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Comparison of R-CHOP-14 and R-mini-CHOP in older adults with diffuse large B-cell lymphoma—A retrospective multicenter cohort study

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma entity, and its incidence increases with age. There is a paucity of data regarding use of biweekly R-CHOP (R-CHOP-14) in patients ≥80 years of age. We performed a retrospective cohort study of patients with DLBCL aged ≥80 years treated with R-CHOP-14 and R-miniCHOP in two academic tertiary centers in Germany between 01/01/2005 and 12/30/2019. Overall, 79 patients were included. Median age was 84 years (range 80–91). Despite higher CR rates with R-CHOP-14 (71.4% vs. 52.4%), no statistically significant difference could be found between patients treated with R-CHOP-14 and R-miniCHOP regarding overall survival (OS) ($p = .88$, HR 0.94, 95% CI = 0.47–1.90) and progression-free survival (PFS) ($p = .26$, HR 0.66, 95% CI = 0.32–1.36). At a median follow-up of 40 months, the 2-year OS rates were 56% with R-CHOP-14 and 53% with R-miniCHOP. Two-year PFS rates were 46% for R-CHOP-14 and 50% for R-mini-CHOP. Relative dose intensity of chemotherapy did not correlate with OS ($p = .72$). With the caveat of a retrospective cohort study, we conclude that lacking a difference in OS, R-miniCHOP should be preferred for most patients with untreated DLBCL aged ≥80 years.

KEYWORDS
aged 80 and over, diffuse large B-cell lymphoma, dose intensity, R-CHOP-14, R-miniCHOP

Novelty statements

What is the new aspekt of your work?

This is the first study to provide data on dose dense biweekly R-CHOP-14 in old adults with DLBCL aged >80 years.

Funding information
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What is the central finding of your work?
There is no difference in survival outcomes between R-CHOP-14 and R-miniCHOP.

What is the specific clinical relevance of your work?
Dose reduced regimens such as R-miniCHOP should remain the standard of care for older adults with DLBCL. Dose intensification does not improve outcomes.

1 | INTRODUCTION

Non-Hodgkin lymphoma (NHL) ranks as the fifth most prevalent cancer among men and the sixth among women.[1] Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype of NHL, and its frequency increases steadily with age.[2] Approximately 40% of patients with DLBCL are ≥70 years old. Due to demographic change, the number of elderly people in the population will increase in the coming decades,[3] with estimates suggesting that by 2030, women may live up to 85 years and men up to 80 years.[4] Consequently, individuals over the age of 65 years will soon make up over 20% of the global population.[5] As a result, the number of elderly patients with DLBCL will increase significantly in the coming decades. In contrast to younger patients, only a small proportion of elderly patients are treated in clinical trials.[6]

The inclusion of the anti-CD20 antibody rituximab into the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) for older adults with DLBCL, leading to the development of the R-CHOP-21 regimen, marked a significant advancement.[7] The RICOVER-60 trial established 6 cycles of biweekly dose-dense R-CHOP-14 regimen in patients with DLBCL aged 60–80 years as a standard of care.[8] Subsequently, randomized clinical trials failed to demonstrate a benefit of the dose dense biweekly R-CHOP-14 regimen as compared to R-CHOP given every three weeks (R-CHOP-21), so that R-CHOP-21 is more frequently used in clinical practice.[9,10] Nevertheless, with increasing age additional difficulties arise, as not all older adults are able to tolerate full-dose R-CHOP.

Thus, in certain older adults with DLBCL, it is necessary to consider dose reduction of chemotherapy. A retrospective analysis of the RICOVER-60 trial and CHOP-R-ESC trials conducted by the DSHNHL (German High-Grade Non-Hodgkin's Lymphoma Study Group) revealed that treatment-related mortality is notably higher in patients aged 75 years and above who received full-dose R-CHOP treatment.[11] It is estimated that approximately 20%–25% of all DLBCL patients are not suitable candidates for full-dose frontline R-CHOP treatment.[12] As a result, in older adults, attenuated dose regimens are preferred. In 2011, Peyrade et al. conducted a landmark trial that established the R-miniCHOP regimen as a viable alternative for patients aged over 80 years.[13] A total of 149 patients were treated with the R-miniCHOP protocol in this study, the ORR was 78%, overall survival (OS) at 2 years was 59%, and 2-year progression-free survival (PFS) was 47%. The study concluded that R-miniCHOP offers a good balance between efficacy and safety in elderly patients aged over 80 years with diffuse large B-cell lymphoma and suggests considering R-miniCHOP as the new standard treatment for this subgroup of patients. However, even with this regimen, outcomes remain modest underlining the need for more effective treatment in this population.

To our knowledge, no study has specifically demonstrated the role of dose dense biweekly R-CHOP-14 regimen in this age group. Our retrospective analysis aims to examine the use of R-CHOP-14 and compare it to dose attenuated regimens (e.g., R-miniCHOP) while taking into account both patient- and disease-related characteristics to allow for adequate risk stratification.

2 | METHODS

This is a retrospective cohort study of older adults with DLBCL treated with dose dense chemotherapy with R-CHOP-14 or R-miniCHOP at two academic tertiary centers in Germany in which biweekly R-CHOP (R-CHOP-14) was systematically preferred over R-CHOP every three weeks (R-CHOP-21), regardless of patient age. We performed an electronic medical record search of institutional records for all patients with DLBCL ≥ 80 years old treated between January 2005 and December 2019. All patients with diagnosis of DLBCL ≥ 80 years old at the time point of diagnosis for whom the decision to treat with R-CHOP-like immunochemotherapy was made including at least rituximab, doxorubicin, and either cyclophosphamide or vincristine were included. Informed consent was an additional prerequisite for study inclusion for patients who were still alive at the time of the analysis. Patients were grouped retrospectively into two cohorts (R-CHOP-14 or R-miniCHOP) according to the intended dose intensity as applied during the first treatment cycle. Two patients who received R-CHOP-21 were allocated in the R-CHOP-14 cohort.

Endpoints were overall (OS), progression-free (PFS), and event-free survival (EFS) as well as outcomes according to relative dose intensity (RDI). OS was defined as time from start of treatment to death, PFS at the time from start of treatment to disease progression/relapse, or death. Event-free survival was defined as time from start of treatment to death, progression/relapse, or treatment discontinuation. Dose intensity was defined as the dose in mg per m^2 per week. RDI was calculated as the percentage of the dose intensity achieved divided by the intended dose intensity for doxorubicin, cyclophosphamide, and vincristine separately, the average value was calculated for each patient. The biweekly R-CHOP-14 regimen was used as a reference for the calculation (RDI 100%), so that the RDI is 67% for a patient who receives full dose R-CHOP-21 regimen without delays/dose reduction and 30% for R-miniCHOP every three weeks. Patient data, including baseline characteristics, histology, dose intensity, and treatment outcomes, such as response, survival, relapse, or treatment

discontinuation, were extracted from the hospital medical electronic records. In the absence of a documented death and/or cause and/or date of death in the hospital records, information was obtained by the local health departments. The Charlson Comorbidity Index (CCI) was retrospectively calculated for each patient at the time of diagnosis, whereas the diagnosis of lymphoma was not included in the calculation. Treatment-related mortality was defined as any death which occurred during the planned course of immunochemotherapy which was not related to lymphoma. This study was approved by the ethics committee of Saarland (approval number 16/21). Study conduct and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[14] recommendations for cohort studies.

For all analyses, SPSS Statistics version 28.0.1.0 (IBM Corp. Released 2021, Armonk) was used. Baseline characteristics were analyzed with descriptive statistics, Cox regression, comparisons among cohorts were done using Fisher's exact test, Chi-square test, *t*-test for categorical and continuous variables, and log-rank test. Survival curves were generated using Kaplan–Meier estimates, with a *p*-value of .05 used as significance level. To identify factors associated with survival, we performed univariate analysis using log-rank tests. Each variable was individually examined for its association with survival, and variables showing a significant association (*p*-value <.05) were included in the multivariate analysis. All analyses were performed separately by cohorts as in total cohort, R-CHOP-14 cohort, and R-miniCHOP cohort.

The Forest Plot was created with StatsDirect, version 3.3.6 (StatsDirect Ltd, Wirral, UK), presenting a comparative OS analysis between two cohorts, R-miniCHOP and R-CHOP-14, across various characteristics. The hazard ratios and corresponding 95% confidence intervals were used to describe the results.

3 | RESULTS

The database search identified 108 potentially eligible patients. Of those, 29 were excluded due to primary central nervous system lymphoma ($n = 9$), age <80 years ($n = 5$), insufficient data ($n = 4$), non-R-CHOP-like treatment ($n = 4$), therapy and participation rejection (n = 4), and others (n = 3) resulting in an analysis set of 79 patients.

Relevant patient characteristics are summarized in Table 1. In total, 55 (70%) patients received R-CHOP-14 and 24 (30%) patients received R-miniCHOP. Median age across all patients was 83 years (range 80–91). Patients in the R-CHOP-14 cohort were younger (patients aged >82 years 47.2% vs. 75%, $p = .079$), more often female (60% vs. 37.5%, $p = .065$), and less often diagnosed after 2015 (34.5% vs. 83.3%, $p = .058$). Furthermore, patients in the R-CHOP-14 cohort had more often Eastern Cooperative Oncology Group performance status (ECOG) 2–4 (58.2% vs. 37.5%, $p = .022$) and advanced stage disease (60.1% vs. 41.7%, $p = .046$).

With a median follow-up of 40 months (range 0–109), the 2-year OS, PFS, and EFS rates across all patients were 55%, 46%, 40%, respectively. Median OS, PFS, and EFS were 37, 22, and 12 months, respectively.

When comparing the two treatment cohorts, R-CHOP-14 and R-miniCHOP, no statistically significant difference could be found regarding OS ($p = .88$, HR 0.94, 95%CI = 0.47–1.90), PFS ($p = .26$, HR 0.66, 95% CI = 0.32–1.36), and EFS ($p = .27$, HR 0.70, 95% CI = 0.37–1.32) (Figure 1). Two-year OS for patients treated with R-CHOP-14 was 56% versus 53% with R-miniCHOP. The median follow-up for R-CHOP-14 was 49 months and for R-miniCHOP 32 months.

Median OS and the 2-year OS rates were 37 months and 56% with R-CHOP-14 and not reached, and 53% with R-miniCHOP. Median PFS and 2-year PFS rates were 22 months and 46% for R-CHOP-14 and 17 months and 50% for R-mini-CHOP. Median EFS and 2-years EFS rates were 9 months and 39% for R-CHOP-14 as opposed to 17 months and 43% for R-miniCHOP.

Forty-four patients (56%) died within the follow-up period in the whole cohort. In R-CHOP-14 cohort 33 (60%) died during follow-up, 12 (36%) deaths were reported due to lymphoma progression, 3 (9%) due to infection, 4 (12%) due to cardiac disease, 2 (6%) due to other reasons, and 13 (36%) patients for unknown reasons. In R-miniCHOP cohort 11 (45%) deaths were reported, 6 (55%) due to lymphoma progression, 1 due to sepsis (4%), and for 4 deaths (36%) the cause of death remained unknown. The cumulative incidence of deaths over time according to cause of death is shown in Figure S1. Treatment-related mortality was 9% (5/55) in the R-CHOP-14 cohort versus 4% (1/24) during treatment with R-miniCHOP.

Progressive disease/relapse was reported in 18 patients total (23%), of those 11 (20%) patients in R-CHOP-14 cohort and 7 (29%) R-miniCHOP cohort in total. During the first year of follow-up, progressive disease/relapse events occurred in 5 patients (45%) treated with R-CHOP-14 and in all 7 patients (100%) who relapsed in the R-miniCHOP cohort. Beyond the 12-month mark post-therapy, relapses were only observed in the R-CHOP-14 cohort, specifically in 6 (55%) patients. Treatment discontinuation due to toxicity occurred in 22 patients total (28%), 16 patients (29%) treated with R-CHOP-14 versus 6 (25%) in the R-miniCHOP cohort.

After treatment completion, 71.4% of patients treated with R-CHOP-14 had a complete remission (CR) as opposed to 52.4% in the R-miniCHOP cohort ($p \leq 001$) (Table 2).

In the total cohort, patients aged between 80 and 82 years had numerically longer median survival than patients aged above 82 (51 vs. 36 months, $p = .059$). The univariate analyses for total cohort, R-CHOP-14 cohort, and R-miniCHOP are shown in Tables S1–S3. Patients who discontinued treatment due to toxicity ($n = 21$, 26%) had poor survival, with a median OS of 9 months (univariate $p = .033$). Patients with CCI of 1–5 had only numerically shorter median survival than patients with CCI of 0 (19 and 75 months, respectively) ($p = .255$). An ECOG score >1 was associated univariately with shorter OS, PFS, and EFS ($p \leq .001$; .001; .002), with 2-year OS and PFS rates of 70% versus 38% and 59% versus 37%, respectively (Figure 2). Elevated LDH levels were associated univariately with shorter OS and EFS ($p = .007$; .004) (Table 3). In the multivariate model, only an ECOG score >1 was significantly

TABLE 1 Patients' characteristics at diagnosis.

Characteristics	R-CHOP-14, *n* (%)	R-mini-CHOP, *n* (%)	*p*-Value	Total, *n* (%)
Age			.079	
80–82	29 (52.7%)	6 (25%)		35 (44.3%)
>82	26 (47.3%)	18 (75%)		44 (55.7%)
Gender			.065	
Male	22 (40%)	15 (62.5%)		37 (46.8%)
Female	33 (60%)	9 (37.5%)		42 (53.2%)
Year of diagnosis			.058	
≤2015	36 (65.5%)	4 (16.7%)		40 (50.6%)
>2015	19 (34.5%)	20 (83.3%)		39 (49.4%)
ECOG performance status			**.022**	
0–1	23 (41.8%)	15 (62.5%)		33 (41.8%)
2–4	32 (58.2%)	9 (37.5%)		46 (58.2%)
CCI			.557	
0	19 (34.5%)	10 (41.7%)		29 (36.7%)
1–5	36 (65.5%)	14 (58.3%)		50 (63.3%)
Stage			**.046**	
1–2	15 (27.2%)	14 (58.3%)		29 (36.7%)
3–4	38 (60.1%)	10 (41.7%)		48 (60.8%)
Transformation	2 (3.6%)	0		2 (2.5%)
IPI score			.875	
0–1	8 (15.1%)	2 (8.3%)		10 (13%)
2–5	45 (84.9%)	22 (91.7%)		67 (87%)
B-Symptoms			.793	
Absent	40 (75.5%)	18 (78.3%)		58 (76.3%)
Present	13 (24.5%)	5 (21.7%)		18 (23.7%)
Extranodal			.887	
Absent	21 (42%)	7 (38.9%)		28 (41.2%)
Present	29 (58%)	11 (61.1%)		40 (58.8%)
RDI			.185	
<80%	24 (47.1%)	18 (94.7%)		42 (60%)
≥80%	27 (52.9%)	1 (5.3%)		28 (40%)
Albumin			.485	
≤34 g/L	17 (30.9%)	11 (50%)		28 (36.4%)
>34 g/L	38 (69.1%)	11 (50%)		49 (63.6%)
LDH			.492	
≤Normal value	18 (32.7%)	6 (25%)		24 (30.4%)
>Normal value	37 (67.3%)	18 (75%)		55 (69.6%)
Vitamin D			.329	
<10 ng/mL.	26 (89.7%)	9 (100%)		35 (92.1%)
≥10 ng/mL	3 (10.3%)	0		3 (7.9%)
ß2-Mikroglobulin				
≤3.0 mg/L	11 (20.7%)	1 (9.1%)	.847	12 (18.7%)
>3.0 mg/L	42 (79.3%)	10 (90.9.6%)		52 (81.3%)
BMI before therapy			.638	
<18.5	2 (4.4%)	1 (8.3%)		3 (5.3%)
18.5–25.0	18 (40%)	3 (25%)		21 (36.8%)
>25.0	25 (55.5%)	8 (66.7%)		33 (57.9%)

TABLE 1 (Continued)

Characteristics	R-CHOP-14, *n* (%)	R-mini-CHOP, *n* (%)	*p*-Value	Total, *n* (%)
BMI after therapy			.984	
<18.5	4 (9.3%)	6 (60%)		10 (18.9%)
18.5–25.0	27 (62.8%)	4 (40%)		31 (58.5%)
>25.0	12 (27.9%)	0		12 (22.6%)

Note: Bold indicates significant *P* values.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

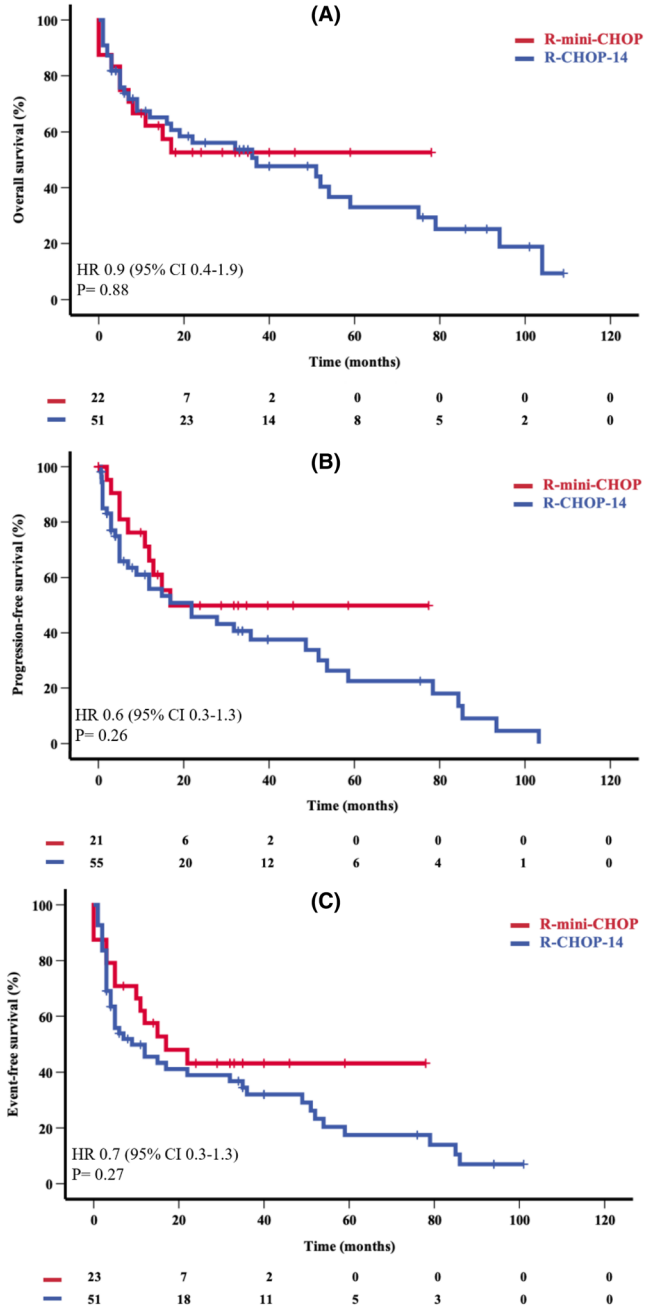

FIGURE 1 Comparison of outcomes of the R-CHOP-14 and R-mini-CHOP cohorts. Kaplan–Meier curves of overall survival (A), progression-free survival (B), and event-free survival (C) for all analyzed patients in the cohorts of R-CHOP-14 and R-mini-CHOP.

associated with shorter OS and EFS ($p < .001$, HR 2.2, 95% CI = 1.4–3.4, and $p = .002$, HR 1.7, 95% CI = 1.2–2.5) (Table 3).

In the R-CHOP-14 cohort, an ECOG score >1 and an LDH value above normal were univariately associated with shorter OS as well as PFS, and OS as well as EFS ($p = .004$; .009; .011; .002) (Table S2). Only the association with ECOG remained significant in the multivariate model ($p = .006$, HR 2.2, 95% CI = 1.2–4) (Table 3).

For the R-miniCHOP cohort, the univariate analysis revealed a statistically significant association of age with shorter OS ($p = .041$) and ECOG > 1 with shorter OS, PFS, and EFS ($p = .019$; .016; .012) (Table S3). In the same cohort, the multivariate analysis showed only statistically significant association between ECOG < 1 and OS ($p = .025$, HR 1.9, 95% CI = 1.0–3.6) (Table 3).

Median RDI and median treatment duration in R-CHOP-14 cohort were 83%; 16 months and in R-miniCHOP cohort 37%; 21 months. Relative dose intensity (RDI) was not associated with OS, PFS, or EFS in a statistically significant manner neither in the whole cohort nor in the two treatment groups. Overall, the patients who received an RDI ≥80% achieved a 2-year overall survival (OS) rate of 60% and a median survival of 36 months, whereas those with less than 80% had a 2-year OS rate of 57% and a median OS of 51 months (Figure 2). The PFS with an RDI of ≥80 was 22 months numerically higher than RDI of <80% with 13 months, but this difference did not reach statistical significance ($p = .84$) (Figure 2).

In the forest plot comparing OS between R-CHOP-14 versus R-miniCHOP in subgroups defined by various factors (Figure 3), no significant difference in outcome was found in any subgroup. Some factors, such as age of 80–82 years, an ECOG status of 0–1, and extranodal involvement showed a non-significant inclination toward favoring R-miniCHOP. An LDH value within the normal range, IPI of 0–1, and the absence of extranodal involvement tended to favor R-CHOP-14.

4 | DISCUSSION

Our study is to our knowledge, the first to examine dose-dense R-CHOP-14 in patients aged >80 years with DLBCL. We assessed the outcomes and prognostic factors associated with R-CHOP-14 and R-miniCHOP treatment in this population.

The current study cohort is representative of the very elderly population with a median age of 83 years. The high incidence of

TABLE 2 Response rates of total cohort, R-CHOP-14 cohort, R-mini-CHOP cohort.

Response rate	R-CHOP-14 *n* (%)		Mini-R-CHOP *n* (%)		Total cohort *n* = (%)	
	Interim restaging	Final restaging	Interim restaging	Final restaging	Interim restaging	Final restaging
PR	29 (66%)	10 (23.9%)	9 (56.2%)	6 (28.6%)	38 (63.3%)	16 (25.4%)
CR	11 (25%)	30 (71.4%)	5 (31.2%)	11 (52.4%)	16 (26.7%)	41 (65.1%)
PD	4 (9%)	2 (4.7%)	2 (12.6%)	4 (19%)	6 (10%)	6 (9.5%)

Abbreviations: CR, complete remission; PD, progredient disease; PR, partial remission.

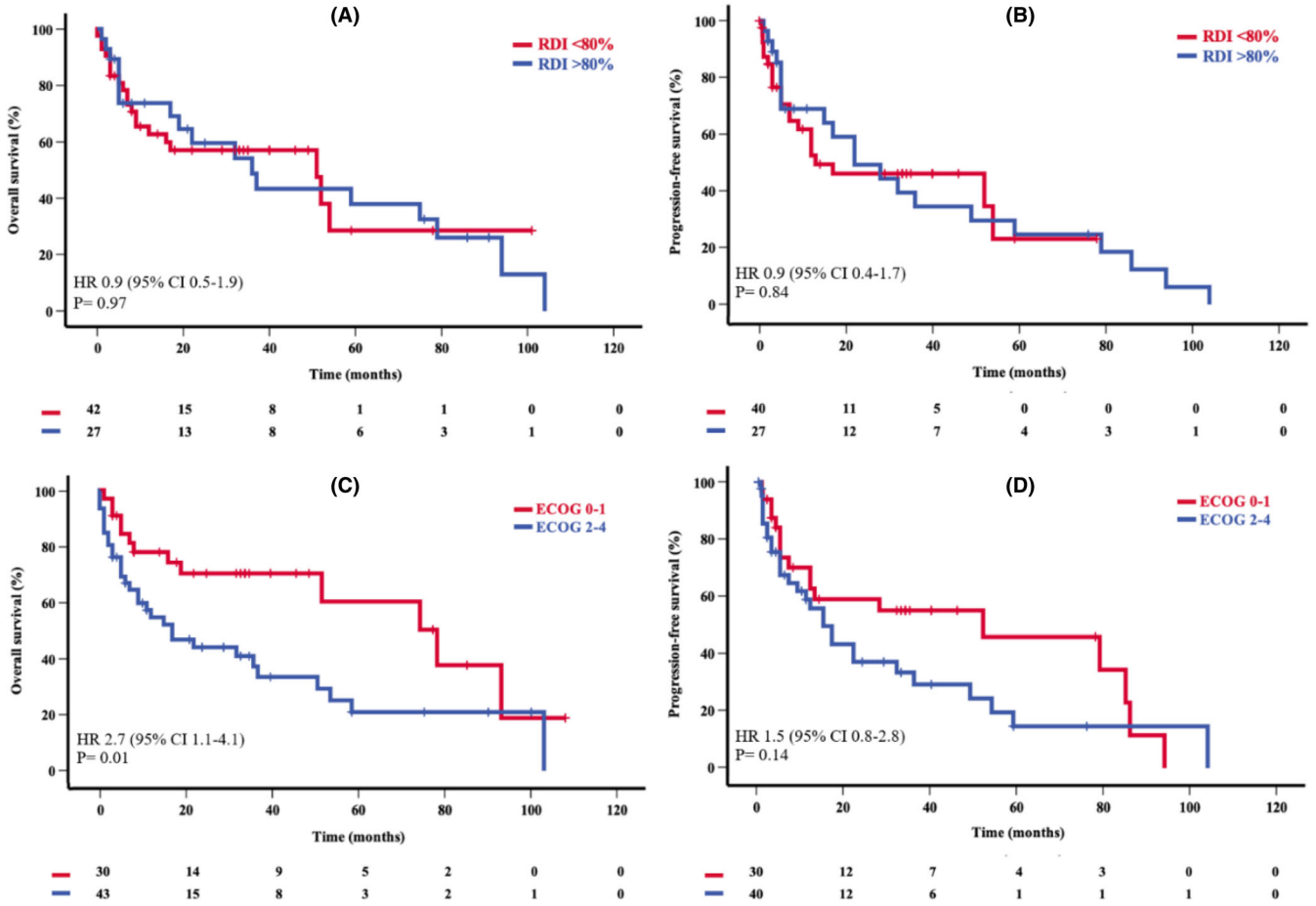

FIGURE 2 Comparison of outcomes according to relative dose intensity and to ECOG performance status. Kaplan–Meier curves for overall survival (A) and progression-free survival (B) for relative dose intensity (RDI) ≥80% and < 80% in the total cohort. Kaplan–Meier curves for overall survival (C) and progression-free survival (D) for ECOG 0–1 versus 2–4 for all analyzed patients in the total cohort.

patients presenting with IPI 2–5 (87%) is indicative of advanced disease at the time of diagnosis. However, notable imbalances between the two treatment cohorts exist due to the retrospective nature of this analysis. Patients in the R-CHOP-14 cohort were younger and had less comorbidities than patients treated with R-miniCHOP. This most likely represents selection bias, typically encountered in retrospective studies, when patients are not allocated to treatment randomly but based on the physician's assessment. In the current study, this may have led to frailer patients receiving reduced dose chemotherapy. Interestingly, similar rates of treatment discontinuation were observed in the two cohorts. This can probably be at least in part attributed to selection bias rather than solely to comparable tolerability of the two regimens. Nevertheless, patients in this study who received R-CHOP-14 or R-miniCHOP had similar OS, PFS, and EFS. Patients who received R-miniCHOP achieved 2-year OS and PFS rates of 53% and 50%, respectively. These results are overall comparable to outcomes previously published. For example, Peyrade et al. reported in 2011 2-year OS and PFS rates of 59% and 47%, respectively, in the prospective trial which established R-miniCHOP. A more recently conducted prospective trial (SENIOR[15]) reported slightly better outcomes with the R-miniCHOP regimen (2-year OS: 66%, 2-year PFS: 56.2%).

TABLE 3 Multivariate analyses of OS and EFS.

	OS		EFS	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Total cohort				
ECOG	2.2 (1.4–3.4)	**<.001**	1.7 (1.2.-2.5)	**.002**
LDH (>normal value)	1.3 (0.6–2.6)	.267	1.2 (0.7–2.2)	.425
Treatment discontinuation	1.5 (0.8–3.1)	.185		
R-mini CHOP				
Age	1.2 (0.9–1.6)	.058		
ECOG	1.9 (1.0–3.6)	**.025**		
R-CHOP-14				
ECOG	2.2 (1.2–4.0)	**.006**		
LDH	1.4 (0.6–3.2)	.331		

Note: Bold indicates significant *P* values.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Neither the intended dose intensity succeeded in improving outcomes in a statistically significant manner nor the achieved dose intensity, expressed as RDI. Patients who received 80% of the intended dose intensity or more (RDI ≥ 80%) had similar 2-year OS rates as those who received less than 80% (60% and 57%, respectively). This is in line with previous studies in patients >80 years in whom dose intensification has not been shown to be associated with improved survival. For example, an analysis of the Danish National Lymphoma Registry, which included 1011 patients aged 75 years and older, estimated that in the age groups of 75–79, 80–85, and 85 years and above, 83%, 65%, and only 32% of patients received full-dose R-CHOP treatment, respectively. In patients aged 80 years and above and only in those, similar OS regardless of the intended R-CHOP dose was demonstrated.[16] Furthermore, a similar analysis of 690 patients aged ≥70 years was performed between 2009 and 2018 across eight centers in the UK by Eyre et al.[17] The study found that achieving an 80% or higher intended dose intensity with R-CHOP treatment on patients aged 80 years and above no difference in PFS ($p = .88$) or OS ($p = .75$) could be shown versus lower dose intensities.

Markedly higher CR rates were achieved with R-CHOP-14 (71.4% vs. 52.4%) as would be expected with the difference in the relative dose intensity between the two cohorts (R-CHOP-14: 83% vs. R-miniCHOP 37%). However, this did not translate into improved survival due to a higher rate of treatment-related deaths in the R-CHOP-14 cohort (9% vs. 4%) and because later relapses continued to occur. Treatment-related deaths for both cohorts are relatively low (Peyrade et al. reported 8% treatment-related mortality for R-miniCHOP), which can be explained by advancements in supportive therapy, including prephase therapy, antimicrobial prophylaxis against pneumocystis, and herpes viruses as well fluoroquinolone prophylaxis during nadir. Nonetheless, the lower CR rates in the R-miniCHOP cohort are directly associated with higher rates of primary progressive disease and/or relapse within the first year of follow-up. In fact, all progression events observed in patients treated with R-miniCHOP occurred within the first year of follow-up. However, the shorter median follow-up in the R-miniCHOP cohort may also contribute to late PFS events being missed. Furthermore, since this is a retrospective study without PET-CT as a standard examination, it may be assumed that the CR rate in general is underestimated.

With the advent of new agents in the treatment landscape of DLBCL, salvage therapy options have dramatically improved for frail patients. Regimens such as tafasitamab/lenalidomid,[18] rituximab/bendamustin/polatuzumab,[19] and even CAR-T cell therapies[20,21] are viable options for patients relapsing after a less intensive first-line therapy. Most of these options were probably not available for the patients of this study since it included patients whose first-line treatment was delivered between 2005 and 2019. Thus, the disadvantage of R-miniCHOP having higher rates of primary treatment failure /early relapses can be expected to be mitigated with the current standard of care.

Nevertheless, our study is the first to our knowledge to specifically report outcomes according to dose intensity in patients ≥80 years treated with R-CHOP-14. Even with higher dose density, outcomes remain similar despite potential selection bias of patients in better condition treated with full-dose therapy. A benefit for dose intensification with the biweekly R-CHOP application over every three weeks could neither be demonstrated in several randomized controlled clinical trials across different age groups[9,10,22-24] nor in a meta-analysis including 2956 patients.[25] Both regimens have been systematically shown to be similar in terms of OS and PFS. R-CHOP-14 remains an option when a shorter therapy course is preferred. Nonetheless, in our study, the absence of a statistically significant difference between full-dose R-CHOP-14 and attenuated R-miniCHOP suggests that both regimens are viable options and offer comparable outcomes. Reducing cycle intervals to a biweekly regimen (R-miniCHOP-14) and thus reducing overall treatment duration regardless of the total chemotherapy dose is another option.

The most important prognostic factor in this octogenarian cohort was the ECOG score being more impactful than disease-related parameters such as stage or IPI. A previous study by Carson shown similar results.[26] Prognostic impact of functional status highlights that

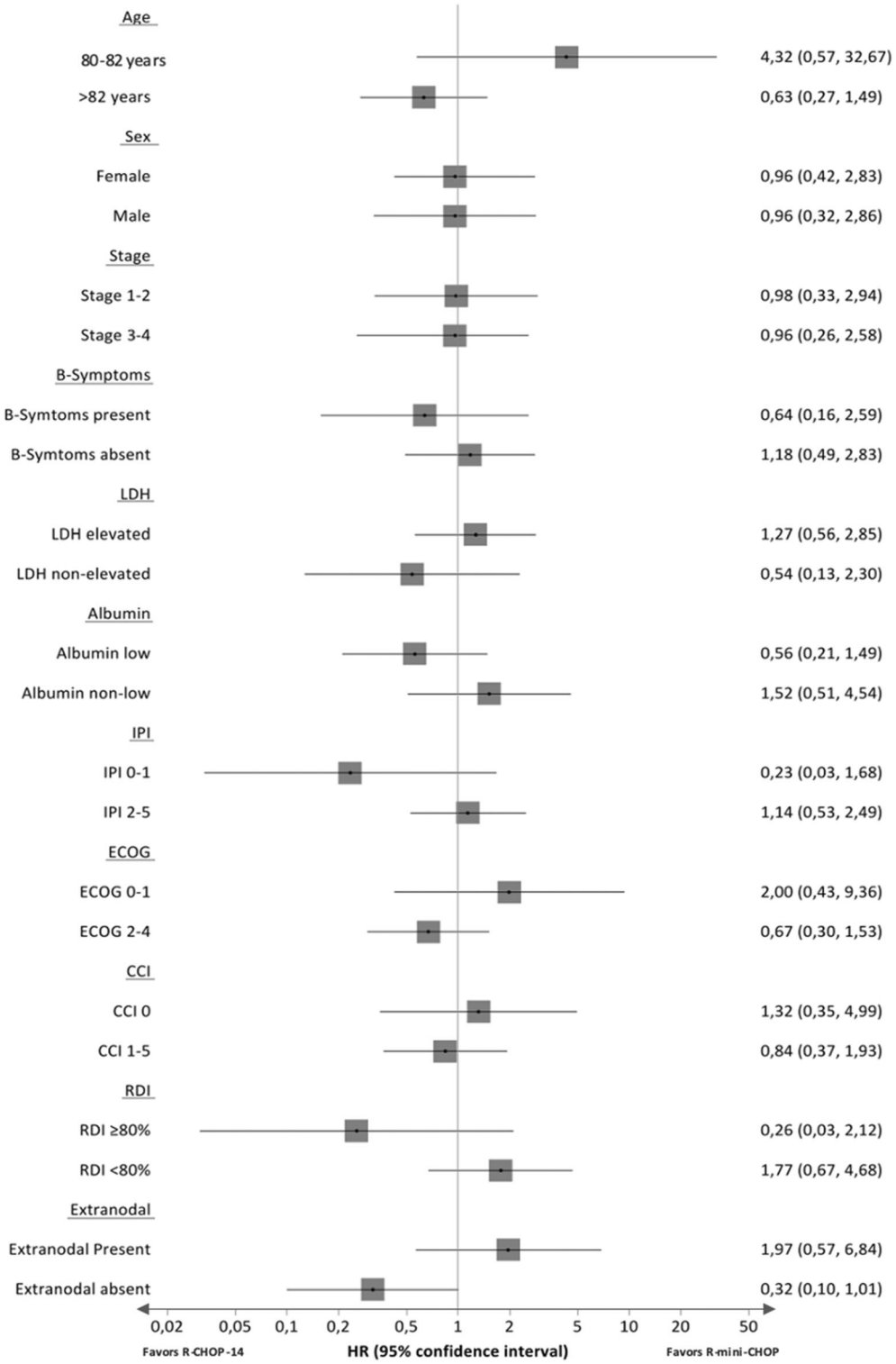

FIGURE 3 Forest plot of OS in R-CHOP-14 and R-mini-CHOP cohorts. The hazard ratios, including 95% confidence intervals, are shown for OS for known prognostic factors for survival. The gray boxes represent HR values, and the lines the range of the 95% confidence intervals. A value below 1 represents lower risk of death with R-CHOP-14 treatment, whereas a value >1 represents a lower risk of death with R-mini-CHOP.

performing accurate geriatric evaluation at the start of treatment of the very old adult may be more informative than performing a PET CT scan to determine the exact disease stage. The prognostic value of serum vitamin D or albumin levels, as shown in earlier studies,[27–30] could not be confirmed in our cohort.

Despite the strengths of our study, which include long follow-up time in a real-world scenario and detailed information of dosing and timing of treatment, there are notable limitations. Median follow-up is lower in patients treated with R-miniCHOP; thus, events in this group may be underreported. Because the study was restricted to centers which systematically applied R-CHOP-14 instead of R-CHOP-21, center-specific biases cannot be excluded. Furthermore, no standardized functional geriatric assessment was performed in these patients. Finally, the R-mini-CHOP cohort is relatively small, thus limiting the confidence in the results. Despite this fact, previous datasets are concordant with our results.[16,17]

Summarizing, our study demonstrated that dose intensity does not influence survival outcomes in the octogenarian population, even with the densest R-CHOP-14 regimen. Outcomes are similar to those achieved with the standard of care R-miniCHOP. To improve survival, other strategies beyond an increase in dose intensity are required. One such strategy is adjusted dosing according to frailty status / comorbidities. Spina et al.[31] performed a prospective trial in which the selection of chemoimmunotherapy dose was based on factors such as age, geriatric assessment, and comorbidities. A total of 100 patients aged 70 years or older were included. The 5-year disease-free, OS, and cancer-specific survival (CSS) rates were 80%, 60%, and 74%, respectively. In addition, a Japanese study involving 109 patients aged 70 years or older employed a strategy of reducing R-CHOP doses based on age. Patients in their 70s received 70% of the initial dose, while those aged 80 years or older received 50%. This approach yielded 2-year overall survival rates surpassing 60%, and only five deaths were linked to therapy-related toxicity.[32] These results offer valuable insights for potential trial designs that include factors such as age, geriatric assessment, and comorbidities.

Another promising approach is the integration of newer agents into the standard of care. Although some prospective trials conducted so far following this strategy have shown promising results, none so far were able to achieve their primary endpoints. Peyrade et al. replaced rituximab with ofatumumab in a single-arm phase II trial and achieved a 2-year OS of 64.7%.[33] More recently, Verner et al. showed in another phase II single-arm study that the addition of ibrutinib to R-miniCHOP leads to a respectable 2-year OS rate of 68%. The only phase III study published in this patient group so far was conducted by the French LYSA group and compared R-miniCHOP with lenalidomid to R-miniCHOP alone. The addition of lenalidomid did not lead to improved survival.[15]

Nonetheless, a rising number of trials are currently ongoing in this patient group. Some explore the addition of newer agents to R-miniCHOP such as acalabrutinib,[34] azacitidin,[35] epcoritamab,[36] and polatuzumab vedotin,[37] while others the substitution of traditional immunochemotherapy with regimens including bispecific antibodies such as glofitamab[38] and mosunetuzumab.[39] Interestingly, the number of trials with targeted agents currently running outnumbers the number of prospective trials published in the last two decades. Beyond exploring the potential of novel agents, modern approaches in this age group should focus on providing robust data on geriatric assessment prior to therapy, as well as information on quality of life and functional decline during therapy.

AUTHOR CONTRIBUTIONS

ZD and KC wrote the manuscript draft. KC, DKM, JB, MB, LT, VP, SS, and IKN designed and supervised the analyses. ZD, SD, CA, SH, and AK performed the analyses. KC and ZD are responsible for data analysis. All authors revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study will be shared by the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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