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Age, Comorbidity Burden and Treatment Outcomes in Mature B-Cell Lymphoproliferative Disorders: A Real-World Study

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Received: 30 April 2026 | **Revised:** 20 October 2026 | **Accepted:** 24 October 2026

Keywords: frail | mature B-cell lymphoproliferative disorders | older adult | treatment

ABSTRACT

Introduction: Treatment decisions in older patients with mature B-cell lymphoproliferative disorders (MBLD) are frequently guided by chronological age and comorbidity burden, although their ability to predict clinically relevant outcomes remains uncertain.

Methods: We conducted a retrospective real-world study including 172 patients with MBLD between 2016 and 2021, assessing the association of age and comorbidity burden (standardised using the Cumulative Illness Rating Scale for Geriatrics, CIRS-G score) with treatment intensity, toxicity, and clinical outcomes.

Results: Treatment intensity decreased significantly with both age ($p = 0.003$) and CIRS-G score ($p < 0.001$). However, neither age nor CIRS-G score was associated with an increased rate of treatment-related toxic events. In contrast, older age was associated with worse overall survival and lower response rates (all $p < 0.05$), whereas CIRS-G score was not significantly associated with these outcomes. Similar associations between age and outcomes were observed in the DLBCL subgroup.

Conclusion: In this real-world cohort of patients with MBLD, chronological age was more consistently associated with treatment patterns and clinical outcomes than comorbidity burden as measured by the CIRS-G score. These findings suggest that chronological age alone may not adequately capture the heterogeneity of older patients and support the use of more comprehensive assessments of frailty and functional status to inform treatment decisions.

1 | Introduction

The ageing of the population represents a significant challenge for healthcare systems in Western countries, as 24% to 28% of the western population is projected to be aged 65 years or older by 2060 [1]. According to the recommendations of the European Society of Medical Oncology (ESMO), the International Society of Geriatric Oncology (SIOG) and the European Organization for Research and Treatment of Cancer (EORTC), older patients are defined as those aged 70 years or older [1–3]. Mature B-cell Lymphoproliferative Disorders (MBLD) are particularly affected by population ageing, with a median age at diagnosis of 67–70 years and 30% of patients being older than 75 years [4–6]. This heterogeneous group of lymphoid malignancies is classified according to the World Health Organization (WHO) system and includes aggressive subtypes such as Diffuse Large B-Cell Lymphoma (DLBCL), whereas follicular lymphoma (FL) and chronic lymphocytic leukaemia (CLL) often have an indolent

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course [1, 7]. Ageing is a complex process characterised by multiple structural and functional changes that may lead to an increased burden of comorbidities and functional dependency. However, the relationship between these changes and chronological age can vary considerably between patients, highlighting the need for a comprehensive assessment of functional status. Assessment of comorbidities using validated scores is a key component of this evaluation and may form part of a Comprehensive Geriatric Assessment (CGA) [1, 8]. These considerations are particularly relevant when selecting therapeutic strategies. In this context, anti-CD20 monoclonal antibodies such as rituximab and obinutuzumab represent a cornerstone of MBLD treatment, alone or in combination with chemotherapy depending on disease and patient characteristics. More recently, novel targeted approaches, including bispecific antibodies and CAR-T cells, have expanded the range of treatment options. However, balancing treatment efficacy and tolerability remains challenging, particularly in patients with significant comorbidities [1]. We aimed to assess whether chronological age or comorbidity burden better predicts treatment tolerance and clinical outcomes in patients with MBLD in a real-world setting.

2 | Material and Methods

2.1 | Study Design and Patients' Population

This retrospective, single-center, observational study included adult patients (≥18 years) with MBLD treated at the Department of Oncology, HFR Fribourg Hospital, Switzerland. Consecutive patients who received at least one dose of the anti-CD20 monoclonal antibodies rituximab and/or obinutuzumab between January 1, 2016, and December 31, 2021, were eligible for inclusion. Patients were excluded if they received anti-CD20 therapy for a non-oncological disease, were lost to follow-up or had a follow-up of less than 1 month, had incomplete medical records, or had not consented to the use of their medical data (see Figure S1 for the study flowchart). Clinical data were extracted from the Medfolio electronic medical record system, pseudonymised, and stored in a secure REDCap database hosted by the University of Fribourg.

2.2 | Data Collection

The following data were collected: baseline characteristics including demographic data, laboratory values (including serum creatinine, albumin, calcium, liver function tests, lactate dehydrogenase (LDH), complete blood count and hepatitis and HIV serologies), comorbidity burden (evaluated by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score) and details of MBLD diagnosis (histological subtype and prognostic score when available; see Tables S1 and S2). The CIRS-G score is a validated tool used to measure medical and psychiatric impairment in older adults. It consists of an organ-system-based rating scale, in which the most severe condition in each of the 14 organ systems is assigned a severity score ranging from 0 (no problem) to 4 (extremely severe), resulting in a final cumulative score [9] (see Table S3). We used 70 years as the threshold to categorise patients into two groups: younger (<70 years) and older (≥70 years). Treatment-related data were collected, including treatment type, number of cycles, treatment line, and total number of treatments. The total number of treatments was defined as the cumulative total of all therapies administered to a patient, regardless of treatment line. This distinction is particularly relevant for multimodal therapies (e.g., a combination of chemotherapy and radiotherapy is considered a single treatment line but comprises two separate treatments). Treatment adaptation was defined as either the use of the standardised reduced-dose protocol R-mini-CHOP or non-standardised treatment modifications of existing treatment regimens (i.e., reduction in the planned dose or omission of one or more drugs). Treatment history was reviewed from the available medical records, including all treatments administered before, during, and after the first anti-CD20 treatment captured by the study inclusion criteria. Data were also collected on treatment-related toxic events, including grade (grade ≥3 according to CTCAE v5.0), type, timing, and management strategies (see Tables S4 and S5). Patient outcomes—including Objective Response Rates (ORR), Disease Control Rate (DCR), and Overall Survival (OS) – were calculated from the date of diagnosis. When available, outcome data were collected at 6- and 12-months post-diagnosis, and annually thereafter until either the end of the data collection period (January 1, 2024; follow-up ranging from 1 month to 8 years), or the patient's death. Immediate treatment response was also recorded. Outcomes were evaluated using disease-specific scoring systems based on the underlying malignancy (see Tables S6–S8).

2.3 | Statistics

Statistical analyses and figures were performed in R 4.4.3, and the *survival, ggsurvfit, and contsurvplot* packages [10, 11]. To assess the impact of age class at diagnosis (<70 vs. ≥70 years), Chi-squared tests were used for categorical variables, including R-mini-CHOP use, toxicity grade, haematological toxic events, DCR and ORR at 6, 12, and 24 months. For continuous variables including CIRS-G score, number of toxic events, treatment lines, total number of treatments and toxicity rates per treatment line and total number of treatments, Kruskal–Wallis tests were applied.

To increase statistical power in selected analyses, age was also treated as a continuous variable. Generalised linear models (binomial, quasibinomial or quasipoisson, as appropriate) were used to assess the association between age and treatment patterns, treatment-related toxic events and clinical outcomes.

As there is no established consensus on how to categorise comorbidity burden using the CIRS-G score and to enhance statistical power, the CIRS-G score was analysed as a continuous variable. Generalised linear models (binomial, quasibinomial or quasipoisson, as appropriate) were used to assess its association with treatment patterns, treatment-related toxic events and clinical outcomes.

Multivariable analyses were performed to assess the independent associations of age and CIRS-G score with clinical outcomes. Logistic regression models for DCR and ORR at 6, 12, and 24 months were adjusted for age at diagnosis, CIRS-G score, and Ann Arbor stage. Overall survival was analysed using Cox proportional hazards models adjusted for the same covariates. Survival analyses were represented by Kaplan–Meier curves.

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Subgroup analyses were performed in patients with Diffuse Large B-Cell Lymphoma (DLBCL) using the same statistical approach as in the overall cohort. Multivariable analyses of DCR, ORR, and overall survival were adjusted for age at diagnosis, CIRS-G score, and Ann Arbor stage.

All statistical tests were two-sided and a p-value <0.05 was considered statistically significant.

3 | Results

3.1 | Study Population

3.1.1 | General Characteristics

Of the 322 patients screened, 172 were included. The mean age was 67 years; 41% ($n=70$) were <70 years and 59% ($n=102$) were ≥ 70 years. Sixty percent ($n=103$) were male, while 40% ($n=69$) were female. The mean CIRS-G score was 9.3 ± 3.4 and was significantly higher in patients aged ≥ 70 years ($p<0.001$; Figure S2). The most frequent diagnoses were DLBCL (35%), FL (22%), and CLL (12%), with no significant difference between age groups ($p=0.691$; Figure S3). Overall, 72% ($n=101$) had advanced-stage disease (Ann Arbor Stage III–IV, when applicable) at diagnosis (Table 1).

3.1.2 | Treatment Modalities in the Entire Population

Patients received a mean of 2 treatment lines (SD = 1.9). Systemic therapies accounted for 81% of all treatments, with chemo-immunotherapy being the most frequent approach (57%, $n=246$) and R-CHOP the most frequent regimen (21%, $n=52$). R-mini-CHOP represented 11% ($n=26$) of combined chemo-immunotherapy regimens. Non-standard treatment modifications were applied in 11% ($n=28$) of systemic treatments (Tables 2, S9, and S10).

3.1.3 | Treatment-Related Toxic Events in the Entire Population

The mean number of significant toxic events per patient was 1.8 (SD = 2.6) with infectious (41%, $n=127$) and haematological (31%, $n=97$) toxic events being the most frequent. Among grade ≥ 3 toxic events, Grade 3 events predominated (52%, $n=162$) (Table 3).

3.2 | Analysis of Treatment Tolerance

3.2.1 | Impact of Age on Treatment Type and Toxic Event

Treatment intensity decreased with age, reflected by a fewer total number of treatments ($p=0.003$; Figure S4), while the number of treatment lines remained unchanged ($p=0.422$; Figure S5).

R-CHOP was more frequently used in younger patients ($p=0.008$), whereas R-mini-CHOP was more frequent in older patients ($p<0.001$; Figure 1A,B). Non-standard treatment modifications were not associated with age ($p=0.271$; Figure S6).

Toxicity rates per treatment line and per total number of treatments did not differ significantly with age ($p=0.126$ and $p=0.286$, respectively; Figures 1C and S7). Older age was associated with a lower proportion of haematological toxic events ($p=0.02$; Figure S8), while toxicity severity differed between age groups ($p=0.005$; Figure 1D), with more Grade 3 and Grade 5 events among older patients. Grade 5 toxic events remained uncommon (5% of adverse events in older patients; Table 3).

3.2.2 | Impact of CIRS-G Score on Treatment Type and Toxicity

Increasing CIRS-G score was associated with fewer treatment lines and total number of treatments (both $p<0.001$; Figure 2A,B respectively) but not with R-mini-CHOP use ($p=0.084$; Figure S9) or non-standard treatment modifications ($p=0.076$; Figure S10).

CIRS-G score was not associated with the number of toxic events overall ($p=0.111$; Figure S11), per treatment line or per total number of treatments ($p=0.589$; Figure 2C and $p=0.443$; Figure 2D respectively). No significant associations were observed with toxicity type ($p=0.176$; Figure S12) or severity ($p=0.867$; Figure S13).

3.3 | Analysis of Patient's Outcomes

3.3.1 | Impact of Age on Outcomes

Overall mortality was higher in older patients ($p=0.002$; Figure S14) while DCR and ORR decreased significantly with age at 6, 12, and 24 months (all $p<0.05$; Figure S15).

3.3.2 | Impact of CIRS-G Score on Outcomes

CIRS-G score was not associated with ORR ($p=0.912$, 0.661, and 0.944), DCR ($p=0.361$, 0.919, and 0.988) or survival probability ($p=0.083$) at 6, 12, and 24 months respectively.

3.4 | Additional Subgroup and Multivariable Analyses

3.4.1 | Multivariable Analyses in the Overall MBLD Cohort

In multivariable analyses adjusted for age at diagnosis, CIRS-G score, and Ann Arbor stage, age remained significantly associated with poorer ORR at 6, 12, and 24 months ($p=0.008$, 0.003, and 0.005, respectively) while CIRS-G score was not significantly associated with ORR ($p=0.500$, 0.345, and 0.228, respectively; Figure 3A).

Similarly, age remained significantly associated with poorer DCR at 6, 12, and 24 months ($p=0.003$, <0.001, and 0.006, respectively),

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TABLE 1 | Baseline characteristics.

General characteristics	All ($N=172$) Mean ± SD AF (RF in %)[a]	< 70 years ($N=70$) Mean ± SD AF (RF in %)[a]	≥ 70 years ($N=102$) Mean ± SD AF (RF in %)[a]
Age (years)	67 ± 13.6	54 ± 10.3	74 ± 8
Female	69 (40%)	31 (44%)	38 (37%)
BMI (kg/m^2)	26.3 ± 5.2	26.2 ± 5.6	26.3 ± 4.9
CIRS-G	9.3 ± 3.4	7.8 ± 3.1	10.3 ± 3.2
Creatinine (μmol/L)	86.8 ± 31.6	82.8 ± 33.3	89.8 ± 30.2
Haemoglobin (g/L)	125.7 ± 23.5	131.1 ± 22.1	122 ± 23.9
Leucocytes (G/L)	7.4 (4.65)	7 (5.4)	7.65 (4.45)
Thrombocytes (G/L)	245.5 ± 115.6	241.7 ± 108.3	248.1 ± 120.8
Elevated LDH	85 (51%)	33 (49%)	52 (52%)
Calcium (mmol/L)	2.35 ± 0.15	2.33 ± 0.12	2.36 ± 0.17
Albumin (g/L)	39.4 ± 6.2	41.1 ± 6.2	38.3 ± 5.9
Histology			
Diffuse large B-cell lymphoma (DLBCL)	60 (35%)	21 (30%)	39 (38%)
Follicular lymphoma (FL)	37 (22%)	16 (23%)	21 (21%)
Chronic lymphocytic leukaemia (CLL)	21 (12%)	12 (17%)	9 (9%)
Mantle cell lymphoma (MCL)	15 (9%)	4 (6%)	11 (11%)
Marginal zone lymphoma (MZL)	14 (8%)	5 (7%)	9 (9%)
Waldenström's macroglobulinaemia	10 (6%)	1 (1%)	9 (9%)
Burkitt lymphoma (BL)	5 (3%)	3 (4%)	2 (2%)
Other	10 (6%)	8 (11%)	2 (2%)
Stage[b]			
I	19 (14%)	9 (16%)	10 (12%)
II	20 (14%)	9 (16%)	11 (13%)
III	29 (21%)	9 (16%)	20 (24%)
IV	72 (51%)	29 (52%)	43 (51%)
B-symptoms	46 (27%)	20 (29%)	26 (26%)
High grade transformation	17 (10%)	10 (14%)	7 (7%)
Prognostic score[c]			
R-IPI	2.45 ± 1.36	1.92 ± 1.35	2.78 ± 1.27
FLIPI	2.21 ± 1.26	1.75 ± 1.34	2.52 ± 1.12
Binet/Rai[d]			
A/0	9 (43%)	6 (50%)	3 (33%)
A/I	5 (24%)	2 (17%)	3 (33%)
B/I	3 (14%)	3 (25%)	0 (0%)
B/II	2 (10%)	1 (8%)	1 (11%)
C/III	2 (10%)	0 (0%)	2 (22%)

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TABLE 1 | (Continued)

General characteristics	All ($N=172$) Mean ± SD AF (RF in %)[a]	<70 years ($N=70$) Mean ± SD AF (RF in %)[a]	≥70 years ($N=102$) Mean ± SD AF (RF in %)[a]
MIPI	5.47 ± 1.39	4.7 ± 2.04	5.75 ± 1.06
HPLLs/ABC	1.8 ± 1.32	1 ± 1.41	2.33 ± 1.03
IPSSWM	1.9 ± 0.99	1	2 ± 1
BL-IPI	1.8 ± 0.84	1.33 ± 0.58	2.5 ± 0.71
MALT-IPI	1.5 ± 0.71	2	1
IPS	3 ± 2.83	3 ± 2.83	
IELSG	2	2	

Abbreviations: AF, absolute frequency; RF, relative frequency; SD, standard deviation.
[a]For Leucocytes (G/L) we used median + interquartile difference.
[b]According to Ann Arbor staging system, calculated only for solid tumours (e.g., DLBCL, FL, etc.).
[c]More details in appendix.
[d]Only for CLL.

whereas CIRS-G score was not significantly associated with DCR ($p=0.690$, 0.121, and 0.170, respectively; Figure 3B). Age was also independently associated with poorer overall survival ($p=0.016$), whereas CIRS-G score was not ($p=0.701$; Figure 3C).

3.4.2 | DLBCL Subgroup Analyses

As DLBCL was the most frequent histological subtype, subgroup analyses were performed in the 60 patients with DLBCL. R-mini-CHOP use increased significantly with age ($p<0.001$; Figure S16), while R-CHOP use was not associated with age ($p=0.143$). Neither R-mini-CHOP nor R-CHOP use was significantly associated with CIRS-G score ($p=0.099$ and 0.795 respectively). The total number of treatments decreased with increasing age ($p=0.038$) and CIRS-G score ($p=0.023$). Toxicity rates per treatment line and per total number of treatments were not significantly associated with age ($p=0.339$ and 0.545 respectively) or CIRS-G score ($p=0.897$ and 0.607 respectively). Toxicity grade did not significantly differ according to age ($p=0.071$) or CIRS-G score ($p=0.46$).

Clinical outcomes showed a broadly similar pattern to the overall cohort. DCR decreased with age at 6, 12, and 24 months ($p=0.051$, 0.007, and 0.048, respectively; Figure S17), but was not associated with CIRS-G score ($p=0.151$, 0.524 and 0.744, respectively). Similarly, ORR decreased with age at 6, 12, and 24 months ($p=0.030$, 0.007, and 0.015, respectively; Figure S18), but was not associated with CIRS-G score ($p=0.11$, 0.524 and 0.538, respectively). Survival was worse with increasing age ($p=0.002$; Figure S19), whereas CIRS-G score was not associated with survival ($p=0.427$).

Multivariable analyses adjusted for age at diagnosis, CIRS-G score, and Ann Arbor stage showed that age remained significantly associated with ORR and DCR at 6, 12, and 24 months (ORR: $p=0.030$, 0.004, and 0.006; DCR: $p=0.032$, 0.004, and 0.011, respectively), whereas CIRS-G score was not significantly associated with ORR ($p=0.906$, 0.147, and 0.186) or DCR ($p=0.971$, 0.147, and 0.152). For overall survival, age remained significantly associated with poorer survival ($p=0.004$), whereas CIRS-G score was not ($p=0.350$). Given the limited sample size and number of events, these subgroup analyses should be interpreted cautiously.

3.4.3 | CLL Subgroup Analyses

The CLL subgroup comprised 21 patients, including 12 (57.1%) aged <70 years and 9 (42.9%) aged ≥70 years, with a median CIRS-G score of 9 (IQR 7–11). Patients received a median of 2 treatment lines (IQR 1–4), with a median total number of 3 treatments per patient (IQR 2–4). In the first-line setting, chemoimmunotherapy accounted for 60.7% ($n=17$) of treatments, whereas targeted therapies were uncommon (3.6%, $n=1$). Beyond first line, targeted therapies—mainly Bruton Tyrosine Kinase inhibitors (BTKi) such as ibrutinib, acalabrutinib, and Zanubrutinib and venetoclax-based regimens—became more frequent, representing 35.8% ($n=19$) of treatments compared with 30.2% ($n=16$) for chemoimmunotherapy.

4 | Discussion

In this real-world cohort, increasing age was associated with reduced treatment intensity and poorer clinical outcomes, while comorbidity burden, as measured by the CIRS-G score, did not predict toxicity or survival. These findings suggest that comorbidity burden alone may be insufficient to guide treatment decisions in patients with MBLD. Importantly, these associations persisted in multivariable analyses adjusted for age at diagnosis, CIRS-G score, and Ann Arbor stage, with age remaining independently associated with DCR, ORR, and overall survival, whereas CIRS-G score was not.

The two age groups were comparable in terms of disease distribution, supporting the internal consistency of the cohort.

Treatment intensity decreased with age, as illustrated by the increased use of R-mini-CHOP and the reduction in the total number of treatments, while the number of treatment lines remained stable. A similar decrease in treatment exposure was observed

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TABLE 2 | Treatment modalities.

Treatment modalities	All ($N=172$) AF (RF in %)	<70 years ($N=70$) AF (RF in %)	≥70 years ($N=102$) AF (RF in %)
Total number of treatments	531	262	269
Number of treatment lines	345	168	177
Systemic therapy	430 (81%)	201 (77%)	229 (85%)
Chemotherapy combined with monoclonal antibody	246 (57%)	103 (51%)	143 (62%)
Non-standard treatment modification			
Decrease in the theoretical dose	11 (5%)	3 (3%)	8 (6%)
Exclusion of a molecule	17 (7%)	6 (6%)	11 (8%)
Type of treatment			
R-CHOP[a]	52 (21%)	25 (24%)	27 (19%)
R-mini-CHOP	26 (11%)	2 (2%)	24 (17%)
Other regimens[b]	168 (69%)	76 (74%)	92 (64%)
Maintenance therapy[c]	57 (13%)	20 (10%)	37 (16%)
Sole monoclonal antibody[d]	32 (7%)	19 (10%)	13 (6%)
Non-standard treatment modification (decrease in the theoretical dose)[e]	1 (3%)	1 (5%)	0 (0%)
Type of treatment			
Rituximab	27 (84%)	15 (79%)	12 (92%)
Obinutuzumab	1 (3%)	0 (0%)	1 (8%)
Other regimens[f]	4 (12%)	4 (21%)	1 (8%)
Chemotherapy without monoclonal antibody	40 (9%)	20 (10%)	20 (9%)
Non-standard treatment modification (decrease in the theoretical dose)[e]	1 (3%)	0 (0%)	1 (5%)
Type of treatment			
Corticosteroids alone	14 (35%)	5 (25%)	9 (45%)
Anthracycline-based	4 (10%)	4 (20%)	0 (0%)
Other regimens[g]	22 (55%)	11 (55%)	11 (55%)
Targeted treatment	30 (7%)	21 (10%)	9 (4%)
Non-standard treatment modification (decrease in the theoretical dose)[e]	1 (3%)	0 (0%)	1 (11%)
Type of treatment			
BTKi	17 (56%)	10 (47%)	7 (78%)
Venetoclax	9 (30%)	8 (38%)	1 (11%)
Idelalisib	4 (13%)	3 (14%)	1 (11%)
Stem cell autograft	17 (4%)	13 (6%)	4 (2%)
CAR T-cell therapy	4 (1%)	2 (1%)	2 (1%)
Other systemic treatment	4 (1%)	3 (2%)	1 (1%)
Radiotherapy	54 (10%)	31 (12%)	23 (9%)

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TABLE 2 | (Continued)

Treatment modalities	All ($N=172$) AF (RF in %)	<70 years ($N=70$) AF (RF in %)	≥ 70 years ($N=102$) AF (RF in %)
Intrathecal therapy	40 (8%)	28 (11%)	12 (5%)
Other non-systemic treatments[h]	7 (1%)	2 (1%)	5 (2%)

Abbreviations: AF, absolute frequency; BTKi, Bruton Tyrosin Kinase inhibitors (ibrutinib, acalabrutinib, zanubrutinib); R-(mini)-CHOP, rituximab, cyclophosphamide, hydroxyadriamycine, Oncovin (vincristine), prednisone; RF, relative frequency.
[a]Includes 4 treatments as part of alternating R-CHOP/R-DHAP cycles and 2 treatments as part of alternating R-CHOP/R-DHAOx cycles.
[b]Other regimens include R-ESHAP (rituximab, etoposide, Solumedrol (methylprednisolone), high-dose cytarabine, cisplatin), R-CODOX-M-IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and high-dose cytarabine), R/O-Bendamustine.
[c]Defined as treatment with a monoclonal antibody alone following a "chemotherapy combined with monoclonal antibody" regimen, while remaining within the same line of treatment.
[d]Defined as a treatment in which a monoclonal antibody is the sole systemic therapy within a given line of treatment.
[e]There were no exclusions of specific molecules across the different treatment regimens in these therapies.
[f]Other regimens include pembrolizumab, alemtuzumab, glofitamab.
[g]Other regimens include methotrexate alone, ESHAP, chlorambucil based therapies.
[h]1 intraocular treatment and 6 surgeries.

TABLE 3 | Toxic events.

Significant toxic events[a]	All ($N=172$) AF (RF in %)	<70 years ($N=70$) AF (RF in %)	≥ 70 years ($N=102$) AF (RF in %)
Total count	309	174	135
Infectious	127 (41%)	73 (42%)	54 (40%)
Febrile neutropenia[b]	65 (51%)	39 (53%)	26 (48%)
Respiratory infection	21 (17%)	12 (16%)	9 (17%)
Sepsis/septic shock	16 (13%)	7 (10%)	9 (17%)
Haematological	97 (31%)	57 (33%)	40 (30%)
Afebrile neutropenia	27 (28%)	19 (33%)	8 (20%)
Anaemia	27 (28%)	12 (21%)	15 (38%)
Thrombopenia	23 (24%)	15 (26%)	8 (20%)
Bicytopenia/pancytopenia	12 (12%)	7 (12%)	5 (13%)
Digestive	18 (6%)	9 (5%)	9 (7%)
Malnutrition	6 (33%)	2 (20%)	4 (50%)
Nausea/diarrhoea	5 (28%)	3 (30%)	2 (25%)
Cardiac	15 (5%)	8 (5%)	7 (5%)
Atrial fibrillation	4 (27%)	3 (38%)	1 (14%)
Hypervolemia	4 (27%)	2 (25%)	2 (29%)
Heart failure	4 (27%)	2 (25%)	2 (29%)
Nephrological	5 (2%)	2 (1%)	3 (2%)
Acute kidney injury	5 (100%)	2 (100%)	3 (100%)
Neurological	3 (1%)	0 (0%)	3 (2%)
Dermatological	3 (1%)	2 (1%)	1 (1%)
Other	41 (13%)	23 (13%)	18 (13%)
Toxicity grade			
G3	162 (52%)	87 (50%)	75 (56%)
G4	139 (45%)	86 (50%)	53 (39%)
G5	8 (3%)	1 (1%)	7 (5%)

Abbreviations: AF, absolute frequency; RF, relative frequency.
[a]Only Grade 3 or higher toxic events (according to CTCAE v5.0) were collected during data collection.
[b]See Methods section for definition.

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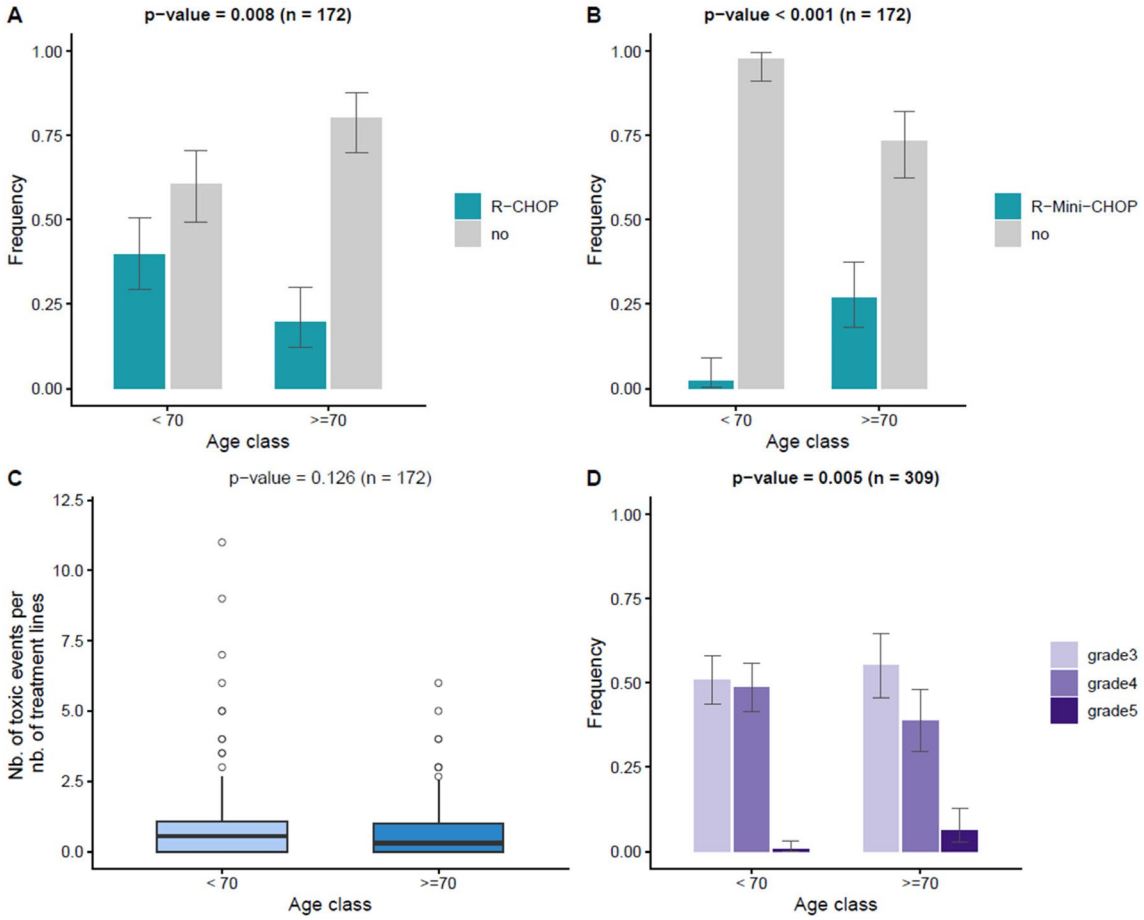


FIGURE 1 | Association between age, treatment patterns and treatment-related toxic events. (A) Proportion of patients receiving R-CHOP according to age group (< 70 years vs. ≥ 70 years). (B) Proportion of patients receiving R-mini-CHOP according to age group (< 70 years vs. ≥ 70 years). (C) Number of treatment-related toxic events per number of treatment lines according to age group (< 70 years vs. ≥ 70 years). Horizontal lines represent the median, boxes the interquartile range (IQR), whiskers extend to 1.5 × IQR, and circles indicate outliers. (D) Distribution of the grade of treatment-related toxicity according to age group, based on CTCAE version 5.0. *p*-Values are shown for each comparison.

with increasing comorbidity burden. However, neither age nor comorbidity burden was associated with a higher rate of toxic events when adjusted for treatment exposure. The lower treatment intensity observed in older patients may have contributed to their poorer clinical outcomes and represents an important potential confounding factor. However, the association between age and clinical outcomes persisted after adjustment for CIRS-G score and disease stage. Although older patients experienced a different distribution of toxicity grades, with more Grade 3 and Grade 5 events, the latter's incidence remained low (5% vs. 56% for Grade 3 toxic events).

Notably, the absence of an association between CIRS-G score and toxicity or clinical outcomes suggests that comorbidity burden alone may be insufficient to guide therapeutic decision-making. While comorbidity indices are widely used in oncogeriatry, our findings suggest that they may not adequately capture patient vulnerability in the context of MBLD.

In contrast, chronological age remained associated with poorer overall survival and response rates. This may reflect a combination of oncological factors, such as disease biology and treatment intensity, as well as non-oncological factors including frailty, functional decline, and competing risks of mortality [1, 2, 8]. Unfortunately, the design of our study does not allow us to clearly separate their respective impact.

4.1 | Comparison With Existing Data

Our findings are overall consistent with previous studies showing that older and/or frail patients are more likely to receive less intensive treatment due to concerns about toxicity [2, 8]. Importantly, in our cohort, reduced treatment intensity was not associated with increased toxicity, suggesting that adapted therapeutic strategies may allow acceptable tolerance in older patients [12–15]. These results extend existing evidence by highlighting that comorbidity burden alone does not explain variations in toxicity or outcomes [1, 3, 8, 15]. Our findings further suggest that the association between chronological age and clinical outcomes cannot be fully explained by comorbidity burden or disease stage alone.

These observations support the need for multidimensional frailty assessment beyond comorbidity scores alone. Comprehensive geriatric assessment (CGA) remains the reference standard

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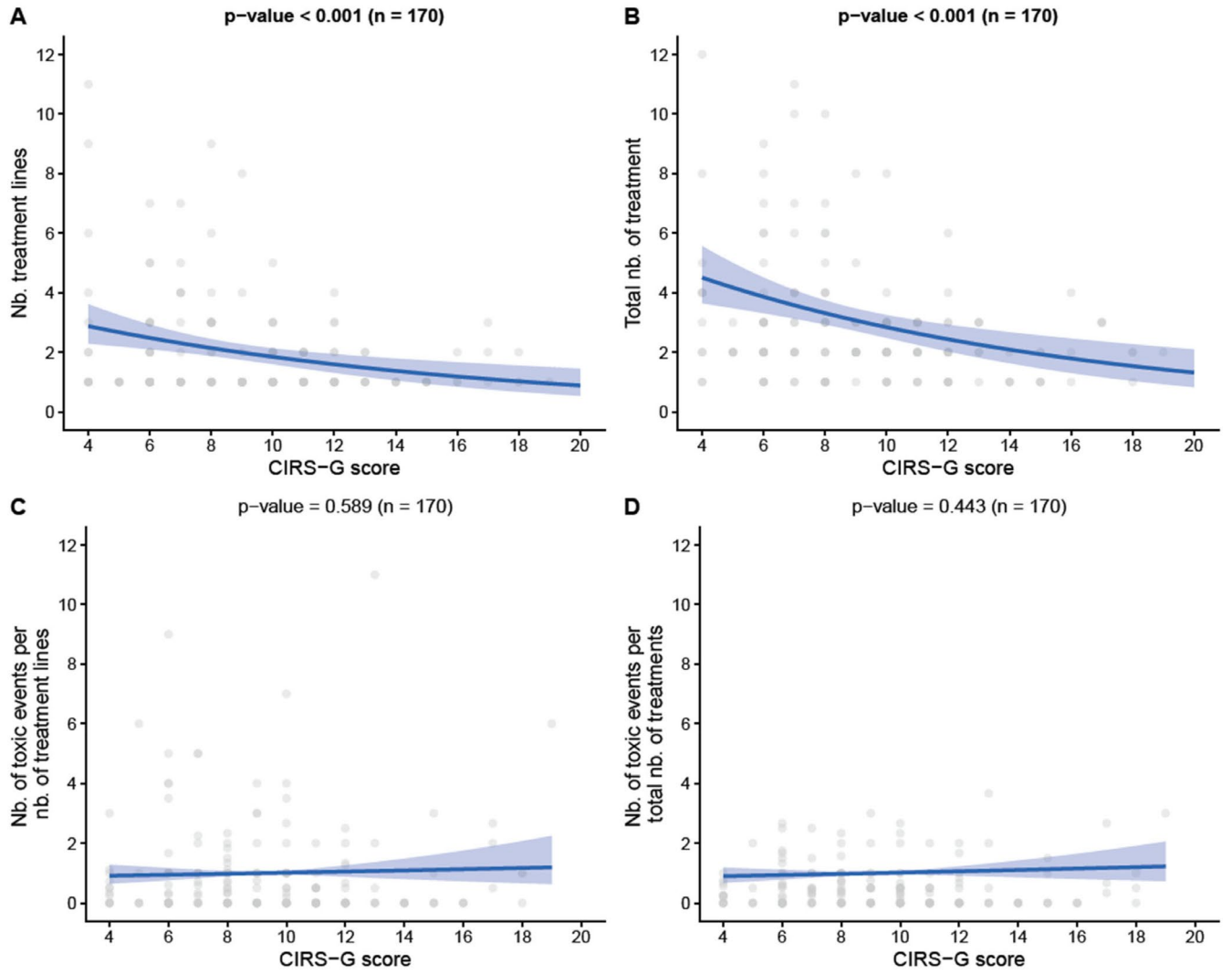


FIGURE 2 | Association between CIRS-G score, treatment patterns and treatment-related toxic events. (A) Number of treatment lines according to CIRS-G score. (B) Total number of treatments according to CIRS-G score. (C) Number of treatment-related toxic events per number of treatment lines according to CIRS-G score. (D) Number of treatment-related toxic events per total number of treatments according to CIRS-G score. Solid blue lines represent the fitted regression curves, dashed red lines indicate the 95% confidence intervals, and *p*-values are shown for each association. CIRS-G, Cumulative Illness Rating Scale–Geriatric.

to evaluate functional status, cognition, and social factors, although its implementation in routine practice can be challenging. In this context, screening tools such as the G8 may help identify patients who would benefit from a full geriatric evaluation [16–18].

4.2 | Strengths and Limitations

This study has several strengths, including its real-world design and the inclusion of patients with multiple comorbidities who are often underrepresented in clinical trials. Comorbidity burden was assessed using a validated tool in oncogeriatric populations [3, 9, 19, 20].

However, several limitations should be acknowledged. The retrospective single-center design limits causal inference and may introduce selection bias. The heterogeneity of MBLD subtypes, with distinct disease biology, prognostic factors, and treatment strategies, may also have introduced residual confounding. Although multivariable analyses were adjusted for Ann Arbor stage, histological subtype could not be included in the final models. The absence of a standardised measure of treatment intensity also limits our ability to determine to what extent differences in treatment intensity contributed to the poorer outcomes observed with increasing age.

In addition, only patients receiving anti-CD20 therapy were included, potentially excluding a subset of frailer or untreated patients. The requirement for prior exposure to rituximab and/or obinutuzumab may have resulted in underrepresentation of CLL patients receiving BTKi or other targeted therapy monotherapy, and the CLL subgroup should therefore not be considered representative of the contemporary CLL population. As CLL accounted for only 21 of 172 patients (12.2%) in our cohort, this selection is unlikely to have substantially influenced the overall findings.

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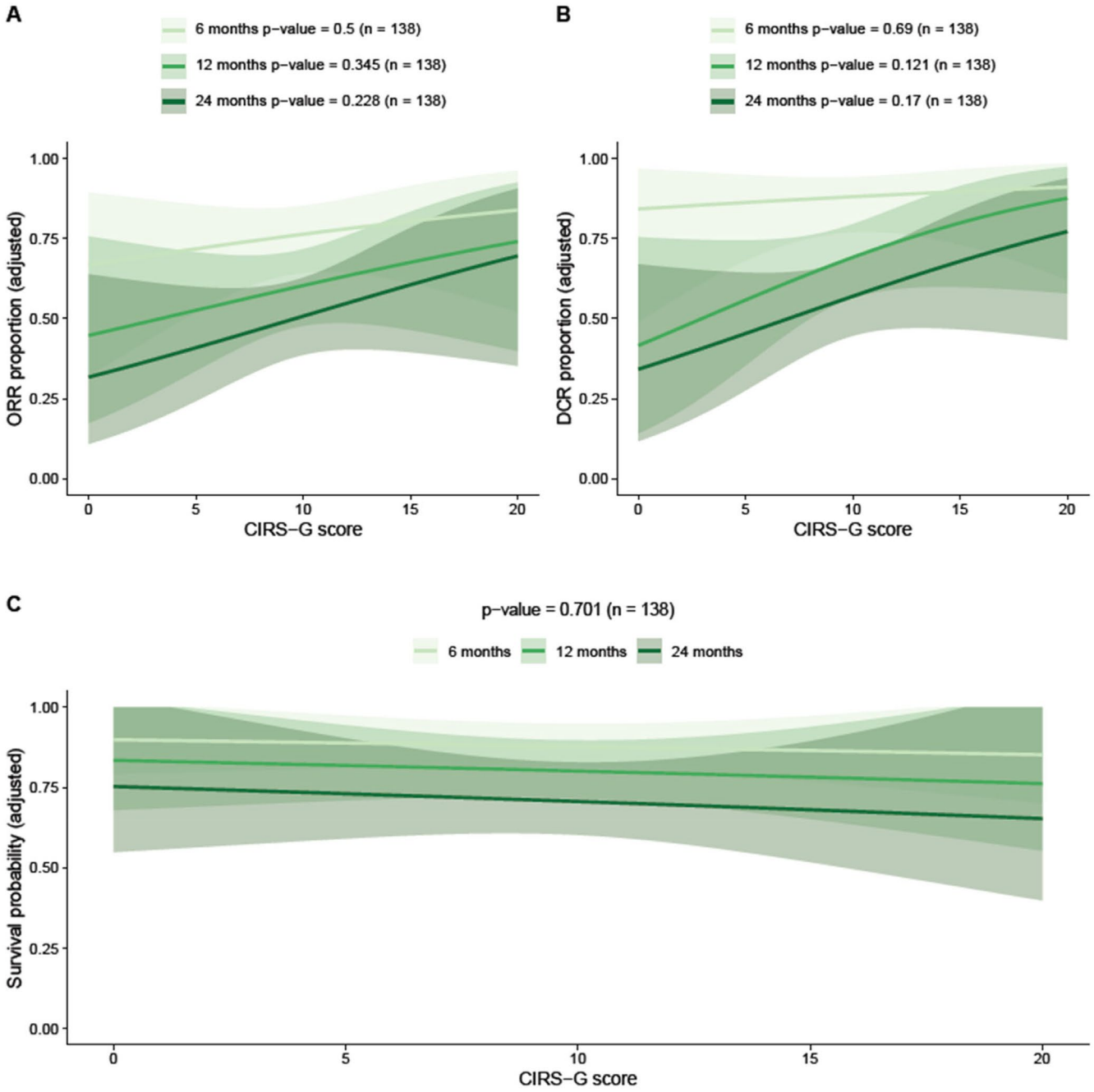


FIGURE 3 | Multivariable analysis of clinical outcomes according to CIRS-G score. (A) Adjusted ORR at 6, 12, and 24 months according to CIRS-G score. (B) Adjusted DCR at 6, 12, and 24 months according to CIRS-G score. (C) Adjusted survival probability according to CIRS-G score. Analyses were adjusted for age at diagnosis, CIRS-G score, and Ann Arbor stage. Solid lines represent fitted regression curves and shaded areas indicate 95% confidence intervals. *p*-values are shown for each association. CIRS-G, Cumulative Illness Rating Scale–Geriatric; DCR, disease control rate; ORR, objective response rate.

The DLBCL subgroup analysis was limited by the relatively small sample size and number of events, particularly for multivariable survival analyses, and should therefore be considered exploratory. Finally, late-onset toxic events may have been underestimated due to limited follow-up. It is also worth noting that only 1% of patients with MBLD received CAR T-cell therapy in our cohort. This low proportion is likely due to the study period (2016–2021), during which CAR T cells had not yet become established as a standard practice in Switzerland.

5 | Conclusion

In this real-world study, chronological age—but not comorbidity burden—was associated with poorer clinical outcomes in patients with MBLD. The lack of association between CIRS-G and both toxicity and survival highlights its limitations as a decision-making tool. These findings support the integration of comprehensive geriatric assessment to better guide treatment strategies in this growing patient population.

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Author Contributions

Kevin Nasrinfar: conceptualization, methodology, investigation, software, writing – original draft, project administration, data curation, visualization. **Harrison Wildhaber:** investigation, writing – original draft, data curation. **Rudolf Rohr:** methodology, formal analysis, visualization. **Gaëlle Rhyner Agocs:** writing – review and editing, validation. **Urban Novak:** validation, writing – review and editing. **Alessandra Curioni-Fontecedro:** conceptualization, funding acquisition, resources, validation, writing – review and editing, supervision. **Vérène Dougoud-Chauvin:** conceptualization, validation, supervision, resources, writing – review and editing, funding acquisition, methodology.

Acknowledgments

The authors thank the physicians of the Department of Oncology at HFR Fribourg Hospital for their support throughout this study.

Funding

The authors have nothing to report.

Ethics Statement

The study was approved by the CER-VD Ethics Committee (Protocol ID: 2023-01789; approval date: December 21, 2023) and was conducted in accordance with the Declaration of Helsinki and applicable national regulations. Written informed consent was obtained from all living participants. For deceased patients, the local ethics committee granted a waiver of informed consent. Participants' privacy and confidentiality were protected throughout the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analysed during the current study are not publicly available due to patient confidentiality and data protection regulations but may be available from the corresponding author on reasonable request and with appropriate ethical approval.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flow chart of patient inclusion. **Table S1:** Summary of collected data. **Table S2:** Prognostic scores. **Table S3:** The CIRS-G score. **Table S4:** Details about toxic events collection. **Table S5:** Details about Grade 5 toxic events. **Table S6:** Criteria used for definition of response, general. **Table S7:** Criteria used for definition of response, detailed. **Table S8:** The 2014 Lugano Classification. **Table S9:** Details of surgical treatments. **Table S10:** Details of non-standard treatment modifications. **Figure S2:** Association between age category and CIRS-G score. **Figure S3:** Association between age category and histological subtypes. **Figure S4:** Association between age category and total number of treatments. **Figure S5:** Association between age category and treatment lines. **Figure S6:** Association between age category and non-standard treatment modification. **Figure S7:** Association between age category and toxic events per total number of treatments. **Figure S8:** Association between age and haematological toxic events. **Figure S9:** Association between CIRS-G score and R-mini-CHOP. **Figure S10:** Association between CIRS-G score and non-standard treatment modification. **Figure S11:** Association between CIRS-G score and toxic events. **Figure S12:** Association between CIRS-G score and haematological toxic events. **Figure S13:** Association between CIRS-G score and toxic events severity. **Figure S14:** Survival analysis as a function of the age category. **Figure S15:** Distribution of clinical outcomes according to age category at 6, 12, and 24 months. **Figure S16:** Association between age category and R-mini-CHOP in DLBCL patients. **Figure S17:** Association between age category and DCR in DLBCL patients. **Figure S18:** Association between age category and ORR in DLBCL patients. **Figure S19:** Association between age and survival probability in DLBCL patients.

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