

Efficacy and safety of rituximab in the treatment of primary central nervous system lymphoma: A meta-analysis and systematic review of 1,388 patients

LICHAOYUE SUN^{1*}, WENSHU LI^{2*}, WEI CHEN³, CHUNXING LI¹,
ZHAO REN¹, QING XIE¹ and DONGXIAO WANG¹

¹Department of Pharmacy, Aerospace Center Hospital, Beijing 100049, P.R. China; ²Department of Pharmacy, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, P.R. China; ³Department of Pharmacy, Emergency General Hospital, Beijing 100028, P.R. China

Received December 5, 2025; Accepted August 3, 2026

DOI: 10.3892/ol.2026.15843

Abstract. Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of non-Hodgkin's lymphoma with a generally poor prognosis, and the median age at diagnosis is 65 years. The clinical value of rituximab in the treatment of PCNSL remains controversial. The present study aimed to evaluate the therapeutic benefits and safety of rituximab in patients with newly diagnosed PCNSL. The EMBASE, PubMed, Web of Science and Cochrane Library were systematically searched from database inception to May 5, 2025, without any language restrictions. Efficacy outcomes included complete remission (CR), overall survival (OS) and progression-free survival (PFS). Safety outcomes were assessed by adverse drug reactions. Statistical analysis was performed using Review Manager 5.3 and Stata16 software to calculate relative risks and 95% confidence intervals (CIs) for categorical data and to analyze survival data. The meta-analysis included 15 studies with 1,388 patients, with a relatively high proportion of males and elderly individuals, and comparable baseline characteristics between rituximab-containing chemotherapy group and the standard chemotherapy-alone control group. Compared with the control group, the rituximab combination group achieved a significantly improved 3-year OS, with an odds ratio (OR) of 2.01 (95% CI: 1.42-2.84, $P<0.00001$). The combined hazard ratio (HR) for OS was 0.57 (95% CI: 0.36-0.91, $P=0.02$). The 3-year PFS also showed significant improvement in the rituximab group with an OR of 2.3 (95%

CI: 1.47-3.58, $P=0.0002$), and the combined PFS-HR was 0.54 (95% CI: 0.37-0.79, $P=0.002$). The rate of CR was significantly higher with an OR of 2.04 (95% CI: 1.5-2.77, $P<0.00001$). For safety outcomes, the OR for grade ≥ 3 leukopenia was 1.74 (95% CI: 0.92-3.27, $P=0.09$) and the OR for any-grade hepatic toxicity was 1.42 (95% CI: 0.98-2.05, $P=0.06$). In subgroup analyses, the OR for 3-year OS was 2.62 (95% CI: 1.16-5.91) for Asians and 1.69 (95% CI: 1.23-2.32) for Caucasians; the OR for 3-year PFS was 2.98 (95% CI: 1.17-7.6) for Asians and 2.02 (95% CI: 1.22-3.34) for Caucasians. In conclusion, based on this meta-analysis, rituximab significantly improved the prognosis of patients with PCNSL without a significant difference in safety compared to the existing treatment regimens. Further high-quality randomized controlled trials are warranted to confirm these findings.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare subtype of diffuse large B-cell lymphoma characterized by its confinement to the brain, spinal cord, meninges and/or eyes at the time of diagnosis (1,2). Despite various treatment modalities, the 5-year survival rate for PCNSL remains only 30-40% (3). The underlying pathophysiological mechanisms of PCNSL are still elusive, but recent studies suggest that immunoglobulins binding to self-proteins within the CNS, along with genetic alterations in pathways such as B-cell receptors, toll-like receptors and NF- κ B signaling, play critical roles (4,5).

Over the past decades, the introduction of high-dose methotrexate (HD-Mtx) has significantly improved the prognosis for patients with PCNSL. Nevertheless, a substantial proportion of patients either do not respond to HD-Mtx-based chemotherapy (15-25%) or relapse after initial response (25-50%). Furthermore, the late-stage neurotoxicity of HD-Mtx remains a concern (1,6). A prior cohort study reported that patients with early disease relapsed after first-line therapy exhibited dismal outcomes, with a median OS of merely 3.7 months, comparable to patients with refractory PCNSL [median overall survival (OS)=2.1 months] (7). There is an ongoing

Correspondence to: Dr Dongxiao Wang, Department of Pharmacy, Aerospace Center Hospital, 15 Yuquan Road, Haidian, Beijing 100049, P.R. China
E-mail: baixiao301@163.com

*Contributed equally

Key words: primary central nervous system lymphoma, efficacy, safety, rituximab, meta-analysis

need for more evidence-based treatment options for patients with PCNSL.

Rituximab, a monoclonal antibody targeting the CD20 antigen, has shown significant improvements in the treatment of systemic diffuse large B-cell lymphoma, including enhanced progression-free survival (PFS) and OS (8,9). The PFS benefit of rituximab in PCNSL has been observed with median PFS times extended by 4-12 months in certain studies compared to standard chemotherapy alone, while OS improvements have ranged from 6 to >24 months depending on the specific regimen and patient population (10,11). However, its efficacy in the treatment of PCNSL remains controversial, primarily due to its high molecular weight and the limited penetration of the blood-brain barrier (12). The European Society for Neuro-Oncology's guidelines for PCNSL treatment recognize the conflicting evidence regarding the use of intravenous rituximab in combination with chemotherapy for PCNSL. The ongoing divergence in expert opinions underscores the necessity for further clinical investigations and robust evidence-based research. Such studies are essential to determine the potential role of rituximab as an adjunct to conventional therapeutic regimens for PCNSL (13).

Most prior meta-analyses have mainly focused on the efficacy of rituximab in PCNSL treatment (14), while comprehensive quantitative synthesis of treatment safety data remains scarce. The present meta-analysis innovatively incorporates safety profiles as key secondary outcomes. In addition, updated long-term follow-up data (years 2022-2024) from the landmark IELSG32 trial were integrated, providing contemporary evidence to inform the clinical application of rituximab in PCNSL management.

Materials and methods

Registration. This study's protocol was duly registered with the International Prospective Register of Systematic Reviews (registration no. CRD42023458837) (14) and was executed in strict compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15).

Search strategy. To identify relevant studies, a systematic search was conducted in the PubMed, EMBASE, Web of Science and Cochrane Library (16) databases. All prospective randomized controlled trials (RCTs) and retrospective comparative cohort studies evaluating frontline rituximab therapy for PCNSL were included, with publication dates spanning from database inception to May 5, 2025. Eligible studies were required to report clinical response or survival endpoints.

The search employed a combination of keywords, subject terms and free-text terms to ensure a comprehensive retrieval of pertinent literature. The simplified search string utilized the following terms: 'Rituximab' OR 'rituximab' OR 'CD20 monoclonal antibody (rituximab)' AND 'primary central nervous system lymphoma' OR 'PCNSL' OR 'PCNSLs'. The specific search formula is provided in detail in Table S1.

Criteria for inclusion and exclusion. The inclusion criteria were as follows: i) Studies should be high-quality retrospective analyses or RCTs; ii) studies should compare a

rituximab-containing treatment protocol vs. the same treatment protocol without rituximab; iii) studies should provide complete data sets for analysis; and iv) a minimum sample size of 10 cases was required.

The following exclusion criteria were applied: i) Editorials, single-arm trials, reviews, case reports and animal studies were excluded; ii) studies on recurrent or secondary CNSL (SCNSL) were not considered; and iii) studies with incomplete data were excluded.

Data extraction. A total of two authors (LCYS and WSL) extracted data by using one of three methods: Direct extraction from the original text, contacting original authors for permission to obtain raw data and utilizing Engauge Digitizer Version 4.1 (17) to extract data from Kaplan-Meier (K-M) survival curves if necessary. For studies that directly reported hazard ratios (HRs) with 95% CIs, HRs were extracted from the published values. For studies that did not report HRs explicitly, the validated survival curve reconstruction method established by Tierney *et al* (18) in 2007 was applied to estimate HRs and their corresponding standard errors. This method accounts for the number of patients at risk and the number of events at each time interval via the following workflow: i) Engauge Digitizer Version 4.1 was used to digitize the published K-M curve and extract numerical coordinates of survival probability at multiple discrete follow-up time-points; ii) combined with the numbers at risk and event counts reported at each time interval in the original study, the algorithm reconstructed the number of events and censored observations within each follow-up interval; iii) the observed minus expected number of events and its variance were calculated for each treatment arm based on log-rank theory, from which the hazard ratio and its 95% CI were finally derived; iv) the uncertainty associated with indirectly estimated HRs was quantified using the standard error derived from the K-M curve reconstruction. Raw individual patient-level survival data were obtained by contacting the corresponding authors of Dina *et al* (19) from 2019; these data were used directly for HR calculation without curve digitization.

Literature quality assessment. The quality of RCTs was assessed using the Cochrane risk of bias (RoB) tool (20). Retrospective studies were evaluated with the Newcastle-Ottawa scale (NOS), which assigns a total score of 0-9, with studies scoring ≥ 5 considered high quality (21). Quality assessments were conducted independently by two researchers (LCYS and WSL), with a third researcher (DXW) involved in cases of disagreement. Only studies meeting predefined quality thresholds were incorporated into the meta-analysis.

Outcomes and statistical analysis. Quantitative meta-analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration) and Stata16 software (StataCorp LP) (22) for statistical analysis. The Eastern Cooperative Oncology Group performance status (ECOG-PS) was used to assess the baseline status of patients before participating in the clinical trials, with lower ECOG-PS scores indicating better patient status (23).

The primary outcome measures focused on efficacy indicators, namely OS, PFS and complete remission (CR). Given that certain studies only reported ~3-year OS and PFS

following rituximab treatment, this study conducted a binary variable analysis of patients achieving 3-year OS and 3-year PFS to investigate whether the addition of rituximab benefits patients in reaching these milestones. The clinical efficacy of PCNSL treatment, with or without rituximab, was evaluated using the OR along with the 95% CI. The secondary outcome measure was the incidence of adverse drug reactions (ADRs) and serious adverse events (SAEs; Grade $\geq$ III), which were primarily quantified using the OR.

OS was defined as the time from randomization (or treatment initiation in single-arm trials) to death from any cause (24). PFS was defined as the time from randomization (or treatment initiation in single-arm trials) to tumour progression or death from any cause, whichever occurred first (25). According to the International PCNSL Collaborative Group (IPCG) criteria for evaluating PCNSL efficacy, CR is defined as no detectable lesions on enhanced imaging, normal ophthalmologic examination results and negative cerebrospinal fluid cytology (26,27).

All pooled analyses were conducted using a random-effects model, regardless of the magnitude of the I^2 statistic. Heterogeneity across included studies was quantified using the I^2 statistic test. The heterogeneity threshold was predefined as follows: Low heterogeneity ($I^2 \leq 50\%$, $P \geq 0.10$) and substantial heterogeneity ($I^2 > 50\%$). Subsequently, sensitivity analysis and subgroup analysis were conducted to further explore and explain the observed heterogeneity. Furthermore, funnel plots (Fig. S1) were employed to assess the potential for publication bias within the included studies. A two-sided P -value < 0.05 was considered statistically significant. All pooled results were graphically displayed as forest plots.

Results

Systematic review and characteristics. The initial literature search retrieved a total of 653 unique citations. After the removal of duplicates and the exclusion of reviews and case reports, a total of 101 papers remained under consideration. Following a thorough review of the titles and abstracts, 61 studies were excluded, narrowing down the selection to 40 full-text references. Upon further assessment of these full-text references, studies were excluded based on several criteria: The absence of a control group in single-arm studies, the exclusion of basic and animal studies and the non-fulfilment of data requirements for experimental interventions. This meticulous evaluation process culminated in the inclusion of 15 studies in the systematic review. The PRISMA flow diagram, illustrating the study selection process, is presented in Fig. 1.

The study included 15 articles, comprising 3 RCTs and 12 retrospective trials. Details of the study characteristics were presented in Table I. The three RCTs, including HOVON105/ALLGNHL24 (28) (ACTRN12610000908033), IELSG32 (11) (NCT01011920) and Luo *et al* (29) from 2016, were complemented by cohort studies. Studies such as Luo *et al* (29) from 2016, Chen *et al* (30) from 2019, Dina *et al* (19) from 2019, Mou *et al* (31) from 2017, Sun *et al* (32) from 2017, Patekar *et al* (33) from 2019 and Pang *et al* (34) from 2021, have investigated the impact of rituximab on individuals of Asian descent. Conversely, ALLGNHL24 (28), IELSG32 (11), Birnbaum *et al* (35) from

2012, Gregory *et al* (36) from 2013, Houillier *et al* (37) from 2017, Kansara *et al* (38) from 2015, Holdhoff *et al* (39) from 2014 and Mocikova *et al* (40) from 2016 mainly focused on studying the effects of rituximab on Caucasians.

The mean age of the study population exceeded 50 years, with a predominance of elderly patients (Table I). Except for Luo *et al* (29) from 2016 and Gregory *et al* (36) from 2013, most studies exhibited a higher proportion of male participants ($>50\%$). The proportion of patients with ECOG-PS ≤ 1 in the rituximab group was like that in the control group, indicating comparable baseline characteristics. The treatment regimens in this study encompassed methotrexate-based protocols for both control and experimental cohorts, potentially augmented with additional therapeutic modalities such as whole brain radiotherapy and autologous stem cell transplantation. Furthermore, based on specific experimental designs and groupings, patients were assessed for the addition of rituximab to these treatments. Most literature reported OS, PFS and CR rates, while ADRs were documented across all studies. Due to the different outcome indicators reported in various trials, some lacked data for certain metrics, such as PFS-HR and OS-HR results from 5 trials, 3-year OS from 10 trials, 3-year PFS from 9 trials and CR results from 12 trials.

RoB and publication assessment

RoB assessment. The Cochrane RoB tool was utilized to assess the quality of the three RCTs included in the present review. Fig. 2A (RoB graph) categorizes seven domains (e.g., random sequence generation, allocation concealment) according to risk level (low: Green; unclear: Yellow; high: Red). Most domains had a low risk, but allocation concealment included high-risk cases and the blinding domains had unclear-risk instances. Fig. 2B (RoB summary) profiles three studies: IELSG32 (11) was at low risk across all domains; ALLGNHL24 (28) had a high risk (in allocation concealment) and an unclear risk (in outcome assessment blinding); Luo *et al* (29) from 2016 had a high risk (in allocation concealment) along with an unclear risk (in participant blinding, incomplete outcome data). Both the ALLGNHL24 (28) and Luo *et al* (29) from 2016 trials did not report allocation concealment measures. The ALLGNHL24 (28) study provided an incomplete description of random sequence generation, while Luo *et al* (29) from 2016 stated the use of computer-generated randomization but disclosed no methodological details. For retrospective studies, the NOS was employed and the results are summarized in Table SII. These assessments confirmed that all 15 studies satisfied the inclusion criteria for this meta-analysis. The NOS scores ranged from 5 to 8, with all studies meeting the pre-specified quality threshold of ≥ 5 . A total of eight studies scored ≥ 7 , indicating high methodological quality [Holdhoff *et al* (39) from 2014: 8; Kansara *et al* (38) from 2015: 8; Pang *et al* (34) from 2021: 8; Birnbaum *et al* (35) from 2012: 7; Chen *et al* (30) from 2019: 7; Dina *et al* (19) from 2019: 7; Patekar *et al* (33) from 2019: 7; Sun *et al* (32) from 2017: 7]. Four studies scored 5-6 [Gregory *et al* (36) from 2013: 6; Houillier *et al* (37) from 2017: 6; Mocikova *et al* (40) from 2016: 6; Mou *et al* (31) from 2017: 5].

Publication bias. Funnel plots were used to assess publication bias for effectiveness and safety indicators separately

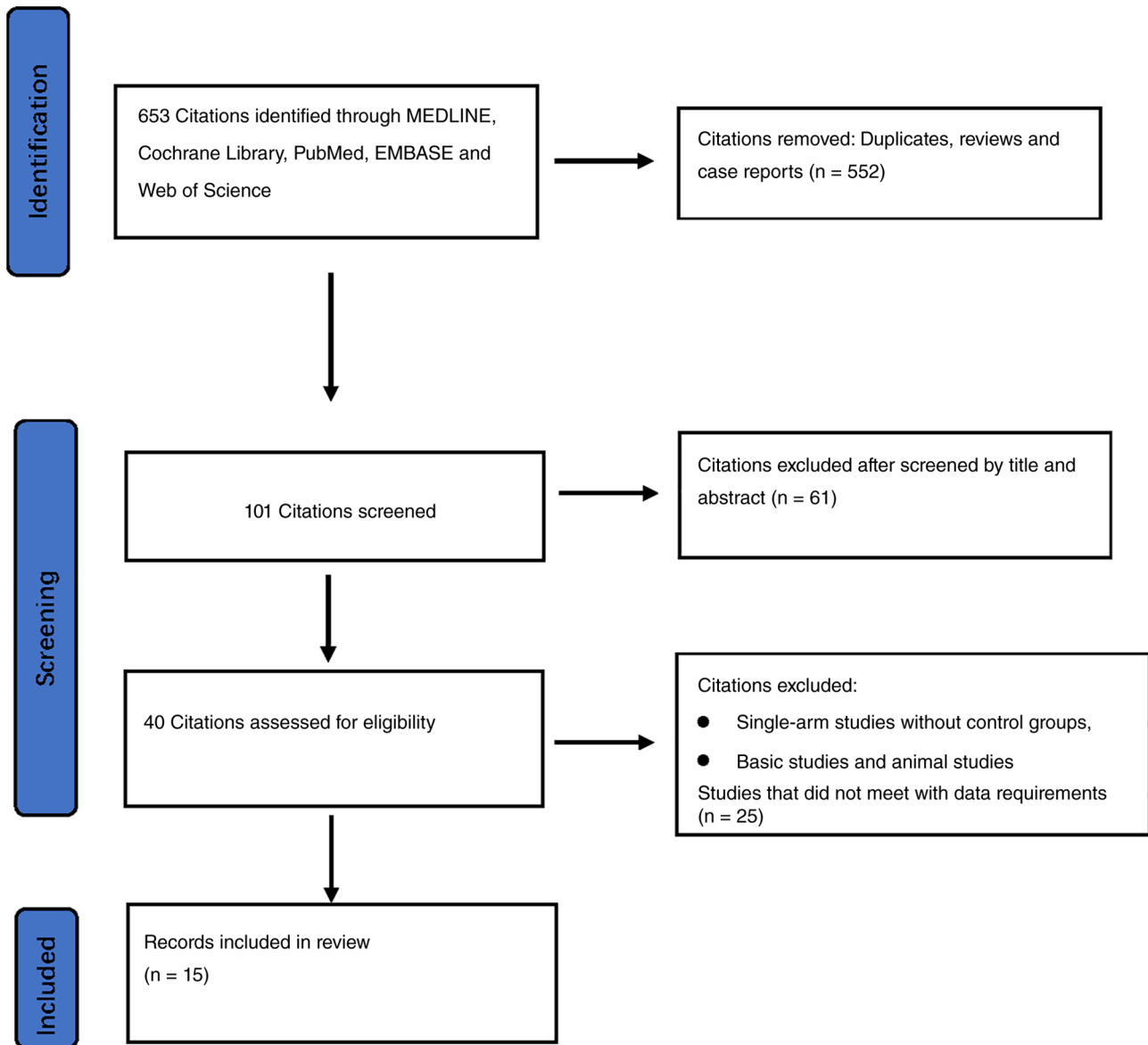


Figure 1. Flowchart of literature search and screening process. This diagram shows the process of retrieving and screening the research studies in this article. The present study followed the PRISMA guidelines for systematic reviews and meta-analyses.

(Fig. S1), and their funnel plots were generally symmetrical, with no evidence of publication bias. Funnel plots for 3-year OS and 3-year PFS were generally symmetrical with no obvious asymmetry. Egger's linear regression test for 3-year OS yielded $P=0.32$, and Begg's rank correlation test gave $P=0.47$. For 3-year PFS, Egger's test yielded $P=0.41$ and Begg's test $P=0.59$. These results suggest no significant evidence of publication bias for the primary outcomes. Nevertheless, given the relatively small number of studies included in certain analyses, the possibility of unpublished negative trials cannot be entirely excluded. First, omission of studies with null or unfavorable effects may overestimate the pooled survival benefit of rituximab; inclusion of missing negative trials could potentially attenuate the effect size and eliminate the statistical significance of primary outcomes. Second, conventional publication bias tests have limited power with small study sets. Accordingly, these conclusions should be interpreted with caution, and

further large, well-designed multicenter RCTs are required to confirm the survival benefit of rituximab in PCNSL. The detailed Egger's and Begg's test results are presented in Table SIII.

Efficacy analysis

Comparisons of OS. This study focused on the 3-year OS rate and the HR of OS, as illustrated in Fig. 3. The studies ALLGNHL24 (28), Dina *et al* (19) from 2019, IELSG32 (11), Kansara *et al* (38) from 2015 and Pang *et al* (34) from 2021 were pooled for the OS analysis. The combined HR was 0.57 (95%CI: 0.36-0.91, $P=0.02$), as shown in Fig. 3A. This suggests a favourable effect of rituximab on OS when used in conjunction with standard chemotherapy. As depicted in Fig. 3B, the incorporation of rituximab into the treatment regimen significantly enhanced patients' OS outcomes [odds ratio (OR)=2.01, 95%CI: 1.42-2.84, $P<0.0001$], indicating a highly statistically significant improvement.

Table I. Baseline characteristics of studies included in the meta-analysis.

Study	Study design	Recruitment period	Location	Median age (range), years	Male sex, %	ECOG PS≤1 (Rtx: No-Rtx)	Sample size (Rtx: No-Rtx)	Dosage and cycles of Rtx	Rtx group	No-Rtx group	Outcome (Refs.)
ALLGNHL24	RCT	2010-2016	Netherlands, Australia and New Zealand	61 (56-67)	54.8	71: 73	199 (99:100)	375 mg/m ² 2 cycles	HD-Mtx + Teniposide + Carmustine + Prednisone + Rtx	HD-Mtx + Teniposide + Carmustine + Prednisone	OS, PFS, CR, ADRs (28)
Birbaum, 2012	Cohort study	2007-2010	Germany	66 (36-79)	61.1	5: 6	36 (17:19)	375 mg/m ² 6 cycles	HD-Mtx + Ifosfamide + Rtx	HD-Mtx + Ifosfamide	OS, PFS, CR, ADRs (35)
Chen, 2019	Cohort study	2005-2015	China	54 (29-77)	51.6	11: 11	62 (32:30)	375 mg/m ² 6-8 cycles	HD-Mtx + Tmz + Rtx	HD-Mtx + Tmz	OS, PFS, CR (30)
Dina, 2019	Cohort study	2012-2015	China	56 (36-75)	63	21: 17	73 (38:35)	375 mg/m ² 6 cycles	HD-Mtx + Rtx	HD-Mtx	OS, PFS, CR, ADRs (19)
Gregory, 2013	Cohort study	1996-2011	Australia	65 (21-81)	49.6	14: 34	117 (18:99)	NA	X + Rtx	X, HD-Mtx and Ara-C, other combination chemotherapy with/without HD-Mtx	OS, CR (36)
Holdhoff, 2014	Cohort study	1995-2012	Australia	66 (32-85)	51.9	18: 35	81 (27:54)	375 mg/m ²	HD-Mtx + Rtx	HD-Mtx	OS, PFS, CR, ADRs (39)
IELSG32	RCT	2010-2014	Denmark, Germany, Italy, Switzerland and the UK	57 (50-64)	62.5	46: 48	144 (69:75)	375 mg/m ² 4 cycles	Mtx + cytarabine + Rtx	Mtx + cytarabine	OS, PFS, CR, ADRs (11)
Kansara, 2015	Cohort study	2000-2013	Canada	61 (18-80)	61.0	15: 16	86 (29:57)	375 mg/m ² ≤8 cycles	HD-Mtx + Rtx	HD-Mtx	OS, PFS, CR (38)
Luo, 2016	RCT	2008-2011	China	64 (51-79)	41.3	NA	58 (29:29)	375 mg/m ² 2-6 cycles	Mtx + Rtx	Mtx	OS, CR, ADRs (29)
Houillier, 2017	Cohort study	2010-2013	French	68 (60-87)	36.7	NA	90 (39:51)	375 mg/m ²	R-Mpv-AAA	Mpv-AAA	CR, ADRs (37)

Table I. Continued.

Study	Study design	Recruitment period	Location	Median age (range), years	Male sex, %	ECOG PS≤1 (Rtx: No-Rtx)	Sample size (Rtx: No-Rtx)	Dosage and cycles of Rtx	Rtx group	No-Rtx group	Outcome	(Refs.)
Mocikova, 2016	Cohort study	2002-2012	Czech	63 (31-79)	51.8	29: 44	164 (49:115)	375 or 500 mg/m ² 5-7 cycles	Mtx + cytarabine + Rtx	Mtx + cytarabine	OS, PFS	(40)
Mou, 2017	Cohort study	2013-2015	China	47 (36-56)	56.0	NA	100 (50:50)	375 mg/m ² 2-5 cycles	HD-Mtx+ Rtx	HD-Mtx	PFS, CR	(31)
Pang, 2021	Cohort study	2010-2017	China	58 (21-77)	57.1	13: 9	42 (25:17)	375 mg/m ² 6-8 cycles	HD-Mtx + Temozolo- mide+ Rtx	HD-Mtx + Temozolo mide	OS, PFS, CR	(34)
Patekar, 2019	Cohort study	2001-2017	India	50 (13-70)	65.5	11:20	76 (27:49)	375 mg/m ² 2-5 cycles	Mtx + Carmustine + Teniposide + Prednisone+ Rtx	Mtx + Carmustine + Teniposide + Prednisone	OS, PFS, CR	(33)
Sun, 2017	Cohort study	2010-2016	China	57 (11-83)	60%	6:4	60 (36:24)	375 mg/m ² ≤6 cycles	HD-Mtx + Dexametha- sone + Rtx	HD-Mtx + Dexametha- sone	OS, PFS, CR, ADRs	(32)

RCT, randomized controlled trial; CR, complete remission; OS, overall survival; PFS, progression-free survival; NA, information not available; HD-MTX, high-dose Methotrexate; Rtx, Rituximab; WBRT, whole brain radiotherapy; ASCT, autologous stem cell transplantation; PS, performance status; ADR, adverse drug reaction; ECOG, Eastern Cooperative Oncology Group; Tmz, Temozolomide; X, HD-MTX alone; Ara-C, Cytarabine; AAA, three rounds of Ara-C consolidation.

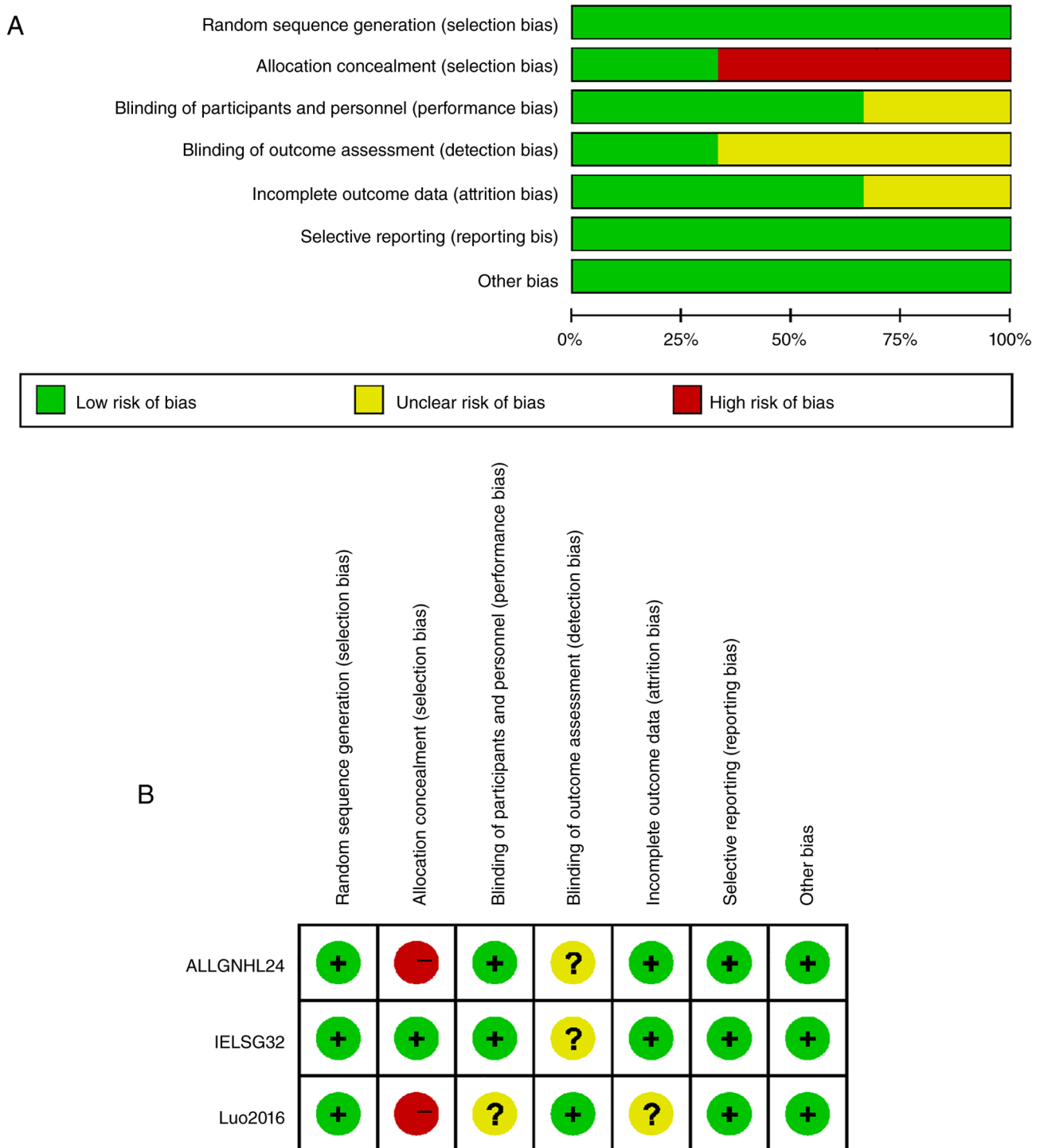


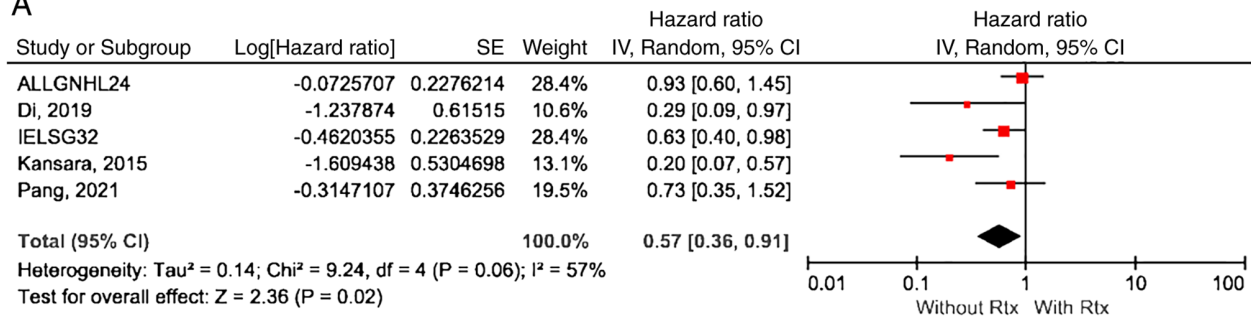
Figure 2. Cochrane risk of bias tool analysis. (A) The authors' judgment of each methodological quality item for each included study is presented. Performance bias and detection bias are bias risks. (B) The authors' judgment of the quality of each method, expressed as a percentage of all included studies.

Comparisons of PFS. For this study, the 3-year PFS data were primarily extracted from 9 studies: ALLGNHL24 (28), Birnbaum *et al* (35) from 2012, Chen *et al* (30) from 2019, Holdhoff *et al* (39) from 2014, IELSG32 (11), Kansara *et al* (38) from 2015, Mocikova *et al* (40) from 2016, Mou *et al* (31) from 2017 and Patekar *et al* (33) from 2019. Additionally, the HR of PFS was derived from an analysis of 5 studies: ALLGNHL24 (28), Dina *et al* (19) from 2019, IELSG32 (11), Kansara *et al* (38) from 2015 and Pang *et al* (34) from 2021. As shown in Fig. 4A, the combined HR after applying the

random-effects model was 0.54 (95%CI: 0.37-0.79, $P=0.002$), suggesting a heterogeneous yet robust and high-certainty benefit of incorporating rituximab into the treatment regimen for patients with PCNSL. Furthermore, the results, as depicted in Fig. 4B, indicated that the addition of rituximab significantly improved the 3-year PFS in patients with PCNSL (OR=2.30, 95% CI: 1.47-3.58, $P=0.0002$).

Comparisons of CR. In the present study, an analysis of CR rates was performed. The results from 12 studies were pooled

A



B

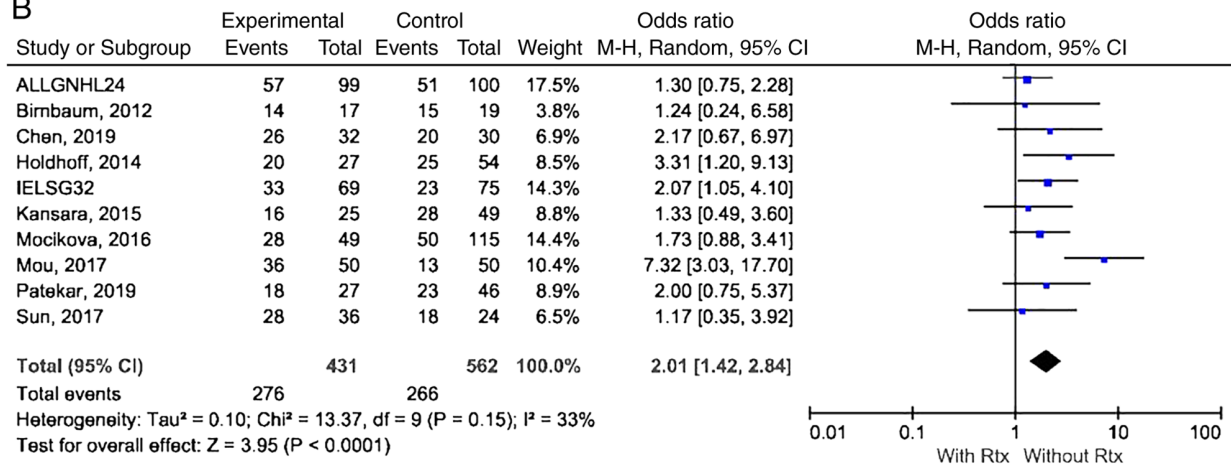
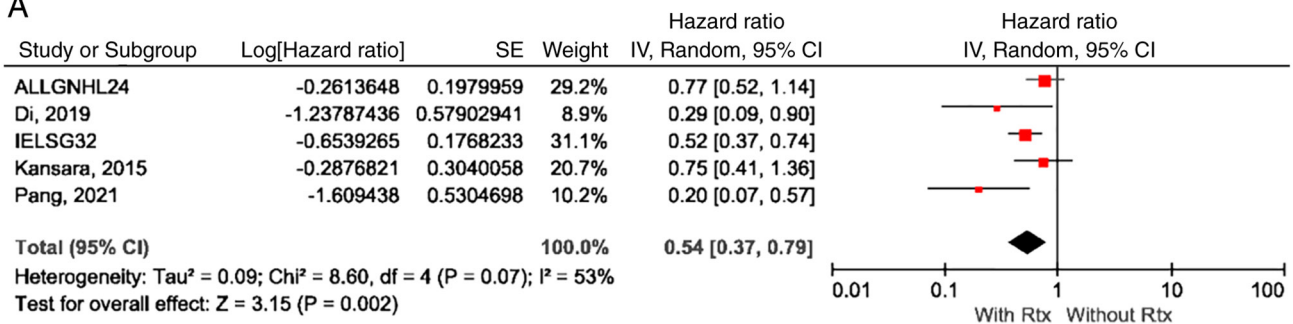


Figure 3. Forest plot of OS in the rituximab group vs. the control group. (A) Forest plot of OS-HR in the rituximab group vs. the control group. (B) Forest plot of 3-year OS in the rituximab group vs. the control group. OS-HR, overall survival hazard ratio; IV, inverse variance; df, degrees of freedom; SE, standard error; Rtx, rituximab; M-H, Mantel-Haenszel.

A



B

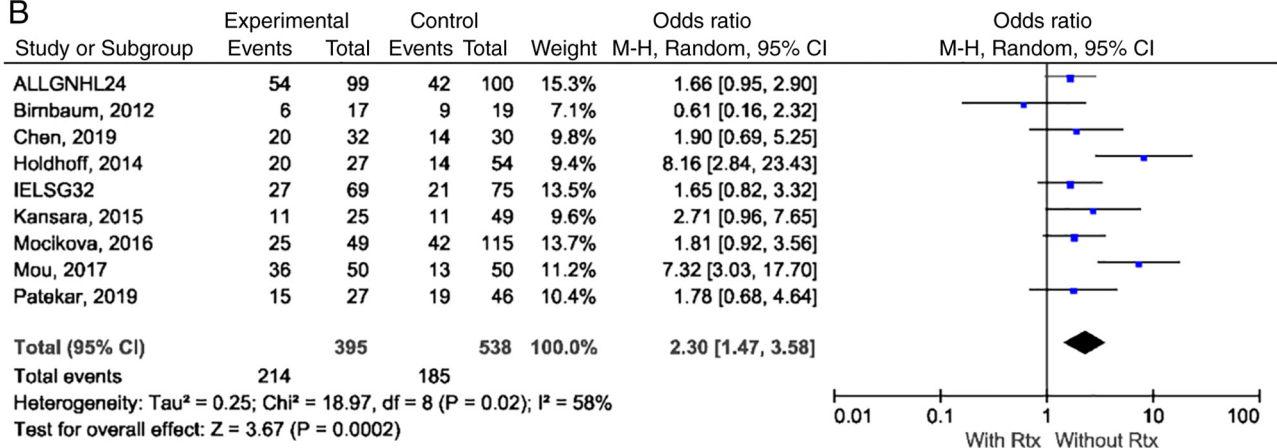


Figure 4. Forest plot of PFS in the rituximab group vs. the control group. (A) Forest plot of PFS-HR in the rituximab group vs. the control group. (B) Forest plot of 3-year PFS in the rituximab group vs. the control group. PFS, progression-free survival; HR, hazard ratio; IV, inverse variance; df, degrees of freedom; SE, standard error; Rtx, rituximab; M-H, Mantel-Haenszel.

Table II. Pooled analysis of G $\geq$ 3 serious adverse events in patients with primary central nervous system lymphoma treated with rituximab-containing vs. non-rituximab-containing regimens.

Adverse Event	OR	95% CI	P-value	I ² , %	Model
Neutropenia $\geq$ G3	1.06	0.65-1.73	0.83	0	Random effects
Leukopenia $\geq$ G3	1.74	0.92-3.27	0.09	0	Random effects
Thrombocytopenia $\geq$ G3	1.26	0.8-1.99	0.32	0	Random effects
Infection $\geq$ G3	0.96	0.61-1.50	0.84	0	Random effects
Hepatic toxicity $\geq$ G3	0.81	0.46-1.41	0.45	45	Random effects
Renal toxicity $\geq$ G3	1.43	0.63-3.27	0.39	0	Random effects
Anemia $\geq$ G3	0.88	0.34-2.25	0.79	63	Random effects

OR, odds ratio; CI, confidence interval; G3, grade 3.

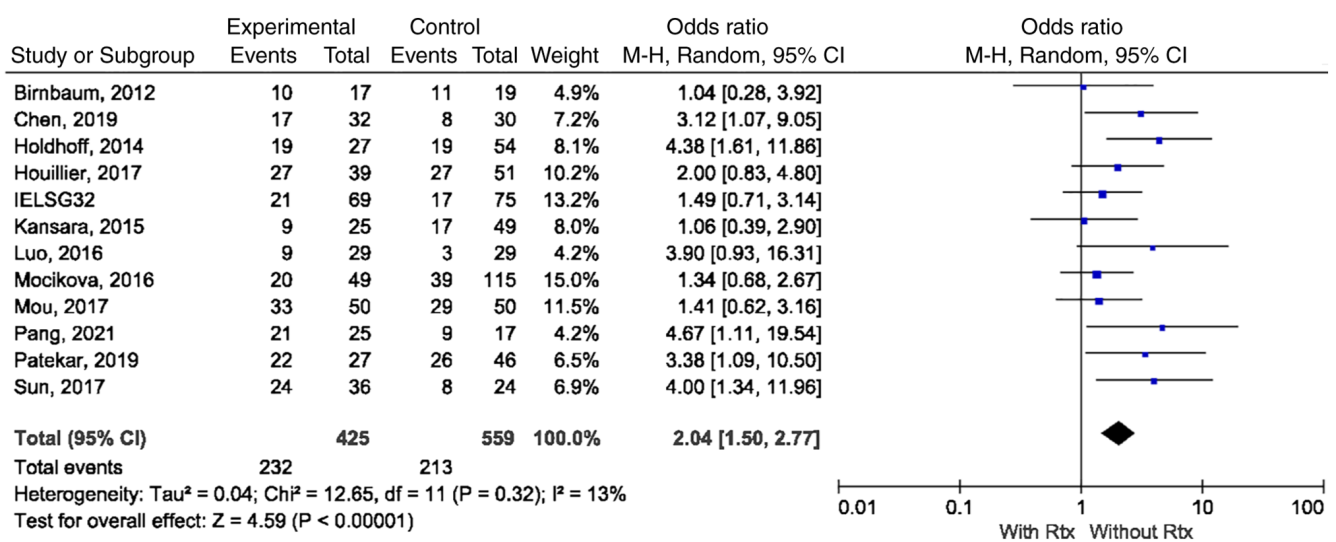


Figure 5. Forest plot of complete remission in the rituximab group vs. the control group. df, degrees of freedom; SE, standard error; Rtx, rituximab; M-H, Mantel-Haenszel.

and are illustrated in Fig. 5. The inclusion of rituximab in the treatment protocol was associated with a significantly higher CR rate among patients with PCNSL (OR=2.04, 95% CI: 1.50-2.77, P<0.00001, I²=13%), indicating a substantial and statistically significant benefit.

Safety analysis. The safety of rituximab in treating patients with PCNSL was comprehensively assessed for the following grade $\geq$ 3 adverse events: Neutropenia, leukopenia, thrombocytopenia, infection, hepatic toxicity, renal toxicity, neurotoxicity and anemia. The results are summarized in Tables II and SIV. Study-level availability of grade $\geq$ 3 SAE data is summarized in Table SIV. Of the 8 included studies, 3 studies [ALLGNHL24 (28), IELSG32 (11), Kansara *et al* (38) from 2015] reported complete data across all 8 SAE categories. Pooled analyses for all grade $\geq$ 3 SAE endpoints showed no statistically significant differences between the rituximab and control groups. Figs. S2 and S3 present the grade $\geq$ 3 SAEs from the combined studies.

For neutropenia $\geq$ grade 3, the OR was 1.06 (95% CI: 0.65-1.73, P=0.83; I²=0%), indicating no significant difference.

For leukopenia $\geq$ grade 3, the OR was 1.74 (95% CI: 0.92-3.27, P=0.09; I²=0%), showing a trend toward increased risk in the rituximab group but not reaching statistical significance. Thrombocytopenia $\geq$ grade 3 showed an OR of 1.26 (95% CI: 0.80-1.99, P=0.32; I²=0%) and Anemia $\geq$ grade 3 and OR of 0.88 (95% CI: 0.34-2.25, P=0.79; I²=63%). Forest blots for specific hematological SAEs are provided in Fig. S2.

Infection $\geq$ grade 3 had an OR of 0.96 (95% CI: 0.60-1.51, P=0.84; I²=0%). Hepatic toxicity $\geq$ grade 3 had an OR=0.81 (95% CI: 0.46-1.41, P=0.45; I²=45%) and renal toxicity $\geq$ grade 3 an OR of 1.43 (95% CI: 0.63-3.27, P=0.39; I²=0%). None of the grade $\geq$ 3 SAEs reached statistical significance, indicating that rituximab did not substantially increase the risk of SAEs compared to chemotherapy alone. Forest blots for non-hematological SAEs are provided in Fig. S3.

For any-grade adverse events (Fig. 6), the comparative analysis revealed no significant differences in the incidence of gastrointestinal toxicity (OR=1.21, 95% CI: 0.47-3.11), thrombocytopenia (OR=1.22, 95% CI: 0.79-1.87) and neurotoxicity (OR=0.72, 95% CI: 0.45-1.15) between rituximab users and controls. An elevated risk of hepatic toxicity was observed

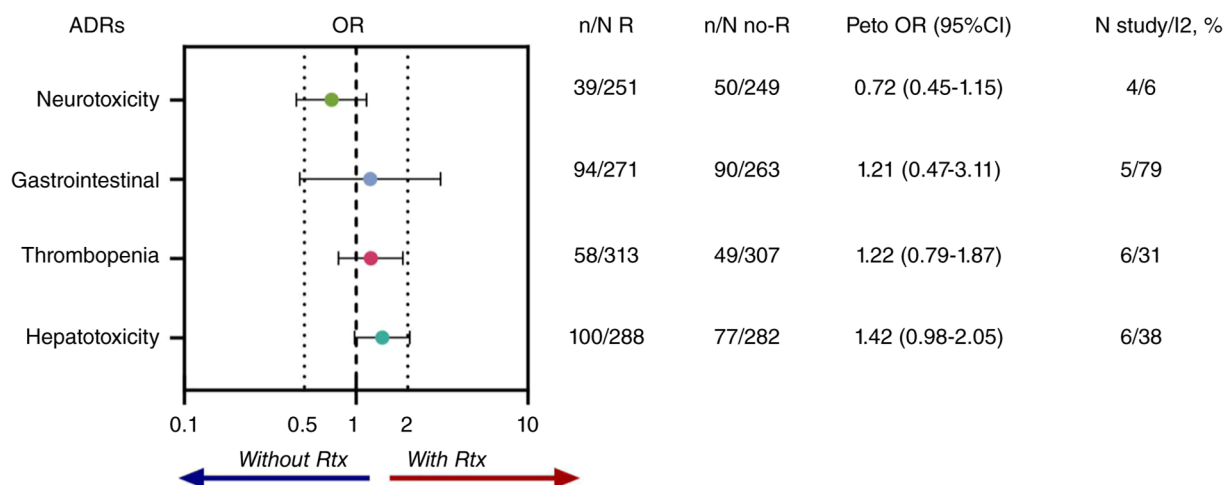


Figure 6. Forest plot of a pooled analysis of adverse events vs. control risks arising from rituximab treatment of primary central nervous system lymphoma. n/N is the number of events observed (n) relative to the total number of patients in each group (N). The circle size is proportional to the number of studies used to estimate the total Peto OR. CI, confidence interval; R/Rtx, rituximab; no-R, no rituximab; ADRs, adverse drug reaction; Peto OR, Peto Odds Ratio.

but it did not reach statistical significance (OR=1.42, 95% CI: 0.98-2.05, $P=0.06$).

Subgroup analysis. The study populations exploring the role of rituximab in PCNSL have focused on Asians and Caucasians, so in this paper, the 3-year OS and 3-year PFS in which heterogeneity exists were stratified by ethnicity, and the specific results were shown in Fig. 7 and Table SV. In this study, the Asian subgroup comprises populations from East Asia (Han Chinese) and South Asia (Indian subcontinent).

In the 3-year OS assessment, a combined analysis of four studies showed an OR of 2.62 (95% CI: 1.16-5.91, $P=0.02$) for Asians and a combined analysis of six studies showed an OR of 1.69 (95% CI: 1.23-2.32, $P=0.001$) for Caucasians; for the 3-year PFS, a combined analysis of three studies showed an OR of 2.98 (95% CI: 1.17-7.60, $P=0.02$) for Asians, while a six-study meta-analysis yielded an OR of 2.02 (95% CI: 1.22-3.34, $P=0.006$) for Caucasians, suggesting that rituximab may have more pronounced efficacy in Asians compared to Caucasians.

This study evaluated the efficacy of rituximab in patients with PCNSL based on study type. As illustrated in Fig. 8A and B, for OS, the HR for cohort studies was 0.38 (95% CI: 0.16-0.88, $P=0.02$), while the HR for RCTs was 0.76 (95% CI: 0.52-1.12, $P=0.17$). The I^2 statistic between groups was found to be 54.9%, indicating no significant difference between them ($P=0.14$). Regarding PFS, the HR for cohort studies was 0.39 (95% CI: 0.16-0.93, $P=0.03$), whereas the HR for RCTs was 0.63 (95% CI: 0.43-0.92, $P=0.02$), with an I^2 value of 0% between groups ($P=0.32$). These findings suggest that rituximab may demonstrate superior efficacy in retrospective cohort studies compared to RCTs; however, this difference is not statistically significant across groups.

Sensitivity analysis. Sensitivity analyses were performed by sequentially excluding individual studies from each pooled analysis. For 3-year OS, the pooled OR ranged from 2.01 to 2.51 upon sequential exclusion and no single study substantially altered the overall effect direction or statistical significance.

For PFS-HR, exclusion of the Pang *et al* (34) from 2021 study (which reported the most extreme HR of 0.20) resulted in a pooled HR of 0.67 (95% CI: 0.50-0.89, $P=0.005$), still indicating significant benefit. Sensitivity analyses excluding studies with NOS scores <7 yielded consistent results: 3-year OS OR=2.36 (95% CI: 1.42-3.93, $P=0.0008$) and 3-year PFS OR=2.14 (95% CI: 1.54-2.97, $P<0.0001$). Excluding HRs estimated from K-M curves [Dina *et al* (19) from 2019 and Kansara *et al* (38) from 2015], the OS-HR was 0.56 (95% CI: 0.39-0.82, $P=0.003$). Detailed sensitivity analysis results are presented in Table SVI.

Heterogeneity summary. Table SVII provides a comprehensive summary of heterogeneity statistics and the effect model used for each pooled analysis. All meta-analyses in this study used the random-effects model, regardless of the I^2 -value found. Substantial heterogeneity ($I^2>50\%$) was observed for OS-HR ($I^2=57\%$), 3-year PFS ($I^2=58\%$), PFS-HR ($I^2=53\%$) and anemia ($I^2=63\%$), necessitating the use of random-effects models. Low heterogeneity ($I^2\leq 50\%$) was observed for 3-year OS ($I^2=33\%$), hepatic toxicity ($I^2=45\%$), CR ($I^2=13\%$), neutropenia ($I^2=0\%$), leukopenia ($I^2=0\%$), thrombocytopenia ($I^2=0\%$), infection ($I^2=0\%$) and renal toxicity ($I^2=0\%$).

For efficacy outcomes (3-year OS, OS-HR, 3-year PFS and PFS-HR), the observed between-study heterogeneity was primarily attributed to differences in study design (RCTs vs. retrospective cohorts) and variations in the ethnic composition of included populations. For the safety endpoint of grade ≥ 3 anemia, the substantial heterogeneity was likely driven by inconsistent adverse event grading and reporting standards across the included studies.

Discussion

PCNSL represents a rare, highly aggressive subtype of B-cell lymphoma with a generally unfavorable prognosis, predominantly affecting elderly patients, with increasing age correlating with higher incidence rates (41). Optimization of HD-Mtx-based frontline regimens has long constituted the core focus of

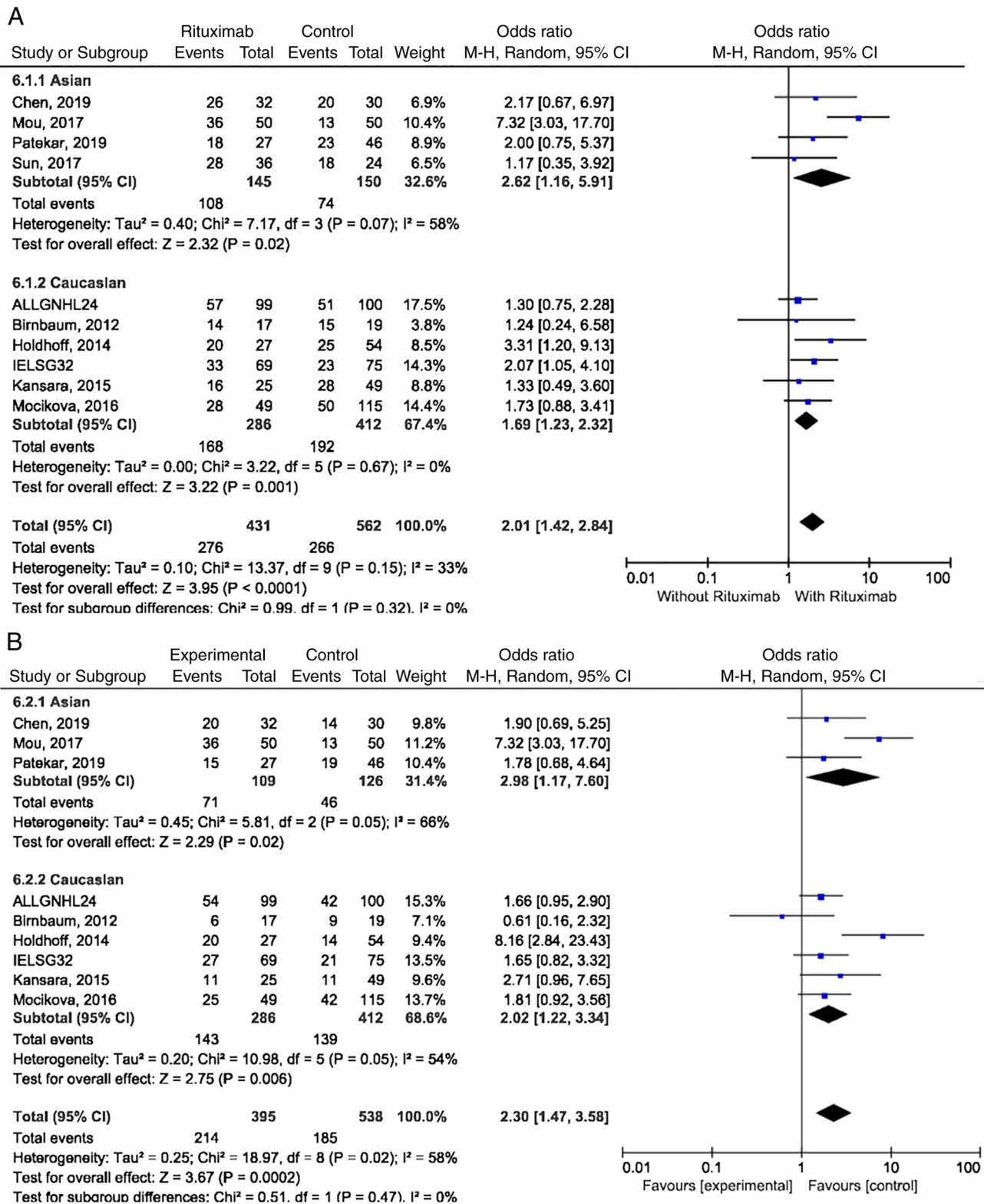


Figure 7. Forest plot for 3-year survival by ethnicity subgroups. (A) Forest plot of 3-year OS in the rituximab group vs. the control group. (B) Forest plot for 3-year PFS in the rituximab group vs. the control group. OS, overall survival; PFS, progression-free survival; df, degrees of freedom; M-H, Mantel-Haenszel.

clinical PCNSL research. Data from the Centralized Brain Tumor Registry of the United States indicated that the 3-year survival rate for patients with PCNSL stands at 39.6% (95% CI: 39.2-39.9) (42).

This study analyzed outcome indicators in >1,000 patients with newly diagnosed PCNSL, both those treated with

rituximab and those without it in their initial chemotherapy regimen. The findings indicate that the incorporation of rituximab significantly enhances OS and PFS, as well as increases the CR rate, while no significant SAEs were reported. In addition, the subgroup meta-analysis of the relationship between ethnicity and the prognosis of patients with PCNSL treated

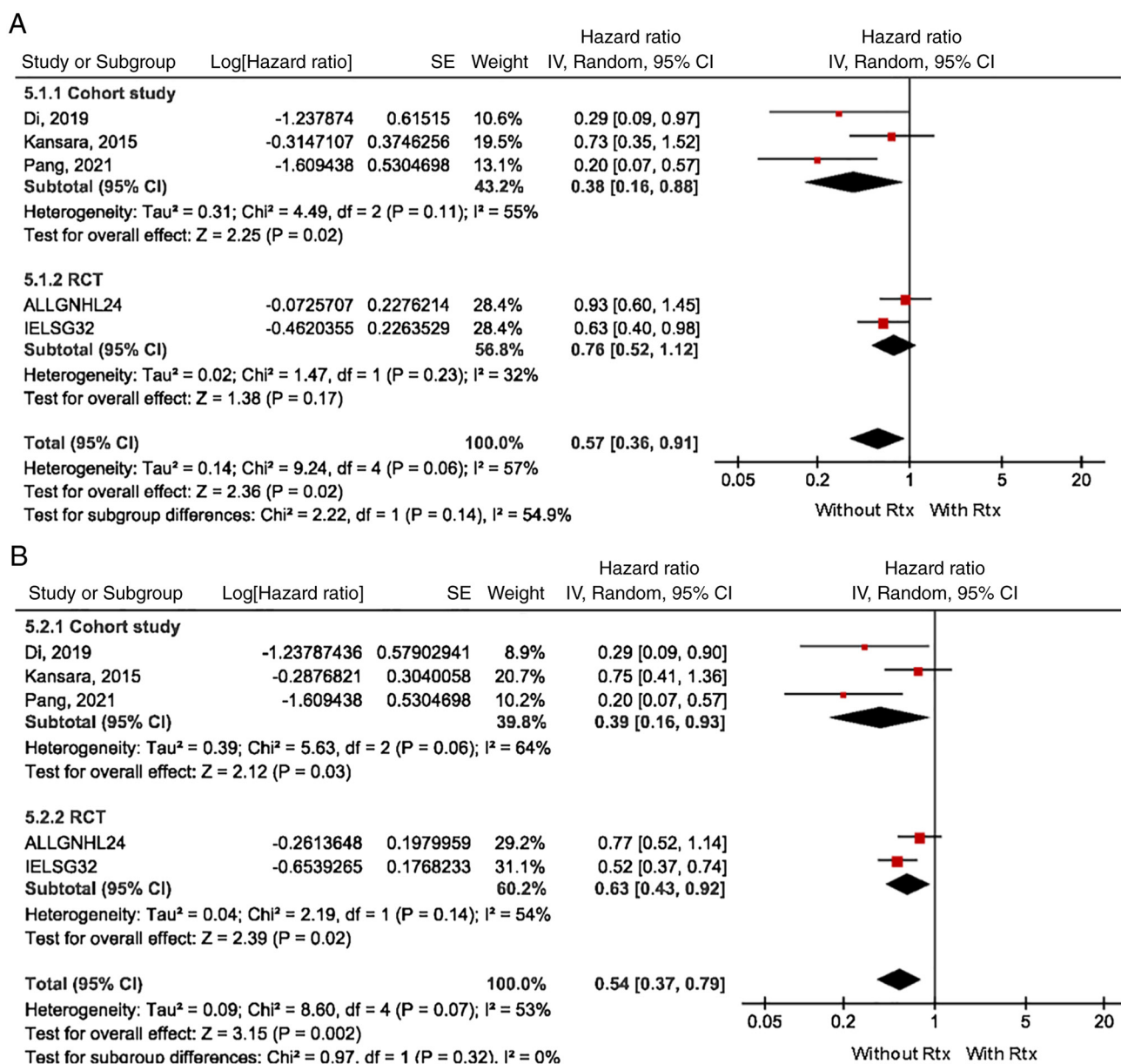


Figure 8. Forest plot for survival by study type. (A) Forest plot of OS-HR subgroup in the rituximab group vs. the control group. (B) Forest plot for PFS-HR subgroup analysis in the rituximab group vs. the control group. OS, overall survival; PFS, progression-free survival; HR, hazard ratio; df, degrees of freedom; SE, standard error; IV, inverse variance; RCT, randomized controlled trial; Rtx, rituximab.

with rituximab and found that rituximab was more effective in Asians than in Caucasians. Rituximab showed a numerically greater effect in patients with PCNSL from retrospective cohort studies than in RCTs, although this difference was not statistically significant. In the future, more high-quality RCTs are needed to explore the efficacy and safety of rituximab in PCNSL.

Given the ethnic heterogeneity in rituximab efficacy for PCNSL, this study further clarifies its mechanistic basis via pharmacogenomics comparison. Rituximab exerts antitumor activity predominantly through antibody-dependent cellular cytotoxicity, which relies on Fcγ receptors encoded by Fcγ receptor IIIa (FCGR3A) and FCGR2A, alongside CD20 encoded by membrane spanning 4-domains A1 (MS4A1) (43). Asians frequently harbor high-response FCGR3A V158F and FCGR2A R131H alleles coupled with high-expression MS4A1

genotypes, boosting CD20 surface density and cytotoxic efficacy (44,45). By contrast, Caucasians possess a higher prevalence of low-affinity variants that diminish drug bioactivity (46). These pharmacogenomic differences underpin the improved OS and PFS seen in Asian PCNSL patients receiving rituximab combined with HD-Mtx.

Beyond therapeutic heterogeneity, ethnicity also exhibits significant epidemiological correlations with PCNSL incidence and early mortality risk. A population-based epidemiological analysis by Pulido *et al* (47) reported a significantly higher incidence of PCNSL in the white population compared to Asians (0.94:0.64, per 100,000 per year). Furthermore, an analysis of risk factors for PCNSL in a different study by a different group suggested that ethnicity may be a contributing factor to early mortality among patients (48). Consistent with real-world study conclusions, subgroup analysis showed that

males comprised a higher proportion of patients with PCNSL, indicating that gender bias might influence this study's conclusions (49). Hence, it is essential to consider the impact of gender on the efficacy and safety of rituximab.

Multiple prior meta-analyses have been performed in the past to explore the efficacy of rituximab in patients with newly diagnosed PCNSL (14,50). A total of two quantitative syntheses indicated that rituximab might positively affect the prognosis of patients with PCNSL and recommended its inclusion in existing treatment regimens (50,51). Another meta-analysis, including only RCTs, showed that rituximab could improve PFS in patients with PCNSL, although it had limited impact on OS (14). However, these studies predominantly concentrated on measures of efficacy, yielding inconsistent conclusions, and often neglecting a comprehensive analysis of the safety profile associated with rituximab use. This study demonstrated that the incorporation of rituximab can enhance therapeutic efficacy while maintaining patient safety in individuals with first-episode PCNSL. However, for recurrent PCNSL, the effectiveness of rituximab remains uncertain and requires further validation (52).

The potential synergy of rituximab in conjunction with chimeric antigen receptor T-cell therapy presents a promising avenue for future research (53). However, safety remains a paramount concern. Rituximab has been shown to elevate the risk of liver damage, although this finding was not statistically significant ($P>0.05$), aligning with the study by Bessone and Björnsson (54). This suggests a need for heightened vigilance regarding hepatic function in patients undergoing rituximab treatment. Clinicians should closely monitor hepatic function parameters, particularly the levels of transaminases, to detect any significant deviations early. In cases where liver injury is evident, the consideration of hepatoprotective therapies may become necessary (55). Similarly, leukopenia and neutropenia could potentially hinder the use of rituximab in patients with PCNSL, necessitating more individualized dosing regimens to mitigate these risks (56).

Of note, the present study had certain strengths. The study has updated the timeliness of the included literature by extending the publication date of the included studies to May 2025. Additionally, it has incorporated indicators of ADRs and conducted a systematic review on the safety of rituximab in patients with PCNSL. Methodological rigor was enhanced using validated tools for RoB assessment (Cochrane RoB and NOS), formal heterogeneity quantification (I^2 test), sensitivity analyses and publication bias testing (Egger's and Begg's tests).

However, several inherent limitations must be acknowledged. Firstly, the rarity of PCNSL and the prohibitive cost of rituximab present significant barriers to conducting large-scale RCTs. Consequently, the limited sample size across studies may impact on the precision of the current findings. Secondly, the presence of heterogeneity in certain outcome measures introduces uncertainty, even after conducting sensitivity analyses to assess the robustness of the results. Additionally, the scope of this paper is confined to the treatment of PCNSL with rituximab and does not encompass data pertaining to SCNSL. Therefore, there is

a clear necessity for future research to broaden the scope of included studies to encompass a wider range of CNSL treatments. Given fewer than 10 studies for OS and PFS, unpublished negative trials may overestimate rituximab's survival benefit and reduce bias detection power. Subtle small-study effects may remain undetected. Missing negative trials may involve underrepresented subgroups, which could overstate the generalizability of the present findings. Large multicenter RCTs are required for validation. Lastly, the ethnic composition of the treated population is largely limited to Asians and Caucasians, highlighting the need for RCTs involving patients with PCNSL in Africa to explore the relationship between ethnicity and rituximab efficacy.

In conclusion, the aggregate findings of the present meta-analysis, encompassing a cohort of 1,388 patients diagnosed with PCNSL, underscore the beneficial role of rituximab when integrated into first-line therapeutic regimens. Rituximab significantly improved 3-year OS (OR=2.01), 3-year PFS (OR=2.3) and CR rate (OR=2.04), with no significant increase in grade ≥ 3 adverse events. Rituximab benefited both ethnic subgroups, with greater efficacy in Asians (3-year OS OR, 2.62 vs. 1.69; 3-year PFS OR, 2.98 vs. 2.02). Consistent with the pharmacogenomic basis of its cytotoxicity in Asians, this supports a particular advantage in Asian patients despite a smaller subgroup and wider CIs. Despite moderate-to-substantial heterogeneity in survival outcomes, sensitivity analyses confirmed the robustness of these findings. Further large-scale, multi-ethnic RCTs are warranted to confirm the long-term efficacy and safety of rituximab in PCNSL, particularly in Asian and other underrepresented populations.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in this study may be requested from the corresponding author.

Authors' contributions

LS and WL conceived and designed the study. LS, WC and WL performed the systematic literature search and study selection. LS, WC, CL, DW and ZR extracted data from the included studies. WL, CL, DW and ZR assessed the risk of bias in the included studies and contributed to the interpretation of the pooled results. WC conducted formal statistical analysis. LS drafted the manuscript. WL, LS, QX, DW and WC critically revised the manuscript for important intellectual content. QX conceived and designed the study with LS and WL and provided critical input on the analytical strategy. LS, WL and DW confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

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.

References

- Ferreri AJM, Calimeri T, Cwynarski K, Dietrich J, Grommes C, Hoang-Xuan K, Hu LS, Illerhaus G, Nayak L, Ponzoni M and Batchelor TT: Primary central nervous system lymphoma. *Nat Rev Dis Primers* 9: 29, 2023.
- Soussain C, Choquet S, Blonski M, Leclercq D, Houillier C, Rezai K, Bijou F, Houot R, Boyle E, Gressin R, *et al*: Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. *Eur J Cancer* 117: 121-130, 2019.
- Schaff LR and Grommes C: Primary central nervous system lymphoma. *Blood* 140: 971-979, 2022.
- Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, Smith JR, Korfel A, Soussain C, DeAngelis LM, *et al*: Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol* 23: 5034-5043, 2005.
- de Koning ME, Hof JJ, Jansen C, Doorduijn JK, Bromberg JEC and van der Meulen M: Primary central nervous system lymphoma. *J Neurol* 27: 2906-2913, 2024.
- Grommes C and DeAngelis LM: Primary CNS lymphoma. *J Clin Oncol* 35: 2410-2418, 2017.
- Langner-Lemerrier S, Houillier C, Soussain C, Ghesquière H, Chinot O, Taillandier L, Soubeyran P, Lamy T, Morschhauser F, Benouaich-Amiel A, *et al*: Primary CNS lymphoma at first relapse/progression: Characteristics, management, and outcome of 256 patients from the French LOC network. *Neuro Oncol* 18: 1297-1303, 2016.
- Rancea M, Will A, Borchmann P, Monsef I, Engert A and Skoetz N: Fifteenth biannual report of the Cochrane Haematological Malignancies Group-focus on non-Hodgkin's lymphoma. *J Natl Cancer Inst* 105: 1159-1170, 2013.
- Rubenstein JL, Combs D, Rosenberg J, Levy A, McDermott M, Damon L, Ignoffo R, Aldape K, Shen A, Lee D, *et al*: Rituximab therapy for CNS lymphomas: Targeting the leptomeningeal compartment. *Blood* 101: 466-468, 2003.
- van der Meulen M, Dirven L, Habets EJJ, Bakunina K, Smits M, Achterberg HC, Seute T, Cull G, Schouten H, Zijlstra JM, *et al*: Neurocognitive functioning and radiologic changes in primary CNS lymphoma patients: Results from the HOVON 105/ALLG NHL 24 randomized controlled trial. *Neuro Oncol* 23: 1315-1326, 2021.
- Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, Celico C, Falautano M, Nonis A, La Rosée P, Binder M, *et al*: Long-term efficacy, safety and neurotoxicity of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. *Leukemia* 36: 1870-1878, 2022.
- Therkelsen KE, Schaff LR, Nandakumar S, Omuro AMP, DeAngelis LM and Grommes C: Long-term outcomes in primary CNS lymphoma after R-MVP and High-dose chemotherapy with autologous hematopoietic stem cell transplant. *Neurology* 101: e710-e716, 2023.
- Hoang-Xuan K, Deckert M, Ferreri AJM, Furtner J, Gallego Perez-Larraya J, Henriksson R, Hottinger AF, Kasenda B, Lefranc F, Lossos A, *et al*: European Association of Neuro Oncology (EANO) guidelines for treatment of primary central nervous system lymphoma (PCNSL). *Neuro Oncol* 25: 37-53, 2023.
- Schmitt AM, Herbrand AK, Fox CP, Bakunina K, Bromberg JEC, Cwynarski K, Doorduijn JK, Ferreri AJM, Illerhaus G, Issa S, *et al*: Rituximab in primary central nervous system lymphoma-A systematic review and meta-analysis. *Hematol Oncol* 37: 548-557, 2019.
- Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D and Vohra S; PRISMA Harms Group: PRISMA harms checklist: Improving harms reporting in systematic reviews. *BMJ* 352: i157, 2016.
- Frandsen TF, Moos C, Marino C and Eriksen MB: Supplementary databases increased literature search coverage beyond PubMed and Embase. *J Clin Epidemiol* 181: 111704, 2025.
- Zhao S, Lu Z, Zhao F, Tang S, Zhang L and Feng C: Assessing the impact of probiotics on immunotherapy effectiveness and antibiotic-mediated resistance in cancer: A systematic review and meta-analysis. *Front Immunol* 16: 1538969, 2025.
- Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR: Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 8: 16, 2007.
- Dina S, Xu XP, Chen BB, Chen T, Li P, Ding TL, Ma L, Yuan Y, Lin ZG and Wang G: The therapeutic effect of high-dose methotrexate (HD-MTX) with rituximab in newly diagnosed primary central nervous system lymphoma (PCNSL). *Fudan Univ J Med Sci* 46: 14-22, 2019.
- Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, *et al*: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343: d5928, 2011.
- Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 25: 603-605, 2010.
- Debray TP, Damen JA, Snell KI, Ensor J, Hooft L, Reitsma JB, Riley RD and Moons KG: A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 356: i6460, 2017.
- Curry LD, Munker R, Li N, Yan D, Pryor P, Nozad S, Keller P, Monohan GP, Iragavarapu C and Krem MM: Performance status, comorbidities, and cycles of methotrexate exert the greatest influence on outcomes of primary and secondary CNS lymphomas: The Lexington experience. *Ann Hematol* 102: 141-154, 2023.
- Bergner N, Monsef I, Illerhaus G, Engert A and Skoetz N: Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL). *Cochrane Database Syst Rev* 11: CD009355, 2012.
- Wang CC, Carnevale J and Rubenstein JL: Progress in central nervous system lymphomas. *Br J Haematol* 166: 311-325, 2014.
- Barajas RF, Politi LS, Anzalone N, Schöder H, Fox CP, Boxerman JL, Kaufmann TJ, Quarles CC, Ellingson BM, Auer D, *et al*: Consensus recommendations for MRI and PET imaging of primary central nervous system lymphoma: Guideline statement from the International Primary CNS Lymphoma Collaborative Group (IPCG). *Neuro Oncol* 23: 1056-1071, 2021.
- Abla O, Weitzman S, Blay JY, O'Neill BP, Abrey LE, Neuwelt E, Doolittle ND, Baehring J, Pradhan K, Martin SE, *et al*: Primary CNS lymphoma in children and adolescents: a descriptive analysis from the International Primary CNS Lymphoma Collaborative Group (IPCG). *Clin Cancer Res* 17: 346-352, 2011.
- Bromberg JEC, Issa S, Bakunina K, Minnema MC, Seute T, Durian M, Cull G, Schouten HC, Stevens WBC, Zijlstra JM, *et al*: Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): A randomised, open-label, phase 3 inter-group study. *Lancet Oncol* 20: 216-228, 2019.
- Luo W, Ji LH, Geng H, Ma XJ, Xiong H, Yin QC, Yin YJ, Yu L and Ma J: Clinical therapeutic efficacy of rituximab combined with methotrexate on primary central nervous system lymphoma. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 24: 444-447, 2016 (In Chinese).
- Chen C, Sun P, Cui J, Yan S, Chen H, Xia Y, Bi X, Liu P, Wang Y, Yang H, *et al*: High-dose Methotrexate plus temozolomide with or without rituximab in patients with untreated primary central nervous system lymphoma: A retrospective study from China. *Cancer Med* 8: 1359-1367, 2019.
- Mou K, Gu WW, Gu CH and Qi JD: Curative efficacy of high dose MTX combined with rituxan for treatment primary CNS lymphoma. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 25: 1406-1409, 2017 (In Chinese).
- Sun X, Liu J, Wang Y, Bai X, Chen Y, Qian J, Zhu H, Liu F, Qiu X, Sun S, *et al*: Methotrexate-cytarabine-dexamethasone combination chemotherapy with or without rituximab in patients with primary central nervous system lymphoma. *Oncotarget* 8: 49156-49164, 2017.

33. Patekar M, Adhikari N, Biswas A, Raina V, Kumar L, Mohanti BK, Gogia A, Sharma A, Batra A, Bakhshi S, *et al*: Primary CNS Lymphoma in India: A 17-year experience from the all India institute of medical sciences. *J Global Oncol* 5: 1-9, 2019.
34. Pang DW, Chen FL, Guo HG, *et al*: Clinical Efficacy of High Dose Methotrexate, Temozolomide and Rituximab in the Treatment of Patients with Primary Central Nervous System Lymphoma. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 29: 1175-1180, 2021 (In Chinese).
35. Birnbaum T, Stadler EA, von Baumgarten L and Straube A: Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. *J Neuro Oncol* 109: 285-291, 2012.
36. Gregory G, Arumugawamy A, Leung T, Chan KL, Abikhair M, Tam C, Bajel A, Cher L, Grigg A, Ritchie D and Opat S: Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. *Neuro Oncol* 15: 1068-1073, 2013.
37. Houillier C, Ghesquière H, Chabrot C, Soussain C, Ahle G, Choquet S, Nicolas-Virelizier E, Bay JO, Vargaftig J, Gaultier C, *et al*: Rituximab, methotrexate, procarbazine, vincristine and intensified cytarabine consolidation for primary central nervous system lymphoma (PCNSL) in the elderly: A LOC network study. *J Neuro Oncol* 133: 315-320, 2017.
38. Kansara R, Shenkier TN, Connors JM, Sehn LH, Savage KJ, Gerrie AS and Villa D: Rituximab with high-dose methotrexate in primary central nervous system lymphoma. *Am J Hematol* 90: 1149-1154, 2015.
39. Holdhoff M, Ambady P, Abdelaziz A, Sarai G, Bonekamp D, Blakeley J, Grossman SA and Ye X: High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. *Neurology* 83: 235-239, 2014.
40. Mocikova H, Pytlík R, Sykorova A, Janikova A, Prochazka V, Vokurka S, Berkova A, Belada D, Campr V, Buresova L, *et al*: Role of rituximab in treatment of patients with primary central nervous system lymphoma: A retrospective analysis of the Czech lymphoma study group registry. *Leuk Lymphoma* 57: 2777-2783, 2016.
41. Hernández-Verdin I, Kirasic E, Wienand K, Mokhtari K, Eimer S, Loiseau H, Rousseau A, Paillasa J, Ahle G, Lerintiu F, *et al*: Molecular and clinical diversity in primary central nervous system lymphoma. *Ann Oncol* 34: 186-199, 2023.
42. Östrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the united states in 2009-2013. *Neuro Oncol* 18 (Suppl 5): v1-v75, 2016.
43. Mata-Molanes JJ, Rebollo-Liceaga J, Martínez-Navarro EM, Manzano RG, Brugarolas A, Juan M and Sureda M: Relevance of Fc gamma receptor polymorphisms in cancer therapy with monoclonal antibodies. *Front Oncol* 12: 926289, 2022.
44. Lee YH and Song GG: Association between functional FCGR3A F158V and FCGR2A R131H polymorphisms and responsiveness to rituximab in patients with autoimmune diseases: A meta-analysis. *Pharmacogenomics J* 23: 210-216, 2023.
45. Murphy KE, Niederer HA, King KS, Harris EC, Glass SM and Cox CJ: Accurate interrogation of FCGR3A rs396991 in European and Asian populations using a widely available TaqMan genotyping method. *Pharmacogenet Genomics* 25: 569-572, 2015.
46. Chen S, Chen H and Xu S: Population genomics insights into pharmacogenomic differentiation between east asians and europeans. *Clin Pharmacol Ther* 120: 510-519, 2026.
47. Pulido JS, Vierkant RA, Olson JE, Abrey L, Schiff D and O'Neill BP: Racial differences in primary central nervous system lymphoma incidence and survival rates. *Neuro Oncol* 11: 318-322, 2009.
48. Zhou X, Niu X, Li J, Zhang S, Yang W, Yang Y, Mao Q and Liu Y: Risk Factors for early mortality in patients with primary central nervous system lymphoma: A large-cohort retrospective study. *World Neurosurg* 138: e905-e912, 2020.
49. Fox CP, Phillips EH, Smith J, Linton K, Gallop-Evans E, Hemmaway C, Auer DP, Fuller C, Davies AJ, McKay P, *et al*: Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. *Br J Haematol* 184: 348-363, 2019.
50. Song Y, Wen Y, Xue W, Zhang Y and Zhang M: Effect of rituximab on primary central nervous system lymphoma: A meta-analysis. *Int J Hematol* 106: 612-621, 2017.
51. Zhang Y, Liu Z, Gao C, Bian H, Ma Y, Jing F and Zhao X: Role of rituximab in treatment of patients with primary central nervous system lymphoma (PCNSL): A systematic review and meta-analysis. *Clin Lymphoma Myeloma Leuk* 23: 733-741, 2023.
52. Miyakita Y, Ohno M, Takahashi M, Muragaki Y, Katai H and Narita Y: Immunochemotherapy using rituximab (RTX) and high-dose methotrexate (HD-MTX): An evaluation of the addition of RTX to HD-MTX in recurrent primary central nervous system lymphoma (PCNSL). *Jpn J Clin Oncol* 47: 919-924, 2017.
53. Cook MR, Dorris CS, Makambi KH, Luo Y, Munshi PN, Donato M, Rowley S, Saad A, Goy A, Dunleavy K and Ali A: Toxicity and efficacy of CAR T-cell therapy in primary and secondary CNS lymphoma: A meta-analysis of 128 patients. *Blood Adv* 7: 32-39, 2023.
54. Bessone F and Björnsson ES: Drug-induced liver injury due to biologics and immune check point inhibitors. *Med Clin North Am* 107: 623-640, 2023.
55. Reddy KR, Beavers KL, Hammond SP, Lim JK and Falck Ytter YT: American Gastroenterological Association Institute: American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 148: 215-219, 2015.
56. Athni TS and Barmettler S: Hypogammaglobulinemia, late-onset neutropenia, and infections following rituximab. *Ann Allergy Asthma Immunol* 130: 699-712, 2023.



Copyright © 2026 Sun et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.