

Diffuse large B-cell lymphoma: 10 years' real-world clinical experience with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone

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Abstract. Treatment with rituximab plus a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for patients with diffuse large B-cell lymphoma (DLBCL) has proven efficacy in clinical trials. The present study investigated its application in clinical practice. This single-center, retrospective database analysis included patients with DLBCL treated at the Slovenian Institute of Oncology Ljubljana between 2004 and 2013. Overall survival (OS) and progression-free survival (PFS) were assessed according to International Prognostic Index (IPI) and revised IPI (R-IPI) categories. Overall, 573 patients with DLBCL were included in the study (median follow-up, 45.3 months; range, 0.1-143.0). Patients were categorized as IPI 'low' (n=170; 30%), 'low-intermediate' (n=134; 23%), 'high-intermediate' (n=129; 23%) and 'high' (n=140; 24%) risk. R-IPI groups were indicated with 'very good' (n=59; 10%), 'good' (n=245; 43%) and 'poor' (n=269; 47%) prognosis. Ten-year OS and PFS rates were 51 and 72%, respectively; median OS was 124 months and median PFS was not reached. Ten-year OS rates were 80 and 87% in low-risk and 'very good' prognosis groups, respectively, and 30 and 37% in high-risk and poor prognosis patients, respectively. This analysis of patients with DLBCL indicated that many patients treated with R-CHOP and R-CHOP-like regimens in the real-world setting have excellent outcomes.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphomas, constituting up to 40%

of cases globally (1). Global epidemiological data on DLBCL are limited, but the estimated incidence is 7 per 100,000 in the USA (2). In Slovenia, the annual incidence of non-Hodgkin lymphomas was 374 in 2013 (3); 36% of these cases are believed to be DLBCL (3). Although most commonly observed in older patients, DLBCL can affect any age group, including children (4).

DLBCL is an aggressive condition and many patients have advanced disease at diagnosis (5). The prognosis of a patient with DLBCL can be predicted using their International Prognostic Index (IPI) score. The IPI score is calculated based on age, serum lactate dehydrogenase level, Eastern Cooperative Oncology Group performance score, disease stage, and the number of extranodal disease sites (6).

Treatment for patients with DLBCL generally consists of a combination of chemotherapy [cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)] and rituximab (R-CHOP). Although many clinical trials have demonstrated the efficacy and tolerability of R-CHOP in patients with DLBCL, (7-9) less is known about the use of this regimen in the real-world setting.

Real-world studies can complement the results of clinical trials and provide additional information that can help guide physicians making treatment decisions. Clinical trial data may not be generalizable to the broad range of patients commonly encountered in the clinical setting, as they may be limited to younger patients with good baseline characteristics. Patients encountered in real-world clinical practice may be older and have comorbidities that would have excluded their participation in rigorously designed clinical trials. Consequently, real-world studies can provide a valuable insight into these less widely studied patients.

We previously described the real-world use of R-CHOP in patients with DLBCL in Slovenia (10). We now present the results of extended follow-up in an expanded patient group.

Materials and methods

This was a single-center retrospective database analysis. Records were searched for all patients with DLBCL who were treated at the Institute of Oncology Ljubljana between 2004 and 2013 for inclusion in this analysis.

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All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2000. Individual patient consent was not collected for this study as this was a retrospective database analysis and the institutional informed consent form for treatment included consent to use the patient's data, materials and/or test results for research purposes. The study was approved as such by the institutional review board of the Institute of Oncology Ljubljana.

Patient characteristics, pathohistological diagnosis, disease stage, and response to treatment were taken from patient records. Survival data were retrieved from the Cancer Registry of the Republic of Slovenia [www.slora.si]. Treatment response was evaluated according to Cheson criteria, with the exception of criteria regarding positron-emission tomography (PET) evaluation, which was not routinely used in Slovenia before January 2016 (11). Progression-free survival (PFS) and Overall survival (OS) were calculated using Kaplan-Meier survival curves. PFS, which was determined for patients receiving first-line treatment only, was defined as the time from the beginning of treatment to disease progression for patients achieving complete or partial remission; OS was defined as the time from the beginning of treatment to the time of death or the end of observation for all patients.

Patients were categorized according to IPI (6) and revised IPI (R-IPI) (12) scores. We also compared younger patients (aged <60 years) with good (IPI 0 or 1) vs. poor (IPI \geq 2) prognosis and we compared older (aged \geq 60 years) vs. younger (aged <60 years) patients. Statistically significant differences were calculated using log-rank and χ^2 tests.

Results

Patients. Between 2004 and 2013, 624 patients with DLBCL were treated at the Institute of Oncology Ljubljana, Slovenia. The diagnosis of DLBCL was established histologically in 523 patients (84%) and cytologically in 101 patients (16%). Patient characteristics are summarized in Table I.

All patients received first-line chemotherapy; 607 patients (97%) whose tumors were CD20 positive received rituximab with their chemotherapy. Chemotherapy consisted of CHOP or a CHOP-like regimen in 575 patients (92%); a further 32 patients (5%) received another non-anthracycline chemotherapy regimen in combination with rituximab and the remaining 17 patients (3%) received chemotherapy alone. A total of 136 patients (22%) received second-line therapy and 56 patients (9%) received third-line therapy. The average number of treatment cycles was 6.7 in the first line, 3.7 in the second line, and 2.4 in the third line. Overall, 26 patients (4%) were receiving maintenance or consolidation treatment with rituximab because of an associated follicular lymphoma component to their disease.

IPI risk category and R-IPI prognosis category were assessed in 573 patients. When categorized according to the IPI system, 170 patients (30%) were considered 'low' risk, 134 (23%) were 'low-intermediate' risk, 129 (23%) were 'high-intermediate' risk, and 140 (24%) were 'high' risk. According to the R-IPI prognostic system, 59 patients (10%)

Table I. Patient clinical and demographic characteristics at the start of treatment (n=624).

Characteristic	Value
Sex, n (%)	
Male	297 (48)
Female	327 (52)
Median age, years (range)	67.0 (19-89)
<50 years, n (%)	77 (12)
<60 years, n (%)	208 (33)
>65 years, n (%)	338 (54)
>75 years, n (%)	167 (27)
ECOG performance status, n (%)	
0	299 (48)
1	183 (29)
2	90 (14)
3	33 (5)
4	19 (3)
Disease stage, n (%)	
I	73 (12)
II	178 (29)
III	111 (18)
IV	245 (39)
Elevated LDH level, n (%)	311 (50)
Extranodal involvement, n (%)	113 (18)
Nodal and extranodal involvement, n (%)	326 (52)
Nodal involvement, n (%)	179 (29)
Treatment regimen, n (%)	
Rituximab + CHOP ^a	575 (92)
Rituximab + other chemotherapy ^b	32 (5)
Chemotherapy alone ^c	17 (3)
IPI score, n (%) ^d	
0	63 (10)
1	122 (20)
2	143 (23)
3	141 (23)
4	108 (17)
5	44 (7)

^aCHOP and CHOP-like regimens (R-CHOP or R-CHOP + methotrexate, n=557; R-ACVBP, n=10; R-CHOEP, n=8). ^bR-COEP, n=20; R-CVP, n=6; other (some other form of rituximab-chemotherapy combination), n=6. ^cCHOP chemotherapy without rituximab, n=13; other chemotherapy without rituximab, n=4. ^dIPI score could not be determined in 3 patients. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisone; R-CHOEP, rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-COEP, rituximab, cyclophosphamide, vincristine, etoposide, and prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone; R-IPI, revised International Prognostic Index.

Table II. Response to treatment.

Group (number of patients)	Patients, n (%)				
	CR	PR	SD	PD	Undefined
IPI risk group					
Low (n=170)	101 (59)	67 (39)	0	0	2 (1)
Low-intermediate (n=134)	62 (46)	64 (48)	1 (1)	3 (2)	4 (3)
High-intermediate (n=129)	56 (43)	56 (43)	0	4 (3)	13 (10)
High (n=140)	50 (36)	61 (44)	2 (1)	7 (5)	20 (14)
R-IPI prognostic group					
Very good (n=59)	36 (61)	23 (39)	0	0	0
Good (n=245)	127 (52)	108 (44)	1 (<1)	3 (1)	6 (2)
Poor (n=269)	106 (39)	117 (43)	2 (1)	11 (4)	33 (12)
All patients (n=573) ^a	269 (47)	248 (43)	3 (1)	14 (2)	39 (7)

IPI risk groups: Low risk, IPI=0 or 1; low-intermediate risk, IPI=2; high-intermediate risk, IPI=3; high risk, IPI=4 or 5. R-IPI prognostic groups: Very good prognosis, R-IPI=0; good prognosis, R-IPI=1 or 2; poor prognosis, R-IPI=3-5. ^aIPI score could not be determined in 2 patients receiving R-CHOP or R-CHOP-like regimens. CR, complete response; IPI, International Prognostic Index; PR, partial response; SD, stable disease; PD, progressive disease; R-IPI, revised International Prognostic Index.

Table III. Progression-free survival rates according to IPI and R-IPI categories.

Patient category	Progression-free survival rate (%)					Median progression-free survival (months)
	1-year	2-year	3-year	5-year	10-year	
All patients	86	82	81	80	72	NR
IPI risk group						
Low	93	90	88	87	75	NR
Low-intermediate	89	84	83	82	75	NR
High-intermediate	79	76	75	75	64	NR
High	78	73	71	71	71	NR
R-IPI prognostic group						
Very good	95	95	95	95	84	NR
Good	89	85	84	82	73	NR
Poor	78	75	73	73	66	NR

IPI risk groups: Low risk, IPI=0 or 1; low-intermediate risk, IPI=2; high-intermediate risk, IPI=3; high risk, IPI=4 or 5. R-IPI prognostic groups: Very good prognosis, R-IPI=0; good prognosis, R-IPI=1 or 2; poor prognosis, R-IPI=3-5. IPI, International Prognostic Index; NR, not reached; R-IPI, revised International Prognostic Index.

fell into the 'very good' prognosis group, 245 patients (43%) into the 'good' prognosis group, and 269 patients (47%) into the 'poor' prognosis group.

Response to treatment. The median follow-up time was 45.3 months (range, 0.1-143.0 months). The overall response rate in all patients was 90%. In the IPI 'low-risk' group, 168 patients (99%) had a complete or partial response. The overall response rates in the 'low-intermediate', 'high-intermediate', and 'high-risk' groups were 94, 87, and 79%, respectively (χ^2 test; $P<0.0001$) (Table II). In the R-IPI 'very good' prognosis group, 59 patients (100%) had a complete or

partial response (Table II). The overall response rates in the R-IPI 'good' and 'poor' prognosis groups were 96 and 83%, respectively; the difference between R-IPI groups was statistically significant ($P<0.0001$).

Progression-free survival. PFS was only determined in patients undergoing first-line treatment. The median PFS was not reached in the overall population, as shown in Table III, nor in any of the subgroups analyzed. PFS according to IPI and R-IPI category is shown in Fig. 1; PFS rates are shown in Table III. Among patients classified as IPI 'low risk', 75% were progression-free 10 years after treatment; 10-year PFS

Table IV. Outcomes according to age and prognosis.

Outcome	Survival rate (%)					Median survival (months)
	1-year	2-year	3-year	5-year	10-year	
Progression-free survival						
Age, <60 years	88	85	84	83	79	NR
Age. ≥60 years	84	80	79	78	70	NR
Age, <60 years, IPI 0 or 1	93	90	89	87	77	NR
Age, <60, IPI ≥2	83	79	79	79	79	NR
Overall survival						
Age, <60 years	93	85	81	81	76	NR
Age, ≥60 years	82	70	64	56	41	80.1
Age, <60 years, IPI 0 or 1	98	95	91	91	87	NR
Age, <60, IPI ≥2	87	76	71	71	67	NR

IPI, International Prognostic Index; NR, not reached.

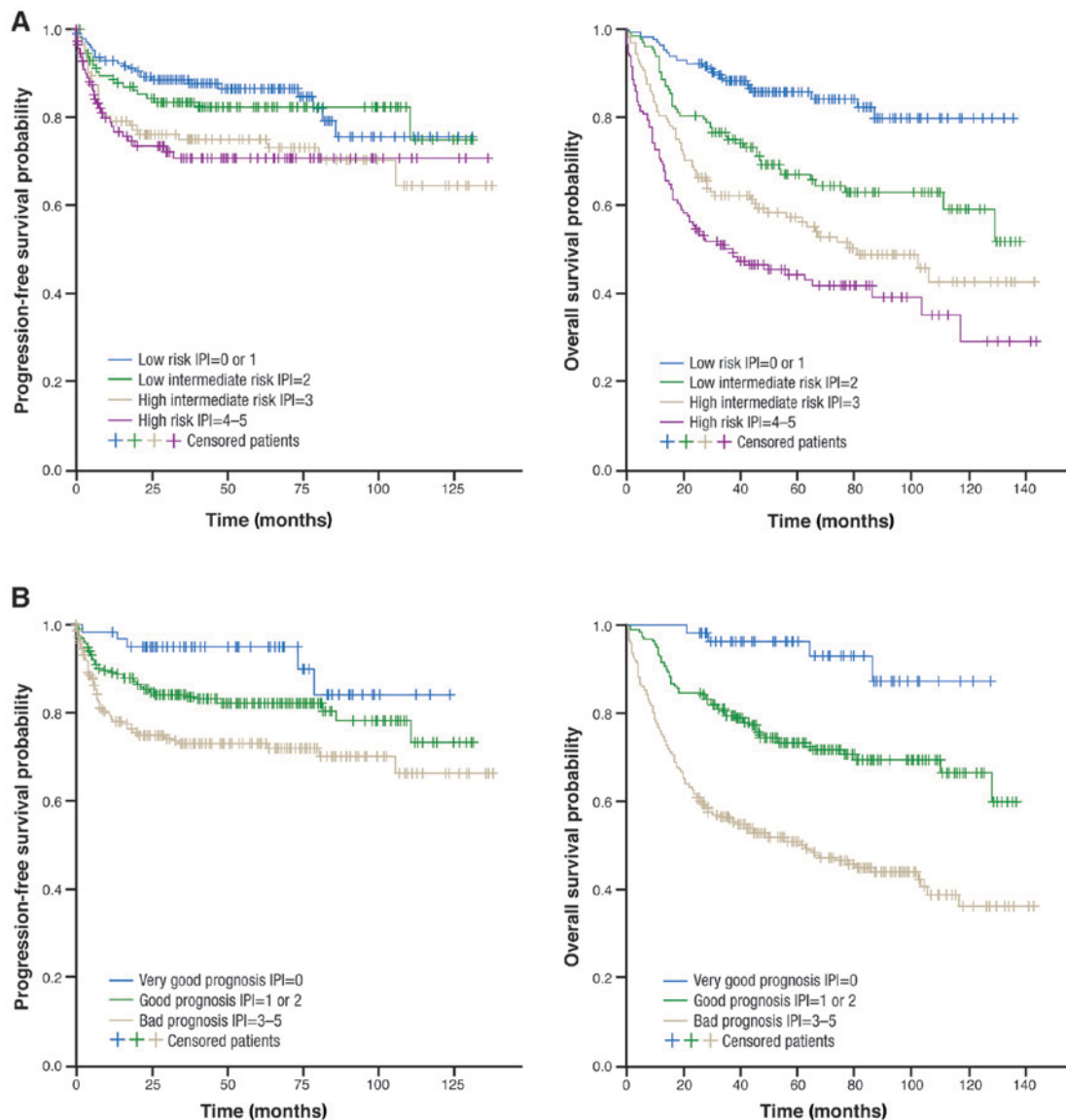


Figure 1. Progression-free and overall survival according to (A) IPI and (B) R-IPI categories. IPI, International Prognostic Index; R-IPI, revised International Prognostic Index.

Table V. Overall survival rates according to IPI and R-IPI categories.

Patient category	Overall survival					Median overall survival (months)
	1-year	2-year	3-year	5-year	10-year	
All patients	85	74	69	63	51	123.7
IPI risk group						
Low	97	92	88	86	80	NR
Low-intermediate	90	81	75	67	60	NR
High-intermediate	81	68	63	58	43	80.6
High	71	56	50	45	30	35.9
R-IPI prognostic group						
Very good	100	98	96	96	87	NR
Good	93	85	79	73	67	NR
Poor	76	62	56	51	37	62.3

IPI risk groups: Low risk, IPI=0 or 1; low-intermediate risk, IPI=2; high-intermediate risk, IPI=3; high risk, IPI=4 or 5. R-IPI prognostic groups: Very good prognosis, R-IPI=0; good prognosis, R-IPI=1 or 2; poor prognosis, R-IPI=3-5. IPI, International Prognostic Index; NR, not reached; R-IPI, revised International Prognostic Index.

rates in the 'low-intermediate', 'high-intermediate', and 'high-risk' groups were 75, 64, and 71%, respectively. Among those classified as having an R-IPI 'very good' prognosis, 84% were progression-free at 10 years after treatment; 10-year PFS rates in the good and poor prognosis groups were 73 and 66%, respectively. The PFS difference between groups was statistically significant for the IPI (log-rank $P=0.01$) and R-IPI groups ($P=0.001$).

When analyzed according to age alone, no statistically significant difference was seen in PFS rates between older and younger patients. Survival outcomes were also evaluated in younger patients (aged <60 years) with good vs. poor prognosis (IPI 0 or 1 and IPI ≥ 2 , respectively) (Table IV and Fig. 2). PFS rates were similar in both groups of patients.

Overall survival. OS was determined in all patients undergoing treatment. The median OS was 124 months in the overall population. OS according to IPI and R-IPI category is shown in Fig. 1; OS rates are shown in Table V. Among patients classified as having an IPI 'low risk', 80% were alive at 10 years; the 10-year OS rates in the 'low-intermediate', 'high-intermediate', and 'high-risk' groups were 60, 43, and 30%, respectively. Ten-year OS for the R-IPI 'very good prognosis' group was 87%; 10-year rates in the good and poor prognosis groups were 67 and 37%, respectively. Between-group differences were statistically significant for OS for the IPI (log-rank test $P<0.0001$) and R-IPI groups (log-rank test $P<0.0001$).

Median OS was not reached in younger patients and was 81 months in older patients. The difference in OS rates between the younger and older groups was statistically significant ($P<0.0001$). Regarding OS in younger patients (aged <60 years), outcomes were statistically significantly better in those with a good vs. poor prognosis (IPI 0 or 1 vs. IPI ≥ 2 , respectively) ($P=0.001$; Table IV and Fig. 2).

Discussion

Long-term follow-up data for patients with DLBCL are scarce, particularly among patients treated in the real-world setting. We have described the use of rituximab-based regimens in over 600 patients of varying ages and disease stages over a prolonged follow-up period. To the best of our knowledge, no other studies have assessed outcomes in patients with DLBCL in the real-world setting.

In our patient population, an overall 10-year PFS rate of 72% was observed, ranging from 64% in patients classed according to IPI as 'high-intermediate' risk (IPI 3) to 75% in patients with low risk (IPI 0 or 1) and from 66% in patients with R-IPI poor prognosis (R-IPI 3-5) to 84% in those with very good prognosis (R-IPI 0). Median PFS was not reached in any of the IPI risk categories. PFS rates were numerically but not statistically significantly higher in patients aged <60 years compared with those aged ≥ 60 years, with 79% of younger patients and 70% of older patients free from progression after 10 years. Coiffier *et al* reported a 10-year PFS rate of 37% in their group of patients aged 60-80 years in the LNH-98.5 trial (13) lower than the 10-year rates seen in our older patients. The median PFS was 4.8 years in the LNH-98.5 trial; median PFS has not yet been reached in our group of patients after a median follow-up of 45 months. However, differences between the two patient populations and study designs call for caution when comparing the results of the two studies.

With regard to OS, we observed a 10-year OS rate of 51% in the overall population and 41% in older patients, the latter being comparable with the 43.5% reported for patients aged ≥ 60 years in the LNH-98.5 study (13). Purroy *et al* reported a 10-year OS rate of 64% in their group of patients with DLBCL, with little difference between older and younger patients (64% for those aged <60 years and 63% for those aged ≥ 60 years) in contrast to the present study (14). They also reported a

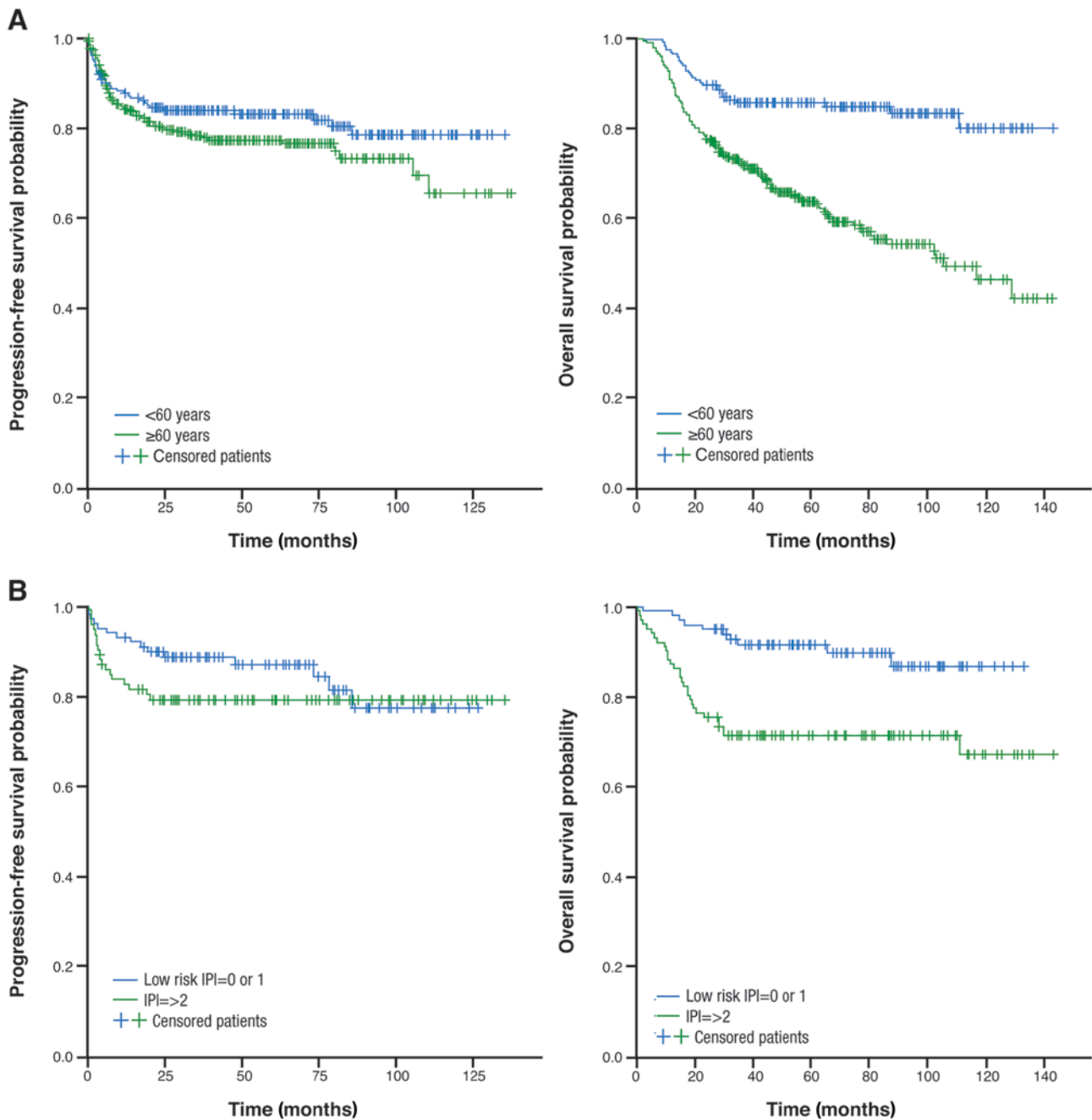


Figure 2. Progression-free and overall survival according to age and prognosis: (A) Patients aged <60 years and ≥60 years; (B) Patients aged <60 years and IPI 0 or 1 and <60 years and IPI ≥2. IPI, International Prognostic Index.

10-year OS rate of 59% in patients with high-risk disease (IPI score ≥3), somewhat higher than the rates we observed in our patients. Once again, however, cross-study comparisons are complicated by many factors, including differences in the treatment settings and patient populations.

We observed a statistically significant difference in OS between younger patients with good vs. poor prognosis, with 10-year OS rates of 87 and 67%, respectively. This was in line with our observations at the 5-year timepoint (10). Younger, high-risk patients clearly represent a population for whom better treatment options are needed. Intensive regimens such as R-CHOEP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone) and megaCHOEP (high-dose cyclophosphamide, doxorubicin, vincristine,

etoposide, and prednisolone) (15,16) and R-ACVBP (rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisolone) (17) are frequently used (18) but have not been shown to be superior to R-CHOP in this patient population (19). Consequently, European treatment guidelines currently recommend recruitment into clinical trials for young 'high-risk' and 'high-intermediate' risk patients (18). In the activated B-cell subtype of DLBCL that is more commonly seen in older patients, the addition of bortezomib, lenalidomide, or ibrutinib to standard therapy has provided encouraging indications of activity in early (20,21). Results from ongoing studies such as ROBUST (NCT02285062) and PHOENIX (NCT01855750) will provide an indication as to whether this is a valid approach for this poor-prognosis group of patients.

A plateau was observed in our PFS curves according to IPI category, with few relapses after 6 years in patients with 'low-intermediate' and 'high-risk' disease. This mirrors observations in the LNH-98.5 study (13). In contrast, an analysis of the SWOG S8736 and S0014 studies, which only included patients with limited-stage disease, revealed a pattern of late relapse in those patients (22). Patients with limited-stage disease comprised 40% of our patient population; in our group of 'low-risk' patients, some evidence of late disease progression was evident at 5-7 years post therapy, highlighting the need for continued observation of these patients.

Five-year OS rates ranged from 86% in IPI 'low-risk' patients to 45% in IPI 'high-risk' patients. Our OS rates were higher than the 5-year OS rates reported for patients in a large validation study by Olszewski *et al* those authors reported 5-year OS of 74, 58, 49, and 33% for 'low-risk', 'low-intermediate', 'high-intermediate' and 'high-risk' patients, compared with 86, 67, 58, and 45%, respectively, in the present study (23). Five-year OS rates in our study were higher in all three R-IPI categories compared with the validation study ('very good' prognosis: 96% vs. 87%; 'good' prognosis: 73% vs. 64%; 'poor' prognosis: 51% vs. 41%, respectively), differences that may have been due to the characteristics of the two patient populations.

Some limitations of the present study should be considered in addition to those inherent in retrospective observational studies. PET was not used for disease staging until 2016; consequently, some patients may have been understaged at diagnosis. Since the introduction of diagnostic PET, we have observed discrete paraspinal lymphomatous masses in some patients that might have been overlooked with computed tomography. This has the potential to affect our survival data.

Although many studies have examined the efficacy of R-CHOP and similar regimens in patients with DLBCL, real-world data are scarce for these patients. We have shown that many patients treated with R-CHOP and R-CHOP-like regimens in the real-world setting can have excellent outcomes; however, accurate disease staging is essential to confidently assign prognostic scores and assess likely outcomes for patients.

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