Efficacy and safety of blinatumomab combination therapy in high-risk B-cell acute lymphoblastic leukemia: A systematic review and meta-analysis

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Abstract. The present study aimed to evaluate the efficacy and safety of blinatumomab-based combination therapy for high-risk B-cell acute lymphoblastic leukemia (B-ALL). PubMed, Embase, Web of Science and the Cochrane Library were searched for clinical studies on blinatumomab. The primary endpoints were complete remission (CR), minimal residual disease (MRD) and complete molecular remission (CMR). The secondary endpoint was overall survival (OS). Safety outcomes included adverse events (AEs), cytokine release syndrome, neurological events and hematological toxicity. A total of 11 studies involving 402 patients were included. The pooled CR rate was 87% (95% CI, 78-95%), the MRD negativity rate was 81% (95% CI, 75-87%) and the CMR rate was 81% (95% CI, 69-92%). The 1-year OS rate was 91% (95% CI, 78-100%), the 2-year OS rate was 87% (95% CI, 71-100%) and the 3-year OS rate was 52% (95% CI, 36-66%). Regarding safety, 86% (95% CI, 77-96%) of patients experienced all-grade AEs. Grade ≥3 AEs were generally consistent with known safety profiles, with the most common events being neutropenia (38%; 95% CI, 0-84%), febrile neutropenia (26%; 95% CI, 10-43%), and hyperglycemia (21%; 95% CI, 5-36%). In conclusion, blinatumomab-based combination therapy is an effective treatment for high-risk B-ALL with manageable toxicity.

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Introduction

Acute lymphoblastic leukemia (ALL) is a severe hematological malignancy characterized by impaired lymphocyte differentiation, which causes the proliferation of leukemic blasts in the bone marrow, peripheral blood and extramedullary tissues (1,2). ALL primarily affects children, with an incidence peaking between the ages of 1 and 4. The disease accounts for ~20% of adult leukemias, and ~60% of patients with ALL are diagnosed before the age of 20 (3-5). According to immunophenotypic classification, B-cell acute lymphoblastic leukemia (B-ALL) is the most common type, accounting for ~75% of cases (6).

High-risk B-ALL primarily comprises relapsed/refractory (R/R) cases and Philadelphia chromosome-positive (Ph^+) cases. In R/R B-ALL, conventional chemotherapy has limited efficacy, low complete remission (CR) rates and high toxicity. For example, in pediatric patients receiving conventional four-drug regimens, the incidence of life-threatening infections reaches 39.8%, and treatment-related mortality is 5%, while long-term survival in adult patients is only 20-40% (7,8). Ph^+ B-ALL accounts for 22-31% of adult ALL cases. Standard treatment regimens include intensive chemotherapy combined with tyrosine kinase inhibitors (TKIs). However, mutations in the ABL1 kinase domain (e.g., Thr315Ile) often lead to TKI resistance, significantly shortening post-relapse survival (9,10). Furthermore, elderly patients have a worse prognosis due to a poor tolerance to high-intensity chemotherapy. Analysis of the Surveillance, Epidemiology and End Results database (https://seer.cancer.gov/) shows that the median overall survival (mOS) time in this population is only 7-8 months. The disease in this group often exhibits aggressive biological characteristics, including complex karyotypes and TP53 mutations, which complicate treatment (11,12).

Over the past decade, targeted treatments utilizing B-cell targeted drugs and TKIs have demonstrated significant clinical efficacy in B-ALL (13,14). The anti-CD22 antibody-drug conjugate inotuzumab ozogamicin (INO) exhibits potent anti-leukemic activity and lower myelosuppression compared with conventional chemotherapy (15-18). Additionally, the

bispecific T-cell engager blinatumomab has shown promising results in relapsed or refractory B-ALL cases (19).

Blinatumomab is a bispecific T-cell engager antibody that simultaneously binds CD19 on B cells and CD3 on T cells. This dual binding activates T cells and redirects their cytotoxic activity against CD19-positive tumor cells, leading to targeted cell lysis (20-22). CD19 is uniformly expressed on malignant B cells but absent on hematopoietic stem cells (HSCs), making it an optimal therapeutic target for B-ALL. Due to this mechanism, blinatumomab has demonstrated clinical efficacy in R/R B-ALL and received U.S. Food and Drug Administration approval for this indication in 2014 (16,20,23,24). In a phase 2 trial of adults with newly diagnosed Ph^+ B-ALL, dasatinib and blinatumomab yielded a 98% CR rate. At the 18-month median follow-up, the OS rate was 95% and the disease-free survival (DFS) rate was 88% (25).

Blinatumomab has been studied in combination with other therapies. When added to low-intensity chemotherapy [mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone (mini-Hyper-CVD)] plus INO, blinatumomab prolonged the interval between inotuzumab administration and HSC transplantation (HSCT). This approach may decrease the risk of veno-occlusive disease/sinusoidal obstruction syndrome. Importantly, no cytokine release syndrome (CRS) or neurotoxicity was reported with this regimen (26). In patients with Ph^+ B-ALL, the chemotherapy-free combination of blinatumomab and ponatinib has shown promising results. This regimen can induce sustained deep remissions, potentially eliminating the need for allogeneic HSCT in some patients (27).

Despite advances with targeted therapies (such as the third-generation TKI ponatinib) and immunotherapies (including bispecific antibody blinatumomab and antibody-drug conjugate INO), single-agent treatment has yielded limited response rates and duration (19). For example, blinatumomab monotherapy achieves only a 36% overall response rate and 7.1-month mOS time in R/R Ph^+ B-ALL (28). Therefore, investigating combination regimens to enhance the depth of response, reduce treatment toxicity and address drug resistance has become a key direction for improving the prognosis of patients with high-risk B-ALL.

Given these factors and the severity of the condition, a meta-analysis of clinical trials on high-risk B-ALL was conducted. The present study aimed to evaluate the efficacy and safety of blinatumomab-based combination therapy in patients with high-risk B-ALL.

Methods

Study registration. The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (29). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews database (https://www.crd.york.ac.uk/prospero/), with registration number CRD420251108271.

Search strategy. A search of the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Web of Science (https://www.webofscience.com/), and the Cochrane Library (https://www.cochranelibrary.com/) databases was performed from inception to July 20, 2025. To ensure comprehensive coverage, no language restrictions were applied to the initial database search. The search strategy combined Medical Subject Headings terms and free-text words, including: 'blinatumomab' AND ('precursor cell lymphoblastic leukemia-lymphoma' OR 'acute lymphoblastic leukemia' OR 'acute lymphoid leukemia' OR 'leukemia, lymphoblastic, acute'). Additionally, reference lists of included studies were reviewed to identify further relevant studies.

Inclusion and exclusion criteria

Inclusion criteria. Eligible studies could be either prospective (covering randomized controlled trials and single-arm trials) or retrospective in design. The intervention under investigation needed to be blinatumomab in combination with other therapies. The target study population had to consist of patients with high-risk B-ALL. Lastly, only English-language studies were considered eligible for inclusion.

Exclusion criteria. Publication types such as reviews, conference abstracts, letters, guidelines, case reports, as well as cellular or animal experiments were excluded. Additionally, studies with unavailable full texts were excluded. Duplicate studies, including those involving secondary analyses, were also excluded. Furthermore, studies of very low quality or with severe design flaws, as evaluated by the Newcastle-Ottawa Scale (NOS) (30) or Methodological Index for Non-Randomized Studies (MINORS) (31), were excluded from the study.

Two researchers independently screened articles to evaluate their eligibility based on predefined inclusion and exclusion criteria. Discrepancies in study selection were resolved through discussions between the two researchers. If no consensus was reached, a third researcher was consulted for further resolution.

Data extraction and quality assessment. Two researchers independently extracted data from included studies and evaluated their quality. In the present study, CR was defined as bone marrow leukemic blasts ≤5% with or without complete blood cell recovery. Minimal residual disease (MRD) response was defined as a negative MRD status, with bone marrow leukemic blasts <0.01%. Complete molecular remission (CMR) was defined as sustained negative MRD, specifically bone marrow leukemic blasts <0.01% confirmed by sensitive testing at time points defined by individual study protocols. The Common Terminology Criteria for Adverse Events (CTCAE) version 5 (32) was used to categorize adverse events (AEs). Other outcomes assessed were 1-, 2- and 3-year OS rates.

Statistical analysis. The present meta-analysis used Stata 14.0 software to conduct the data analysis (StataCorp LP). Heterogeneity among studies was assessed using Cochran's Q test and I^2 statistic. Given the inherent clinical and methodological diversity among the included studies, a random-effects model was employed for all meta-analyses to account for potential between-study heterogeneity, in accordance with the Cochrane Handbook recommendations (33). Sensitivity analysis was performed to assess the robustness of the results. The test of potential publication bias was performed using Begg's test and Egger's test. A two-sided $P<0.05$ was considered

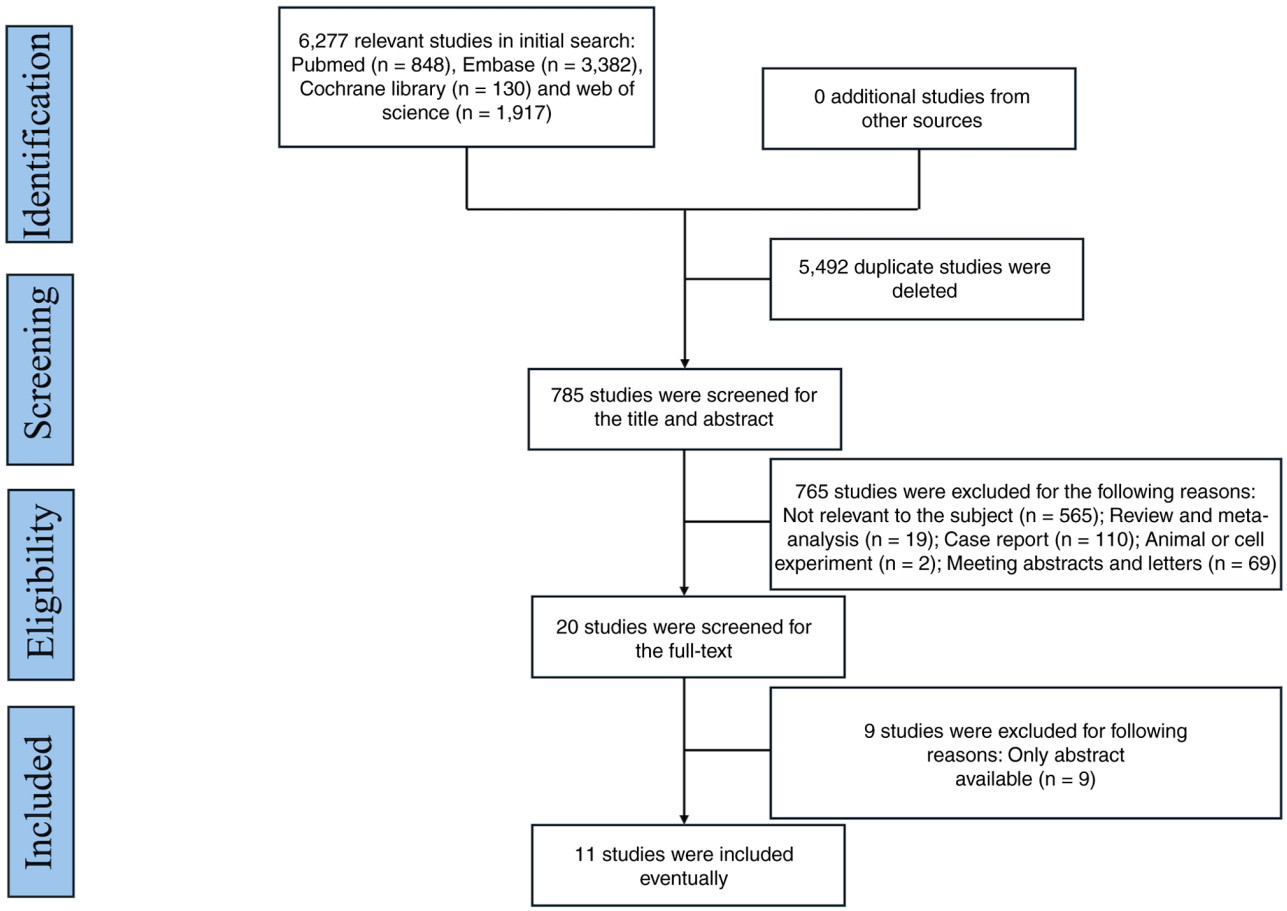

Figure 1. Flow diagram of the meta-analysis for the inclusion/exclusion of studies.

statistically significant. Data were presented as pooled rates (ES) with 95% confidence intervals (CIs).

Results

Study selection. An initial search of four databases yielded 6,277 relevant studies: 848 studies in PubMed, 3,382 in Embase, 130 in the Cochrane Library and 1,917 in Web of Science. After potential duplicates were eliminated, titles and abstracts were screened and a total of 20 studies were selected for full-text review. A subsequent full-text evaluation led to the exclusion of 9 studies due to the unavailability of full texts. Ultimately, 11 studies (19,25,34-42) involving 402 patients met the inclusion criteria and were included in this meta-analysis. The study selection process is shown in Fig. 1, and detailed information on each included study is provided in Table I.

Quality assessment. Quality assessment of 4 cohort studies (comprising prospective and retrospective designs) was performed using the NOS (30). The scale evaluates three domains (selection of study groups, comparability of groups and outcome/exposure determination for cohort/case-control studies) based on eight specific criteria, awarding a maximum of 9 stars. Studies with a score of ≥7 were considered high quality. For 7 single-arm studies, the MINORS tool (31) was applied. This index scores 8 items from 0 (not reported) to 2 (reported and adequate), giving a maximum total score of 16 for non-comparative studies, with higher scores indicating better methodological quality. Detailed results are also shown in Table II.

NOS for prospective and retrospective cohort studies. The numerical labels Q1-Q8 in the Table II headers for the scoring system correspond to the following criteria: i) Representativeness of the exposed cohort; ii) representativeness of the non-exposed cohort; iii) selection of the exposed cohort; iv) absence of the outcome of interest at baseline; v) comparability of cohorts in design or analysis; vi) assessment of outcomes; vii) sufficiency of follow-up duration for outcome occurrence; and 8) adequacy of cohort follow-up completion.

MINORS for single-arm studies. The numerical labels Q1-Q8 in the Table II header for the scoring system correspond to the following criteria: i) Clear statement of research objective; ii) consistency of patient inclusion; iii) prospective data collection; iv) appropriateness of outcome indicators to reflect research objective; v) objectivity of outcome indicator evaluation; vi) sufficiency of follow-up duration; vii) follow-up loss rate <5%; and viii) sample size estimation.

Efficacy

CR. A total of 10 studies reported the CR rate of blinatumomab-based combination therapy for treating high-risk B-ALL. High heterogeneity was observed among these studies (I^2=77.0%; P<0.001). Using a random-effects model,

Table I. Characteristics of the studies included in the meta-analysis.

First author, year	Country	Study design	Phase	Median age (range), years	Treatment 1	Treatment 2	Blinatumomab group, n	Safety analysis, n	Ph^+, % (n/total n)	Prior HSCT, % (n/total n)	Dose of Blinatumomab	Median follow-up time, months	Treatment Setting	(Refs.)
Jabbour *et al*, 2023	USA	Prospective study	II	68 (60-87)	Blinatumomab + mini-Hyper-CVD + fractionated low-dose INO	mini-Hyper-CVD + standard-dose INO	31	31	-	-	Blinatumomab: 9 μg/day for first 4 days, then 28 μg/day for 4 weeks per cycle (total 4 cycles)	29.7(8.8-41.0)	First-line	(19)
Foà *et al*, 2020	Italy	Prospective study	II	54 (24-82)	Blinatumomab + Dasatinib	-	63	60	100 (63/63)	0 (0/63)	Blinatumomab: 28 μg/day for 4 weeks per cycle (minimum 2 cycles)	18.0 (1.0-25.0)	First-line	(25)
Sokolov *et al*, 2017	Russia	Retrospective study	-	32 (24-49)	Blinatumomab + TKI	-	11	11	73 (8/11)	-	Blinatumomab: 9 mcg/day in first week of first cycle, then 28 mcg/day for subsequent three weeks; subsequent cycles of 28 mcg/day for 4 weeks	12.0 (3.0-19.0)	R/R	(34)
Assi *et al*, 2017	USA	Retrospective study	-	65 (30-77)	Blinatumomab + TKI	-	9	9	100 (9/9)	-	Blinatumomab: 9 mcg/day in first week of first cycle, then 28 mcg/day by continuous infusion for 3 weeks; second cycle and onwards at	8.0 (2.0-14.0)	R/R	(35)

Table I. Continued.

First author, year	Country	Study design	Phase	Median age (range), years	Treatment 1	Treatment 2	Blinatumomab group, n	Safety analysis, n	Ph^+, % (n/total n)	Prior HSCT, % (n/total n)	Dose of Blinatumomab	Median follow-up time, months	Treatment Setting	(Refs.)
											28 mcg/day for 4 weeks, repeated every 6 weeks			
Couturier *et al*, 2021	France	Retrospective study	-	58 (18-81)	Blinatumomab + ponatinib	-	26	26	100 (26/26)	34.6 (9/26)	Blinatumomab: 9 mg/day for first week of cycle 1, then escalated to 28 mg/day, and 28 mg/day for subsequent cycles	34.4 58.7) -58.7)	R/R	(36)
Gibson *et al*, 2024	USA	Retrospective study	-	8.5 (2-17)	Blinatumomab + Mini-Hyper-CVD	-	9	5	-	0 (0/5)	Blinatumomab and rituximab: Median, 1 cycle (1-2 cycles)	17.1 (4.8-39.4)	R/R	(37)
Hogan *et al*, 2023	USA	Prospective study	III	11 (1-30)	Blinatumomab + Chemotherapy	Chemotherapy	127	121	-	0 (0/255)	Blinatumomab: 15 μg/m^2/day for 28 days per cycle (3 cycles)	3.5 (0.1-6.6)	R/R	(38)
Jabbour *et al*, 2023	USA	Prospective study	II	51 (36-68)	Blinatumomab + ponatinib	-	54	54	100 (54/54)	-	Blinatumomab: 9 μg per day on days 1-4 of cycle one, then 28 μg per day on days 5-28, 28 μg per day for cycles two to five (28 days each cycle), in up to five 42-day cycles	16.0 (11.0 -24.0)	First-line	(39)

Table I. Continued..

First author, year	Country	Study design	Phase	Median age (range), years	Treatment 1	Treatment 2	Blinatumomab group, n	Safety analysis, n	Ph^+, % (n/total n)	Prior HSCT, % (n/total n)	Dose of Blinatumomab	Median follow-up time, months	Treatment Setting	(Refs.)
Kantarjian *et al*, 2023	USA	Prospective study	II	37 (17-87)	Blinatumomab + Mini-Hyper-CVD + fractionated low-dose inotuzumab	Mini-Hyper-CVD + standard-dose inotuzumab	43	43	-	5 (2/43)	Blinatumomab: 9 μg/day for first 4 days of course 1, then 28 μg/day thereafter, and 28 μg/day for subsequent courses	48.0 (9.0-115.0)	R/R	(40)
King *et al*, 2019	USA	Retrospective study	-	61.2 (27-72.1)	Blinatumomab + TKI	-	11	11	100 (11/11)	27 (3/11)	Blinatumomab: 9 mcg/day in first week of cycle 1, then 28 mcg/day for 3 weeks; subsequent cycles of 28 mcg/day for 4 weeks. MRD dosing: 28 mcg/day for 4 weeks, repeated every 6 weeks (1 patient transitioned to conventional dosing)	10.8 (3.5-20.0)	R/R	(41)

Table I. Continued.

First author, year	Country	Study design	Phase	Median age (range), years	Treatment 1	Treatment 2	Blinatumomab group, n	Safety analysis, n	Ph+, % (n/total n)	Prior HSCT, % (n/total n)	Dose of Blinatumomab	Median follow-up time, months	Treatment Setting	(Refs.)
Stolz *et al*, 2025	Switzerland	Retrospective study	-	65(18+)	Blinatumomab + TKI	TKI + chemotherapy	18	18	100 (18/18)	-	Blinatumomab: 28 μg/day for 28 days per cycle (2-6 cycles)	24.0 (2.0-100.0)	R/R	(42)

Data are presented as n (%) or median (range). Ph+, Philadelphia chromosome-positive; HSCT, hematopoietic stem cell transplantation; mini-hyper-CVD, mini-hyperfractionated cyclophosphamide, vincristine and dexamethasone; INO, inotuzumab-ozogamicin; TKI, tyrosine kinase inhibitor; MRD, minimal residual disease; AE, adverse event; ES, effect size; CI, confidence interval; R/R, relapsed/refractory.

the meta-analysis showed a pooled CR rate of 87% [95% confidence interval (CI), 78-95%] (Fig. 2A).

Subgroup analyses were conducted based on study type (prospective vs. retrospective), age group (<18 vs. >18 years), combination therapy regimen (plus TKI vs. plus chemotherapy), stratification by Philadelphia chromosome status (all-Ph+ cohort vs. non-all Ph+ cohort) and treatment setting (first-line vs. R/R). The latter was pre-specified given the distinct prognosis of newly diagnosed vs. R/R patients.

For study type, the pooled CR rates were 92% (95% CI, 83-100%; I^2=34.8%; P=0.175) in 6 retrospective studies and 83% (95% CI, 67-99%; I^2=90.4%; P<0.001) in 4 prospective studies (Fig. 2B). For age groups, the pooled CR rates were 80% (95% CI, 28-99%) in patients <18 years and 87% (95% CI, 78-95%; I^2=79.2%; P<0.001) in patients >18 years (Fig. 2C). For combination therapy, the pooled CR rates were 89% (95% CI, 79-98%; I^2=76.3%; P<0.001) in the plus TKI subgroup and 81% (95% CI, 61-100%; I^2=75.5%; P=0.017) in the plus chemotherapy subgroup (Fig. 2D). In the analysis stratified by Ph status, the pooled CR rates were 88% (95% CI, 78-99%; I^2=80.1%; P<0.001) in the all Ph+ subgroup and 84% (95% CI, 69-98%; I^2=64.6%; P=0.037) in the non-all Ph+ subgroup (Fig. 2E). For treatment setting, the pooled CR rates were 88% (95% CI, 72-100%; I^2=89.2%; P<0.001) in the first-line subgroup and 85% (95% CI, 73-97%; I^2=68.2%; P=0.004) in the R/R subgroup (Fig. 2F).

MRD response. A total of 8 studies were included to analyze the effect of blinatumomab-based combination therapy on MRD response rate in high-risk B-ALL, with a pooled MRD response rate of 81% (95% CI, 75-87%; I^2=0.0%; P=0.871) (Fig. 3A). For subgroup analyses by study type, the pooled MRD response rates were 84% (95% CI, 74-93%; I^2=0.0%; P=0.795) in 5 retrospective studies and 80% (95% CI, 72-87%; I^2=0.0%; P=0.567) in 3 prospective studies (Fig. 3B). By age group, the pooled MRD response rates were 80% (95% CI, 28-99%) in patients <18 years and 81% (95% CI, 75-87%; I^2=0.0%; P=0.791) in patients >18 years (Fig. 3C). By combination therapy regimen, the pooled MRD response rates were 82% (95% CI, 75-89%; I^2=0.0%; P=0.700) in the subgroup with TKI addition and 79% (95% CI, 67-91%; I^2=0.0%; P=0.962) in the subgroup with chemotherapy addition (Fig. 3D). When stratified by Ph status (all-Ph+ vs. non-all Ph+), the pooled MRD response rates were 82% (95% CI, 75-89%; I^2=0.0%; P=0.557) in the all Ph+ subgroup and 80% (95% CI, 69-91%; I^2=0.0%; P=0.981) in the non-all Ph+ subgroup (Fig. 3E). By treatment setting, the pooled MRD response rates were 80% (95% CI, 70-90%; I^2=10.1%; P=0.292) in the first-line subgroup and 82% (95% CI, 74-90%; I^2=0.0%; P=0.854) in the R/R subgroup (Fig. 3F).

CMR. A total of 5 studies were included that analyzed the effect of blinatumomab-based combination therapy on CMR in high-risk B-ALL, with a pooled CMR rate of 81% (95% CI, 69-92%; I^2=57.9%; P=0.050) (Fig. 4A). The pooled CMR rates of 3 retrospective studies and 2 prospective studies were 88% (95% CI, 77-98%; I^2=0.0%; P=0.852) and 71% (95% CI, 42-100%; I^2=85.9%; P=0.008), respectively (Fig. 4B). For the all Ph+ subgroup and non-all Ph+ subgroup, the pooled CMR rates were 81% (95% CI, 67-94%; I^2=68.4%; P=0.023) and 82% (95% CI, 48-98%), respectively (Fig. 4C). For the R/R subgroup and the first-line subgroup, the pooled CMR rates

Table II. Quality assessment of the studies included in the meta-analysis.

A, NOS for prospective and retrospective cohort studies

First author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total	(Refs.)
Kantarjian *et al*, 2023	1	1	1	1	1	1	2	1	9	(40)
Jabbour *et al*, 2023	1	1	1	1	1	1	2	1	9	(19)
Stolz *et al*, 2025	0.5	1	1	1	0.5	0.5	2	1	7.5	(42)
Hogan *et al*, 2023	1	1	1	1	1	1	2	1	9	(38)

B, MINORS for single-arm studies

First author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total	(Refs.)
Gibson *et al*, 2024	2	2	1	2	2	2	1	1	13	(37)
Couturier *et al*, 2021	2	1	2	2	2	2	2	1	14	(36)
Jabbour *et al*, 2023	2	2	2	2	2	2	1	1	16	(39)
Foà *et al*, 2020	2	2	2	2	2	2	1	1	16	(25)
King *et al*, 2019	2	1	2	2	2	2	2	1	14	(41)
Assi *et al*, 2017	2	1	2	2	2	2	2	1	14	(35)
Sokolov *et al*, 2017	2	1	2	2	2	2	2	1	14	(34)

NOS, Newcastle-Ottawa Scale; MINORS, Methodological Index for Non-Randomized Studies.

were 88% (95% CI, 77-98%; I^2=0.0%; P=0.852) and 71% (95% CI, 42-100%; I^2=85.9%; P=0.008), respectively (Fig. 4D).

Survival. A meta-analysis was conducted using a random-effects model, with results showing a pooled 1-year OS rate of 91% (95% CI, 78-100%; I^2=43.7%; P=0.183), a 2-year OS rate of 87% (95% CI, 71-100%) and a 3-year OS rate of 52% (95% CI, 36-66%) (Fig. 5). Heterogeneity statistics (I^2 and P-value) were not applicable for the 2-year and 3-year estimates as data were derived from single studies.

Toxicities. An analysis of the incidence of the most common all-grade AEs associated with blinatumomab combination therapy for high-risk B-ALL showed an overall incidence of 86% (95% CI, 77-96%; I^2=91.2%; P<0.001) (Fig. 6A), with results summarized in Table III. Most patients experienced AEs, which were generally well-tolerated. The most common AEs were thrombocytopenia, neutropenia and infections, with incidence rates of 64% (95% CI, 36-92%), 39% (95% CI, 0-86%) and 37% (95% CI, 16-59%), respectively. Notably, grade ≥3 AE incidence rates were much lower, with few exceeding an incidence rate of 20%. In particular, the occurrence rates of the most frequent grade ≥3 AEs (neutropenia, febrile neutropenia and hyperglycemia) were 38% (95% CI, 0-84%), 26% (95% CI, 10-43%) and 21% (95% CI, 5-36%), respectively.

Furthermore, a focused analysis of the hallmark toxicities of the blinatumomab, CRS and neurological events (Nes), was conducted. As detailed in Table III, the pooled incidence rate of all-grade CRS was 11.2%. Notably, severe CRS (grade ≥3) was exceptionally rare, with a pooled incidence of only 1.6%. Regarding neurological toxicity, while the pooled incidence of all-grade Nes was 27.5%, the incidence of grade ≥3 Nes remained low at 5.4%. Importantly, the heterogeneity for grade ≥3 Nes was 0.0%, indicating a consistently low risk of severe neurotoxicity across the included studies.

To further investigate the sources of toxicity, the analysis was stratified on the basis of combination therapy regimen. As shown in Fig. 6, the pooled incidence of all-grade AEs in the blinatumomab + chemotherapy subgroup was 99% (95% CI, 96-100%), with an I^2 value of 0.0% (P=0.631). By contrast, the pooled incidence of AEs in the blinatumomab + TKI subgroup was 73% (95% CI, 47-99%), with an I^2 value of 92.3% (P<0.001). The difference between subgroups approached but did not reach statistical significance (P=0.060) (Fig. 6B).

Sensitivity analysis. Sensitivity analysis was performed by removing studies one at a time to determine the effect of this on the pooled results. It was determined that the removal of a single study made no significant difference to the pooled outcome and its 95% confidence, which indicates the general accuracy of the meta-analysis (Fig. 7).

Publication bias. Publication bias was assessed using Egger's and Begg's tests. Both tests were applied to evaluate publication bias for different outcomes with the following results. For MRD response: Egger's test, P=0.05; and Begg's test, P=0.10 (Fig. S1A). For CMR: Egger's test, P=0.36; and Begg's test, P=0.22 (Fig. S1B). For AEs: Egger's test, P=0.09; and Begg's test, P=0.06 (Fig. S1C). No significant publication bias was observed for these outcomes as aforementioned. However, upon examining CR, publication bias was identified, with the following results: Egger's test, P=0.02; and Begg's test, P=0.05 (Fig. S1D). The observed publication bias in CR outcomes may be attributed to heterogeneity in study design, patient characteristics or treatment regimens.

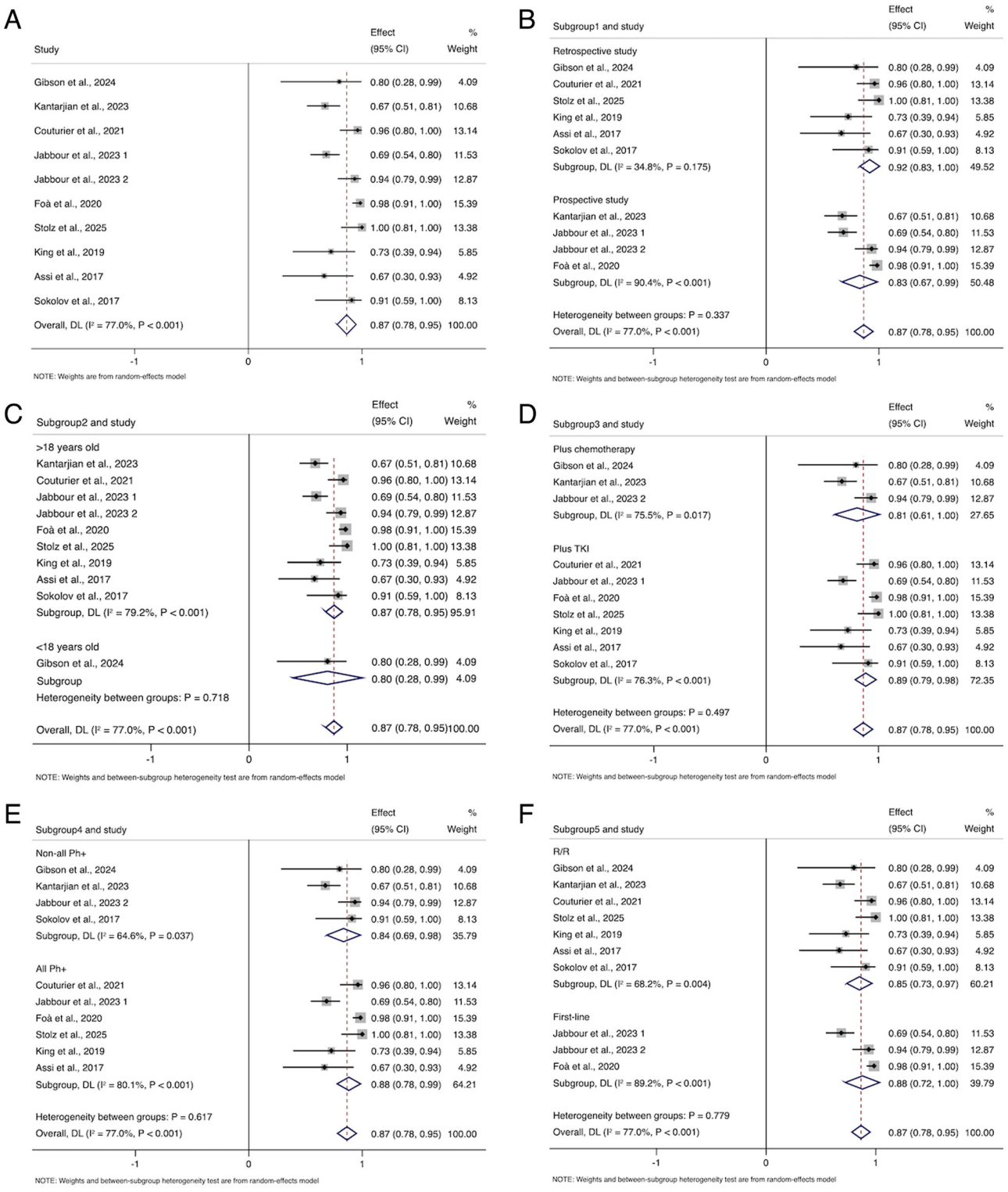

Figure 2. Forest plot of the pooled CR rate. (A) Forest plot of all the studies. (B-F) Forest plots for CR rates based on (B) study types (prospective studies and retrospective studies), (C) different age groups (<18 and >18 years old), (D) different combination therapy regimens (plus TKI and plus chemotherapy), (E) different Ph-positive expression rates (all Ph$^+$ and non-all Ph$^+$) and (F) different treatment settings (first-line and R/R). CR, complete remission; Ph$^+$, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor; R/R, relapsed/refractory; CI, confidence interval; ES, effect size; DL, DerSimonian-Laird.

Discussion

ALL, especially R/R, MRD-positive or Ph$^+$ B-ALL, remains a high-risk hematological malignancy. The pivotal TOWER study demonstrated that blinatumomab was significantly superior to chemotherapy in R/R B-ALL patients, with mOS times of 7.7 and 4.0 months, respectively [hazard ratio (HR), 0.71] (20). The BLAST study showed that blinatumomab induced a negative status for MRD in 78% of MRD-positive patients, effectively bridging them to HSCT (43). The ALCANTARA study further validated the efficacy of blinatumomab in adult patients with R/R Ph$^+$

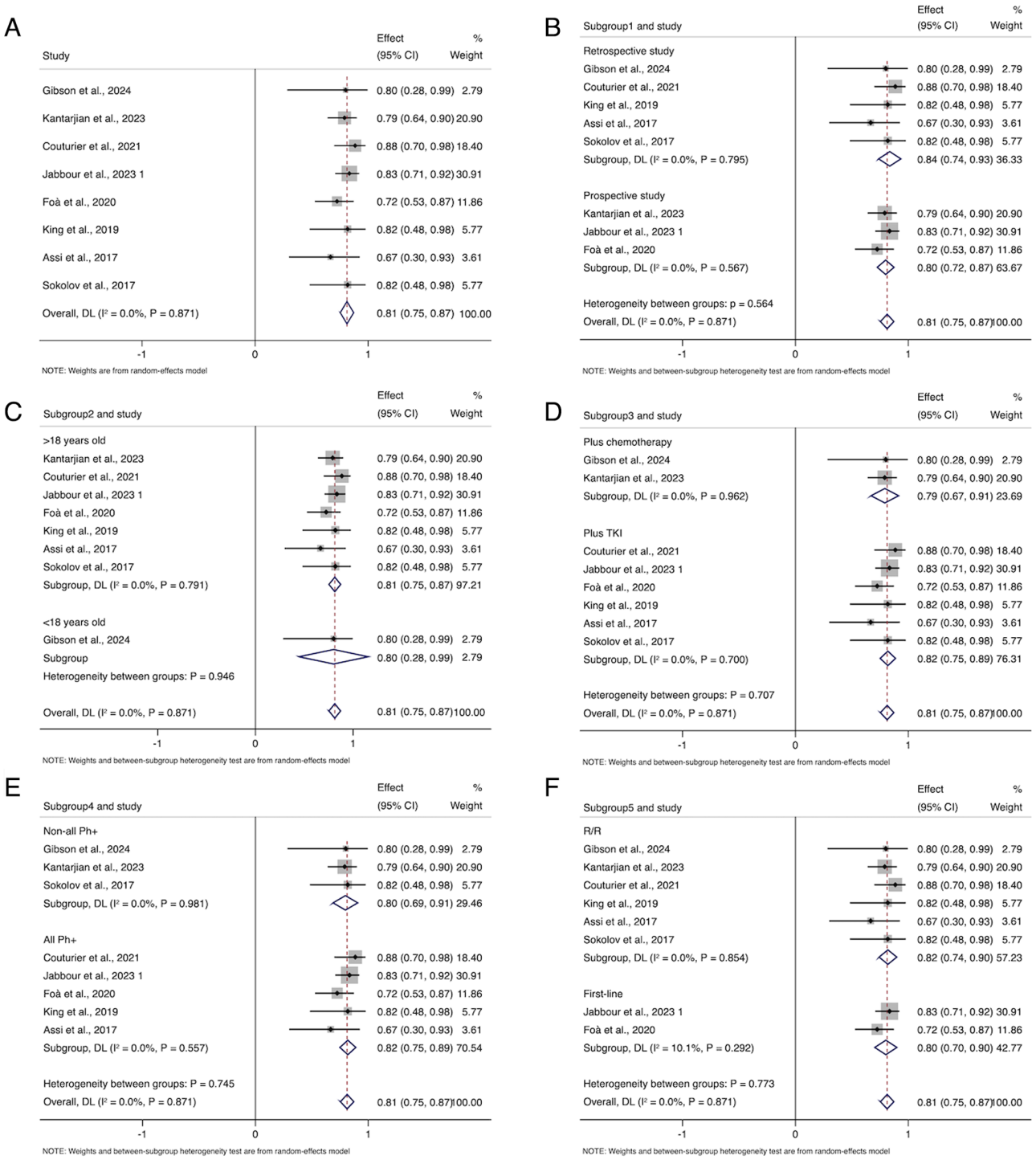

Figure 3. Forest plot of the pooled MRD response rates. (A) Forest plot of all the studies. (B-F) Forest plots for MRD response rates based on (B) study types (prospective studies and retrospective studies), (C) different age groups (<18 and >18 years old), (D) different combination therapy regimens (plus tyrosine kinase inhibitor and plus chemotherapy), (E) different Ph-positive expression rates (all Ph$^+$ and non-all Ph$^+$) and (F) different treatment settings (first-line and relapsed/refractory). MRD, minimal residual disease; Ph$^+$, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor; R/R, relapsed/refractory; CI, confidence interval; ES, effect size; DL, DerSimonian-Laird.

B-ALL, with a CR rate of 35.6% and a negative MRD rate as high as 87.5% (44). In children with R/R B-ALL, the AALL1331 trial showed that blinatumomab significantly improved 2-year OS rate compared with chemotherapy (79.4 vs. 59.2%) (45). Even though there is strong effectiveness of blinatumomab monotherapy, it does not ensure the long-term survival among the high-risk groups, necessitating combination therapy strategies.

Combination therapy based on blinatumomab has shown a synergistic effect in B-ALL. This is primarily attributed to the immunomodulatory properties of the bispecific antibody, which can enhance the antitumor activity of other drugs (36). Blinatumomab can activate T cells to kill leukemia cells by simultaneously binding to CD3 on the surface of T cells and CD19 on the surface of B cells, thereby triggering immunogenic cell death and enhancing antigen presentation and T

Table III. AEs of the studies included in the meta-analysis.

Adverse Event	n/N (All grade)	All grades ES % (95% CI)	I^2 (%)	n/N (Grade ≥3)	Grade ≥3 ES % (95% CI)	I^2 (%)
CRS	27/206	11.2 (4.9-17.5)	28.5	2/127	1.6 (0.0-4.3)	-
Neutropenia	67/160	39.0 (0.0-86.3)	98.0	65/160	38.1 (0.0-83.6)	97.8
Febrile Neutropenia	63/270	26.4 (10.1-42.7)	87.1	63/270	26.4 (10.1-42.7)	87.1
Infections	125/285	37.4 (16.2-58.5)	91.5	30/175	18.7 (7.3-30.1)	55.9
Hyperglycemia	77/260	28.5 (6.1-51.0)	94.3	59/260	20.7 (3.5-36.2)	88.9
Sepsis	11/210	5.9 (0.0-14.6)	72.7	11/210	5.9 (0.0-14.6)	72.7
Thrombocytopenia	165/207	64.2 (36.1-92.4)	95.6	3/17	17.6 (3.8-43.4)	-
Neurotoxicity/Neurological Events	42/143	27.5 (9.8-45.2)	64.0	8/132	5.4 (1.1-9.7)	0.0
Hepatic SOS/VOD	18/200	8.7 (4.4-12.9)	0.0	17/200	8.0 (3.9-12.1)	0.0
Liver Toxicity	73/223	34.3 (9.8-58.9)	91.9	24/200	11.8 (7.0-16.6)	0.0
Hypokalemia	50/190	28.3 (0.0-57.8)	95.0	28/190	14.6 (9.3-20.0)	0.0
Hyperbilirubinemia	56/190	32.7 (0.0-75.9)	97.8	21/190	11.0 (6.2-15.9)	0.0
Headache	48/140	32.2 (4.8-59.6)	92.0	7/140	4.7 (0.6-8.8)	0.0
Neuropathy	38/91	33.9 (8.1-59.8)	73.2	1/80	1.3 (0.0-6.8)	-
Constipation	47/90	34.7 (11.8-81.3)	92.9	4/80	5.0 (0.0-10.5)	-
CMV Reactivation or Infection	9/74	13.3 (0.0-27.6)	32.3	6/63	9.5 (1.5-17.5)	-
All	266/320	86.3 (77.0-96.0)	91.2	104/121	85.0 (78.0-92.0)	-

AE, adverse event; CRS, cytokine release syndrome; SOS/VOD, hepatic sinusoidal obstruction syndrome/veno-occlusive disease; CMV, cytomegalovirus; ES, effect size; CI, confidence interval.

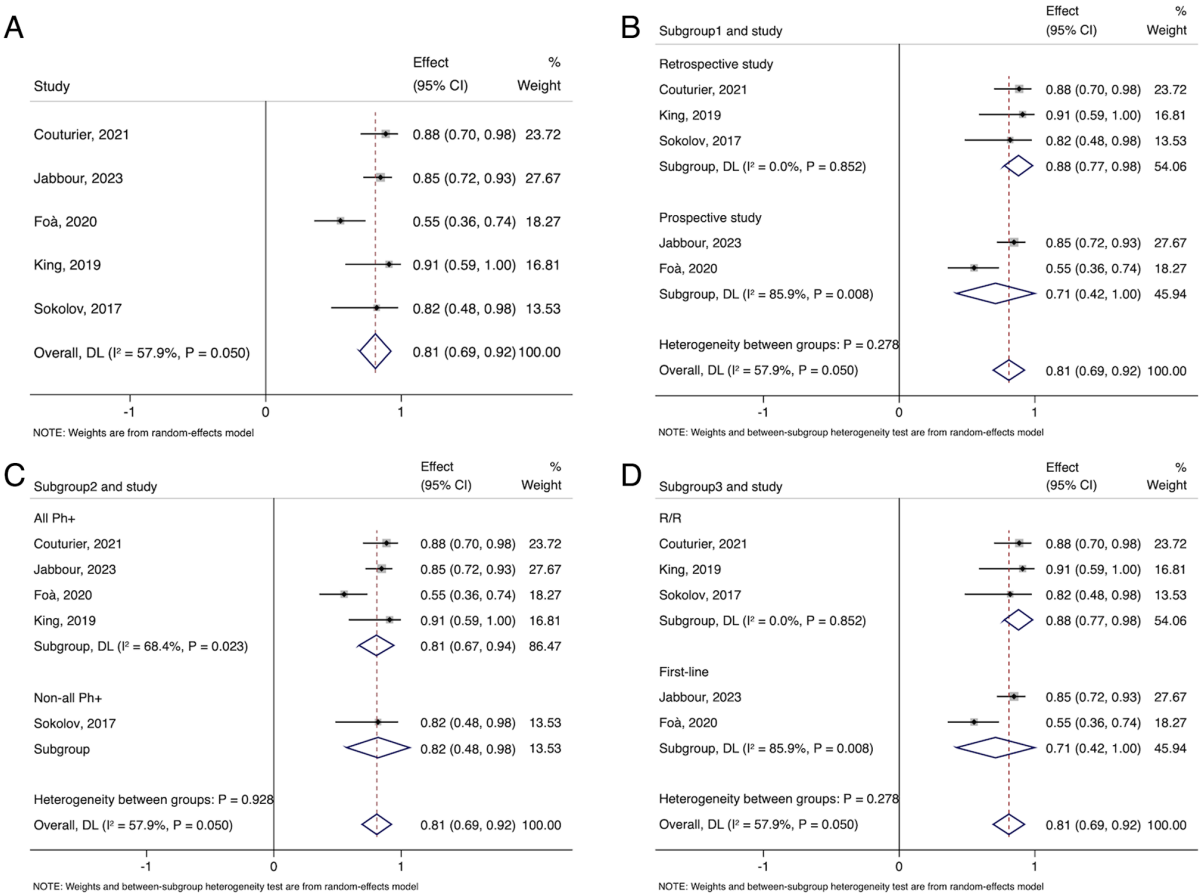

Figure 4. Forest plot of the pooled CMR rates. (A) Forest plot of all the studies. (B-D) Forest plots for CMR rates based on (B) study types (prospective studies and retrospective studies), (C) different Ph^+ expression rates (all Ph^+ and non-all Ph^+) and (D) different treatment settings (first-line and R/R). CMR, complete molecular remission; Ph^+, Philadelphia chromosome-positive; R/R, relapsed/refractory; CI, confidence interval; ES, effect size; DL, DerSimonian-Laird.

Table IV. Ongoing trials of blinatumomab combination therapy in high-risk acute lymphoblastic leukemia.

NCT ID	Phase	Design	Target enrollment, n	Primary endpoint
NCT02744768	II	Blinatumomab + dasatinib	60	MRD
NCT04329325	II	Blinatumomab + TKI	17	CMR
NCT05645718	II	Blinatumomab + INO + rituximab	27	AEs
NCT04524455	I	Blinatumomab + AMG 404	17	DLT
NCT03160079	II	Blinatumomab + pembrolizumab	16	ORR
NCT03512405	II	Blinatumomab + pembrolizumab	36	AE/CR
NCT05182385	II	Blinatumomab + pembrolizumab	39	MTD/MRD
NCT06308588	II	Blinatumomab + asciminib	40	AEs
NCT03739814	II	Blinatumomab + INO	64	EFS
NCT05931757	II	Blinatumomab + olverembatinib	22	CR
NCT03751709	I	Blinatumomab + HMCT	22	DLT
NCT03595917	I	Blinatumomab + ABL001 + dasatinib	40	MTD of ABL001
NCT03263572	II	Blinatumomab + ponatinib	90	CMR/ORR/OS/EFS/RFS
NCT02879695	I	Blinatumomab + ipilimumab + nivolumab	28	AEs
NCT06124157	III	Blinatumomab + dasatinib/imatinib	222	EFS/AEs
NCT04722848	III	Blinatumomab + ponatinib	236	EFS
NCT03518112	II	Blinatumomab + chemotherapy	6	EFS/CR/CRi/PR
NCT03147612	II	Blinatumomab + chemotherapy + ponatinib	22	CMR/OR
NCT04546399	II	Blinatumomab + nivolumab	461	EFS/AEs/PR
NCT04872790	I	Blinatumomab + dasatinib	20	AEs

NCT, national clinical trial; MRD, minimal residual disease; CMR, complete molecular remission; AE, adverse event; ORR, overall response rate; CR, complete remission; MTD, maximum tolerated dose; EFS, event-free survival; DLT, dose-limiting toxicity; INO, inotuzumab-ozogamicin; HMCT, haploidentical hematopoietic cell transplantation; OS, overall survival; RFS, relapse-free survival; Cri, complete remission with incomplete hematological recovery; PR, partial response.

cell activity in tumors (46). In addition, combination therapy can upregulate the expression of tumor cell surface-associated antigens, thereby improving their sensitivity to targeted drugs. This synergistic effect may overcome some drug resistance mechanisms associated with blinatumomab monotherapy in B-ALL. For example, chemotherapy-induced changes in the tumor microenvironment, including increased T cell infiltration and enhanced antigen presentation, may help overcome barriers and increase the proportion of patients benefiting from combination therapy (20,47,48). Ongoing and future clinical trials are expected to provide high-level evidence supporting the efficacy and safety of blinatumomab combination therapy in high-risk B-ALL (Table IV). These studies are crucial for future clinical practice and reshaping the prospects of high-risk B-ALL treatment.

Research on blinatumomab-based combination therapies for B-ALL has yielded promising results, with different combination regimens demonstrating certain efficacy. In pediatric R/R B-ALL, the Pedi-cRIB regimen (mini-Hyper-CVD chemotherapy combined with INO, blinatumomab and/or rituximab) achieved an objective response rate (ORR) of 75%, with no CRS or neurotoxicity observed (37). At a median follow-up time of 17.1 months, 67% of patients remained alive and in remission (37). For adult R/R B-ALL, the ORR of mini-Hyper-CVD combined with INO with or without blinatumomab was 83%, with a 3-year OS rate of 40%. Specifically, for patients receiving blinatumomab, the 3-year OS was 52%, and the incidence of

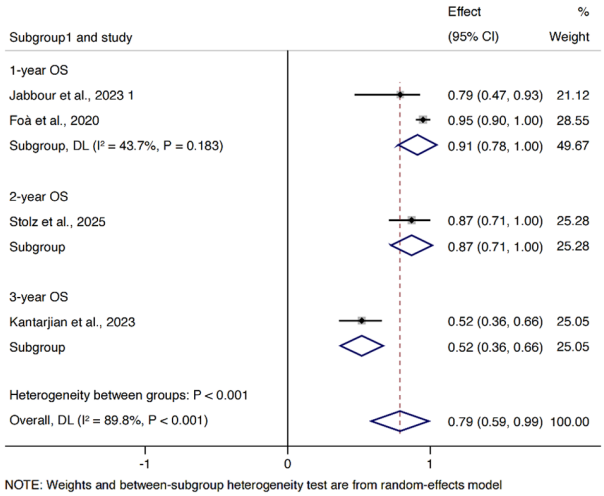

Figure 5. Forest plot of the pooled 1-, 2- and 3-year OS rate. OS, overall survival; CI, confidence interval; DL, DerSimonian-Laird.

sinusoidal obstruction syndrome decreased from 13 to 2% (40). In Ph$^+$ B-ALL, blinatumomab combined with ponatinib in R/R adult patients resulted in a 96.2% CR rate and an 88.5% CMR rate, with a mOS of 20 months and favorable tolerability (36). In elderly patients with newly diagnosed B-ALL, mini-Hyper-CVD combined with INO with or without blinatumomab achieved a 2-year progression-free survival (PFS)

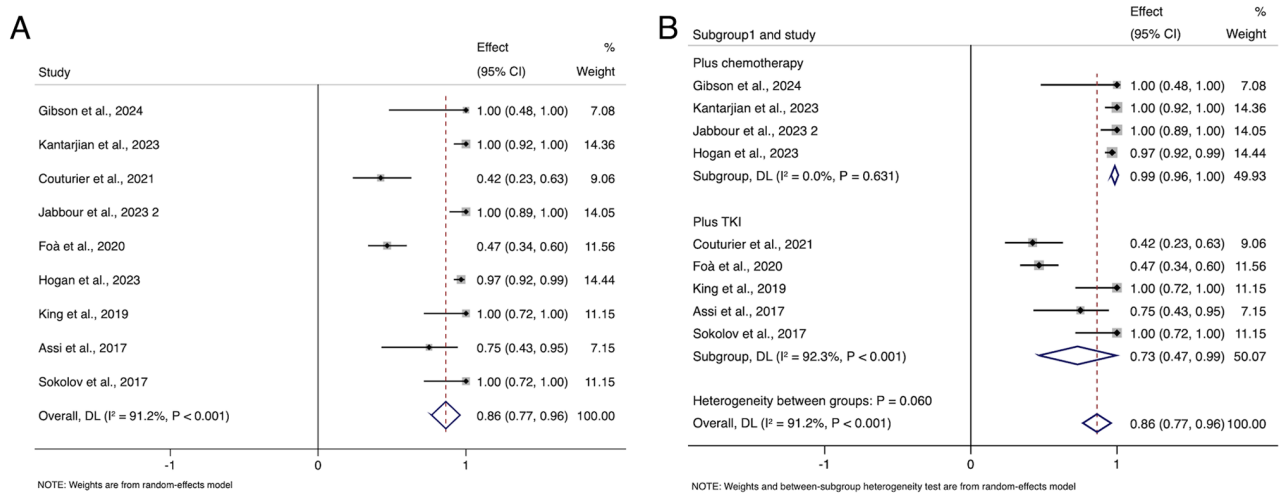

Figure 6. Forest plot of the pooled AEs. (A) Forest plot of all the studies. (B) Forest plot for AEs based on different combination strategies (plus chemotherapy and plus TKI). AEs, adverse events; TKI, tyrosine kinase inhibitor; CI, confidence interval; ES, effect size; DL, DerSimonian-Laird.

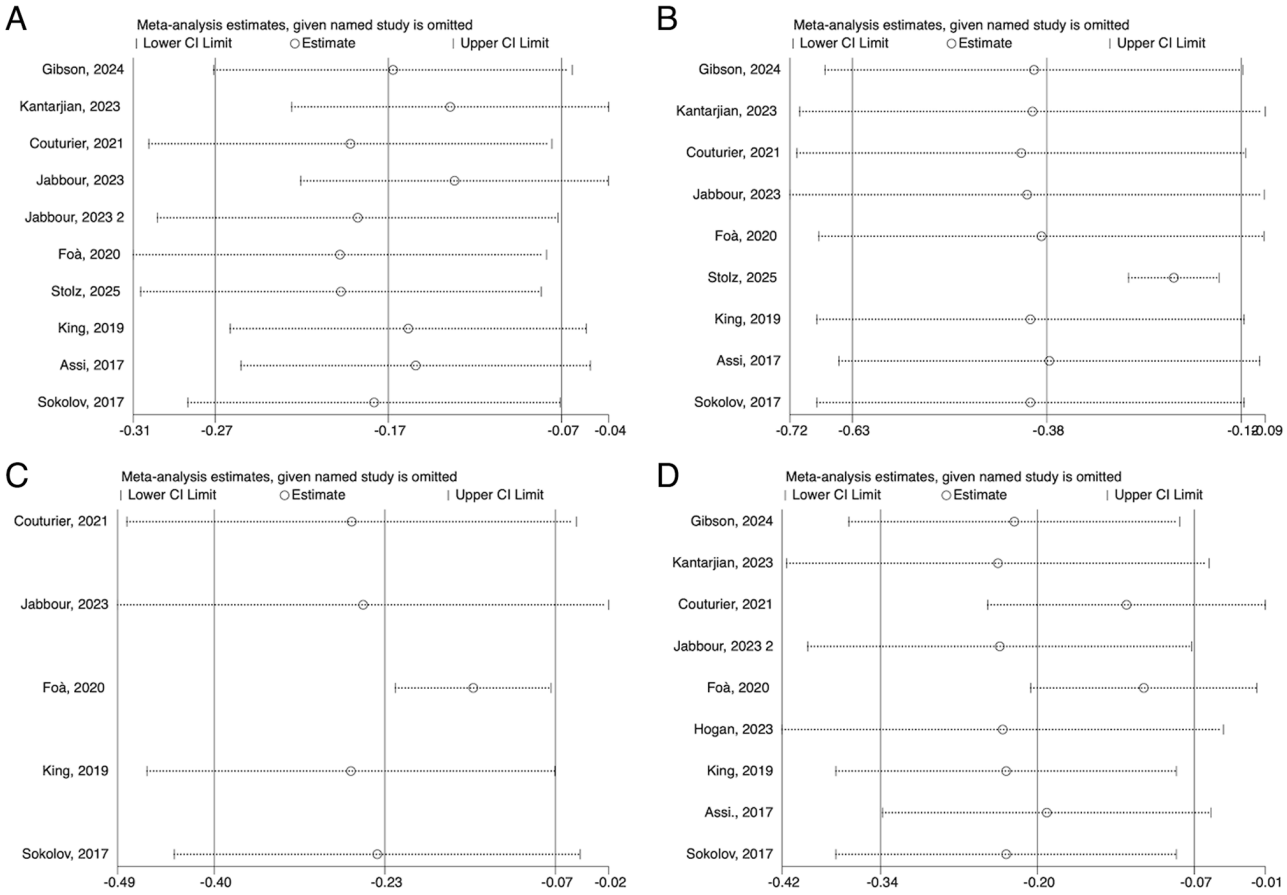

Figure 7. Sensitivity analysis based on (A) complete remission, (B) minimal residual disease, (C) complete molecular remission and (D) adverse events. CI, confidence interval.

rate of 58.2% and a 5-year PFS rate of 44%, with an ORR of 99%. However, vigilance is required regarding AEs, such as infections and secondary myeloid neoplasms, which require close monitoring (39). Furthermore, in children, adolescents and young adults with B-ALL, blinatumomab combined with chemotherapy achieved a 4-year DFS rate of 72.7% and an OS rate of 97.1% in patients with bone marrow relapse (with or without extramedullary relapse), which was significantly better than chemotherapy alone. Nevertheless, this therapy was not as effective in individuals who experienced an isolated extramedullary relapse (38). Such studies propose that combination therapy can enhance the remission and survival rates, yet the treatment options would have to be tailored according to the age of the patient, the type of relapse and other clinical factors.

Table V. AEs for subgroups and TOWER trial.

AEs	Blinatumomab combination n/N	ES % (95% CI)	TOWER trial (N=267) n	%	P-value
CRS	27/206	11.2 (4.9-17.5)	38	14.2	0.84
Neutropenia	67/160	39.0 (0.0-86.3)	53	19.9	0.87
Febrile Neutropenia	63/270	26.4 (10.1-42.7)	64	24.0	0.98
Infections	125/285	37.4 (16.2-58.5)	91	34.1	0.95
Hyperglycemia	77/260	28.5 (6.1-51.0)	20	7.5	0.35
Sepsis	11/210	5.9 (0.0-14.6)	13	4.9	0.96
Neurotoxicity/Neurological Events	42/143	27.5 (9.8-45.2)	25	9.4	0.45
Liver Toxicity	73/223	34.3 (9.8-58.9)	34	12.7	0.70
Hypokalemia	50/190	28.3 (0.0-57.8)	45	16.9	0.84
Headache	48/140	32.2 (4.8-59.6)	77	28.8	0.99
Constipation	47/90	34.7 (11.8-81.3)	34	12.7	0.75
All AEs	266/320	86.3 (77.0-96.0)	263	98.5	0.45

n/N, number of events/total number of patients in studies reporting this event. AEs, adverse events; CRS, cytokine release syndrome; TKI, tyrosine kinase inhibitors; ES, effect size; CI, confidence interval.

The present meta-analysis reveals distinct efficacy characteristics of combination treatment plans as compared with the historical standards. There was a marked increase in the pooled CR rate (87%) compared with the historical 34-44% CR rate reported with the blinatumomab monotherapy in the TOWER trial (20), validating the synergistic effect of adding a TKI or chemotherapy. Regarding MRD clearance, the pooled rate of 81% in the present meta-analysis is close to the 78% reported in the BLAST study (43). However, long-term survival differed significantly: The 3-year OS rate in the present meta-analysis was 52%, which was significantly lower than the 85% in MRD-negative patients receiving blinatumomab consolidation therapy in the E1910 trial (49). This difference may stem from patient baseline characteristics, number of prior lines of therapy (the present analysis included many R/R patients, while the E1910 study focused on consolidation therapy) and heterogeneity in subsequent maintenance therapy strategies. Specifically, in the TKI combination therapy subgroup, while the high CR rate (89%) was consistent with the ALCANTARA study results (44), the observed decline in 3-year survival highlighted a key message: Durable targeted maintenance therapy may be necessary to maintain remission, despite the effectiveness of chemotherapy-free induction therapy in Ph^+ B-ALL. The cross-study disparity highlights the importance of individualized treatment approaches based on disease stage and an individual risk profile.

Furthermore, the present subgroup analysis according to treatment stage clarified the optimal timing for blinatumomab administration. Deep molecular response rates regarding MRD negativity were comparable between patients receiving first-line combination therapy and R/R patients (80 vs. 82%). Of note, the pooled CMR rate was numerically higher in the R/R subgroup compared with the first-line subgroup (88 vs. 71%), although morphological CR rates were similar (88 vs. 85%). While the biological principle that lower tumor burden and a more intact immune system contribute to optimal blinatumomab activity supports the potential benefits of early intervention (46), the lower pooled CMR rate observed in the first-line subgroup may be attributable to significant heterogeneity among the included studies (I^2=85.9%). Conversely, the high deep remission rates achieved in the R/R setting underscore the potent anti-leukemic efficacy of blinatumomab-based combinations, demonstrating their ability to induce deep molecular remission even in patients with advanced disease.

Crucially, indirect comparisons of survival outcomes provide a clearer perspective on the long-term benefits of early intervention. First-line studies [e.g., Jabbour *et al* (39) and Foà *et al* (25)] typically report significantly higher 2-year OS rates compared with the 41% reported in the R/R study by Couturier *et al* (36). Therefore, despite the variations in molecular response rates observed in this meta-analysis, the optimal window to achieve durable survival remains at the earliest instance where blinatumomab combination therapy is administered. This approach could potentially eliminate the need to continue with intensive chemotherapy or serve as an improved bridge to HSCT. While safety is generally manageable in both settings, clinicians must remain vigilant regarding the accumulating toxicity in R/R patients who possess extensive prior treatment histories.

In terms of safety, it is important to delineate the source of toxicity. A notable difference was identified in the present stratified analysis: The pooled incidence of all-grade AEs was 99% (I^2=0.0%) in chemotherapy-containing regimens, compared with 73% in TKI-based regimens. This consistent and near-universal toxicity in the chemotherapy subgroup suggests that the adverse event burden is primarily driven by the cytotoxic drug backbone rather than blinatumomab itself. By contrast, the TKI-based strategy showed a significantly improved toxicity profile. Furthermore, regarding the hallmark toxicities specific to blinatumomab, the incidence of grade ≥3 CRS and Nes was low in all combination therapy trials (2.1 and 5.4%, respectively). These rates are within the range reported in prior blinatumomab monotherapy studies,

including the TOWER trial (20). Compared with the TOWER trial, the incidence of CRS in the current meta-analysis was similar (11.2 vs. 14.2%), with no apparent increase in CRS signal in the combination setting. Several non-CRS adverse events were higher, including hyperglycemia (28.5 vs. 7.5%) and neurological events (27.5 vs. 9.4%), whereas febrile neutropenia (26.4 vs. 24.0%) and infections (37.4 vs. 34.1%) were broadly comparable. These cross-trial differences should be interpreted cautiously given heterogeneity in patient populations, AE ascertainment and concomitant agents; importantly, these toxicities are generally monitorable and treatable with standard supportive measures, supporting an overall manageable safety profile (Table V). This favorable safety profile is possibly due to the pre-emptive cytoreductive effect of the adjuvant (TKI or chemotherapy), which reduces tumor burden prior to T-cell involvement, thereby mitigating the intensity of immune-related inflammatory responses.

Contextualizing these findings within the current therapeutic landscape is essential. While CAR-T cell therapy demonstrates efficacy in R/R cases (23), its clinical application is often restricted by manufacturing delays, high costs and the requirement for specialized centers to manage severe toxicities (such as high-grade CRS and neurotoxicity) (50,51). By contrast, blinatumomab-based combinations offer immediate availability and a generally manageable safety profile (20,52), making them particularly valuable in resource-limited settings lacking CAR-T infrastructure. Furthermore, for patients ineligible for transplantation, such as the elderly or those with marked comorbidities, combining blinatumomab with TKIs or low-intensity chemotherapy offers a viable, potentially curative and less toxic alternative to high-dose chemotherapy and HSCT (25,53). Future research continues to evolve beyond current immunotherapies. Emerging CD19/CD22 bispecific antibodies address antigen escape, while novel nanocarrier-based drug delivery systems are being explored to enhance the pharmacokinetics and safety of therapeutic agents (54,55). These technological innovations may further optimize the delivery of combination therapies. Thus, current blinatumomab-based strategies represent a robust and accessible clinical standard that precedes these next-generation advancements.

The present study has several limitations. First, the absence of randomized controlled trials (RCTs) limits causal inferences and the ability to definitively compare efficacy with that of standard regimens. Second, data availability was limited for long-term survival outcomes and specific subgroup analyses. Notably, the estimates for 2- and 3-year OS were derived from single studies, precluding the execution of a pooled meta-analysis for these instances. Consequently, these results reflect findings from individual studies rather than synthesized evidence, and it remains to be confirmed whether high response rates definitively translate into long-term survival benefits. Third, high heterogeneity was observed among the included studies. The subgroup analysis revealed that clinical heterogeneity, particularly differences in efficacy between first-line and R/R treatments, and differences in safety between chemotherapy and TKI regimens, is a significant contributing factor. Furthermore, inconsistencies in MRD response assessment methods (flow cytometry vs. next-generation sequencing) and safety reporting methods (such as different CTCAE versions) may also contribute to residual heterogeneity. Fourth, some of the studies used small sample sizes, reducing the statistical power. As such, large-scale, multicenter, RCTs with the use of standardized assessment techniques and long-term follow up would be necessary to confirm these findings.

In conclusion, the present meta-analysis shows that blinatumomab-based combination therapy is an effective and well-tolerated treatment option for high-risk B-ALL, exhibiting high remission rates, durable remission and manageable toxicity. The combination of blinatumomab and TKIs or low-intensity chemotherapy has the potential to improve the prognosis of B-ALL. Even though additional RCTs are required to confirm these results and optimize treatment options, current evidence has established blinatumomab combination therapy as a valuable alternative. This offers a potential shift in the therapeutic paradigm of high-risk B-ALL, especially for patients ineligible for intensive chemotherapy or transplantation. Further investigations are needed on how to optimize combination therapy regimens and to define the optimal regimen and timing of combination therapy to ensure better patient selection, as well as increase long-term survival rates.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article. The raw pooled data generated in the present study may be requested from the corresponding author.

Authors' contributions

Conceptualization was performed by XLY. Data curation, encompassing the independent screening of articles for eligibility, data extraction, and quality assessment of the included studies, was performed by MW, XLY, ZQZ, YH, LLC and YL. Formal analysis and investigation were performed by MW, XLY, LLC and YL. Methodology design was the responsibility of MW, XLY, ZQZ, YH, LLC and YL. Software was employed by XLY for statistical analysis. Supervision was provided by YL and LLC. Data validation was performed by YL and LLC. Visualization (preparation of figures and tables) was the responsibility of MW, XLY, ZQZ, LLC and YL. The original draft was written by MW and XLY. The manuscript was reviewed and edited by MW, XLY, LLC and YL. All authors have read and approved the final manuscript. MW and XLY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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