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Pola-R-CHP versus R-CHOP in newly diagnosed diffuse large B-cell lymphoma: a systematic review of efficacy, safety, and patient selection

Moontasir Ahmed [1]*, Shadman Newaz [2], Jannat Ara Tina [1], Md Hasanuzzaman [3], Supritom Sarker [1], Mst Samanta Hoque [4], Maruf Mustakim Fahim [5], Afsana Tasnim [6], Faiyaz Saqif Khan [7]

[1] Tangail Medical College Hospital, Tangail, Bangladesh

[2] Tangail Medical College, Tangail, Bangladesh

[3] Chattogram Medical College Hospital, Chattogram, Bangladesh

[4] Rajshahi Medical College, Rajshahi, Bangladesh

[5] Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh

[6] Comilla Medical College Hospital, Comilla, Bangladesh

[7] Green life Medical College Hospital, Dhaka, Bangladesh

Abstract

Introduction: The combination of polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) has emerged as a potential frontline therapy for diffuse large B-cell lymphoma (DLBCL). This systematic review synthesizes the current evidence comparing the efficacy and safety of Pola-R-CHP versus the standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen.

Materials and methods: We systematically searched PubMed and Science Direct from inception to September, 2025 for studies reporting on Pola-R-CHP versus R-CHOP in previously untreated DLBCL. Data on study characteristics, efficacy outcomes, safety, and biomarker analyses were extracted. The risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials.

Results: 23 studies were included, comprising the pivotal phase 3 POLARIX trial, its subgroup and long-term follow-up analyses, real-world evidence, and biomarker studies. Pola-R-CHP demonstrated a consistent and significant improvement in progression-free survival (PFS) compared to R-CHOP (hazard ratio (HR) range: 0.64-0.77), with a 5.8% absolute PFS benefit at 5 years. Overall survival (OS) data showed a positive but non-significant trend (5-year HR: 0.85). The benefit was most pronounced in higher-risk patients, including those aged ≥70, with International Prognostic Index (IPI) scores 3-5, and those with activated B-cell (ABC) subtype DLBCL (PFS HR: 0.34). The safety profile was manageable but distinct, with a higher incidence of febrile neutropenia requiring granulocyte colony-stimulating factor (G-CSF) prophylaxis but fewer dose reductions. Patient-reported outcomes indicated no detriment in quality of life.

Conclusion: Pola-R-CHP represents a significant advance in the first-line treatment of DLBCL, offering a superior PFS benefit over R-CHOP with a manageable toxicity profile. Its use is most favorable in higher-risk and biologically defined patient subgroups. Future research should focus on long-term OS and validating predictive biomarkers for precision-based patient selection.

Keywords: Diffuse Large B-Cell Lymphoma, DLBCL, Polatuzumab Vedotin, R-CHOP, Pola-R-CHP, Systematic Review, Frontline Therapy

Corresponding Author: Moontasir Ahmed

✉ Email: moontasir22@gmail.com

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma worldwide (1, 7, 15). For over two decades, the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been the standard first-line therapy, curing approximately 60-70% of patients (3, 7). However, outcomes for patients with high-risk clinical or molecular features remain suboptimal, highlighting a critical unmet need (2, 9, 22). Polatuzumab vedotin is an antibody-drug conjugate (ADC) targeting CD79b, a component of the B-cell receptor, and delivering a potent microtubule inhibitor (26, 30). The substitution of vincristine in R-CHOP with polatuzumab vedotin creates the Pola-R-CHP regimen, designed to enhance efficacy by targeting a DLBCL-specific antigen and avoiding the dose-limiting neurotoxicity associated with vincristine (1, 26).

The phase 3 POLARIX trial was the first study in two decades to demonstrate a statistically significant improvement in progression-free survival (PFS) over R-CHOP in previously untreated DLBCL (1). This breakthrough came after numerous attempts to improve upon R-CHOP by adding novel agents like bortezomib, lenalidomide, or ibrutinib, which largely failed to show consistent benefit in unselected populations in phase 3 trials (24, 25, 28). Since its publication, numerous subgroup, biomarker, and real-world studies have been conducted to refine our understanding of which patients derive the most benefit from this new regimen (2, 3, 6, 7, 15).

This systematic review aims to provide a comprehensive synthesis of the global evidence for Pola-R-CHP versus R-CHOP, integrating data from the pivotal trial, subsequent analyses, and real-world evidence to offer a definitive overview of efficacy, safety, and optimal patient selection for clinicians and researchers.

Materials and methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Selection Criteria

A systematic search was performed in PubMed and Science Direct from database inception to September, 2025. The search strategy combined terms related to ("polatuzumab vedotin" OR "Pola-R-CHP") AND ("R-CHOP") AND ("diffuse large B-cell lymphoma" OR "DLBCL") AND ("first-line" OR "previously untreated").

Studies were included if they: (1) compared Pola-R-CHP to R-CHOP in adult patients with previously untreated DLBCL; (2) provided original data on efficacy, safety, or biomarker analysis; and (3) were published in English. Randomized controlled trials (RCTs), subgroup analyses of RCTs, and real-world observational studies were eligible.

Data Extraction and Quality Assessment

Two reviewers independently screened titles, abstracts, and full-text articles. Data were extracted using a standardized form, capturing information on study design, patient demographics, efficacy outcomes (PFS, OS, overall response rate (ORR), complete response rate (CRR)), safety outcomes, and biomarker data. The risk of bias for RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool.

Data Synthesis

Given the heterogeneity in study designs and reporting (e.g., RCTs vs. real-world evidence), a narrative synthesis was conducted. Data are presented in summary tables and descriptive text.

Results

Study Selection and Characteristics

The initial search yielded 476 records. After screening titles and abstracts, 29 full-text articles were assessed for eligibility. Ultimately, 23 studies were included in the final synthesis.

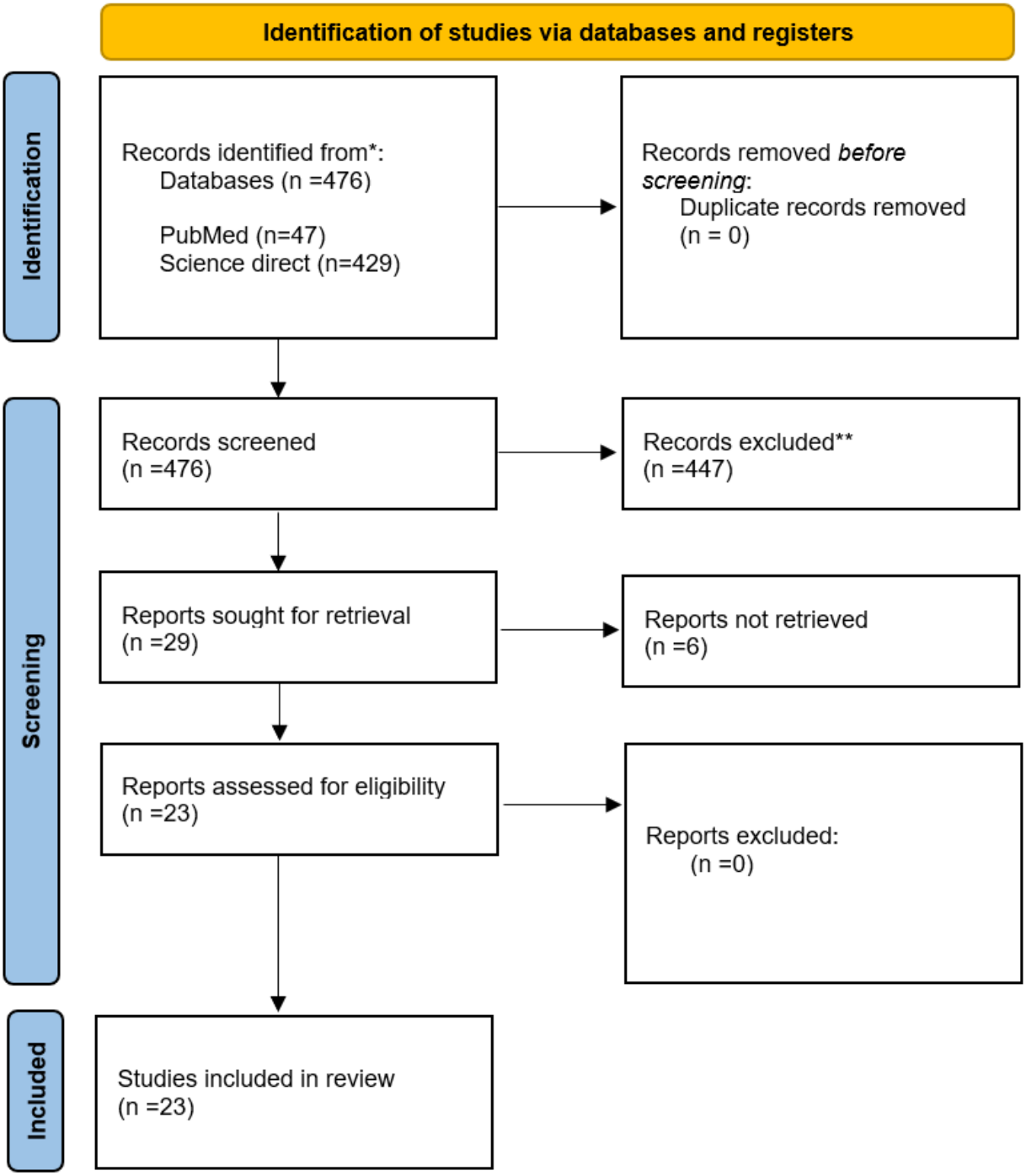


Figure 1. PRISMA 2020 flow diagram for the systematic review

Table 1 provides a clear overview of the evidence base, showing the global scope of the research and the various methodological approaches used to evaluate Pola-R-CHP versus R-CHOP.

Table 1. Study characteristics of included articles.

Study reference	Year	Study Design	Country / Region	Population / Sample Size (Pola-R-CHP vs R-CHOP)
Tilly H et al. (1)	2022	Phase 3 RCT (Randomized, Double-blind, Placebo-controlled)	International (Multinational)	Previously untreated DLBCL; N=879 (440 vs 439)
Song Y et al. (2)	2023	Subpopulation Analysis of Phase 3 RCT	Asia (Mainland China, Japan, Republic of Korea, Taiwan)	Asian subpopulation with previously untreated DLBCL; N=281 (141 vs 140)
Hu B et al. (3)	2025	Post hoc Subgroup Analysis of Phase 3 RCT	Multinational	Patients ≥60 years with untreated DLBCL; N=629 (311 vs 318)
Franck Morschhauser et al. (4)	2025	Phase 3 RCT (Long-Term Follow-up)	Multinational (22 countries)	Previously untreated DLBCL; Global N=879 (440 vs 439); Expanded N=1000 (500 vs 500)
Thompson C et al. (5)	2025	PRO Analysis of Phase 3 RCT	International (Multinational)	Previously untreated DLBCL; N=879 (440 vs 439)
Russler-Germain DA et al. (6)	2023	Letter/Commentary (on Phase 3 RCT data)	International	Previously untreated DLBCL; References POLARIX population N=879 (440 vs 439)
Peiqi Z et al. (7)	2024	Retrospective Cohort Study	China	Previously untreated DLBCL; Total N=600 (131 vs 469); After matching: 115 pairs
Salles G et al. (8)	2024	RCT (Follow-up Analysis)	Multinational (North America, Europe, Asia)	Previously untreated DLBCL; Global N=879 (440 vs 439); Expanded N=1000 (500 vs 500)
Friedberg JW et al. (9)	2022	Phase 3 RCT (PRO Analysis)	Multinational	Previously untreated DLBCL; N=879 (440 vs 439)
Flowers C et al. (10)	2022	Phase 3 RCT	Multinational	Previously untreated DLBCL; N=879 (440 vs 439)
Tilly H et al. (11)	2021	Phase 3 RCT	Multinational	Previously untreated DLBCL; N=879 (440 vs 439)
Song Y et al. (12)	2023	Subpopulation Analysis of Phase 3 RCT	Asia (Mainland China, Japan, Republic of Korea, Taiwan)	Asian subpopulation with previously untreated DLBCL; N=281 (141 vs 140)
Hotta M et al. (13)	2023	Retrospective Observational Study	Japan	Previously untreated DLBCL; N=130 (Pola-R-CHP: 30 vs Control: 100)
Boissard F et al. (14)	2022	Ad hoc Analysis of Phase 3 RCT	Multinational (6 countries)	Patients from POLARIX requiring 2L therapy; Pola-R-CHP n=78; R-CHOP n=109
Morschhauser F et al. (15)	2023	Post hoc Exploratory Analysis of Phase 3 RCT	Multinational (North America, Europe)	Patients from POLARIX with biomarker data; WES: N=594 (292 vs 302); GEP: N=665 (331 vs 334)
Shenmiao Yang et al. (16)	2024	Retrospective Matched Comparison Study	China (Beijing)	DLBCL with extranodal involvement; N=129 (41 vs 88)
Tmény M et al. (17)	2025	Phase 3 RCT (Descriptive Analysis)	Multinational	Previously untreated DLBCL; Safety Population N=873 (435 vs 438)
Herrera AF et al. (18)	2022	Prespecified Exploratory Analysis of Phase 3 RCT	Multinational	Patients from POLARIX with ctDNA data; N=618 (319 vs 299)
Jardin F et al. (19)	2023	Sub-analysis of Phase 3 RCT	Multinational	Patients from POLARIX with both WES and ctDNA data; N=443
Hu B et al. (20)	2025	Post hoc Subgroup Analysis of Phase 3 RCT	Multinational	Patients ≥60 years with untreated DLBCL; N=629 (311 vs 318)
Westin JR et al. (21)	2024	Phase 2 RCT (Ongoing)	United States (primarily)	Patients with LBCL and MRD post-first-line therapy; Planned N=240
Lugtenburg PJ,	2023	Review Article	The Netherlands	Overview of evidence; references

Mutsaers PGNJ (22)				POLARIX and other studies
Thompson C et al. (23)	2025	PRO Analysis of Phase 3 RCT	International (Multinational)	Previously untreated DLBCL; N=879 (440 vs 439)

Abbreviations: RCT: Randomized Controlled Trial; PRO: Patient-Reported Outcome; DLBCL: Diffuse Large B-Cell Lymphoma; WES: Whole Exome Sequencing; GEP: Gene Expression Profiling; MRD: Minimal Residual Disease; LBCL: Large B-Cell Lymphoma.

A taxonomy of the evidence base is provided in Table 2.

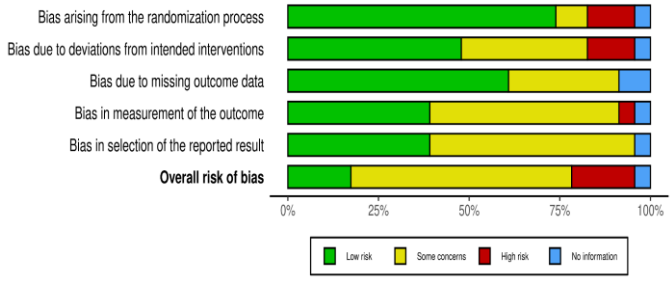
Table 2. Overview of included studies.

Study Category	Primary Focus	Representative References	Study Design
Pivotal RCT & Long-Term Follow-up	Primary efficacy & safety of Pola-R-CHP vs R-CHOP	Tilly et al. 2022 (1); Salles et al. 2024/25 (4)	Phase 3 Randomized Controlled Trial (RCT)
Regional & Subpopulation Analyses	Efficacy and safety in specific geographic or demographic groups	Song et al. 2023 (Asia) (2); Hu et al. 2025 (Older pts) (3)	Subgroup Analysis of RCT
Biomarker & Translational Studies	Role of molecular subtypes and ctDNA in predicting outcomes	Russler-Germain et al. 2023 (COO) (6); Herrera et al. 2022 (ctDNA) (18)	Exploratory Analysis of RCT
Real-World Evidence (RWE)	Effectiveness and safety in routine clinical practice	Peiqi Z et al. 2024 (7); Hotta M et al. 2023 (13)	Retrospective Cohort Study
Patient-Reported Outcomes (PROs)	Impact of treatment on patient quality of life and symptoms	Thompson et al. 2025 (5)	PRO Analysis of RCT
Reviews & Commentaries	Expert interpretation and contextualization of trial data	Lugtenburg et al. 2023 (22)	Review Article

This taxonomy of the included literature demonstrates the multi-faceted and mature nature of the evidence for Pola-R-CHP (1-23). The foundation is the high-quality, Phase 3 POLARIX RCT (1, 11), which provides the highest level of evidence for efficacy. The subsequent long-term follow-up studies (4, 8) are crucial, as they confirm the durability of the PFS benefit and provide more mature, albeit still not significant, OS data. The subpopulation and biomarker analyses (2, 3, 6, 12, 15, 18, 20) represent a critical evolution from a "one-size-fits-all" approach to precision medicine, identifying which patients are most likely to benefit. The Real-World Evidence (RWE) studies (7, 13, 16) act as a vital validation bridge, demonstrating that the efficacy observed in a controlled trial translates to heterogeneous, unselected patient populations in clinical practice, where comorbidities and management practices may differ. The inclusion of PROs (5, 9, 23) elevates the assessment beyond traditional efficacy endpoints, addressing the patient's experience and quality of life, which are paramount in modern oncology. Finally, review articles and commentaries (22) provide expert synthesis and highlight ongoing debates, such as the clinical interpretation of a PFS benefit without a clear OS advantage. This comprehensive evidence base, spanning from rigorous RCTs to practical RWE, allows for a robust and nuanced evaluation of Pola-R-CHP's role in the DLBCL treatment landscape.

3.2. Risk of Bias Assessment

The methodological quality of the included randomized studies was assessed using the Cochrane RoB 2 tool. The overall risk of bias was low for the pivotal RCT. Common limitations in other study types included their exploratory, post-hoc, or retrospective nature.



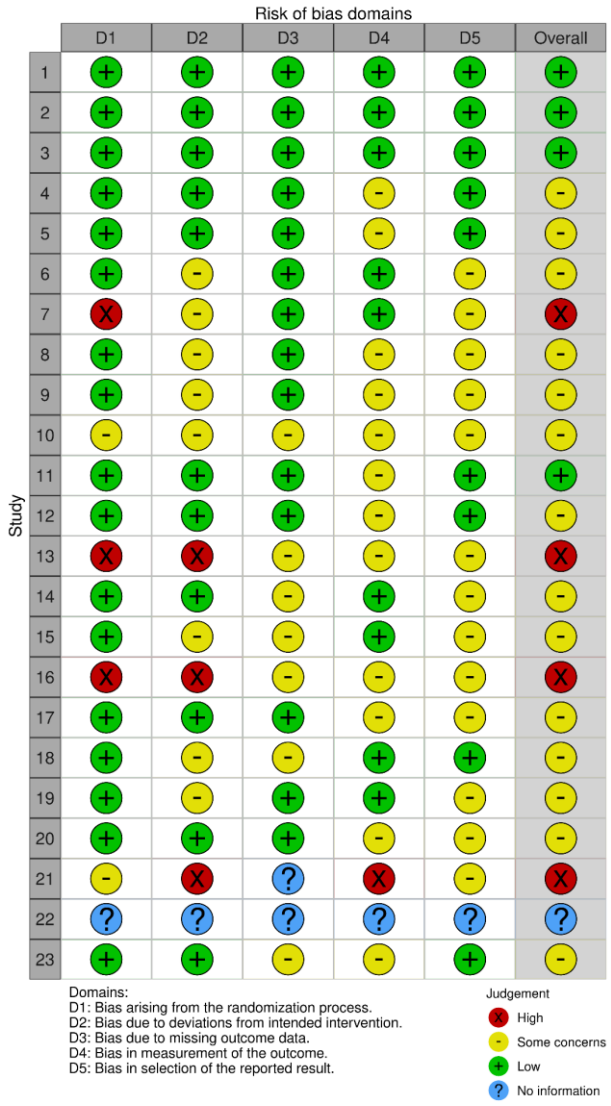


Figure 2. a shows the proportion of studies assessed for various domains of bias, including: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each domain is color-coded to represent the assessed level of bias: Low risk (green), Unclear risk (yellow), High risk (red), Critical risk (dark red), and No information (blue). Figure 2b provides a study-wise breakdown of risk of bias assessments, allowing a granular comparison across individual studies.

Key Efficacy Outcomes

The core efficacy data from the POLARIX trial and its follow-ups are summarized in Table 3.

The data in this table form the core efficacy argument for Pola-R-CHP (1, 4, 8). The consistent PFS hazard ratios (HRs) significantly below 1.0 across time and populations indicate a robust and sustained reduction in the risk of disease progression, relapse, or death (1, 2, 4, 8). The 2-year PFS absolute improvement of 6.5% (76.7% vs 70.2%) consolidates into a 5.8% absolute improvement at 5 years (64.9% vs 59.1%), demonstrating that the benefit is not only statistically significant but also clinically meaningful and durable (4, 8). The trend in the OS HR moving from 0.94 at 2 years to 0.85 at 5 years is noteworthy (1, 4, 8). While still not statistically significant, this positive drift suggests that preventing progression early may be translating into a longer-term survival advantage. This is further supported by data (14) showing a 37.8% reduction in the use of subsequent therapies in the Pola-R-CHP arm, implying that patients who avoid relapse are spared the toxicity and potentially lower efficacy of salvage regimens. The numerically higher ORR and CRR across all analyses, particularly in the Asia subpopulation (2, 12), reinforce the enhanced anti-tumor activity of the polatuzumab vedotin-containing regimen. The Asia-specific data, while not statistically powered, show a notably strong trend (HR 0.64), potentially reflecting the different biological distribution of DLBCL subtypes in that region.

Table 3. Key efficacy outcomes from the POLARIX trial and follow-ups.

Study Reference (Year)	Population	PFS HR (95% CI)	OS HR (95% CI)	ORR (%) (Pola / R-CHOP)	CRR (%) (Pola / R-CHOP)
Tilly et al. (2022) (1)	Global (2-yr)	0.73 (0.57-0.95)	0.94 (0.65-1.37)	85.5 / 83.8	78.0 / 74.0
Salles et al. (2024/25) (4)	Global (5-yr)	0.77 (0.62-0.97)	0.85 (0.63-1.15)	NR	NR
Song et al. (2023) (2)	Asia (2-yr)	0.64 (0.40-1.03)	0.64 (0.29-1.42)	90.1 / 81.4	82.3 / 77.9

Safety and Tolerability Profile

The safety profile of Pola-R-CHP was manageable but distinct from R-CHOP.

The safety profile comparison reveals a nuanced but important shift in toxicity management (1, 6, 17). The most critical finding is the distinct toxicity signature.

Pola-R-CHP exchanges the cumulative, often dose-limiting, neurotoxicity of vincristine for the more acute, but manageable, hematological toxicity of polatuzumab vedotin. This is evidenced by the significantly higher rate of febrile neutropenia (14.3% vs 8.0%) but a markedly lower rate of dose reductions (9.2% vs 13.0%) (1, 6). This suggests that while Pola-R-CHP requires more vigilant supportive care (specifically, mandatory G-CSF prophylaxis), it is less likely to require dose modifications due to chronic toxicities, potentially allowing for more consistent drug exposure. The similar rates of high-grade peripheral neuropathy and treatment discontinuation are reassuring, indicating that neither regimen is overwhelmingly more toxic than the other (1, 17). The comparable treatment-related mortality underscores that the increased febrile neutropenia does not translate into a higher death rate, likely due to effective modern supportive care (1). In summary, the safety profile of Pola-R-CHP is not "better" but "different," and its successful administration requires a proactive management strategy focused on preventing and managing myelosuppression.

The overall incidence of Grade ≥3 adverse events was comparable between arms (~60%). However, Pola-R-CHP was associated with a higher rate of febrile neutropenia (14.3% vs. 8.0%), necessitating G-CSF prophylaxis (6). A key differentiating factor was the lower rate of dose reductions with Pola-R-CHP (9.2% vs. 13.0%), attributed to the avoidance of cumulative vincristine-induced neurotoxicity (1). Rates of treatment discontinuation and treatment-related mortality were similar between the two regimens (1) (Table 4).

Table 4. Key safety and tolerability profile (pivotal trial).

Safety Parameter	Pola-R-CHP (n=435)	R-CHOP (n=438)	Clinical Implication
Grade ≥3 Adverse Events	264 (60.7%)	262 (59.8%)	Comparable overall toxicity burden
Febrile Neutropenia	14.3% (6)	8.0% (6)	Higher with Pola; mandates G-CSF prophylaxis
Peripheral Neuropathy (All Grades)	230 (52.9%)	236 (53.9%)	Similar overall incidence
Peripheral Neuropathy (Grade ≥3)	7 (1.6%)	5 (1.1%)	Low rate of severe events in both arms
Dose Reduction (due to AE)	40 (9.2%)	57 (13.0%)	Fewer dose reductions with Pola-R-CHP
Treatment Discontinuation (due to AE)	6.2%	6.6%	Comparable treatment delivery
Treatment-Related Mortality	13 (3.0%)	10 (2.3%)	No significant difference

Efficacy in Key Demographic and Clinical Subgroups

Subgroup analyses revealed that the PFS benefit was not uniform across all patient types.

This subgroup analysis is pivotal for defining the target population for Pola-R-CHP (1, 3, 20). The data compellingly show that the benefit is concentrated in patients with higher-risk disease features. The striking efficacy in patients aged 70 and older (HR 0.63) is clinically highly significant (3, 20). This population often has reduced tolerance for aggressive chemotherapy and poorer outcomes with R-CHOP. Pola-R-CHP appears to offer a more effective and manageable option for these vulnerable patients. Similarly, the consistent benefit in the IPI 3-5 subgroup addresses a major unmet need in DLBCL, where outcomes with R-CHOP remain suboptimal (1). The lack of a clear benefit in low-risk (IPI 0-2) patients and those with bulky disease suggests that for these groups, the incremental benefit may not justify the increased cost and specific toxicity profile (e.g., febrile neutropenia) of Pola-R-CHP over R-CHOP (1). This risk-adapted interpretation is essential for cost-effective and personalized healthcare, arguing for the use of Pola-R-CHP not as a universal replacement for R-CHOP, but as a superior frontline option for well-defined, higher-risk subgroups.

The magnitude of benefit was strongest in higher-risk subgroups, including patients aged 70 years and older (HR: 0.63, 95% CI: 0.41-0.96) (3, 20) and those with IPI scores of 3-5 (1). In contrast, patients with low-risk

disease (IPI 0-2) or bulky disease derived minimal benefit (1) (Table 5).

Table 5. Efficacy in key demographic and clinical subgroups.

Subgroup	Study Reference	PFS Hazard Ratio (95% CI)	Magnitude of Benefit
Age ≥60 years	Hu et al. 2025 (3)	0.76 (0.57-1.01)	Moderate to Strong
Age ≥70 years	Hu et al. 2025 (3)	0.63 (0.41-0.96)	Strong
IPI Score 3-5	Tilly et al. 2022 (1)	Favors Pola-R-CHP	Strong
IPI Score 0-2	Tilly et al. 2022 (1)	Neutral	Minimal
Bulky Disease (≥7.5cm)	Tilly et al. 2022 (1)	Neutral	Minimal

Efficacy by Biological Subtypes

Biomarker analyses provided critical insights for precision medicine.

Table 6 represents the frontier of precision medicine in DLBCL (6, 15). The dramatic efficacy in the ABC subtype (HR 0.34) is biologically plausible (6). As an antibody-drug conjugate targeting CD79b, a component of the B-cell receptor (BCR), polatuzumab vedotin may have a dual mechanism of action in ABC-DLBCL: direct cytotoxicity via microtubule disruption and inhibition of chronic active BCR signaling, a key oncogenic driver in this subtype. This stands in stark contrast to the GCB subtype, where there is no benefit (HR 1.18) (6). This finding is critical and should strongly influence treatment decisions; using Pola-R-CHP in a GCB patient may expose them to unnecessary toxicity and cost without any efficacy gain. The benefit in more refined genetic subtypes like DZsig+ (HR 0.47) further sharpens our ability to identify "Pola-responsive" disease beyond the simpler ABC/GCB classification (15). These findings make a compelling argument for the mandatory implementation of cell-of-origin testing, and where available, broader molecular profiling, to guide the rational selection of first-line therapy in DLBCL.

A profound PFS benefit was observed in patients with the activated B-cell (ABC) subtype (HR: 0.34, 95% CI: 0.13-0.85) (6). Conversely, no benefit was observed in the germinal center B-cell (GCB) subtype (HR: 1.18, 95% CI: 0.75-1.84) (6). Significant benefit was also seen in other high-risk molecular subtypes, such as the DZsig+ genetic subgroup (HR: 0.47) (15).

Table 6. Efficacy by biological subtypes.

Biomarker / Subtype	Study Reference	PFS Hazard Ratio (95% CI) for Pola-R-CHP vs R-CHOP	Conclusion
Cell-of-Origin: ABC	Russler-Germain et al. 2023 (6)	0.34 (0.13-0.85)	Major Benefit
Cell-of-Origin: GCB	Russler-Germain et al. 2023 (6)	1.18 (0.75-1.84)	No Benefit / Potential Harm
Molecular: DZsig+	Morschhauser et al. 2023 (15)	0.47 (0.24-0.95)	Major Benefit
Molecular: EZB	Morschhauser et al. 2023 (15)	0.61 (0.33-1.13)	Trend towards Benefit
Double-Expressor Lymphoma	Salles et al. 2024/25 (4)	Favors Pola-R-CHP	Benefit

Real-World Evidence

Real-world studies from China and Japan confirmed the effectiveness and safety of Pola-R-CHP in routine clinical practice.

Real-world evidence is crucial for validating RCT results in "real-life" clinical settings (7, 13, 16). The RWE presented here largely confirms and, in some cases (like the Chinese study with HR 0.30), amplifies the efficacy signal from POLARIX (7). This could be due to various factors, including different patient mix, practice patterns, or the inherent limitations of retrospective studies. Importantly, these studies demonstrate that the safety profile holds up outside a controlled trial, with no new signals emerging and specific tolerability advantages (like low peripheral neuropathy) being confirmed (7, 13). The study by Shenmiao Yang et al., while showing a non-significant P-value, still demonstrates a strong numerical trend

favoring Pola-R-CHP, consistent with the overall body of evidence (16). The collective message from RWE is that Pola-R-CHP is not just an "ivory tower" regimen but is implementable, effective, and safe in diverse healthcare systems, thereby strengthening the case for its adoption into standard practice.

These studies reported PFS benefits consistent with or even greater than the pivotal trial, with no new safety signals, supporting the generalizability of the RCT findings (Table 7).

Table 7. Real-world evidence (RWE) outcomes.

Study Reference	Design (Sample Size)	Key Efficacy Finding (PFS)	Key Safety Finding
Peiqi Z et al. (2024)	Retrospective Matched Cohort (115 pairs)	HR: 0.30 (0.16-0.56); p=0.0002 12-mo PFS: 90.1% vs 68.1%	Well tolerated; no AE-related deaths
Hotta M et al. (2023)	Retrospective Cohort (Pola: 30, Control: 100)	6-mo PFS: 93.3% vs 80.0%; p=0.017	Low rate of Grade 3-4 PN (3.3%)
Shenmiao Yang et al. (2024)	Retrospective Matched (Pola: 41, R-CHOP: 88)	12-mo PFS: 92% vs 87% (p=0.311)	Not reported

Treatment Delivery and Dose Modifications

Treatment delivery metrics were favorable for Pola-R-CHP.

The high rates of treatment completion and low rates of discontinuation for both regimens confirm that both Pola-R-CHP and R-CHOP are feasible to administer in the frontline setting (1). The most telling comparison, however, is in the dose reduction rates. The statistically significant lower rate of dose reductions with Pola-R-CHP (9.2% vs 13.0%) is a direct reflection of its differentiated toxicity profile (1). Vincristine in R-CHOP often causes cumulative peripheral neuropathy, leading clinicians to reduce doses in subsequent cycles to prevent severe, long-lasting toxicity. Polatuzumab vedotin, while causing more hematological toxicity, does not cause this type of cumulative non-hematological toxicity, allowing for more consistent dosing. This ability to deliver the full planned dose intensity may be a contributing factor to its superior efficacy, particularly in achieving deeper responses (1, 20). The similar interruption rates are likely related to the management of acute, reversible events like neutropenia, which can be managed with growth factors and brief delays.

Over 90% of patients in both arms received all six planned cycles. The lower dose reduction rate with Pola-R-CHP, as noted in the safety analysis, suggests a potentially more consistent delivery of the intended drug intensity (1) (Table 8).

Table 8. Treatment delivery and dose modifications.

Parameter	Pola-R-CHP	R-CHOP	Interpretation
Received all 6 planned doses	91.7% (1)	88.5% (1)	High completion rate in both
Discontinued any drug due to AE	6.2% (1)	6.6% (1)	Comparable low discontinuation
Dose Reduction (Blinded Drug)	9.2% (1)	13.0% (1)	Fewer reductions with Pola
Dose Interruption (Blinded Drug)	18.6% (≥60 yrs) (20)	17.7% (≥60 yrs) (20)	Comparable interruption rates

Patient-Reported Outcomes and Quality of Life

Analysis of PROs from the POLARIX trial found no clinically meaningful difference in global health status/quality of life between Pola-R-CHP and R-CHOP over time. The PRO data from POLARIX are a critical component of the value proposition for Pola-R-CHP (5, 9, 23). They answer a fundamental question: does the significant PFS benefit come at the cost of a worse patient experience? The data resoundingly show that it does not (5, 23). The absence of a clinically meaningful difference in Global Health Status/QoL indicates that, from the patient's perspective, the experience of undergoing Pola-R-CHP is not perceived as more burdensome than that of R-CHOP. This is a powerful finding, as it dissociates improved efficacy from increased treatment burden. The high PRO completion rates lend considerable weight to this

conclusion (5). Furthermore, the observed discrepancies between PROs and clinician-reported AEs underscore that these are complementary tools; clinicians may under-report certain subjective symptoms, while patients provide a direct account of their experience (5, 23). This supports the integration of PROs as a standard endpoint in future oncology trials to fully capture the treatment's impact.

This indicates that the PFS benefit was achieved without a detrimental impact on the patient's quality of life (Table 9).

Table 9. Patient-reported outcomes (PROs) and quality of life.

PRO Domain	Findings from POLARIX (Thompson et al. 2025 (5))	Interpretation
Global Health Status / QoL	No clinically meaningful difference between arms over time	Pola-R-CHP provides a PFS benefit without compromising overall quality of life.
PRO Completion Rates	High (>90% during treatment, >80% during follow-up)	Data reliability is strong.
Comparison to Clinician AE Reporting	PROs provided complementary data; some symptomatic AEs (e.g., decreased appetite, constipation) were reported more frequently by clinicians.	Highlights the importance of collecting both PROs and clinician-reported outcomes.

The Role of Circulating Tumor DNA

Studies investigating ctDNA demonstrated its power as a prognostic and predictive tool.

The ctDNA analyses from POLARIX offer a glimpse into the future of lymphoma management (18, 19). ctDNA emerges as a dynamic, sensitive, and highly prognostic "liquid biopsy" tool. Its ability to identify high-risk patients independently of the IPI is a major advance, potentially allowing for the upfront intensification of therapy for the highest-risk group (18). Most importantly, the finding that early ctDNA clearance is a powerful predictor of outcome is paradigm-shifting (18). It suggests that molecular response can be assessed within the first few cycles of therapy, long before a mid-treatment PET-CT. This opens the door for response-adapted trials where patients with poor molecular response could be "switched" to alternative therapies earlier, while those with rapid clearance could be de-escalated. Finally, the ability to perform molecular classification from plasma could overcome the logistical and technical challenges of tumor biopsies, making precision medicine more accessible (19). While prospective validation is needed, ctDNA is poised to become a cornerstone of risk stratification and response monitoring in DLBCL.

High baseline ctDNA levels identified high-risk patients, and early ctDNA clearance (by cycles 1-3) was strongly associated with superior PFS and OS, suggesting its potential for dynamic risk adaptation and early response assessment (18) (Table 10).

Table 10. Role of circulating tumor DNA (ctDNA).

ctDNA Metric	Study Reference	Association with Outcome	Clinical Implication
High Baseline ctDNA	Herrera et al. 2022 (18)	Independent predictor of inferior PFS/OS	Identifies high-risk patients beyond IPI.
Early ctDNA Clearance (Cycle 1-3)	Herrera et al. 2022 (18)	Strongly associated with superior PFS/OS	Potential for early response-adapted therapy.
ctDNA for Molecular Classification	Jardin et al. 2023 (19)	High concordance with tissue genotyping	Plasma can be an alternative to tumor biopsy.

Summary of Limitations and Recommendations

A critical appraisal of the evidence base is provided in Table 11.

A critical appraisal of the evidence must acknowledge its limitations to provide a balanced conclusion (1, 3-8, 13, 15). The most significant limitation remains the lack of a statistically significant overall survival benefit, though the positive trend at 5 years is

encouraging (1, 4, 8). The subgroup and biomarker findings, while practice-informing, are hypothesis-generating due to their exploratory nature and require validation in prospective studies (3, 6, 15). The exclusion of certain patient populations (e.g., >80 years, transformed lymphoma) from POLARIX means the evidence in these groups is limited to real-world studies (7, 13). The RWE itself is constrained by its retrospective nature (7, 13). Despite these limitations, a clear consensus emerges. Pola-R-CHP represents a significant advance and a new standard of care for a defined subset of patients—specifically, those with intermediate- or high-risk disease, particularly with ABC biology or advanced age (1, 3, 6, 20). The recommendations emphasize a precision-based approach: using biomarkers to guide patient selection and implementing mandatory supportive care to manage the specific toxicity profile (1, 6). Future research should focus on validating biomarkers, exploring combinations, and assessing outcomes in the excluded populations.

Key limitations include the immature and non-significant OS data from the primary trial (1, 4, 8), the exploratory nature of the subgroup and biomarker analyses (3, 6, 15), and the inherent biases of real-world evidence (7, 13). Based on the synthesized evidence, Pola-R-CHP is recommended as a new standard of care for first-line treatment of intermediate- and high-risk DLBCL, particularly for patients with ABC subtype, age ≥70, or IPI 3-5 (1, 3, 6, 20). Mandatory G-CSF prophylaxis is advised (1, 6).

Table 11. Summary of limitations and recommendations across studies.

Study Type	Common Limitations	Common Recommendations
Pivotal RCT (POLARIX)	- Immature OS data - Not powered for subgroup analyses - Excluded transformed lymphoma, PMBL, >80 years	Pola-R-CHP is a new, effective, and well-tolerated first-line option for intermediate/high-risk DLBCL.
Subgroup & Biomarker Analyses	- Post-hoc, exploratory nature - Small sample sizes in subgroups - Requires prospective validation	Use is most favorable in ABC, DZsig+, older (≥70), and high-risk (IPI 3-5) patients. Mandate G-CSF prophylaxis.
Real-World Evidence	- Retrospective design - Potential selection bias - Short follow-up	Confirms real-world effectiveness and safety, supporting use in clinical practice.
PRO Studies	- PROs not collected after progression - Lack of specific PRO instruments (e.g., for fatigue)	Incorporate PROs and standardize their measurement in future clinical trials.

Discussion

Summary of Evidence

This systematic review of 23 studies (1-23) establishes Pola-R-CHP as a superior frontline regimen to R-CHOP for a defined subset of patients with DLBCL. The regimen provides a statistically significant and clinically meaningful improvement in PFS, a benefit that is sustained over 5 years of follow-up (1, 4, 8). The safety profile is distinct and manageable, requiring a shift in supportive care focus towards hematological toxicity management (1, 6). Crucially, this efficacy benefit does not come at the cost of reduced patient quality of life (5, 23).

Interpretation in the Context of Existing Literature

The findings of this review consolidate the paradigm shift in first-line DLBCL treatment initiated by the POLARIX trial (1). The consistent PFS benefit across multiple analyses, including real-world settings (7, 13, 16), provides robust confirmation of Pola-R-CHP's efficacy. The most impactful finding is the identification of patient subgroups that derive the greatest benefit, moving towards a precision-based approach (3, 6, 15, 20). The dramatic efficacy in the ABC subtype is biologically plausible, as polatuzumab vedotin's target, CD79b, is part of the chronically active B-cell receptor signaling pathway that drives this DLBCL subtype (6).

The lack of a significant OS benefit remains a point of discussion (1, 4, 8). However, the positive trend at 5 years and the significant reduction in the use of subsequent therapies in the Pola-R-CHP arm (4, 14) suggest that a survival advantage may emerge with longer follow-up.

Limitations

This review has limitations. The evidence is anchored by a single, albeit large and well-conducted, phase 3 trial (1). The subgroup and biomarker findings, while practice-informing, are largely exploratory and require prospective validation (3, 6, 15). The generalizability to certain populations excluded from POLARIX (e.g., patients over 80, those with transformed lymphoma) relies on more limited real-world data (7, 13).

Clinical Implications

The findings from this review have immediate implications for clinical practice:

1. Patient Selection: Pola-R-CHP should be strongly considered as the preferred first-line regimen for patients with untreated DLBCL who have high-risk features, particularly those with an ABC subtype (mandating cell-of-origin testing) (6), age ≥70 (3, 20), or IPI score 3-5 (1).

2. Toxicity Management: Proactive management, including mandatory G-CSF prophylaxis, is essential to mitigate the increased risk of febrile neutropenia (1, 6).

3. Precision Medicine: The integration of biomarker testing (cell-of-origin, potentially ctDNA) is now critical for optimizing first-line therapy choice in DLBCL (6, 18, 19).

Future Research: Efforts should focus on validating predictive biomarkers, exploring combinations in high-risk molecular groups, and collecting long-term outcomes in real-world populations.

Conclusion

ThisPola-R-CHP represents the most significant advance in the first-line treatment of DLBCL since the introduction of R-CHOP over two decades ago. It offers a superior progression-free survival benefit over R-CHOP, with a manageable and distinct toxicity profile. The evidence supports its use as a new standard of care, particularly for patients with higher-risk clinical or biological disease features. A precision medicine approach, guided by clinical risk factors and molecular subtypes, is essential to maximize the benefit of this novel therapy.

Author contribution

MA developed the methodology and wrote the methodology section. MA also conducted data extraction using a predesigned Excel spreadsheet, capturing key study details. Additionally, MA oversaw the entire review process and coordinated the writing of the manuscript. **SN** independently verified 50% of the extracted data to ensure accuracy and consistency. SN also wrote the results section, contributed to the final review of the manuscript, played a role in developing the study design, and assisted in refining the methodology section. **JT** contributed to refining the search strategy, participated in the full-text review process, and assisted in synthesizing the extracted data. JT also built the tables and diagrams for the manuscript and helped review the methodology section. **MH** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. MH also conducted the full-text review for studies meeting the inclusion criteria and wrote the discussion section. **SS** independently verified 50% of the extracted data alongside SN to enhance data accuracy. SS also contributed to refining the study methodology and participated in manuscript revisions. **MF** wrote the introduction section and assisted in optimizing the search strategy. MF also played a role in screening fulltext articles and contributed to drafting and reviewing the discussion section. **MSH** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. MSH also wrote the conclusion section and participated in discussions regarding study inclusion and exclusion criteria. **AT** contributed to writing the discussion section and provided critical revisions to improve clarity and coherence. AT also participated in reviewing the final manuscript to ensure consistency and accuracy. **FK** played a role in the quality assessment of included studies and assisted in synthesizing the extracted data. FK also contributed to reviewing the discussion and conclusion sections to ensure alignment with the study objectives. All authors contributed to the conception and design of the study,

provided input on data interpretation, and participated in manuscript revisions. All authors approved the final version before submission.

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