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A Modified Simplified Frailty Score Predicts Survival, Toxicity, and Treatment Selection in Elderly Patients with Diffuse Large B-Cell Lymphoma: A Retrospective Cohort Study

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Simple Summary

Diffuse large B-cell lymphoma frequently affects older adults, yet treatment intensity decisions often lack systematic frailty assessment. We applied a modified simplified frailty score (mSFS)—based on age, performance status, and comorbidity burden—to 117 elderly patients treated at community hospitals. The mSFS revealed substantial discordance with oncologist-assessed frailty. Frail patients receiving full-dose R-CHOP experienced worse survival, higher toxicity, and more treatment discontinuations, while fit patients receiving dose-reduced R-mini-CHOP had significantly lower complete response rates. Dose-attenuated therapy appeared to mitigate the adverse impact of frailty. These findings support the mSFS as a practical, electronic medical record-integrable tool to auto-calculate frailty and guide treatment intensity in community oncology practice.

Abstract

Background/Objectives: Treatment decisions for elderly patients with diffuse large B-cell lymphoma (DLBCL) often rely on subjective clinical impression rather than systematic frailty assessment. We evaluated whether a modified simplified frailty score (mSFS)—a binary adaptation of the Isaksen score—predicts treatment selection, toxicity, and survival. Methods: In this retrospective study of 117 patients aged ≥65 years with DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or dose-attenuated R-CHOP (R-mini-CHOP) at MedStar Health community hospitals (2000–2025), the mSFS assigned one point each for age ≥80, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, and ≥5 comorbidities; score ≥2 defined frailty. Results: Among 86 R-CHOP recipients, 17 (19.8%) were mSFS-frail; among 31 R-mini-CHOP recipients, 15 (48.4%) were mSFS-fit. In R-CHOP recipients, frailty independently predicted worse overall survival (adjusted hazard ratio [aHR] 7.67, 95% confidence interval [CI] 2.36–24.97), progression-free survival (aHR 2.90, 95% CI 1.18–7.13), grade ≥3 adverse events (adjusted odds ratio [aOR] 3.90, p = 0.035), and early discontinuation (aOR 4.41, p = 0.034). Frail R-CHOP patients had lower complete response rates (aOR 0.24, p = 0.038). Fit R-mini-CHOP patients had 88% lower odds of complete response versus fit R-CHOP patients (aOR 0.12, p = 0.003). Among R-mini-CHOP recipients, frailty was not significantly associated with outcomes. Conclusions: The mSFS revealed bidirectional discordance with oncologist-assessed frailty and independently predicted survival, toxicity, and response, supporting its integration into community oncology practice.

Keywords: diffuse large B-cell lymphoma; frailty; elderly; geriatric assessment; R-CHOP; R-mini-CHOP; modified simplified frailty score; community oncology

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (NHL), accounting for approximately 30% of all cases in Western populations, with a median age at diagnosis of 70 years. Despite advances in immunochemotherapy, outcomes for elderly patients remain substantially inferior to those of younger patients [1]. In a National Cancer Database (NCDB) analysis, median overall survival (OS) for patients aged ≥80 years was only 11.6 months compared with 61.0 months for those aged 65–79 years, and more than one-third of patients aged ≥80 years do not receive any systemic therapy [2]. These findings underscore an urgent unmet need in this rapidly growing patient population.

The National Comprehensive Cancer Network (NCCN) Guidelines for B-Cell Lymphomas recommend rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) (for International Prognostic Index [IPI] ≥2) as preferred first-line regimens (both category 1) for advanced-stage DLBCL [3]. However, the guidelines identify a distinct treatment category for "patients who are very frail and patients >80 years of age with comorbidities," for whom the recom-mended regimens include dose-attenuated R-CHOP (R-mini-CHOP), cyclophos-phamide, doxorubicin (liposomal), vincristine (or etoposide), prednisone, and rituximab (CDOP-R), and gemcitabine, cyclophosphamide, vincristine, and predni-solone with rituximab (GCVP-R) [3]. R-mini-CHOP was established as a feasible regimen in this population by the Lymphoma Study Association (LYSA) phase 2 trial, which demonstrated a 2-year overall survival of 59% with an acceptable toxicity profile in patients aged >80 years [4]. Despite this guideline-defined frail category, the NCCN provides limited guidance on how to systematically identify patients who should receive these attenuated regimens, and frailty assessment in community oncology practice relies predominantly on chronologic age, Eastern Cooperative Oncology Group (ECOG) performance status, and the clinician's general impression of comor-bidity burden rather than on validated tools [1,3].

Comprehensive geriatric assessment (CGA) is the gold standard for evaluating frailty in older cancer patients and has been shown to predict chemotherapy toxicity and survival outcomes [1,5]. Several validated frailty scores have been developed for this population: the simplified geriatric assessment (sGA) and Elderly Prognostic Index (EPI) from the Fondazione Italiana Linfomi (FIL) Elderly Project, which classify patients as fit, unfit, or frail with significantly different 3-year OS of 75%, 58%, and 43%, re-spectively; the Isaksen simplified frailty score, which identified three frailty groups with distinct 2-year OS (fit 82%, unfit 47%, frail 14%); the Cancer and Aging Research Group (CARG) chemotherapy toxicity calculator, which incorporates geriatric as-sessment variables, laboratory values, and treatment characteristics to predict grade 3–5 toxicity risk; the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), which accounts for the specific chemotherapy regimen along with func-tional, nutritional, and cognitive assessments; and the Vijenthira population-based frailty index, which demonstrated that frailty was independently associated with 1-year mortality (adjusted hazard ratio [HR] 1.5; 95% confidence interval [CI] 1.3–1.7) in a cohort of 5,527 DLBCL patients [2,6–9]. However, despite their validation, these tools are not widely utilized in community oncology practice, potentially because they are time-intensive and complex—some require patient questionnaires, use of online calculators, or access to administrative databases—making routine implementation impractical in busy clinical settings [5,9,10].

To address this gap, we adapted the simplified frailty score developed by Isaksen et al., which consists of three components—age ≥80 years, ECOG performance status ≥2, and ≥5 comorbidities—all of which are readily available in the patient's medical chart and can be auto-calculated from the electronic medical record (EMR) to identify frailty at the point of care [7]. We conducted a retrospective cohort study to evaluate the impact of this modified simplified frailty score (mSFS) on treatment selection and outcomes in elderly patients with DLBCL treated at MedStar Health, a large community-based hospital network. Our objectives were threefold: (1) to evaluate whether the mSFS predicts treatment selection between R-CHOP and R-mini-CHOP in routine practice; (2) to assess the

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association between frailty status and clinical outcomes in-cluding survival and toxicity; and (3) to examine whether the effect of treatment regimen on outcomes differs by frailty status, which would support the use of frailty assessment to guide individualized treatment decisions.

2. Materials and Methods

2.1. Study Design and Setting

We conducted a retrospective cohort study of patients with newly diagnosed DLBCL treated at MedStar Health community hospitals in the Baltimore-Washington metropolitan area between January 2000 and December 2025. MedStar Health is an integrated healthcare delivery system comprising multiple community hospitals serving a diverse patient population. The study was approved by the MedStar Health Institutional Review Board (IRB) with a waiver of informed consent given the retrospective nature of the analysis.

2.2. Patient Population

Inclusion criteria: Patients were eligible if they were (1) aged ≥65 years at diagnosis; (2) had histologically confirmed DLBCL, not otherwise specified, according to World Health Organization (WHO) classification criteria; and (3) received first-line treatment with R-CHOP or R-mini-CHOP regimens.

Exclusion criteria: We excluded patients with (1) transformed lymphoma from a known indolent precursor; (2) primary central nervous system lymphoma; (3) primary mediastinal B-cell lymphoma; (4) high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit/triple-hit lymphoma); (5) human immunodeficiency virus (HIV)-associated DLBCL; (6) prior treatment for DLBCL; or (7) insufficient medical record documentation to determine frailty status or treatment outcomes. The overall study design, including patient identification, frailty assessment, treatment group allocation, and outcome evaluation, is summarized in Figure 1.

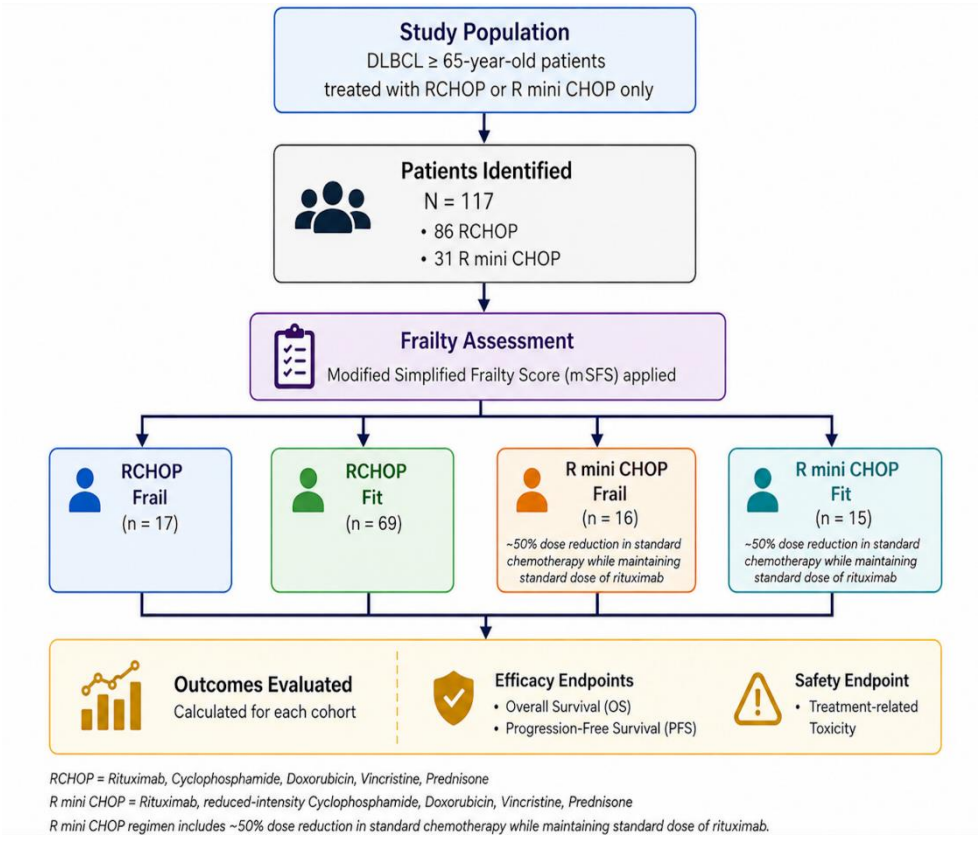

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Figure 1. Study design and patient allocation.

2.3. Modified Simplified Frailty Score (mSFS)

Frailty was assessed using a modified version of the simplified frailty score developed by Isaksen et al. The original score assigns one point for each of the following characteristics present at diagnosis:

- Age ≥80 years
- ECOG performance status ≥2
- ≥5 comorbidities across 14 organ system categories defined by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)

The Isaksen score uses only the binary presence or absence of comorbidity per organ system (rather than full CIRS-G severity grading) and classifies patients into three groups: fit (score 0), unfit (score 1), and frail (score 2–3). In this study, we made two modifications. First, comorbidities were ascertained retrospectively through systematic review of the EMR—including the problem list, active medication list, and clinical documentation—rather than through prospective CIRS-G assessment. Second, patients were dichotomized as fit (score 0–1) or frail (score ≥2) rather than using the original three-tier classification, to facilitate analysis given the sample size. This modified score is hereafter referred to as the modified simplified frailty score (mSFS).

2.4. Treatment Regimens

R-CHOP consisted of rituximab 375 mg/m² intravenously on day 1, cyclophosphamide 750 mg/m² intravenously on day 1, doxorubicin 50 mg/m² intravenously on day 1, vincristine 1.4 mg/m² (maximum 2 mg) intravenously on day 1, and prednisone 100 mg orally on days 1–5, administered every 21 days for a planned 6–8 cycles.

R-mini-CHOP consisted of the same agents with approximately 50% dose reduction: rituximab 375 mg/m² (full dose), cyclophosphamide 400 mg/m², doxorubicin 25 mg/m², vincristine 1 mg (not capped), and prednisone 40 mg on days 1–5, administered every 21 days for a planned 6–8 cycles.

2.5. Data Collection

Data were abstracted from the EMR by trained research personnel using a standardized case report form (CRF). Baseline characteristics included demographics (age, sex, race/ethnicity), disease characteristics (Ann Arbor stage, B symptoms, bulky disease ≥7.5 cm, lactate dehydrogenase [LDH], serum albumin, IPI score, serum creatinine), and frailty score components. Treatment data included regimen received, number of cycles completed, dose modifications, treatment delays, and early discontinuation. Toxicity data were abstracted according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, including hematologic toxicity (neutropenia, anemia, thrombocytopenia), infectious complications, and hospitalizations. Response assessment was based on treating physician documentation using Lugano criteria, with responses categorized as complete response (CR), partial response (PR), stable disease, or progressive disease [11]. Survival data were obtained through medical record review and supplemented by query of the Social Security Death Index (SSDI), with follow-up censored on 31 December 2025.

2.6. Outcome Definitions

- Primary outcomes: Overall survival (OS) and progression-free survival (PFS).
- Secondary outcomes: Overall response rate (ORR), complete response rate (CRR), treatment-related toxicity and delivery, such as grade ≥3 adverse events, dose reductions, treatment delays, and early discontinuations.

2.7. Statistical Analysis

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Baseline characteristics were summarized using descriptive statistics and compared between groups using chi-square tests or Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The association between frailty status and treatment selection (R-CHOP vs. R-mini-CHOP) was assessed using Fisher's exact test, with odds ratios (OR) and 95% CI calculated. Survival outcomes were estimated using the Kaplan–Meier method, and survival curves were compared using log-rank tests. HR and 95% CI were estimated using Cox proportional hazards regression. The proportional hazards assumption was verified using Schoenfeld residuals. All statistical tests were two-sided with significance set at $p < 0.05$. Analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient Characteristics and Treatment Selection

Between January 2000 and December 2025, 117 patients aged ≥65 years with newly diagnosed DLBCL met eligibility criteria and were included in the analysis. The median age was 75 years (range 65–90), and 52.1% were female. Eighty-six patients (73.5%) received R-CHOP, and 31 (26.5%) received R-mini-CHOP. Using the mSFS, 33 patients (28.2%) were classified as frail (mSFS ≥2) and 84 (71.8%) as fit (mSFS 0–1).

Baseline characteristics stratified by treatment regimen and frailty status are presented in Table 1. Frail patients were significantly more likely to receive R-mini-CHOP compared with fit patients (48.5% vs. 17.9%; OR 4.33, 95% CI 1.79–10.45, p = 0.001). However, despite meeting frailty criteria, 51.5% of frail patients (17/33) still received full-dose R-CHOP, suggesting that frailty may be underrecognized in routine clinical practice and that treatment intensity decisions are not consistently guided by systematic frailty assessment. Among R-CHOP recipients, frail patients (n = 17) were older (median age 77 vs. 73 years), more likely to have ECOG ≥2 (58.8% vs. 14.5%), and had similar disease stage and IPI risk distribution compared with fit patients (n = 69). Among R-mini-CHOP recipients, frail patients (n = 16) were also older (median age 80.5 vs. 79 years) and more likely to have ECOG ≥2 (68.8% vs. 20.0%) compared with fit patients (n = 15). High-risk IPI scores (3–5) were common across all groups (60.0–73.3%), with no significant differences between frailty categories within each treatment regimen. One fit R-mini-CHOP patient had incomplete data and was excluded from survival, toxicity, and response analyses, yielding an evaluable sample of 14 for that subgroup.

Table 1. Baseline characteristics of elderly patients with DLBCL treated with R-CHOP or R-mini-CHOP stratified by frailty status.

Variable	R-CHOP Frail (n=17)	R-CHOP Fit (n=69)	R-mini-CHOP Frail (n=16)	R-mini-CHOP Fit (n=15)
Demographics				
Age, median (range)	77 (68–88)	73 (65–86)	80.5 (69–89)	79 (68–90)
Female, n (%)	9 (52.9%)	36 (52.2%)	10 (62.5%)	6 (60.0%)
Male, n (%)	8 (47.1%)	33 (47.8%)	6 (37.5%)	4 (40.0%)
Race/Ethnicity				
White	11 (64.7%)	42 (60.9%)	8 (50.0%) †	8 (53.3%) †
Black	6 (35.3%)	14 (20.3%)	1 (6.3%)	0 (0%)
Asian	0 (0%)	4 (5.8%)	0 (0%)	0 (0%)
Other	0 (0%)	7 (10.1%)	1 (6.3%)	1 (6.7%)
Multiple	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)

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Unknown	0 (0%)	1 (1.4%)	6 (37.5%)	6 (40.0%)
Disease Characteristics				
ECOG <2, n (%)	7 (41.2%)	59 (85.5%)	5 (31.3%)	12 (80.0%)
ECOG ≥2, n (%)	10 (58.8%)	10 (14.5%)	11 (68.8%)	3 (20.0%)
Stage I/II, n (%)	6 (35.3%)	18 (26.1%)	5 (31.3%)	5 (35.7%) ‡
Stage III/IV, n (%)	11 (64.7%)	51 (73.9%)	11 (68.8%)	9 (64.3%) ‡
IPI 0–2, n (%)	6 (35.3%)	26 (40.0%)	4 (26.7%)	4 (26.7%) §
IPI 3–5, n (%)	11 (64.7%)	39 (60.0%)	11 (73.3%)	11 (73.3%) §
B symptoms, n (%)	3 (17.6%)	12 (17.4%)	4 (25.0%)	3 (20.0%)
Bulky disease (≥7.5 cm), n (%)	8 (47.1%)	15 (21.7%)	6 (37.5%)	6 (40.0%)
Laboratory Values				
Albumin, median (range)	3.6 (2.5–4.9)	3.7 (2.2–4.9)	3.55 (2.5–4.7)	3.5 (1.6–4.4)
Albumin < 3.5, n (%)	7 (41.2%)	21 (32.3%)	7 (43.8%)	7 (46.7%)
LDH, median (range)	202 (134–835)	248 (108–1146)	317 (119–1034)	267 (145–2349)
LDH elevated, n (%)	7 (43.8%) ‖	37 (66.1%)	11 (73.3%) ‖	10 (66.7%)
Creatinine, median (range)	0.8 (0.4–1.53)	0.8 (0.4–2.1)	0.65 (0.4–1.64)	0.9 (0.6–1.8)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-mini-CHOP, dose-attenuated R-CHOP. †For R-mini-CHOP cohorts, race data were available for only 10 of 16 (Frail) and 10 of 15 (Fit) patients; percentages are calculated using the full-cohort denominators. ‡Stage data were available for 14 of 15 fit R-mini-CHOP patients; percentages for this subgroup are calculated using a denominator of 14. §IPI data were available for 15 of 16 frail R-mini-CHOP patients; percentages for this subgroup are calculated using a denominator of 15. ‖LDH elevation data were available for 16 of 17 frail R-CHOP patients and 15 of 16 frail R-mini-CHOP patients; percentages for these subgroups are calculated using denominators of 16 and 15, respectively.

3.2. Survival Outcomes

OS and PFS were evaluated by frailty status within each treatment group using Kaplan–Meier analysis with log-rank tests and Cox proportional hazards regression. Multivariable models were adjusted for IPI risk category.

3.2.1. R-CHOP Cohort

Among R-CHOP recipients (n = 86; 15 OS events, 24 PFS events), frailty was significantly associated with inferior OS on univariable analysis (HR 4.28, 95% CI 1.58–11.56, p = 0.0007). On multivariable Cox regression adjusted for IPI risk category, frailty remained independently associated with a 7.67-fold increased risk of death (adjusted HR [aHR] 7.67, 95% CI 2.36–24.97; likelihood ratio test p = 0.0009). For PFS, frailty was associated with a 2.31-fold increased risk of progression or death on univariable analysis (HR 2.31, 95% CI 1.04–5.14, p = 0.021), which strengthened after multivariable adjustment (aHR 2.90, 95% CI 1.18–7.13; likelihood ratio test p = 0.03). Kaplan–Meier curves (Figure 2, Figure 3) demonstrated significant separation between frail and fit R-CHOP patients for both OS (log-rank p = 0.00045) and PFS (log-rank p = 0.019).

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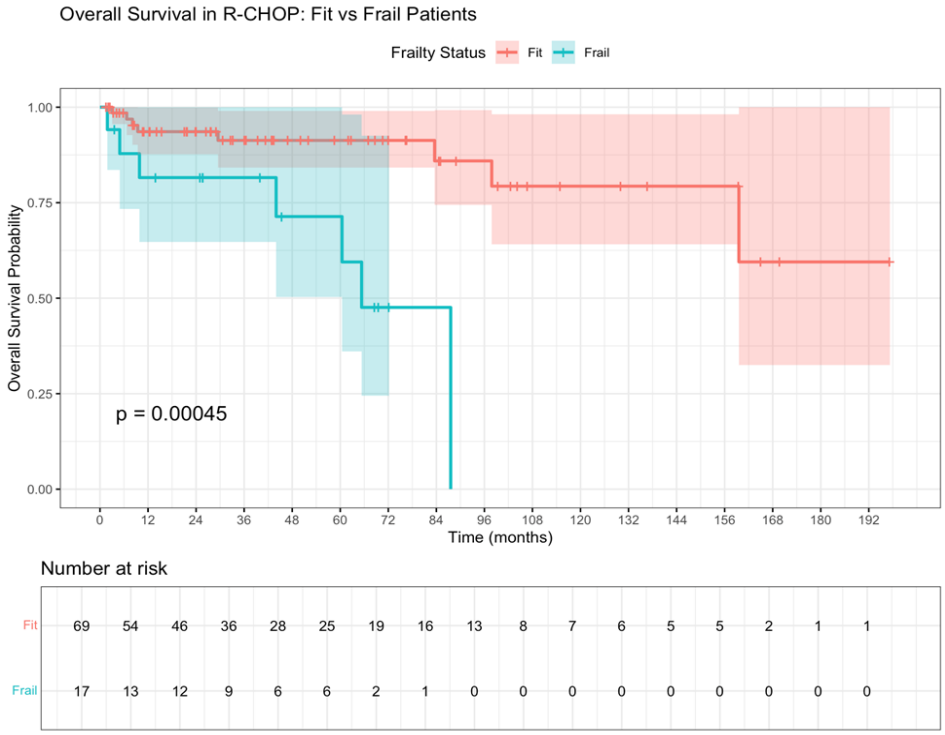

Figure 2. Kaplan–Meier curves for overall survival (OS) in patients treated with R-CHOP stratified by mSFS frailty status. Frail patients demonstrated significantly worse OS compared to fit patients in univariate analysis.

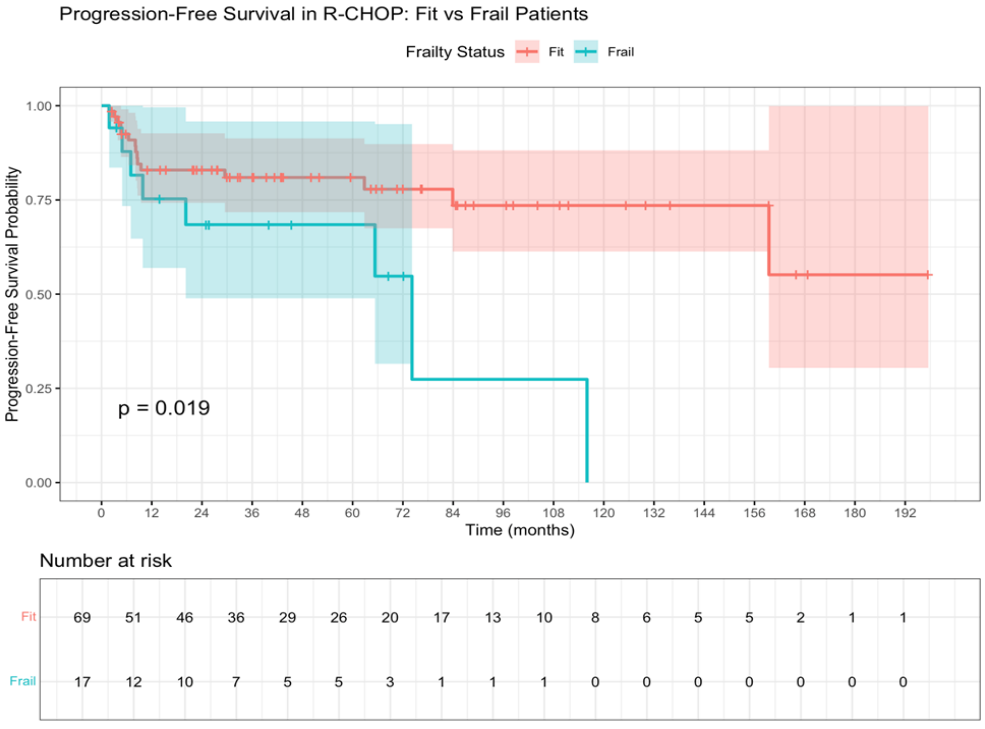

Figure 3. Kaplan–Meier curves for progression-free survival (PFS) in patients treated with R- CHOP stratified by mSFS frailty status. Frail patients demonstrated significantly worse PFS than fit patients in the univariate analysis.

3.2.2. R-mini-CHOP Cohort

Among R-mini-CHOP recipients (n = 31; 11 OS events, 14 PFS events), one fit patient had incomplete data and was excluded from survival analyses, yielding an evaluable fit subgroup of 14. Frailty was not significantly associated with OS on univariable analysis (HR 3.12, 95% CI 0.98–9.94,

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p = 0.493) or after multivariable adjustment for IPI risk category (aHR 1.53, 95% CI 0.45–5.18; likelihood ratio test p = 0.2) as demonstrated in Figure 4. Similarly, frailty was not significantly associated with PFS on univariable analysis (HR 2.87, 95% CI 0.94–8.76, p = 0.260) or after adjustment (aHR 1.89, 95% CI 0.62–5.71; likelihood ratio test p = 0.2) as demonstrated in Figure 5.

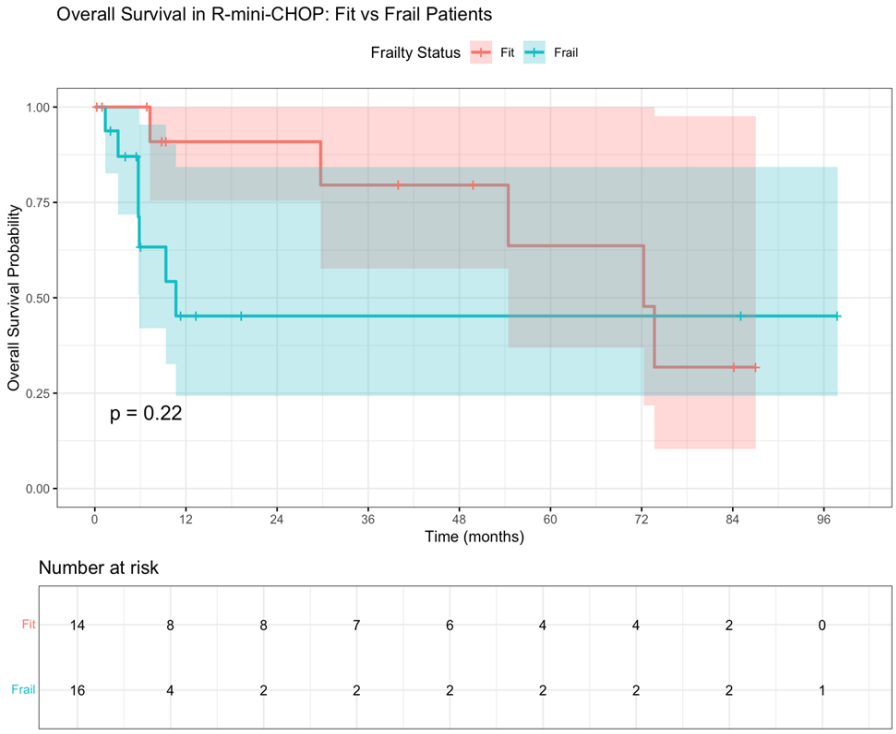

Figure 4. Kaplan–Meier curves for overall survival (OS) in patients treated with R- mini-CHOP stratified by mSFS frailty status.

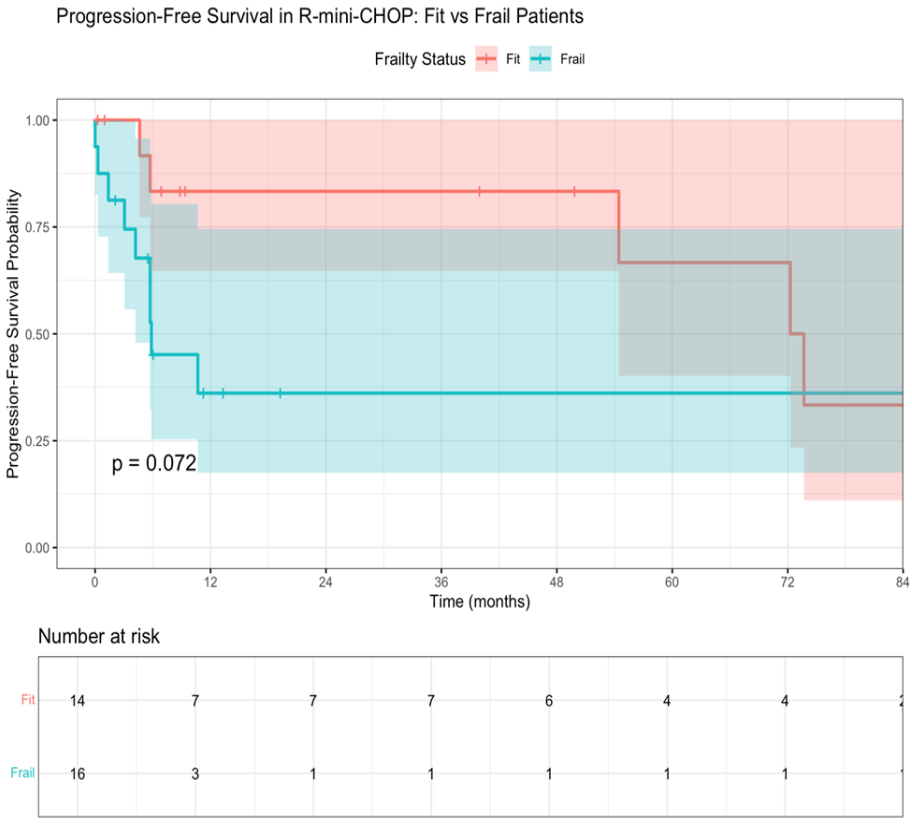

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Figure 5. Kaplan–Meier curves for progression-free survival (PFS) in patients treated with R-mini-CHOP stratified by mSFS frailty status.

3.3. Treatment-Related Toxicity

Treatment-related toxicity was compared between frail and fit patients within each treatment group. Unadjusted comparisons used chi-square and Fisher's exact tests. Adjusted analyses employed IPTW using propensity scores estimated from logistic regression models including IPI risk category, baseline albumin, and baseline creatinine as covariates. Weighted logistic regression was used to estimate adjusted odds ratios (aOR).

3.3.1. R-CHOP Cohort

Among R-CHOP recipients, frail patients (n = 17) experienced significantly higher rates of grade ≥3 adverse events compared with fit patients (n = 69) (76.5% vs. 40.6%, p = 0.01) and early treatment discontinuation (29.4% vs. 8.7%, p = 0.03). Dose reduction (35.3% vs. 20.3%, p = 0.21) and treatment interruption (35.3% vs. 18.8%, p = 0.14) were numerically higher in frail patients but did not reach statistical significance. After IPTW adjustment for IPI risk category, albumin, and creatinine, frailty remained independently associated with grade ≥3 adverse events (aOR 3.90, 95% CI 1.13–13.51, p = 0.035) and early treatment discontinuation (aOR 4.41, 95% CI 1.14–17.00, p = 0.034), while dose reduction (aOR 2.97, 95% CI 0.87–10.12, p = 0.086) and treatment interruption (aOR 2.65, 95% CI 0.79–8.91, p = 0.120) remained non-significant.

3.3.2. R-mini-CHOP Cohort

One fit patient had incomplete data and was excluded from toxicity analyses, yielding an evaluable fit subgroup of 14. No significant differences in toxicity endpoints were observed between frail (n = 16) and fit (n = 14) patients: grade ≥3 adverse events (43.8% vs. 35.7%, p = 0.054), treatment interruption (31.3% vs. 14.3%, p = 0.40), and early discontinuation (18.8% vs. 7.1%, p = 0.61). No dose reductions were observed in either group. After IPTW adjustment for IPI risk category, albumin, and creatinine, no toxicity endpoint was significantly associated with frailty: grade ≥3 adverse events (aOR 1.30, 95% CI 0.27–6.26, p = 0.75), treatment interruption (aOR 2.20, 95% CI 0.32–15.09, p = 0.43), and early discontinuation (aOR 3.16, 95% CI 0.26–37.82, p = 0.37). The wide confidence intervals reflect the limited sample size in this subgroup. Unadjusted and IPTW-adjusted toxicity outcomes for both cohorts are summarized in Table 2.

Table 2. Treatment-related toxicity by mSFS frailty status among R-CHOP and R-mini-CHOP recipients: unadjusted rates and IPTW-adjusted odds ratios.

Endpoint	Frail, n (%)	Fit, n (%)	Unadjusted p	Adjusted OR (95% CI)‡	Adjusted p
R-CHOP (Frail n=17; Fit n=69)					
Grade ≥3 AE	13 (76.5%)	28 (40.6%)	0.01	3.90 (1.13–13.51)	0.035
Dose Reduction	6 (35.3%)	14 (20.3%)	0.21	2.97 (0.87–10.12)	0.086
Treatment Interruption	6 (35.3%)	13 (18.8%)	0.14	2.65 (0.79–8.91)	0.120
Early Discontinuation	5 (29.4%)	6 (8.7%)	0.03	4.41 (1.14–17.00)	0.034
R-mini-CHOP (Frail n=16; Fit n=14†)					

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Grade ≥3 AE	7 (43.8%)	5 (35.7%)	0.054	1.30 (0.27–6.26)	0.75
Dose Reduction §	0 (0%)	0 (0%)	—	—	—
Treatment Interruption	5 (31.3%)	2 (14.3%)	0.40	2.20 (0.32–15.09)	0.43
Early Discontinuation	3 (18.8%)	1 (7.1%)	0.61	3.16 (0.26–37.82)	0.37

Abbreviations: AE, adverse event; CI, confidence interval; IPTW, inverse probability of treatment weighting; IPI, International Prognostic Index; OR, odds ratio; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-mini-CHOP, dose-attenuated R-CHOP; mSFS, modified simplified frailty score. † One R-mini-CHOP fit patient had incomplete data and was excluded; evaluable n = 14 for toxicity analyses. ‡ Adjusted ORs were estimated using IPTW with propensity scores derived from IPI risk category, baseline albumin, and baseline creatinine. § No dose reductions were observed in either group; statistical comparison was not performed.

3.4. Response Rates

Response rates were evaluated using two sets of comparisons: (1) frail versus fit within each treatment group, and (2) R-mini-CHOP versus R-CHOP within each frailty stratum. Unadjusted comparisons used Fisher's exact tests. IPTW-adjusted analyses were performed using the same propensity model covariates (IPI risk category, albumin, creatinine).

3.4.1. Frail Versus Fit Within Treatment Groups

R-CHOP cohort (unadjusted): ORR were similar between frail (n = 16) and fit (n = 69) patients (93.8% vs. 91.3%). CRR were numerically lower in frail patients (68.8% vs. 85.5%) but did not reach significance on unadjusted analysis.

R-CHOP cohort (IPTW-adjusted): After adjustment, no significant difference in ORR was observed (aOR 0.54, 95% CI 0.06–4.45, p = 0.57). However, frailty was associated with significantly lower odds of achieving CR (aOR 0.24, 95% CI 0.07–0.90, p = 0.038), corresponding to 76% lower odds of CR in frail compared with fit R-CHOP patients.

R-mini-CHOP cohort (unadjusted): ORR was 100% (14/14) in frail patients and 78.6% (11/14) in fit patients (Fisher's exact p = 1.000). CRR was 50.0% (7/14) in frail and 35.7% (5/14) in fit patients (p = 0.296).

R-mini-CHOP cohort (IPTW-adjusted): Adjusted analysis for ORR was not feasible due to complete separation (100% ORR in the frail subgroup). No significant difference in CRR was observed between frail and fit R-mini-CHOP patients after adjustment (aOR 1.08, 95% CI 0.22–5.24, p = 0.92).

3.4.2. R-mini-CHOP Versus R-CHOP Within Frailty Strata

Frail patients (unadjusted): Among frail patients, ORR was similar between R-CHOP and R-mini-CHOP (93.8% vs. 100%, p = 1.000). CRR was numerically higher with R-CHOP (68.8% vs. 50.0%) but did not reach significance (p = 0.296).

Frail patients (IPTW-adjusted): Adjusted ORR analysis was not feasible due to complete separation (100% ORR in R-mini-CHOP). No significant difference in CRR was observed between regimens (aOR 0.48, 95% CI 0.10–2.19, p = 0.35).

Fit patients (unadjusted): Among fit patients, ORR was 91.3% (63/69) with R-CHOP and 78.6% (11/14) with R-mini-CHOP (p = 0.175). CRR was markedly higher with R-CHOP (85.5% vs. 35.7%, p = 0.001).

Fit patients (IPTW-adjusted): R-mini-CHOP was associated with numerically lower ORR compared with R-CHOP, though this did not reach significance (aOR 0.34, 95% CI 0.04–2.52, p = 0.29). Fit patients receiving R-mini-CHOP had 88% lower adjusted odds of achieving CR compared with fit R-CHOP patients (aOR 0.12, 95% CI 0.03–0.47, p = 0.003), confirming the unadjusted finding. Unadjusted and IPTW-adjusted response outcomes are summarized in Table 3 (by frailty status within treatment groups) and Table 4 (by treatment regimen within frailty strata).

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Table 3. Response rates by mSFS frailty status within treatment groups: unadjusted rates and IPTW-adjusted odds ratios.

Endpoint	Frail, n/N (%)	Fit, n/N (%)	Unadjusted p #	Adjusted OR (95% CI) ¶	Adjusted p
R-CHOP (Frail† n=16; Fit n=69)					
ORR	15/16† (93.8%)	63/69 (91.3%)	—	0.54 (0.06–4.45)	0.57
CRR	11/16† (68.8%)	59/69 (85.5%)	—	0.24 (0.07–0.90)	0.038
R-mini-CHOP (Frail‡ n=14; Fit§ n=14)					
ORR	14/14‡ (100%)	11/14§ (78.6%)	1.000	NE‖	—
CRR	7/14‡ (50.0%)	5/14§ (35.7%)	0.296	1.08 (0.22–5.24)	0.92

Abbreviations: CI, confidence interval; CRR, complete response rate; IPI, International Prognostic Index; IPTW, inverse probability of treatment weighting; mSFS, modified simplified frailty score; NE, not estimable; OR, odds ratio; ORR, overall response rate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-mini-CHOP, dose-attenuated R-CHOP. † One R-CHOP frail patient had missing response data; evaluable n = 16 of 17 for response analyses.| ‡ Two R-mini-CHOP frail patients had missing response data; evaluable n = 14 of 16 for response analyses. § One R-mini-CHOP fit patient had incomplete data and was excluded; evaluable n = 14 of 15 for response analyses. ‖ Adjusted OR and corresponding p-value not estimable due to complete separation (100% ORR in one subgroup). # Unadjusted p values not reported; IPTW-adjusted analysis was used as the primary comparison. ¶ Adjusted ORs were estimated using IPTW with propensity scores derived from IPI risk category, baseline albumin, and baseline creatinine.

Table 4. Response rates by treatment regimen within mSFS frailty strata: unadjusted rates and IPTW-adjusted odds ratios.

Endpoint	R-CHOP, n/N (%)	R-mini-CHOP, n/N (%)	Unadjusted p	Adjusted OR (95% CI) ¶ ‖	Adjusted p
Frail Patients (R-CHOP† n=16; R-mini-CHOP‡ n=14)					
ORR	15/16† (93.8%)	14/14‡ (100%)	1.000	NE‖	—
CRR	11/16† (68.8%)	7/14‡ (50.0%)	0.296	0.48 (0.10–2.19)	0.35
Fit Patients (R-CHOP n=69; R-mini-CHOP§ n=14)					
ORR	63/69 (91.3%)	11/14§ (78.6%)	0.175	0.34 (0.04–2.52)	0.29

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CRR	59/69 (85.5%)	5/14§ (35.7%)	0.001	0.12 (0.03–0.47)	0.003

Abbreviations: CI, confidence interval; CRR, complete response rate; IPI, International Prognostic Index; IPTW, inverse probability of treatment weighting; mSFS, modified simplified frailty score; NE, not estimable; OR, odds ratio; ORR, overall response rate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-mini-CHOP, dose-attenuated R-CHOP. † One R-CHOP frail patient had missing response data; evaluable n = 16 of 17 for response analyses. ‡ Two R-mini-CHOP frail patients had missing response data; evaluable n = 14 of 16 for response analyses. § One R-mini-CHOP fit patient had incomplete data and was excluded; evaluable n = 14 of 15 for response analyses. ‖ Adjusted OR and corresponding p-value not estimable due to complete separation (100% ORR in one subgroup). ¶ Adjusted ORs were estimated using IPTW with propensity scores derived from IPI risk category, baseline albumin, and baseline creatinine.

4. Discussion

This retrospective cohort study demonstrates that the mSFS adapted from Isaksen et al. is a practical and prognostically meaningful tool for elderly patients with DLBCL treated in a community-based hospital network [7].

A central finding of this study is the substantial discordance between frailty as classified by the mSFS and frailty as implicitly assessed by treating oncologists through their treatment selection decisions. Among the 86 patients who received R-CHOP—indicating that the treating oncologist considered them fit for full-dose therapy—17 (19.8%) were classified as frail by the mSFS (score ≥2). Conversely, among the 31 patients who received R-mini-CHOP—suggesting the oncologist perceived them as too frail for full-dose therapy—15 (48.4%) were classified as fit by the mSFS. This bidirectional discrepancy highlights that the unstructured clinical assessment currently used in community oncology practice both overestimates fitness in a substantial proportion of patients (leading to potentially harmful overtreatment) and overestimates frailty in others (leading to potentially suboptimal undertreatment). These findings are consistent with the broader literature documenting suboptimal treatment selection in elderly DLBCL patients [1,12]. In the National Cancer Database analysis, patients aged ≥80 years were more likely to receive treatment at non-academic centers (71% vs. 48% for patients aged <65 years), and not receiving systemic therapy was the strongest risk factor for mortality (HR 3.26) [2]. The Vijenthira population-based study similarly demonstrated that half of older DLBCL patients were classified as frail, with frailty independently associated with 1-year mortality (adjusted HR 1.5; 95% CI 1.3–1.7), and frail patients incurred higher healthcare utilization and costs [10,13]. Di et al. have highlighted that wider application of geriatric assessments may help identify fit older patients who benefit from standard immunochemotherapy without unnecessary dose reductions, while attenuated regimens may provide a better balance of risk and benefit for selected unfit or frail patients [14]. A recent systematic review and meta-analysis by Pearce et al. confirmed that frailty is independently associated with worse survival outcomes in adults undergoing systemic anticancer treatment across multiple tumor types, reinforcing the importance of routine frailty screening [15]. These patterns underscore the dual challenge of both undertreatment and inappropriate treatment intensity in the absence of systematic frailty screening.

The clinical consequences of this frailty misclassification were substantial. Among R-CHOP recipients, frail patients (as defined by the mSFS) experienced significantly inferior outcomes across multiple domains after adjusting for confounding variables. For survival, frailty was independently associated with a 7.67-fold increased risk of death (aHR 7.67, 95% CI 2.36–24.97) and a 2.90-fold increased risk of progression or death (aHR 2.90, 95% CI 1.18–7.13) after multivariable adjustment for IPI risk category. For treatment-related toxicity, frail R-CHOP recipients experienced significantly higher rates of grade ≥3 adverse events (76.5% vs. 40.6%; adjusted OR 3.90, 95% CI 1.13–13.51) and early treatment discontinuation (29.4% vs. 8.7%; adjusted OR 4.41, 95% CI 1.14–17.00) compared with fit patients. These findings are consistent with the original Isaksen et al. validation study, which demonstrated markedly different 2-year OS rates across frailty groups (fit 82%, unfit 47%, frail 14%)

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in a population-based Norwegian cohort of 784 patients aged ≥70 years [7]. Yagi et al. confirmed the utility of the frailty score in a Japanese single-center cohort of 337 patients, reporting 5-year OS of 73.1%, 60.2%, and 29.7% for fit, unfit, and frail patients, respectively, with frailty also predicting treatment-related mortality (5-year TRM: 0%, 5.4%, and 16.8%) [16]. The electronic FRAIL score study by Zhang et al. similarly showed that patients with high frailty scores were 12.5 times more likely to require dose reduction or treatment delay due to toxicity [17]. The CARG chemotherapy toxicity calculator has also been shown to predict grade 3-5 toxicity in elderly patients receiving immunochemotherapy [18].

A systematic review and meta-analysis by Horiuchi et al. confirmed the predictive value of the Cancer and Aging Research Group (CARG) score for grade 3–5 toxicity across cancer types, and Rosko et al. demonstrated its applicability specifically in hematologic malignancies [18,19]. Ortland et al. compared the performance of the CARG and Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) scores in older cancer patients and found that both tools provided meaningful toxicity prediction, though with differing strengths across patient populations, and Frelaut et al. further evaluated the external validity of both scores in the ELCAPA prospective cohort of older patients with solid tumors [20,21]. Collectively, these data reinforce that frailty assessment provides prognostic information and that administering full-dose R-CHOP to frail patients results in excess toxicity without commensurate survival benefit.

The consequences of the reverse misclassification—fit patients receiving dose-attenuated therapy—were also clinically meaningful. Among fit patients, R-mini-CHOP was associated with significantly lower complete response rates compared with R-CHOP in both unadjusted (35.7% vs. 85.5%, p = 0.001) and IPTW-adjusted analyses (adjusted OR 0.12, 95% CI 0.03–0.47, p = 0.003), corresponding to 88% lower odds of achieving complete response. This finding is consistent with the Isaksen et al. observation that fit patients clearly benefited from full-dose R-CHOP over R-mini-CHOP (2-year OS: 86% vs. 70%; P = .012), and with Yagi et al., who demonstrated that initial dose intensity and relative dose intensity had a significant impact on OS in fit patients but no significant effect on survival in non-fit patients [7,16]. Al-Sarayfi et al. similarly reported in a propensity-matched population-based study that R-CHOP was associated with superior outcomes compared with R-mini-CHOP in patients who were fit enough to tolerate full-dose therapy [22]. These data suggest that fit patients who are inappropriately de-escalated to R-mini-CHOP may be denied the full curative potential of standard-dose therapy.

Additionally, among frail patients receiving R-CHOP, complete response rates were significantly lower after adjusting for confounding variables (adjusted OR 0.24, 95% CI 0.07–0.90, p = 0.038), corresponding to 76% lower odds of CR compared with fit R-CHOP patients. In contrast, among R-mini-CHOP recipients, frailty was not significantly associated with survival, toxicity, or response outcomes, suggesting that dose-attenuated therapy may mitigate the adverse prognostic impact of frailty. This pattern parallels the LYSA phase 2 trial by Peyrade et al., which established R-mini-CHOP as a feasible regimen in patients aged >80 years, and the subsequent LYSA phase 3 trial by Oberic et al. in patients aged ≥80 years, which reported a 2-year OS of 66% with R-mini-CHOP and demonstrated that this regimen provides meaningful disease control in the very elderly population [4,23]. Dilbaz et al. similarly found no significant difference in OS between R-CHOP-14 and R-mini-CHOP in patients aged ≥80 years (2-year OS 56% vs. 53%), concluding that R-mini-CHOP should be preferred for most patients in this age group [24]. A recent real-world study by Romagnoli et al. found comparable overall response rates between R-mini-CHOP and R-CHOP (88.7% vs. 92.6%) despite worse baseline characteristics in the R-mini-CHOP group [25]. Lugtenburg and Mutsaers have similarly advocated for a frailty-guided approach to frontline DLBCL treatment in older patients, emphasizing that treatment intensity should be calibrated to the individual patient's functional reserve rather than chronologic age alone [26]. The European Hematology Association (EHA) Clinical Practice Guidelines for large B-cell lymphoma also recommend consideration of dose-attenuated regimens for frail elderly patients, further supporting this approach [27]. These findings collectively indicate that the relative benefit of treatment intensity is modified by frailty status and

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that frailty-guided treatment selection may optimize the balance between disease control and treatment tolerability.

The mSFS used in this study represents a simplified binary adaptation of the original Isaksen frailty score [7]. Whereas Isaksen et al. classified patients into three groups—fit (score 0), unfit (score 1), and frail (score 2–3)—we dichotomized patients as fit (score 0–1) or frail (score ≥2) to facilitate analysis given our sample size. Despite this simplification, the mSFS retained its prognostic value, demonstrating significant associations with survival, toxicity, and response outcomes. The binary classification may in fact be advantageous for clinical implementation, as it provides a clear, actionable decision point: patients flagged as frail warrant consideration for dose-attenuated therapy, while those classified as fit can be treated with standard-dose R-CHOP.

The mSFS has several practical advantages over other validated frailty tools that make it particularly suited for community oncology practice. The American Society of Clinical Oncology (ASCO) Guideline Update on Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy recommends that geriatric assessment (GA), including all essential domains, should be used for all patients over 65 years old with cancer, and that GA-guided management should be included in the care plan [28]. However, the complexity of comprehensive GA tools remains a barrier to routine implementation, particularly in community settings [5,10].

The Fondazione Italiana Linfomi (FIL) simplified geriatric assessment (sGA), prospectively validated in 1,163 patients, requires evaluation of activities of daily living (ADL), instrumental activities of daily living (IADL), and CIRS-G, necessitating patient questionnaires and dedicated clinician time for administration [6]. While the sGA has the strongest prospective evidence base in DLBCL, its multi-domain assessment may be impractical in busy community settings where geriatric oncology expertise is limited. The CRASH accounts for the specific chemotherapy regimen along with functional (ECOG), nutritional (Mini Nutritional Assessment), and cognitive (Mini-Mental State Examination) assessments, adding further complexity [6,20]. The Vijenthira population-based frailty index, while demonstrating robust prognostic value in 5,527 DLBCL patients, requires access to administrative databases and linked healthcare data, making it unsuitable for point-of-care clinical decision-making [10]. The abbreviated CGA (aCGA), recently evaluated by Hung et al. in 91 DLBCL patients, demonstrated good discrimination (area under the curve [AUC] 0.846) but still requires assessment of multiple geriatric domains [29]. The Vulnerable Elders Survey-13 (VES-13), a self-reported screening tool evaluated by Johnson et al., showed similar sensitivity and specificity to the FIL GA for predicting toxicity and mortality in aggressive lymphoma but requires patient self-administration [30].

In contrast, the mSFS consists of only three components—age ≥80 years, ECOG performance status ≥2, and ≥5 comorbidities—all of which are routinely documented in the electronic medical record (EMR) and require no patient questionnaires, no dedicated assessment time, and no online calculators. Despite this simplicity, the prognostic performance of the mSFS in our community-based cohort is broadly comparable to results produced by more complex tools. The aHR of 7.67 for OS in frail R-CHOP patients in our study compares favorably with the prognostic discrimination reported by the FIL sGA (3-year OS: fit 75%, unfit 58%, frail 43%), the Isaksen score in its original three-tier classification (2-year OS: fit 82%, unfit 47%, frail 14%), and the electronic FRAIL score (5-year OS: 60%, 60%, and 0% for scores 0–1, 2, and 3–5, respectively) [6,7,17]. The mSFS also predicted treatment-related toxicity (adjusted OR 3.90 for grade ≥3 adverse events), consistent with the electronic FRAIL score's OR of 12.5 for treatment-limiting toxicity [17].

A key advantage of the mSFS is its amenability to automated calculation within the EMR. All three components—age, ECOG performance status, and comorbidity count across CIRS-G organ systems—can be extracted from structured EMR data fields (date of birth, documented performance status, and problem list/International Classification of Diseases, Tenth Revision [ICD-10] codes mapped to CIRS-G categories). The CIRS-G, which evaluates 14 organ system categories, was originally developed by Miller et al. for rating chronic medical illness burden in geriatric populations

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and has been validated as a reliable indicator of health status with good interrater reliability (intraclass correlation coefficients of 0.78–0.88) and predictive validity for mortality and rehospitalization in elderly patients [31]. Benderra et al. recently confirmed the reliability of the CIRS-G for assessing multimorbidity in older cancer patients in the ELCAPA cohort [32]. Since the Isaksen score uses only the binary presence or absence of comorbidity per organ system (rather than the full CIRS-G severity grading), mapping ICD-10 codes to CIRS-G categories for automated scoring is straightforward. Unlike the unstructured approach currently used by community oncologists—which relies on subjective clinical impression and chronologic age—an EMR-integrated mSFS would provide a standardized, reproducible, and objective frailty assessment for every eligible patient.

The findings of this study support the prospective evaluation of EMR-integrated frailty screening to guide treatment intensity decisions in elderly DLBCL patients. A logical next step would be a prospective, multicenter study in which the mSFS is integrated into the EMR as an automated clinical decision support tool, with the frailty score calculated and displayed at the point of care for all patients aged ≥65 years with newly diagnosed DLBCL. Such a study would allow external validation of the mSFS in diverse community oncology settings and assessment of whether systematic frailty screening improves treatment selection concordance and clinical outcomes.

Several limitations should be acknowledged. First, the retrospective design introduces potential for selection bias and unmeasured confounding. Second, the sample size, particularly in the R-mini-CHOP subgroups (frail n = 16, fit n = 15), limits statistical power and contributes to wide confidence intervals, precluding definitive conclusions about the absence of frailty effects in this group. Third, this study was conducted within a single healthcare system, and external validation in other community practice settings is needed. Fourth, residual confounding bias remains a concern, as multivariable models for survival outcomes were adjusted only for IPI risk category; other variables that differed between groups at baseline—including bulky disease and laboratory values—were not included in the survival models due to sample size constraints. Finally, variable follow-up across patients may affect the reliability of long-term survival estimates.

5. Conclusions

In this community-based retrospective cohort of elderly patients with DLBCL, the mSFS—a binary adaptation of the Isaksen et al. score using three readily available clinical variables (age ≥80 years, ECOG ≥2, and ≥5 comorbidities)—independently predicted survival, toxicity, and treatment selection [7]. The mSFS revealed substantial bidirectional discordance with unstructured oncologist assessment: frail patients who received full-dose R-CHOP experienced significantly worse survival, higher toxicity, and lower complete response rates, while fit patients who received R-mini-CHOP had significantly lower complete response rates. Notably, among R-mini-CHOP recipients, frailty did not significantly affect survival, toxicity, or response outcomes, suggesting that dose-attenuated therapy may mitigate the adverse impact of frailty when treatment intensity is appropriately matched. These findings support prospective evaluation of the mSFS as an EMR-integrated clinical decision support tool to provide standardized, objective frailty assessment and guide individualized treatment intensity decisions for elderly patients with DLBCL.

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Abbreviations

The following abbreviations are used in this manuscript:

aCGA	Abbreviated comprehensive geriatric assessment
ADL	Activities of daily living
AE	Adverse event
aHR	adjusted hazard ratio
aOR	Adjusted odds ratio
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
CARG	Cancer and Aging Research Group
CDOP-R	cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CR	Complete response
CRASH	Chemotherapy Risk Assessment Scale for High-Age Patients
CRF	Case report form
CRR	Complete response rate
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-cell Lymphoma
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Association
EMR	Electronic Medical Record
EPI.	Elderly Prognostic Index
GCVP-R	Gemcitabine, cyclophosphamide, vincristine, prednisone, rituximab
HIV	Human immunodeficiency virus
HR	Hazard ratio
IADL	Instrumental activities of daily living
IPI	International prognostic index
IPTW	Inverse probability of treatment weighting
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
mSFS	Modified simplified frailty score
NCDB	National Cancer Database
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin Lymphoma
OR	Odds ratio

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ORR Overall response rate
OS Overall survival
PFS Progression Free survival
Pola-R-CHP polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, prednisone
PR. Partial response
R-CHOP Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-mini-CHOP dose attenuated R-CHOP
TRM Treatment-related mortality
VES-13 Vulnerable Elders Survey-13
WHO World Health Organization

References

1. Sehn, L.H.; Salles, G. Diffuse Large B-Cell Lymphoma. *N. Engl. J. Med.* **2021**, *384*, 842–858. doi:10.1056/NEJMra2027612.
2. Andrade-Gonzalez, X.; Saliba, A.; Fuentes, H.; et al. Survival Trends of Older Adult Patients with Diffuse Large B-Cell Lymphoma: A National Cancer Database Analysis. *J. Clin. Oncol.* **2021**, *39*(Suppl. 15), 7542. doi: 10.1200/JCO.2021.39.15_suppl.7542.
3. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas*; Version 3.2026; NCCN: Plymouth Meeting, PA, USA, 2026. Available online: https://www.nccn.org (accessed on 12 March 2026).
4. Peyrade, F.; Jardin, F.; Thieblemont, C.; et al. Attenuated Immunochemotherapy Regimen (R-miniCHOP) in Elderly Patients Older than 80 Years with Diffuse Large B-Cell Lymphoma: A Multicentre, Single-Arm, Phase 2 Trial. *Lancet Oncol.* **2011**, *12*, 460–468. doi:10.1016/S1470-2045(11)70069-9.
5. Soto-Perez-de-Celis, E.; Li, D.; Yuan, Y.; Lau, Y.M.; Hurria, A. Functional versus Chronological Age: Geriatric Assessments to Guide Decision Making in Older Patients with Cancer. *Lancet Oncol.* **2018**, *19*, e305–e316. doi:10.1016/S1470-2045(18)30348-6.
6. Merli, F.; Luminari, S.; Tucci, A.; et al. Simplified Geriatric Assessment in Older Patients with Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. *J. Clin. Oncol.* **2021**, *39*, 1214–1222. doi:10.1200/JCO.20.02465.
7. Isaksen, K.T.; Mastroianni, M.A.; Rinde, M.; et al. A Simplified Frailty Score Predicts Survival and Can Aid Treatment-Intensity Decisions in Older Patients with DLBCL. *Blood Adv.* **2021**, *5*, 4771–4782. doi:10.1182/bloodadvances.2021004777.
8. Hurria, A.; Togawa, K.; Mohile, S.G.; Owusu, C.; Klepin, H.D.; Gross, C.P.; Lichtman, S.M.; Gajra, A.; Bhatia, S.; Katheria, V.; et al. Predicting Chemotherapy Toxicity in Older Adults with Cancer: A Prospective Multicenter Study. *J. Clin. Oncol.* **2011**, *29*, 3457–3465. doi:10.1200/JCO.2011.34.7625.
9. Extermann, M.; Boler, I.; Reich, R.R.; Lyman, G.H.; Brown, R.H.; DeFelice, J.; Levine, R.M.; Lubiner, E.T.; Reyes, P.; Schreiber, F.J., III; et al. Predicting the Risk of Chemotherapy Toxicity in Older Patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score. *Cancer* **2012**, *118*, 3377–3386. doi:10.1002/cncr.26646.
10. Vijenthira, A.; Mozessohn, L.; Nagamuthu, C.; Guo, Y.; Guo, S.; Engel, E.; Cheung, M.C. Frailty in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma Receiving Curative-Intent Therapy: A Population-Based Study. *J. Natl. Compr. Canc. Netw.* **2022**, *20*, 635–642.e9. doi:10.6004/jnccn.2022.7014.
11. Cheson, B.D.; Fisher, R.I.; Barrington, S.F.; Cavalli, F.; Schwartz, L.H.; Zucca, E.; Lister, T.A. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J. Clin. Oncol.* **2014**, *32*, 3059–3068. doi:10.1200/JCO.2013.54.8800.
12. Merli, F.; Pozzi, S.; Catellani, H.; Barbieri, E.; Luminari, S. The Role of Geriatric Assessment in the Management of Diffuse Large B-Cell Lymphoma. *Cancers* **2023**, *15*, 5845. doi:10.3390/cancers15245845.
13. Vijenthira, A.; Calzavara, A.; Nagamuthu, C.; Guo, Y.; Guo, S.; Engel, E.; Cheung, M.C. Health Care Utilization and Costs for Frail vs Nonfrail Patients with Diffuse Large B-Cell Lymphoma. *Blood Adv.* **2024**, *8*, 4625–4632. doi:10.1182/bloodadvances.2024013158.

 doi:10.20944/preprints202605.1257.v1

14. Di, M.; Huntington, S.F.; Olszewski, A.J. Challenges and Opportunities in the Management of Diffuse Large B-Cell Lymphoma in Older Patients. *Oncologist* **2021**, *26*, 120–132. doi:10.1002/onco.13610.
15. Pearce, J.; Martin, S.; Heritage, S.; Swain, A.; Batty, J.; Hewitt, J.; Lund, J.; Todd, A. Frailty and Outcomes in Adults Undergoing Systemic Anticancer Treatment: A Systematic Review and Meta-Analysis. *J. Natl. Cancer Inst.***2025**, *117*, 1316–1339. doi:10.1093/jnci/djaf017.
16. Yagi, Y.; Kanemasa, Y.; Sasaki, Y.; Hiramatsu, Y.; Komatsu, D.; Imoto, W.; Kida, J.; Sugimoto, T.; Koh, H.; Nakamae, H. Utility of the Frailty Score for Predicting Prognosis and Individualizing Treatment Intensity in Elderly Patients with Diffuse Large B Cell Lymphoma. *Ann. Hematol.* **2023**, *102*, 1485–1500. doi:10.1007/s00277-023-05233-2.
17. Zhang, J.; Disperati, P.; Elinder-Camburn, A.; et al. Electronic FRAIL Score as a Predictor of Treatment Outcomes in Older Patients with Diffuse Large B-Cell Lymphoma. *J. Geriatr. Oncol.* **2022**, *13*, 505–510. doi:10.1016/j.jgo.2021.12.005.
18. Horiuchi, K.; Kuno, T.; Takagi, H.; Ueno, N.T.; Afezolli, D. Predictive Value of the Cancer and Aging Research Group Score for Chemotherapy Toxicities in Older Adults with Cancer: A Systematic Review and Meta-Analysis. *Support. Care Cancer* **2026**, *34*, 85. doi:10.1007/s00520-025-10271-9.
19. Rosko, A.E.; Huang, Y.; Wall, S.A.; et al. Predictive Ability of the Cancer and Aging Research Group Chemotherapy Toxicity Calculator in Hematologic Malignancy. *J. Geriatr. Oncol.* **2025**, *16*, 102144. doi:10.1016/j.jgo.2024.102144.
20. Ortland, I.; Mendel Ott, M.; Kowar, M.; Reitter, E.M.; Siebenhofer, A.; Goisser, S. Comparing the Performance of the CARG and the CRASH Score for Predicting Toxicity in Older Patients with Cancer. *J. Geriatr. Oncol.* **2020**, *11*, 997–1005. doi:10.1016/j.jgo.2019.12.016.
21. Frelaut, M.; Paillaud, E.; Beinse, G.; Gisselbrecht, M.; Caillet, P.; Poisson, J.; Tournigand, C.; Boudou-Rouquette, P.; Canoui-Poitrine, F.; Aparicio, T.; et al. External Validity of Two Scores for Predicting the Risk of Chemotherapy Toxicity among Older Patients with Solid Tumors: Results from the ELCAPA Prospective Cohort. *Oncologist* **2023**, *28*, e341–e349. doi:10.1093/oncolo/oyad050.
22. Al-Sarayfi, D.; Brink, M.; Chamuleau, M.E.D.; et al. R-miniCHOP versus R-CHOP in Elderly Patients with Diffuse Large B-Cell Lymphoma: A Propensity Matched Population-Based Study. *Am. J. Hematol.* **2024**, *99*, 216–222. doi:10.1002/ajh.27151.
23. Oberic, L.; Peyrade, F.; Puyade, M.; et al. Subcutaneous Rituximab-MiniCHOP Compared with Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older. *J. Clin. Oncol.* **2021**, *39*, 1203–1213. doi:10.1200/JCO.20.02666.
24. Dilbaz, Z.G.; Denker, S.; Ankermann, C.; et al. Comparison of R-CHOP-14 and R-mini-CHOP in Older Adults with Diffuse Large B-Cell Lymphoma—A Retrospective Multicenter Cohort Study. *Eur. J. Haematol.* **2024**, *113*, 675–684. doi:10.1111/ejh.14268.
25. Romagnoli, C.; Guerra, V.; Santos-Carrion, L.; et al. Real-World Data of R-mini-CHOP Therapy in Elderly Hispanic Population with Diffuse Large B-Cell Lymphoma and High-Grade Follicular Lymphoma. *Cancers* **2026**, *18*, 1124. doi:10.3390/cancers18071124.
26. Lugtenburg, P.J.; Mutsaers, P.G.N.J. How I Treat Older Patients with DLBCL in the Frontline Setting. *Blood* **2023**, *141*, 2566–2575. doi:10.1182/blood.2020008239.
27. Thieblemont, C.; Gomes Da Silva, M.; Leppä, S.; et al. Large B-Cell Lymphoma (LBCL): EHA Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-Up. *HemaSphere* **2025**, *9*, e7020.
28. Dale, W.; Klepin, H.D.; Williams, G.R.; Alibhai, S.M.H.; Berger, N.A.; Bhatia, S.; Bodge, M.N.; Chapman, A.E.; Cohen, H.J.; Desai, A.V.; et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Update. *J. Clin. Oncol.* **2023**, *41*, 4293–4312. doi:10.1200/JCO.23.00933.
29. Hung, Y.S.; Chang, H.; Kuo, M.C.; Chou, W.C. The Performance of Abbreviated Comprehensive Geriatric Assessment in Elderly Patients with Diffuse Large B Cell Lymphoma. *Support. Care Cancer* **2025**, *33*, 81. doi:10.1007/s00520-024-09142-6.
30. Johnson, P.C.; Newcomb, R.A.; Nipp, R.D.; et al. Evaluating Vulnerable Elders Survey-13 and FIL Geriatric Assessment in Older Adults with Aggressive Lymphomas. *J. Natl. Compr. Canc. Netw.* **2026**, *24*, e257100. doi:10.6004/jnccn.2025.7100.

 doi:10.20944/preprints202605.1257.v1

31. Miller, M.D.; Paradis, C.F.; Houck, P.R.; Mazumdar, S.; Stack, J.A.; Rifai, A.H.; Mulsant, B.; Reynolds, C.F., III. Rating Chronic Medical Illness Burden in Geropsychiatric Practice and Research: Application of the Cumulative Illness Rating Scale. *Psychiatry Res.* **1992**, *41*, 237–248. doi:10.1016/0165-1781(92)90005-N.
32. Benderra, M.A.; Caillet, P.; Aregui, A.; et al. Reliability of the Cumulative Illness Rating Scale for Geriatrics for Assessing Multimorbidity in Older Patients with Cancer: Results from the ELCAPA Cohort.