabine	Dec + Ibrutinib	93	28
Wei, A. H	2020	RCT	211	76 (36–93)	117/34	LDAC	LDAC + Venetoclax	130	81
Pepe,S	2020	Cohort study	110	75 (58–89)	74/36	Decitabine	Aza	62	44
Dohner, H	2021	RCT	666	75 (65–93)	376/290	LDAC	LDAC + Volasertib	344	322
Heuser, M	2021	RCT	116	76.7 (58–92)	82/34	LDAC	LDAC + Glasdegib	56	60
Hu, Y	2021	RCT	15	72 (61–86)	N6/9	LDAC	LDAC + Venetoclax	14	1
Montesinos, P	2021	RCT	316	75 (65–92)	171/145	Decitabine	Dec + Talacotuzumab	213	103
Berdel, Andrew F	2022	RCT	30	76 (60–84)	15/15	LDAC	LDAC + Nintedanib	7	9
Wang, E. S	2022	RCT	123	77 (59–90)	70/53	Azacitidine	Aza + Gilteritinib	*	*
Wang, W	2022	RCT	20	70.3 (60–83)	11/9	Azacitidine	Aza + Venetoclax	*	*
Yamamoto, K	2022	RCT	37	77.3 (67–86)	23/14	Azacitidine	Aza + Venetoclax	30	7
Zeidan, A. M	2022	RCT	129	75.5 (65–89)	71/58	Azacitidine	Aza + Durvalumab	54	75
Laloi,L	2023	Cohort study	111	62 (14–83)	NR	LDAC + Venetoclax	Aza + Venetoclax	37	57
Petit,C	2024	Cohort study	175	66 (55–71.5)	99/76	Azacitidine	Aza + Venetoclax	92	83
Baba,Y	2024	Cohort study	33	78.7 (58–88)	N8/25	Azacitidine	Aza + Venetoclax	17	16
Pratz,K.W	2024	RCT	431	76 (49–90)	259/172	Azacitidine	Aza + Venetoclax	324	107

[*] represents information that is not mentioned in the article

Complete remission (CR), complete remission with incomplete hematologic recovery (CRi), and overall response rate (ORR)

The results indicated that AZA plus venetoclax significantly increased CR and CRi rates compared to AZA monotherapy, with a (RR = 2.58, 95% CrI = 1.1–7.28) and (RR = 3.2, 95% CrI = 1.37–18.88), respectively. LDAC plus glasdegib significantly improved CR rates over LDAC monotherapy (RR = 0.09, 95% CrI = 0.01–0.7). There were no statistically significant differences in CR, CRi, or ORR between venetoclax combination therapy (LDAC + venetoclax or AZA + venetoclax) and decitabine (as shown in Table 2B and Table 2C). Based on cumulative treatment ranking, AZA plus venetoclax demonstrated the highest probability of becoming the most effective measure for CR, CRi, and ORR with SUCRA values of 0.836, 0.829, and 0.911, respectively. For CR, decitabine plus talacotuzumab (SUCRA = 0.832) and decitabine monotherapy (SUCRA = 0.783) ranked second and third, respectively. In terms of CRi, AZA plus gilteritinib (SUCRA = 0.761) and LDAC plus venetoclax (SUCRA = 0.739) ranked second and third, respectively. For ORR, LDAC plus venetoclax (SUCRA = 0.742) and barasertib (SUCRA = 0.699) ranked second and third, respectively. Ranking for additional low-intensity treatments are presented in Table 3 and Fig. 3. A visual representation of SUCRA-OS and SUCRA-ORR is provided in Fig. 4

Adverse events (AEs) (grade ≥ 3)

Among AZA-related treatments, AZA monotherapy ranked first (SUCRA = 0.902), with 93.75% (390/416) of patients experiencing grade 3–5 AEs. AZA plus

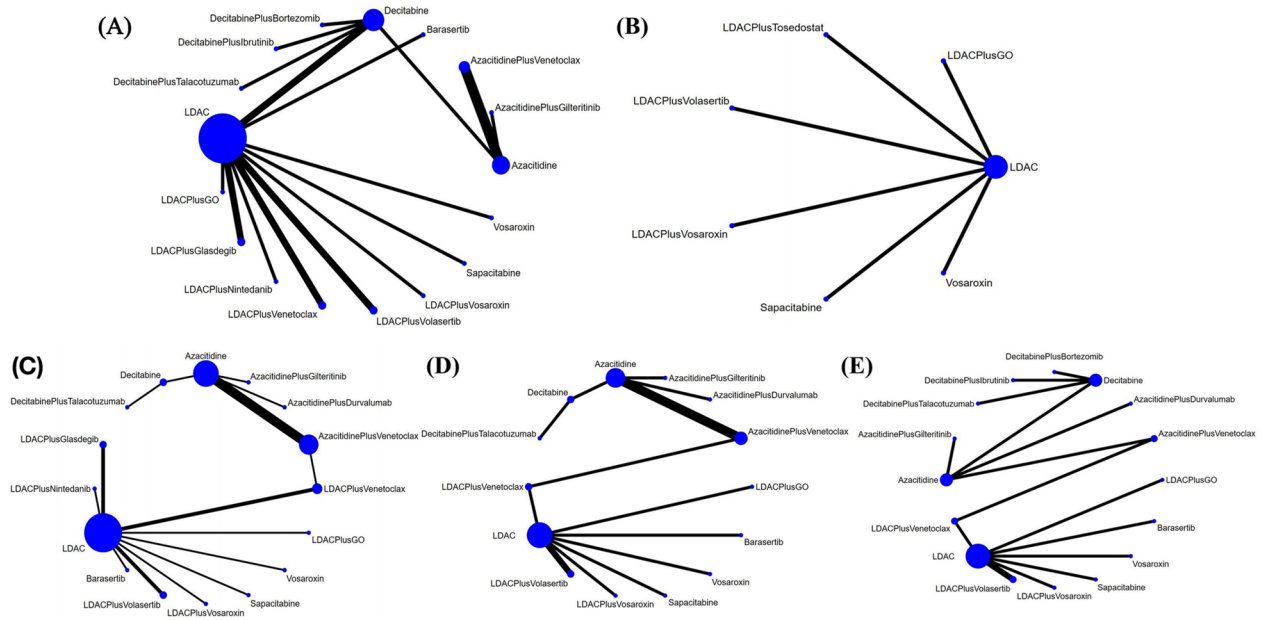

Fig. 2 Network Evidence plot for eligible comparisons (**A**: OS, **B**: RFS, **C**: CR, **D**:CRi, **E**: ORR). Each node represents an intervention, and the connecting lines between 2 nodes represents 1 or more researches in which the 2 interventions have been compared directly. The size of each node is proportional to the number of randomly assigned participants, and the thickness of the lines connecting 2 nodes is weighted according to the number of studies that directly compared the interventions it connected

venetoclax ranked second (SUCRA = 0.548); however, the difference between these two treatments was not statistically significant (Table 2C, Fig. 5C). Regarding LDAC-based related therapies, LDAC in combination with nintedanib and LDAC monotherapy ranked highest in safety (SUCRA = 0.743 and 0.720, respectively), followed by LDAC plus glasdegib (SUCRA = 0.710), barasertib (SUCRA = 0.387), LDAC plus venetoclax (SUCRA = 0.308), and LDAC plus volasertib (SUCRA = 0.133) (Fig. 5D). These findings suggested that LDAC monotherapy was associated with a lower risk of AEs compared to LDAC plus volasertib, with (RR = 0.66, 95% CrI = 0.44–0.98) Table 2C. The network plots and relative rankings are presented in Fig. 5.

Publication bias

The deviance information criterion (DIC) was calculated for both consistency and inconsistency models across all outcomes. The results revealed that the differences in DIC were consistently less than five, indicating good model consistency across all outcomes. Funnel plots and Egger's tests revealed no evidence of publication bias, as presented in Supplementary Figure S2. The p values obtained from the test were 0.497 for OS, 0.690 for RFS, 0.717 for CR, 0.148 for CRi, and 0.747 for ORR, further supporting the absence of publication bias in the analysis.

Discussion

To the best of our knowledge, this NMA is the first to comprehensively compare low-intensity treatment regimens for old patients with AML. Despite the availability of various treatment options, no previous studies have provided a comparative evaluation of their efficacy and safety. This study addresses this gap by indirectly comparing all available low-intensity treatments for old AML patients ineligible for intensive chemotherapy. The results highlight several important findings.

First, when combined with venetoclax, both LDAC and HMA regimens demonstrated improved effectiveness compared to monotherapy, with combination therapies ranking higher overall. Notably, AZA plus venetoclax demonstrated superior outcomes in OS, CR, Cri, and ORR among all treatments and showed no statistically significant differences in AEs compared to AZA monotherapy. These findings suggest that AZA plus venetoclax may be a preferable option over LDAC plus venetoclax and other monotherapy for old patients ineligible for intensive chemotherapy. These results align with a recently published meta-analysis, which has demonstrated that AZA plus venetoclax improves OS and is associated with significantly higher ORR rates [50]. Nevertheless, the prior study focused solely on venetoclax-based therapies and did not include AEs

Table 2 Cumulative ranking probability plots (A: OS and RFS, B: CR and CRi, C: ORR and AEs), significant results are highlighted in the following tables

A	RFS								
OS	Aza								
	1.09 (0.55, 2.15)	Aza + Gilteritinib							
	1.66 (1.23, 2.36)	1.53 (0.73, 3.3)	Aza + Venetoclax						
	0.82 (0.31, 2.34)	0.75 (0.23, 2.66)	0.49 (0.18, 1.45)	Barasertib					
	0.81 (0.45, 1.47)	0.74 (0.3, 1.85)	**0.49 (0.24, 0.94)**	0.98 (0.41, 2.17)	Dec				
	0.69 (0.33, 1.48)	0.63 (0.23, 1.76)	**0.42 (0.18, 0.92)**	0.84 (0.31, 2.08)	0.85 (0.53, 1.37)	Dec + Bortezomib			
	0.92 (0.4, 2.12)	0.85 (0.29, 2.5)	0.55 (0.22, 1.33)	1.12 (0.39, 2.95)	1.14 (0.64, 2.02)	1.33 (0.63, 2.77)	Dec + Ibrutinib		
	0.78 (0.36, 1.7)	0.71 (0.26, 2.04)	0.47 (0.2, 1.07)	0.95 (0.35, 2.38)	0.96 (0.58, 1.6)	1.13 (0.56, 2.24)	0.84 (0.39, 1.83)	Dec + Talacotuzumab	
	0.72 (0.37, 1.54)	0.66 (0.26, 1.86)	**0.43 (0.2, 0.97)**	0.88 (0.43, 1.8)	0.88 (0.62, 1.42)	1.04 (0.59, 2.06)	0.78 (0.4, 1.67)	0.92 (0.51, 1.88)	LDAC
	1.43 (0.66, 3.37)	1.31 (0.47, 3.98)	0.86 (0.37, 2.11)	1.73 (0.76, 3.94)	**1.75 (1.04, 3.28)**	**2.05 (1.04, 4.58)**	1.54 (0.73, 3.67)	1.82 (0.89, 4.15)	**1.98 (1.33, 2.95)**
	0.71 (0.32, 1.76)	0.65 (0.23, 2.04)	0.43 (0.18, 1.09)	0.87 (0.37, 2.03)	0.88 (0.5, 1.74)	1.02 (0.5, 2.39)	0.77 (0.35, 1.9)	0.91 (0.43, 2.18)	0.99 (0.62, 1.59)
	0.61 (0.2, 1.91)	0.56 (0.15, 2.14)	0.37 (0.12, 1.17)	0.74 (0.23, 2.3)	0.75 (0.29, 2)	0.88 (0.31, 2.59)	0.66 (0.22, 2.09)	0.78 (0.27, 2.39)	0.85 (0.35, 2)
	1.04 (0.46, 2.63)	0.95 (0.33, 3.05)	0.62 (0.25, 1.63)	1.27 (0.53, 3.06)	1.28 (0.71, 2.61)	1.5 (0.71, 3.57)	1.12 (0.5, 2.85)	1.33 (0.62, 3.24)	1.44 (0.88, 2.41)
	0.83 (0.41, 2.07)	0.77 (0.29, 2.43)	0.5 (0.23, 1.29)	1.02 (0.47, 2.38)	1.02 (0.65, 2.02)	1.19 (0.65, 2.81)	0.9 (0.44, 2.24)	1.06 (0.56, 2.55)	1.15 (0.83, 1.78)
	0.56 (0.22, 1.5)	0.51 (0.16, 1.72)	**0.33 (0.13, 0.93)**	0.68 (0.26, 1.76)	0.69 (0.34, 1.52)	0.8 (0.35, 2.05)	0.6 (0.25, 1.62)	0.71 (0.3, 1.84)	0.77 (0.41, 1.44)
	0.6 (0.25, 1.57)	0.55 (0.18, 1.83)	**0.36 (0.14, 0.98)**	0.73 (0.29, 1.85)	0.74 (0.38, 1.58)	0.87 (0.39, 2.15)	0.65 (0.27, 1.71)	0.77 (0.34, 1.95)	0.83 (0.47, 1.49)
	0.37 (0.15, 0.98)	0.34 (0.11, 1.13)	**0.22 (0.09, 0.61)**	0.45 (0.18, 1.14)	**0.46 (0.23, 0.99)**	0.54 (0.24, 1.33)	0.4 (0.17, 1.06)	0.47 (0.21, 1.21)	**0.51 (0.28, 0.94)**

A	RFS							
OS								
		0.9 (0.28, 2.94)			1.37 (0.38, 4.87)	0.41 (0.1, 1.63)	0.73 (0.19, 2.77)	2.06 (0.52, 8.19)
	LDAC + Glasdegib							
	0.5 (0.27, 0.93)	LDAC + GO			1.52 (0.27, 8.57)	0.45 (0.07, 2.79)	0.81 (0.14, 4.79)	2.28 (0.38, 13.84)
	0.43 (0.16, 1.09)	0.85 (0.32, 2.24)	LDAC + Nintedanib					
	0.73 (0.39, 1.4)	1.46 (0.74, 2.92)	1.7 (0.64, 4.71)	LDAC + Venetoclax				
	0.59 (0.35, 1.06)	1.16 (0.68, 2.25)	1.37 (0.55, 3.68)	0.8 (0.45, 1.57)	LDAC + Volasertib	0.3 (0.05, 1.98)	0.53 (0.08, 3.37)	1.5 (0.23, 9.87)
	0.39 (0.19, 0.82)	0.78 (0.36, 1.7)	0.92 (0.31, 2.71)	0.54 (0.24, 1.18)	0.67 (0.31, 1.33)	LDAC + Vosaroxin	1.78 (0.27, 12.23)	5.06 (0.71, 35.89)
	0.42 (0.21, 0.85)	0.84 (0.4, 1.76)	0.99 (0.35, 2.82)	0.58 (0.26, 1.23)	0.72 (0.34, 1.39)	1.08 (0.46, 2.53)	Sapacitabine	2.83 (0.42, 19.19)
	0.26 (0.13, 0.53)	0.52 (0.24, 1.11)	0.61 (0.21, 1.78)	**0.36 (0.16, 0.78)**	**0.44 (0.21, 0.86)**	0.67 (0.28, 1.59)	0.62 (0.27, 1.42)	Vosaroxin

Table 2 (continued)

B	CRi							
CR	**Aza**	1.02 (0.15, 7.05)	2.89 (0.44, 20.41)	**3.2 (1.37, 18.88)**	0.93 (0.02, 77.03)	0.97 (0.14, 6.4)	1.21 (0.08, 17.36)	0.61 (0.03, 21.03)
	1.33 (0.1, 17.82)	**Aza + Durvalumab**	2.86 (0.19, 44.06)	3.2 (0.47, 51.54)	0.9 (0.01, 115.36)	0.95 (0.06, 14)	1.19 (0.04, 31.36)	0.6 (0.02, 36.48)
	0.84 (0.06, 11.57)	0.63 (0.02, 24.96)	**Aza + Gilteritinib**	1.12 (0.16, 17.75)	0.32 (0, 39.5)	0.33 (0.02, 4.82)	0.41 (0.01, 10.72)	0.21 (0.01, 12.41)
	0.27 (0.07, 0.87)	0.21 (0.01, 3.26)	0.32 (0.02, 5.42)	**Aza + Venetoclax**	0.28 (0.01, 12.71)	0.3 (0.02, 1.9)	0.37 (0.01, 4.62)	0.18 (0.01, 3.26)
	0.56 (0, 122.61)	0.42 (0, 166.51)	0.66 (0, 265.7)	2.08 (0.01, 420.17)	**Barasertib**	1.04 (0.01, 69.98)	1.31 (0.01, 128.16)	0.67 (0.05, 6.28)
	0.29 (0.02, 4.38)	0.22 (0.01, 9.24)	0.35 (0.01, 15.41)	1.07 (0.06, 23.76)	0.52 (0, 209.1)	**Dec**	1.25 (0.19, 8.07)	0.63 (0.02, 39.48)
	0.2 (0, 8.01)	0.15 (0, 13.88)	0.24 (0, 22.33)	0.72 (0.02, 40.41)	0.36 (0, 233.82)	0.68 (0.06, 8.49)	**Dec + Talacotuzumab**	0.49 (0.01, 48.78)
	7.09 (0.2, 542.59)	5.33 (0.07, 860.95)	8.57 (0.11, 1423.47)	26.21 (0.99, 1784.56)	12.44 (0.59, 709.21)	24.58 (0.29, 4160.37)	36.02 (0.23, 11763.89)	**LDAC**
	0.6 (0.01, 72.42)	0.45 (0, 104.79)	0.72 (0, 174.38)	2.24 (0.04, 247.13)	1.05 (0.02, 102.03)	2.09 (0.01, 522.37)	3.05 (0.01, 1291.4)	**0.09 (0.01, 0.7)**
	3.29 (0.04, 505.94)	2.49 (0.02, 751.61)	3.95 (0.03, 1183.72)	12.14 (0.22, 1818.25)	5.88 (0.11, 656.54)	11.46 (0.07, 3649.93)	16.67 (0.06, 9339.91)	0.46 (0.04, 5.55)
	20.48 (0.13, 7740.3)	15.34 (0.06, 10108.27)	24.71 (0.09, 15802.87)	76.37 (0.61, 27335.11)	36.17 (0.31, 11236.99)	71.06 (0.24, 46802.56)	103.62 (0.21, 107575.69)	2.71 (0.08, 188.34)
	1.04 (0.04, 25.57)	0.79 (0.01, 45.16)	1.27 (0.02, 73.16)	3.84 (0.24, 78.72)	1.86 (0.03, 147.36)	3.64 (0.05, 229.55)	5.37 (0.04, 638.05)	0.15 (0.01, 1.03)
	4.6 (0.08, 461.34)	3.45 (0.03, 707.64)	5.53 (0.04, 1141.96)	16.85 (0.38, 1580.4)	8.06 (0.21, 633.18)	15.92 (0.12, 3445.04)	23.26 (0.1, 8981.88)	0.66 (0.09, 3.68)
	5.29 (0.07, 855.53)	3.99 (0.02, 1272.3)	6.3 (0.04, 2033.96)	19.49 (0.32, 2939.19)	9.51 (0.17, 1155.35)	18.5 (0.11, 6087.1)	27.01 (0.09, 15469.12)	0.75 (0.05, 10.01)
	12.93 (0.17, 2007.36)	9.73 (0.06, 2933.58)	15.5 (0.1, 4768.79)	47.34 (0.81, 6900.01)	22.92 (0.42, 2733.23)	45.07 (0.28, 14415.65)	65.91 (0.23, 36405.82)	1.8 (0.13, 23.67)
	7.36 (0.09, 1236.37)	5.58 (0.04, 1794.41)	8.91 (0.06, 2883.68)	27.36 (0.46, 4214.85)	13.32 (0.24, 1625.64)	25.63 (0.15, 8328.38)	37.7 (0.13, 20726.41)	1.03 (0.08, 14.69)

B	CRi							
CR		0.89 (0.02, 50.19)		2.39 (0.18, 41.86)	1.61 (0.05, 77.1)	0.58 (0.01, 35.76)	0.23 (0, 16.15)	0.49 (0.01, 30.83)
		0.87 (0.01, 81.69)		2.3 (0.1, 79.75)	1.56 (0.03, 124.65)	0.57 (0.01, 56.91)	0.22 (0, 25.78)	0.48 (0.01, 48.74)
		0.3 (0.01, 28.26)		0.8 (0.03, 27.25)	0.54 (0.01, 42.97)	0.2 (0, 19.8)	0.08 (0, 8.58)	0.17 (0, 16.96)
		0.27 (0.01, 8.23)		0.71 (0.05, 5.91)	0.48 (0.01, 12.1)	0.17 (0, 5.84)	0.07 (0, 2.7)	0.15 (0, 4.97)
		0.98 (0.04, 17.61)		2.54 (0.1, 52.36)	1.77 (0.09, 25.36)	0.64 (0.02, 12.67)	0.24 (0.01, 6.17)	0.54 (0.02, 10.98)
		0.91 (0.02, 88.39)		2.42 (0.11, 84.61)	1.65 (0.04, 135.07)	0.6 (0.01, 61.1)	0.23 (0, 27.51)	0.51 (0.01, 54.25)
		0.72 (0.01, 104.64)		1.91 (0.06, 112.69)	1.3 (0.02, 163.53)	0.47 (0.01, 72.29)	0.18 (0, 31.84)	0.4 (0, 63.92)
		1.46 (0.23, 9.4)		3.77 (0.54, 29.65)	2.63 (0.67, 10.97)	0.96 (0.13, 6.85)	0.38 (0.03, 3.73)	0.82 (0.11, 6.08)
	LDAC + Glasdegib							
	5.43 (0.22, 203.08)	**LDAC + GO**		2.59 (0.17, 40.63)	1.8 (0.18, 18.82)	0.65 (0.04, 9.83)	0.26 (0.01, 4.83)	0.56 (0.04, 8.56)
	33.08 (0.52, 4438.47)	5.9 (0.08, 758.01)	**LDAC + Nintedanib**					
	1.74 (0.05, 40.99)	0.33 (0.01, 6.41)	0.05 (0, 2.99)	**LDAC + Venetoclax**	0.7 (0.06, 7.97)	0.25 (0.01, 4.11)	0.1 (0, 1.98)	0.21 (0.01, 3.62)
	7.5 (0.42, 177.33)	1.42 (0.06, 28.26)	0.24 (0, 11.55)	4.25 (0.3, 123.54)	**LDAC + Volasertib**	0.36 (0.03, 3.99)	0.14 (0.01, 2.02)	0.31 (0.03, 3.54)
	8.7 (0.31, 357.63)	1.6 (0.04, 58.65)	0.27 (0, 21.61)	4.93 (0.23, 266.23)	1.15 (0.05, 31.24)	**LDAC + Vosaroxin**	0.39 (0.02, 8)	0.85 (0.05, 14.2)
	21.4 (0.79, 837.53)	3.91 (0.1, 142.33)	0.66 (0, 52.05)	11.89 (0.57, 634.3)	2.78 (0.13, 73.12)	2.44 (0.06, 95.83)	**Sapacitabine**	2.16 (0.1, 56.45)
	12.18 (0.44, 508.21)	2.24 (0.06, 86.19)	0.38 (0, 30.73)	6.87 (0.32, 383.34)	1.58 (0.07, 44.9)	1.4 (0.03, 58.23)	0.57 (0.01, 23.43)	**Vosaroxin**

Table 2 (continued)

C	AE							
ORR	**Aza**	1.08 (0.94, 1.26)	1.11 (0.95, 1.34)	1.03 (0.97, 1.13)				
	1.13 (0.26, 4.89)	**Aza + Durvalumab**	1.03 (0.82, 1.29)	0.95 (0.82, 1.13)				
	0.52 (0.12, 2.25)	0.46 (0.06, 3.63)	**Aza + Gilteritinib**	0.93 (0.77, 1.12)				
	0.19 (0.02, 1.07)	0.17 (0.01, 1.59)	0.36 (0.03, 3.52)	**Aza + Venetoclax**				
	0.44 (0.01, 12.24)	0.39 (0.01, 14.36)	0.85 (0.02, 31.36)	2.34 (0.13, 40.49)	**Barasertib**			
	0.71 (0.16, 3.15)	0.63 (0.08, 5.09)	1.37 (0.17, 11.35)	3.74 (0.39, 54.69)	1.63 (0.04, 82.54)	**Dec**		
	0.74 (0.09, 5.86)	0.66 (0.05, 8.21)	1.42 (0.11, 18.35)	3.91 (0.27, 79.28)	1.7 (0.03, 108.19)	1.04 (0.24, 4.42)	**Dec + Bortezomib**	
	0.94 (0.12, 7.5)	0.83 (0.07, 10.41)	1.81 (0.14, 23.05)	4.95 (0.34, 103.14)	2.15 (0.04, 140.66)	1.32 (0.31, 5.62)	1.27 (0.17, 10)	**Dec + Ibrutinib**
	0.92 (0.12, 7.27)	0.82 (0.07, 10.31)	1.77 (0.14, 23.3)	4.86 (0.33, 99.82)	2.1 (0.04, 135.13)	1.29 (0.31, 5.49)	1.25 (0.16, 9.68)	0.98 (0.13, 7.73)
	1.53 (0.07, 27.27)	1.36 (0.04, 33.66)	2.94 (0.1, 74.04)	8.05 (0.93, 81.16)	3.4 (0.63, 23.17)	2.15 (0.07, 54.06)	2.06 (0.05, 71.97)	1.63 (0.04, 56.31)
	0.88 (0.03, 21.43)	0.78 (0.02, 25.82)	1.68 (0.04, 57.18)	4.6 (0.35, 67.67)	1.95 (0.22, 20.8)	1.23 (0.03, 41.08)	1.18 (0.02, 52.38)	0.93 (0.02, 42.18)
	0.41 (0.03, 4.79)	0.36 (0.02, 6.16)	0.78 (0.04, 13.48)	2.11 (0.44, 12.22)	0.91 (0.1, 9.9)	0.57 (0.02, 9.93)	0.55 (0.02, 13.36)	0.43 (0.01, 10.62)
	0.83 (0.03, 17.12)	0.74 (0.02, 20.46)	1.61 (0.04, 45.37)	4.4 (0.37, 52.75)	1.86 (0.24, 15.6)	1.18 (0.03, 33.56)	1.13 (0.02, 43.06)	0.89 (0.02, 34.18)
	1.34 (0.04, 33.94)	1.19 (0.03, 40.9)	2.57 (0.06, 89.66)	7.09 (0.52, 110.66)	2.99 (0.32, 33.5)	1.89 (0.05, 65.84)	1.81 (0.03, 83.6)	1.43 (0.03, 66.15)
	2.73 (0.09, 69.28)	2.41 (0.06, 82.3)	5.22 (0.13, 180.64)	**14.47 (1.03, 222.11)**	6.1 (0.64, 69.04)	3.84 (0.09, 132.7)	3.67 (0.07, 169.36)	2.91 (0.05, 135.03)
	1.73 (0.05, 44.27)	1.52 (0.04, 53.61)	3.3 (0.08, 115.2)	9.06 (0.65, 141.85)	3.83 (0.41, 42.91)	2.43 (0.06, 86.26)	2.32 (0.04, 108.71)	1.84 (0.03, 85.15)

C	AE							
ORR			**Barasertib**					
			1.22 (0.79, 1.99)	**LDAC**				
			1.22 (0.73, 2.13)	1 (0.76, 1.31)	**LDAC + Glasdegib**			
			1.45 (0.51, 4.22)	1.17 (0.46, 3.1)	1.17 (0.45, 3.19)	**LDAC + Nintedanib**		
	Dec + Talacotuzumab		0.94 (0.5, 1.77)	0.76 (0.48, 1.16)	0.76 (0.45, 1.25)	0.64 (0.23, 1.82)	**LDAC + Venetoclax**	
	1.66 (0.04, 55.82)	**LDAC**	0.81 (0.44, 1.51)	**0.66 (0.44, 0.98)**	0.66 (0.4, 1.07)	0.56 (0.2, 1.53)	0.86 (0.48, 1.58)	**LDAC + Volasertib**
	0.96 (0.02, 41.97)	0.57 (0.14, 2.38)	**LDAC + GO**					
	0.44 (0.01, 10.72)	0.27 (0.06, 1.16)	0.47 (0.06, 3.63)	**LDAC + Venetoclax**				
	0.91 (0.02, 34.45)	0.55 (0.18, 1.49)	0.96 (0.15, 5.29)	2.04 (0.32, 12.35)	**LDAC + Volasertib**			
	1.45 (0.03, 65.96)	0.88 (0.2, 3.8)	1.53 (0.2, 11.97)	3.27 (0.41, 27.77)	1.59 (0.28, 10.62)	**LDAC + Vosaroxin**		
	2.98 (0.05, 131.81)	1.77 (0.39, 8.1)	3.1 (0.39, 24.72)	6.67 (0.82, 57.73)	3.23 (0.54, 22.2)	2.03 (0.25, 16.93)	**Sapacitabine**	
	1.87 (0.03, 85.23)	1.12 (0.25, 5.06)	1.95 (0.25, 15.64)	4.2 (0.52, 36.45)	2.04 (0.35, 13.82)	1.28 (0.16, 10.49)	0.63 (0.08, 5.36)	**Vosaroxin**

Table 3 SUCRAs of different results

OS			RFS			CR			CRi			ORR		
Rank	Treatments	SUCRA	Rank	Treatments	SUCRA	Rank	Treatments	SUCRA	Rank	Treatments	SUCRA	Rank	Treatments	SUCRA
1	Aza + Venetoclax	0.93604687	**1**	LDAC + Vosaroxin	0.8590825	**1**	Aza + Venetoclax	0.8359187	**1**	Aza + Venetoclax	0.8293585	**1**	Aza + Venetoclax	0.9112827
2	LDAC + Glasdegib	0.89751	**2**	Sapacitabine	0.6310483	**2**	Dec + Talacotuzumab	0.8317783	**2**	Aza + Gilteritinib	0.7611027	**2**	LDAC + Venetoclax	0.7422793
3	LDAC + Venetoclax	0.7176025	**3**	LDAC + Tosedostat	0.5755125	**3**	Dec	0.7833813	**3**	LDAC + Venetoclax	0.7392035	**3**	Barasertib	0.6990053
4	Aza + Gilteritinib	0.69129688	**4**	LDAC + GO	0.5290508	**4**	LDAC + Glasdegib	0.7058453	**4**	LDAC + Volasertib	0.6509977	**4**	Aza + Gilteritinib	0.6659057
5	Aza	0.66444344	**5**	LDAC	0.4547225	**5**	Barasertib	0.6998757	**5**	Dec + Talacotuzumab	0.5283492	**5**	Dec	0.573313
6	Dec + Ibrutinib	0.61098719	**6**	LDAC + Volasertib	0.2996467	**6**	Aza + Gilteritinib	0.6102677	**6**	Barasertib	0.4812181	**6**	Dec + Bortezomib	0.544716
7	LDAC + Volasertib	0.54861938	**7**	Vosaroxin	0.1509367	**7**	LDAC + Venetoclax	0.6091527	**7**	Aza + Durvalumab	0.4728412	**7**	LDAC + Volasertib	0.5319947
8	Barasertib	0.51440781	**AE (LDAC)**			**8**	Aza	0.5745067	**8**	LDAC + GO	0.4720338	**8**	LDAC + GO	0.5109247
9	Dec	0.51347906	**Rank**	**Treatments**	**SUCRA**	**9**	Aza + Durvalumab	0.5182353	**9**	Aza	0.454975	**9**	Dec + Talacotuzumab	0.4557177
10	Dec + Talacotuzumab	0.46664344	**1**	LDAC + Nintednib	0.743295	**10**	LDAC + GO	0.4051167	**10**	Dec	0.4500496	**10**	Dec + Ibrutinib	0.4481013
11	LDAC + GO	0.38059437	**2**	LDAC	0.719868	**11**	LDAC + Volasertib	0.3378537	**11**	LDAC + Vosaroxin	0.3491758	**11**	Aza	0.4183773
12	LDAC	0.37945469	**3**	LDAC + Glasdegib	0.709557	**12**	LDAC + Vosaroxin	0.3092167	**12**	LDAC	0.3385215	**12**	Aza + Durvalumab	0.384702
13	Dec + Bortezomib	0.34478437	**4**	Barasertib	0.386796	**13**	Vosaroxin	0.246066	**13**	Vosaroxin	0.3068208	**13**	LDAC + Vosaroxin	0.362992
14	LDAC + Nintedanib	0.31004531	**5**	LDAC + Venetoclax	0.307944	**14**	LDAC	0.224422	**14**	Sapacitabine	0.1653527	**14**	LDAC	0.2994807
15	Sapacitabine	0.25912375	**6**	LDAC + Volasertib	0.13254	**15**	LDAC + Nintedanib	0.1554207				**15**	Vosaroxin	0.2854667
16	LDAC + Vosaroxin	0.21596437	**AE (AZA)**			**16**	Sapacitabine	0.1529527				**16**	Sapacitabine	0.165741
17	Vosaroxin	0.04899656	**Rank**	**Treatments**	**SUCRA**									
			1	Aza	0.9026517									
			2	Aza + Venetoclax	0.548455									
			3	Aza + Durvalumab	0.3192317									
			4	Aza + Gilteritinib	0.2296617									

Aza: Azacitidine; Ven: Venetoclax; LDAC: Low-dose Cytarabine; Dec: Decitabine; GO: Gemtuzumab Ozogamicin; AE: Adverse Event

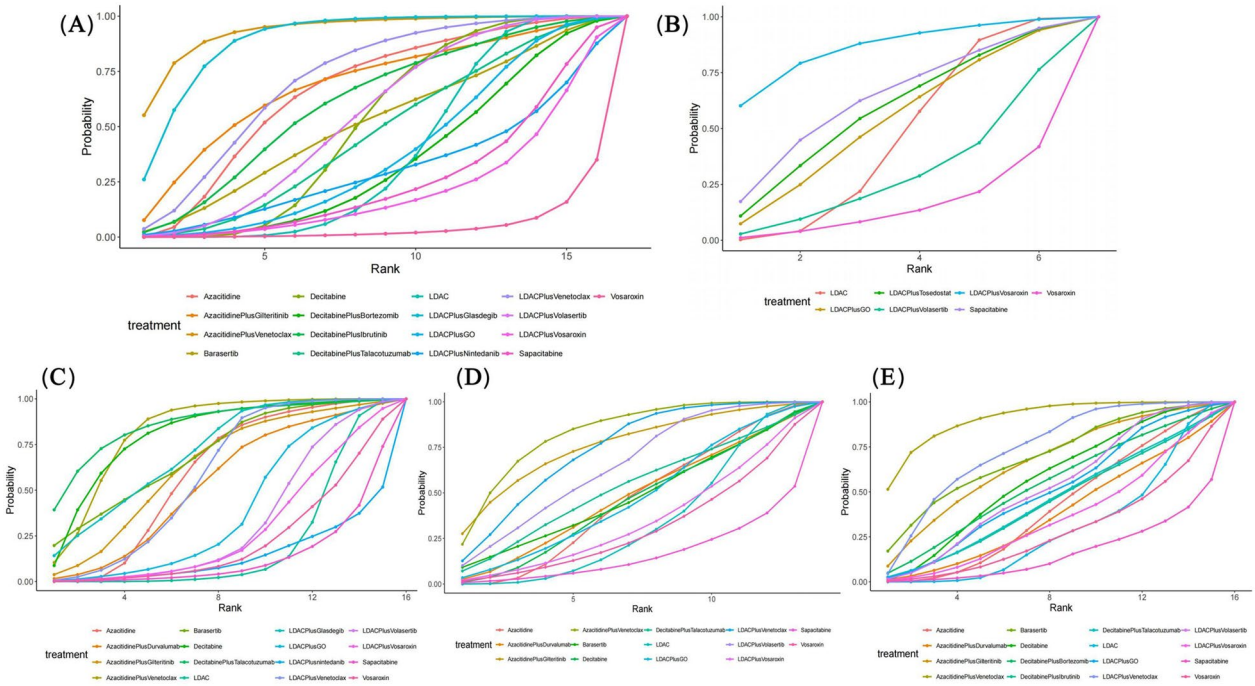

Fig. 3 Cumulative ranking probability plots (**A**: OS, **B**: RFS, **C**:CR, **D**:CRi, **E**:ORR), The horizontal axis represents the possible rank of each treatment (from best to worst according to the outcome). The vertical axis represents the cumulative probability for each treatment to be the best option, the best of 2 options, the best of 3 options, and so on

as a potential outcome, limiting its ability to provide a comprehensive assessment of low-intensity treatment for old patients.

Furthermore, LDAC plus glasdegib demonstrated statistically significant advantages over LDAC monotherapy, LDAC plus GO, and LDAC plus vosaroxin in improving OS. This indirect comparison addresses the limitation of lacking direct head-to-head trial results. Although the league table did not reveal differences in OS and CR, LDAC plus glasdegib ranked significantly higher than LDAC plus venetoclax. Additionally, LDAC plus glasdegib showed a lower risk of death compared to decitabine monotherapy. These findings corroborate the conclusions drawn by Tremblay et al. who used indirect or simulated treatment comparison methods to suggest that LDAC in combination with glasdegib significantly improves OS compared to azacitidine or decitabine [51]. Given the widespread use of HMA in combination with venetoclax, LDAC plus glasdegib deserves greater consideration as a treatment option.

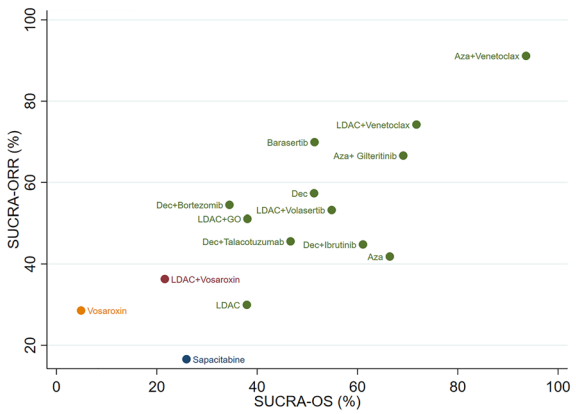

Fig. 4 A visual representation of SUCRA-OS and SUCRA-ORR

Regarding the safety profile of LDAC-related combination therapies, despite LDAC plus nintedanib is highly safe, it does not improve survival, similar to other anti-VEGF drugs. Hence, it is an unsatisfactory treatment option overall. Additionally, when LDAC is combined with either glasdegib or venetoclax, its higher incidence of AEs may be attributable to longer treatment durations. However, LDAC plus volasertib has been associated with significantly higher rates of fatal infections, likely due to pronounced myelosuppression, as confirmed in Phase III clinical trials. Given the poor intolerability of the regimen, it is considered the least favorable in term of safety [23]. For AZA-related combination therapies, although AZA plus venetoclax and durvalumab ranked lower than AZA monotherapy in term of safety, they did not negatively impact patients' quality of life and maintained a manageable safety profile. The lowest-ranked combination, AZA plus gilteritinib, despite having the highest

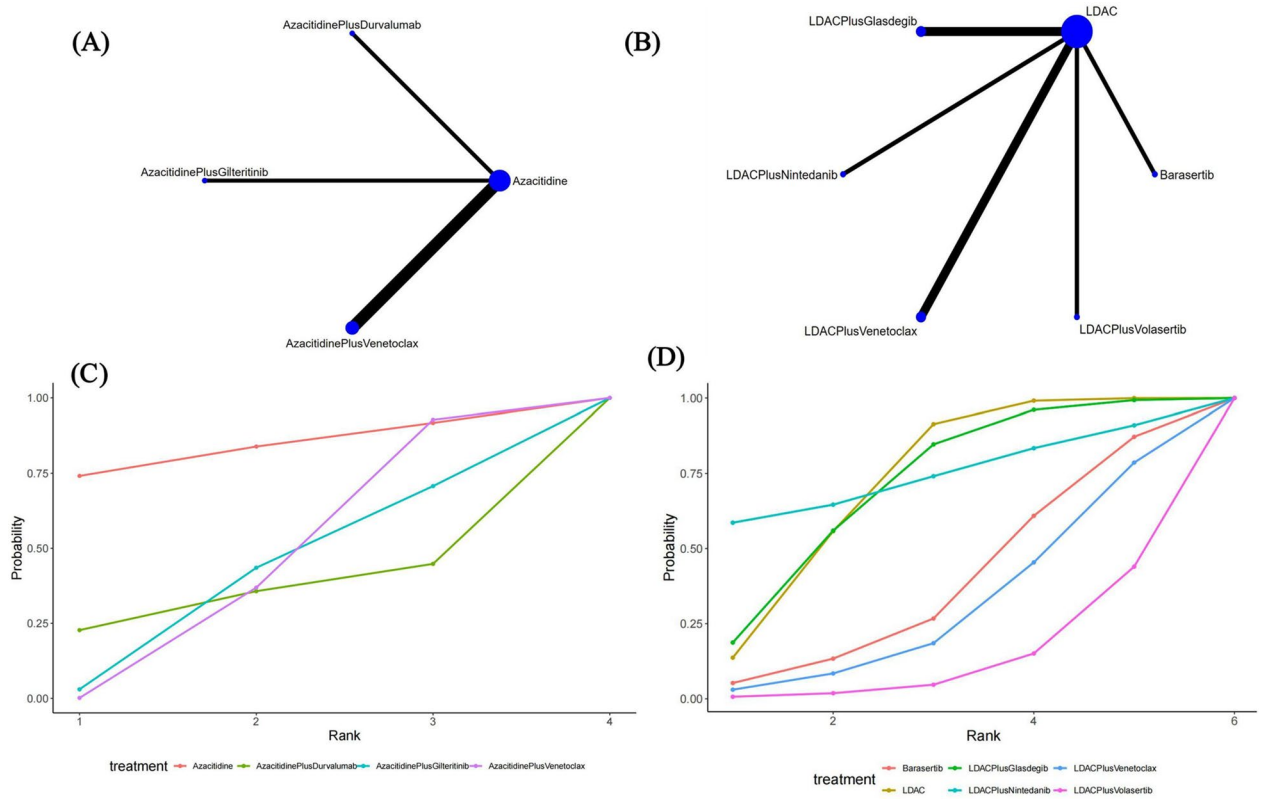

Fig. 5 **A , B** Network Evidence plot for AEs; **C, D** Cumulative ranking probability plots for AEs

probability of AEs, exhibited a comparable mortality rate to monotherapy. Therefore, with careful monitoring of bone marrow suppression and infections, old patients may still benefit from this treatment.

With advancing age, treatment limitations arise due to poorer tolerance and lower CR rates associated with adverse cytogenetics and molecular markers. The addition of venetoclax to HMAs has significantly improved outcomes in AML. Venetoclax (ABT-199) is a second-generation BH3 mimetic that selectively inhibits B-cell lymphoma-2 (BCL-2), thereby disrupting energy metabolism and targeting leukemic stem cells (LSCs), leading to substantial clinical benefits [52, 53]. Our study verifies the idea that AZA plus venetoclax is an effective and safe option for old AML patients with relapsed/refractory (R/R) disease or newly diagnosed cases unfit for standard therapy. Clinical trials have further shown that this combination elicits similar responses in patients with Nucleophosmin-1-mutation and FMS-like Tyrosine Kinase 3 –mutation [54, 55]. However, acquired resistance to venetoclax poses a significant challenge for maintaining long-term remission in venetoclax-sensitive patients. The restoration of pre-existing dominant mutations is the primary mechanism of resistance [56]. Combining venetoclax with LDAC may serve as a potential strategy to mitigate resistance while enhancing CR and CRi rates in AML. For patients previously treated with HMA for myelodysplastic syndromes (MDS) who subsequently develop AML, transitioning from HMA plus venetoclax to alternating combination therapies may improve treatment responses [53]. A recently proposed regimen, known as the VAA (venetoclax, azacitidine, and LDAC) regimen, combines LDAC with venetoclax and azacitidine. This combination regimen has demonstrated therapeutic advantages against both venetoclax-resistant and venetoclax-sensitive AML cells in vitro, with high response rates (CR: 83.3%) and good tolerability in clinical practice. Prospective multicenter clinical trials are currently underway to further evaluate its efficacy and safety in treating R/R AML and MDS-related AML [57].

Glasdegib is an oral inhibitor of the transmembrane protein Smoothened (SMO) involved in the Hedgehog (Hh) signaling pathway. It was approved by the Food and Drug Administration (FDA) in November 2018 and by the European Medicines Agency (EMA) in June 2020 for use in combination with LDAC in newly diagnosed AML patients aged ≥ 75 years or those unfit for intensive induction chemotherapy. When combined with LDAC, glasdegib has demonstrated improved OS and

clinical efficacy. Since the Hedgehog signaling pathway is not essential for normal adult hematopoietic stem cell function, targeting LSCs with glasdegib can effectively reduce tumor burden while preserving normal hematopoietic function, thereby improving clinical outcomes. This may explain why old patients tolerate glasdegib better than other treatment options [58, 59]. Furthermore, a study by Heuser et al. found that LDAC plus glasdegib provides greater benefits to secondary AML patients, with a median OS surpassing previously reported values for decitabine (7.1 months) and LDAC plus venetoclax (4.0 months) [35]. Therefore, we speculate that alternating treatment with AZA plus venetoclax and LDAC plus glasdegib may represent a promising strategy to overcome acquired venetoclax resistance.

Therefore, direct head-to-head double-blind RCTs are sincerely desired to compare AZA plus venetoclax, LDAC plus venetoclax, and LDAC plus glasdegib. Additionally, further research should extend beyond old patients ineligible for standard treatment to explore broader patient populations. Given the challenge of acquired venetoclax resistance, evaluating the clinical feasibility of the VAA regimen and the alternative use of LDAC plus glasdegib with LDAC plus venetoclax is crucial. Further investigation is warranted to determine whether these novel combination therapies can replace the conventional AZA plus venetoclax regimen and improve the survival outcome in older AML patients who are unfit for standard intensive chemotherapy. We believe that these emerging and exciting treatments can make the future of old AML patients brighter than ever before.

This network meta-analysis has several limitations. First, direct (head-to-head) treatment comparisons remain lacking, despite the use and validation of indirect treatment comparison analyses to compare outcomes from RCTs. Prospective comparative trial data are limited, restricting the ability of network meta-analyses to fully inform patient selection for different treatment strategies, and further research is warranted. Second, the number of studies is limited and sample sizes for certain interventions are small, which may have influenced the findings. Additionally, in the analysis of AEs, the incomplete reporting of side effects across included studies limited direct comparison. Nevertheless, this study systematically synthesizes data from RCTs and cohort studies on low-intensity treatments, providing a comprehensive evaluation of the efficacy and safety of currently available clinical or approved experimental protocols.

Conclusions

In this network meta-analysis, both LDAC and AZA combined with venetoclax significantly improved OS and ORR compared to monotherapy. Additionally, LDAC with the SMO inhibitor glasdegib demonstrated better OS and CR rates compared with other low-intensity induction regimens including LDAC plus venetoclax, offering a new perspective on treatment strategies under the leading role of venetoclax. However, high-quality, large-scale prospective RCTs directly comparing different low-intensity treatments remain scarce, and our NMA study addresses this gap. To overcome resistance issues and determine the optimal low-intensity treatment regimen for old AML patients, we strongly encourage further research into feasible multi-drug combination therapies to expand and strengthen the treatment network.

Critical view

This review comprehensively evaluates the efficacy and safety of low-intensity treatments for old patients with AML through a systematic review and network meta-analysis. While previous studies have explored individual therapies in RCTs and observational studies, this analysis integrates indirect comparisons across a broad spectrum of treatment modalities. This approach addresses the gap of no head-to-head clinical trials, providing a more nuanced understanding of relative treatment effects. AZA plus venetoclax is established as the most effective and well-tolerated regimen for old patients unfit for intensive chemotherapy, and other alternatives such as LDAC plus glasdegib should be further investigated. These findings have the potential to shape clinical guidelines and inform personalized treatment strategies, particularly for high-risk subgroups. Additionally, it is necessary to conduct direct head-to-head RCTs and further investigation into multi-drug regimens, such as alternating therapies to combat resistance. It proposes innovative strategies, including the VAA regimen (venetoclax, AZA, and LDAC), as promising avenues for improving outcomes in this patient population. In conclusion, this review provides a critical and actionable insight into this field by synthesizing existing evidence and identifying key gaps. It serves as a valuable resource for clinicians and researchers to optimize care for old AML patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02476-9.

Supplementary Material 1.

Supplementary Material 2: Figure S1. Risk of bias for the studies included in this network meta-analysis. Figure S2. Funnel plots, Egger's publication bias plot of different endpoints. A: Funnel plots and Egger's publication of OS. B: Funnel plots and Egger's publication of recurrence-free survival. C: Funnel plots and Egger's publication of CR. D: Funnel plots and Egger's publication of CRi. E: Funnel plots and Egger's publication of ORR. Table S1. Brief table of the various medication included in RCTs. Table S2. Search strategies. Table S3 Quality assessment for cohort studies.

Author contributions
Wenze Li, Sijing Kang designed the study and developed the retrieval strategy. Yu Jiao and Sijng Kang executed the systematic evaluation as the first and second reviewers, respectively; Pengjie Yue and Rui Ge searched and screened the summaries and titles, assessed the inclusion and exclusion criteria, generated the data collection forms; Wenze Li, Weilin Dong extracted the data, and evaluated the quality of the study. Disagreements were arbitrated by Xiaojing Yan and Ziyi Wang. Wenze Li and Sijing Kang performed the meta-analysis, and drafted the article, which was reviewed and revised by Xiaojing Yan.

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Data availability
All data is available in the manuscript.

Declarations

Ethics approval and consent to participate
This meta-analysis strictly follows academic norms and ethical principles, performing only a secondary analysis of aggregated data. The privacy and confidentiality of study participants in the original research were not compromised. All included studies were retrieved from scientific databases and subjected to rigorous quality assessments to ensure reliability and validity.

Competing interests
The authors declare no competing interests.

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