A simplified frailty score predicts outcome in curatively treated older patients with classical Hodgkin lymphoma

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Simplified frailty score in elderly classical Hodgkin lymphoma patients

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Authorship

KL, RRKJ and AF: conception and design of the study; KL, BLW, NÖ, ØF, UMF, HB, IBB and AF: data collection and assembly; KL, RRKJ, DM, PW and AF: data analysis and interpretation; KL, RRKF, DM, PW and AF: created figures and tables; SB and AF: supervised; KL and AF: wrote the manuscript. All authors took part in writing the manuscript and reviewed and approved the final version.

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Supplementary Material

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Supplementary methods

Study design

We performed a retrospective population-based cohort study of all patients diagnosed with Hodgkin Lymphoma (HL) at the age of 60 years or older in Norway between 2000-2015 (Supplementary Figure S1) [1]. Since several patients in Norway after 2015 have been included in trials evaluating novel drugs and to allow for long follow-up, we decided to include only patients treated up until the end of 2015. Patients were identified through the Cancer Registry of Norway (CRN) and diagnoses were verified by review of original histology reports.

Patients alive at start of the study in 2016 were informed about the study and given the possibility to object to participation. No survivors objected. For patients who had died prior to study start, ethical approval gave exemption from the need for consent. We retrieved detailed information from clinical records at hospitals and general practitioners concerning medical history, diagnostic work-up and staging, treatment choices and follow-up during and after treatment. Review of clinical records was performed by physicians with help from study nurses.

For the present study, we focused on classical HL (cHL) patients with curatively intended upfront treatment consisting of standard anthracycline-containing regimens used for HL with more than 50% of full dose of doxorubicin (mitoxantrone in one patient) in the first cycle. We also excluded patients with composite lymphomas (defined as a previous or simultaneous finding of another malignant lymphoproliferative disease) or nodular lymphocyte predominant HL (NLPHL), patients never or only palliatively treated for HL, and patients who received anthracycline-free chemotherapy or extended-field irradiation as primary treatment.

From the Swedish Lymphoma Register (SLR) [2], we included an external validation cohort consisting of similar patients diagnosed with cHL at the age of 60 years or older between 2000 and 2015 (Supplementary Figure S2), all receiving anthracycline-containing regimens. Patients never or only palliatively treated were excluded. The patients were registered in the SLR and included in the LymphomaBase cohort, where the data from the lymphoma register is cross checked with several other health care registers. In this dataset, patients with composite lymphomas or NLPHL, were already excluded.

The study was approved by the Regional Committee for Medical Research Ethics South East Norway (REK 2016/1202) and Data Protection Officers at all participating hospitals and performed according to the Declaration of Helsinki.

Norwegian analysis cohort

Patient-related variables from time of diagnosis included age, sex, Eastern cooperative oncology group performance status (ECOG PS) [3], body mass index (BMI) and smoking habits. The burden of comorbidity was determined by Cumulative Illness Rating Score for Geriatrics (CIRS-G) [4], which assesses basic chronic medical illnesses taking into account the severity of each, and validated to reflect common geriatric problems. Dependency of help was determined according to Katz Index of Independence in Activities of Daily Living (ADL) [5]. For the latter two parameters, the status of the patient prior to debut of lymphoma symptoms was assessed from the medical records prior to the diagnosis of lymphoma, i.e. the impact of the lymphoma on organ function and self-reliance would be ignored as best possible.

Diagnostic procedures and curative treatment of patients ≥60 years followed national guidelines [6]. We recorded histological subtype and disease extent, based on computed tomography (CT) scan and bone marrow biopsy, and only rarely by fluorodeoxyglucose positron emission tomography CT (PET-CT), presence of B-symptoms or bulky disease (lesion ≥10 cm in largest diameter on CT scans) and relevant blood tests. For stages I-IIA (limited disease), these were erythrocyte sedimentation rate (ESR) and for stages IIB-IV (advanced disease), hemoglobin, albumin, leucocyte and lymphocyte counts as part of the international prognostic score (IPS) [7].

Principles for curatively intended treatment in Norwegian cHL patients over 60 years of age are detailed in national recommendations [6]. A risk-adapted strategy as for younger patients has been used, with 2-4 cycles of doxorubicin-containing chemotherapy and involved site radiotherapy in limited disease. Two cycles were recommended for those without risk factors (bulky disease ≥10 cm in diameter, ESR ≥50 mm/h or ≥3 involved lymph node regions). At the time, in advanced stage disease, 6-8 cycles of chemotherapy were recommended with possible consolidation radiotherapy. Due to toxicity observed with regimens used in younger patients, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) administered every three weeks was the standard for curative treatment from 2000 to 2015. Patients deemed suitable could receive ABVD, with the option to omit bleomycin if there were concerns about pulmonary toxicity [1].

Other curative chemotherapy options included BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), ABOP (Doxorubicin, bleomycin, oncovin, prednisone, AVOP (Doxorubicin, etoposide, oncovin, prednisone) and CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone). For classical Hodgkin Lymphoma (cHL), radiotherapy alone was not recommended, except for a small number of patients with stage I-IIA disease without risk factors prior to 2000.

Therapy was recorded by choice of regimen. Dose intensity of doxorubicin was recorded for the first cycle and total treatment as dose delivered divided by standard full dose for the chosen regimen and the preplanned number of cycles. For the first cycle, treatment intensity was dichotomized as ≥80% intensity or 50-79% of standard doxorubicin in the first cycle, disregarding other or later dose modifications. For the total treatment, dose intensity of doxorubicin was categorized as ≥80%, 50-79% or <50%. Patients with treatment-related mortality (TRM) were excluded from the analysis of total doxorubicin doses. Use of radiotherapy as part of primary treatment was documented.

Tumor response was documented according to Cheson et al [8]. Final response assessment was usually done within 1-2 months after treatment (or earlier in case of suspected progression) and included CT scans, supplemented with a bone marrow trephine biopsy if needed. PET-CT for evaluation was gradually introduced starting in 2008 but not used for response assessment in this analysis. TRM was defined as death of any cause during or within three months after treatment not clearly due to cHL.

Swedish validation cohort

SLR was initiated in 2000 with the aim to monitor quality of care in adult lymphoma patients [2]. Swedish treatment guidelines for older cHL patients are based on anthracycline-containing regimens in line with Norwegian recommendations [9]. Patients 60-70 years of age: Patients with limited stage (I-IIA) disease and no risk factor (bulky disease, erythrocyte sedimentation rate >50 mm or more than two involved sites) were given two courses of ABVD followed by radiotherapy to 30 Gy fractions or, later in the period, to 20 Gy. Limited stage patients with any risk factor were treated with 4 ABVD, followed by radiotherapy to approximately 30 Gy. Stage IB patients were treated according to the same principles as patients with limited stage and any risk factor or as advanced stage (IIB-IV) disease.
Advanced stage (IIB-IV) patients were recommended 6-8 courses of ABVD.

Patients ≥71 years: Limited stage disease without risk factors, was treated with 2 cycles of CHOP followed by 30 Gy. Limited stage disease with any risk factor received 4 CHOP and 30 Gy. Stage IB was either given 4 cycles of CHOP and 30 Gy or 6 cycles of CHOP. Advanced stages were initially recommended 6 cycles of CHOP, however, some centers also used ABVD in patients >70 years of age. Comorbidities were scored with Charlson comorbidity index (CCI) and calculated within the LymphomaBase framework, based on diagnoses retrieved from the Swedish National Patient Register [10, 11]. Diagnostic codes were mapped to the comorbidity conditions and a weighted score assigned to each condition according to the standard CCI scoring system [11]. The total CCI was then computed by summing the individual scores. The CCI cutoff in analysis was 0-2 versus ≥3 based on the percentiles for the CIRS-G score in the Norwegian cohort. Sensitivity analyses of the frailty score were performed in a subset of patients with complete treatment data (Supplementary methods).

Statistical analysis

Progression-free survival (PFS) was calculated from date of diagnosis to time of progression, relapse or death of any cause, whichever occurred first, censored at date of last follow-up. Similarly, overall survival (OS) was calculated for date of diagnosis to death of any cause, censored at time of the last update from Statistics Norway (December 31st 2021) who provided dates of death for all deceased patients.

Survival times were calculated by the Kaplan-Meier method and survival curves compared by log-rank test and Cox regression analysis with hazard ratios (HR) in univariate and multivariable analyses. Requirements for constant proportional hazards with time necessitated right truncating of survival times at five years from diagnosis. Sex and all variables univariately associated with outcome at p-values <0.05 were chosen for multivariable models but excluded when collinearity with other independent variables was observed. Performance measures used to assess the final frailty model were concordance index (C-index) and time-varying area under the curve (AUC), evaluated for 5-year PFS and OS. Internal validation was done by pooling estimates in a 10-fold cross-validation. All statistical tests were two sided and p-values <0.05 were considered significant. Analyses were performed using SPSS v28.0. and R 4.1.1. (Supplementary Table S1).

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Supplementary Table S1: Specific packages used for R software version 4.1.1. (R Foundation for Statistical Computing, Vienna, Austria)

Package	**Functions**	**Package Versions**
haven	read_sav	2.43
survminer	ggsurvplot	0.4.9
survival	survfit, survdiff	3.4-0
networkD3	sankeyNetwork	0.4
prodlim	prodlim	2019.11.13
cmprsk	cuminc	2.2-11

Supplementary Table S2: Baseline demographics and clinical characteristics Norwegian training cohort

Characteristic	**All patients N= 279**
	n (%)
Age at diagnosis/years	
Median (range)	69 (60-90)
Sex	
Female	128 (45.9)
Male	151 (54.1)
Histology	
Nodular sclerosis	126 (45.2)
Mixed cellularity	48 (17.2)
Lymphocyte-depleted	6 (2.2)
Lympocyte-rich	30 (10.8)
cHL NOS	69 (24.7)
Stage (Ann Arbor)	
I - II	116 (41.6)
III - IV	163 (58.4)
B-symptoms	
Absent	143 (51.3)
Present	136 (48.7)
cHL risk groups	90 (32.3)
Limited disease favorable	51 (18.3)
Limited disease unfavorable	38 (13.6)
Limited disease, missing	1 (0.4)
Advanced disease	189 (67.7)
IPS (1 - 2)	65 (23.3)
IPS (3 - 4)	93 (33.3)
IPS (5 - 7)	31 (11.1)
ECOG PS	
0 - 1	214 (76.7)
≥ 2	62 (22.2)
Missing	3 (1.1)
ADL	
Independent	237 (84.9)
Dependent	37 (13.3)
Missing	5 (1.8)
Weight loss	
No	160 (57.3)
Yes	108 (38.7)
Missing	11 (3.9)
BMI/kgm^{-2}	
Median (range)	25.2 (15.2-43.0)
Missing	16 (5.7)
Cognitive failure	
No	271 (97.1)
Yes	5 (1.8)
Missing	3 (1.1)
CIRS-G	
Median (range)	6 (0-23)
< 8	188 (67.4)
≥ 8	87 (31.2)
Missing	4 (1.4)
Smoking	
No	111 (39.8)
Yes, current	78 (28.0)

Yes, previously	64 (22.9)
Missing	26 (9.3)
Primary treatment regimen	
CHOP	219 (78.5)
ABVD/ABOP	53 (19.0)
BEACOPP	4 (1.4)
Other anthracycline-based[b]	3 (1.1)
Initial dose doxorubicin (%)	
Median (range)	100 (50-100)
50 - 79 %	40 (14.3)
≥ 80 %	239 (85.7)
Total doxorubicin dose (%)	
Median (range)	100 (8.3-100)
≤ 49 %	25 (9.7)
50 - 79 %	45 (17.4)
≥ 80 %	188 (73)
Irradiation	
Consolidation limited disease	81 (90.0)[a]
Consolidation advanced disease	38 (20.1)[a]
Response primary treatment	
CR	206 (73.8)
PR	32 (11.5)
SD	3 (1.1)
PD	9 (3.2)
TRM	21 (7.5)
Missing	8 (2.9)

Continuous variables described as median and range, categorical data described with numbers and proportions. [a]proportion within limited and advanced disease group, respectively. [b]other anthracycline-based regimens included AVOP (doxorubicin, etoposide, vincristine, oncovin, prednisone) in 2 and CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone) in one patient.

Abbreviations: ADL: activity of daily living; ABOP: doxorubicin, bleomycin, vincristine and prednisone; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BMI: body mass index; cHLNOS: classical Hodgkin lymphoma not otherwise specified; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CIRS-G: cumulative illness rating scale for geriatrics; CR: complete response; ECOG PS: performance status by Eastern Cooperative Oncology Group; IPS: international prognostic score; PD: progression disease; PR: partial response; SD: stable disease; TRM: treatment related mortality.

Supplementary Table S3: Response rates and treatment-related mortality Norwegian training cohort.

Patients (n)	Response	n	Percent (%)	95%CI
All patients (279)	CR	206	73.8	68.3-78.7
	PR	32	11.5	8.2-15.8
	SD	3	1.1	0.3-3.3
	PD	9	3.2	1.7-6.1
	TRM	21	7.5	5.0-11.3
	Unknown	8	2.9	1.4-5.7
Limited disease (90)	CR	78	86.7	77.8-92.4
	PR	9	10	5.2-18.3
	SD	0	0	0
	PD	1	1.1	0.2-7.7
	TRM	2	2.2	0.5-8.7
	Unknown	0	0	0
Advanced disease (189)	CR	128	67.7	60.7-74.1
	PR	23	12.2	8.2-17.7
	SD	3	1.6	0.5-4.9
	PD	8	4.2	2.1-8.3
	TRM	19	10.1	6.5-15.3
	Unknown	8	4.2	2.1-8.3

Abbreviation: CI: confidence interval; CR: complete response; PD: progression disease; PR: partial response; SD: stable disease; TRM: treatment-related mortality.

Supplementary Table S4: Multivariable Cox regression analysis on progression-free and overall survival up until 5 years for all patients with age, BMI and CIRS-G as continuous variables Norwegian training cohort

	5-year progression-free survival		5-year overall survival	
	multivariable analysis		multivariable analysis	
Characteristic (n)	HR (95% CI)	*p*	HR (95% Cl)	*p*
Patient-related variables				
Age at diagnosis/years (279)	1.04 (1.0-1.1)	**0.011**	1.1 (1.0-1.1)	**<0.001**
Sex		0.12		0.12
Female (128)	ref		ref	
Male (151)	1.4 (0.9-2.0)		1.4 (0.9-2.2)	
ECOG PS		**0.040**		0.24
0-1 (214)	ref		ref	
≥ 2 (62)	1.6 (1.0-2.5)		1.3 (0.8-2.1)	
ADL		0.71		0.47
Independent (237)	ref		ref	
Dependent (37)	1.1 (0.6-1.9)		1.2 (0.7-2.2)	
BMI/kgm^{-2} (263)	1.0 (0.9-1.0)	0.12	1.0 (0.9-1.0)	0.13
CIRS-G (275)	1.1 (1.0-1.1)	**0.007**	1.1 (1.0-1.1)	**<0.001**
Disease-related variables				
Histology		**0.005**		**0.001**
Nodular sclerosis (126)	ref		ref	
Mixed cellularity (48)	0.7 (0.4-1.3)	0.26	0.8 (0.4-1.5)	0.48
Lymphocyte-rich (30)	0.2 (0.1-0.6)	**0.006**	0.3 (0.1-0.9)	**0.028**
Lymphocyte-depleted/ cHL NOS (75)	1.4 (0.9-2.1)	0.15	1.9 (1.2-3.0)	**0.009**
Risk groups		**0.003**		**0.005**
Limited disease (90)	ref		ref	
Advanced disease (189)	2.2 (1.3-3.6)		2.3 (1.3-4.0)	

Sums of n may not add to the total in each group, n is given for valid cases only.

Multivariable Cox regression analysis was performed for progression-free and overall survival right truncated at 5 years. P-values are indicated in bold when below the 5% significance threshold. Sex was included in the multivariable model although p-values was not significant in univariate analysis.

Stage and presence of B-symptoms omitted from the multivariable analysis due to collinearity with risk group. Treatment omitted from the multivariate analysis as not relevant for developing a prediction model consisting of variables present prior to start of treatment.

Abbreviations: ADL: activity of daily living; BMI: Body mass index; CI: confidence interval; CIRS-G: cumulative illness rating scale for geriatrics; cHL NOS: Classical Hodgkin lymphoma not otherwise specified; ECOG PS: performance status by Eastern Cooperative Oncology Group; HR: hazard ratio; Ref: reference.

Supplementary Table S5: Univariate and multivariable Cox regression analysis on progression-free and overall survival up until 5 years for patients with limited or advanced disease separately Norwegian training cohort

	5-year progression-free survival				5-year overall survival			
	univariate analysis		multivariable analysis		univariate analysis		multivariable analysis	
Characteristic (n)	HR (95% Cl)	*p*	HR (95% Cl)	*p*	HR (95% Cl)	*p*	HR (95% Cl)	*p*
Patients with limited disease (90)								
Age at diagnosis/years		**0.008**		0.09		**0.002**		**0.034**
< 70 years (51)	ref							
≥ 70 years (39)	3.4 (1.4-8.2)		2.3 (0.9-6.0)		5.6 (1.8-16.9)		3.6 (1.1-11.8)	
Sex		0.67		0.67		0.27		0.12
Female (40)	ref							
Male (50)	1.2 (0.5-2.8)		1.2 (0.5-3.0)		1.7 (0.6-4.6)		2.3 (0.8-6.6)	
ECOG PS		**<0.001**		0.053		**0.009**		0.61
0-1 (84)	ref							
≥ 2 (5)	7.8 (2.6-23.5)		3.6 (1.0-13.0)		5.3 (1.5-18.4)		1.5 (0.3-6.7)	
ADL		0.42				0.63		
Independent (74)	ref							
Dependent (13)	1.6 (0.5-4.7)				1.4 (0.4-4.8)			
BMI/kgm^{-2}		0.76				0.34		
≤ 26 (43)	ref							
≥ 26 (42)	0.9 (0.4-2.0)				0.6 (0.2-1.6)			
CIRS- G		**0.007**		**0.046**		**<0.001**		**0.010**
< 8 (63)	ref							
≥ 8 (25)	3.3 (1.4-7.7)		2.5 (1.0-6.0)		5.5 (2.0-15.0)		3.9 (1.4-11.0)	
Histology		0.39				0.99		
Nodular sclerosis (45)	ref							
Mixed cellularity (15)	0.6 (0.2-2.0)	0.38			1.2 (0.4-3.8)	0.78		
Lymphocyte-rich (14)	0.2 (0.0-1.5)	0.11			0.0 (0.0-0.0)	0.97		
Lymphocyte-depleted/ cHL NOS (16)	0.8 (0.3-2.4)	0.67			1.2 (0.4-3.8)	0.76		
Risk group		0.75				0.87		
Early favorable (51)	ref							
Early unfavorable (39)	1.1 (0.5-2.6)				1.1 (0.4-2.7)			
Doxorubicin dose 1. cycle		**0.009**				**0.005**		
50-79% (5)	ref							
≥ 80% (85)	0.2 (0.1-0.7)				0.2 (0.0-0.6)			
Total Doxorubicin dose		0.77				0.88		
≥ 80% (68)	ref							
50-79% (18)	1.5 (0.5-4.0)	0.47			1.3 (0.4-4.2)	0.61		
≤ 49% (2)	0.0 (0.0-0.0)	0.98			0.0 (0.0-0.0)	0.99		
Irradiation		**0.015**				**0.045**		
No (9)	ref				ref			

Yes, consolidation (81)	0.3 (0.1-0.8)				0.3 (0.1-1.0)			
Patients with advanced disease (189)								
Age at diagnosis/years < 70 years (98)	ref	**0.002**		0.058		**<0.001**		**0.015**
≥ 70 years (91)	1.9 (1.3-2.8)		1.5 (1.0-2.3)		2.2 (1.4-3.4)		1.8 (1.1-2.8)	
Sex Female (88)	ref	0.49		0.88		0.57		0.98
Male (101)	1.1 (0.8-1.7)		1.0 (0.6-1.5)		1.1 (0.7-1.7)		1.0 (0.6-1.6)	
ECOG PS 0-1 (130)	ref	**<0.001**		0.12		**<0.001**		0.26
≥ 2 (57)	2.1 (1.4-3.2)		1.4 (0.9-2.2)		2.2 (1.5-3.4)		1.3 (0.8-2.1)	
ADL Independent (163)	ref	**0.025**		0.37		**0.009**		0.57
Dependent (24)	1.8 (1.1-3.0)		1.3 (0.7-2.3)		2.0 1.2-3.4)		1.2 (0.7-2.2)	
BMI/kgm^{-2} < 26 (121)	ref	0.10				0.28		
≥ 26 (58)	0.7 (0.4-1.1)				0.8 (0.5-1.2)			
CIRS-G < 8 (125)	ref	0.10				**0.006**		**0.008**
≥ 8 (62)	1.4 (0.9-2.1)				1.8 (1.2-2.7)		1.8 (1.2-2.8)	
Histology Nodular sclerosis (81)		**0.003**		0.054		**0.001**		0.06
Mixed cellularity (33)	1.0 (0.6-1.7)	0.93	0.9 (0.5-1.6)	0.74	0.8 (0.4-1.6)	0.58	0.8 (0.4-1.6)	0.50
Lymphocyte-rich (16)	0.3 (0.1-0.9)	**0.036**	0.2 (0.0-0.8)	**0.028**	0.5 (0.2-1.4)	0.20	0.4 (0.1-1.2)	0.10
Lymphocyte-depleted/ cHL NOS (59)	1.7 (1.1-2.7)	**0.014**	1.3 (0.8-2.1)	0.22	2.0 (1.3-3.2)	**0.003**	1.5 (0.9-2.5)	0.13
International prognostic score 1-2 (65)	ref	**<0.001**		**0.007**		**<0.001**		**0.008**
3-4 (93)	2.6 (1.6-4.2)	**<0.001**	2.4 (1.4-4.1)	**0.002**	2.6 (1.5-4.5)	**<0.001**	2.2 (1.2-4.1)	**0.004**
5-7 (31)	3.4 (1.9-6.2)	**<0.001**	2.3 (1.1-4.5)	**0.020**	4.6 (2.4-8.6)	**<0.001**	2.9 (1.4-6.0)	
Doxorubicin dose 1. cycle 50-79% (35)	ref	**<0.001**				**<0.001**		
≥ 80% (154)	0.4 (0.3-0.7)				0.4 (0.3-0.6)			
Total Doxorubicin dose ≥ 80% (120)	ref	**0.004**				**<0.001**		
50-79% (27)	2.2 (1.3-3.8)	**0.002**			2.8 (1.6-4.8)	**<0.001**		
≤ 49% (23)	1.9 (1.0-3.5)	**0.041**			2.2 (1.2-4.2)	**0.016**		
Irradiation No (151)	ref	0.058			ref	**0.034**		
Yes, consolidation (38)	0.6 (0.4-1.0)				0.5 (0.3-1.0)			

Sums of n may not add to the total in each group, n is given for valid cases only.

Univariate and multivariable Cox regression analyses were performed for progression-free and overall survival right truncated at 5 years. P-values are indicated in bold when below the 5% significance threshold. Sex was included in the multivariable model although p-values was not significant in univariate analysis.

Treatment omitted from the multivariable analysis as not seen relevant for developing a prediction model consisting of variables present prior to start of treatment.

Abbreviations: ADL: activity of daily living; BMI: body mass index; cHL NOS: classical Hodgkin lymphoma not otherwise specified; CI: confidence interval; CIRS- G: cumulative illness rating scale for geriatrics; ECOG PS: performance status by Eastern Cooperative Oncology Group; HR: hazard ratio.

Supplementary Table S6: Construction of a geriatric frailty index in the Norwegian training cohort

Independent variables predicting PFS	HR from multivariable analysis (95% CI)	*p*	Score in frailty index
Age at diagnosis/years			
< 70	ref		0
≥ 70	1.7 (1.1-2.5)	**0.012**	1
ECOG PS			
0-1	ref		0
≥ 2	1.6 (1.0-2.5)	**0.037**	1
CIRS-G			
< 8	ref		0
≥ 8	1.7 (1.2-2.5)	**0.007**	1

Frailty score (0-3) is calculated by adding scores for age, ECOG PS status and CIRS-G.

Abbreviations: CI: confidence interval; CIRS-G: cumulative illness rating scale for geriatrics; ECOG PS: performance status by Eastern Cooperative Oncology Group; HR: hazard ratio; PFS: progression-free survival; Ref: reference.

Supplementary Table S7: Baseline demographics and clinical characteristics Swedish validation cohort

Characteristic	**All patients N= 792**
	n (%)
Age at diagnosis/years	
Median (range)	71 (60-99)
Sex	
Female	354 (44.7)
Male	438 (55.3)
Histology	
Nodular sclerosis	305 (38.5)
Mixed cellularity	223 (28.2)
Lymphocyte-depleted	16 (2.0)
Lympocyte-rich	46 (5.8)
cHL NOS	202 (25.5)
Stage (Ann Arbor)	
I - II	324 (40.9)
III - IV	414 (52.3)
Missing	54 (6.8)
B-symptoms	
Absent	358 (45.2)
Present	423 (53.4)
Missing	11 (1.4)
cHL risk groups	
Limited disease	217 (27.4)
Advanced disease	551 (69.6)
Missing	24 (3.0)
ECOG PS	
0 - 1	602 (76.0)
≥ 2	173 (21.8)
Missing	17 (2.1)
Weight loss	
No	519 (65.5)
Yes	273 (34.5)
CCI	
Median (range)	1 (0-13)
≤ 2	645 (81.4)
≥ 3	147 (18.6)
Primary treatment regimen	
CHOP	188 (23.7)
ABVD/AVD	166 (21.0)
BEACOPP	15 (1.9)
Missing	423 (53.4)
Irradiation	
Yes	116 (14.6)
No	326 (41.2)
Missing	350 (44.2)
Response primary treatment	
CR/CRu	299 (37.8)
PR	50 (6.3)
SD	7 (0.9)
PD	34 (4.3)
Missing	402 (50.8)

Continuous variables described as median and range, categorical data described with numbers and proportions.

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD: doxorubicin, vinblastine, and dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CCI: Charlson Comorbidity Index; cHL NOS: classical Hodgkin lymphoma not otherwise specified; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CR: complete response; CRu: complete response unconfirmed; ECOG PS: performance status by Eastern Cooperative Oncology Group; PD: progression disease; PR: partial response; SD: stable disease.

Supplementary Table S8: Univariate and multivariable Cox regression analysis on progression-free and overall survival up until 5 years for all patients in the Swedish validation cohort

	5-year progression-free survival				5-year overall survival			
	univariate analysis		multivariable analysis		univariate analysis		multivariable analysis	
Characteristic (n)	HR (95% Cl)	*p*	HR (95% Cl)	*p*	HR (95% Cl)	*p*	HR (95% Cl)	*p*
Patient-related variables								
Age at diagnosis/years		**<0.001**		**<0.001**		**<0.001**		**<0.001**
< 70 (331)	ref							
≥ 70 (461)	2.7 (2.2-3.3)		2.2 (1.6-3.0)		2.9 (2.3-3.7)		2.5 (1.8-3.5)	
Sex		0.29		**0.045**		0.30		0.053
Female (354)	ref							
Male (438)	1.1 (0.9-1.4)		1.4 (1.0-1.8)		1.1 (0.9-1.4)		1.4 (1.0-1.8)	
ECOG PS		**<0.001**		**<0.001**		**<0.001**		**<0.001**
0-2 (602)	ref							
≥ 2 (181)	3.8 (3.1-4.7)		2.3 (1.6-3.3)		4.1 (3.4-5.1)		2.6 (1.8-3.8)	
CCI		**<0.001**		0.10		**<0.001**		0.066
≤ 2 (645)	ref							
≥ 3 (147)	2.0 (1.6-2.5)		1.3 (1.0-1.9)		2.1 (1.7-2.6)		1.4 (1.0-2.0)	
Disease-related variables								
Histology								
Nodular sclerosis (305)	ref							
Mixed cellularity (223)	1.0 (0.8-1.3)	0.94	0.9 (0.6-1.3)	0.44	1.1 (0.8-1.4)	0.54	0.9 (0.6-1.4)	0.71
Lymphocyte-rich (46)	0.6 (0.3-1.0)	**0.033**	0.7 (0.3-1.4)	0.27	0.6 (0.4-1.0)	0.07	0.8 (0.4-1.6)	0.50
Lymphocyte-depleted/ cHL NOS (218)	1.6 (1.2-2.0)	**<0.001**	1.0 (0.7-1.4)	0.89	1.6 (1.3-2.1)	**<0.001**	1.0 (0.7-1.5)	0.94
Stage (Ann Arbor)								
I (129)	ref							
II (195)	1.8 (1.2-2.6)	**0.003**			1.8 (1.2-2.7)	**0.003**		
III (227)	2.1 (1.5-3.0)	**<0.001**			2.3 (1.6-3.3)	**<0.001**		
IV (187)	3.0 (2.1-4.2)	**<0.001**			3.0 (2.0-4.3)	**<0.001**		
B-symptoms		**<0.001**				**<0.001**		
Absent (358)	ref							
Present (423)	2.1 (1.7-2.6)				2.0 (1.7-2.5)			
Risk groups		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Limited disease (180)	ref							
Advanced disease (204)	2.5 (1.8-3.4)		1.9 (1.3-2.6)		2.4 (1.8-3.3)		1.8 (1.3-2.6)	

Sums of n may not add to the total in each group, n is given for valid cases only.

Sex was included in the multivariable model although p-values was not significant in univariate analysis.

Abbreviations: cHL NOS: classical Hodgkin lymphoma not otherwise specified; CI: confidence interval; CCI; Charlson Comorbidity Index; ECOG PS: performance status by Eastern Cooperative Oncology Group; HR: hazard ratio.

Supplementary Table S9: Cox regression analysis of frailty score on 5-year progression-free survival and overall survival in the Swedish validation cohort

Frailty score	Frailty group (n)	5-year progression-free survival		5-year overall survival	
		univariate analysis		univariate analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
0	Fit (255)	ref		ref	
1-2	Unfit (505)	3.7 (2.8-4.8)	**<0.001**	4.3 (3.2-5.7)	**<0.001**
3	Frail (23)	9.5 (5.8-15.5)	**<0.001**	11.8 (7.2-19.4)	**<0.001**

Sums of n may not add to the total in each group, n is given for valid cases only.

Univariate Cox regression analysis was performed with HR shown for progression-free and overall survival right truncated at 5 years. P-values below 5% significance threshold are indicated in bold.

Abbreviations: CI: confidence interval; HR: hazard ratio.

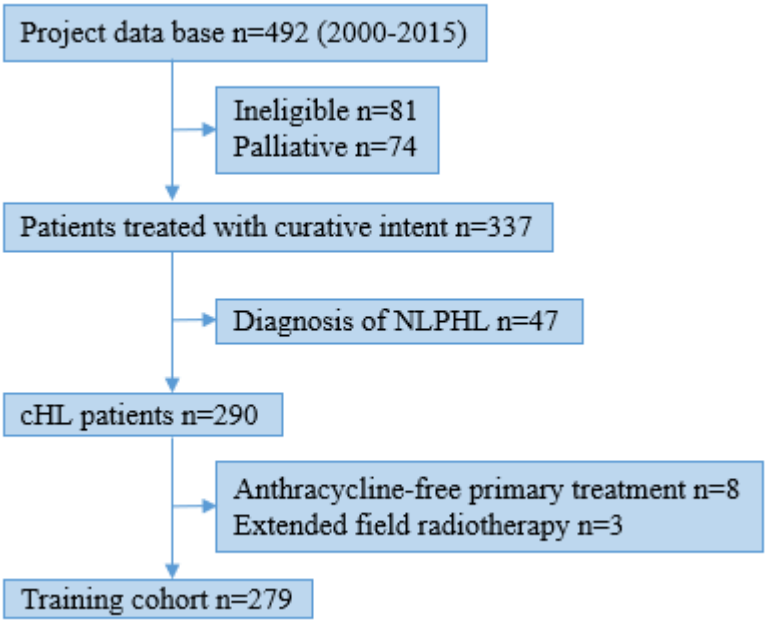
Supplementary Table S10: Cox regression analysis of frailty score on 5-year progression-free survival and overall survival in patients from the Swedish validation cohort with complete treatment data

Frailty score	Frailty group (n)	5-year progression-free survival univariate analysis		5-year overall survival univariate analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
0	Fit (116)	ref		ref	
1-2	Unfit (152)	2.4 (1.5-3.6)	**<0.001**	3.2 (2.0-5.2)	**<0.001**
3	Frail (3)	5.9 (1.8-19.6)	**0.003**	9.1 (2.7-30.8)	**<0.001**

Sums of n may not add to the total in each group, n is given for valid cases only.

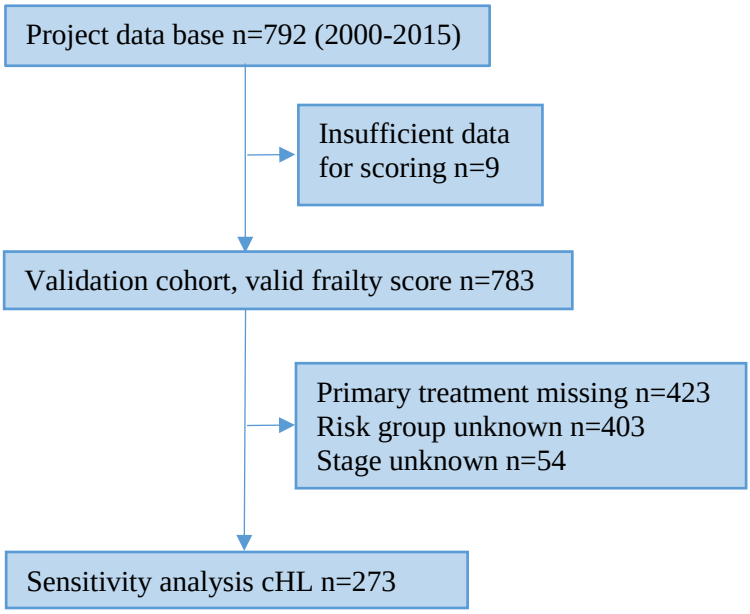
Univariate Cox regression analysis was performed with HR shown for progression-free and overall survival right truncated at 5 years. P-values below 5% significance threshold are indicated in bold.

Abbreviations: CI: confidence interval; HR: hazard ratio.



Supplementary Figure S1: Flowchart of patients with classical Hodgkin lymphoma in Norway from 2000-2015

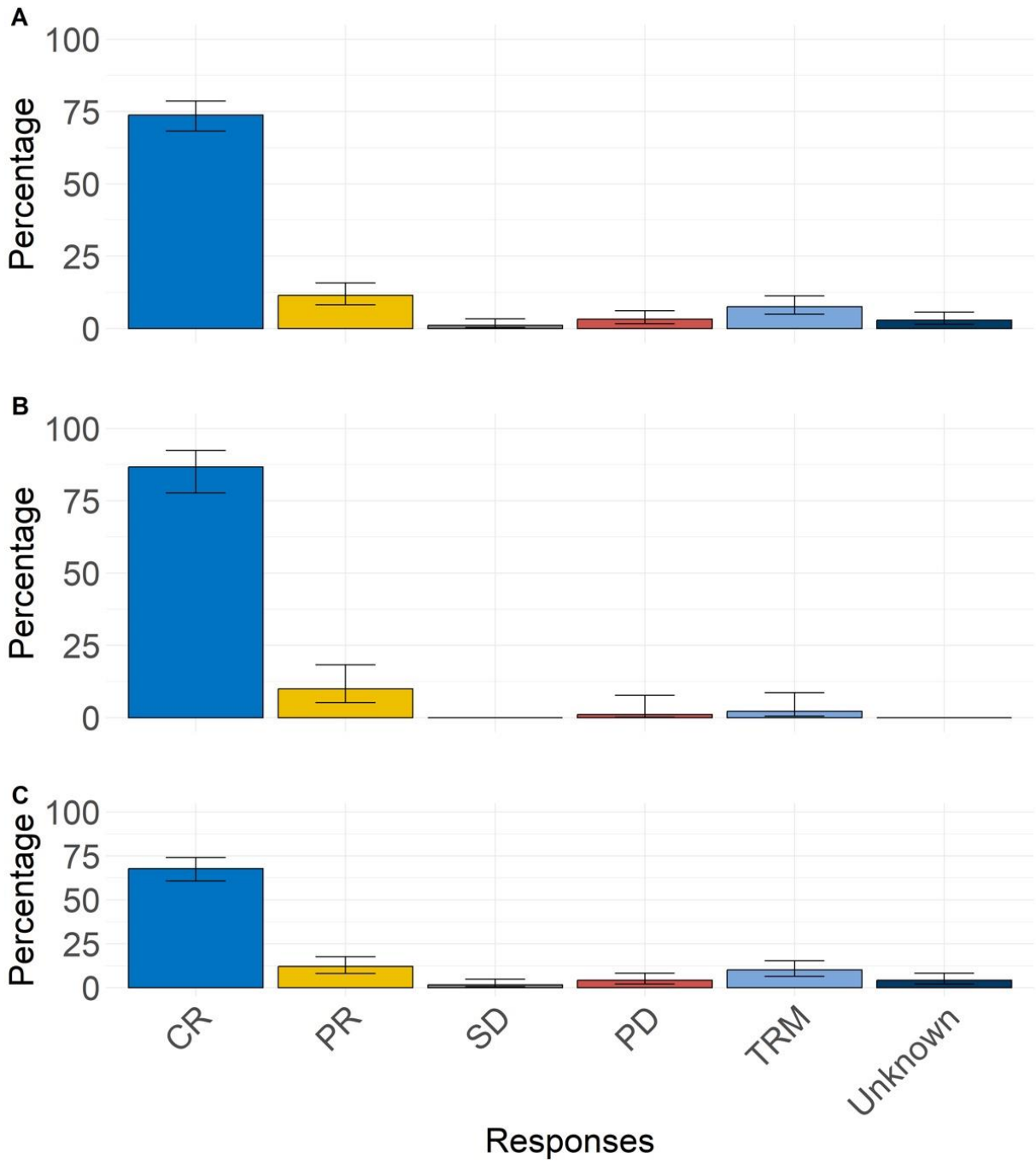
Abbreviations: cHL: classical Hodgkin lymphoma; CRN: Cancer Registry Norway; NLPHL: nodular lymphocyte predominant Hodgkin lymphoma.



Supplementary Figure S2: Flowchart of Swedish validation cohort with classical Hodgkin lymphoma from 2000-2015

Abbreviations: cHL: classical Hodgkin lymphoma.

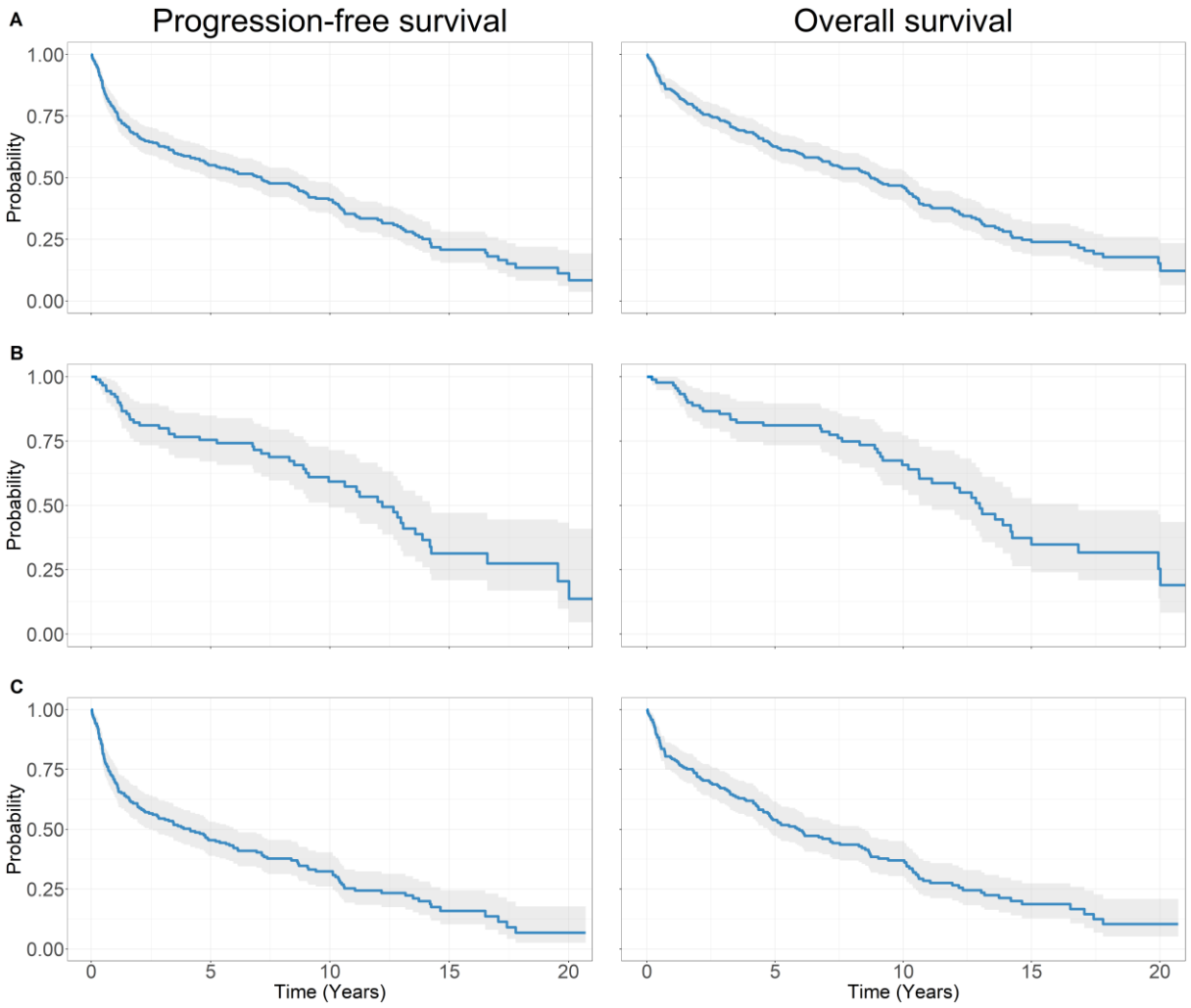
Sensitivity analyses of the frailty score were performed in a subset of patients with complete treatment data. The patients who had either primary treatment missing, risk group or stage, were excluded. One patient could have more than one missing variable.



Supplementary Figure S3: Response rates primary treatment and treatment related mortality.

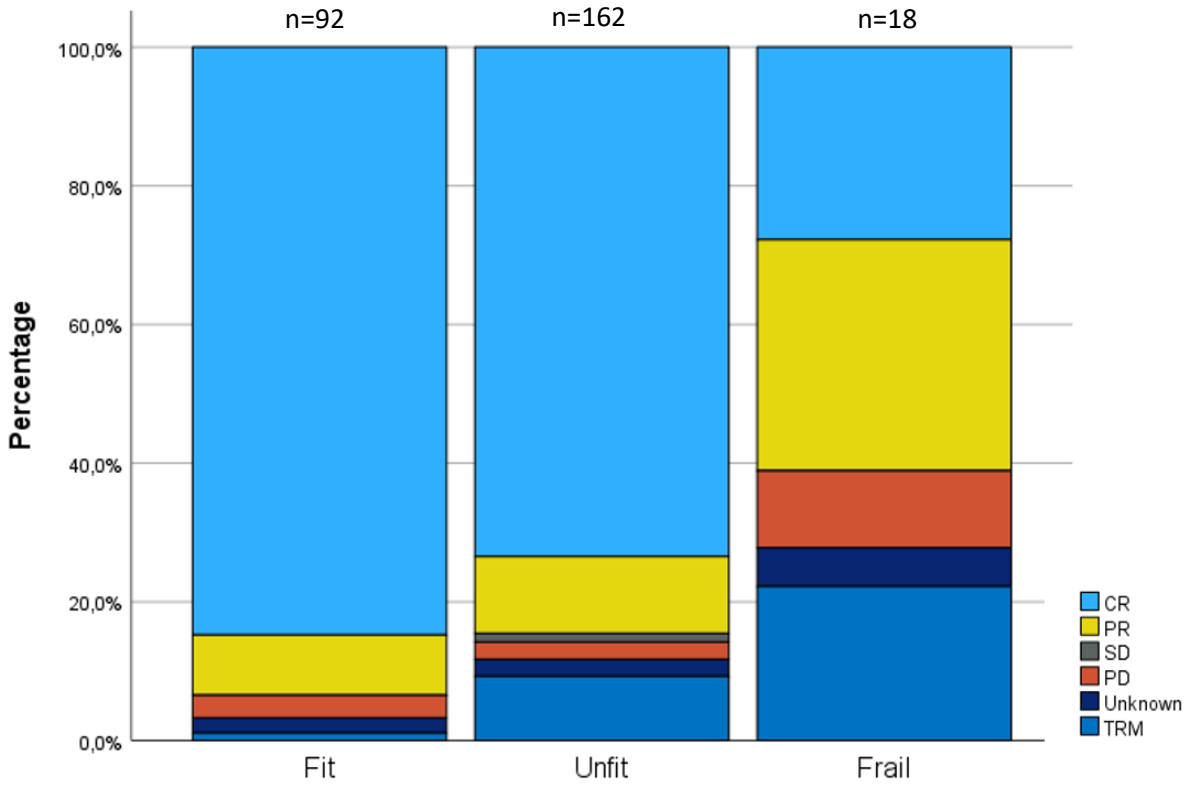
Response rates from primary treatment and treatment related mortality. (A) All patients n=279. (B) Patients with limited disease n=90. (C) Patients with advanced diseased n=189.

Abbreviations: CR: complete response; PD: progression of disease; PR: partial response; SD: stable disease; TRM: treatment-related mortality.



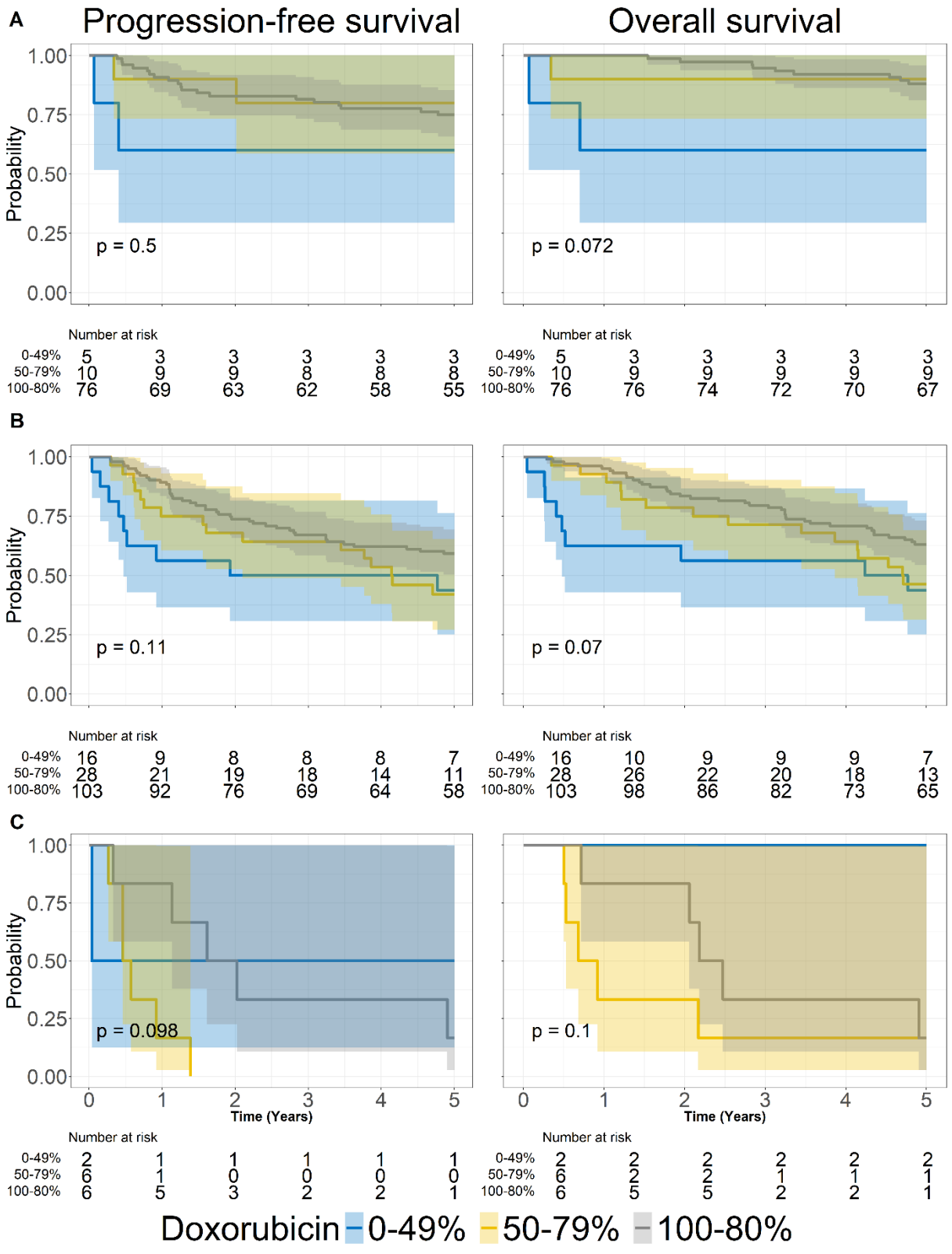
Supplementary Figure S4: Progression-free and overall survival.

(A) In all patients. (B) Patients with limited. (C) Patients with advanced disease.



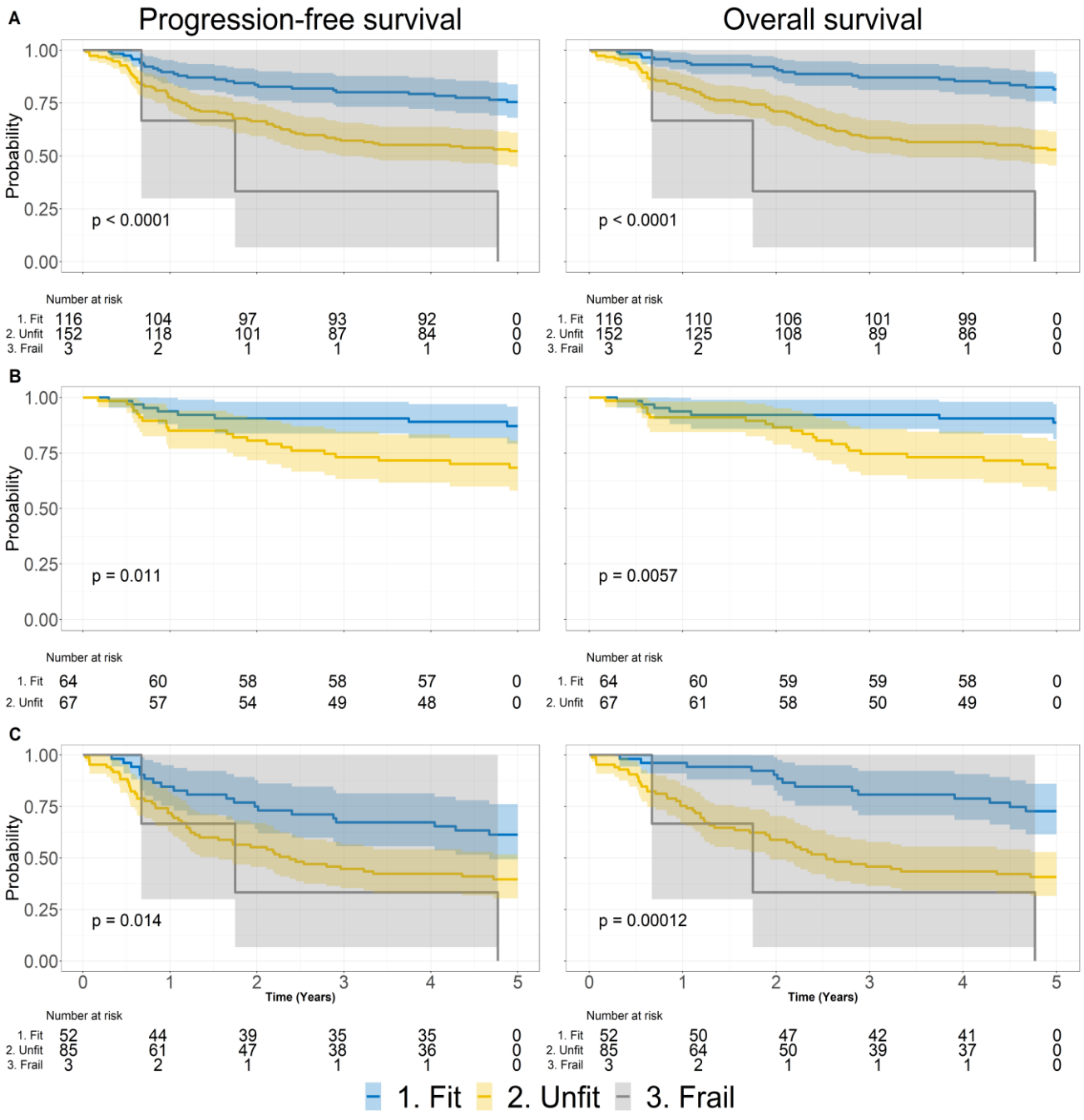
Supplementary Figure S5: Responses to therapy in the different frailty groups. (A) Fit patients. (B) Unfit patients. (C) Frail patients.

Abbreviations: CR: complete response; PD: progression of disease; PR: partial response; SD: stable disease; TRM: treatment-related mortality.



Supplementary Figure S6: Progression-free survival up until 5 years of patients according to frailty score and total dose of doxorubicin

(A) Fit. (B) Unfit. (C) Frail patients.



Supplementary Figure S7: Progression-free and overall survival up until 5 years according to frailty groups in the patients from the validation cohort with complete treatment data. (A) All patients. (B) Patients with limited disease. (C) Patients with advanced disease.