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RESEARCH ARTICLE

Limited Efficacy of Salvage R-ICE Therapy in Relapsed Diffuse Large B-Cell Lymphoma: A Real-World Study from Iraq

Amer Shareef Mohamed

Department of Internal Medicine, College of Medicine, University of Thi Qar, Nasiriyah, Dhi Qar, Iraq.

Abstract

Background: Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) remains challenging to treat. Despite widespread use of salvage R-ICE, real-world data on outcomes and response predictors are limited, with a notable scarcity of regional data from low-resource settings. **Objectives:** This study aimed to characterize the profile and outcomes of relapsed DLBCL patients, evaluate the efficacy of salvage R-ICE therapy, and identify factors associated with treatment response and overall survival. **Methods and Materials:** Data from 59 consecutive adult patients with recurrent DLBCL at a tertiary center in Iraq (2017–2022) were analyzed in this retrospective cohort research. Of these, 49 were treated with salvage R-ICE. Data on survival, treatment response, laboratory, and clinical parameters were extracted. Logistic regression, log-rank tests, and Kaplan-Meier survival curves were among the statistical analyses used. **Results:** The cohort had a median age of 54 years, with 52.5% presenting with stage IV disease. Most patients were poor responders to first-line R-CHOP (interim: 71.2%; end-of-therapy: 79.7%). The response rate to R-ICE after 2 cycles was low (10.2%). Receiving R-ICE did not confer a survival benefit compared to no R-ICE (mean survival 15.82 vs. 14.5 months, p=0.877). However, patients who responded to R-ICE had significantly longer survival than non-responders (34.4 vs. 13.7 months, p=0.002). Response to first-line R-CHOP was a powerful prognostic factor for overall survival after relapse (p<0.001). No baseline clinical or laboratory factor significantly predicted R-ICE response, though a non-significant trend suggested prior chemosensitivity may be associated. **Conclusion:** Salvage R-ICE showed limited efficacy in this real-world cohort. Response to R-ICE, though uncommon (10.2%), was associated with marked survival advantage. Initial chemosensitivity to R-CHOP remained a key prognostic factor. However, the small number of responders limited statistical power and precludes definitive conclusions. These findings underscore the urgent need for improved patient selection strategies and the integration of novel therapies, such as CAR-T cells and bispecific antibodies, for patients unlikely to benefit from conventional salvage chemotherapy. These results emphasize the limited effectiveness of traditional salvage chemotherapy in unselected populations and highlight the necessity of predictive biomarkers to inform more individualized treatment selection.

Keywords: Diffuse large B-cell lymphoma- Relapsed- R-ICE- Salvage therapy- Overall survival- Treatment response

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent histologic subtype of B-cell non-Hodgkin lymphomas, which pose a significant clinical burden [1]. A considerable percentage of patients relapse or develop refractory illness, despite the fact that immunochemotherapy, particularly the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), has greatly improved results [2, 3]. Since patients with recurrent or refractory DLBCL typically have a poor prognosis and need efficient salvage techniques, managing these individuals is a huge clinical challenge. In order to bridge the gap to potentially curative procedures, such stem cell transplantation, for eligible patients, this clinical setting requires second-line therapeutic protocols that can elicit deep responses [4].

Clinical practice has embraced the R-ICE regimen

Corresponding Author:
Dr. Amer Shareef Mohamed
Department of Internal Medicine, College of Medicine, University of Thi Qar, Nasiriyah, Dhi Qar, Iraq.
Emails: aamer.shreef.78@gmail.com, amer@utq.edu.iq

(rituximab, ifosfamide, carboplatin, and etoposide) among salvage chemotherapy treatments [5]. Nevertheless, response rates to salvage therapy vary, and many patients either do not respond well enough or relapse too soon after treatment. The importance of determining which patients stand to gain the most from intensive salvage techniques such as R-ICE is highlighted by this diversity. To improve overall results, tailor treatment plans, and optimize patient selection, a thorough grasp of the clinical and pathological variables that predict treatment response and survival in this context is necessary [6-8].

Even with R-ICE's well-established use, more detailed real-world data is still required, especially from local regional healthcare contexts, in order to describe patient characteristics, treatment trends, and results outside of controlled clinical trials. Additionally, since it may provide important prognostic information, the connection between initial responsiveness to first-line therapy and future sensitivity to salvage regimens needs to be clarified [9]. This study, therefore, aimed to characterize the profile and outcomes of relapsed DLBCL patients, evaluate the efficacy of salvage R-ICE therapy, and identify factors associated with treatment response and overall survival. By addressing these objectives, this research seeks to contribute valuable evidence to guide clinical decision-making and prediction for patients with this aggressive disease, ultimately aiding in the implementation of more tailored and effective management strategies.

Materials and Methods

Study Design and Setting

This was a retrospective cohort study conducted at the hematology outpatient clinic of Al Nasiriya Teaching Hospital, a major tertiary-care government hospital in Nasiriya, Iraq. Serving a sizable population from the city and the nearby rural areas, Al Nasiriya Teaching Hospital is the main referral facility for difficult medical and surgical specialties in the Thi-Qar governorate. Board-certified hematologists, nurses with training in oncology, and supportive care staff work in the hospital's specialty hematology clinic, which treats a broad range of benign and malignant hematologic illnesses. For the purpose of identifying cases and retrieving data, the clinic has a special electronic registry for patients with lymphoma. The study examined the medical records of every adult patient treated at this center for six years, from January 1, 2017, to December 31, 2022, who had been diagnosed with relapsed diffuse large B-cell lymphoma (DLBCL).

Participants / Inclusion and Exclusion Criteria

The final study cohort comprised 59 adult patients with histologically confirmed DLBCL who experienced relapse after first-line therapy. Patients with a confirmed diagnosis of DLBCL, a documented relapse after first-line treatment with R-CHOP, and full medical records covering treatment and follow-up were eligible to participate. Patients had to be at least 18 years old. Patients with incomplete medical records or loss to follow-up prior to salvage therapy evaluation, a diagnosis of another lymphoma subtype, or a history of salvage therapy other than R-ICE before data collection were excluded.

Sample Size Calculation

A formal sample size calculation was not performed for this retrospective study. All eligible patients identified during the six-year study period were enrolled, resulting in a final cohort of 59 relapsed DLBCL patients, of whom 49 received salvage therapy with R-ICE.

Procedure and Data Collection

Retrospective data extraction was done using the hospital's integrated electronic medical records system. The following variables were systematically collected using a standardized data extraction sheet:

• Demographic and Clinicopathological Data: Age at diagnosis, sex, disease stage at diagnosis (Ann Arbor staging), baseline laboratory values (hemoglobin, white blood cell count, absolute monocyte count).

• Treatment and Response Data: Response to first-line R-CHOP therapy (assessed after 3 cycles [interim] and after 6 cycles [end-of-therapy]), receipt of salvage R-ICE therapy, response to R-ICE after 2 cycles, and relapse timing post-R-ICE (early: <1 year; late: ≥1 year).

• Survival Data: Date of diagnosis, date of relapse, date of last follow-up, and vital status at last contact for overall survival analysis.

Response Assessment Criteria

Response to first-line R-CHOP therapy was assessed using standardized criteria based on the Lugano classification. Response evaluations were performed after 3 cycles (interim assessment) and after completion of 6 cycles (end-of-therapy assessment).

Good response was defined as achievement of complete response (CR) or partial response (PR) based on imaging assessment.

Poor response was defined as stable disease (SD) or progressive disease (PD) at the time of evaluation. Response assessments were conducted using contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, as positron emission tomography-computed tomography (PET-CT) was not routinely available at our center during the study period.

Response to salvage R-ICE therapy was assessed after 2 cycles using the same Lugano classification criteria.

Good responders were defined as patients who achieved either complete response (CR) or partial response (PR) after 2 cycles of R-ICE.

Poor responders were defined as patients with stable disease (SD) or progressive disease (PD) after 2 cycles. All response assessments were performed by board-certified hematologists and radiologists based on available imaging studies.

Post-R-ICE Management

Following salvage R-ICE therapy, patients who achieved a response (CR or PR) were considered candidates for high-dose chemotherapy followed by

autologous stem cell transplantation (ASCT). However, due to limited availability of transplant facilities and resources in our region, only a small proportion of eligible patients ultimately proceeded to ASCT. Specific data on ASCT receipt were not systematically captured in this retrospective analysis.

All data abstraction was performed by two trained clinicians to ensure accuracy and consistency, with any discrepancies resolved by a third senior hematologist. The extracted data were entered into a structured Microsoft Excel spreadsheet specifically designed for this study to facilitate organization and preliminary analysis.

Ethical Considerations

The Institutional Review Board (IRB) of Thi Qar Medical College examined and approved the study protocol (Reference Log Number: IQ.UTQ.MED.2025.031). The IRB waived the need for individual informed consent because the study was retrospective in nature. To maintain anonymity, all patient data was de-identified and anonymized before analysis. The Declaration of Helsinki's ethical guidelines were followed when conducting the study.

Statistical Analysis

Statistical analysis was done by SPSS version 28 (IBM Co., Armonk, NY, USA). Numerical data were presented as median and interquartile range (Q1, Q3) and analyzed using Mann-Whitney test. Categorical data were presented as the frequency and percentage and analyzed using the Chi-square test or exact test, as appropriate. Overall survival was analyzed using Kaplan-Meier curve with Log-rank test. Logistic regression analysis was performed to assess factors associated with response to R-ICE. A two tailed P-value < 0.05 was considered statistically significant.

Results

The demographic and clinicopathological characteristics of relapsed DLBCL patients are presented in Table 1 and Figures 1-3. Among the 59 patients, the cohort was nearly evenly distributed by sex, with 30 males (50.8%) and 29 females (49.2%). The median age at diagnosis was 54 years (interquartile range [IQR]: 41, 66). Laboratory values at presentation included a median hemoglobin (Hb) level of 10.4 g/dL (IQR: 9.75, 13) and a median white blood cell (WBC) count of 7 x10^3/µl (IQR: 5.25, 10.3). Disease staging revealed that the majority of patients presented with advanced disease; 31 patients (52.5%) were in stage IV, while stages I, II, and III accounted for 11.9%, 15.3%, and 20.3% of patients, respectively. The response to first-line R-CHOP therapy was predominantly poor; at the interim assessment after 3 cycles, 42 patients (71.2%) were poor responders, and at the end of therapy after 6 cycles, 47 patients (79.7%) were poor responders. A large majority of patients (49, 83.1%) received the new salvage protocol (R-ICE). Among these 49 patients, the response rate to R-ICE after 2 cycles was low, with only 5 patients (10.2%) responding positively. For those who received R-ICE, the pattern of relapse was skewed towards early recurrence, with 37 patients (75.5%) experiencing relapse within one year. The median absolute monocyte count (AMC) was 0.8 x10^9/L (IQR: 0.4, 1.7).

The association between baseline characteristics and response to the new therapy (R-ICE) in relapsed DLBCL patients is presented in Table 2. Among the 49 patients who received R-ICE, no statistically significant differences were found between poor responders (n=44) and good responders (n=5) across the variables analyzed. The distribution by sex was comparable between groups, with 59.1% of poor responders being male compared to 40% of good responders (P-value=0.639). The median age at diagnosis was similar, at 54 years (IQR: 40, 64) for poor responders and 48 years (IQR: 38.5, 70.5) for good responders (P-value=0.962). Baseline laboratory parameters also showed no significant association with response: median hemoglobin levels were 10.15 g/dL (IQR: 9.7, 12.8) in poor responders and 12 g/dL (IQR: 10.15, 14.5) in good responders (P-value=0.263), while median white blood cell counts were 6.97 x10^3/µl (IQR: 5.29, 10.75) and 4 x10^3/µl (IQR: 3.5, 11), respectively (P-value=0.293). Although not statistically significant, a trend toward higher hemoglobin and lower white blood cell counts was observed among good responders. The distribution of disease stage was not significantly different between the two response groups (P-value=0.890). Similarly, the median absolute monocyte count was 0.8 x10^9/L (IQR: 0.41, 1.8) in poor responders and 0.63 x10^9/L (IQR: 0.3, 1.5) in good responders (P-value=0.619).

The association between response to first-line therapy (R-CHOP) and subsequent response to the salvage therapy (R-ICE) in relapsed DLBCL patients is presented in Table 3 and Figures 4 and 5. Among poor responders to R-ICE (n=44), the majority were also poor responders to the first-line R-CHOP regimen, with 32 patients (72.7%) classified as poor responders at the interim assessment and 36 patients (81.8%) as poor responders at the end of therapy. Conversely, among the good responders to R-ICE (n=5), a higher proportion exhibited a prior good response to R-CHOP, with 3 patients (60%) being good responders at the interim assessment and 3 patients (60%) at the end of therapy. The association between interim response to R-CHOP and subsequent response to R-ICE did not reach statistical significance (P-value=0.160). Similarly, the association between end-of-therapy response to R-CHOP

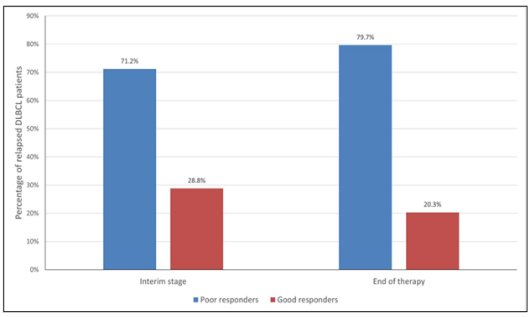

Figure 1. Distribution of Relapsed DLBCL Patients According to Interim and end of Therapy Responses to 1st Line Treatment (R-CHOP)

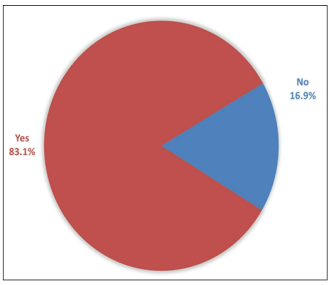

Figure 2. Distribution of Relapsed DLBCL Patients According to Receiving the New Protocol (R-ICE)

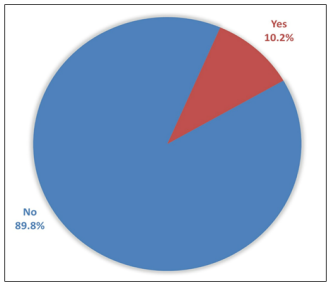

Figure 3. Rate of Response to the New Protocol (R-ICE) among Relapsed DLBCL Patients

and response to R-ICE approached, but did not meet, the threshold for statistical significance (P-value=0.068).

The overall survival analysis of relapsed DLBCL patients according to stage, interim and end of therapy responses to 1st line treatment and response to salvage therapy (R-ICE) are presented in Table 4 and Figures 6-10. Survival outcomes did not differ significantly according to disease stage at presentation (log-rank P-value =0.828), with mean survival times ranging from 14.35 months for stage IV to 17.92 months for stage III. In contrast, response to first-line R-CHOP treatment was significantly associated with overall survival. Patients who were good responders at the interim assessment after 3 cycles had a significantly longer mean survival of 24.76 months compared to 11.88 months for poor interim responders (HR=0.19, 95% CI=0.10 to 0.36, p<0.001). This significant association was also observed for end-of-therapy response, where good responders had a mean survival of 27.25 months compared to 12.62 months for poor responders (HR=0.23, 95% CI=0.12 to 0.44, p<0.001). Receiving the salvage R-ICE protocol was not associated with a survival benefit, with a mean survival of 15.82 months for those who received R-ICE compared to 14.5 months for those who did not (HR=1.06, 95% CI=0.50 to 2.24, P-value=0.877). However, among patients who received R-ICE, a positive response to the protocol after 2 cycles was a significant prognostic factor. Good responders to R-ICE had a markedly longer mean survival of 34.4 months, whereas poor responders had a mean survival of 13.7 months (HR=0.30, 95% CI=0.14 to 0.65, P-value=0.002).

The logistic regression analysis of factors associated with good response to salvage therapy (R-ICE) in relapsed DLBCL patients is presented in Table 5. In the univariate analysis, none of the examined demographic or clinicopathological factors demonstrated a statistically significant association with a positive response to R-ICE. Female sex showed a non-significant trend towards higher odds of good response compared to male sex (unadjusted OR=2.17, 95% CI=0.33 to 14.31, P-value=0.422). Age at diagnosis (unadjusted OR=1.00, 95% CI=0.94 to 1.06, P-value=0.958), disease stage, and absolute monocyte count (AMC) (unadjusted OR=0.71, 95% CI=0.16 to 3.13, P-value=0.647) were not significant predictors. The factor with the strongest association in univariate analysis was a good response to first-line treatment at the end of therapy, which approached but did not reach statistical significance (unadjusted OR=6.75, 95% CI=0.96 to 47.27, P-value=0.054). In the multivariable analysis adjusting for all listed variables, the pattern of results remained consistent, with no factor achieving statistical significance. The association between a good end-of-therapy response to first-line R-CHOP and a subsequent good response to R-ICE remained non-significant in the adjusted model (adjusted OR=6.73, 95% CI=0.81 to 55.64, P-value=0.077).

Table 1. Demographic and Clinicopathological Characteristics of Relapsed DLBCL Patients (n=59)

Item	Relapsed DLBCL patients (n=59)
Sex	
Male	30 (50.8%)
Female	29 (49.2%)
Age at diagnosis (years)	54 (41, 66)
Hb (g/dL)	10.4 (9.75, 13)
WBCs (x10^3/µl)	7 (5.25, 10.3)
Stage	
I	7 (11.9%)
II	9 (15.3%)
III	12 (20.3%)
IV	31 (52.5%)
Response to first line treatment (R-CHOP)	
Interim response (after 3 cycles)	
Poor responders	42 (71.2%)
Good responders	17 (28.8%)
End of therapy response (after 6 cycles)	
Poor responders	47 (79.7%)
Good responders	12 (20.3%)
Receiving the new protocol (R-ICE)	
No	10 (16.9%)
Yes	49 (83.1%)
Response to R-ICE after 2 cycles	(n=49)
No	44 (89.8%)
Yes	5 (10.2%)
Relapse after R-ICE	
Early relapse (<1 year)	37 (75.5%)
Late relapse (>1 year)	12 (24.5%)
AMC (x10^9/L)	0.8 (0.4, 1.7)

Hb: Hemoglobin, WBCs: White blood cells, CR: Complete response, R-ICE: Rituximab+Ifosfamide+Carboplatin+Etoposide, AMC: Absolute Monocyte Count

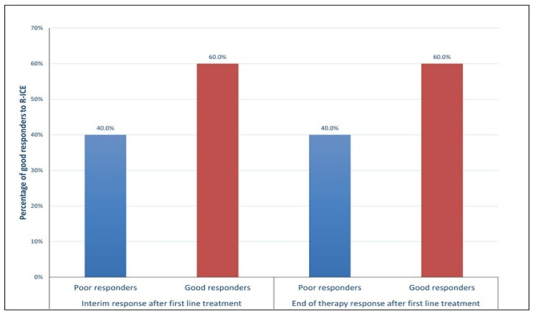

Figure 4. Percentages of Poor and Good Responders to the Old Protocol (R-CHOP) among Poor Responders to the New Protocol (R-ICE)

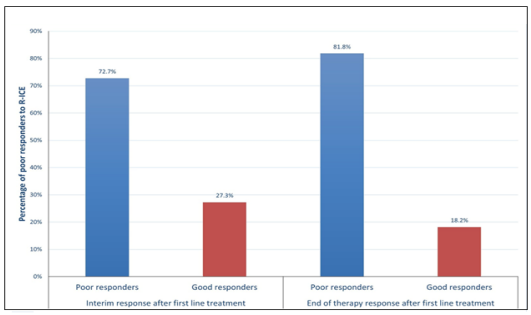

Figure 5. Percentages of Poor and Good Responders to the Old Protocol (R-CHOP) among Good Responders to the New Protocol (R-ICE)

Discussion

The management of relapsed or refractory DLBCL continues to represent a therapeutic challenge, with heterogeneous outcomes that underscore the need for improved patient stratification and more effective salvage strategies. Even if regimens like R-ICE have a proven role, an important percentage of patients only experience minor benefits, indicating a serious weakness in our capacity to forecast therapeutic response and survival in this high-risk group. Investigating the clinical characteristics, treatment results, and prognostic factors of relapsed DLBCL patients treated with salvage R-ICE was the goal of this retrospective research of a real-world cohort from a tertiary center in Nasiriyah, Iraq.

A striking finding in our cohort was the high burden of advanced disease at initial presentation, with over half of the patients (52.5%) diagnosed with Stage IV disease. This characteristic likely contributed to the observed high rate of treatment failure with first-line R-CHOP, as a substantial majority of patients were classified as poor responders both at the interim assessment (71.2%) and at the end of therapy (79.7%). This high primary failure rate underscores the aggressive nature of the disease in this cohort and sets the stage for the challenging clinical scenario of managing refractory or early-relapsing disease, a finding that mirrors the high incidence of primary refractory disease (22.6%) reported in the large Italian STRIDER study (Dogliotti et al., 2024) [10]. Consequently, salvage therapy was a central component of management, with the majority of patients (83.1%) proceeding to receive the R-ICE regimen. Despite this broad application, the objective response rate to R-ICE was low, at only 10.2% after two cycles. Furthermore, among those who received R-ICE, the pattern of relapse was skewed heavily towards early treatment failure, with 75.5% of patients relapsing within one year. This triad of findings, a high proportion of advanced-stage disease, profound resistance to first-line immunochemotherapy, and a minimal response to second-line salvage, collectively paints a picture of a particularly poor-prognosis subset of relapsed DLBCL patients encountered in our clinical setting. Our observed outcome aligns more closely with the poor prognosis documented in population-based studies, such as the report from Ontario where the 2-year overall survival from second-line therapy was only 33% [11].

These results are in contrast to the outcomes reported by Haque et al. (2024), who observed a much higher overall response rate of 64.8% to ICE/R-ICE [12]. This discrepancy may be attributed to differences in patient

Table 2. Association between Baseline Characteristics and Response to the New Therapy (R-ICE) in Relapsed DLBCL Patients (n=49)

Item	Response to the new protocol (R-ICE)		P-value
	Poor responders (n=44)	Good responders (n=5)	
Sex			
Male	26 (59.1%)	2 (40%)	0.639
Female	18 (40.9%)	3 (60%)	
Age at diagnosis (years)	54 (40, 64)	48 (38.5, 70.5)	0.962
Hb (g/dL)	10.15 (9.7, 12.8)	12 (10.15, 14.5)	0.263
WBCs ($x10^3/\mu l$)	6.97 (5.29, 10.75)	4 (3.5, 11)	0.293
Stage			
I	4 (9.1%)	1 (20%)	0.89
II	7 (15.9%)	1 (20%)	
III	8 (18.2%)	1 (20%)	
IV	25 (56.8%)	2 (40%)	
AMC ($x10^9/L$)	0.8 (0.41, 1.8)	0.63 (0.3, 1.5)	0.619

Numerical data are presented as median (Q1, Q3) and categorical data are presented as frequency (%), Statistical significance at P-value<0.05

Table 3. Association between Response to First-line Therapy (R-CHOP) and Subsequent Response to the Salvage Therapy (R-ICE) in Relapsed DLBCL Patients (n=49)

Item	Response to the new protocol (R-ICE)		P-value
	Poor responders (n=44)	Good responders (n=5)	
Interim response after the old protocol (R-CHOP)			
Poor responders	32 (72.7%)	2 (40%)	0.16
Good responders	12 (27.3%)	3 (60%)	
End of therapy response after the old protocol (R-CHOP)			
Poor responders	36 (81.8%)	2 (40%)	0.068
Good responders	8 (18.2%)	3 (60%)	

Numerical data are presented as median (Q1, Q3) and categorical data are presented as frequency (%), Statistical significance at P-value<0.05

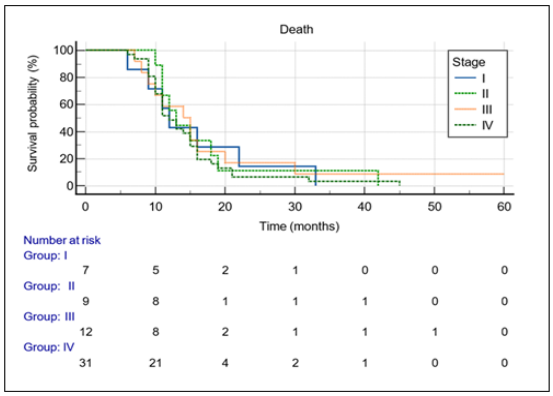

Figure 6. Kaplan-Meier Curve for Overall Survival Analysis of Relapsed DLBCL Patients According to Stage

selection, the proportion receiving rituximab with ICE, or regional treatment practices. Collectively, these results immediately highlight the critical need to understand the determinants of this poor outcome and to identify which patients, if any, might derive meaningful benefit from intensive salvage protocols like R-ICE.

The implications of these findings are particularly stark in low-resource settings, such as our center in Iraq, where access to novel agents like CAR-T cell therapy and bispecific antibodies is severely limited or nonexistent. In such contexts, conventional salvage chemotherapy like R-ICE remains the only available option for patients with relapsed DLBCL, despite its limited efficacy. This reality underscores the urgent need for: better patient selection strategies to identify the minority who may benefit from intensive salvage regimens, optimization of supportive care to improve outcomes in those receiving conventional therapy, and advocacy for increased access to novel therapies in low-resource regions. Furthermore, these findings highlight the importance of regional real-world data to inform evidence-based guidelines that account for the practical constraints of healthcare delivery in resource-limited environments.

The analysis demonstrated that conventional baseline characteristics, including demographics, disease stage, and standard laboratory values, held no significant predictive power for response to salvage R-ICE therapy. This lack of significant associations indicates that the likelihood of responding to R-ICE in this relapsed setting cannot be reliably estimated using these readily available clinical and pathological features alone. This finding is clinically important as it suggests that traditional prognostic markers, which may hold value in the first-line setting, lose their discriminatory power in predicting sensitivity to salvage chemotherapy. This aligns with the work of Jiang et al. (2020), whose multivariate models for outcomes in R/R DLBCL did not identify disease stage as an independent predictor [13]. The trend observed towards higher median hemoglobin (12 vs. 10.15 g/dL) and lower median WBC counts (4 vs. 6.97 x10^3/µl) in good responders, while not statistically significant, may hint at a better pre-treatment performance status or lesser tumor burden. However, the observed laboratory differences themselves did not reach the threshold for clinical utility in our cohort. This inability to predict response using standard metrics underscores the complex biology of chemorefractory DLBCL and points to the potential role of more sophisticated determinants, such as molecular subtypes, genetic alterations, or tumor microenvironment features, which were not captured in this analysis but are central to the contemporary shift toward biomarker-driven, personalized management of DLBCL [14]. Consequently, the selection of patients for intensive salvage therapy remains a significant clinical challenge, lacking guidance from conventional clinical parameters.

While baseline clinical factors failed to predict R-ICE response, an analysis of prior treatment outcomes revealed a clinically suggestive, though statistically non-significant, trend. Patients who ultimately responded to salvage R-ICE were more likely to have shown sensitivity to first-line R-CHOP therapy. Specifically, 60% of R-ICE good responders had also been good responders at the end of

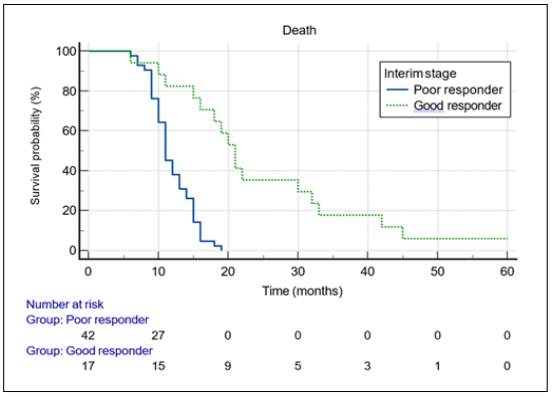

Figure 7. Kaplan-Meier Curve for Overall Survival Analysis of Relapsed DLBCL Patients According to Response to 1st Line Treatment at Interim Stage

Table 4. Overall Survival Analysis of Relapsed DLBCL Patients According to Stage, Interim and End of Therapy Responses to 1st Line Treatment and Response to Salvage Therapy (R-ICE)

Item	N of events (%)	N. Censored (%)	Mean (months)	HR (95%CI)	Log-rank P-value
Stage					
I	7 (100%)	0 (0%)	15.57	Ref	0.828
II	9 (100%)	0 (0%)	16.78	0.97	
				(0.38 to 2.51)	
III	11 (91.67%)	1 (8.33%)	17.92	0.91	
				(0.37 to 2.24)	
IV	31 (100%)	0 (0%)	14.35	1.19	
				(0.53 to 2.68)	
Response to first line treatment (R-CHOP)					
Interim response (after 3 cycles)					
Poor responder	42 (100%)	0 (0%)	11.88	Ref	<0.001
Good responder	16 (94.12)	1 (5.88%)	24.76	0.19	
				(0.1 to 0.36)	
End of therapy response (after 6 cycles)					
Poor responder	47 (100%)	0 (0%)	12.62	Ref	<0.001
Good responder	11 (91.67%)	1 (8.33%)	27.25	0.23	
				(0.12 to 0.44)	
Receiving the new protocol (R-ICE)					
No	10 (100%)	0 (0%)	14.5	Ref	0.877
Yes	48 (97.96%)	1 (2.04)	15.82	1.06	
				(0.50 to 2.24)	
Response to R-ICE after 2 cycles					
No	44 (100%)	0 (0%)	13.7	Ref	0.002
Yes	4 (80%)	1 (20%)	34.4	0.3	
				(0.14 to 0.65)	

HR: Hazard ratio, CI: Confidence interval, Statistical significance at P-value<0.05

their first-line therapy, compared to only 18.2% of R-ICE poor responders: where this association approached but did not meet the conventional threshold for statistical significance (P-value=0.068). A similar pattern was observed for interim response (P-value=0.160). This finding suggests a potential phenotype of consistent chemosensitivity, where tumors retain some degree of treatment susceptibility across therapeutic lines. The trend is biologically coherent, as it may reflect an underlying tumor biology that is inherently less aggressive or lacks robust multidrug resistance mechanisms. The failure to reach statistical significance is likely influenced by the very small number of good responders to R-ICE (n=5), which severely limits the statistical power of the comparison. Nonetheless, the observation that a good end-of-therapy response to first-line R-CHOP was approximately three times more common among patients who subsequently responded to R-ICE carries important clinical implications. This pattern aligns with and is strengthened by the work of Jiang et al. (2020), who, in a larger cohort, identified prior response to front-line treatment as a significant independent predictive factor for second-line efficacy (OR=4.50, P-value=0.001) [13]. This suggests that a patient's initial response to R-CHOP may hold more predictive value for salvage success than static baseline characteristics, arguing for a prognostic assessment that incorporates dynamic treatment response. However, the counterpoint remains that 40% of R-ICE responders were initial poor responders, indicating that primary resistance does not universally rule out salvage success, and clinical decisions cannot rely solely on this historical factor.

The survival analysis yielded critical insights with significant clinical implications. First, the quality of response to initial R-CHOP therapy emerged as a powerful and independent determinant of long-term outcome, even after disease relapse. Patients who achieved a good interim response enjoyed a more than twofold

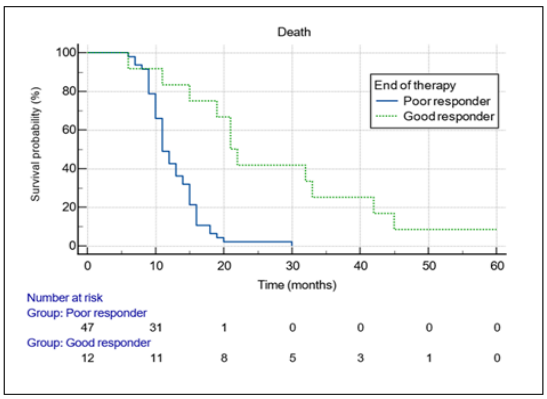

Figure 8. Kaplan-Meier Curve for Overall Survival Analysis of Relapsed DLBCL Patients According to Response to 1st Line Treatment at End of Therapy

Table 5. Logistic Regression Analysis of Factors Associated with Good Response to Salvage Therapy (R-ICE) in Relapsed DLBCL Patients (n=49)

Item	Univariate analysis			Multivariable analysis		
	Unadjusted OR	95%CI	P-value	Adjusted OR	95%CI	P-value
Sex						
Male	Ref			Ref		
Female	2.17	0.33 to 14.31	0.422	2.02	0.24 to 16.67	0.515
Age at diagnosis (years)	1	0.94 to 1.06	0.958	0.99	0.93 to 1.06	0.812
Stage						
I	Ref			Ref		
II	0.57	0.03 to 11.85	0.718	0.95	0.04 to 23.71	0.974
III	0.5	0.02 to 10.25	0.653	1.38	0.04 to 44.28	0.856
IV	0.32	0.02 to 4.41	0.394	0.61	0.04 to 10.04	0.732
AMC ($x10^9$/L)	0.71	0.16 to 3.13	0.647	0.58	0.1 to 3.39	0.543
Response to 1st line treatment at end of therapy						
Poor responders	Ref			Ref		
Good responders	6.75	0.96 to 47.27	0.054	6.73	0.81 to 55.64	0.077

OR: Odds ratio, CI: Confidence interval, Statistical significance at P-value<0.05

longer mean survival compared to poor responders (24.76 vs. 11.88 months), corresponding to a substantial 81% reduction in the risk of death (HR=0.19, 95% CI 0.10-0.36, p<0.001). This prognostic strength was even more pronounced for end-of-therapy response, where good responders lived a median of 27.3 months versus 12.6 months for poor responders, with a 77% risk reduction (HR=0.23, 95% CI 0.12-0.44, p<0.001). This underscores that the disease biology dictating initial chemosensitivity continues to exert a dominant influence on the ultimate clinical trajectory, overshadowing other factors. Conversely, the initial disease stage, a cornerstone of prognostic stratification in newly diagnosed DLBCL, lost all predictive value in this relapsed cohort (log-rank P-value=0.828), suggesting that upon relapse, aggressive tumor behavior and acquired treatment resistance become more important determinants of mortality than the original disease stage, a finding consistent with prior research in R/R DLBCL, where multivariate analyses have not identified disease stage as an independent predictor of survival (Jiang et al., 2020) [13].

The analysis of salvage therapy outcomes revealed a fundamental and somewhat paradoxical distinction. Merely receiving the R-ICE protocol did not confer a survival benefit; the hazard ratio was neutral at 1.06 (95% CI 0.50-2.24, P-value=0.877), with mean survival times nearly identical between those who did and did not receive the regimen (15.8 vs. 14.5 months). However, this comparison should be interpreted with caution, as the group that did not receive R-ICE (n=10) was small and likely confounded by factors such as poor performance status, comorbidities, or patient preference that precluded receipt of salvage chemotherapy. This finding critically differentiates treatment administration from treatment efficacy and is consistent with the extremely poor median overall survival of 6.7 months after relapse reported in the STRIDER study [10], where no survival difference was observed between platinum-based regimens and other salvage therapies. However, for the small subset of patients who did achieve a response to R-ICE, the survival benefit was profound and represented the strongest positive association in our study. Responders to R-ICE had a mean survival of 34.4 months, more than double

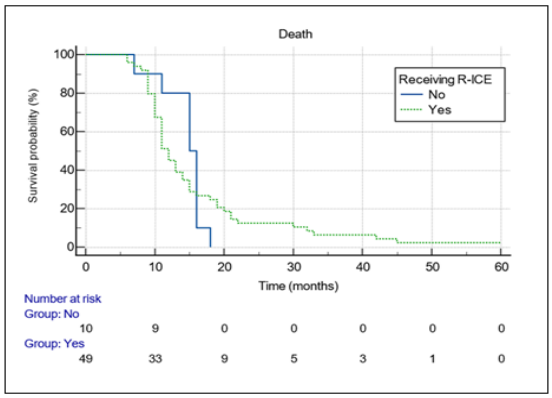

Figure 9. Kaplan-Meier Curve for Overall Survival Analysis of Relapsed DLBCL Patients According to Receiving the New Protocol (R-ICE)

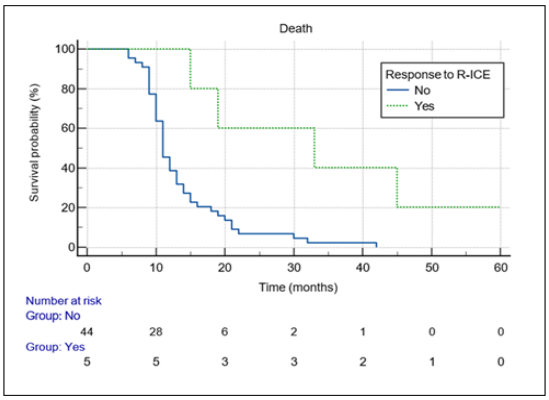

Figure 10. Kaplan-Meier Curve for Overall Survival Analysis of DLBCL Patients According to Response to the New Protocol (R-ICE)

that of non-responders (13.7 months), translating to a 70% reduction in mortality risk (HR=0.30, 95% CI 0.14-0.65, P-value=0.002). This creates a critical distinction in the relapsed setting: a patient's survival is not improved simply by receiving salvage chemotherapy, but only if their tumor responds to it. This underscores the urgent need for novel predictive biomarkers and supports the shift toward genetically guided therapies [15] and novel agents like CAR-T cells and bispecific antibodies for patients unlikely to respond to conventional salvage therapy [10, 14].

The final, consolidated statistical model reinforced and refined the earlier findings. A multivariable logistic regression analysis, which adjusts for potential confounding between variables, confirmed that none of the studied demographic, clinical, or laboratory factors emerged as a statistically significant independent predictor of a good response to salvage R-ICE therapy. All adjusted p-values exceeded the significance threshold. This definitive analysis underscores that the inability to predict R-ICE response is not an artifact of simpler bivariate comparisons but persists even when accounting for multiple factors simultaneously. The most compelling, though still non-significant, signal within the model came from the patient's historical response to first-line therapy. A good end-of-treatment response to R-CHOP was associated with an approximately 6.7-fold increased odds of responding to R-ICE in the adjusted model (Adj. OR=6.73, 95% C=- 0.81–55.64). While this association did not reach conventional statistical significance (P-value=0.077), the magnitude of the odds ratio and its consistency from the univariate analysis (OR=6.75, P-value=0.054) strongly suggests a genuine biological relationship that our study was underpowered to definitively prove due to the very low number of positive R-ICE response events (n=5). The exceptionally wide confidence intervals for this and other estimates further highlight the instability of the model stemming from this limited sample size within the response group. The clinical implications are twofold. First, clinicians currently lack a reliable, multi-factor clinical algorithm to select candidates for R-ICE, reinforcing the call for advanced prediction tools, such as the machine learning models incorporating lactate dehydrogenase (LDH) and treatment response history shown to be highly predictive by Zhu et al. (2025) [16]. Second, the consistent trend pointing to prior chemosensitivity as the strongest candidate variable provides a rational, though not yet definitive, clinical guideline: a patient who responded well to first-line therapy may represent a more favorable candidate for a second intensive regimen, whereas a patient with primary refractory disease should be approached with heightened caution and consideration of alternative strategies including novel agents or clinical trials. This directly informs the critical need for incorporating biological markers, such as cell-of-origin classification or specific genetic alterations like MYC/BCL2 rearrangements, which were not assessed here but are increasingly recognized as key determinants of treatment resistance in DLBCL. This approach is validated by studies showing that outcomes can be significantly improved by tailoring therapy to genetic subtypes [15] and that the cell of origin remains a critical factor for both prognosis and predicting response to specific salvage regimens [17, 18].

Strengths and Limitations

This study provides unique real-world insights into the outcomes and predictive parameters related with salvage R-ICE therapy for recurrent DLBCL in a specific regional healthcare context, filling a significant gap in the literature. Its merits stem from a well-defined, sequential cohort of patients managed at a single tertiary referral institution, ensuring consistency in diagnostic criteria, treatment methods, and follow-up practices. The adoption of a systematic data extraction method led by professional doctors improved the reliability and accuracy of retrospective data collecting. However, the study is inherently limited by its retrospective, observational design, which is susceptible to biases related to patient selection and unmeasured confounding factors. A significant limitation is the very small number of patients who responded to R-ICE (n=5), which severely restricted statistical power and rendered the study underpowered to detect meaningful associations, particularly in multivariable models. Consequently, the generalizability of our findings is limited, and the results should be interpreted as hypothesis-generating rather than definitive. This constraint is apparent in the large confidence intervals found for several estimations and the inability to achieve statistical significance for clinically suggestive trends. Furthermore, the study was limited to commonly acquired clinical and laboratory variables; critical molecular and genetic data, such as cell-of-origin classification, double-hit status (assessed by FISH for MYC, BCL2, and BCL6 rearrangements), or comprehensive genetic subtyping, were unavailable. This absence of molecular and genomic information represents a major limitation, particularly given the contemporary shift toward precision medicine in DLBCL management. Importantly, the lack of these biological markers directly contributes to our inability to identify predictive factors for R-ICE response, as molecular subtypes are increasingly recognized as key determinants of treatment sensitivity and resistance. The absence of these biological markers restricts the depth of prognostic and predictive insights that can be obtained and underscores the need for prospective studies incorporating routine molecular profiling.

In conclusion, poor response to first-line R-CHOP was found to be strongly linked to later relapse in this trial. Although there was a trend that suggested it would affect response to salvage R-ICE, this was not statistically significant. All things considered, R-ICE produced a poor response rate and no overall survival improvement for the treated group. Importantly, only the tiny proportion that reacted to R-ICE saw an improvement in survival. These results emphasize the limited effectiveness of traditional salvage chemotherapy in an unselected population and show that initial chemosensitivity is still a significant prognostic factor. They also highlight the necessity of predictive biomarkers to inform more individualized

treatment selection.

Future Recommendations

Prospective, multi-center studies with larger cohorts should be given priority in future research. To identify physiologically defined subgroups that may benefit from R-ICE or require other therapy, it is crucial to incorporate complete molecular profiling, which includes cell-of-origin categorization, genetic changes, and tumor microenvironment indicators. Furthermore, in comparable regional healthcare environments, comparative effectiveness studies comparing R-ICE to more recent salvage options such as innovative medicines like bispecific antibodies and CAR-T cell therapy are necessary. Finally, in order to support continuous, population-level outcome analysis and quality enhancement in the treatment of relapsed DLBCL, attempts should be undertaken to create organized regional lymphoma registries.

Acknowledgments

Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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