The Geriatric Prognostic Index: a clinical prediction model for survival of older diffuse large B-cell lymphoma patients treated with standard immunochemotherapy

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Abstract

The International prognostic Index (IPI) is the most widely used clinical prediction model for diffuse large B-cell lymphoma (DLBCL) patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), but may be suboptimal in older patients. We aimed to develop and externally validate a clinical prediction model for older, R-CHOP-treated DLBCL patients by examining geriatric assessment and lymphoma-related parameters in real-world cohorts. A population-based training set of 365 R-CHOP-treated DLBCL patients ≥70 years was identified through the Cancer Registry of Norway. The external test set consisted of a population-based cohort of 193 patients. Data on candidate predictors were retrieved from the Cancer Registry and through review of clinical records. Cox regression models for 2-year overall survival were used for model selection. Activities of daily living, the Charlson Comorbidity Index, age, sex, albumin, stage, Eastern Cooperative Oncology Group performance status and lactate dehydrogenase level were identified as independent predictors and combined into a Geriatric Prognostic Index (GPI). The GPI demonstrated good discrimination (optimism-corrected C-index 0.752), and identified low-, intermediate- and high-risk groups with significantly different survivals (2-year overall survival, 94%, 65%, and 25%, respectively). At external validation, the continuous and grouped GPI demonstrated good discrimination (C-index 0.727 and 0.710, respectively) and the GPI groups had significantly different survivals (2-year overall survival 95%, 65%, and 44%, respectively). Both the continuous and grouped GPI showed better discrimination than the IPI, revised-IPI and National Comprehensive Cancer Network (NCCN)-IPI (C-index 0.621, 0.583, and 0.670, respectively). In conclusion, we have developed and externally validated a GPI for older DLBCL patients treated with R-CHOP that outperformed the IPI, revised-IPI and NCCN-IPI. A web-based calculator is available at *https://wide.shinyapps.io/GPIcalculator/*.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy with almost half the patients being 70 years or older at diagnosis.[1] R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) has remained standard treatment for over two decades, curing about 60% of patients. Although survival improved for all age groups after the introduction of rituximab, relative- and disease-specific survival is still markedly poorer for older

patients.[2-4] This is mainly due to comorbidity and age-related organ changes compromising delivery of standard, curative treatment and increasing the risk of adverse events. However, there is a large heterogeneity in fitness among older patients and the evidence base for guiding treatment decisions is limited as clinical trials often exclude older patients or select only the fittest older patients.[5,6] Based on phase II trials, an attenuated R-miniCHOP regimen has been suggested as standard treatment for patients over 80 years to balance efficacy and risk of treatment toxicity.[7,8] Treatment stratification based on age alone is inaccurate and to optimize treatment outcome for older DLBCL patients it is crucial to improve the selection of patients for R-CHOP or R-miniCHOP. This is especially relevant in older patients who have few curative options at progression or relapse. More precise prognostic tools are also crucial for improving the design of clinical trials in older DLBCL patients.

The International Prognostic Index (IPI), its revised version (R-IPI) and the National Comprehensive Cancer Network (NCCN)-IPI are the most widely used clinical prediction models for DLBCL patients treated with R-CHOP.[9-11] However, the IPI was developed and refined in cohorts including all age groups, not focusing on domains of special importance in older patients, and agnostic to the increasing age-related heterogeneity above the age of 60 years. Accumulating evidence shows that prognostic factors change with older age, with non-lymphoma-related factors gaining increased importance.[12]

A geriatric assessment (GA) is a systematic and multidimensional evaluation of older patients which has emerged as an important tool to assess older patients' fitness for cancer treatment and to predict survival and toxicity.[13-18] A full GA is resource-demanding and we and others have shown that a simplified GA can readily and precisely predict survival in older DLBCL patients.[19-21]

Here, we aimed to develop and externally validate a clinical prediction model especially suited for older (≥ 70 years) DLBCL patients who are considered candidates for curative treatment. For this purpose, we used a population-based, R-CHOP-treated cohort to examine candidate predictors of special importance in older patients, including GA variables, in addition to established lymphoma predictors and routine tumor markers. We aimed to create a predictive model with easy accessible parameters that can be applied in a routine oncology practice, and to compare the model with the IPI, R-IPI and NCCN-IPI.

Methods

Study design and patients

We used the Cancer Registry of Norway to identify a population-based training set of DLBCL patients aged ≥70 years and treated with R-CHOP during 2006-2016 in the administrative region of South-Eastern Norway. The patients included in the training set were treated at seven independent hospitals. For the external test set, DLBCL patients aged ≥70 years treated with R-CHOP during 2003-2016 at two independent hospitals in South-Eastern and two in Western Norway were included (Figure 1). The study was approved by the Norwegian Regional Health Research Ethics Committee (REK 2017/1861) and Data Protection Officers at all participating hospitals.

Candidate predictors and outcome

Data on candidate predictors were retrieved from data prospectively reported to the Cancer Registry of Norway and through review of clinical records. Parameters of the GA were registered retrospectively by review of clinical records and included a modified Katz Activities of Daily Living (ADL) scale,[22] Charlson Comorbidity Index (CCI)[23], Geriatric Nutritional Risk Index (GNRI)[24], albumin, body mass index and polypharmacy (≥ 5 regular medications). These parameters were chosen as they could be scored from data routinely collected in clinical practice, they cover key domains of a GA and have been validated in cancer patients.[14,25] ADL was scored as "dependent" if the patient had impairments in any of the six categories (bathing, dressing, toileting, transferring, continence, and eating), lived in an institution or received help from home nursing.

Additional candidate predictors examined for association with survival were age, sex, disease stage, Eastern Cooperative Oncology Group performance status (ECOG PS), extranodal sites, B-symptoms, bulky disease (>7 cm), heart disease, heart failure, hypertension, coronary artery disease, lactate dehydrogenase (LDH) level, hemoglobin concentration, lymphocytes, monocytes, neutrophils, lymphocyte/monocyte ratio (LMR), monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), alanine aminotransferase, as well as cell-of-origin (COO),[26] Ki67, BCL2 expression and CD5 expression (all determined by immunohistochemistry).

Two-year overall survival (OS) was chosen as the primary endpoint to limit dilution of non-lymphoma-related deaths, while 5-year OS and 2-year progression-free survival (PFS) were secondary endpoints.

Statistical methods and model development

For the training set, OS was calculated from the date of diagnosis to death from any cause or censored at the end of follow-up on 30 June, 2020. PFS was calculated from the date of diagnosis to progression, relapse or death from any cause or censored after 2 years of follow-up. OS and PFS were estimated using the Kaplan-Meier method and the log-rank test was used to compare curves. The

median follow-up for OS was estimated with the reverse Kaplan-Meier method.[27]

In the training set, missing values were imputed with multivariate imputation by chained equations to preserve representativeness and statistical power.[28,29] Continuous values were primarily analyzed as continuous, as recommended in guidelines,[30] but were (log) transformed if deemed necessary to avoid an overly large impact of outliers. For categorical variables, subgroups were collapsed based on clinical reasoning and to create sufficiently large groups. Univariate and multivariable Cox proportional hazard models for 2-year OS were used for model development.

Model performance was assessed with discrimination and calibration. Discrimination was quantified using the Harrell C-index and calibration was assessed with a calibration slope and calibration plots.[31,32] In the training set, model performance was corrected for optimism with 200 bootstrap resamples.[30]

All statistical analyses were performed using R version 4.1.3. Further details are provided in the *Online Supplementary Material*.

Results

Characteristics of the patients in the training set

A total of 365 patients were included in the training set (Figure 1). Their median age was 76 years (range, 70-91), 56% had stage III/IV disease and 33% an ECOG PS ≥2 (Table 1). Ten percent were ADL dependent, 30% had a CCI ≥2, 32% regularly used ≥5 medications and 29% had moderate to severe nutritional risk according to the GNRI. The majority

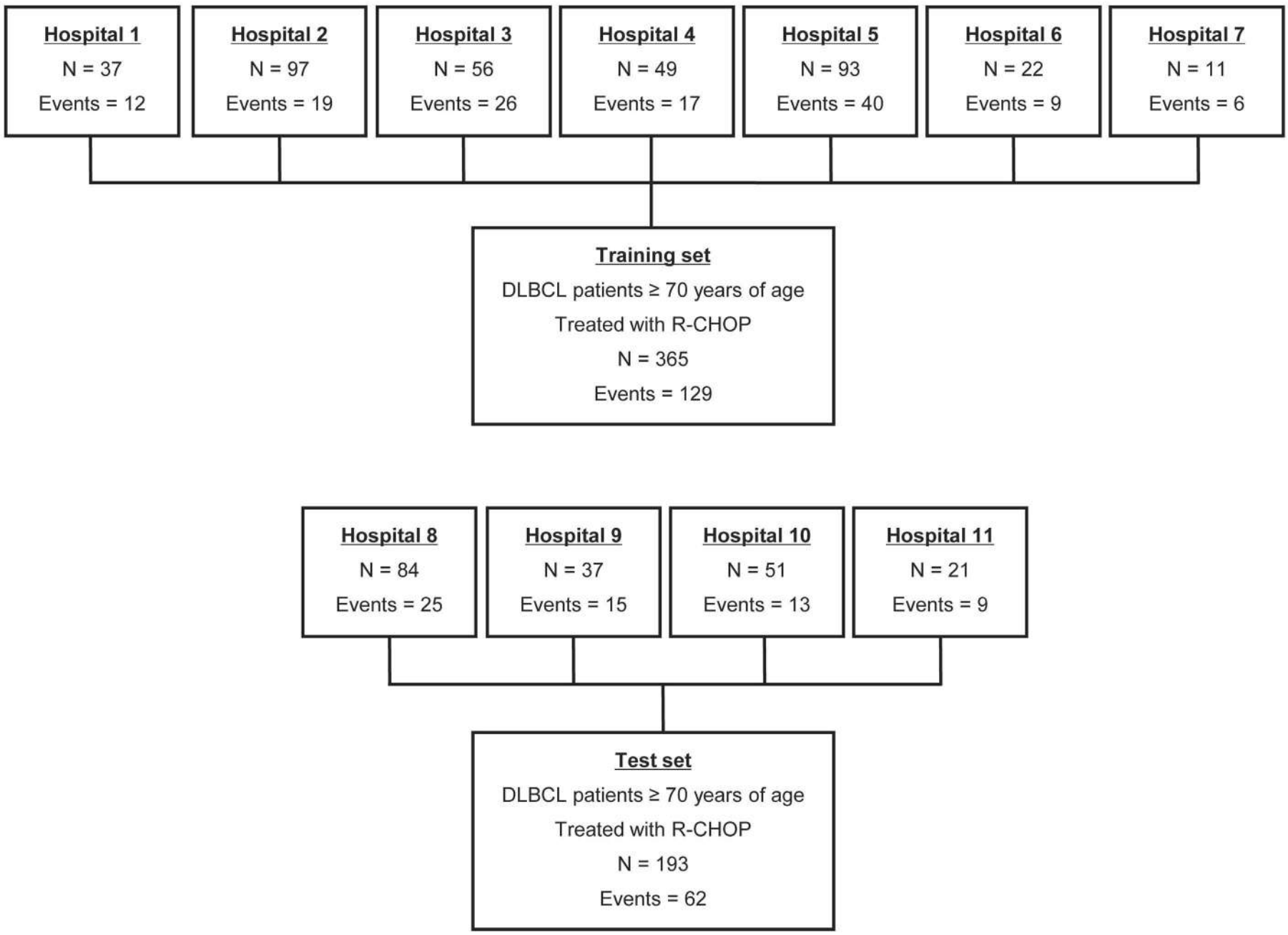

Figure 1. Flow chart of patients included in the training and test sets. All hospitals are from the administrative regions of South-Eastern (hospitals 1-9) or Western (hospitals 10-11) Norway and include hospitals at both the local and university hospital levels. Patients from hospitals 1-9 were identified through the Cancer Registry of Norway and include all patients diagnosed with diffuse large B-cell lymphoma in the period 2006-2016 who were ≥70 years of age at diagnosis and had received rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone as first-line treatment. Patients from hospitals 10 and 11 were diagnosed in the period 2003-2008 and identified locally. Number of events is the number of deaths at 2 years of follow-up (2-year overall survival). DLBCL: diffuse large B-cell lymphoma; R-CHOP: received rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Table 1. Characteristics of the patients in the training and test sets.

Characteristics	Training set (N=365)	Test set (N=193)	*P*
Age, years			
Median (range)	76 (70-91)	77 (70-95)	0.154
70-79 years, N (%)	273 (75)	134 (69)	
80-84 years, N (%)	77 (21)	47 (24)	
≥85 years, N (%)	15 (4)	12 (6)	
Sex, male, N (%)	187 (51)	102 (53)	0.716
ADL, dependent, N (%)	38 (10)	24 (13)	0.431
Missing, N	0	3	
CCI ≥2, N (%)	111 (30)	45 (24)	0.088
Missing, N	0	2	
GNRI			0.192
Absent, N (%)	159 (44)	71 (41)	
Low, N (%)	96 (27)	39 (22)	
Moderate/severe, N (%)	105 (29)	64 (37)	
Missing, N	5	19	
Albumin, g/L			
Median (range)	38 (17-49)	37 (18-49)	0.426
Albumin <36 g/L, N (%)	130 (36)	81 (43)	0.101
Missing, N	5	6	
Stage III/IV, N (%)	204 (56)	101 (52)	0.422
ECOG PS ≥2, N (%)	118 (33)	68 (37)	0.354
Missing, N	3	7	
LDH, units			
Median (range)	257 (71-10,105)	260 (104-4,355)	0.438
Not elevated, N (%)	179 (50)	91 (49)	0.876
Elevated 1-3 x ULN, N (%)	151 (42)	81 (44)	
Elevated >3 x ULN, N (%)	31 (9)	14 (8)	
Missing, N	4	7	
Extranodal sites >1, N (%)	85 (23)	27 (14)	0.010
Missing, N	0	1	
IPI			0.016
Low (1), N (%)	93 (26)	44 (24)	
Low-intermediate (2), N (%)	73 (20)	57 (31)	
High-intermediate (3), N (%)	100 (28)	34 (19)	
High (4-5), N (%)	93 (26)	47 (26)	
Missing, N	6	11	
R-IPI			0.042
Good (1-2), N (%)	166 (46)	101 (56)	
Poor (3-5), N (%)	193 (54)	81 (45)	
Missing, N	6	11	
NCCN-IPI			0.934
Low-intermediate (2-3), N (%)	103 (29)	53 (29)	
High-intermediate (4-5), N (%)	166 (46)	86 (47)	
High (6-8), N (%)	90 (25)	43 (24)	
Missing, N	6	11	
Frailty group*			0.647
Fit, N (%)	166 (46)	78 (45)	
Unfit, N (%)	148 (41)	67 (39)	
Frail, N (%)	46 (13)	27 (16)	
Missing, N	0	2	
Treatment intensity**			0.925
R-CHOP >80%, N (%)	235 (64)	119 (64)	
R-CHOP ≤80%, N (%)	130 (36)	67 (36)	
Missing	0	7	
2-year OS, % (95% CI)	65 (60-70)	68 (62-75)	

(64%) received full-dose R-CHOP (initial dosage >80%), while the remainder received attenuated R-CHOP (initial dosage ≤80%). For patients receiving attenuated R-CHOP, the median initial dose was 75% (interquartile range [IQR], 50-75%). The median follow-up time was 104 months (IQR, 72-136) and 2-year OS was 65% (95% confidence interval [95% CI]: 60-70%). At the 2-year follow-up 129 patients had died; the causes of death included lymphoma (53%), treatment-related toxicity (32%), other non-lymphoma-related causes (12%) and unknown cause (3%).

Model development

Candidate predictors that showed a significant association with 2-year OS (cutoff $P<0.10$) in the training set were age, sex, ADL, CCI, GNRI, albumin, ECOG PS, disease stage, specific extranodal sites (bone marrow, liver, lung), bulky tumor, B-symptoms, LDH, hemoglobin, lymphocytes, monocytes, neutrophils, LMR, MLR, NLR, eGFR and CRP (Table 2; *Online Supplementary Table S1*, *Online Supplementary Figure S1*). Extranodal sites >1 were not *per se* predictive of reduced survival; however bone marrow, liver and lung infiltration did have a negative impact on survival both independently and when merged into one common parameter. Albumin and GNRI were the predictors with the lowest *P* values in univariate analyses, followed by ECOG PS, LDH, inflammatory markers (CRP, NLR, LMR and MLR), ADL and CCI. Of note, none of the biological immunhistochemical markers from the pathology reports, including COO, was significantly associated with 2-year OS.

Significant candidate predictors from univariate analyses were included in Cox multivariable models for 2-year OS. Further variable selection was performed using stepwise backward elimination with the Akaike information criterion as the stopping criterion and age forced to stay in the model due to its biological relevance. With this strategy a model with the following nine variables was identified: age (continuous), sex, ADL dependent, CCI ≥2, GNRI (absent, low, moderate/severe), stage III-IV, ECOG PS ≥2, LDH (log) and NLR (log) (*Online Supplementary Table S2*). The same model was also identified when using forward selection or a combination of forward and backward selection. Likewise, when applying backward elimination to 200 bootstrap resamples of the training set, the nine variables were included in the final model in over 60% of the bootstrap resamples.

The nine-variable model was then critically examined for

*Frailty status assessed with our previously published frailty calculator: Isaksen *et al.*, Blood Advances 2021, *https://wide.shinyapps.io/app-frailty/*. **Treatment intensity defined by the initial dosage of R-CHOP. Further details are provided in the *Online Supplementary Material*. ADL: activities of daily living; CCI: Charlson Comorbidity Index; GNRI: Geriatric Nutritional Risk Index; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; IPI: International Prognostic Index; R-IPI: revised IPI; NCCN-IPI: National Comprehensive Cancer Network IPI; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; OS: overall survival; 95% CI: 95% confidence interval.

clinical robustness and potential simplification while retaining predictive power. NLR was associated with some uncertainties because of significant differences in lymphocyte counts between hospitals and a risk of neutrophil counts being affected by steroid treatment initiated prior to the registered blood sample analysis. Including NLR in the model would also make it less suitable to apply after pre-phase treatment with steroids commonly given to older patients. We therefore examined a model without NLR, which showed only a marginal loss in discrimination (C-index 0.764 *vs*. 0.765), thus NLR was removed from the final model. When running stepwise selection again without the NLR, the same eight variables were identified with no other candidate predictor chosen as a replacement for NLR.

As albumin and GNRI (as a continuous score) showed a

Table 2. Univariate Cox regression analyses for the association between candidate predictors and 2-year overall survival in the training set.

Candidate predictors	HR (95% CI)	*P*
Age, years, continuous	1.04 (1.00-1.08)	0.06
ADL dependent	3.06 (1.98-4.75)	5.5e-07
CCI ≥2	2.41 (1.70-3.41)	6.5e-07
Polypharmacy*	1.33 (0.93-1.91)	0.12
Body mass index, continuous	0.98 (0.94-1.02)	0.31
GNRI		
Low *vs*. absent	1.98 (1.20-3.27)	0.008
Moderate/severe *vs*. absent	5.05 (3.25-7.84)	5.3e-13
Albumin <36 g/L	3.93 (2.74-5.63)	9.3e-14
ECOG PS ≥2	3.28 (2.31-4.66)	3.2e-11
Stage III/IV	2.40 (1.63-3.54)	9.9e-06
Extranodal sites >1	1.34 (0.91-1.97)	0.137
Bone marrow, liver or lung infiltration**	1.89 (1.28-2.80)	0.00135
Male	1.44 (1.01-2.05)	0.0412
Bulky disease (≥7 cm)	1.64 (1.16-2.33)	0.00543
B-symptoms	2.17 (1.53-3.08)	1.3e-05
Heart failure	1.52 (0.86-2.69)	0.154
Hypertension	1.26 (0.89-1.78)	0.194
Coronary artery disease	1.13 (0.76-1.69)	0.548
Heart disease***	1.14 (0.80-1.63)	0.473
Non-GCB cell-of-origin (IHC)	1.00 (0.65-1.53)	0.995
Ki67 (IHC), continuous	1.00 (0.99-1.01)	0.626
BCL2 positive (cutoff 1%) (IHC)	1.13 (0.63-2.02)	0.678
CD5 positive (IHC)	1.54 (0.80-2.96)	0.197
Lactate dehydrogenase		
Elevated 1-3 x ULN *vs.* not elevated	1.86 (1.25-2.76)	0.00208
Elevated >3 x ULN *vs*. not elevated	5.11 (3.06-8.52)	4.04e-10
Hemoglobin, g/dL, continuous	0.83 (0.77-0.91)	2.4e-05
LMR, continuous (log transformed)	0.51 (0.40-0.66)	2.2e-07
MLR, continuous	2.00 (1.56-2.56)	3.2e-08
NLR, continuous (log transformed)	1.71 (1.43-2.04)	3.2e-09
eGFR, mL/min/1.73 m^2, continuous	0.99 (0.98-1.00)	0.0036
CRP, mg/L, continuous (log transformed)	1.45 (1.28-1.64)	2.3e-09
ALAT, U/L, continuous (log transformed)	1.08 (0.82-1.43)	0.581

*Polypharmacy: ≥ 5 regular medications *vs.* <5 regular medications. **See *Online Supplementary Figure S1* for details on Cox univariate analyses for specific extranodal sites. ***Includes heart failure, coronary artery disease, cardiac arrhythmia, operated valve disease or an implanted pacemaker. Further details are provided in the *Online Supplementary Material* and *Online Supplementary Table S1*. HR: hazard ratio; 95% CI: 95% confidence interval; ADL: activities of daily living; CCI: Charlson Comorbidity Index; GNRI: Geriatric Nutritional Risk Index; ECOG PS: Eastern Cooperative Oncology Group performance status; GCB: germinal center B-cell like; IHC: immunohistochemistry; ULN: upper limit of normal; LMR: lymphocyte/monocyte ratio; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; eGFR, estimated glomerular filtration rate; CRP: C-reactive protein; ALAT: alanine aminotransferase.

high degree of correlation (Spearman correlation >0.90), a simpler model with albumin (as a continuous or categorical variable [<36 g/L or <38 g/L]) was compared to the model with GNRI. LDH as a continuous variable was also compared to LDH as a categorical variable with two cutoffs as defined in the NCCN-IPI (elevated 1-3 x upper reference level of normal [ULN] and elevated >3 x ULN). Age as a continuous variable was compared to age as a categorical variable with a cutoff at 80 years. A simplified model with age as a continuous variable, albumin as a categorical variable (<36 g/L) and LDH with two cutoffs showed the best discrimination (optimism-corrected C-index 0.752) and acceptable calibration (optimism-corrected calibration slope 0.89) (*Online Supplementary Figure S2*), and was selected as the final model (Table 3A). Further details are provided in the *Online Supplementary Material*.

Development of a Geriatric Prognostic Index and risk groups

A Geriatric Prognostic Index (GPI) was then constructed from the weighted sum of regression coefficients for the eight variables in the final model (the linear predictor) (Table 3A). Age was counted as years over 70 to create a score starting at zero. As we planned for an online calculator for the GPI, regression coefficients with five decimals were used to preserve prognostic information. Accordingly, the GPI was calculated as follows:

GPI = (years >70 years x 0.04103) + 0.48169 (if ADL dependent) + 0.74504 (if CCI ≥2) + 0.90446 (if albumin <36 g/L) + 0.45541 (if ECOG PS ≥2) + 0.52298 (if stage III-IV) + 0.33396 (if male) + 0.12446 (if LDH 1-3 x ULN) + 0.65823 (if LDH >3 x ULN)

This resulted in a GPI ranging from 0 to 3.9893 (median, 1.5156) in 355 patients in the training set with available data for the selected variables.

For division into three risk groups, objective cutoffs at the 30th and 80th percentiles (cutoff GPI 0.98003 and 2.39963) were chosen. With these cutoffs, low-, intermediate- and high-risk groups with significantly different 2-year OS (94%, 65%, and 25%, respectively; P<0.001) were identified, and the model with the three GPI groups demonstrated good discrimination with a C-index of 0.726 (Figure 2; Table 3B). The GPI groups also showed significantly different 5-year OS (84% [95% CI: 77-91%], 49% [95% CI: 42-57%] and 18% [95% CI: 11-30%]) and 2-year PFS (92% [95% CI: 87-97%], 60% [95% CI: 53-68%] and 23% [95% CI: 15-35%]) (*Online Supplementary Figure S3*). Survival was similar when analyses were limited to patients receiving full-dose R-CHOP (2-year OS 95%, 69%, and 30%; P<0.001), and slightly poorer for patients receiving attenuated R-CHOP (2-year OS 88%, 58%, and 18%; P<0.001) (*Online Supplementary Figure S4*; *Online Supplementary Table S3*). The GPI groups were also predictive for survival when restricted to patients over and under 80 years of age (*Online Supplementary Figure S5*). The predictive value of the GPI groups also exceeded that of our previously developed frailty classification[19] (C-index frailty grouping: 0.697).

Table 3. (A) Multivariable Cox regression model for 2-year overall survival in the training set and (B) the Geriatric Prognostic Index risk groups in the training set (N=355, number of events =122)

A				
Predictor	**β**	**SE**	**HR (95% CI)**	***P***
Age >70 years	0.04103	0.02080	1.04 (1.00-1.09)	0.0486
ADL dependent	0.48169	0.25612	1.62 (0.98-2.67)	0.0600
CCI ≥2	0.74504	0.18873	2.11 (1.46-3.05)	<0.001
Albumin <36 g/L	0.90446	0.21018	2.47 (1.64-3.73)	<0.001
ECOG PS ≥2	0.45541	0.21912	1.58 (1.03-2.42)	0.0377
Stage III/IV	0.52298	0.21781	1.69 (1.10-2.59)	0.0163
Male	0.33396	0.19184	1.40 (0.96-2.03)	0.0817
Lactate dehydrogenase				
1-3 x ULN	0.12446	0.22784	1.13 (0.72-1.77)	0.5849
>3 x ULN	0.65823	0.32334	1.93 (1.02-3.64)	0.0418
B				
GPI risk group	**N (%)**	**2-year OS (95% CI)**	**HR (95% CI)**	***P***
Low risk	108 (30)	94 % (89-98)	1	
Intermediate risk	176 (50)	65 % (58-72)	6.46 (2.96-14.1)	<0.001
High risk	71 (20)	25 % (17-38)	20.3 (9.22-44.9)	<0.001
High risk *vs.* intermediate risk			3.15 (2.17-4.56)	<0.001

(A) Performance of the multivariable Cox model in the training set: optimism-corrected C-index after applying the final Cox model to 200 bootstrap resamples of the training set: 0.752. (B) C-index of the model with three Geriatric Prognostic Index risk groups: 0.726. Survival estimated from Kaplan-Meier curves. β: regression coefficient; SE: standard error; HR: hazard ratio; 95% CI: 95% confidence interval; ADL: activities of daily living; CCI: Charlson Comorbidity Index; ECOG PS: Eastern Cooperative Oncology Group performance status; ULN: upper limit of normal; GPI: Geriatric Prognostic Index; OS: overall survival.

External validation of the Geriatric Prognostic Index and comparison with the International Prognostic Index and its modifications

A total of 193 patients were included in the test set (Figure 1). Their median age was similar to that of the training set (77 years; range, 70-95) (Table 1). The test set had a lower frequency of patients with >1 extranodal sites, fewer patients with IPI 3 and more with IPI 2. There was also a trend towards fewer patients with CCI ≥2 and more patients with albumin <36 g/L in the test set, otherwise the distribution of baseline characteristics was similar in the training and test sets. The proportion of patients receiving full-dose R-CHOP (64%) and the median dose for attenuated R-CHOP (75% of full-dose; IQR, 53-75) was the same as in the training set. The median follow-up time was 127 months (IQR, 83-163) and 2-year OS was similar to that in the training set (68% *vs.* 65%).

In the test set, the median GPI was 1.43900 (range, 0.04103 to 4.47104) in 174 patients with complete data for the eight included variables. Applying the fixed cutoffs for the GPI groups from the training set, 33% (n=57), 41% (n=71) and 26% (n=46) of patients were assigned to the low-, intermediate- and high-risk group, respectively. Both the continuous GPI and GPI groups showed good discrimination for 2-year OS with a C-index of 0.727 and 0.710, respectively, and the GPI groups showed significantly different 2-year OS (95%, 65%, and 44%; *P*<0.001) (Figure 3A; Table 4). The GPI groups were also predictive for 5-year OS (75% [95% CI: 65-87%], 49% [95% CI: 38-62%] and 32% [95% CI: 21-49%]) and 2-year PFS (91% [95% CI: 84-99%], 59% [95% CI: 49-72%] and 41% [95% CI: 29-58%]).

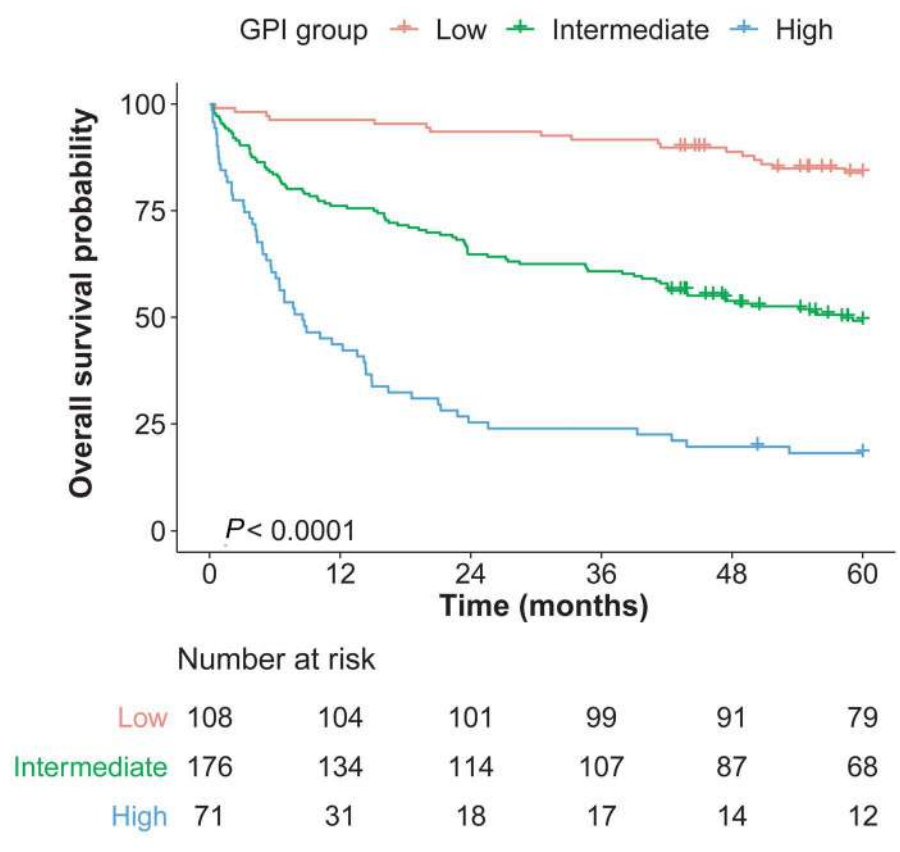

Figure 2. Overall survival of patients in the different Geriatric Prognostic Index groups in the training set. GPI: Geriatric Prognostic Index.

A calibration slope of 0.73 for the GPI indicates some overestimation of risk for the high-risk patients in the test set. When comparing observed and predicted survival for the GPI groups, mean predictions for the low- and intermediate-risk groups were in line with estimated survival, while the high-risk group had a slightly better survival than predicted (*Online Supplementary Figure S6*).

The GPI and GPI groups outperformed IPI, R-IPI and NCCN-IPI in terms of model discrimination in both the training set (C-index: IPI 0.665, R-IPI 0.628, and NCCN-IPI 0.671) and test set (C-index: IPI 0.621, R-IPI 0.583, and NCCN-IPI 0.670) (Figure 3; Table 4), and reallocated a substantial proportion of patients into different risk groups (Figure 4). In particular, the GPI identified a large low-risk group with a very favorable prognosis (GPI low-risk group: 33% of patients, 95% 2-year OS *vs.* IPI low-risk group: 24% of patients, 85% 2-year OS) (Table 4). The predictive value of the GPI also exceeded that of our previously developed frailty score[19] (C-index 0.64).

Characteristics of the Geriatric Prognostic Index risk groups

The characteristics of the patients in the GPI risk groups were similar in the training and test sets (*Online Supplementary Tables S4* and *S5*). In the test set, the majority of patients in the low-risk group had stage I/II disease (n=43, 75%), were 70-79 years old (n=43, 75%) and fit (n=48, 91%) according to our previously published frailty calculator.[19] The majority had also received full-dose R-CHOP (n=50, 88%) (*Online Supplementary Table S4*). Patients in the GPI low-risk group were reallocated from all four IPI groups (Figure 4).

In the intermediate-risk group the majority of patients had stage III/IV disease (n= 38, 54%), were 70-79 years old (n=51, 72%), were either fit (n=29, 45%) or unfit (n=28, 44%), and had received full-dose R-CHOP (n=47, 68%) (*Online Supplementary Table S4*). Also here, patients were reallocated from all four IPI groups.

In the high-risk group, 61% of patients (n=28) were 70-79 years old, 87% (n=40) had stage III/IV disease, all patients were either unfit (n=29, 64%) or frail (n=16, 36%), and 64% had received attenuated R-CHOP (n=27) (*Online Supplementary Table S4*). The majority of patients were IPI high-risk, but patients from the remaining IPI groups were also reallocated to the GPI high-risk group. When comparing the high-risk group in the training and test sets, the high-risk group in the test set had a lower proportion of patients who were classified as frail (36% *vs.* 48%), and a lower median GPI score (2.74 *vs.* 2.94) (*Online Supplementary Tables S4* and *S5*).

Discussion

We have developed, and externally validated, the GPI based on large, population-based Norwegian cohorts. This index is especially suited for predicting survival of older

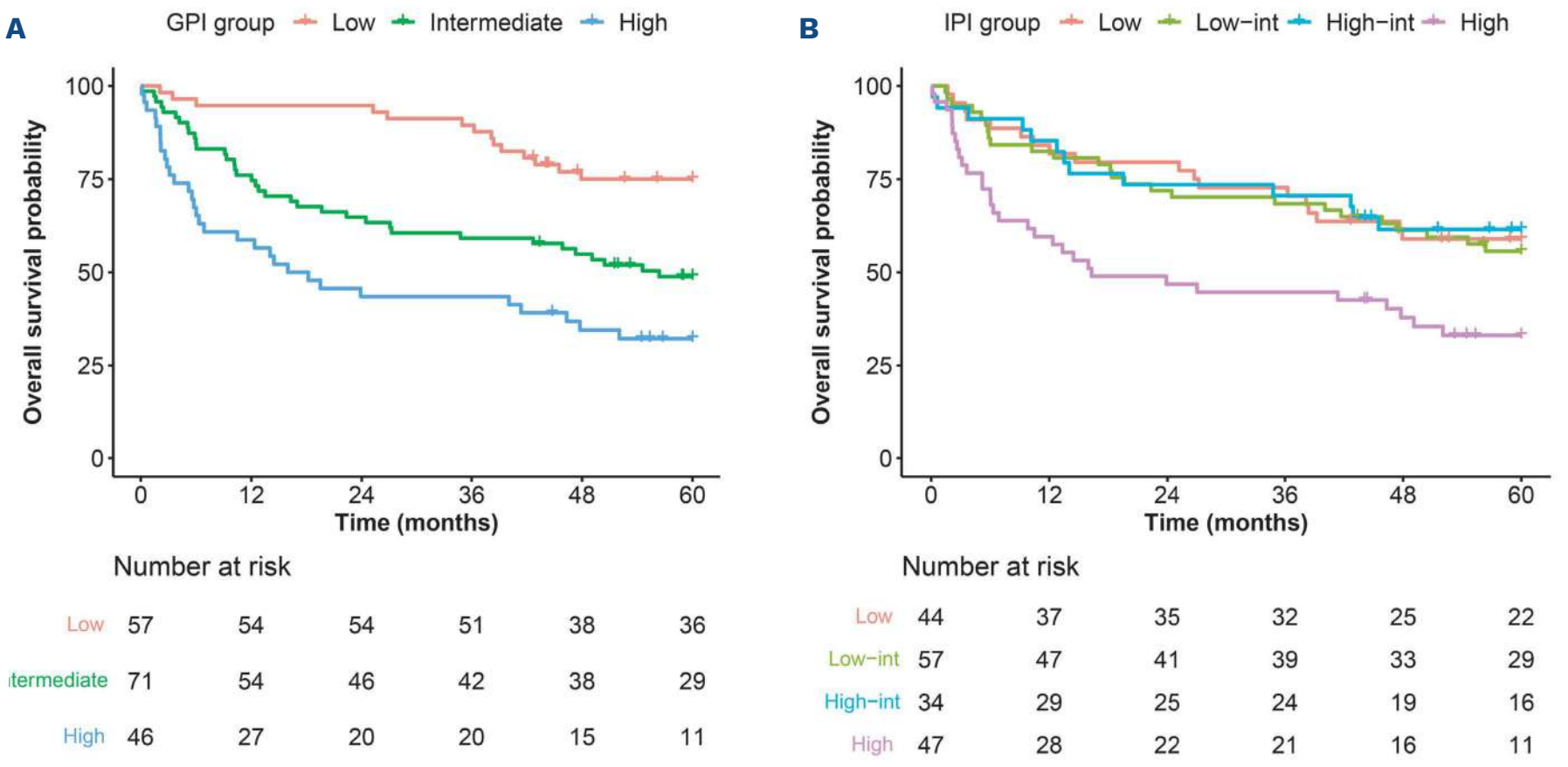

Figure 3. External validation. Overall survival of patients in the (A) Geriatric Prognostic Index groups, (B) International Prognostic Index (IPI) groups, (C) revised IPI groups and (D) National Comprehensive Cancer Network IPI groups in the test set. GPI: Geriatric Prognostic Index; IPI: International Prognostic Index; R-IPI: revised IPI; NCCN-IPI: National Comprehensive Cancer Network IPI.

(≥70 years) DLBCL patients who are candidates for curative intent treatment with R-CHOP. The GPI combines known prognostic factors in DLBCL with impairments in GA parameters to integrate a patient's fitness into the prognostication. The GPI showed good discrimination and outperformed the IPI, R-IPI and NCCN-IPI in both the training and test sets.

The GPI identified three risk groups with significantly different survival in the test set, in contrast to the IPI, R-IPI and NCCN-IPI that only identified two groups with significantly different survival. Importantly, the GPI was superior in identifying a substantial proportion of older patients (~1/3) with a very favorable prognosis following R-CHOP treatment. Patients in the GPI low-risk group were reallocated from all IPI groups, including the high-intermediate and high-risk groups. The GPI is more complex than the IPI, but our results underline the importance of a broader assessment of older lymphoma patients. The ADL and CCI

Table 4. External validation. Performance of the Geriatric Prognostic Index in the test set and comparison with the International Prognostic Index and its modifications.

Prognostic model	N (%)	2-year OS, % (95% CI)	HR (95% CI)	*P*	C-index
GPI, continuous index	174			<0.001	0.727
GPI risk groups	174				0.710
Low risk	57 (33)	95 (89-100)	1		
Intermediate risk	71 (41)	65 (55-77)	7.77 (2.34-25.7)	<0.001	
High risk	46 (26)	44 (31-60)	15.3 (4.62-50.5)	<0.001	
High risk *vs.* intermediate risk			1.97 (1.14-3.41)	0.016	
IPI	182				0.621
Low (1)	44 (24)	80 (69-92)	1		
Low-intermediate (2)	57 (31)	72 (61-85)	1.40 (0.62-3.16)	0.423	
High-intermediate (3)	34 (19)	74 (60-90)	1.31 (0.52-3.30)	0.568	
High (4-5)	47 (26)	47 (35-64)	3.32 (1.55-7.13)	0.002	
R-IPI	182				0.583
Good (1-2)	101 (56)	75 (67-84)	1		
Poor (3-5)	81 (44)	58 (48-70)	1.93 (1.15-3.24)	0.013	
NCCN-IPI	182				0.670
Low-intermediate (2-3)	53 (29)	85 (76-95)	1		
High-intermediate (4-5)	86 (47)	71 (62-81)	2.03 (0.92-4.51)	0.081	
High (6-8)	43 (24)	40 (27-57)	5.88 (2.66-13.0)	<0.001	

Survival estimated from Kaplan-Meier curves and hazard ratios estimated from Cox regression in the test set. OS: overall survival; 95% CI: 95% confidence interval; HR: hazard ratio; GPI: Geriatric Prognostic Index; IPI: International Prognostic Index; R-IPI: revised IPI; NCCN-IPI: National Comprehensive Cancer Network IPI.

are relatively simple parameters that are easily assessed in routine oncology practice, and with the use of an online calculator, the GPI is quickly available.

The GPI low- and intermediate-risk groups had similar survival in the training and test sets, but the high-risk group had better survival in the test set than in the training set. This is likely due to differences in selection of patients for R-CHOP and treatment management at different hospitals. As the high-risk group includes the majority of frail patients, the composition of this group may differ between hospitals. The heterogeneity of the high-risk group, together with this group being the smallest risk group (n=46 in the test set), makes the survival estimates for the high-risk group subject to variation within the group. This is reflected in the wider confidence interval for 2-year OS for the high-risk group (Table 4).

An Elderly Prognostic Index (EPI) that combines a simplified GA with IPI and hemoglobin has been proposed by the Italian Lymphoma Foundation.[21] The EPI was developed for patients treated with both palliative and curative regimens and not restricted to R-CHOP. The GPI is also slightly easier and faster to perform than the EPI. The EPI includes the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), which is more comprehensive than the CCI, and also includes instrumental activities of daily living (IADL) in addition to ADL. Their prospective study design is a strength, but also increases the risk of selection bias in this older patient population. A direct comparison between the GPI and EPI was not possible in our study as we did not have data on CIRS-G and IADL. An Elderly IPI (E-IPI) for patients over 60 years has also been suggested.[33] However, the only modification from the standard IPI is an age cutoff at 70 years, and no GA parameters were included.

Four of the prognostic factors from the IPI were included in our GPI (age, stage, ECOG PS and LDH), while extranodal sites were not. Bone marrow, liver and/or lung infiltration were associated with adverse survival in univariate analyses, but lost significance when combined with the other IPI variables in multivariable analysis. Decreased prognostic value of extranodal sites in older DLBCL patients has also been demonstrated by others.[7,34] Age was forcibly maintained in the model due to its biological relevance, but was not highly significant. This may partly be due to selection bias whereby only the fitter among the oldest patients receive R-CHOP. On the other hand, chronological age may also be of less importance among older patients in whom fitness evaluation may better reflect a patient's biological age. Age was not dichotomized in the GPI as a continuous variable is more likely to reflect the biological effect of increased age. However, a commonly used cutoff at 80 years was also tested in the final model, but resulted in poorer model performance.

GNRI and albumin showed a high degree of correlation and gave similar results when included in the final model. Albumin was thus chosen for a simpler model. Several studies

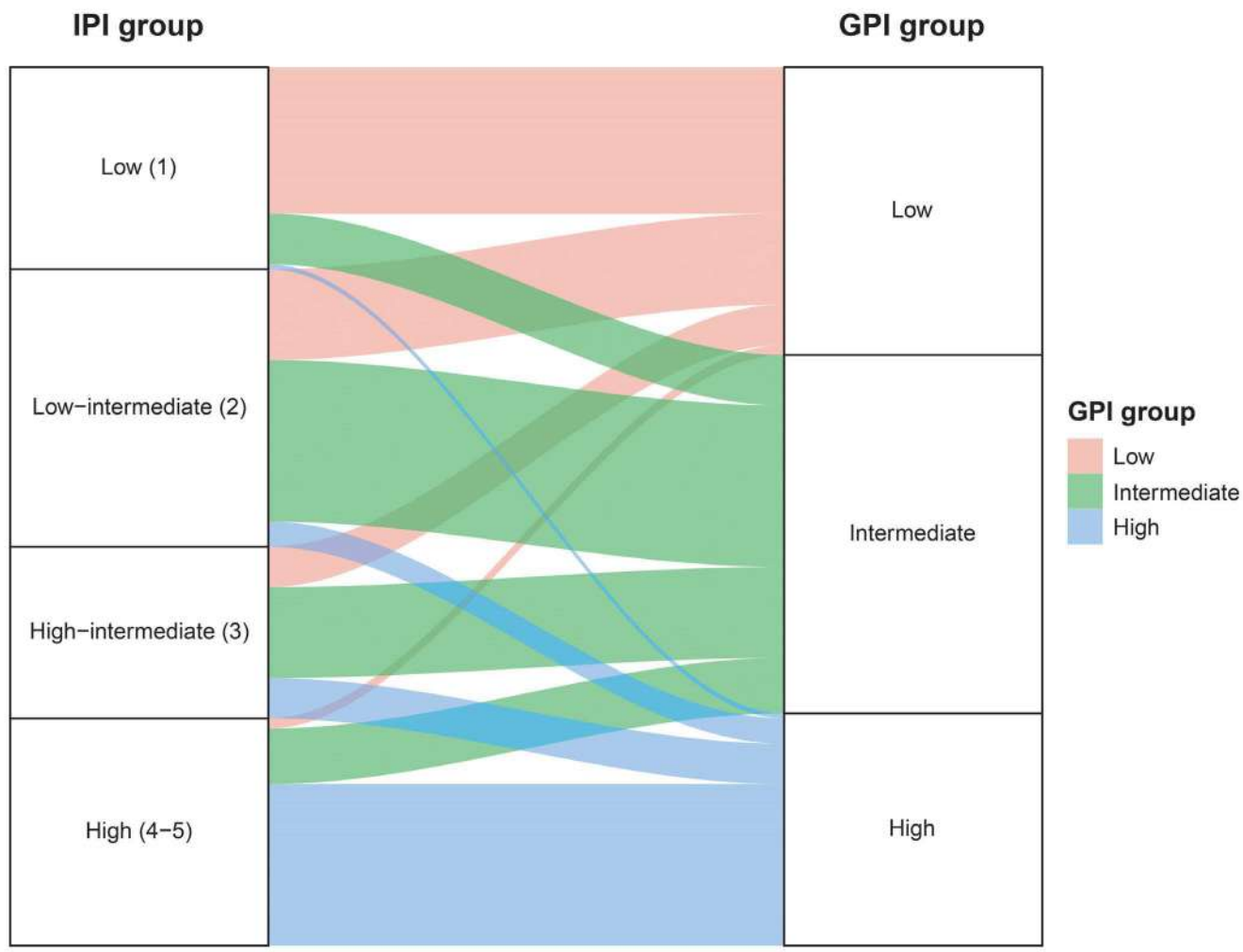

Figure 4. Alluvial plot showing the flow of patients from International Prognostic Index groups to Geriatric Prognostic Index groups in the test set (N=174). IPI: International Prognostic Index; GPI: Geriatric Prognostic Index.

have identified albumin as a strong prognostic marker for survival in older DLBCL patients.[7,34,35] Decreased albumin could be part of a general dysregulation of protein synthesis and metabolism linked to frailty.[36] Albumin is also likely linked to other aspects, including poor nutritional status, inflammation and lymphoma aggressiveness.[37]

CCI was highly significant in the model. The prognostic value of comorbidity in older DLBCL patients has been demonstrated in several studies.[15,34] However, some prospective studies on older patients have not shown this association.[8,38] This is likely caused by selection bias for fit patients, and highlights the importance of a representative cohort when identifying prognostic factors in an older age group. ADL dependence was, as expected, not as high in this older patient population selected for receiving R-CHOP treatment, compared to an unselected older population.[19] Nevertheless, ADL showed prognostic value independent of ECOG PS, a finding that has also been demonstrated by others.[15,20,21,38] Poorer prognosis for male sex has also been shown in several studies.[34,39-41]

Chronic, low-grade, systemic inflammation has been linked to frailty, and several serum markers linked to inflammation have been suggested as potential biomarkers for frailty.[36] Inflammatory markers were also highly significant in univariate analyses in our data. However, after removal of NLR, no other inflammatory marker contributed significantly to the model. This may partly be due to a strong correlation with albumin and other variables in the model linked to inflammation, frailty and tumor aggressiveness.

None of the examined tumor-related parameters from the routine pathology report was significant, including COO. Other studies have also demonstrated the lack of prognostic value of COO in older DLBCL patients.[8,34] Our results indicate that factors linked to frailty override known tumor biological variations in older DLBCL patients treated with R-CHOP. However, the lack of prognostic significance of COO in our cohort may also be due to the fact that COO was determined by immunohistochemistry, not by gene expression.[38]

Inclusion of other biological markers, such as double-hit or double-expression of MYC and BCL2, might improve the model. However, genetic complexity is associated with increasing age and biological markers may have less prognostic value among older patients.[42] An aggressive tumor biology could also partly be reflected in clinical parameters. Inclusion of newly identified molecular subtypes[43,44] could add prognostic information, but may be of less prognostic relevance in older patients and makes the model less feasible to apply in routine clinical practice.

Limitations of our study include the retrospective study design with a restricted number of GA parameters. However, prospective studies and meta-studies have identified the GA domains included in the GPI (functional status, comorbidity and nutrition) as key domains in a GA for capturing

frailty and predicting survival in older hematology patients.[14,15] The retrospective study design also increases the risk of registration bias. In particular, the retrospective collection of ADL could be subjected to underreporting. Biological features such as double-hit status could also not be tested in the model because of the high number of missing observations. The selection of patients for R-CHOP treatment and the dosage of R-CHOP administered may also vary between doctors and hospitals, which could affect the accuracy of the GPI. Furthermore, the 2-year OS predicted by the GPI may have improved in the current era with increasing approval of novel therapies in later-line settings. In a constantly moving treatment landscape, prognostic scores such as the GPI need to be continuously validated or revised, and survival predictions may need to be re-calibrated. Strengths include the population-based study design with quality-checked and few missing data, enabling identification of a representative, "real-world" older DLBCL population. This is difficult to achieve in a prospective setting, as many older patients are treated at smaller, local hospitals not involved in prospective trials. Limiting the analysis to patients treated with R-CHOP allowed testing of known disease- and treatment-related predictors. This, in combination with predictors of special importance in older patients, including GA variables, makes the study well suited for modeling a robust prognostic index in older DLBCL patients treated with R-CHOP. The GPI was also externally validated and its performance compared to that of IPI, R-IPI and NCCN-IPI.

Before the start of treatment, we and others suggest assessing frailty status by using an objective GA to help evaluate patients' fitness for R-CHOP treatment.[16-19,21] Alternatives for frailty assessment include our previously proposed frailty score that is easily accessible together with the GPI in an online calculator.[19] Of note, frailty status should be re-evaluated after pre-phase treatment to allow for improvement in frailty status for patients with reduced fitness mainly caused by their lymphoma. A comprehensive GA also includes non-oncological interventions for identified impairments to optimize patients' fitness prior to oncological treatment.[45]

For possible R-CHOP candidates, according to our data the GPI provides a more accurate estimation of prognosis following R-CHOP than the IPI, R-IPI and NCCN-IPI. The prognostic information from the GPI also exceeded that of a simplified frailty assessment alone, and can thus together with frailty status provide a more solid ground for dose adaptions in individual patients. It can also form a basis for shared decision-making conversations with patients and their families. Importantly, the GPI could provide a platform for risk-adapted treatment approaches in clinical trials in older DLBCL patients. The very favorable outcome for the low-risk patients reinforces R-CHOP as the gold standard for this group. For the intermediate- and high-risk patients, chemotherapy-free agents that have shown potential in DLBCL, including bi-specific antibodies, immunomodulatory agents, targeted agents and chimeric antigen receptor T-cell-based therapy could be considered in a clinical trial setting, either alone or in combination with R-CHOP.[46-50]

In conclusion, we have developed and externally validated the GPI suited for older (≥70 years) DLBCL patients who are considered candidates for curative treatment with R-CHOP. The GPI combines GA variables with well-established prognostic factors in DLBCL. The model outperformed the IPI, R-IPI and NCCN-IPI and could be a tool for informed treatment decisions and for stratifying older DLBCL patients for clinical trials. The GPI consists of easy accessible parameters that can be obtained in routine oncology practice, and can be calculated with an online calculator available at *https://wide.shinyapps.io/GPIcalculator/*. Although the GPI has been externally validated, validation in a prospective setting is warranted.

Disclosures

No conflicts of interest to disclose.

Contributions

MB, HH, EBS and KTI designed the research study. KTI, HH, MAM, MR, LSR, DB, FR, MS, ØF, RG and PM participated in collection of clinical data. KTI, MB, HH, EBS, OCL and KL analyzed and interpreted the data. KTI generated all the tables and figures and drafted the manuscript. All authors critically reviewed and approved the final manuscript.

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Data-sharing statement

The original data included in this study cannot be shared publicly due to Norwegian regulations, but can be shared upon reasonable request to the corresponding author if this divulgation is accepted by the Norwegian Regional Committees for Medical and Health Research Ethics and Data Protection Officers at participating hospitals.

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