

Original Article

A study comparing the efficacy of R-CHOP and R-DA-EPOCH regimens in young, high-risk treatment-naïve diffuse large B-cell lymphoma patients: a multicenter retrospective analysis

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Abstract: Background: Patients with high-risk diffuse large B-cell lymphoma (DLBCL) have poor prognoses, and the comparative efficacy between R-CHOP and R-DA-EPOCH regimens remains controversial. Objective: To compare the efficacy and safety of R-CHOP and R-DA-EPOCH regimens in young, treatment-naïve patients with high-risk DLBCL. Methods: This multicenter retrospective cohort study included 148 young, treatment-naïve, high-risk DLBCL patients treated at five tertiary hospitals between March 2023 and March 2025. Patients were divided into the R-CHOP group (n=98) and the R-DA-EPOCH group (n=50). Baseline characteristics, treatment responses, treatment completion, dose intensity, adverse events, and supportive care information were collected. Intergroup comparisons were performed using the Mann-Whitney U test, chi-square test, or Fisher's exact test. Results: Baseline characteristics were generally balanced between the two groups, except for a significantly higher proportion of ECOG score 1 in the R-DA-EPOCH group (76.0% vs. 50.0%, P=0.007); subsequent multivariate analysis was used to adjust for this difference. The complete response (CR) rate was 46.0% in the R-DA-EPOCH group versus 36.7% in the R-CHOP group, but the difference was not statistically significant (P=0.313); the objective response rates were 58.0% and 61.2%, respectively (P=0.313). Subgroup analysis showed higher CR rates with R-DA-EPOCH in most subgroups, though none reached statistical significance. The relative dose intensity was significantly lower in the R-DA-EPOCH group compared to the R-CHOP group ($\$0.84 \pm 0.06$ vs. $\$0.92 \pm 0.04$, P<0.001), with significantly higher rates of dose reduction (52.0% vs. 18.4%, P<0.001) and treatment delay (46.0% vs. 18.4%, P=0.001). The R-DA-EPOCH group had significantly higher usage rates of G-CSF (50.0% vs. 31.6%, P=0.033), platelet transfusions (28.0% vs. 8.2%, P=0.003), and a longer median length of hospital stay (7.1 days vs. 4.9 days, P<0.001). Baseline LDH levels showed no significant correlation with treatment response (P=0.561). Conclusion: Compared with R-CHOP, the R-DA-EPOCH regimen showed a trend toward higher CR rates in young, treatment-naïve, high-risk DLBCL patients, but this did not reach statistical significance. Moreover, R-DA-EPOCH was associated with significantly increased hematological toxicity and supportive care burden. Clinicians should carefully weigh the potential benefits against the risks when selecting this regimen.

Keywords: Diffuse large B-cell lymphoma, R-CHOP, R-DA-EPOCH, young adult, high-risk

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma subtype in adults [1, 2]. It accounts for approximately 30%-40% of non-Hodgkin lymphomas in Western countries and an even higher proportion, reaching 40%-50%, in China and other Asian

nations [3-5]. This disease exhibits significant clinical and biological heterogeneity, manifesting in diverse morphologies, immunophenotypes, genetic alterations, and treatment responses [6, 7].

Despite the advent of rituximab, where the R-CHOP regimen (rituximab, cyclophosphami-

de, doxorubicin, vincristine, and prednisone) has become the standard first-line therapy, approximately 30%-40% of patients eventually develop refractory disease or relapse. The majority of these patients face a dismal prognosis, with long-term survival rates below 30% [8, 9].

Prognosis in DLBCL is influenced by multiple factors. The International Prognostic Index (IPI) and its revised version, the NCCN-IPI, are the most widely used clinical tools for risk stratification. According to IPI scoring, high-risk patients (IPI ≥ 3) have a 5-year progression-free survival (PFS) rate of only 40%-50%, significantly lower than the 70%-80% observed in low-risk patients. The NCCN-IPI further refines the weighting of age and LDH levels, allowing for more precise identification of high-risk cohorts. Patients with an NCCN-IPI score ≥ 4 are classified as high-risk and exhibit a 5-year overall survival (OS) rate of less than 50% [5, 10, 11].

Furthermore, molecular markers identified in recent years—such as double-expression (immunohistochemical positivity $\geq 40\%$ for MYC and $\geq 50\%$ for BCL2) and genetic rearrangements of MYC, BCL2, and/or BCL6 (“double-hit” or “triple-hit” lymphomas)—are closely associated with poor outcomes following R-CHOP therapy [12, 13]. The presence of these high-risk features suggests that the intensity of the conventional R-CHOP regimen may be insufficient, necessitating the exploration of more effective initial therapeutic strategies [14].

For high-risk DLBCL patients, intensified chemotherapy or novel drug delivery approaches are highly anticipated. Among these, the R-DA-EPOCH regimen (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) holds theoretical promise. By employing a 96-hour continuous infusion and individualized dose adjustment based on the nadir blood counts from the preceding cycle, this regimen aims to overcome tumor cell resistance, increase drug exposure, and enhance efficacy. Based on pharmacokinetic principles, continuous infusion allows the drug to act on tumor cells for a prolonged duration, offering potential advantages against highly proliferative aggressive lymphomas [15].

Early single-arm studies demonstrated that R-DA-EPOCH achieved overall response rates exceeding 80% and long-term event-free sur-

vival (EFS) rates of 60%-70% in treatment-naïve DLBCL. However, subsequent randomized controlled trials have not consistently confirmed its superiority over R-CHOP. The US CALGB 50303 study, which enrolled 524 treatment-naïve DLBCL patients randomized to receive either R-CHOP or R-DA-EPOCH, showed no significant differences in progression-free survival or overall survival between the two groups. Intriguingly, a subgroup analysis suggested a trend toward improved survival with R-DA-EPOCH in patients with an IPI ≥ 3 (HR=0.81, P=0.18), indicating that high-risk populations might derive benefit from intensified therapy. Moreover, a real-world study from the UK involving 185 high-risk DLBCL patients found that the R-DA-EPOCH regimen significantly improved EFS in the “double-hit” lymphoma subgroup [16].

Notably, existing data are predominantly derived from Western populations, and most studies have not specifically analyzed young (age ≤ 60 years) high-risk patients. Younger patients generally tolerate chemotherapy better, with a relatively lower risk of severe adverse events following intensified regimens, theoretically allowing for a greater net clinical benefit. However, real-world data regarding the R-DA-EPOCH regimen in young, treatment-naïve, high-risk DLBCL patients in China remain extremely limited, warranting further validation of its efficacy and safety [17, 18].

Based on the aforementioned context, this multicenter retrospective cohort study systematically compares the short-term efficacy, treatment completion rates, and safety of R-CHOP versus R-DA-EPOCH in young, treatment-naïve, high-risk DLBCL patients. We also explore differences in treatment response across molecular subtypes to provide real-world evidence for clinical, individualized treatment decision-making.

Materials and methods

Study design and ethics

This study is a multicenter retrospective cohort study designed to compare the efficacy and safety of the R-CHOP and R-DA-EPOCH regimens in young, treatment-naïve, high-risk patients with diffuse large B-cell lymphoma (DLBCL). This study was approved by the Ethics Committee of Lishui Municipal Central Hospital. All

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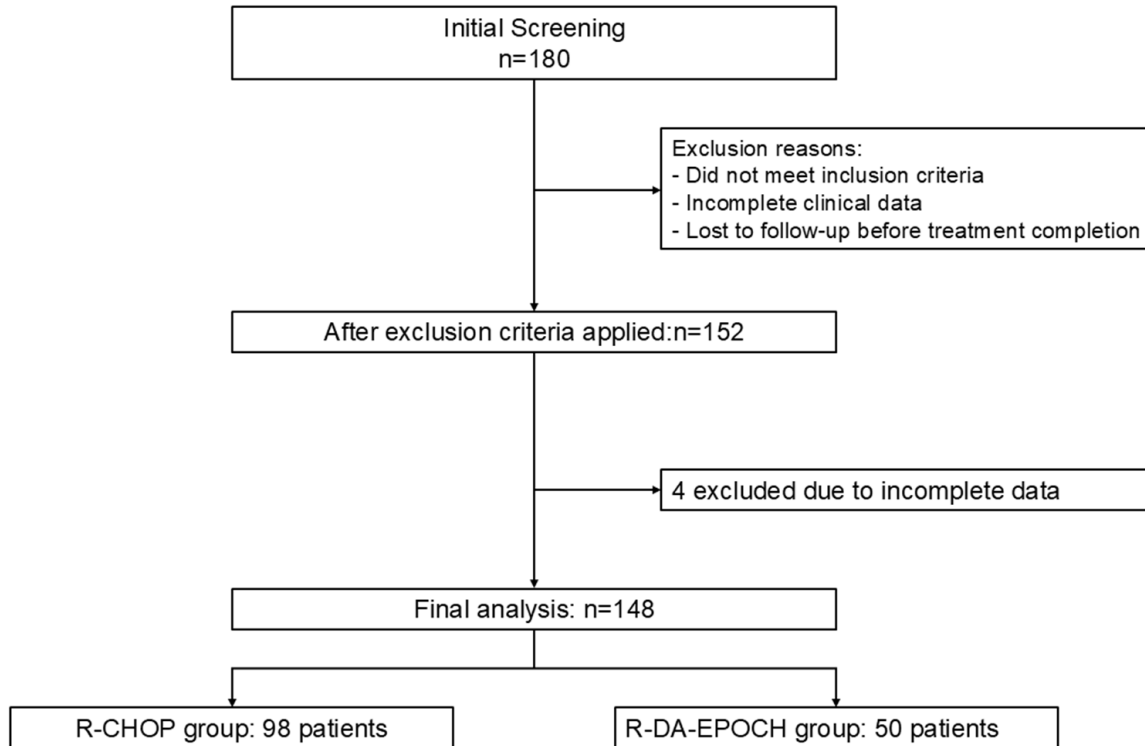


Figure 1. Flowchart of patient selection. Abbreviation: DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab.

procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

Consecutive patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) treated between March 2023 and March 2025 across the hematology departments of five tertiary hospitals were enrolled. Patients were eligible for inclusion if they met all of the following criteria: (1) Age ≥ 18 years with histopathologically confirmed CD20-positive diffuse large B-cell lymphoma (DLBCL); (2) Presence of high-risk features, defined as an International Prognostic Index (IPI) score ≥ 3 or a NCCN-IPI score ≥ 4 ; (3) Receipt of at least two cycles of first-line chemotherapy with either the R-CHOP or R-DA-EPOCH regimen; and (4) Availability of complete baseline data and at least one post-treatment radiological assessment. Exclusion criteria were: (1) Primary central nervous system lymphoma or other lymphoma subtypes (e.g., transformed follicular lymphoma, Burkitt lymphoma);

(2) Prior anti-tumor treatment (including radiotherapy, chemotherapy, targeted therapy, or immunotherapy); (3) Concomitant active malignancies; (4) Pregnancy or lactation; (5) Severe cardiac, hepatic, or renal insufficiency, or active infection; and (6) HIV infection or active hepatitis B/C (Figure 1).

Treatment regimens

The R-CHOP regimen consisted of rituximab 375 mg/m² on day 0, cyclophosphamide 750 mg/m² on day 1, doxorubicin 50 mg/m² on day 1, vincristine 1.4 mg/m² (maximum dose 2 mg) on day 1, and prednisone 100 mg daily on days 1-5, administered every 21 days. The R-DA-EPOCH regimen consisted of rituximab 375 mg/m² on day 1, etoposide 50 mg/m²/day on days 1-4, prednisone 60 mg/m²/day on days 1-5, vincristine 0.4 mg/m²/day (maximum dose 2 mg) on days 1-4, cyclophosphamide 750 mg/m² on day 5, and doxorubicin 10 mg/m²/day on days 1-4, also administered every 21 days with dose adjustments based on the absolute neutrophil count nadir. R-DA-EPOCH regimen was

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dose-adjusted according to the neutrophil nadir of the previous cycle as follows: if nadir $<0.5 \times 10^9/L$, the doses of etoposide, cyclophosphamide, and doxorubicin were reduced by 20% for the next cycle; if nadir $\geq 0.5 \times 10^9/L$, doses were maintained or escalated by 20% as per the original protocol (Wilson et al., JCO 2008).

Vincristine was capped at a maximum dose of 2 mg per cycle, applied to all patients regardless of body surface area, consistent with clinical routine to avoid neurotoxicity.

All patients were scheduled to complete 6 cycles, although this could be adjusted based on therapeutic response and tolerability. Supportive care, including antiemetics and hepatoprotection, was administered routinely. The use of G-CSF and blood product transfusions followed the clinical guidelines of each participating center.

Data collection and evaluation endpoints

Baseline characteristics: Data were retrospectively collected via electronic medical records, including: Demographics: Age, sex, ECOG (Eastern Cooperative Oncology Group) performance status.

Disease characteristics: Ann Arbor stage, B symptoms, number of extranodal sites, serum lactate dehydrogenase (LDH) level (expressed as the ratio of measured value to the upper limit of normal), maximum diameter of bulky disease (≥ 7.5 cm).

Prognostic scores: IPI and NCCN-IPI scores.

Molecular pathology: Cell of origin (Hans classifier), MYC/BCL2 double-expression (immunohistochemistry $\geq 40\%$ and $\geq 50\%$, respectively), and MYC/BCL2/BCL6 rearrangements (detected by FISH).

Treatment and response evaluation: Treatment details: Number of cycles completed, dose reductions, treatment delays, and treatment completion status (defined as “completed” if $\geq 90\%$ of planned cycles were administered).

Response criteria: The best overall response at mid-treatment and end-of-treatment was evaluated using the Lugano 2014 criteria, including complete response (CR), partial response (PR),

stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR or PR.

Safety endpoints: Toxicity: Grade 3-4 hematological toxicities (neutropenia, febrile neutropenia, anemia, thrombocytopenia) and non-hematological toxicities (infection, neurotoxicity, cardiotoxicity, hepatotoxicity, nephrotoxicity, oral mucositis) were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, along with treatment-related mortality.

Supportive care: Usage of G-CSF, red blood cell/platelet transfusions, antibiotics/antifungals, and length of hospital stay.

This study retrospectively collected information on the use of G-CSF (including whether it was used or not and the frequency of use). However, due to limitations in data sources, it was not possible to distinguish whether G-CSF was used for primary prevention (precautionary use before the start of the first chemotherapy cycle) or secondary prevention (therapeutic use after the occurrence of febrile neutropenia). Centers did not have unified regulations regarding the timing of G-CSF use, the antibiotic prevention regimen, and the transfusion threshold. They all followed their own clinical routines.

Follow-up and survival: Follow-up method: Out-patient review and telephone follow-up; the last follow-up date was March 31, 2025.

Overall survival (OS): Time from treatment initiation to death from any cause or last follow-up.

Progression-free survival (PFS): Time from treatment initiation to first disease progression, relapse, or death.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics: Normally distributed continuous variables are presented as mean \pm standard deviation; non-normally distributed variables are presented as median (interquar-

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tile range). Categorical variables are presented as frequency (percentage).

Group comparisons: Continuous variables were compared using the independent samples t-test (if normally distributed with equal variance) or the Mann-Whitney U test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test (if expected frequency <5).

Subgroup analysis: Forest plots were generated using the forestplot package in R to display the odds ratios (OR) and 95% confidence intervals (CI) for CR in different subgroups.

Survival analysis: Kaplan-Meier curves were generated and compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model to calculate hazard ratios (HR) and 95% CI, adjusting for covariates such as age, LDH, IPI, and treatment regimen.

Predictive factors: Binary logistic regression with forward stepwise selection (entry criterion 0.05, removal criterion 0.10) was used to identify independent predictors of CR.

Significance level: All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics are detailed in **Table 1**. The baseline characteristics of the two groups of patients were basically balanced, except for the difference in the ECOG physical status score: the proportion of patients with an ECOG score of 1 in the R-DA-EPOCH group was significantly higher (76.0% vs. 50.0%, $P = 0.007$). Subsequent multivariate analysis has corrected this difference. Regarding molecular subtypes, the R-CHOP group comprised 21 patients (21.4%) with the GCB subtype and 77 patients (78.6%) with the non-GCB subtype, whereas the R-DA-EPOCH group comprised 19 patients (38.0%) with the GCB subtype and 31 patients (62.0%) with the non-GCB subtype. The distribution of cell-of-origin subtypes approached but did not reach statistical significance ($P = 0.051$). The proportion of double-expressor lymphoma was 38.8% in the R-CHOP group ver-

sus 28.0% in the R-DA-EPOCH group ($P = 0.264$). The corresponding rates for double-hit lymphoma were 10.2% and 12.0%, respectively ($P = 0.335$). Overall, the baseline characteristics were well-balanced and comparable between the two groups.

Treatment response

The best overall response at the end of treatment is shown in **Figure 2**. In the R-CHOP group, the complete response (CR) rate was 36.7% (36/98), the partial response (PR) rate was 24.5% (24/98), and the objective response rate (ORR) was 61.2%. In the R-DA-EPOCH group, the CR rate was 46.0% (23/50), the PR rate was 12.0% (6/50), and the ORR was 58.0%. The overall distribution of responses did not differ significantly between the groups ($\chi^2 = 3.558$, $P = 0.313$). However, the CR rate in the R-DA-EPOCH group represented an absolute increase of 9.3% compared to the R-CHOP group.

Subgroup analysis

The comparison of CR rates across key subgroups is shown in **Figures 3** and **4**. In the overall population, the R-DA-EPOCH group demonstrated a higher CR rate compared to the R-CHOP group. The odds ratio for CR (R-CHOP vs. R-DA-EPOCH) was 0.68 (95% CI 0.34-1.36, $P = 0.292$), which corresponds to an OR of 1.47 for R-DA-EPOCH vs. R-CHOP. Subgroup analyses revealed that the R-DA-EPOCH regimen yielded higher CR rates in multiple subgroups: patients ≤ 60 years (44.2% vs. 35.6%, OR=0.70), patients > 60 years (57.1% vs. 45.5%, OR=0.62), double-expressor lymphoma (42.9% vs. 28.9%, OR=0.54), GCB subtype (47.4% vs. 23.8%, OR=0.35), and non-GCB subtype (45.2% vs. 40.3%, OR=0.82). The most pronounced improvement was observed in patients with the GCB subtype (difference: +23.6%). Although the OR values across all subgroups favored the R-DA-EPOCH group, the confidence intervals crossed 1, indicating that the differences did not reach statistical significance. Given the small sample sizes in certain subgroups (e.g., DHL, $n = 11$; patients aged > 60 years, $n = 18$), these subgroup findings should be interpreted as exploratory and hypothesis-generating.

Treatment completion and dose intensity

Treatment completion data are summarized in **Table 2**. No significant differences were

R-CHOP vs. R-DA-EPOCH in young high-risk DLBCL

Table 1. Baseline clinical characteristics of patients

Variable	Total (N=148)	R-CHOP (N=98)	R-DA-EPOCH (N=50)	U/ χ^2	P value
Age (years)	45.1 ± 11.9	44.1 ± 11.8	46.8 ± 12.0	2130.500	0.196
Extranodal sites	1.7 ± 0.8	1.8 ± 0.8	1.6 ± 0.8	2750.000	0.191
LDH ratio	3.4 ± 1.0	3.4 ± 0.9	3.3 ± 1.1	2552.500	0.679
IPI score	3.8 ± 0.8	3.7 ± 0.8	3.8 ± 0.8	2315.000	0.556
NCCN-IPI score	6.1 ± 1.2	6.0 ± 1.2	6.3 ± 1.2	2188.000	0.275
Gender				0.001	0.989
Female	65 (43.9%)	43 (43.9%)	22 (44.0%)		
Male	83 (56.1%)	55 (56.1%)	28 (56.0%)		
ECOG score				9.894	0.007
0	33 (22.3%)	28 (28.6%)	5 (10.0%)		
1	87 (58.8%)	49 (50.0%)	38 (76.0%)		
2	28 (18.9%)	21 (21.4%)	7 (14.0%)		
Ann Arbor stage				0.074	0.785
III	60 (40.5%)	41 (41.8%)	19 (38.0%)		
IV	88 (59.5%)	57 (58.2%)	31 (62.0%)		
B symptoms				0.001	0.977
No	55 (37.2%)	37 (37.8%)	18 (36.0%)		
Yes	93 (62.8%)	61 (62.2%)	32 (64.0%)		
Extranodal group				3.130	0.077
0-1	55 (37.2%)	31 (31.6%)	24 (48.0%)		
≥2	93 (62.8%)	67 (68.4%)	26 (52.0%)		
Cell of origin: GCB	40 (27.0%)	21 (21.4%)	19 (38.0%)	3.808	0.051
Cell of origin: non-GCB	108 (73.0%)	77 (78.6%)	31 (62.0%)		
Double expression				1.247	0.264
No	96 (64.9%)	60 (61.2%)	36 (72.0%)		
Yes	52 (35.1%)	38 (38.8%)	14 (28.0%)		
Double hit:				0.412	0.335
No	137 (92.6%)	89 (90.8%)	48 (96.0%)		
Yes	11 (7.4%)	9 (9.2%)	2 (4.0%)		

Abbreviation: IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell type; non-GCB, non-germinal center B-cell type; DHL, double-hit lymphoma.

observed between the two groups regarding planned cycles or actual cycles completed ($P=0.440$ and $P=0.193$, respectively). The treatment completion rate (actual/planned cycles) was 0.90 ± 0.10 in the R-CHOP group and 0.92 ± 0.10 in the R-DA-EPOCH group ($P=0.300$). Fifty patients (51.0%) in the R-CHOP group and 30 patients (60.0%) in the R-DA-EPOCH group completed all planned cycles ($\chi^2=0.744$, $P=0.383$, **Figure 5**).

The distribution of relative dose intensity is presented in **Figure 6** and **Table 2**. The R-CHOP group achieved a relative dose intensity of 0.92 ± 0.04 , significantly higher than the 0.84 ± 0.06 observed in the R-DA-EPOCH group

(Mann-Whitney $U=4124.500$, $P<0.001$). The significantly lower dose intensity in the R-DA-EPOCH group was consistent with its higher rates of dose reduction (52.0% vs. 18.4%, $\chi^2=16.353$, $P<0.001$) and treatment delay (46.0% vs. 18.4%, $\chi^2=11.280$, $P=0.001$). In this study cohort, no treatment-related death events occurred in either group (0/98 in the R-CHOP group, 0/50 in the R-DA-EPOCH group). Due to the limited sample size and the relatively small number of CR events, the Logistic regression model was unable to stably estimate the association between dose intensity and CR rate (the confidence interval of the OR was too wide). Descriptive analysis showed that the mean relative dose intensity of CR and non-

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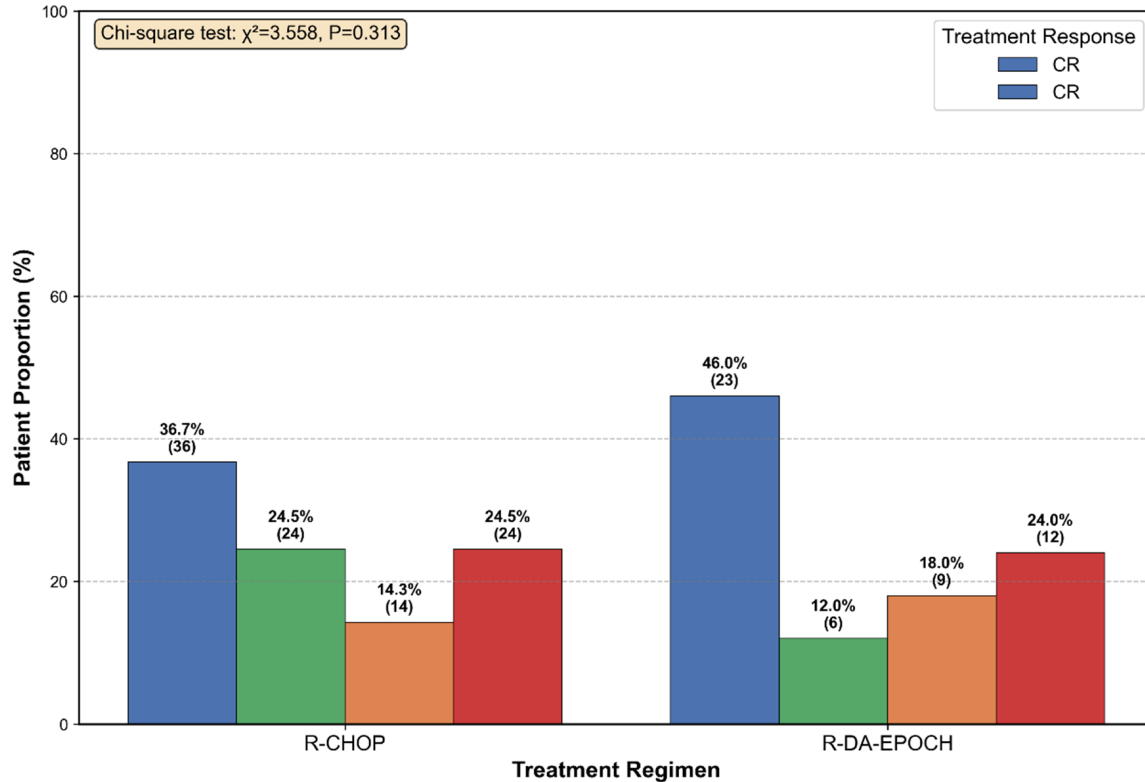


Figure 2. Comparison of best overall response rates at end of treatment. Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

CR patients in both groups was extremely close, suggesting that the impact of dose intensity on the CR rate was limited.

Relationship between LDH levels and treatment response

Figure 7 illustrates the relationship between baseline LDH levels and treatment response. The baseline LDH ratio was 3.46 ± 0.97 in patients who achieved CR and 3.36 ± 0.99 in those who did not, with no statistically significant difference (Welch's t-test, $t=0.583$, $P=0.561$). Stratified analysis by treatment group showed LDH ratios of 3.52 ± 0.84 and 3.37 ± 0.97 for CR and non-CR patients in the R-CHOP group, respectively, and 3.35 ± 1.16 and 3.33 ± 1.05 in the R-DA-EPOCH group, respectively. Baseline LDH levels did not significantly predict treatment response in this study.

Supportive care requirements

Supportive care utilization is detailed in **Table 3** and **Figure 8**. The R-DA-EPOCH group had significantly higher rates of G-CSF use (50.0% vs.

31.6%, $OR=0.463$, $P=0.033$), platelet transfusion (28.0% vs. 8.2%, $OR=0.229$, $P=0.003$) compared to the R-CHOP group. A trend toward higher red blood cell transfusion rates was also observed in the R-DA-EPOCH group (24.0% vs. 15.3%, $OR=0.572$, $P=0.260$). The median length of hospital stay was significantly longer in the R-DA-EPOCH group (7.1 days vs. 4.9 days, Mann-Whitney $U=893.000$, $P<0.001$). These results indicate that while the R-DA-EPOCH regimen may improve CR rates, it is associated with increased hematological toxicity and a higher burden of supportive care.

Discussion

This multicenter retrospective cohort study systematically compared the efficacy and safety of R-CHOP and R-DA-EPOCH regimens in young, treatment-naïve, high-risk DLBCL patients. The results showed that the R-DA-EPOCH group achieved an absolute 9.3% higher complete response (CR) rate compared to the R-CHOP group (46.0% vs. 36.7%); however, this difference did not reach statistical significance ($P=0.313$). The objective response rates (ORR)

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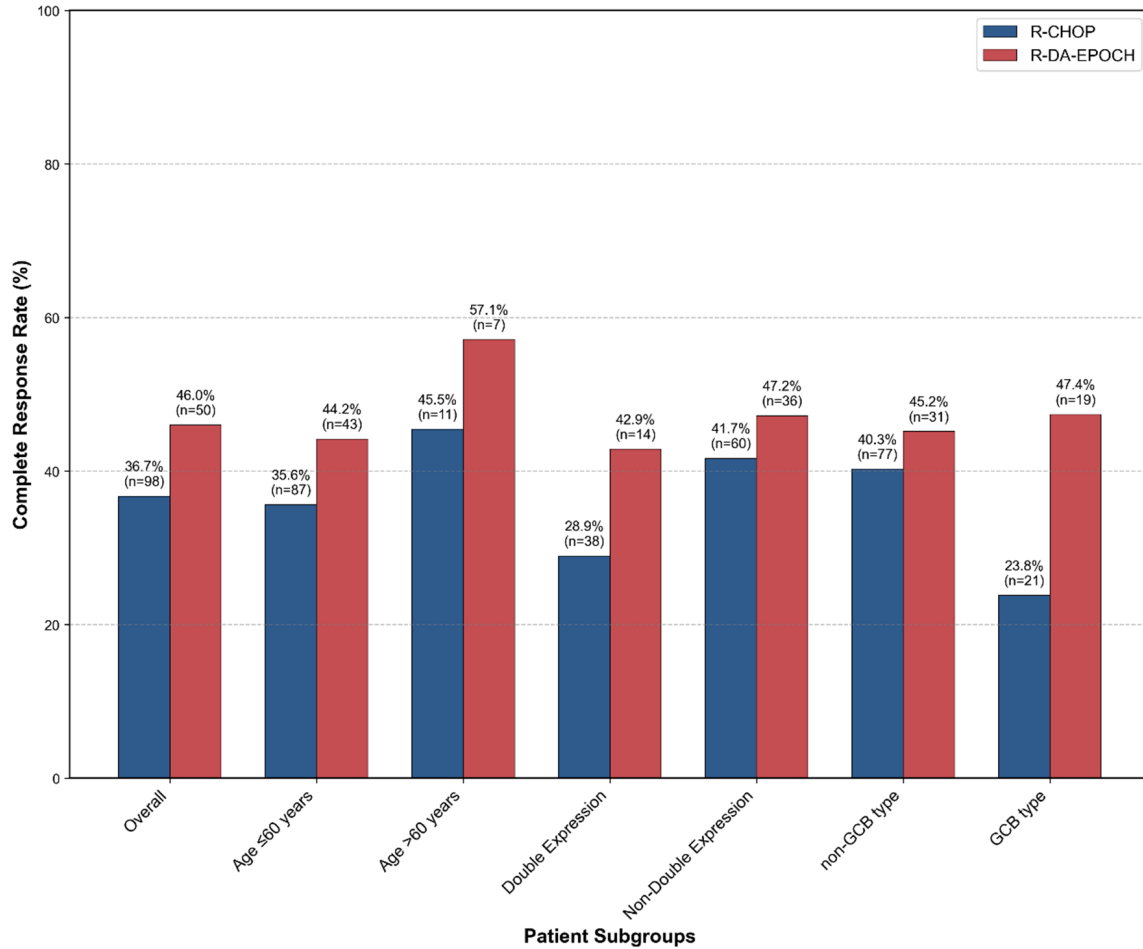


Figure 3. Complete response rates in key subgroups. Abbreviation: GCB, germinal center B-cell type; non-GCB, non-germinal center B-cell type; DHL, double-hit lymphoma.

were comparable between the two groups (58.0% vs. 61.2%), with no significant difference in the overall response distribution. In most prespecified subgroups, the R-DA-EPOCH regimen demonstrated higher CR rates, particularly a 23.6% difference in GCB subtype patients. Nevertheless, the confidence intervals for all subgroups crossed 1, and no statistically significant interaction was observed. Concurrently, the R-DA-EPOCH group exhibited a significantly lower relative dose intensity (0.84 ± 0.06 vs. 0.92 ± 0.04 , $P < 0.001$), along with significantly higher rates of dose reduction (52.0% vs. 18.4%) and treatment delay (46.0% vs. 18.4%), as well as increased demands for supportive care (G-CSF, platelet transfusions, length of hospital stay). These findings indicate that although the R-DA-EPOCH regimen may offer higher CR rates, it is associated with significantly increased hematological toxicity and

treatment burden, necessitating careful consideration in clinical decision-making.

Compared with previous large-scale randomized controlled trials [19-21], our findings are consistent with the overall conclusions of the CALGB 50303 trial, which demonstrated that R-DA-EPOCH did not significantly improve efficacy over R-CHOP in the overall population. However, the subgroup analysis in CALGB 50303 suggested a trend toward benefit in high-risk patients (IPI ≥ 3) (HR=0.81, $P=0.18$), which aligns with the absolute increase in CR rate observed in our study. Notably, the actual relative dose intensity in the R-DA-EPOCH group was significantly lower than that in the R-CHOP group, which may partially explain why the intensified regimen did not translate into a significant efficacy advantage [22-24]. Previous studies have shown that the dose intensity of

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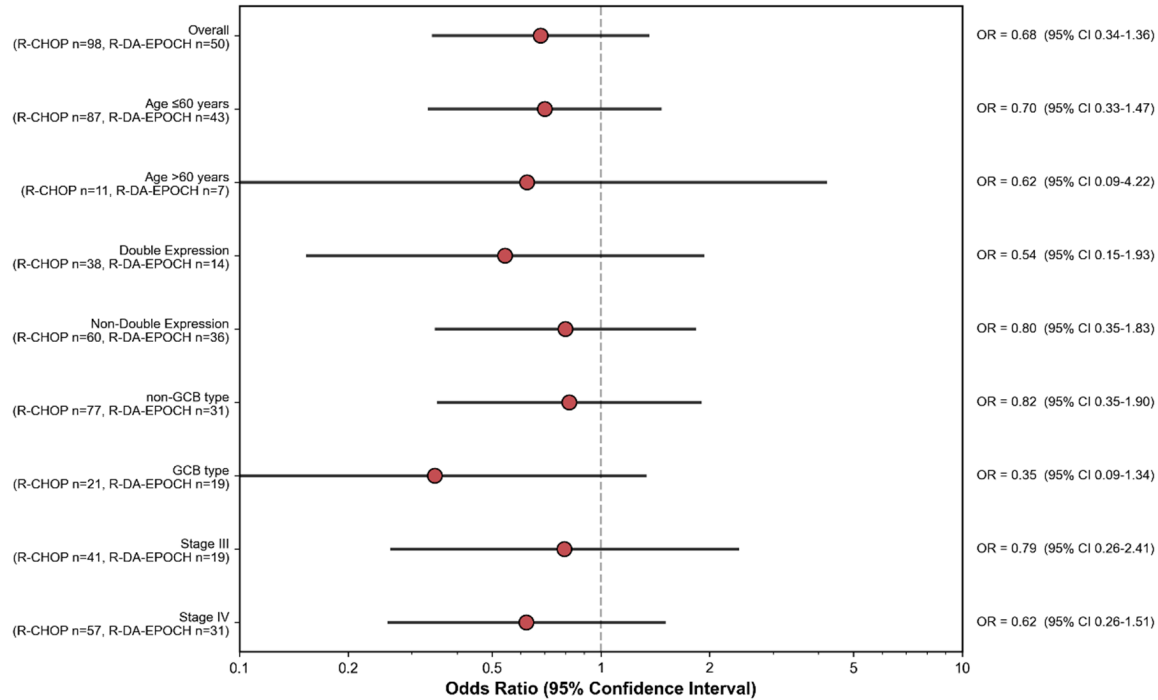


Figure 4. Forest plot of treatment efficacy across subgroups. Abbreviation: OR, odds ratio; CI, confidence interval; GCB, germinal center B-cell type; DHL, double-hit lymphoma.

Table 2. Comparison of treatment completion and dose intensity between the two groups

Metric	R-CHOP (N=98)	R-DA-EPOCH (N=50)	U/ χ^2	P value
Planned cycles	5.19 ± 0.82	5.30 ± 0.81	2273.000	0.440
Actual cycles	4.70 ± 0.94	4.90 ± 0.97	2144.000	0.193
Completion rate	0.90 ± 0.10	0.92 ± 0.10	2217.000	0.300
Relative dose intensity	0.92 ± 0.04	0.84 ± 0.06	4124.500	<0.001
Dose reduction	18 (18.4%)	26 (52.0%)	16.353	<0.001
Treatment delay	18 (18.4%)	23 (46.0%)	11.280	0.001

Abbreviation: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab.

the DA-EPOCH regimen is closely related to efficacy, and insufficient dosing may weaken its antitumor effects. In our study, 52% of patients in the R-DA-EPOCH group experienced dose reductions and 46% had treatment delays, highlighting the tolerability challenges of this regimen in real-world settings. Even in young patients, the high aggressiveness of the disease and treatment intensity may still lead to significant myelosuppression. From a pharmacokinetic perspective, the DA-EPOCH regimen employs a 96-hour continuous infusion, aiming to overcome tumor cell resistance by prolong-

ing the drug exposure time [15]. However, when the actual relative dose intensity is forced to be reduced due to toxicity (in this study, the dose intensity of the R-DA-EPOCH group was only 0.84 ± 0.06), its theoretical advantages may be weakened. Previous studies have shown that the efficacy of the DA-EPOCH regimen is closely related to the achieved dose intensity. When the dose intensity is below a certain threshold, the advantage of continu-

ous infusion is difficult to translate into clinical benefits [25]. The observed dose intensity deficiency and the failure to achieve superiority in efficacy in this study are consistent with the aforementioned mechanistic evidence.

In the subgroup analysis, GCB subtype patients who received R-DA-EPOCH showed a 23.6% increase in CR rate (47.4% vs. 23.8%, OR=0.35). Although this difference was not statistically significant (P=0.186), the large effect size is noteworthy [26-28]. The GCB subtype is traditionally more sensitive to chemotherapy, and

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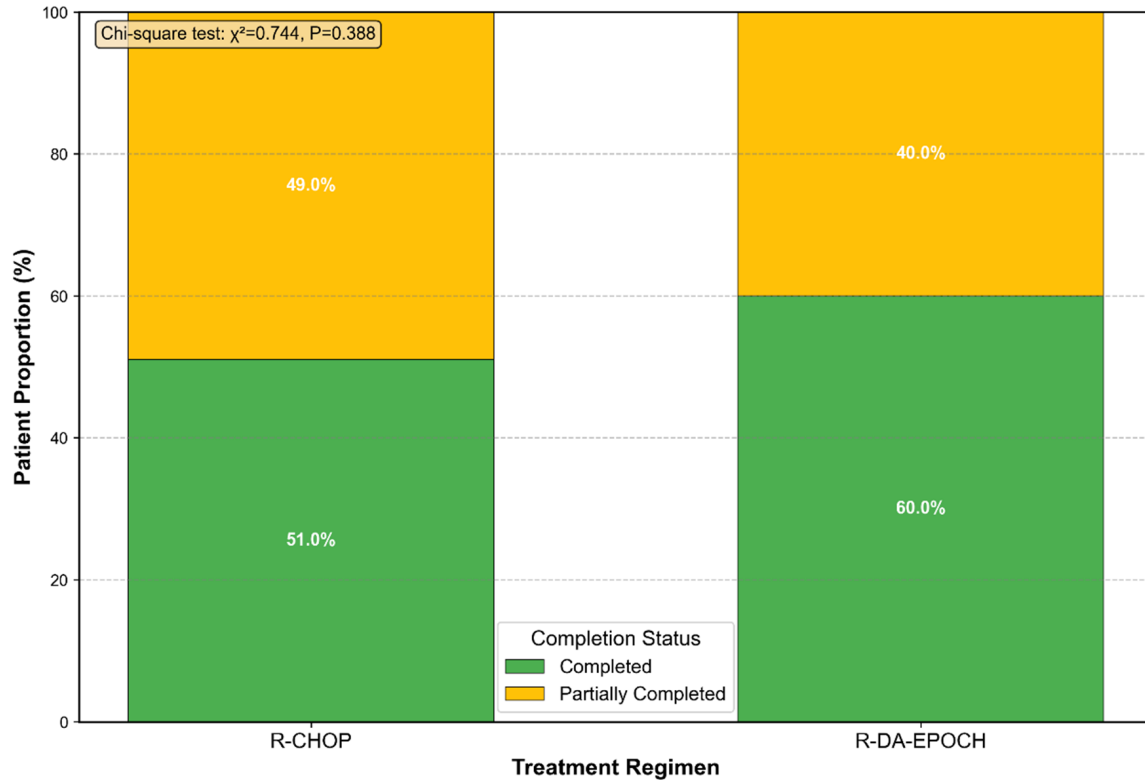


Figure 5. Treatment completion status by regimen. Abbreviation: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. Comparisons of treatment completion status between groups were performed using the chi-square test.

intensified treatment may further amplify this advantage. From the molecular perspective, GCB subtype tumor cells usually have a higher proliferation index and rely on signaling pathways such as PI3K-AKT-mTOR [29]. The continuous infusion of the EPOCH regimen can more effectively kill rapidly dividing GCB tumor cells by prolonging the action time of cell cycle-specific drugs. Moreover, the abnormal expression of genes such as MYC and BCL2 in the GCB subtype is more sensitive to dose intensity [30]. This might explain the significantly higher CR rate observed in GCB subtype patients with R-DA-EPOCH in this study (+23.6%), although statistical significance was not reached due to the sample size limitation. Additionally, the double-expressor lymphoma subgroup showed a 13.9% increase in CR rate (42.9% vs. 28.9%, OR=0.54), also indicating a trend toward benefit. However, due to the small sample sizes in each subgroup, particularly the very limited number of patients aged >60 years or with double-hit lymphoma, the statistical power was insufficient to draw definitive conclusions. Fu-

ture prospective studies targeting specific molecular subtypes are needed to validate these findings.

This study is the first to systematically report the supportive care burden of the R-DA-EPOCH regimen in a real-world domestic population. The results showed that the R-DA-EPOCH group had significantly higher rates of G-CSF use (50.0% vs. 31.6%), platelet transfusions (28.0% vs. 8.2%), and median length of hospital stay (7.1 days vs. 4.9 days) compared to the R-CHOP group, with a total supportive care usage rate as high as 60.0%. These data suggest that the R-DA-EPOCH regimen not only increases hematological toxicity but also significantly elevates healthcare resource consumption and patient financial burden, factors that must be comprehensively considered in clinical practice. The significant increase in treatment burden not only reflects the stronger myelosuppressive effect of the R-DA-EPOCH regimen, but also indirectly confirms that this regimen is more toxic to normal hematopoietic stem cells com-

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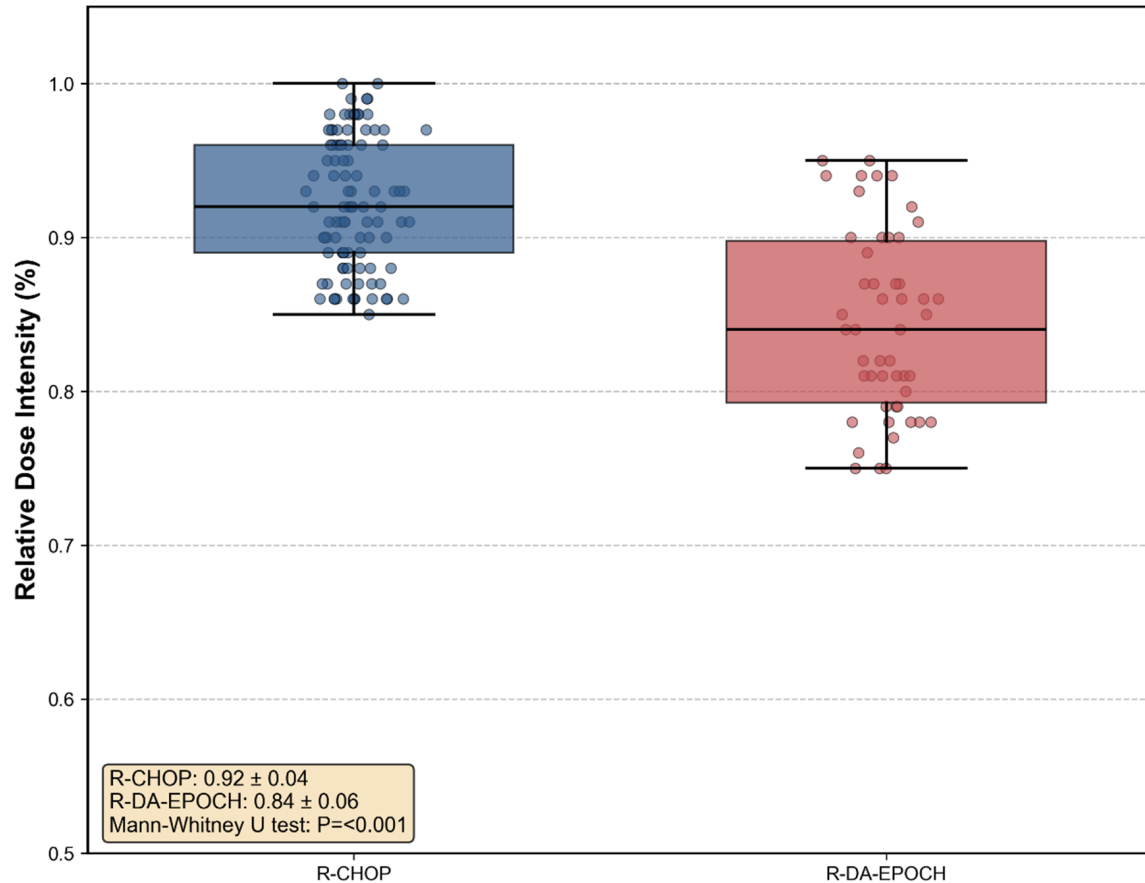


Figure 6. Distribution of relative dose intensity. Abbreviation: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, doseadjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. Distributions of relative dose intensity were compared using the Mann-Whitney U test (non-parametric).

pared to R-CHOP. This toxicity may be achieved by activating inflammatory pathways such as NF- κ B and inducing DNA damage responses [31]. In clinical practice, even in young patients, the hematopoietic function inhibition caused by intensified chemotherapy still requires more intensive supportive treatment intervention. This phenomenon has been clearly demonstrated in the multi-center real-world data of this study.

Furthermore, this study did not observe a significant association between baseline LDH levels and treatment response ($P=0.561$), which contrasts with the findings of some previous reports [32, 33]. Potential reasons include the generally high LDH ratios in our cohort (median 3.4) and the fact that nearly all patients were high-risk; under these circumstances, the predictive value of LDH may have been masked by

other prognostic factors. Stratified analysis also did not reveal an interaction between LDH and the treatment regimen.

This study has several limitations. Firstly, the retrospective design inherently makes it difficult to completely avoid selection bias and information bias. Although the baseline characteristics of the two groups were generally balanced, there was a significant difference in the distribution of ECOG scores ($P=0.007$), with a higher proportion of ECOG 1 patients in the R-DA-EPOCH group (76.0% vs. 50.0%), suggesting that the baseline physical condition of this group was slightly better. Although multivariate analysis was used to correct for residual confounding bias, there may still be residual bias, and caution should be exercised when interpreting the differences in efficacy. Secondly, the sample size was relatively limited, especial-

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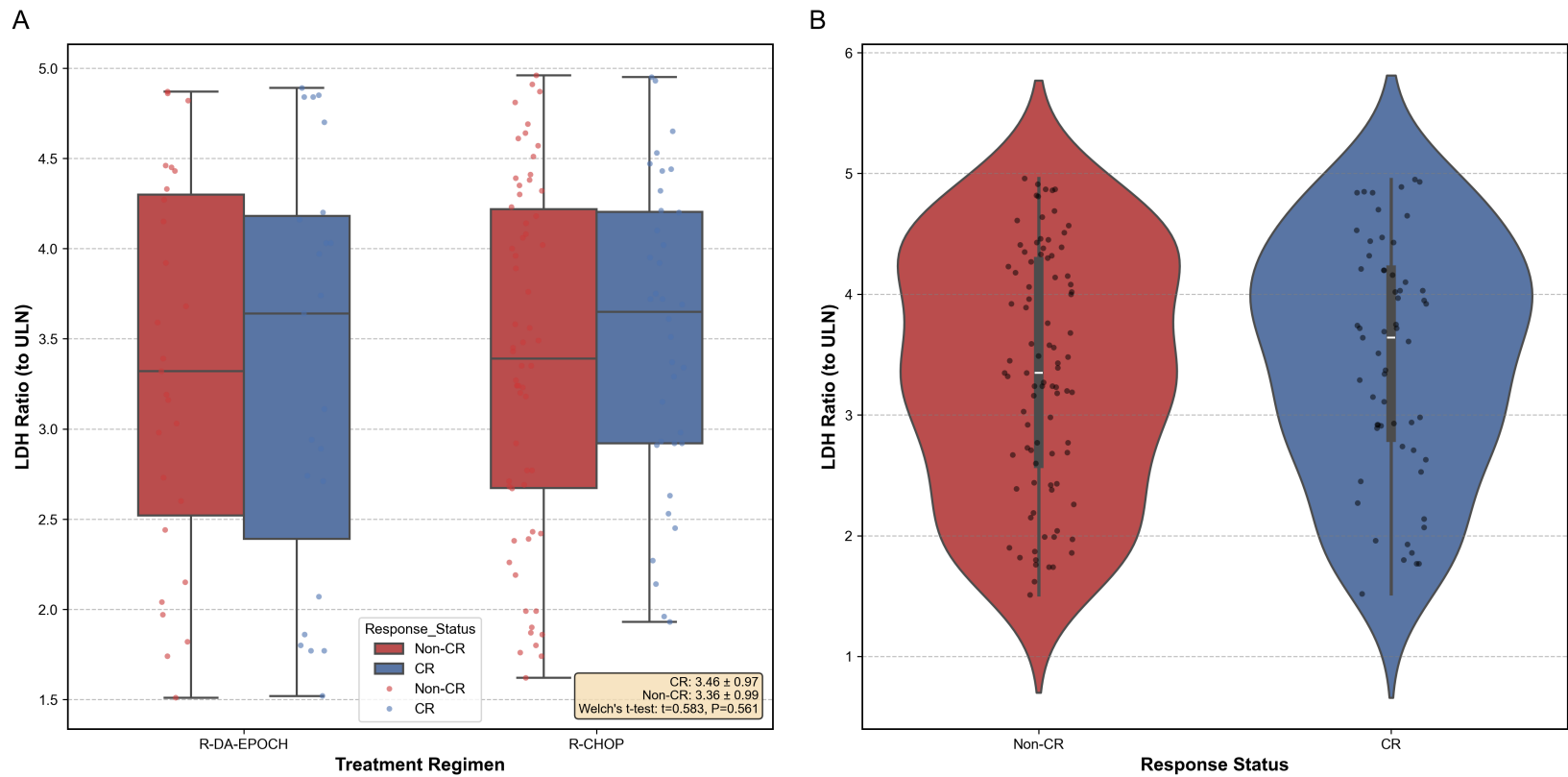


Figure 7. Relationship between LDH levels and treatment response. A. Baseline LDH levels (mean \pm SD) stratified by treatment group and response status. B. Distribution of LDH levels grouped by response status. Abbreviation: LDH, lactate dehydrogenase; SD, standard deviation; CR, complete response.

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Table 3. Comparison of supportive care requirements between the two groups [n (%) or median]

Category	Supportive care	R-CHOP (N=98)	R-DA-EPOCH (N=50)	U/ χ^2	P value
Growth Factors	G-CSF use	31 (31.6%)	25 (50.0%)	0.463	0.033
Transfusion	RBC transfusion	15 (15.3%)	12 (24.0%)	0.572	0.260
Transfusion	Platelet transfusion	8 (8.2%)	14 (28.0%)	0.229	0.003
Hospitalization	Hospitalization days (median)	4.9	7.1	893.000	<0.001

Abbreviation: G-CSF, granulocyte colony-stimulating factor; RBC, red blood cell.

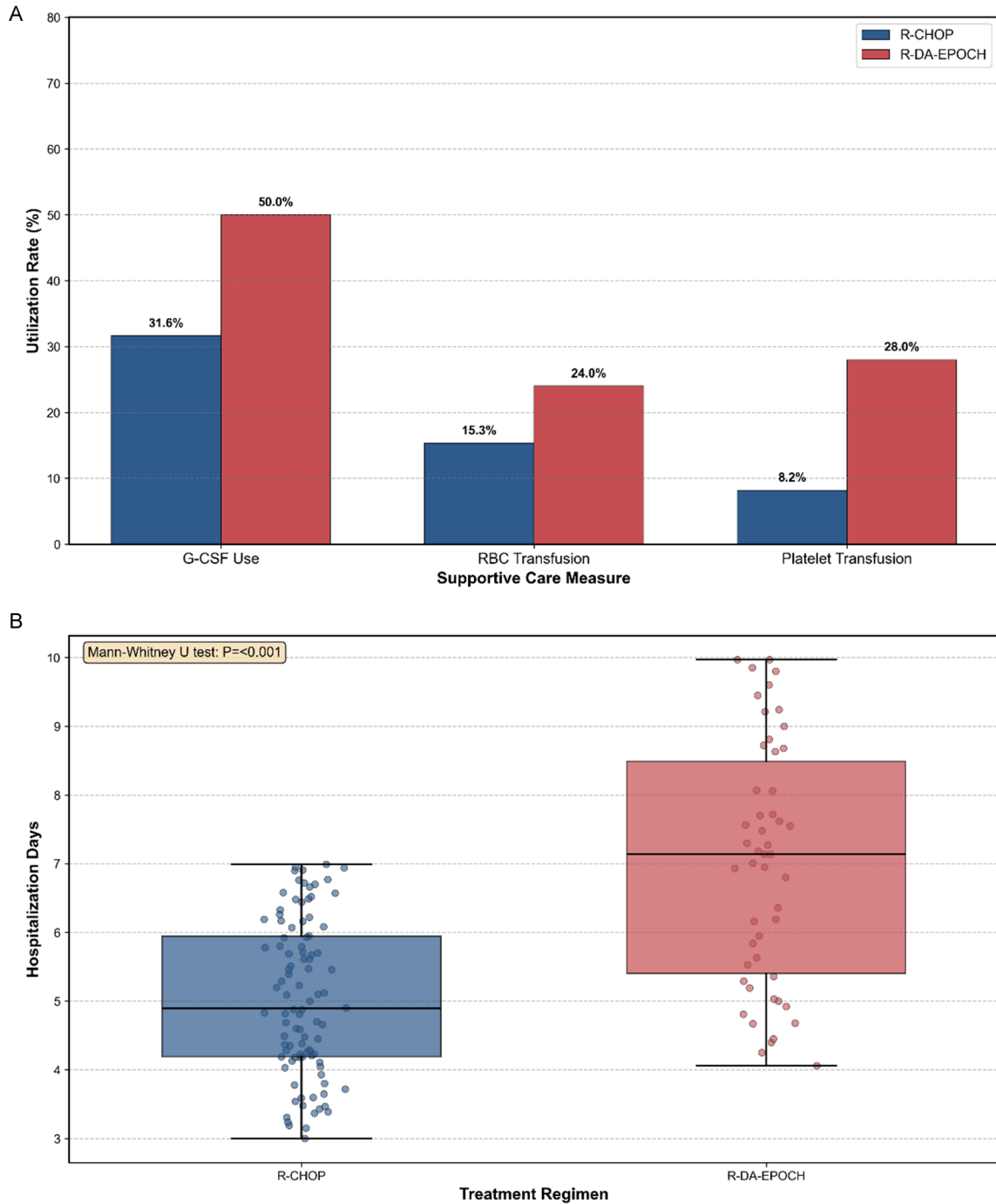


Figure 8. Comparison of supportive care requirements. A. Comparison of supportive care utilization rates between the two groups. B. Distribution of length of hospital stay. Abbreviation: G-CSF, granulocyte colony-stimulating factor; RBC, red blood cell.

ly in the DHL (n=11) and >60 years (n=18) subgroups, where the statistical power was significantly insufficient, making the subgroup analysis results only of exploratory significance. At the same time, due to the short follow-up period, survival analysis could not be conducted, and the differences in progression-free survival and overall survival between the two groups could not be evaluated. Additionally, there were missing values for some variables, and using the median/median number to fill in was a common method, but it may still introduce certain bias; we also did not conduct in-depth causal mediation analysis on dose intensity and efficacy, so it is impossible to clearly determine whether dose reduction is a mediating factor for the efficacy difference. Moreover, this study was a multicenter retrospective design, and the participating centers did not standardize and unify the support treatment (such as the timing of G-CSF use, antibiotic prevention strategies, and transfusion thresholds), nor did they conduct centralized imaging review. These factors may lead to data heterogeneity and affect the accuracy of comparisons between groups. It is worth noting that the G-CSF usage rate in the R-DA-EPOCH group was significantly higher than that in the R-CHOP group (50.0% vs. 31.6%), but since G-CSF was not distinguishable as being used for primary prevention or secondary prevention, it is difficult to clearly determine whether this difference is due to the higher risk of bone marrow suppression in the R-DA-EPOCH regimen itself or the different prevention strategies of each center. This imbalance in support treatment use may indirectly affect the treatment tolerance, treatment completion rate, and efficacy evaluation of patients. The dose adjustment protocols differ between R-CHOP and R-DA-EPOCH due to their distinct pharmacological mechanisms and clinical administration schedules (bolus vs. continuous infusion). This asymmetry limits direct comparability of dose intensity but reflects real-world practice. In response to these limitations, future prospective studies should expand the sample size, extend the follow-up period to include survival endpoints, and use propensity score matching and other methods to control confounding factors. More importantly, randomized controlled trials comparing R-CHOP and R-DA-EPOCH for specific molecular subtypes (such as GCB subtype, double-expression lymphoma) should be designed to provide high-

er-level evidence-based medical evidence for this population.

Conclusion

This multicenter retrospective analysis demonstrates that, in young, treatment-naïve, high-risk DLBCL patients, the R-DA-EPOCH regimen achieved an absolute 9.3% higher complete response rate compared to R-CHOP, although the difference was not statistically significant. The R-DA-EPOCH group was associated with significantly reduced dose intensity, along with higher rates of dose reduction, treatment delay, and supportive care requirements, indicating a greater treatment burden. Although larger efficacy differences were observed in specific subgroups, such as the GCB subtype, none of these comparisons reached statistical significance. Therefore, in the absence of supporting prospective evidence, R-DA-EPOCH should not routinely replace R-CHOP as the standard first-line therapy for this patient population; clinical selection requires individualized decision-making that comprehensively considers the patient's molecular profile, tolerability, and available medical resources. Future prospective studies with larger sample sizes are needed, with a focus on biomarker-guided precision treatment strategies.

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Disclosure of conflict of interest

None.

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