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

Kathrine T. Isaksen,[1,2] Renate Galleberg,[3] Maria Adele Mastroianni,[4] Marit Rinde,[5] Leiv Sindre Rusten,[6] Dlawer Barzenje,[7] Frode Ramslien,[8] Øystein Fluge,[3,9] Marit Slaaen,[10,11] Peter Meyer,[12] Knut Liestøl,[13,14] Erlend B. Smeland,[1,2] Ole Christian Lingjærde,[13,15] Harald Holte[2,16] and Marianne Brodtkorb[1,16]

[1]Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital, Oslo; [2]KG Jebsen Center for B Cell Malignancies, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo; [3]Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen; [4]Department of Hematology, Akershus University Hospital, Lørenskog; [5]Department of Hematology, Vestfold Hospital Trust, Tønsberg; [6]Department of Surgery, Section of Oncology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen; [7]Department of Oncology, Østfold Hospital Trust, Kalnes; [8]Department of Hematology, Telemark Hospital Trust, Skien; [9]Department of Clinical Science, University of Bergen, Bergen; [10]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo; [11]The Research Center for Age Related Functional Decline and Diseases, Innlandet Hospital Trust, Ottestad; [12]Stavanger University Hospital–Rogaland, Stavanger; [13]Department of Informatics, University of Oslo, Oslo; [14]Institute for Cancer Genetics and Informatics, Oslo University Hospital, Oslo; [15]Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, Oslo and [16]Department of Oncology, Oslo University Hospital, Oslo, Norway

Correspondence: M. Brodtkorb
meide@ous-hf.no

Received: December 13, 2022.
Accepted: February 23, 2023.
Ealy view: March 2, 2023.

https://doi.org/10.3324/haematol.2022.282289

©2023 Ferrata Storti Foundation
Published under a CC BY-NC license

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

Supplemental Methods

Study design and patients

The Cancer Registry of Norway (CRN) has an estimated 98.8% completeness on diagnosis and receives data on patients' vital status from the Norwegian Population Registry, and prospectively reported clinical and treatment features from treating physicians.[1] In the current study, patients with primary central nervous system lymphoma or prior lymphoproliferative disease were excluded, while a concurrent diagnosis of indolent lymphoma was allowed.

The division into training- and test set was based on geography/hospitals and independent investigators collecting the data. This was done to create a robust, external validation design that allowed for non-random variation between the training- and test set.[2]

In this study, an exception from informed consent was granted by the Norwegian Regional Health Research Ethics Committee (REK 2017/1861) based on the high age of the patients and the potential benefit for future patients.

Definition of full-dose and attenuated R-CHOP

The cutoff for attenuated R-CHOP was set at an initial "intended" dosage of 80% or lower, in line with cutoffs used in previous studies on older DLBCL patients.[3-7] Doxorubicin was used to define R-CHOP dosage as it is considered a key component of the regimen and dose reduction of cyclophosphamide is seldom done without a concurrent reduction in doxorubicin. The initial dosage was used to define treatment intensity, rather than the mean dose per course or accumulated dose as dose reductions during therapy may have many causes like toxicity and disease progression, especially in older patients.

In the training set, four patients had received R-COP and etoposide (R-CEOP) in the first treatment cycle. Here, treatment intensity was defined by the initial dosage of etoposide and cyclophosphamide.

Candidate predictors

Data on candidate predictors were retrieved from the CRN and through review of clinical records of all patients to quality-check data, collect missing data and obtain information not routinely reported to the CRN.

Geriatric Nutritional Risk Index (GNRI) is an adaption to elderly of the Nutritional Risk Index and consists of albumin and estimated weight loss calculated from current and ideal weight, and has been validated in older DLBCL patients.[8,9] Heart disease included heart failure, coronary artery disease, cardiac arrhythmia, operated valve disease or an implanted pacemaker. Heart failure was defined as a diagnosis of heart failure or clinical or radiological signs of heart failure (ejection fraction <50% measured with echocardiography or multigated acquisition (MUGA) scan) documented in clinical records at the time of diagnosis. Coronary artery disease included prior myocardial infarction, percutaneous coronary intervention, bypass surgery and angina pectoris.

Candidate predictors that were collected as part of the study, but were not included in model development due to a high fraction of missing values were "double hit" status detected by fluorescence in situ hybridization (FISH) for MYC, BCL2 and BCL6, double-protein expression of MYC and BCL2, and EBV positivity. The reason for the high fraction of missing values for double-hit status was that FISH for MYC, BCL2 and BCL6 was not routinely performed for patients in the time period for the training cohort (2006-2016), especially not for older patients who would not be candidates for further treatment intensification.

Outcome variables

In the training set, time of death was retrieved from the CRN, while data on progression, relapse and causes of death were retrieved from clinical records. Date of diagnosis was registered as the day the diagnosis was confirmed by the pathologist. Date of progression or relapse was retrieved from clinical records by the investigators and registered as the date when there was a biopsy-confirmed relapse or progression, radiological findings or a strong clinical suspicion of progression or relapse, whichever came first.

Cause of death was registered retrospectively by the investigators and divided into the following categories: lymphoma, treatment-related toxicity, other non-lymphoma related cause and unknown cause. Death from treatment-related toxicity included deaths occurring during or shortly after treatment where the death was considered likely to have been caused by acute treatment toxicity, or later deaths that were likely a result of long term toxicity.

Statistical methods and model development

Patient characteristics were compared using the χ2 test or Fisher's exact test when indicated for categorical variables, and Mann-Whitney U test for continuous variables when comparing two groups and Kruskal-Wallis test when comparing three groups.

In the training set, the few missing values were assumed to be missing at random (MAR) and imputed using multivariate imputation by chained equations (MICE) creating 21 imputed datasets.[10] To prevent bias in the results, the outcome was not included in the imputation model. For simplicity, the 21 multiply imputed datasets were combined into one dataset during the model-selection process by using the mean of the imputed continuous variables and the most frequent imputed category for categorical variables for each patient with missing values. For the external test set, no imputations of missing values were performed.

For the multivariable Cox models, model selection with stepwise backward elimination was performed using the stepAIC function in the MASS package in R. Candidate predictors showing a high degree of correlation (Spearman correlation >0.90) were examined in separate models (lymphocyte/monocyte ratio (log) and monocyte/lymphocyte ratio). For the final model, dichotomization of continuous variables (age, albumin and LDH) were examined. For age, a cutoff at 80 years decreased model performance and the continuous definition was kept. For albumin, two categorical cutoffs were examined: a cutoff at the median (38 g/L) and a cutoff at 36 g/L as this cutoff had been used in other studies on the same patient population.[11-14] LDH was examined as a continuous predictor and categorized as in NCCN-IPI.

For the final Cox model, the model without imputed data was used for estimation of regression coefficients and calculation of the Geriatric prognostic index (GPI), as there were only a few missing observations (n=10) for the variables included in the final model.

The proportional-hazards assumption for the final model was checked using Schoenfeld residuals and showed violation for stage (p=0.009), while the global test for the model showed no significant violation of the proportional-hazards assumption (p=0.11).[15]

Division into risk groups

When creating 3 risk groups from the Geriatric prognostic index (GPI), three different divisions were examined: cutoffs at the 33th and 66th percentile, at the 25th and 75th percentile and at the 30th and 80th percentile. Further exploration of cutoffs, including an optimal cutoff, was not examined to avoid overfitting of the model to our data. The cutoffs at the 30th and 80th percentile were chosen as unequal group sizes enabled identification of a high-risk group with a more extreme prognoses and a relatively large low-risk group with a very favorable prognosis.

Model performance

Model performance was assessed with discrimination and calibration. Discrimination measures the models' ability to distinguish between patients who experience the outcome or not, and was quantified using Harrell's C-index. Calibration measures the agreement between observed and predicted survival, and was assessed with calibration slope and calibration plots.

Internal validation

Internal validation was performed by applying the final model to 200 bootstrap resamples of the training set with the validate function in the rms package in R. The bootstrap resampling technique simulates the process of repeatedly sampling from an underlying patient population to assess the likely model overfit and correct for the resulting optimism in model performance.[2] For simplicity, optimism was estimated for the final model, not including all modelling steps, and thus the optimism-corrected performance might still include some optimism.

In the training set, this resulted in an optimism-corrected C-index of 0.752, and an optimism-corrected calibration slope of 0.89. A calibration slope <1 indicated some anticipated optimism in the model. When assessing calibration in a calibration plot comparing predicted and observed 2-year overall survival (OS), the model showed fairly good concordance between observed and predicted survival (Figure S2).

Supplemental References

1. Larsen IK, Smastuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-1231.
2. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162(1):W1-73.
3. Eyre TA, Salisbury R, Eyre DW, Watson C, Collins GP, Hatton CS. Results of a large retrospective analysis of the effect of intended dose intensity of R-CHOP on outcome in a cohort of consecutive, unselected elderly patients with de novo diffuse large B cell lymphoma. Br J Haematol. 2016;173(3):487-491.
4. Eyre TA, Martinez-Calle N, Hildyard C, et al. Impact of intended and relative dose intensity of R-CHOP in a large, consecutive cohort of elderly diffuse large B-cell lymphoma patients treated with curative intent: no difference in cumulative incidence of relapse comparing patients by age. J Intern Med. 2019;285(6):681-692.
5. Juul MB, Jensen PH, Engberg H, et al. Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: A Danish population-based cohort study. Eur J Cancer. 2018;99(86-96.
6. Chihara D, Westin JR, Oki Y, et al. Management strategies and outcomes for very elderly patients with diffuse large B-cell lymphoma. Cancer. 2016;122(20):3145-3151.
7. Carson KR, Riedell P, Lynch R, et al. Comparative effectiveness of anthracycline-containing chemotherapy in United States veterans age 80 and older with diffuse large B-cell lymphoma. J Geriatr Oncol. 2015;6(3):211-218.
8. Lidoriki I, Schizas D, Frountzas M, et al. GNRI as a prognostic factor for outcomes in cancer patients: A systematic review of the literature. Nutr Cancer. 2021;73(3):391-403.
9. Kanemasa Y, Shimoyama T, Sasaki Y, Hishima T, Omuro Y. Geriatric nutritional risk index as a prognostic factor in patients with diffuse large B cell lymphoma. Ann Hematol. 2018;97(6):999-1007.
10. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-399.
11. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2011;12(5):460-468.
12. Peyrade F, Bologna S, Delwail V, et al. Combination of ofatumumab and reduced-dose CHOP for diffuse large B-cell lymphomas in patients aged 80 years or older: an open-label, multicentre, single-arm, phase 2 trial from the LYSA group. Lancet Haematol. 2017;4(1):e46-e55.
13. Merli F, Luminari S, Tucci A, et al. Simplified Geriatric Assessment in Older Patients With Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. J Clin Oncol. 2021;39(11):1214-1222.
14. Oberic L, Peyrade F, Puyade M, et al. Subcutaneous Rituximab-MiniCHOP Compared With Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older. J Clin Oncol. 2021;39(11):1203-1213.
15. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression-Model. Biometrika. 1982;69(1):239-241.

Supplemental Tables

Table S1. Univariate Cox regression analyses for the association between candidate predictors and 2-year overall survival in the training set.

Candidate predictors	n (%)	HR (95% CI)	*p*
Age, years, continuous	**365**	1.04 (1.00-1.08)	0.06
Age group	**365**		
70-79 years	273 (75%)	1	
≥80 years	92 (25%)	1.41 (0.97-2.04)	0.07
ADL	**365**		
Independent	327 (90%)	1	
Dependent	38 (10%)	3.06 (1.98-4.75)	5.5e-07
CCI	**365**		
0-1	254 (70%)	1	
≥2	111 (30%)	2.41 (1.70-3.41)	6.5e-07
Polypharmacy	**365**		
<5 regular medications	249 (68%)	1	
≥5 regular medications	116 (32%)	1.33 (0.93-1.91)	0.12
BMI, continuous	**361**	0.98 (0.94-1.02)	0.31
GNRI	**360**		
Absent	159 (44%)	1	
Low	96 (27%)	1.98 (1.20-3.27)	0.008
Moderate/severe	105 (29%)	5.05 (3.25-7.84)	5.3e-13
Albumin g/L, continuous	**360**	0.91 (0.89-0.93)	6.5e-14
Albumin	**360**		
≥36 g/L	230 (64%)	1	
<36 g/L	130 (36%)	3.93 (2.74-5.63)	9.3e-14
ECOG PS	**362**		
ECOG 0-1	244 (67%)	1	
ECOG ≥2	118 (33%)	3.28 (2.31-4.66)	3.2e-11
Stage	**365**		
I/II	161 (44%)	1	
III/IV	204 (56%)	2.40 (1.63-3.54)	9.9e-06
Extranodal sites	**365**		
Extranodal sites 0-1	280 (77%)	1	
Extranodal sites >1	85 (23%)	1.34 (0.91-1.97)	0.137
Bone marrow, liver or lung infiltration*	**360**		
No	293 (81%)	1	
Yes	67 (19%)	1.89 (1.28-2.80)	0.00135
Sex	**365**		
Female	178 (49%)	1	
Male	187 (51%)	1.44 (1.01-2.05)	0.0412

Bulky disease (≥7 cm)	**352**		
No	223 (63%)	1	
Yes	129 (37%)	1.64 (1.16-2.33)	0.00543
B-symptoms	**361**		
No	227 (63%)	1	
Yes	134 (37%)	2.17 (1.53-3.08)	1.3e-05
Heart failure	**365**		
No	338 (93%)	1	
Yes	27 (7%)	1.52 (0.86-2.69)	0.154
Hypertension	**365**		
No	178 (49%)	1	
Yes	187 (51%)	1.26 (0.89-1.78)	0.194
Coronary artery disease	**365**		
No	281 (77%)	1	
Yes	84 (23%)	1.13 (0.76-1.69)	0.548
Heart disease**	**365**		
No	238 (65%)	1	
Yes	127 (35%)	1.14 (0.80-1.63)	0.473
Cell-of-origin (IHC)	**273**		
GCB	156 (57%)	1	
Non-GCB	117 (43%)	1.00 (0.65-1.53)	0.995
Ki67 (IHC), continuous	**339**	1.00 (0.99-1.01)	0.626
Ki67 (IHC), median	**339**		
≤80%	119 (35%)	1	
>80%	220 (65%)	0.88 (0.60-1.28)	0.495
BCL2 positive (cutoff 1%) (IHC)	**319**		
No	44 (14%)	1	
Yes	275 (86%)	1.13 (0.63-2.02)	0.678
CD5 positive (IHC)	**304**		
No	280 (92%)	1	
Yes	24 (8%)	1.54 (0.80-2.96)	0.197
LDH, U/L, continuous (log transformed)	**361**	1.89 (1.56-2.29)	5.2e-11
LDH	**361**		
Not elevated	179 (50%)	1	
Elevated	182 (50%)	2.25 (1.55-3.26)	1.9e-05
LDH	**361**		
Not elevated	179 (50%)	1	
Elevated x 1-3 x ULN	151 (42%)	1.86 (1.25-2.76)	0.00208
Elevated >3 x ULN	31 (8%)	5.11 (3.06-8.52)	4.04e-10
Hb, g/dL, continuous	**365**	0.83 (0.77-0.91)	2.4e-05
Lymphocytes, x10^9/L (log transformed)	**359**	0.52 (0.40-0.67)	8.9e-07
Monocytes, x10^9/L, continuous	**356**	1.62 (0.98-2.69)	0.061
Neutrophils, x10^9/L (log transformed)	**360**	1.90 (1.35-2.67)	0.000226

LMR, continuous (log transformed)	**356**	0.51 (0.40-0.66)	2.2e-07
MLR, continuous	**356**	2.00 (1.56-2.56)	3.2e-08
NLR, continuous (log transformed)	**359**	1.71 (1.43-2.04)	3.2e-09
eGFR, mL/min/1,73m^2, continuous	**363**	0.99 (0.98-1.00)	0.0036
CRP, mg/L, continuous (log transformed)	**348**	1.45 (1.28-1.64)	2.3e-09
ALAT, U/L, continuous (log transformed)	**353**	1.08 (0.82-1.43)	0.581

Abbreviations: ADL, Activities of daily living; ALAT, alanine aminotransferase; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; ; eGFR, estimated glomerular filtration rate; GCB, germinal center B-cell like; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; HR, hazard ratio; IHC, immunohistochemistry; LDH, lactate dehydrogenase; LMR, lymphocyte/monocyte ratio; MLR, monocytes/lymphocyte ratio; NLR, neutrophile/lymphocytes ratio; PS, performance status; ULN, upper limit of normal. *Polypharmacy: ≥ 5 regular medications vs <5 regular medications. **See Figure S1 for details on Cox univariate analyses for spesific extranodal sites. ***Includes heart failure, coronary artery disease, cardiac arrhythmia, operated valve disease or an implanted pacemaker. Further details are provided in the supplemental text.

Table S2. Results from model selection in the training set using Cox multivariable models for 2-year overall survival (OS) and stepwise backward elimination with Akaike's information criterion (AIC) as stopping criterion. **(A)** Prognostic model with missing variables imputed with multivariate imputation by chained equations. **(B)** Prognostic model in the training set without imputed data.

A)

Cox multivariable model with imputed data (n=365)				
	β	**SE**	**HR (95% CI)**	***P***
Years >70 years	0.04117	0.02053	1.04 (1.00-1.09)	0.045
ADL dependent	0.71470	0.24282	2.04 (1.27-3.29)	0.003
CCI ≥2	0.70756	0.18842	2.03 (1.40-2.94)	<0.001
GNRI				
Low	0.35118	0.25815	1.42 (0.86-2.36)	0.174
Moderate/Severe	0.92099	0.24916	2.51 (1.54-4.09)	<0.001
ECOG ≥2	0.36940	0.20784	1.45 (0.96-2.17)	0.076
Stage III/IV	0.48950	0.21429	1.63 (1.07-2.48)	0.022
Male	0.44087	0.18916	1.55 (1.07-2.25)	0.020
LDH (log)	0.21997	0.12758	1.25 (0.97-1.60)	0.085
NLR (log)	0.22009	0.10008	1.25 (1.02-1.52)	0.028

B)

Cox multivariable model without imputed data (n=349)				
	β	**SE**	**HR (95% CI)**	***P***
Years >70 years	0.03821	0.02133	1.04 (1.00-1.08)	0.073
ADL dependent	0.69544	0.24798	2.00(1.23-3.26)	0.005
CCI ≥2	0.68431	0.19548	1.98 (1.35-2.91)	<0.001
GNRI				
Low	0.29455	0.26819	1.34 (0.79-2.27)	0.272
Moderate/Severe	0.86783	0.25823	2.38 (1.44-3.95)	<0.001
ECOG ≥2	0.46088	0.21774	1.59 (1.03-2.43)	0.034
Stage III/IV	0.43911	0.22171	1.55 (1.01-2.40)	0.048
Male	0.42021	0.19507	1.52 (1.04-2.23)	0.031
LDH (log)	0.20115	0.13318	1.22 (0.94-1.59)	0.131
NLR (log)	0.24016	0.10307	1.27 (1.04-1.56)	0.020

Abbreviations: ADL, Activities of daily living; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; GNRI, Geriatric Nutritional Risk Index; LDH, lactate dehydrogenase; NLR, neutrophil/lymphocyte ratio. β indicates the regression coefficient; SE, standard error; HR, hazard ratio; CI, confidence interval.

Table S3. Overall survival (OS) and hazard ratio (HR) for the Geriatric prognostic index (GPI) groups in the training set when **(A)** restricted to patients receiving full-dose R-CHOP (initial R-CHOP dosage >80%) (n=231, number of events =59), and **(B)** restricted to patients receiving attenuated R-CHOP (initial R-CHOP dosage ≤80%) (n=124, number of events =63).

A)

GPI risk group	**n (%)**	**2-year OS (95% CI)**	**HR (95% CI)**	***P***
Low-risk	92 (40)	95 % (90-99)	1	
Intermediate risk	112 (48)	69 % (61-78)	6.72 (2.63-17.1)	<0.001
High-risk	27 (12)	30 % (17-53)	21.7 (8.09-58.5)	<0.001
High-risk vs intermediate risk			3.24 (1.85-5.68)	<0.001

B)

GPI risk group	**n (%)**	**2-year OS (95% CI)**	**HR (95% CI)**	***P***
Low-risk	16 (13)	88 % (73-100)	1	
Intermediate risk	64 (52)	58 % (47-71)	3.93 (0.93-16.5)	0.062
High-risk	44 (35)	18 % (10-34)	10.49 (2.51-43.8)	0.001
High-risk vs intermediate risk			2.67 (1.60-4.45)	<0.001

Survival estimated from Kaplan-Meier curves. HR estimated from Cox regression for the three GPI risk groups in the training set. Abbreviations: HR, hazard ratio; CI, confidence interval.

Table S4. Patient characteristics for the Geriatric prognostic index (GPI) groups in the test set.

Characteristics	**Low risk** n=57 (%)	**Intermediate risk** n=71 (%)	**High risk** n=46 (%)	***p***
Age, years, median (IQR)	76 (72-79)	78 (75-80)	78 (74-81)	0.031
Age ≥80 years	14 (25)	20 (28)	18 (39)	0.253
Stage III-IV	14 (25)	38 (54)	40 (87)	<0.001
ECOG ≥2	1 (2)	26 (37)	37 (80)	<0.001
ADL dependent	2 (4)	7 (10)	13 (28)	<0.001
CCI ≥2	0 (0)	14 (20)	22 (48)	<0.001
IPI				<0.001
Low (1)	29 (51)	10 (14)	1 (2)	
Low-intermediate (2)	18 (32)	32 (45)	5 (11)	
High-intermediate (3)	8 (14)	18 (25)	8 (17)	
High (4-5)	2 (4)	11 (16)	32 (70)	
R-IPI				
Good (1-2)	47	42	6	
Poor (3-5)	10 (18)	29 (41)	40 (87)	<0.001
NCCN-IPI				<0.001
Low-intermediate (2-3)	38 (67)	10 (14)	2 (4)	
High-intermediate (4-5)	19 (33)	48 (68)	15 (33)	
High (6-8)	0 (0.0)	13 (18)	29 (63)	
Frailty status*				<0.001
Fit	48 (91)	29 (45)	0 (0.0)	
Unfit	5 (9)	28 (44)	29 (64)	
Frail	0 (0.0)	7 (11)	16 (36)	
Missing	4	7	1	
Treatment intensity**				
R-CHOP >80%	50 (88)	47 (68)	15 (36)	
R-CHOP ≤80%	7 (12)	22 (32)	27 (64)	
Missing	0	2	4	<0.001

Abbreviations: ADL, Activities of daily living; CCI, Charlson comorbidity index; ECOG Eastern Cooperative Oncology Group; IPI, International Prognostic Index; IQR, interquartile range; NCCN, the National Comprehensive Cancer Network; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-IPI, revised IPI. *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 supplemental text.

Table S5. Patient characteristics for the Geriatric prognostic index (GPI) groups in the training set.

Characteristics	Low risk n=108 (%)	Intermediate risk n=176 (%)	High risk n=71 (%)	*p*
Age, years, median (IQR)	75 [72, 78]	77 [74, 80]	77 [73, 81]	<0.001
Age ≥80 years	15 (14)	47 (27)	24 (34)	0.005
Stage III-IV (%)	27 (25)	111 (63)	60 (85)	<0.001
ECOG ≥2	3 (3)	54 (31)	59 (83)	<0.001
ADL dependent	0 (0)	10 (6)	27 (38)	<0.001
CCI ≥2	2 (2)	66 (38)	39 (55)	<0.001
IPI (%)				<0.001
Low (1)	61 (56)	28 (16)	2 (3)	
Low-intermediate (2)	27 (25)	45 (26)	0 (0)	
High-intermediate (3)	18 (17)	62 (35)	19 (27)	
High (4-5)	2 (2)	41 (23)	50 (70)	
R-IPI (%)				<0.001
Good (1-2)	88 (82)	73 (41)	2 (3)	
Poor (3-5)	20 (18)	103 (59)	69 (97)	
NCCN-IPI (%)				<0.001
Low-intermediate (2-3)	71 (66)	29 (16)	1 (1)	
High-intermediate (4-5)	35 (32)	112 (64)	17 (24)	
High (6-8)	2 (2)	35 (20)	53 (75)	
Frailty status (%)*				<0.001
Fit	103 (95)	62 (35)	1 (1)	
Unfit	4 (4)	105 (60)	36 (51)	
Frail	1 (1)	9 (5)	34 (48)	
Treatment intensity**				
R-CHOP >80%	92 (85)	112 (64)	27 (38)	
R-CHOP ≤80%	16 (15)	64 (36)	44 (62)	
COD (at 2 years follow-up)				<0.001
Censored (alive)	101 (94)	114 (65)	18 (25)	
Lymphoma	3 (3)	30 (17)	30 (42)	
Treatment-related toxicity	4 (4)	20 (11)	16 (23)	
Other cause	0 (0)	11 (6)	5 (7)	
Unknown	0 (0)	1 (1)	2 (3)	

Abbreviations: ADL, Activities of daily living; CCI, Charlson comorbidity index; COD, cause of death; ECOG Eastern Cooperative Oncology Group; IPI, International Prognostic Index; IQR, interquartile range; NCCN, the National Comprehensive Cancer Network; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-IPI, revised IPI. *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 supplemental text.

Supplemental Figures

Figure S1. Forest plot showing results from univariate Cox regression analyses for association between specific extranodal sites and 2-year overall survival (OS) in the training set. HR, hazard ratio; CI, confidence interval.

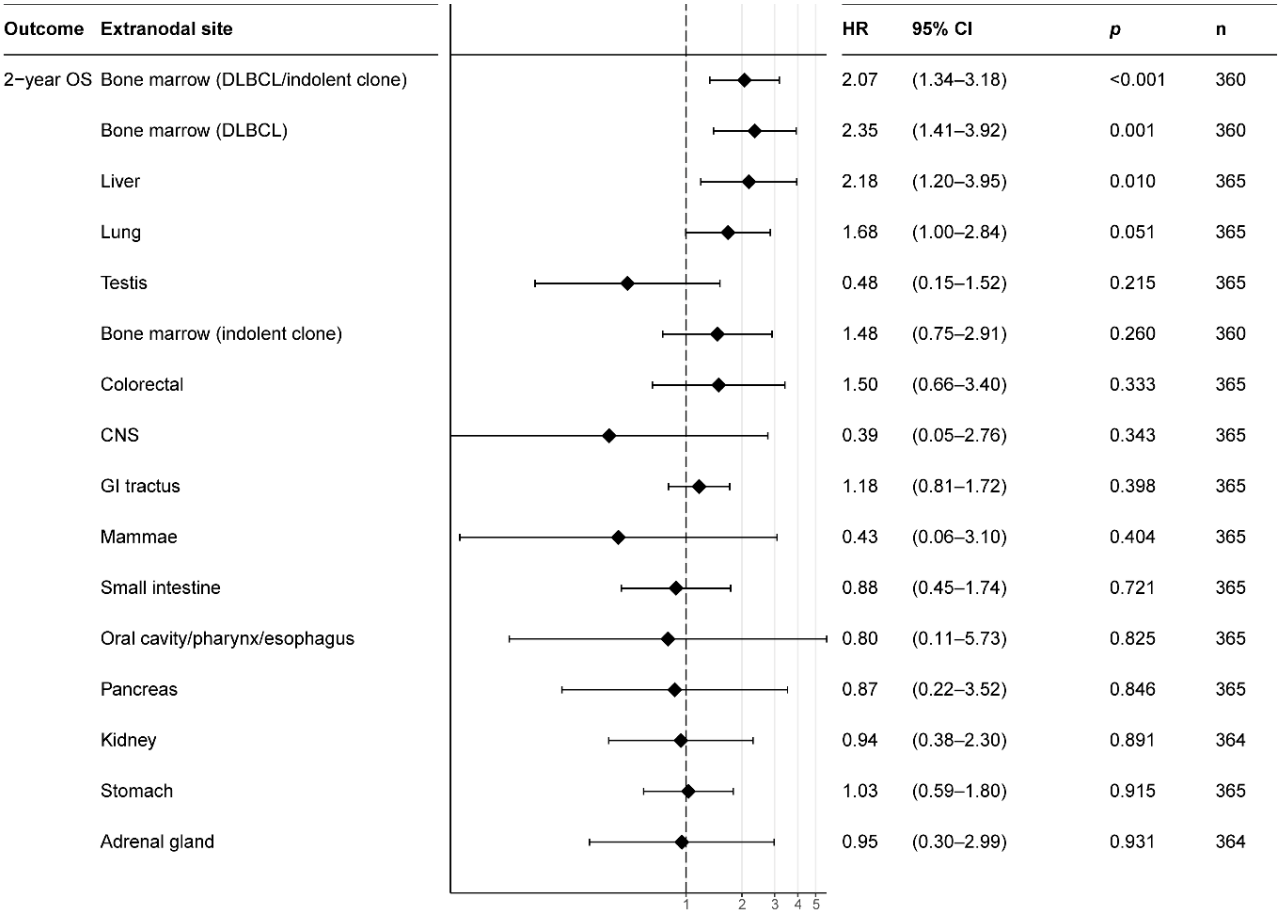


Figure S2. Internal calibration. Calibration plot of the final prognostic model from 200 bootstrap resamples of the training set (n=355). The plot shows comparison of observed and predicted 2-year overall survival (OS) from 200 bootstrap resamples of the training set. The grey line represents perfect predictions where predicted 2-year OS is equal to observed 2-year OS estimated with the Kaplan-Meier method. The black points show mean predicted 2-year OS with corresponding 95% confidence interval for groups of patients with similar prognosis (about 70 cases per group). Crosses represent optimism-corrected 2-year OS. Histogram on top shows number of patients.

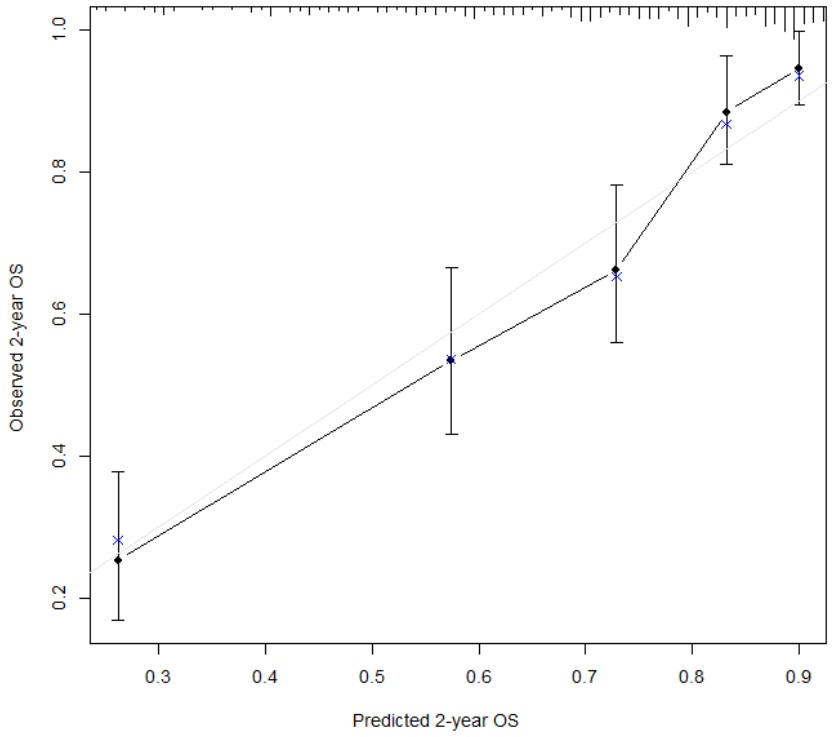


Figure S3. Progression-free survival of the Geriatric prognostic index (GPI) groups in the training set.

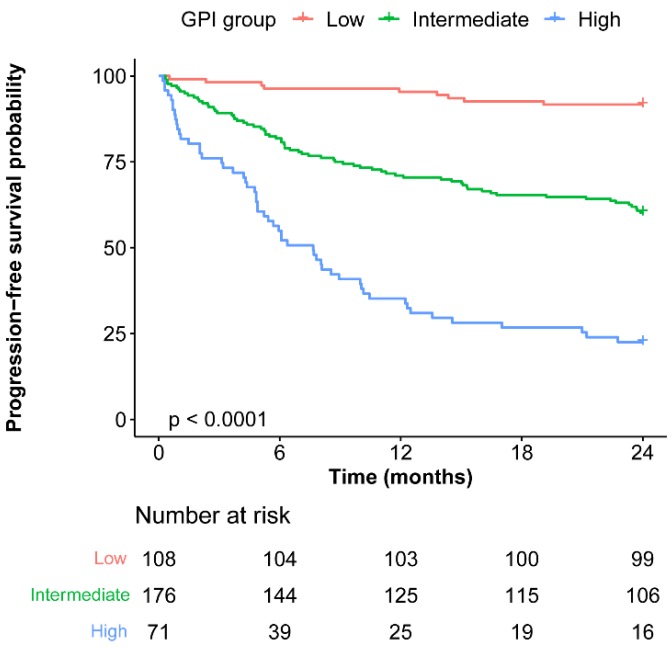


Figure S4. Overall survival of the Geriatric prognostic index (GPI) groups in the training set for patients treated with **(A)** full-dose R-CHOP (initial dosage >80%) and **(B)** attenuated R-CHOP (initial dosage ≤80%)

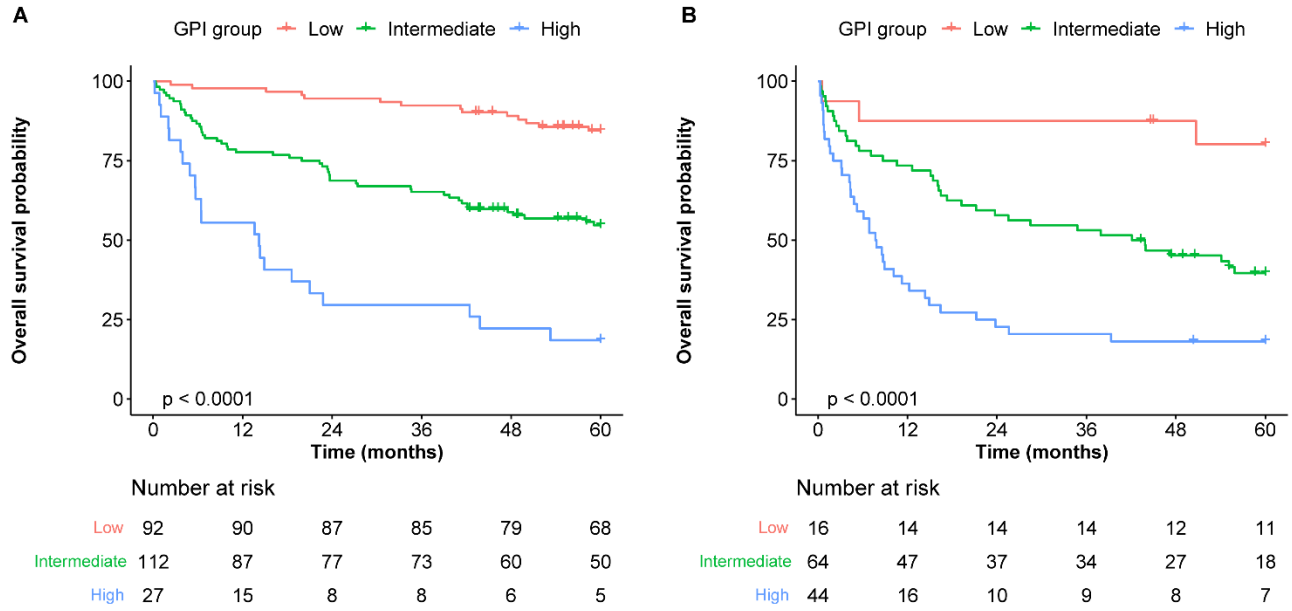


Figure S5. Overall survival of the Geriatric prognostic index (GPI) groups in the training set for patients aged **(A)** 70-79 years and **(B)** ≥ 80 years.

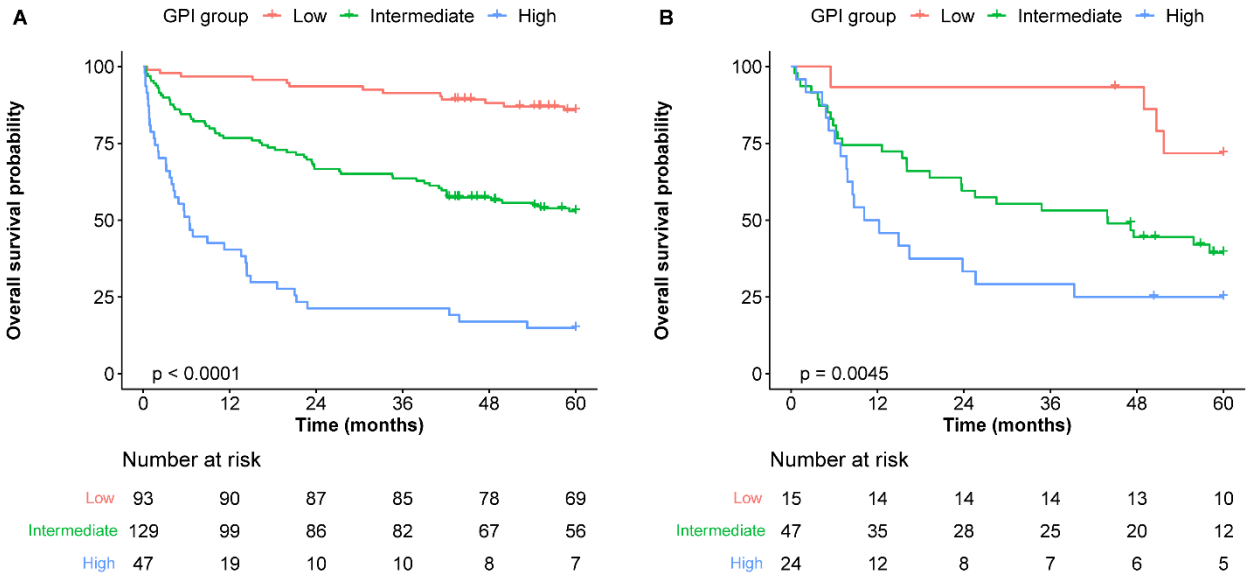
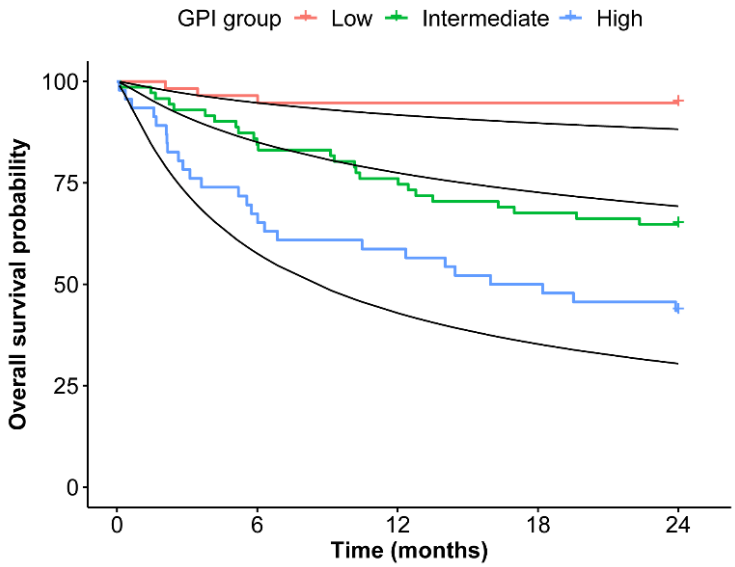


Figure S6. Calibration of survival probabilities for the Geriatric prognostic index (GPI) groups in the test set.



The figure shows observed versus predicted survival for the GPI risk groups in the test set. The colored lines represent observed survival estimated with the Kaplan-Meier method and the smooth lines represent predicted mean survival for the GPI risk groups.