Systematic Review and Meta-Analysis

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Efficacy of decitabine combined with allogeneic hematopoietic stem cell transplantation in the treatment of recurrent and refractory acute myeloid leukemia (AML)

A systematic review and meta-analysis

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Abstract

Background: This analysis aimed to assess the effect of decitabine combined with allogeneic hematopoietic stem cell transplantation (allo-HSCT) in treating recurrent and refractory acute myeloid leukemia.

Method: The present analysis was carried out according to the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline statement. Web of Science, Embase, PubMed, The Cochrane Library, CNKI, VIP, and WanFang Data databases were searched for trials published from their corresponding inception to September 13, 2021. Retrospective research or published randomized controlled trials in Chinese or English were ruled out. The methodological quality of the included studies was assessed using the Physiotherapy Evidence Database scale. Mean differences with 95% confidence intervals were used to analyze continuous data. The I^2 test was used to determine heterogeneity, and the meta-analysis was conducted using Revman 5.4.

Results: Eight studies including 795 participants in total were identified. Decitabine and allo-HSCT showed significant reductions in recurrence after transplantation (odds ratio [OR] = 0.29, 95% confidence interval [CI] (0.17, 0.50), $P < .00001$), leukemia-free survival (OR = 2.17, 95% CI (1.47, 3.21), $P < .0001$), graft related death (OR = 0.50, 95% CI (0.25, 0.98), $P = .04$), and significant improvements in complete remission (OR = 0.39, 95% CI = 0.23–0.68, $P = .0007$) and partial remission (OR = 0.46, 95%CI = 0.27–0.78, $P = .004$). The median follow-up time, acute graft-versus-host disease, and no remission had no significant difference between treatment and control groups (the median follow-up time: OR = –1.76, 95% CI (–6.28, 2.76), $P = .45$; acute graft-versus-host disease: OR = 0.72, 95% CI (0.50, 1.03), $P = .08$; no remission: OR = 3.19, 95%CI = 2.06–4.94, $P = .05$). Overall, the magnitude of the effect was found to be in the small to moderate range.

Conclusion: Decitabine combined with allo-HSCT can obtain lower recurrence risk and longer disease-free survival time, and improve the prognosis of patients. The safety is relatively stable. Due to the varying quality level of the included studies, the validation of multiple high-quality studies still needs improvement.

Abbreviations: aGVHD = acute graft-versus-host disease, allo-HSCT = allogeneic hematopoietic stem cell transplantation, AML = acute myeloid leukemia, CIs = confidence intervals, CR = complete remission, DAC = decitabine, LFS = leukemia-free survival, NR = no remission, OR = odds ratio, PR = partial remission, RCTs = published randomized controlled trials, TRM = graft related death.

Keywords: allo-HSCT, decitabine, meta-analysis, recurrent and refractory AML

The authors have no funding and conflicts of interest to disclose.

The data synthesized and presented in the results section have been well referenced as an update systematic review article. However, raw data (in excel sheet) used in the statistical analysis will be made available on request through the corresponding author (JC).

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1. Introduction

Acute myeloid leukemia (AML) can be defined as a complex hematologic-based cancer with symptomatology, including hemorrhage, anemia, and infections.[1] Most reported AML patients are senior citizens with a median diagnosis age of 67 years.[2] Furthermore, limited therapeutic options in elderly AML patients may explain such a demographic accounting for the bulk of annual AML mortality rates, particularly in individuals with comorbid morbidities and poor treatment response.[3]

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only way to cure refractory and recurrent AML.[4] Relapse remains the leading cause of death in patients after allo-HSCT, accounting for 20% to 50% of deaths.[5–7] Post-transplantation deterioration is associated with a poor prognosis,[8] therefore preventing relapse is critical to improving the outcome of allo-HSCT in high-risk AML patients.

Intensive myeloablative conditioning is a primary therapeutic option that can maximize the reduction of the residual leukemia burden to reduce disease recurrence post-transplantation.[9] Decitabine (DAC) is a deoxycytidine analog that can inhibit DNA methylation and promote the differentiation and apoptosis of cancer cells.[10,11] It can significantly improve the prognosis and the quality of life of AML patients.[12] DAC induces leukemic cell differentiation and re-expression of epigenetically silenced putative tumor suppressor genes,[13] and it exerts synergistic cytotoxicity with Bu in AML cell lines.[14] Furthermore, DAC can up-modulate tumor-associated cell surface antigen expression, which clinically may lead to an increased graft-versus-leukemia effect, but decrease graft-versus-host disease (GVHD) effect through an increase in regulatory T cells.[15] Demethylated drugs, including decitabine, have been used to prevent and treat recurrence after allo-HSCT, but there are few reports at home and abroad. Therefore, to provide evidence-based evidence for clinical treatment, we conducted the present study to systematically evaluate the effectiveness and safety of decitabine combined allo-HSCT in treating recurrent and refractory AML.

2. Materials and Methods

2.1. Search strategy

PubMed, the Web of Science, EMBASE, CNKI, Cochrane Library, CBM, VIP, and Wanfang databases were searched from the date of their respective inception to September 13, 2021. The keywords used for the searching were: ("Decitabine[Mesh]" OR "5-AzadC" OR "Dacogen" OR "5? Deoxyazacytidine" OR "DecitabineMesylate") AND ("Hematopoietic Stem Cells[Mesh]" OR "Hematopoietic Stem Cell" OR "Hematopoietic Progenitor Cell" OR "Hematopoietic Colony-Forming Unit") AND ("Leukemia, Myeloid, Acute[Mesh]" OR "Acute Myeloid Leukemia?" OR "ANLL" OR "Acute Myeloblastic Leukemia?" OR "Acute Myelogenous Leukemia?"). No language limit was applied (Table 1).

2.2. Inclusion criteria

The inclusion criteria were: study type: randomized controlled trials or case-control trial; study participants: patients diagnosed with relapsed refractory AML; treatment methods: patients in the treatment group received decitabine in addition to allo-HSCT, while those in the control group received only allo-HSCT; the outcome indicators had to include: median follow-up time, leukemia-free survival (LFS), graft related death (TRM), acute graft versus host disease (aGVHD), recurrence after transplantation, and as per NCCN guidelines, the efficacy evaluation was divided into partial remission (PR), complete remission (CR), and no remission.[16,17]

2.3. Exclusion criteria

Non-Chinese or non-English literature; If the original data could not be recovered after contacting the author, no raw data could be obtained; multiple publications, duplicate publications, animal experiments, clinical case studies; and studies with inconsistent outcome indicators.

2.4. Data extraction and literature quality evaluation

Two researchers independently screened the literature back-to-back, extracted the data, and cross-checked the results. In case of disagreement, the discrepancy was determined through discussion with a third party. When conducting a literature search, the title and abstract of the publication were first reviewed, and then the whole text was examined to see if the study merited inclusion. The following details were gleaned from the extracted information: baseline information of the included study such as title, first author, year of publication; essential characteristics and treatment methods of control and experimental groups; key information of bias risk assessment; and outcome indicators. The risk of bias for each qualified study was evaluated following the Cochrane reviewer's manual 5.1.0.[18] Bias risks include selection bias (random sequence generation and allocation concealment), implementation and measurement bias (blindness of participants and researchers, blindness of outcome evaluators and statisticians), follow-up bias (incomplete outcome data, systematic differences), reporting bias (selective outcome reporting), and other bias (e.g., conflict of interest, follow-up, different characteristics and representativeness of participants, different types of needles used, intentional treatment analysis, etc).

2.5. Statistical analysis

Revman 5.4 (The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark) was used to conduct the analysis. The

Table 1

The search words and strategy of the PubMed database.

No.	Search strategies
#1	"Hematopoietic Stem Cells"[Mesh]
#2	"Decitabine"[Mesh]
#3	"Leukemia, Myeloid, Acute"[Mesh]
#4	((Hematopoietic Stem Cell[Title/Abstract]) OR (Hematopoietic Progenitor Cell?[Title/Abstract])) OR (Hematopoietic Colony-Forming Unit?[Title/Abstract])
#5	((((((((((5?Aza?2′?deoxycytidine[Title/Abstract]) OR (5-AzadC[Title/Abstract])) OR (AzadC Compound[Title/Abstract])) OR (5AzadC[Title/Abstract])) OR (2′-Deoxy?5?azacytidine[Title/Abstract])) OR (5?Azadeoxycytidine[Title/Abstract])) OR (Dacogen[Title/Abstract])) OR (5?Deoxyazacytidine[Title/Abstract])) OR (NSC 127716[Title/Abstract])) OR (NSC?127716[Title/Abstract])) OR (Decitabine Mesylate[Title/Abstract])
#6	(((((((((Acute Myeloid Leukemia?[Title/Abstract]) OR (ANLL[Title/Abstract])) OR (Acute Myeloblastic Leukemia?[Title/Abstract])) OR (Acute Myelocytic Leukemia?[Title/Abstract])) OR (Acute Nonlymphoblastic Leukemia?[Title/Abstract])) OR (Acute Nonlymphocytic Leukemia?[Title/Abstract])) OR (Acute Myelogenous Leukemia?[Title/Abstract])) OR (Acute Myeloid Leukemia without Maturation[Title/Abstract])) OR (Acute Myeloid Leukemia with Maturation[Title/Abstract])
#7	#1 OR #4
#8	#2 OR #5
#9	#3 OR #6
#10	#7 AND #8 AND #9

data were analyzed with the use of the odds ratio (OR). The weighted mean difference statistic was employed to measure the data, and the results were presented with a 95% confidence interval (CI). The chi-square test (with a significance level of $\alpha = 0.1$) was used to examine the heterogeneity among the included study results. The amount of heterogeneity was quantified by combining it with the I^2 coefficient.[19] Suppose no significant statistical heterogeneity was observed ($I^2 \leq 50\%$, $P \geq .1$), the fixed-effect model was used to merge the data. If there was a significant statistical heterogeneity found ($I^2 > 50\%$, $P < .1$), the random effect model was used to merge the data.[20] Sensitivity analysis was used to determine the origin of heterogeneity. The publication bias test was used in conjunction with Stata 15.1 to find any asymmetry between the studies, and possible publication bias was determined using a funnel chart.[21] Due to the small sample size, funnel plot analysis was not employed to assess publication bias.

2.6. Ethical statement

All authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will be completed based on published literature; therefore, research ethics board approval and consent are waived.

3. Results

3.1. Search results

As is shown in Figure 1, a total of 117 articles were obtained in the initial screening, and 46 pieces were removed for duplication. Through reading titles and abstracts, 49 articles were excluded, and 22 were selected. The full texts of the selected articles were obtained for further evaluation, and 8 articles[22–29] were finally included.

3.2. Patient characteristics

Seven trials included in the present analysis were conducted in China, 1 test run in America, 6 retrospective studies,[23–26,28,29] and 2 randomized controlled trials.[22,27] Seven hundred ninety-five patients were identified, including 294 patients in the treatment group and 501 in the control group. Detailed information about the included trials and patients is listed in Table 2.

3.3. Quality assessment

According to the criteria of Cochrane guidelines, each trial was classified as low bias, unclear (the risk of bias is undefined or unknown), or high bias. The assessment of the risk of bias is shown in Figure 2. Among the included studies, 1 literature studies[22] use reasonable random methods (random number table), which belong to complete randomness. Therefore, the generation of random sequence' is judged as "low risk"; only 2 pieces of literature[22,23] specify the methods of concealing allocation, double-blind of implementers and subjects, and blind outcome measurement. As a result, these items were classified as "low risk." All included studies reported the trial's outcome, demonstrating the trial's integrity. On the whole, this review's effectiveness indicates a minimal risk.

3.4. Meta-analysis results

3.4.1. Median follow-up time. As shown in Figure 3, 7 studies[22–26,28,29] had a total of 747 cases, with homogeneity between the studies ($I^2 = 0\%$, $P = .97$). Using the fixed effect model, the incidence of median follow-up time had no significant difference between treatment and control groups [OR = –1.76, 95% CI (–6.28, 2.76), $P = .45$].

3.4.2. Leukemia-free survival (LFS). As illustrated in Figure 4, 5 investigations[22,23,25,26,29] included a total of 580 cases, with low

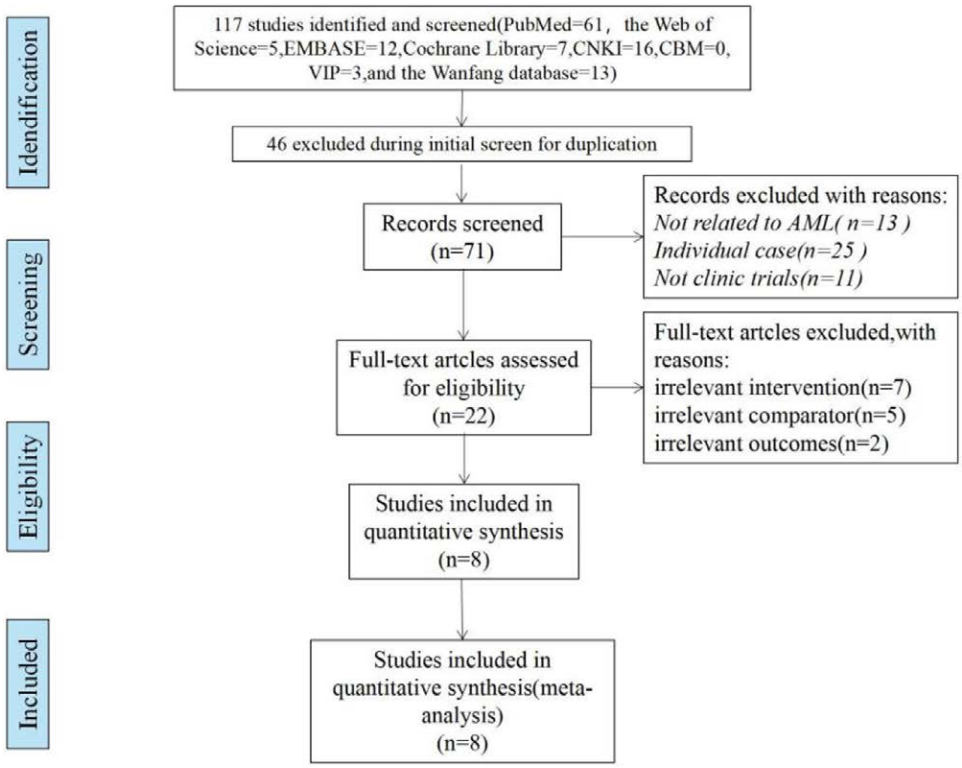

Figure 1. Flowchart of the literature screening process.

Table 2

Main characteristics of the 8 studies included in the meta-analysis.

		Treatment group				Control group				
Name	Year	Intervention	Age: mean (SD)	Male (%)	Female (%)	Intervention	Age: mean (SD)	Male (%)	Female (%)	Outcome
Gao et al[22]	2020	DAC + allo-HSCT	3–62	56 (56.0)	44 (44.0)	Allo-HSCT	2–52	61 (59.8)	41 (40.2)	①②③④⑤⑥⑧
Gangat et al[23]	2021	DAC + allo-HSCT	53–81	9 (64.2)	5 (35.8)	Allo-HSCT	47–81	10 (55.5)	8 (44.5)	②⑤⑥⑧
Xu et al[24]	2019	DAC + allo-HSCT	14–74	22 (62.8)	13 (37.2)	Allo-HSCT	15–64	25 (52.0)	23 (48.0)	⑤⑥
Tang et al[25]	2021	DAC + allo-HSCT	8–61	35 (59)	24 (41)	Allo-HSCT	7–61	106 (60)	71 (40)	②④⑧
Ma et al[26]	2019	DAC + allo-HSCT	10–63	13 (61.9)	8 (31.8)	Allo-HSCT	8–56	37 (58.7)	26 (41.3)	②④⑤⑦⑧
Zheng[27]	2015	DAC + allo-HSCT	9–56	12 (60.0)	8 (40.0)	Allo-HSCT	12–54	19 (67.8)	9 (32.2)	③④⑤⑥⑦⑧
Cheng et al[28]	2017	DAC + allo-HSCT	24–57	15 (83.3)	3 (16.7)	Allo-HSCT	12–52	16 (61.5)	10 (38.5)	③④⑧
Gao[29]	2018	DAC + allo-HSCT	19–67	15 (55)	12 (45)	Allo-HSCT	10–60	25 (64.5)	14 (35.5)	②③④⑧

Outcomes: ① The median follow-up time; ② Leukemia-free survival (LFS); ③ Graft related death (TRM); ④ Acute graft versus host disease (aGVHD); ⑤ complete remission (CR); ⑥ partial remission (PR); ⑦ no remission (NR); ⑧ Recurrence after transplantation.

DAC = decitabine, HSCT = allogeneic hematopoietic stem cell transplantation.

inter-study homogeneity (I^2 = 33%, P = .20). The difference in LFS between the treatment and control groups in the treatment of AML was statistically significant when using the fixed-effect model [OR = 2.17, 95 % CI (1.47, 3.21), P < .0001].

3.4.3. Graft related death (TRM). As displayed in Figure 5, 4 investigations[22,27–29] included a total of 333 patients, with no evidence of heterogeneity between the studies (I^2 = 0%, P = .64). The difference in TRM between the treatment and control groups in the treatment of AML was statistically significant when using the fixed-effect model [OR = 0.50, 95 % CI (0.25, 0.98), P = .04].

3.4.4. Acute graft-versus-host disease (aGVHD). As shown in Figure 6, 7 studies[22,25–29] had a total of 653 cases, with homogeneity between the studies (I^2 = 19%, P = .29). Using the fixed effect model, the incidence of aGVHD had no significant difference between treatment and control groups [OR = 0.72, 95% CI (0.50, 1.03), P = .08].

3.5. Recurrence after transplantation

As illustrated in Figure 7, 4 investigations[22,27–29] included a total of 352 patients, with no evidence of heterogeneity between the studies (I^2 = 0%, P = .98). The difference in recurrence after transplantation between the treatment and control groups was statistically significant [OR = 0.29, 95% CI (0.17, 0.50), P < .0001].

3.6. Efficacy evaluation

As shown in Table 3, the pooled results indicated that patients who received combination therapy achieved considerably higher rates of CR and PR. The results of the heterogeneity tests of the CR were: I^2 = 78%, P = .004, showing significant heterogeneity. The random-effect model was used for analysis (OR = 0.39, 95%CI = 0.23–0.68, P = .0007), showing a significant difference in CR between the 2 groups (P < .05). The outcomes of the heterogeneity tests of the PR were: I^2 = 0%, P = .99, using the fixed-effect model (OR = 0.46, 95%CI = 0.27–0.78, P = .004), which indicated a significant difference in PR between the 2 groups (P < .05). However, no significant differences were observed in no remission between the 2 groups (OR = 3.19, 95%CI = 2.06–4.94, P = .05). The OR rate was evaluated through fixed-effect models because of low heterogeneity.

3.7. Safety

Two studies[22,25] 1 of 8 mentioned unfavorable responses. The most often occurring adverse event associated with treatment was hyperleukocytosis, which occurred primarily during the first 2 rounds of G-Dec medication (Data Supplement). Nausea, vomiting, diarrhea, peripheral edema, abnormal liver function, and abnormal renal function were nonhematologic toxicities. The majority of adverse events were classified as grade 1 or 2 and resolved following symptomatic therapy.

4. Discussion

Hematopoietic stem cell disease AML is a highly diverse illness with multiple cytogenetic or molecular alterations. Chemotherapy and allo-HSCT may cure AML patients,[30] the GVHD-free (relapse-free survival, GRFS) composite outcome is used.[31] Recurrence after transplantation is the leading cause of refractory and recurrent AML, accounting for about half of all transplantation failures.[32] Decitabine is an inhibitor of DNA methyltransferase. Numerous clinical trials have demonstrated that decitabine is more effective than best supportive care (BSC) at improving blood response and reducing blood transfusion reliance in patients with relatively low-risk MDS.[33] In relatively high-risk MDS and AML, decitabine can upsurge the survival benefit and delay the transformation to AML compared with BSC or low-dose cytarabine.[34,35] Hence, decitabine is clinically recommended for treating malignant hematological diseases such as MDS and AML through its antitumor activity, immunomodulatory effect, and good tolerance.[36,37] Some studies have recently applied decitabine to bridging therapy before MDS transplantation[38,39] or maintenance treatment after MDS transplantation,[40] and some progress has been made.

However, different studies have shown that overall survival and recurrence impact is still controversial.[41–43] Previous studies have shown that bridging allo-HSCT with decitabine pretreatment is a safe and feasible treatment.[44,45] Kong-Tim et al[46] believe that applying demethylation drugs before transplantation can reduce the 3-year cumulative recurrence rate and prolong the progression-free survival time. However, other works of the literature suggest that whether chemotherapy and demethylation drugs are used before transplantation does not affect the prognosis of transplantation.[47,48] This meta-analysis showed that decitabine bridging combined with allo-HSCT, or decitabine enhanced pretreatment regimen allo-HSCT is safe and effective in treating refractory recurrent acute leukemia. This strategy can decrease recurrence rates following transplantation, improving overall and disease-free survival rates in patients with refractory recurrent acute leukemia. The meta-analysis revealed that whether decitabine bridging in combination with allo-HSCT or decitabine enhanced pretreatment regimen in combination with allo-HSCT is used to treat refractory and refractory AML patients, decitabine in combination with allo-HSCT demonstrated a significant reduction in recurrence after transplantation, LFS, and TRM (P < .05), as well as

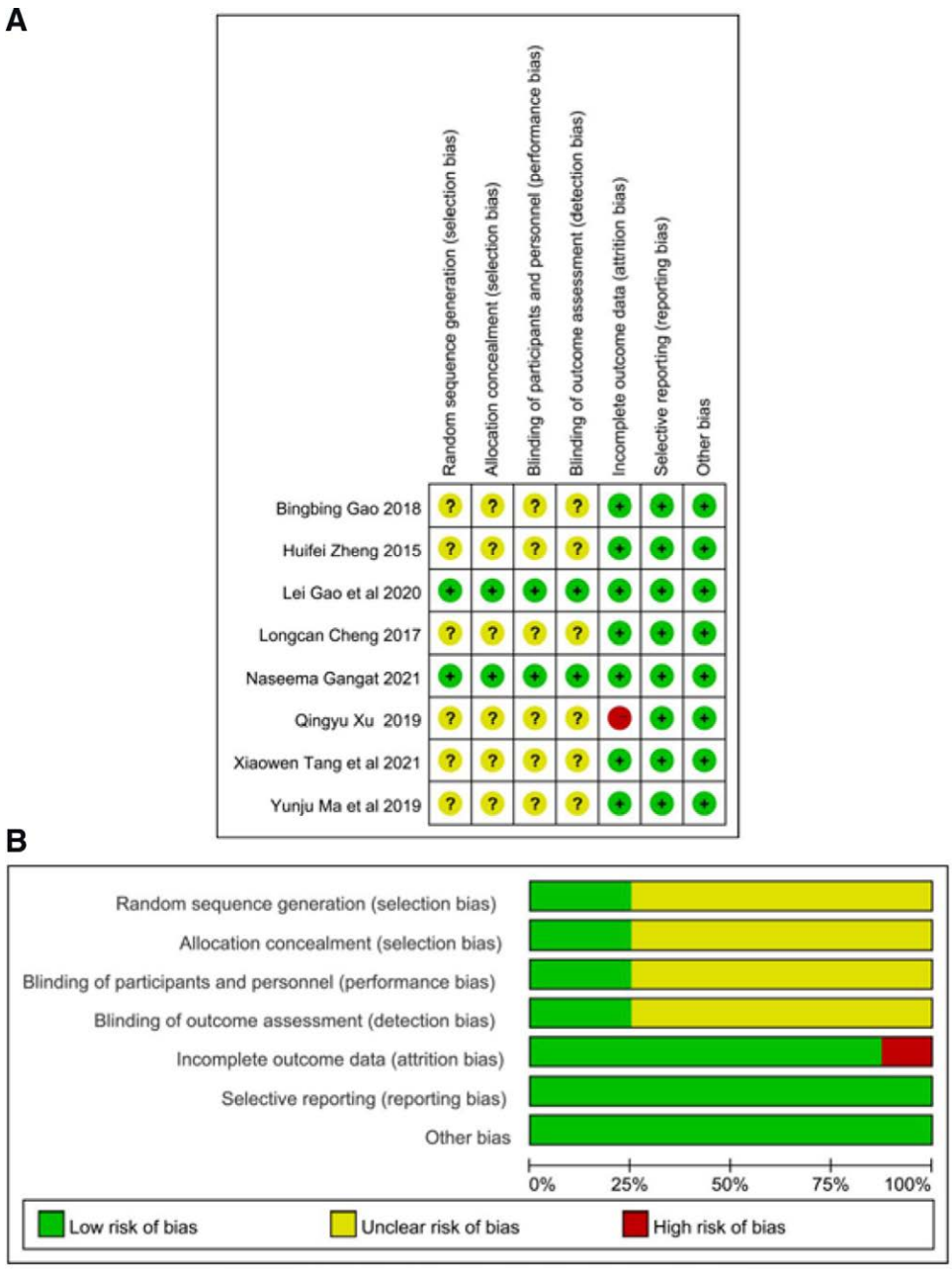

Figure 2. (A) Summary of risk of bias for each included study and (B) bar graph of the risk of bias showing the percentage of risk level for each characterized risks. Each color represents a different level of bias: red for high risk, green for low risk, and yellow for unclear risk of bias.

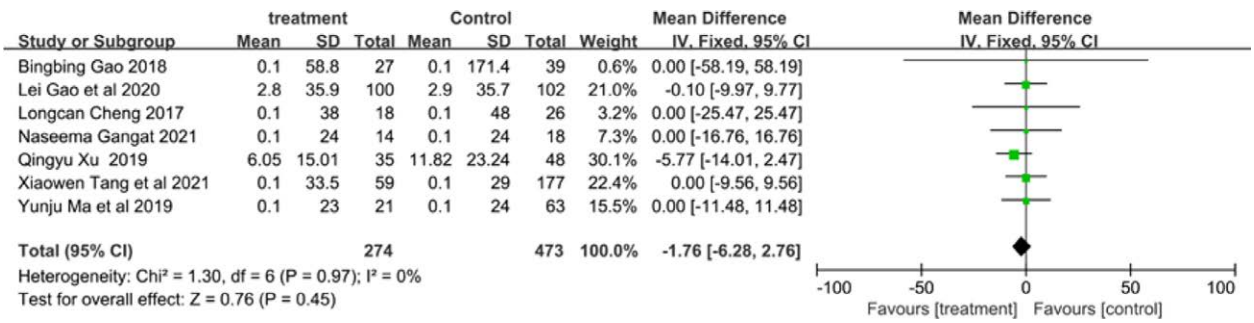

Figure 3. Forest plot of the comparison of median follow-up time between the experimental and control groups.

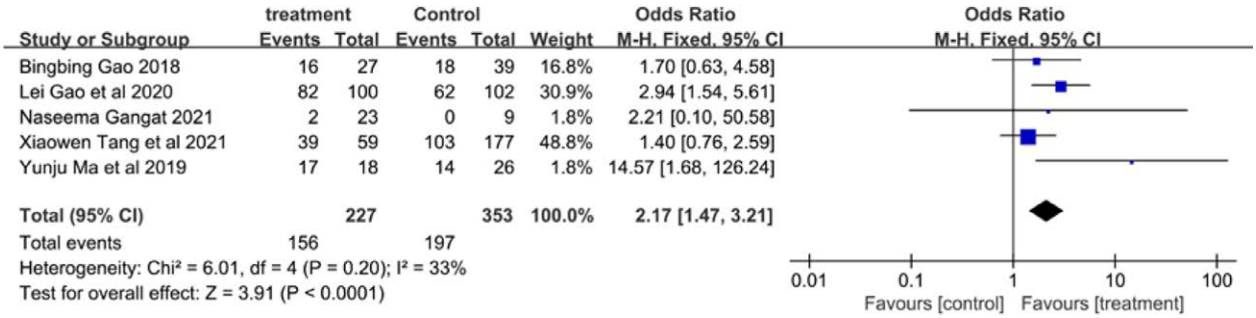

Figure 4. Forest plot of the comparison of recurrence after transplantation between the experimental and control groups.

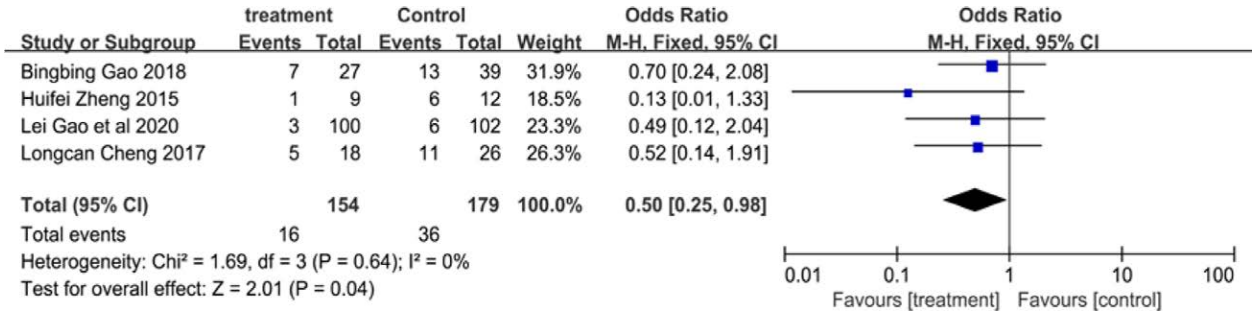

Figure 5. Forest plot of the comparison of leukemia-free survival (LFS) between the experimental and control groups.

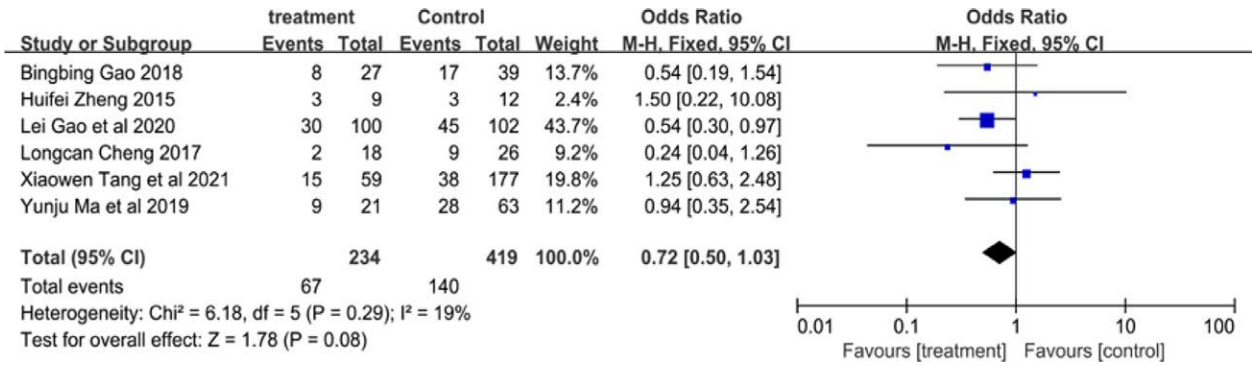

Figure 6. Forest plot of the comparison of graft related death (TRM) between the experimental and control groups.

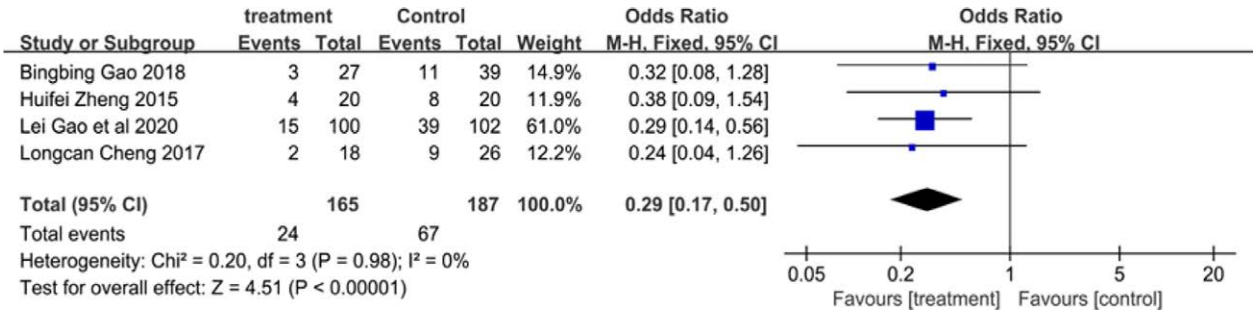

Figure 7. Forest plot of the comparison of acute graft-versus-host disease (aGVHD) between the experimental and control groups.

a significant improvement in CR and PR. It is hypothesized that when decitabine is paired with allo-HSCT, patients with AML will have a lower chance of recurrence and a longer disease-free survival time, thereby improving their prognosis.

However, because of the constraints of varied research designs, sample sources, and sample sizes, decitabine in combination with allo-HSCT transplantation to treat patients with AML is inconsistent, leading to inaccurate compelling conclusions. Additionally, only 2 trials mentioned adverse effects, indicating a lack of statistical accuracy. Future research seeks to increase clinical medicine's awareness of DAC and related adverse events caused by medications to provide AML patients

Table 3

Comparison of CR, PR, and NR between the treatment and control groups.

		Treatment		Control		Heterogeneity		Pooled effect	
Parameter	Studies	Events	Total	Events	Total	I^2 (%)	*P* value	OR (95% CI)	*P* value
CR	4	32	155	77	183	78	.004	0.39 (0.23, 0.68)	.0007
PR	3	40	134	60	120	0	.99	0.46 (0.27, 0.78)	.004
NR	2	7	32	32	72	0	.87	0.38 (0.14, 1.02)	.05

CI = confidence intervals, CR = complete response rates, NR = no remission, OR = odds ratio, PR = partial response rates.

with more remarkable advantages during treatment and lower the risk of recurrence.

5. Conclusion

Decitabine bridging combined with allo-HSCT, or decitabine improved pretreatment regimen allo-HSCT can obtain lower recurrence risk and longer disease-free survival time, and improve the prognosis of patients, the safety is relatively stable. Due to the varying quality level of the included studies, the validation of multiple high-quality studies still needs improvement.

Author contributions

(I) Conception and design: Jiahui Chen.
(II) Administrative support: None.
(III) Provision of study materials or patients: All authors.
(IV) Collection and assembly of data: Donghui Zhang.
(V) Data analysis and interpretation: Jiahui Chen.
(VI) Manuscript writing: All authors.
(VII) Final approval of manuscript: All authors.
Conceptualization: Donghui Zhang, Jiahui Chen.
Data curation: Donghui Zhang, Jiahui Chen.
Formal analysis: Donghui Zhang, Jiahui Chen.
Methodology: Donghui Zhang.
Resources: Donghui Zhang.
Software: Donghui Zhang.
Validation: Donghui Zhang.
Visualization: Jiahui Chen.
Writing – original draft: Donghui Zhang, Jiahui Chen.
Writing – review & editing: Donghui Zhang, Jiahui Chen.

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