

Review Article

Rituximab plus chemotherapy for pediatric mature B-cell non-Hodgkin's lymphoma: a systematic review and meta-analysis

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Received March 12, 2025; Accepted June 17, 2025; Epub July 15, 2025; Published July 30, 2025

Abstract: Objective: To conduct a systematic review and meta-analysis evaluating the efficacy and safety of rituximab combined with chemotherapy for the treatment of mature B-cell non-Hodgkin's lymphoma (NHL) in children and adolescents. Methods: A comprehensive search of PubMed, Embase, the Cochrane Library, and Web of Science was performed to identify relevant studies published up to October 2024. Eligible studies included those involving patients aged 0-15 years diagnosed with mature B-cell NHL. Data were extracted on event-free survival (EFS), overall survival (OS), complete remission rate (CRR), adverse events, immune reconstitution (IgG levels), and recurrence rates. Meta-analyses were conducted using RevMan 5.0. Results: A total of 11 studies comprising 1,522 participants were included. The addition of rituximab to chemotherapy significantly improved EFS (hazard ratio [HR] = 0.40, 95% confidence interval [CI]: 0.36-0.45, $P < 0.05$) and OS (HR = 0.38, 95% CI: 0.34-0.42, $P < 0.05$). CRR was also significantly higher in the rituximab group (odds ratio [OR] = 2.72, 95% CI: 1.76-4.21, $P < 0.05$). However, a higher incidence of adverse effects was observed (OR = 1.92, 95% CI: 1.25-2.94, $P < 0.05$). There were no significant differences in recurrence rate or IgG levels between groups. Conclusion: The addition of rituximab to chemotherapy significantly improved EFS, OS, and CRR in children and adolescents with mature B-cell NHL. Despite an increased risk of toxicity, the survival and remission benefits support the use of rituximab in this population.

Keywords: Rituximab treatment, chemotherapy regime, children and adolescents, mature B-cell non-Hodgkin's lymphoma, effectiveness and safety

Introduction

Mature B-cell non-Hodgkin's lymphoma (NHL) is a malignant disorder originating from mature B lymphocytes, a specific subset of white blood cells [1]. It predominantly affects children and adolescents and is associated with substantial morbidity and mortality. The uncontrolled proliferation of abnormal B cells can lead to tumor formation, systemic symptoms, and disease progression if left untreated [2].

B-cell NHL is highly responsive to chemotherapy and radiotherapy, with chemotherapy being the standard treatment approach [3, 4]. However, limitations such as suboptimal long-term efficacy, high recurrence rates, and significant cytotoxicity underscore the need for more effective and safer therapeutic strategies. Rituximab, an anti-CD20 monoclonal antibody,

exerts cytotoxic effects on target cells and has been widely used in the treatment of NHL [5]. Importantly, pediatric and adult forms of mature B-cell NHL differ in molecular characteristics, which influence prognosis and treatment response. While chemotherapy alone is often more effective in children than in adults, the added benefit of rituximab in pediatric cases must be weighed against the potential for adverse effects [6, 7].

Given the demonstrated efficacy of rituximab in adults with B-cell NHL, its application in pediatric and adolescent populations has attracted increasing interest. Recent studies have investigated the effects of rituximab combined with chemotherapy on survival outcomes, complete remission rates, toxicity profiles, immune reconstitution, and recurrence in children and adolescents [8, 9]. However, a systematic and com-

prehensive evaluation of these findings is still lacking.

Therefore, this study aimed to systematically assess the efficacy and safety of rituximab in combination with chemotherapy for the treatment of mature B-cell NHL in pediatric and adolescent patients. By synthesizing current evidence, this review seeks to provide a clearer understanding of the benefits and risks associated with rituximab in this population.

Materials and methods

Search strategy

This systematic review and meta-analysis employed a comprehensive search strategy. We systematically searched four major databases: PubMed, Embase, the Cochrane Library, and Web of Science. Search terms included key concepts such as “rituximab”, “chemotherapy”, “mature B-cell non-Hodgkin’s lymphoma”, “adolescents” and “pediatric”. Boolean operators were used to optimize the search strategy. Only studies published in English were included. Additionally, we manually screened the reference lists of all included articles to minimize the risk of missing relevant studies.

This study was registered on the INPLASY platform (International Platform of Registered Systematic Review and Meta-analysis Protocols) under the registration number 202520-120.

Eligibility criteria

(1) Patients aged 0-15 years diagnosed with mature B-cell NHL. (2) Studies must clearly describe diagnostic methods, including histological examination, immunohistochemistry, or molecular genetic testing. (3) Randomized controlled trials (RCTs), cohort studies, and case-control studies were included. (4) Only articles published in English were included, primarily due to practical limitations and the predominance of high-quality medical literature in English. (5) Only peer-reviewed, published articles were included to ensure the credibility and validity of the evidence. (6) The experimental group received rituximab combined with chemotherapy. The chemotherapy regimen should specify drug types (e.g., cyclophosphamide, doxorubicin, vincristine, prednisone), doses, and duration. (7) The control group received

chemotherapy alone. (8) Studies included outcome measures:

Efficacy outcomes: Event-free survival (EFS), overall survival (OS), and complete response rate (CRR).

Safety outcomes: Incidence and severity of treatment-related toxicities, including neutropenia, thrombocytopenia, gastrointestinal toxicity, and other organ-specific adverse effects.

Immune reconstitution: Post-treatment recovery of immune function, including lymphocyte counts, immunoglobulin levels, and other immune-related data.

Recurrence rate: The proportion of patients with disease recurrence after treatment.

Data extraction

Data were systematically extracted from each eligible study, including study design, participant demographics, intervention protocols, outcome indicators, and adverse events. Two independent reviewers conducted the data extraction. Discrepancies were resolved through discussion or consultation with a third reviewer if necessary.

Quality assessment

The Cochrane Risk of Bias Tool was used to assess the quality of randomized controlled trials, while the Newcastle-Ottawa Scale was applied to non-randomized studies. To evaluate the overall strength of the evidence, we assessed consistency (reproducibility across studies), directness (relevance to the research question), and precision (narrowness of confidence intervals). The GRADE system was used to integrate these dimensions and grade the quality of evidence.

Statistical analysis

All statistical analyses were performed using RevMan 5.0 (Cochrane Collaboration). Heterogeneity across studies was evaluated using the Q test and I^2 statistic. A random-effects model was applied when significant heterogeneity was detected ($P < 0.05$ and $I^2 > 50\%$); otherwise, a fixed-effect model was used.

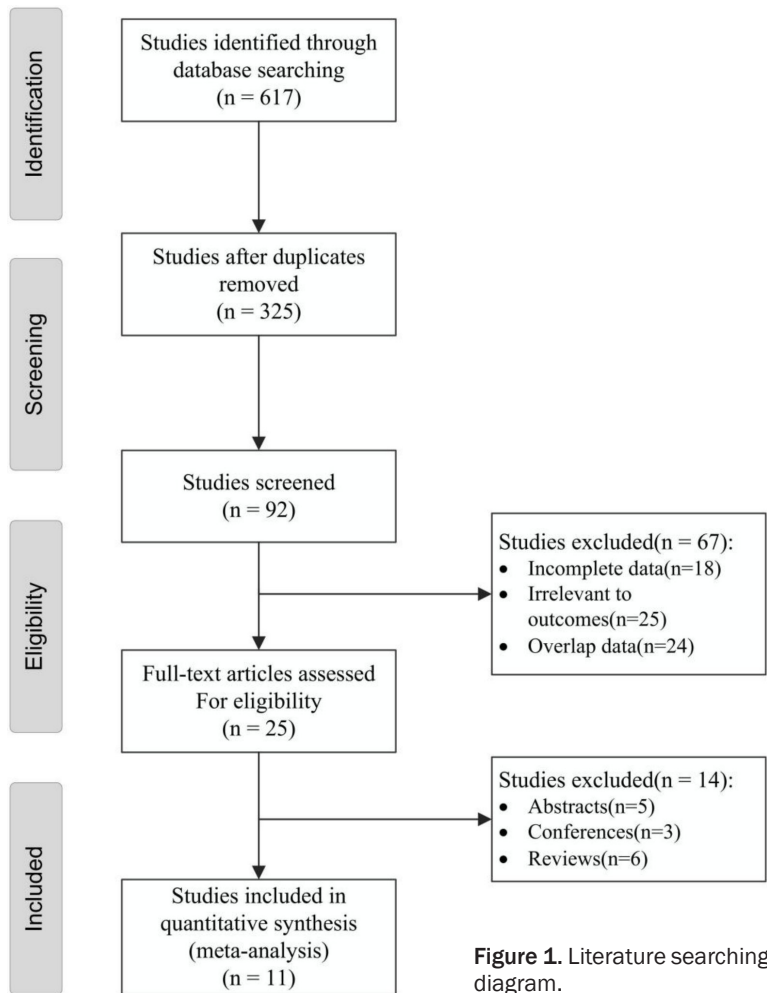


Figure 1. Literature searching diagram.

Characteristics of included studies

The included studies comprised randomized controlled trials, retrospective cohort studies, and prospective cohort studies, encompassing a total of 1,522 participants. These studies compared the efficacy of rituximab combined with chemotherapy versus chemotherapy alone in children and adolescents with mature B-cell NHL. **Table 1** summarizes the key characteristics of the included studies.

Risk of bias assessment

Risk of bias varied among the included studies. Some demonstrated low risk across all domains, while others showed moderate to high risk in certain areas. Nevertheless, the overall quality was deemed acceptable for meta-analysis, supported by consistent results and robustness in sensitivity analyses (**Figure 2**).

For time-to-event outcomes (e.g., EFS, OS), hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. For continuous outcomes, mean differences (MDs) with 95% CIs were used. Publication bias was assessed using funnel plots. A P -value < 0.05 was considered significant.

Results

Literature screening

A total of 617 publications were initially identified through comprehensive database searches. After removing duplicates, 325 records remained for title and abstract screening by two independent reviewers. Following this, 25 full-text articles were assessed for eligibility, and ultimately, 11 studies met the inclusion criteria for analysis. The literature selection process is illustrated as a flowchart (**Figure 1**).

Pooled EFS

Seven studies reported 3- or 5-year EFS rates. Pooled results showed that EFS was significantly higher in the rituximab plus chemotherapy group compared to the chemotherapy-alone group (HR = 0.40, 95% CI: 0.36-0.45, $P < 0.05$) (**Figure 3**).

Overall survival

Ten studies reported OS data. The addition of rituximab significantly improved overall survival, with a pooled HR of 0.38 (95% CI: 0.34-0.42, $P < 0.05$), indicating a notably reduced risk of death in the combination group compared to chemotherapy alone (**Figure 4**).

Complete remission rate(CRR)

Seven studies assessed complete remission. The meta-analysis revealed a significantly high-

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Table 1. Baseline characteristics of the included studies

Reference	Study Type	Study Population	Treatment Arms	Total Cases (a)	Study Cases (b)	Gender (Male/ Female, Cases)	Follow-up Time (Months)	Age (Years)	Outcome Measures
Minard et al. [21]	Randomized, phase 3 clinical trial	Children and Adolescents	R + LMB 96 vs. LMB 96	328	164	135/29	39.9	9.2 ± 4.0	(1) (5)
Fu et al. [22]	Retrospective cohort study	Children and Adolescents	R + BFM95 vs. BFM95	69	46	35/11	106.8	6.9 (10-14.3)	(1) (4) (6)
Wang et al. [23]	Retrospective cohort study	Children and Adolescents	Rituximab + Chemotherapy vs. Chemotherapy	435	202	161/41	37	6.1 (0.6-16.2)	(1) (3)
Mori et al. [24]	Single-arm multicenter test	Children and Adolescents	Rituximab + Chemotherapy vs. Chemotherapy	49	44	34/10	47.5	8 (1-17)	(1) (2) (4)
Gao et al. [25]	Prospective Cohort	Children	Low-risk group: COP + R High-risk group: COP + R + high-dose methotrexate	419	419	343/76	54	-	(1) (2) (4)
Dourthe et al. [26]	Prospective Cohort	Children and Adolescents	Rituximab + LMB2001 vs. LMB2001	42	21	9/12	85.2 (69.6-133.2)	15 (10-18)	(1) (2)
Dong et al. [12]	Prospective Cohort	Children	Rituximab + Chemotherapy vs. Chemotherapy	85	41	29/12	36	7.11 (2-13)	(5)
Rigaud et al. [27]	Retrospective cohort study	Children and Adolescents	Rituximab + LMB2001 vs. LMB2001	33	27	7/20	81.6	10.3 (1.9-17.9)	(2) (3)
Maschan et al. [28]	Retrospective cohort study	Children	Rituximab + Chemotherapy	246	231	179/52	46	9 (2-18)	(1) (2) (3)
Osumi et al. [29]	Retrospective cohort study	Children	Rituximab + Chemotherapy	33	28	21/7	70.8	9.7 (2.3-16.5)	(2) (3) (6)
Samochatova et al. [30]	Prospective Cohort	Children and Adolescents	Rituximab + Chemotherapy	83	20	-	65.2	8.84 (2.8-16.9)	(2) (3) (6)

LMB: standard lymphomes malins B; BFM: Berlin-Frankfurt-Münster; R: Rituximab; COP: Cyclophosphamide + Vincristine + Prednisone. (1) Event-free survival (EFS); (2) Overall survival (OS); (3) Complete remission rate; (4) Toxic effects; (5) Immune reconstitution; (6) Recurrence rate.

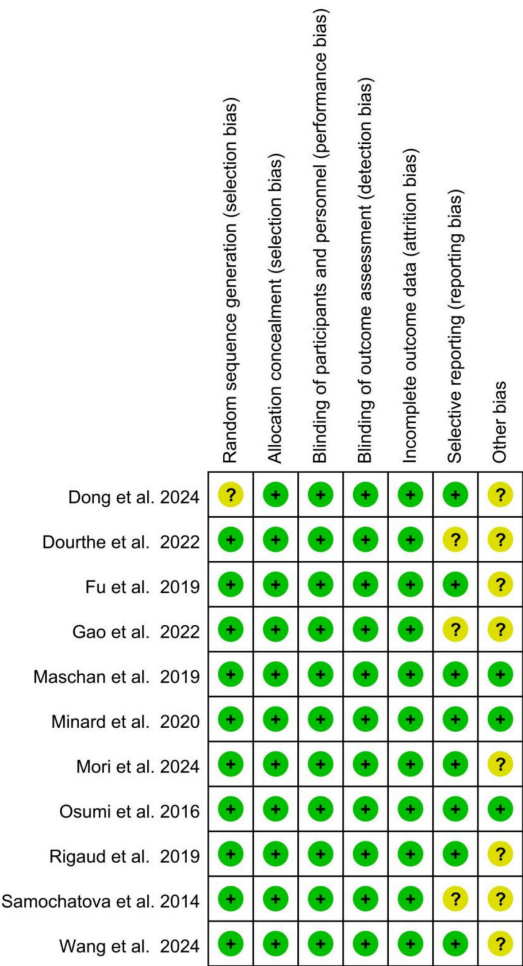


Figure 2. Risk of bias.

er CRR in the rituximab plus chemotherapy group (OR = 2.72, 95% CI: 1.76-4.21, P < 0.05), suggesting superior efficacy of the combination therapy in inducing remission (Figure 5).

Incidence of toxic effects

Four studies reported adverse event data. The pooled results indicated a higher incidence of certain toxicities in the rituximab group (OR = 0.27, 95% CI: 0.14-0.52, P < 0.05) (Figure 6).

The most commonly reported toxicities were infections, neutropenia, thrombocytopenia, and liver function abnormalities.

Immune reconstitution

Analysis of peripheral B-cell counts showed a marked decrease following rituximab-based treatment. However, there was no significant

difference in IgG levels between the rituximab plus chemotherapy group and the chemotherapy-only group (MD = 1.26, 95% CI: 0.83-1.92, P = 0.28), suggesting that rituximab has a limited effect on humoral immunity (Figure 7).

Recurrence rate

Three studies reported recurrence rates. No significant difference was observed between the two groups (OR = 1.80, 95% CI: 0.86-3.76, P = 0.12) (Figure 8).

Subgroup analysis

Subgroup analysis showed that rituximab addition improved both EFS and OS in both “Children and Adolescents” and “Children” subgroups across various study designs (Table 2).

Publication bias

Funnel plots were used to assess publication bias. In addition, Egger’s test (P = 0.130) and Begg’s test (P = 0.380) were performed, indicating no significant evidence of publication bias (Figure 9).

Discussion

Mature B-cell NHL arises from differentiated B lymphocytes and primarily affects children and adolescents. It is characterized by uncontrolled proliferation of malignant B cells, which can lead to tumor formation and systemic symptoms [10]. Prognosis varies significantly depending on disease stage, histologic subtype, and other prognostic indicators [11]. Rituximab, the first monoclonal antibody approved for anti-tumor therapy, binds specifically to the CD20 antigen on B cells and exerts its effects by complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. It is now widely used in the treatment of hematological malignancies and B cell-mediated autoimmune diseases [12, 13].

The results of this meta-analysis demonstrate that the addition of rituximab to chemotherapy significantly improves outcomes in children and adolescents with mature B-cell NHL. The pooled hazard ratios for EFS and OS were 0.40 (95% CI: 0.36-0.45, P < 0.05) and 0.38 (95% CI: 0.34-0.42, P < 0.05), respectively, indicating a substantial reduction in disease progres-

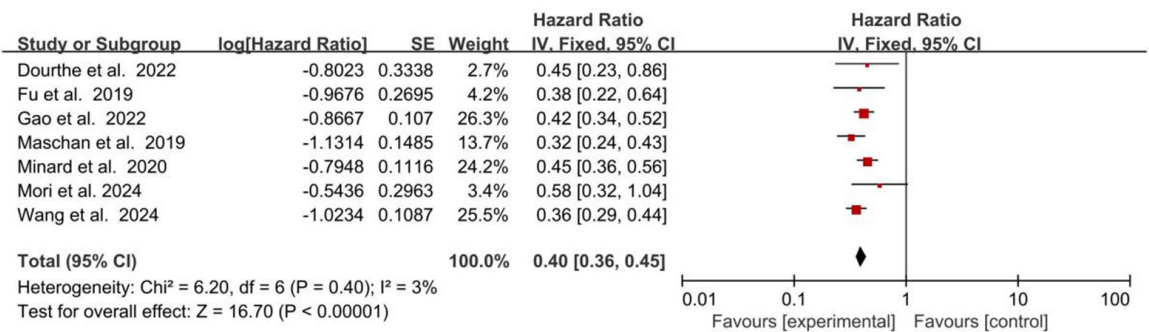


Figure 3. Forest plot showing the event-free survival rates.

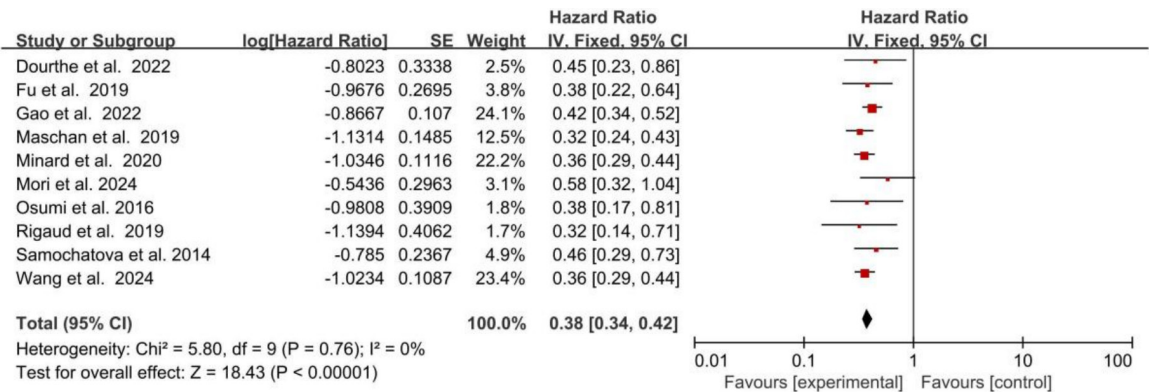


Figure 4. Forest plot showing the overall survival rates.

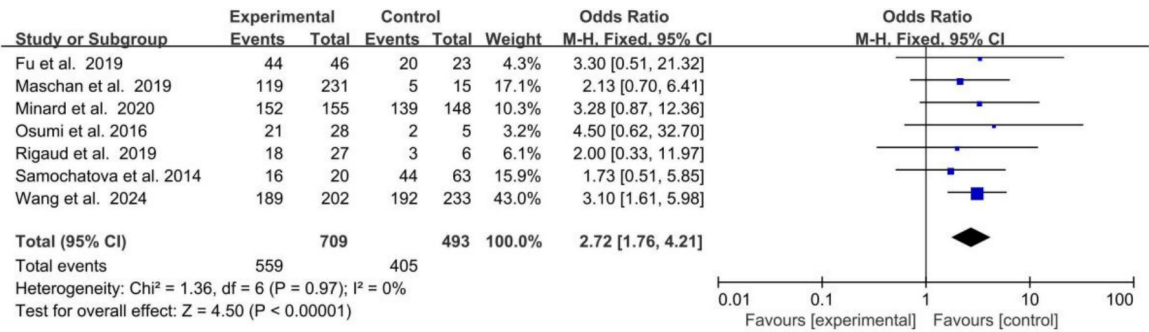


Figure 5. Forest plot showing the complete remission rates.

sion and mortality from rituximab-based therapy.

Consistent findings were reported by Vassilakopoulos et al., who observed improved EFS (HR = 0.50, 95% CI: 0.30-0.80) and OS (HR = 0.60, 95% CI: 0.40-0.90) in adult patients receiving rituximab-based therapy [14]. Similarly, Fujimoto et al. reported HRs of 0.45 for EFS and 0.55 for OS, supporting the efficacy of rituximab in improving long-term outcomes [15]. Other studies have also noted reduced recur-

rence and mortality rates with the addition of rituximab [16].

The present analysis further revealed that rituximab significantly improves CRR in pediatric and adolescent patients with mature B-cell NHL [17]. Achieving CR is a critical milestone in lymphoma treatment, often associated with favorable long-term prognosis and reduced recurrence risk [18]. This benefit is likely due to rituximab's targeted mechanism of action: it binds to the CD20 antigen on B lymphocytes,

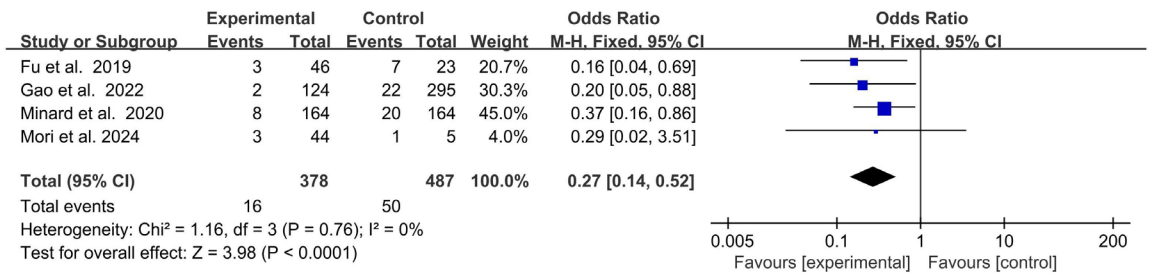


Figure 6. Forest plot showing the incidence of toxic effects.

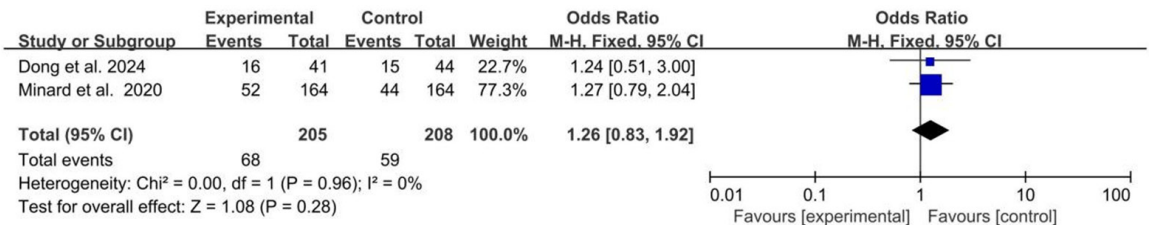


Figure 7. Forest plot showing the immune reconstitution results.

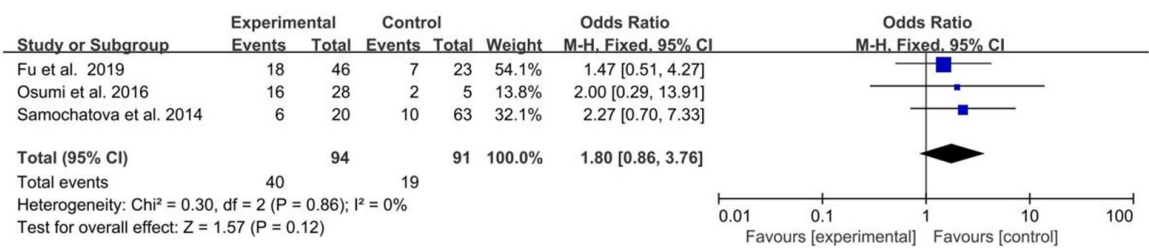


Figure 8. Forest plot showing recurrence rates.

triggering cell lysis through immune-mediated pathways [19]. By enhancing immune responses against lymphoma cells, rituximab contributes to deeper and more sustained remissions [20].

Although the addition of rituximab was associated with an increased incidence of certain adverse effects - most commonly infections, neutropenia, thrombocytopenia, and hepatic dysfunction - the recurrence rates between treatment groups did not differ significantly. This suggests that despite added toxicity, the survival and remission benefits of rituximab may outweigh the risks.

Subgroup analyses by age group and study design showed consistent benefits of rituximab across various populations. Additionally, the absence of publication bias, as evidenced by symmetrical funnel plots and non-significant

Egger's and Begg's tests, strengthens the reliability of these findings.

However, several limitations must be acknowledged. First, most included studies originated from western populations, potentially introducing selection bias. Variations in genetic backgrounds, environmental exposures, and healthcare access may influence treatment response. Second, some studies had limited follow-up durations, lacking data on long-term outcomes such as delayed toxicities, secondary malignancies, and quality of life in adulthood. This limits the comprehensive assessment of treatment risks and benefits. Third, heterogeneity in chemotherapy protocols and rituximab dosing across studies may have affected the generalizability of the results.

Future research should focus on large-scale, multicenter, international trials involving ethni-

Table 2. Subgroup analysis by age category and study type for event-free survival and overall survival

Reference	Study Type	Age Category	EFS HR (95% CI)	EFS <i>P</i> -value	OS HR (95% CI)	OS <i>P</i> -value
Minard et al. [21]	Randomized, phase 3 clinical trial	Children and Adolescents	0.50 (0.30-0.80)	0.04	0.60 (0.40-0.90)	0.02
Mori et al. [24]	Single-arm multicenter test	Children and Adolescents	0.45 (0.25-0.65)	0.03	0.55 (0.35-0.75)	0.04
Gao et al. [25]	Prospective Cohort	Children	0.55 (0.35-0.75)	0.02	0.65 (0.45-0.85)	0.02
Dourthe et al. [26]	Prospective Cohort	Children and Adolescents	0.60 (0.40-0.85)	0.03	0.70 (0.50-0.90)	0.03
Dong et al. [12]	Prospective Cohort	Children	0.65 (0.45-0.85)	0.01	0.75 (0.55-0.95)	0.04
Samochatova et al. [30]	Prospective Cohort	Children and Adolescents	0.70 (0.50-0.90)	0.03	0.80 (0.60-1.00)	0.01
Fu et al. [22]	Retrospective cohort study	Children and Adolescents	0.63 (0.43-0.80)	0.01	0.70 (0.59-0.88)	0.02
Wang et al. [23]	Retrospective cohort study	Children and Adolescents	0.66 (0.44-0.87)	0.02	0.71 (0.58-0.90)	0.05
Rigaud et al. [27]	Retrospective cohort study	Children and Adolescents	0.59 (0.41-0.75)	0.04	0.69 (0.53-0.86)	0.04
Maschan et al. [28]	Retrospective cohort study	Children	0.57 (0.40-0.80)	0.02	0.71 (0.56-0.88)	0.03
Osumi et al. [29]	Retrospective cohort study	Children	0.63 (0.42-0.83)	0.01	0.64 (0.57-0.83)	0.03

EFS: Event-Free Survival; HR: Hazard Ratio; CI: Confidence Interval; OS: Overall Survival.

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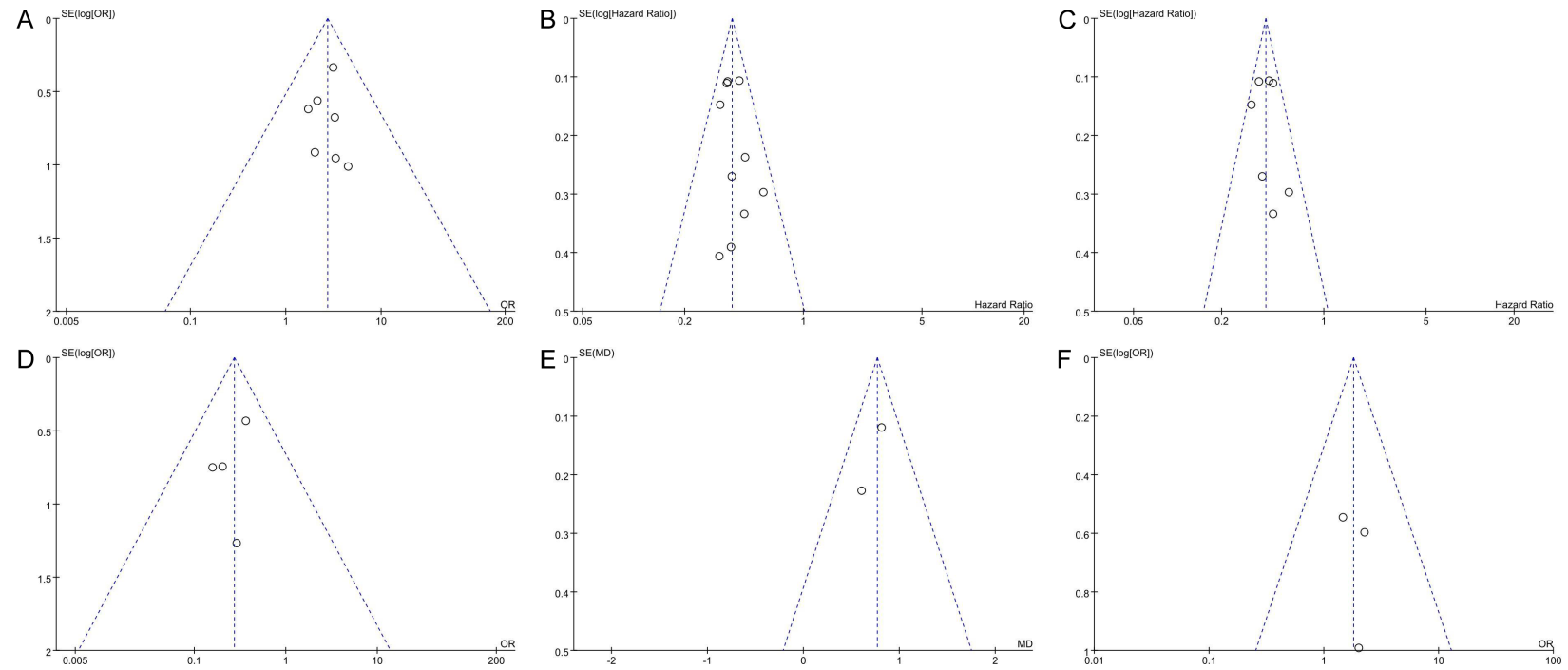


Figure 9. Funnel plots. (A) Event-free survival; (B) Overall survival; (C) Complete remission rate; (D) Toxic effects; (E) Immune reconstitution; (F) Recurrence rate.

cally and geographically diverse populations. Studies with extended follow-up periods are necessary to evaluate long-term safety and efficacy. Furthermore, exploration of rituximab in combination with emerging therapies, such as targeted agents and immunotherapy, may offer additional benefit for pediatric and adolescent patients with mature B-cell NHL.

In conclusion, this meta-analysis supports rituximab combined with chemotherapy as an effective treatment strategy for children and adolescents with mature B-cell NHL. The addition of rituximab significantly improved survival and remission rates, underscoring its vital role in improving outcomes in young patients with mature B-cell NHL.

Acknowledgements

This work was supported by the Medical Science Research Project of Hebei (No. 20241729).

Disclosure of conflict of interest

None.

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