ORIGINAL ARTICLE

Treatment Patterns, Toxicity, and Outcomes in Elderly Patients with Diffuse Large B-Cell Lymphoma Treated with R-CHOP or Alternative Regimens: A Retrospective Cohort Study from Pakistan

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ABSTRACT

Background: Treatment of diffuse large B-cell lymphoma (DLBCL) in elderly patients remains challenging because of comorbidities, frailty, and reduced tolerance to intensive chemotherapy. Data from low- and middle-income countries are limited.

Objective: To evaluate treatment patterns, clinical outcomes, and treatment-related challenges among elderly patients with DLBCL treated at a tertiary care center in Pakistan.

Methods: This retrospective study was conducted at Aga Khan University Hospital, Karachi, Pakistan. The study included 175 patients aged ≥60 years with DLBCL who were treated between January 2018 and December 2022. Continuous variables were summarized using medians and ranges, while categorical variables were reported as frequencies and percentages. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method, with comparisons performed using the log-rank test ($p<0.05$ considered significant). Cox regression analysis was used for prognostic adjustment.

Results: The median age was 66 years (range 60-87). Most patients had an ECOG performance status of 1-2 (77.1%). High IPI scores were present in 37.1%, while 40.6% had a high CNS-IPI ≥ 4. Seventy-six patients received standard R-CHOP and 99 received alternative regimens, with R-CHOP use declining with age. PFS and OS were significantly longer with R-CHOP than with alternative regimens (log-rank $p<0.01$). Median OS for the overall cohort was 59 months (95% CI 43.06-74.64). Treatment modifications occurred in 15% of R-CHOP recipients, dose reductions in 11.4%, and grade 3/4 febrile neutropenia in 20.6%. Nine deaths occurred during treatment.

Conclusion: Management of elderly patients with DLBCL remains challenging in resource-limited settings. R-CHOP was associated with superior survival, while treatment selection was influenced by frailty, age, and toxicity concerns.

Keywords: *Diffuse large B-cell lymphoma, elderly patients, R-CHOP, frailty, Pakistan, lymphoma outcomes.*

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL) and constitutes a substantial proportion of lymphomas seen in routine clinical practice. In Pakistan, the available data from cancer registries reveal that non-Hodgkin lymphoma (NHL) accounts for about 5% of all cancers, which represents its contribution to the burden of cancer in the country [1]. However, population-based data on diffuse large B-cell lymphoma (DLBCL) remain limited, with most available evidence coming from single-institution experiences. DLBCL is more common in older adults, and its incidence rises steadily with increasing age [2].

DLBCL is a biologically heterogeneous disease, and immunophenotypic and molecular studies have shown that elderly patients are more likely to have the nongerminal center (non-GCB) subtype, which is associated with poorer outcomes than the germinal center (GCB) subtype [3, 4]. In addition, Epstein-Barr virus (EBV)- positive DLBCL is a distinct clinicopathologic entity that mainly affects older patients and is associated with aggressive disease and worse prognosis [5].

Management of DLBCL in elderly patients remains challenging because of the combined effects of disease biology, age-related comorbidities, functional decline, and increased susceptibility to treatment-related toxicity

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[6, 7]. Although standard therapy with R-CHOP remains curative for many patients, its tolerability declines with advancing age, often necessitating treatment modification, dose reduction, or alternative regimens in clinical practice [8-10]. Reduced-intensity regimens, particularly R-miniCHOP, have therefore been developed and are increasingly used in selected elderly or frail patients, with population-based studies showing acceptable outcomes and better tolerability compared with full-dose R-CHOP [11, 12]. Another challenge in the management of DLBCL in elderly patients is the lack of a standardized definition of "elderly," along with inconsistent use of functional and geriatric assessment in treatment decision-making [13].

International consensus guidelines recommend that chronological age alone should not guide treatment decisions and that comorbidities, functional status, and structured geriatric assessment should be used to guide individualized treatment selection in older patients with lymphoma [14-17]. In low- and middle-income countries, where access to specialized care may be more variable, it is especially important to understand how these variations affect treatment decisions and outcomes among elderly patients with DLBCL.

METHODOLOGY

This was a retrospective observational study conducted at Aga Khan University Hospital, Karachi, Pakistan. The study was conducted with ethical approval from the institutional ethics review committee (Ref. 2022-7737-22639), and patient data confidentiality was maintained throughout the study. Data were collected retrospectively from patients' physical files and electronic health records, which were reviewed between January 1, 2024, and December 31, 2024.

The study included patients aged 60 years or older with a new diagnosis of diffuse large B-cell lymphoma who initiated treatment between January 2018 and December 2022. Consecutive eligible patients were included according to predefined inclusion and exclusion criteria. Patients were eligible if they had biopsy-proven DLBCL and an ECOG performance status of 0 to 4. Patients with transformed lymphoma, a second primary malignancy, HIV infection, CNS involvement, supportive care only, or loss to follow-up after initial treatment cycles were excluded.

Survival status and follow-up information were updated through December 31, 2024, from available medical record files. No face-to-face interviews or surveys were conducted. The collected variables included baseline demographic and clinical characteristics, staging, ECOG performance status, comorbidities, laboratory parameters, prognostic variables, treatment details, treatment-related toxicities, dose modifications, regimen changes, response assessment, progression, and survival outcomes.

A structured data collection proforma was used as the study tool. The proforma captured clinical and treatment variables such as age, sex, disease stage, ECOG performance status, comorbidities, laboratory results, International Prognostic Index, CNS-IPI, cell of origin, expression markers, first-line treatment regimen, use of growth factors, febrile neutropenia, other toxicities, dose reductions, treatment delays, regimen changes, treatment response, progression-free survival, and overall survival. Age was grouped in 5-year intervals: 60-65, 66-70, 71-75, 76-80, 81-85, and $\geq$ 86. Staging was based on PET-CT and/or bone marrow biopsy according to institutional practice. Cell of origin was determined by immunohistochemistry using the Hans algorithm and classified as germinal center B-cell (GCB) or non-germinal center B-cell (non-GCB) subtype. Treatment selection was at the treating physician's discretion and individualized based on patient fitness, comorbidities, performance status, and overall clinical judgment. As this was a retrospective study, the specific factors influencing treatment selection were not consistently documented in the medical records and therefore could not be analyzed.

Standard R-CHOP consisted of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg) intravenously on day 1, and prednisone 100 mg orally on days 1-5. R-mini-CHOP consisted of rituximab 375 mg/m^2, cyclophosphamide 400 mg/m^2, doxorubicin 25 mg/m^2, vincristine 1 mg intravenously on day 1, and prednisone 40 mg/m^2 orally on days 1-5. Dose modifications and supportive measures, including growth factor support, were implemented at the treating physician's discretion, based on individual patient characteristics and treatment tolerance.

Response assessment was based on PET-CT imaging performed during routine clinical follow-up and categorized according to Lugano response criteria using the Deauville 5-point scale (1: no uptake; 2: uptake $\leq$ mediastinum; 3: uptake > mediastinum but $\leq$ liver; 4: uptake moderately > liver; 5: uptake markedly > liver and/or new FDG-avid lesions). Deauville scores of 1-3 were considered a complete metabolic response; scores of 4-5 with reduced uptake from baseline were considered a partial metabolic response; and increased uptake from baseline or new FDG-avid lesions consistent with lymphoma were considered progressive metabolic disease. In cases of treatment failure, first-line therapy was changed at the physician's discretion. Progression-free survival was defined as the time from treatment initiation to disease progression or death from any cause.

Overall survival was defined as the time from treatmentinitiation to death from any cause. Follow-up was calculated from treatment initiation to death or last documented clinical contact.

Data were analyzed using SPSS version 20. Continuous variables were summarized as medians with ranges, while categorical variables were presented as frequencies and percentages. Kaplan-Meier survival analysis was used to estimate progression-free survival and overall survival. Differences between survival curves were compared using the log-rank test. Median follow-up was estimated using the reverse Kaplan-Meier method. Cox proportional hazards regression analysis was performed to identify factors associated with survival outcomes and to calculate adjusted hazard ratios. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 175 patients aged ≥60 years treated for diffuse large B-cell lymphoma between 2018 and 2022 were included in the analysis. A total of 76 patients received standard R-CHOP and 99 received alternative regimens. Flow diagram of patient selection and treatment group allocation is displayed in Fig. (**1**).

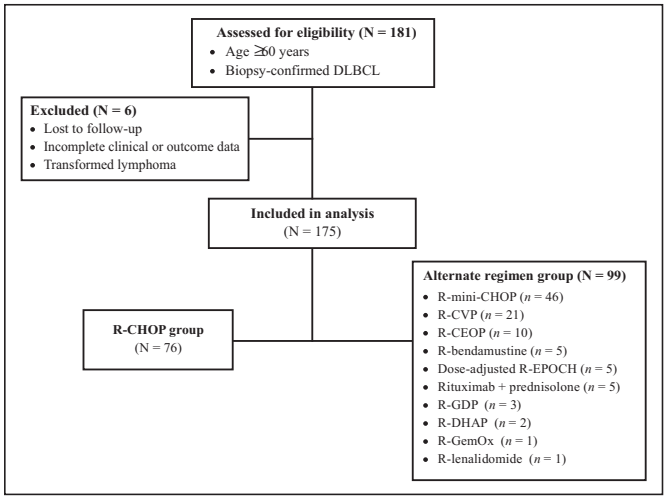

Fig. (1): Flow diagram of patient selection and treatment group allocation. **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; **R-mini-CHOP:** dose-reduced R-CHOP; **R-CVP:** rituximab, cyclophosphamide, vincristine, and prednisone; **R-CEOP:** rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; **R-GemOx:** rituximab, gemcitabine, and oxaliplatin; **R-DHAP:** rituximab, dexamethasone, high-dose cytarabine, and cisplatin; **R-GDP:** rituximab, gemcitabine, dexamethasone, and cisplatin; **R-EPOCH:** rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

The median age was 66 years, and 58.3% of patients were male. Most patients had an ECOG performance status of 1-2 (77.1%). Stage IV disease was present in 52% of patients. High-risk features were common: 37.1% of patients had a high International Prognostic Index (IPI) score, and 40.6% had a high CNS-IPI score. The germinal center B-cell subtype was more frequent than the non-GCB subtype (52.6% *vs.* 35.4%), and extranodal disease was present in 24% of patients. Baseline patient and disease characteristics are summarized in Table **1**.

Table 1: Baseline demographic ,clinical ,and disease characteristics of elderly patients with diffuse large B -cell lymphoma .

Variable	Frequency (%)
Age (years)	
60 - 65	66 (37.7)
66 - 70	43 (24.6)
71 - 75	42 (24.0)
76 - 80	17 (9.7)
80 - 85	5 (2.9)
+86 years	2 (1.1)
Gender	
Male	102 (58.3)
Female	73 (41.7)
Comorbidities	
Diabetes mellitus	69 (39.4)
Hypertension	73 (41.7)
Ischemic heart disease	33 (18.9)
ECOG Performance Status	
0	0 (0)
1	98 (56.0)
2	37 (21.1)
3	32 (18.3)
4	8 (4.6)
Disease Stage	
Stage I	11 (6.3)
Stage II	26 (14.9)
Stage III	32 (18.3)
Stage IV	91 (52.0)
Unknown	15 (8.6)
Cell of Origin	
GCB	92 (52.6)
Non-GCB	62 (35.4)
Unknown	21 (12.0)
IPI Score	
Low (0 - 1)	52 (29.7)
Intermediate (2 - 3)	53 (30.3)
High (4 - 5)	65 (37.1)
Unknown	5 (2.8)
CNS-IPI Score	
0 - 1	46 (26.3)
2 - 3	53 (30.3)
4 - 6	71 (40.6)
Unknown	5 (2.8)

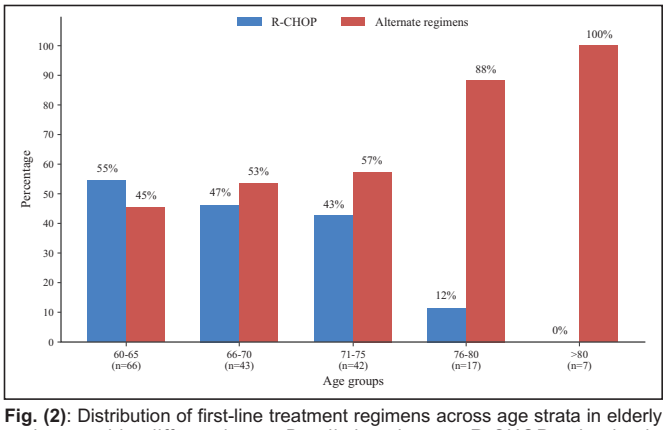

Fig. (2): Distribution of first-line treatment regimens across age strata in elderly patients with diffuse large B-cell lymphoma. R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone .

R-CHOP was more commonly used in the 60-65-year age group. In patients aged 66-75 years, the proportion treated with R-CHOP was lower than that treated with less intensive regimens. However, the use of standard R-CHOP was markedly lower in patients aged >75 years (**Fig. 2**). The average number of cycles administered was six in both groups.

Interim response assessment by PET-CT was available for 106 patients, and most patients in both groups achieved either a complete or a partial metabolic response. Complete and partial responses were observed in 37.5% and 54.2% of patients treated with R-CHOP, compared with 31.0% and 62.1% of those receiving alternate regimens, respectively. End-of-treatment response assessment was available for 169 patients. Complete metabolic response was more frequent in the R-CHOP group than in the alternate-regimen group (58.0% *vs.* 50.5%), while partial response was less frequent (4.0% *vs.* 7.5%). The combined complete or partial metabolic response rate was 61.8% with R-CHOP and 58.1% with alternate regimens. Progressive metabolic disease at the end of treatment did not differ significantly between groups (38.0% *vs.* 42.0%) (**Table 2**).

Table 2: Response assessment at interim analysis and end of treatment.

Response	R-CHOP-Interim (n = 48), n(%)	Other regimens-Interim (n = 58), n(%)	R-CHOP-End of treatment (n = 76), n (%)	Other regimens-End of treatment (n = 93), n (%)	p-value
Complete response (CR)	18 (37.5)	18 (31.0)	44 (58.0)	47 (50.5)	0.020
Partial response (PR)	26 (54.2)	36 (62.1)	3 (4.0)	7 (7.5)	0.001
Progressive disease (PD)	4 (8.3)	4 (6.9)	29 (38.0)	39 (42.0)	0.070

The median follow-up duration, estimated using the reverse Kaplan-Meier method, was 61 months. The median progression-free survival (PFS) for the overall cohort was 59 months (95% CI: 43.4-74.7) (**Fig. 3A**). The median overall survival (OS) for the overall cohort was 59 months (95% CI: 43.0-74.0) (**Fig. 3B**).

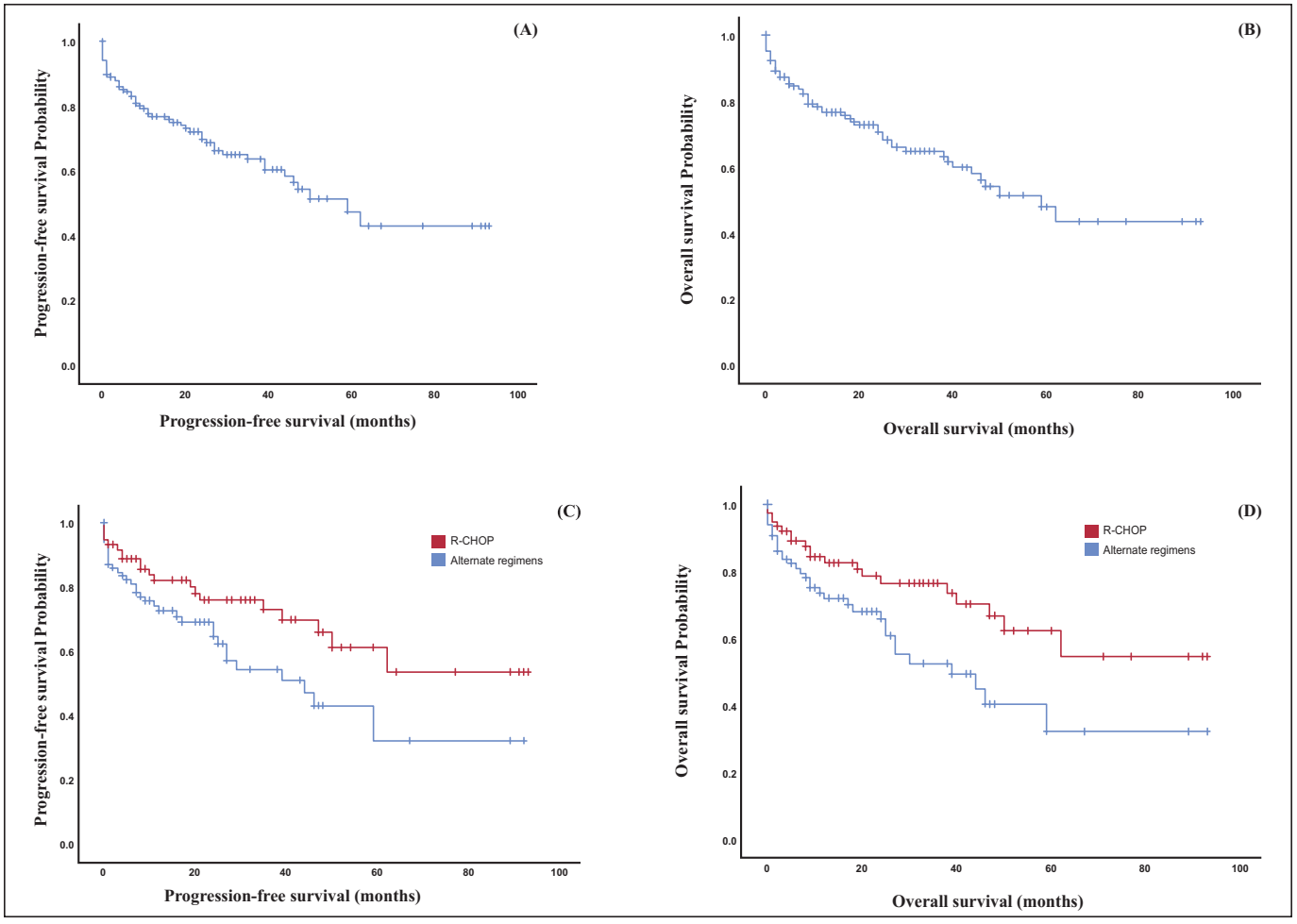

Fig. (3): Kaplan–Meier survival analyses.
(A) Progression-free survival in the overall cohort.
(B) Overall survival in the overall cohort.
(C) Progression-free survival stratified by treatment regimen.
(D) Overall survival stratified by treatment regimen.

Patients treated with R-CHOP demonstrated significantly longer PFS than those receiving alternative regimens (log-rank p < 0.01). The median PFS was not reached in the R-CHOP group. In contrast, it was 44 months in the alternate-regimen group (95% CI: 37.5-57.5) (**Fig. 3C**). Overall survival was also significantly superior in the R-CHOP group compared with the alternate-regimen group (log-rank p < 0.01). The median OS was not reached in the R-CHOP group, whereas it was 45 months in the alternate-regimen group (95% CI: 35.0-65.9) (**Fig. 3D**).

Among patients treated with R-CHOP, 12 (15.7%) were switched to an alternate regimen, most commonly R-mini-CHOP, due to poor treatment tolerance. Dose reductions were required in 20 patients receiving R-CHOP. They were observed across all age groups, with higher frequencies in older patients (**Fig. 4**). Grade 3/4 febrile neutropenia occurred in 36 patients (20.6%) and was the most common severe toxicity. The highest frequencies of grade 3/4 febrile neutropenia were observed in patients aged 60-65 years (28.8%), 76-80 years (29.4%), and >80 years (28.6%), whereas lower frequencies were observed in patients aged 66-75 years. Febrile neutropenia was significantly associated with age group (p=0.001), as shown in Table **3**.

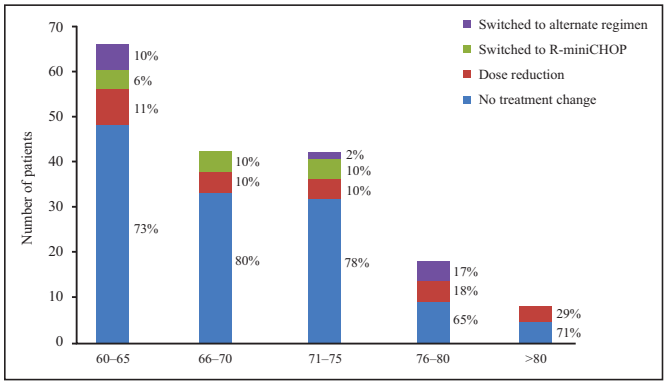

Fig. (4): Treatment modifications across age strata, including dose reductions and switches to **R-mini-CHOP** or alternate regimens. R-mini-CHOP: dose-reduced rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 3: Grade 3/4 febrile neutropenia by age strata.

Ages strata (years)	Febrile neutropenia,n (%)	p-value
60-65	19 (28.8)	0.001
66-70	4 (9.3)	
71-75	6 (14.3)	
76-80	5 (29.4)	
>80	2 (28.5)	

Nine deaths occurred during treatment, including two in the R-CHOP group and seven in the alternate-regimen group; several of these deaths occurred early, after one to two cycles of therapy. Exploratory Cox regression analyses did not identify any comorbidity as significantly associated with overall survival or progression-free survival; all p-values were >0.05, and all 95% confidence intervals included unity (**Table 4**).

Table 4: Exploratory Cox regression analysis of comorbidities for overall survival and progression-free survival.

Comorbidity	Overall survival			Progression-free survival		
	HR	95% CI	p-value	HR	95% CI	p-value
Diabetes mellitus	0.98	0.56-1.71	0.943	0.93	0.53-1.69	0.828
Hypertension	1.20	0.66-2.18	0.549	1.17	0.65-2.12	0.591
Ischemic heart disease	1.11	0.58-2.12	0.751	1.20	0.63-2.27	0.576
Other comorbidities	1.02	0.95-1.11	0.564	1.03	0.95-1.12	0.417

CI: Confidence interval, HR: Hazard ratio.

DISCUSSION

This study provides a real-world view of treatment patterns, toxicity, and outcomes in elderly patients with diffuse large B-cell lymphoma (DLBCL) treated at a tertiary care center in Pakistan. To our knowledge, this is the first detailed report describing this patient population from this region, where data on elderly DLBCL remain limited [18].

One characteristic feature of this patient population was the high burden of advanced disease. More than half of the patients presented with stage IV disease, 37.1% had high International Prognostic Index (IPI) scores, and 40.6% had high CNS-IPI scores. This distribution is consistent with findings from large registry studies in elderly patients, including data from the SEER registry and Latin American cohorts, where delayed presentation and limited access to care are associated with advanced-stage disease at diagnosis [18-20]. These observations place our cohort within the expected spectrum of elderly DLBCL patients treated outside randomized clinical trials.

The choice of treatment showed a clear trend with age. R-CHOP was primarily used in patients aged 60-65 years, with its use declining with increasing age and the use of alternative regimens increasing. This pattern is typical of routine clinical practice where functional status, burden of comorbidity, and expected tolerability of therapy often have more influence on treatment decisions than does chronological age alone [21, 22]. While interim and end-of-treatment response rates were comparable across treatment groups, patients treated with R-CHOP had markedly extended progression-free and overall survival. Most patients receiving alternative regimens were treated with dose-reduced approaches, mainly R-mini-CHOP, due to concerns about tolerability rather than treatment resistance. These findings are consistent with population-based studies showing that, despite improved tolerability, R-mini-CHOP is associated with inferior survival outcomes compared with standard-dose R-CHOP in elderly patients [23-25].

Treatment modification was primarily due to treatment-related toxicity. Overall, about one in six patients treated

with R-CHOP required a regimen change, and dose reductions occurred across all age groups but were more common in older patients. These results highlight the difficulties of administering intensive chemotherapy to older people. The most common adverse event was grade III/IV febrile neutropenia. Poor performance status, advanced-stage disease, elevated LDH, anemia, comorbidities, and bone marrow involvement have been identified in previous studies as predictors of febrile neutropenia in elderly patients receiving R-CHOP, with inconsistent use of primary granulocyte colony-stimulating factor prophylaxis adding to the risk [21, 26]. Together, these findings suggest that treatment-related toxicity may be more related to functional reserve than age per se, highlighting the importance of individualized risk assessment and proactive supportive care.

Response rates were similar between treatment groups, with complete response rates approaching 50% in both cohorts. These results are consistent with data from low- and middle-income settings, where a complete response rate of ~50-55% has been reported among elderly patients treated outside clinical trials [19, 20]. Registry data from high-income countries have reported complete response rates of > 65-70% with R-CHOP [11], in contrast. These differences are likely due to differences in stage at presentation, access to supportive care, availability of growth factor support, and the ability to deliver full-dose chemotherapy rather than intrinsic biological differences.

Overall, the survival outcomes in this cohort were consistent with the existing observational data. Previous studies have reported a median overall survival of 40-60 months in patients aged 60-80 years, with outcomes declining substantially beyond age 80 [19, 20, 22, 24]. The median overall survival in this study was 59 months and is in line with these reports. Importantly, patients treated with R-CHOP had significantly better survival outcomes compared with those receiving other regimens, supporting the continued role of R-CHOP as the preferred curative-intent backbone for medically fit elderly patients [23, 24, 27].

Exploratory analyses did not find any significant association between individual comorbidities and progression-free or overall survival. This finding is consistent with the notion that functional status and disease-related characteristics likely have more prognostic significance than comorbidity burden alone. Similarly, the Geriatric Prognostic Index emphasizes the importance of performance status, albumin, and LDH, rather than individual comorbidities, and the need to integrate frailty into the management of elderly patients with DLBCL [21, 22, 28].

LIMITATIONS

Several limitations of this study should be acknowledged. The retrospective single-center design limits generalizability. Frailty was not formally assessed using standardized geriatric tools, precluding correlation between geriatric parameters and survival outcomes. In addition, treatment allocation was non-randomized and based on physician judgment and baseline fitness, limiting causal interpretation regarding comparative efficacy between regimens. Furthermore, the specific rationale for selecting less commonly used frontline regimens, information regarding subsequent lines of therapy, and growth factor support were not consistently available, precluding further analysis of treatment selection and post-progression management, as well as their potential influence on treatment-related toxicity and survival outcomes. Despite these limitations, the study provides important real-world insight into treatment practices and outcomes among elderly patients with DLBCL in a resource-limited setting.

CONCLUSION

R-CHOP remains associated with superior survival outcomes in elderly patients with diffuse large B-cell lymphoma who can tolerate intensive treatment. Treatment modification and toxicity increase with advancing age, supporting the need for individualized, frailty-informed treatment decisions.

ETHICS APPROVAL

The study was approved by the Ethical Review Committee (ERC) of Aga Khan University Hospital (Ref. 2022-7737-22639). All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

De-identified datasets are available from the corresponding author upon reasonable request.

FUNDING

This study received no specific funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

IMA, WAK, MM, AS, and SRK contributed to study conceptualization, data analysis and interpretation, and

manuscript drafting. TD, MS, and MRS contributed to data acquisition and analysis. NZ and MAH contributed to data interpretation and manuscript writing. YAR and SRK conceived and designed the study. MM prepared the study protocol, critically reviewed the manuscript, and revised it. All authors critically reviewed and approved the final manuscript and are responsible for the content.

GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (GPT-4, OpenAI) only to obtain language suggestions and to perform minor proofreading in some parts of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the published article.

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