Supplemental material for "A simplified frailty score predicts survival and can aid treatment intensity decisions in older DLBCL patients"

Supplemental methods

Study population

Patients belonging to the uptake area to the Hospital of Southern Norway were not included in the study. This was due to practical reasons concerning travel time when collecting data. Approximately 9% of the patient population living in south-eastern Norway belongs to the uptake area to the Hospital of Southern Norway. This population is not expected to differ from the rest of the population in south-eastern Norway, or the rest of Norway.

Twelve patients were excluded from the study due to missing follow-up data for progression-free survival and treatment-related mortality because they moved to a hospital not included in the study during initial diagnostic work-up or initial treatment, or due to technical difficulties accessing clinical records for these patients. Fifty-one patients were excluded due to diagnosis after death. Of these, 16 were diagnosed at autopsy while 35 patients died during or shortly after diagnostic work-up, before the biopsy results were available. None of the patients had started treatment with chemotherapy. We excluded these patients as we thought it would be clinically most relevant to estimate the expected survival time for patients who are alive when they get the diagnosis. Additionally, we wanted to limit the "no chemotherapy" treatment group to patients where an active treatment decision of no chemotherapy had been made.

Definition of treatment groups

Doxorubicin was used to define the R-CHOP dose, as it is considered a key component, and dose reduction of cyclophosphamide is seldom done without a concurrent reduction in doxorubicin. The initial dosage of doxorubicin was used to define the treatment intensity, rather than the mean dose per course or accumulated dose. Dose reductions during therapy may have many causes like toxicity and disease progression, especially in older patients. Using the mean dose per course or accumulated dose would likely create a selection bias where a poor prognostic group of patients who experience toxicity, disease progression or death during treatment are placed in the attenuated R-CHOP group. For decision making, the intended dose was thus chosen as the preferred registration.

The cutoff for attenuated R-CHOP was set at an initial dosage of doxorubicin ≤80% of standard dose (50 mg/m^2) based on cutoffs used in similar studies, clinical reasoning and distribution of dose reductions in our cohort. The majority of dose reductions in our cohort were given at an initial dosage of 75-80%, while a minor group of patients received an initial dosage of 60-70% or ≤50%.

Initial dosage of R-CHOP in patients that received dose reductions in the total cohort

Initial dosage of R-CHOP (%)	Frequency (%)
25	1 (0.5%)
40	1 (0.5%)
50	51 (26.2%)
60	7 (3.6%)
65	4 (2.1%)
70	6 (3.1%)
75	73 (37.4%)
80	33 (16.9%)
85	5 (2.6%)
90	8 (4.1%)
95	6 (3.1%)
Total	195 (100%)

We considered 80% a suitable cutoff to create a sufficiently large attenuated R-CHOP group (176 patients, 22% of all patients in the total cohort). This cutoff was also consistent with definition of attenuated R-CHOP in similar studies.[1-5]

Anthracycline-free regimens included all chemotherapy regimens without anthracycline, including R-COP and trofosfamid (Ixotene®), and the no chemotherapy group included radiotherapy, rituximab, steroids or no treatment. We separated the no chemotherapy group from the anthracycline-free chemotherapy group to allow for a more rational comparison between anthracycline-free chemotherapy and R-CHOP.

Definition of heart disease

For the definition of heart disease we included heart failure, coronary artery disease, cardiac arrhythmia, operated valve disease and an implanted pacemaker. Heart failure was registered as present if a diagnosis of heart failure was documented in clinical records or if there was clinical

or radiological signs of heart failure (ejection fraction <50% measured with echocardiography or multigated acquisition (MUGA) scan) at diagnosis. Coronary artery disease included prior myocardial infarction, percutaneous coronary intervention, bypass surgery and angina pectoris. Cardiac arrhythmia included atrial fibrillation and atrial flutter, while atrioventricular block and sick sinus syndrome was not included. Valve disease was only scored if operated.

Outcome variables

Date of diagnosis was defined as the day the diagnosis was confirmed by the pathologist. Date of relapse or progression was retrieved from clinical records and defined as the date when there was a biopsy-confirmed relapse/progression, radiological findings or a strong clinical suspicion of progression, whichever came first. Treatment-related mortality was registered based on review of medical records and defined as death 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 documented in the clinical records as likely a result of long term toxicity.

Statistical analysis

The assumption of proportional hazard in Cox regression analyses was tested with the use of Schoenfeld residuals. Missing values were assumed to be missing at random (MAR). Sensitivity analyses in the form of E-values were calculated to identify the minimum strength of association a potential unmeasured confounder would need to have with both treatment and outcome to change the observed associations between treatment intensity and survival.[6]

Frailty score development

Aim of the frailty score

To create a robust and generalizable frailty score, we aimed at incorporating existing evidence and clinical reasoning in the model development. Our aim was to create a simplified frailty score that could classify patients into three frailty groups, fit, unfit and frail, based on key elements of a geriatric assessment (GA) that can be scored with high quality from data routinely collected in clinical practice. The definition of fit would relate to likely tolerance of full-dose R-CHOP.

Division into a training and validation cohort

To allow for a temporal validation,[7] the study cohort was divided into a training and validation cohort based on time of diagnosis. A temporal validation is by the TRIPOD guidelines[7] considered an external or an intermediary between internal and external validation.

Selection of candidate GA variables and their cutoffs

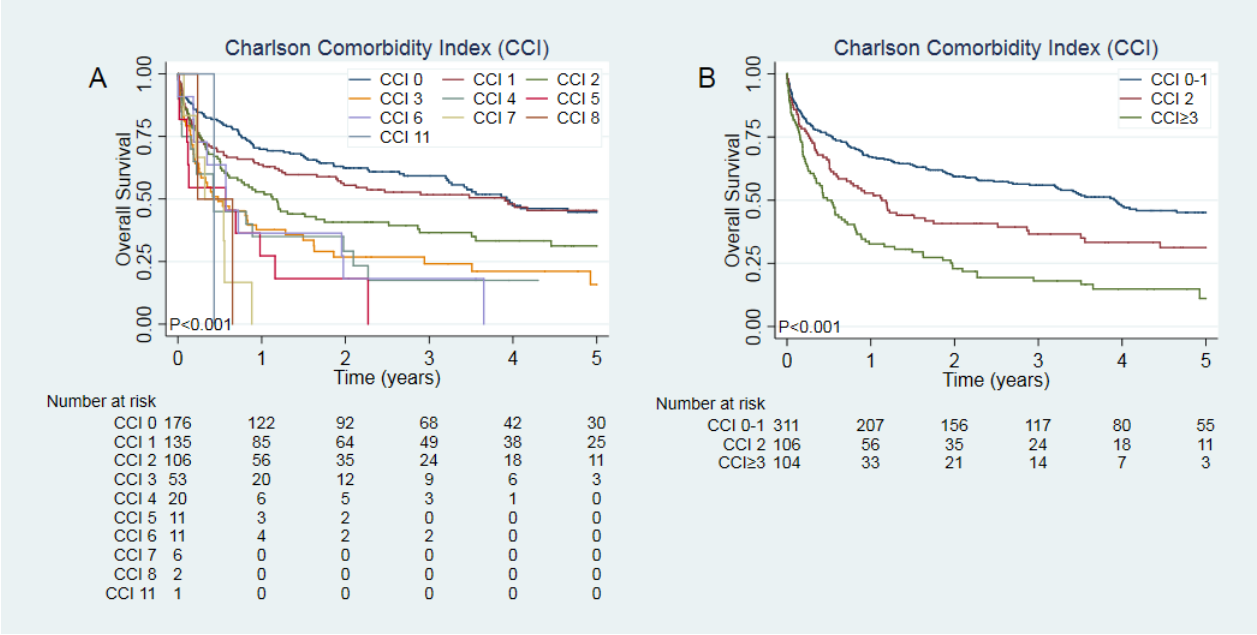
Functional status, comorbidity, nutrition and chronological age are all key elements of a GA[8,9] that have also shown prognostic significance in hematological malignancies,[10] and candidate GA variables were selected to cover these elements. As there is no gold standard on the best instrument to measure the different domains, we used instruments that are validated in cancer patients and possible to score with high quality from data registered in medical records. For functional status, we thus chose a modified version of the Katz Activities of Daily Living (ADL).[11] For comorbidity, we chose the Charlson Comorbidity Index (CCI),[12] as this is the most validated score in cancer patients. For the current paper, the diagnosis of lymphoma was excluded from the score. For nutritional status, we collected data on BMI, albumin and the Geriatric Nutritional Risk Index (GNRI).[13] The GNRI (calculated from body weight, height and albumin) is an adaption to elderly of the well-known Nutritional Risk Index,[14] and has shown prognostic significance in cancer patients, including older DLBCL patients.[15,16]

The cutoff for age as a frailty indicator was set at 85 years based on review of the literature. The prevalence of clinical frailty has been described to increase sharply after 85 years,[17] and this cutoff has been suggested as a frailty indicator in the literature,[18 9] and in expert papers on older DLBCL patients.[19] The cutoff is also in line with clinical experience that few patients over 85 years will tolerate full-dose R-CHOP treatment.

In the modified version of ADL, we scored patients as "dependent" if they had limitations in any of the six categories, lived in an institution or received help from home nursing. The rationale for this cutoff was based on recommendation in the literature where any limitation in ADL can be seen as a frailty indicator,[9] and again the feasibility to score it with high quality based on information in medical records.

The cutoffs for CCI (0-1, 2, ≥3) were based on clinical reasoning and distribution of the score in the training cohort. With these cutoffs we had three sufficiently large groups (60%, 20% and 20%), with a not too strict definition for no/mild comorbidity (0-1) in this older cohort. The grouping was then examined for associations with overall survival (OS) in the training cohort to evaluate its suitability, showing three groups with significantly different OS.

Overall survival in the training cohort for (A) all Charlson Comorbidity Index (CCI) scores, and for (B) CCI with chosen cutoffs (0-1, 2, ≥3)



For GNRI, we used the cutoffs proposed in the original study.[13] However, based on clinical reasoning, we considered only a moderate or severe risk of malnutrition as a frailty indicator. Thus, we analyzed GNRI as a 3-group score with absent/low risk as the reference group. The cutoff for albumin (<36 g/L) was chosen based on cutoffs used in similar studies.[20,21] For BMI, we used the groups defined by the WHO (underweight: BMI <18.5 kg/m^2, normal weight: BMI, 18.5 to <25 kg/m^2, overweight: BMI, 25 to <30 kg/m^2, and obese: BMI ≥30 kg/m^2). As the underweight group only consisted of 3% of the patients and the obese group approximately 15%, we decided to use a binary cutoff at 25 kg/m2, in line with previous studies. [22-24]

Model development

The frailty model was built by including all candidate variables, with the defined cutoffs, in a multivariate Cox regression analysis for OS in the training cohort. As nutritional status and functional status could be affected by lymphoma aggressiveness, we adjusted the model for IPI-score. Variables were then removed in a backward stepwise selection process with a 5% significance level as stopping criteria. BMI and albumin were removed stepwise due to non-significance, and the final model consisted of ADL, CCI, Age ≥85 years and GNRI, as shown in Table 2 in the manuscript. Follow-up was limited to 2 years for GNRI to obtain proportional hazard, otherwise follow-up was limited to 5 years. Further details on the final model are described in the results section of the manuscript.

Supplemental references

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Supplemental Tables

Supplemental Table 1. Patient baseline characteristics for 747 patients in the total cohort, divided by frailty group

Characteristics	Fit (n=228) (31%)	Unfit (n =265) (35%)	Frail (n=254) (34%)	*P*
Age, years				**<0.001**
Median (range)	76 (70-84)	78 (70-94)	83 (70-100)	
70-74 years	90 (40%)	80 (30%)	28 (11%)	
75-79 years	85 (37%)	79 (30%)	46 (18%)	
80-84 years	53 (23%)	74 (28%)	74 (29%)	
≥85 years	0 (0%)	32 (12%)	106 (42%)	
Sex				0.320
Female	117 (51%)	120 (45%)	129 (51%)	
Male	111 (49%)	145 (55%)	125 (49%)	
Stage (Ann Arbor)				**0.004**
I-II	121 (53%)	105 (40%)	100 (40%)	
III-IV	107 (47%)	159 (60%)	151 (60%)	
Missing	0	1	3	
LDH				**<0.001**
Normal	143 (63%)	109 (42%)	72 (32%)	
Elevated	85 (37%)	153 (58%)	152 (68%)	
Missing	0	3	30	
ECOG PS				**<0.001**
0-1	191 (84%)	136 (53%)	40 (16%)	
≥ 2	36 (16%)	120 (47%)	204 (84%)	
Missing	1	9	10	
Extranodal sites				0.037
0-1	187 (82%)	203 (77%)	181 (72%)	
≥ 2	41 (18%)	61 (23%)	70 (28%)	
Missing	0	1	3	
IPI-score				**<0.001**
Low (1)	81 (36%)	46 (18%)	13 (6%)	
Low-intermediate (2)	63 (28%)	50 (20%)	33 (15%)	
High-intermediate (3)	53 (23%)	71 (28%)	58 (26%)	
High (4-5)	30 (13%)	86 (34%)	116 (53%)	
Missing	1	12	34	
ADL				**<0.001**
Independent	228 (100%)	236 (89%)	69 (27%)	
Dependent	0 (0%)	29 (11%)	185 (73%)	
Missing	0	0	0	
CCI				**<0.001**
0-1	228 (100%)	129 (49%)	100 (39%)	

2	0 (0%)	94 (35%)	46 (18%)	
≥3	0 (0%)	42 (16%)	108 (43%)	
Missing	0	0	0	
GNRI				**<0.001**
Absent/Low	228 (100%)	157 (59%)	48 (23%)	
Moderate	0 (0%)	80 (30%)	79 (38%)	
Severe	0 (0%)	28 (11%)	81 (39%)	
Missing	0	0	46	
Treatment regimen				**<0.001**
R-CHOP-like*	214 (94%)	192 (72%)	63 (25%)	
R-CHOP>80%	172 (75%)	113 (43%)	15 (6%)	
R-CHOP≤80%	42 (18%)	78 (30%)	48 (19%)	
Missing	0	1	0	
Anthracycline-free regimen **	8 (3.5%)	46 (17%)	81 (32%)	
No chemotherapy	6 (2.6%)	27 (10%)	110 (43%)	

NOTE. Boldface indicates significance. Abbreviations: LDH: lactate dehydrogenase; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; ADL, Activities of daily living; CCI, Charlson comorbidity index; GNRI, Geriatric Nutritional Risk Index *Includes 3 patients treated with R-CHP, 5 patients treated with EPOCH and 1 with GMALL2002 regimen. **All chemotherapy regimens without anthracycline. Pearson's chi-squared test was used to compare all categorical variables.

Supplemental Table 2. Mortality risk associated with frailty groups for patients that received chemotherapy in the training and validation cohort, unadjusted and adjusted for IPI-score, stage, age group and ECOG PS.

	Training cohort, patients receiving chemotherapy				Validation cohort, patients receiving chemotherapy			
	2-year OS		2-year PFS		2-year OS		2-year PFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Frailty group, unadjusted								
Fit	1		1		1		1	
Unfit	4.53 (2.70-7.58)	**<0.001**	3.81 (2.42-6.02)	**<0.001**	3.02 (1.77-5.13)	**<0.001**	3.07 (1.85-5.10)	**<0.001**
Frail	12.0 (7.09-20.2)	**<0.001**	9.39 (5.89-15.0)	**<0.001**	6.56 (3.84-11.2)	**<0.001**	6.41 (3.82-10.8)	**<0.001**
Frail vs unfit	2.64 (1.90-3.68)	**<0.001**	2.46 (1.78-3.40)	**<0.001**	2.18 (1.42-3.33)	**<0.001**	2.09 (1.38-3.16)	**<0.001**
Frailty group, adjusted*								
Fit	1		1		1		1	
Unfit	2.72 (1.57-4.70)	**<0.001**	2.28 (1.39-3.72)	**0.001**	2.79 (1.55-5.03)	**0.001**	3.01 (1.70-5.31)	**<0.001**
Frail	4.60 (2.44-8.66)	**<0.001**	3.51 (1.95-6.33)	**<0.001**	4.61 (2.36-9.00)	**<0.001**	4.87 (2.53-9.35)	**<0.001**
Frail vs unfit	1.69 (1.14-2.52)	**0.009**	1.54 (1.04-2.28)	**0.031**	1.65 (1.01-2.71)	**0.048**	1.62 (1.00-2.61)	**0.049**

Univariate and multivariate cox regression analysis with hazard ratio (HR) for 2-year OS and 2-year PFS. *Adjusted for all IPI groups (IPI 1, 2, 3 and 4-5), all stages (I, II, III and IV), four age groups (70-74 years, 75-79 years, 80-84 years and ≥85 years) and ECOG PS (0, 1, 2, 3 and 4). All patients in the cohorts that could be classified into a fraily group and had received chemotherapy were included in the analyses (n=398 in the training cohort, n=206 in the validation cohort). Patients that did not receive chemotherapy were excluded from the analyses. This was done to evaluate the prognostic and discriminative power of the frailty grouping in patients that were candidates for chemotherapy, and to avoid exaggerated HR for the frail group due to this poor prognostic group. Missing values were imputed with multiple imputation by chained equations. Follow-up was limited to 2 years to obtain proportional hazard for the frail group. Harrell's C Index for 2-year OS was 0.73 for the unadjusted model and 0.79 for the adjusted model in the training cohort, and 0.69 for the unadjusted model and 0.76 for the adjusted model in the validation cohort.

Supplemental Table 3. Mortality risk associated with frailty groups for all patients and R-CHOP treated patients in the total cohort, unadjusted and adjusted for IPI-score, stage, age group and ECOG PS.

	Total cohort			
	2-year OS, all patients		2-year OS, R-CHOP treated	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Frailty group, unadjusted				
Fit	1		1	
Unfit	3.94 (2.76-5.62)	**<0.001**	3.24 (2.18-4.82)	**<0.001**
Frail	11.3 (8.02-16.0)	**<0.001**	7.02 (4.48-11.0)	**<0.001**
Frail vs unfit	2.88 (2.32-3.58)	**<0.001**	2.16 (1.50-3.13)	**<0.001**
Frailty group, adjusted*				
Fit	1		1	
Unfit	2.53 (1.74-3.68)	**<0.001**	2.28 (1.48-3.50)	**<0.001**
Frail	4.36 (2.88-6.61)	**<0.001**	4.14 (2.36-7.25)	**<0.001**
Frail vs unfit	1.72 (1.33-2.23)	**<0.001**	1.82 (1.18-2.80)	**0.007**

Univariate and multivariate cox regression analysis with hazard ratio (HR) for 2-year OS. *Adjusted for all IPI groups (IPI 1, 2, 3 and 4-5), all stages (I, II, III and IV), four age groups (70-74 years, 75-79 years, 80-84 years and ≥85 years) and ECOG PS (0, 1, 2, 3 and 4). All patients in the total cohort that could be classified into a frailty group were included in the analyses for all patients (n=747), and all patients that could be classified into a frailty group and had received R-CHOP were included in the analyses for R-CHOP treated patients (n=469). Missing values were imputed with multiple imputation by chained equations. Follow-up was limited to 2 years to obtain proportional hazard for the frail group. Harrell's C Index for 2-year OS for the model with all patients was 0.73 for the unadjusted analysis and 0.79 for the adjusted analysis. Harrell's C Index for 2-year OS for the model with only R-CHOP treated patients was 0.69 for the unadjusted analysis and 0.75 for the adjusted analysis.

Supplemental Table 4. Patient baseline characteristics for fit patients that received full-dose R-CHOP vs attenuated R-CHOP.

Characteristics	R-CHOP>80%, N=172 (%)	R-CHOP≤80%, N=42 (%)	*P*
Age, years			**<0.001**
Median (range)	75 (70-83)	79 (71-84)	
70-74 years	86 (50%)	4 (10%)	
75-79 years	65 (38%)	18 (43%)	
80-84 years	21 (12%)	20 (48%)	
≥85 years	0 (0%)	0 (0%)	
Sex			0.122
Female	82 (48%)	26 (62%)	
Male	90 (52%)	16 (38%)	
Stage (Ann Arbor)			0.734
I-II	89 (52%)	23 (55%)	
III-IV	83 (48%)	19 (45%)	
Missing	0	0	
ECOG PS			**<0.001**
0-1	154 (90%)	27 (64%)	
≥ 2	17 (10%)	15 (36%)	
Missing	1	0	
IPI-standard			0.476
Low-intermediate (1-2)	110 (64%)	24 (57%)	
High-intermediate (3-5)	61 (36%)	18 (43%)	
Missing	1	0	
Heart disease*			**0.006**
No	133 (77%)	23 (55%)	
Yes	39 (23%)	19 (45%)	
Heart failure	1 (1%)	0 (0%)	1.000
Coronary artery disease	24 (14%)	12 (29%)	
Cardiac arrhythmia	16 (9%)	10 (24%)	
Valve disease, operated	1 (1%)	1 (2%)	
Pacemaker	4 (2%)	0 (0%)	
Missing	0	0	

NOTE. Boldface indicates significance. Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index. *Further described in supplemental methods. Fisher's exact test was used to compare all categorical variables.

Supplemental Table 5. Cumulative incidence of treatment-related mortality (TRM) associated with different treatment intensity in fit, unfit and frail patients, unadjusted and adjusted for IPI-score, stage, sex and time-period

	Fit patients		Unfit patients		Frail patients	
	2-year cumulative incidence TRM		2-year cumulative incidence TRM		2-year cumulative incidence TRM	
Variables	**SHR (95% CI)**	***P***	**SHR (95% CI)**	***P***	**SHR (95% CI)**	***P***
Treatment, unadjusted						
R-CHOP >80%	1		1		1	
R-CHOP ≤80%	1.83 (0.47-7.14)	0.382	1.06 (0.47-2.39)	0.897	0.82 (0.26-2.52)	0.726
Anthracycline-free regimen	NA	NA	1.45 (0.61-3.44)	0.398	0.39 (0.12-1.26)	0.115
Treatment, adjusted*						
R-CHOP >80%	1		1		1	
R-CHOP ≤80%	1.42 (0.41-4.93)	0.584	1.17 (0.49-2.81)	0.728	0.66 (0.21-2.06)	0.475
Anthracycline-free regimen	NA	NA	1.57 (0.66-3.75)	0.306	0.35 (0.11-1.13)	0.078

Univariate and multivariate cox regression model for 2-year cumulative incidence of treatment-related mortality (TRM). *Adjusted for all levels of IPI-score, all stages, sex and time-period (2006-2011 vs 2012-2016). Analyses are performed on the total cohort and stratified for fit, unfit and frail patients. Only patients that received chemotherapy are included in the analysis and follow-up time is limited to 2 years. Missing values are imputed with multiple imputation by chained equations, except for 1 patient in the unfit group with missing R-CHOP dosage. NA: Not applicable: 2-year cumulative incidence of TRM not calcualted for the fit group due to a small number of patients in this group (8) and no TRM.

Supplemental Table 6. Patient baseline characteristics for unfit patients that received full-dose R-CHOP, attenuated R-CHOP and anthracycline-free regimen

Characteristics	R-CHOP>80%, N=113 (%)	R-CHOP≤80%, N=78 (%)	Anthracycline-free, N=46 (%)	R-CHOP>80% vs R-CHOP≤80%, *P*	R-CHOP≤80% vs anthracycline-free, *P*
Age, years				**<0.001**	**0.013**
Median (range)	74 (70-85)	80 (70-89)	82 (70-90)		
70-74 years	57 (50%)	14 (18%)	4 (9%)		
75-79 years	45 (40%)	25 (32%)	6 (13%)		
80-84 years	10 (9%)	31 (40%)	25 (54%)		
≥85 years	1 (1%)	8 (10%)	11 (24%)		
Sex				0.768	0.355
Female	49 (43%)	32 (41%)	23 (50%)		
Male	64 (57%)	46 (59%)	23 (50%)		
Stage (Ann Arbor)				**0.032**	0.450
I-II	34 (30%)	36 (46%)	17 (38%)		
III-IV	79 (70%)	42 (54%)	28 (62%)		
Missing	0	0	1		
ECOG PS				1.000	0.129
0-1	63 (56%)	41 (56%)	18 (41%)		
≥ 2	49 (44%)	32 (44%)	26 (59%)		
Missing	1	5	2		
IPI-score				0.531	1.000
Low-intermediate (1-2)	38 (34%)	28 (39%)	16 (37%)		
High-intermediate (3-5)	74 (66%)	44 (61%)	27 (63%)		
Missing	1	6	3		
CCI				0.672	0.445
Score 0-1	49 (43%)	36 (46%)	26 (57%)		
Score 2	42 (37%)	31 (40%)	13 (28%)		
Score ≥3	22 (19%)	11 (14%)	7 (15%)		
Missing	0	0	0		
Heart disease*				0.125	**0.041**
No	79 (70%)	46 (59%)	18 (39%)		
Yes	34 (30%)	32 (41%)	28 (61%)		
Heart failure	9 (8%)	10 (13%)	11 (24%)	0.328	0.139
Coronary artery disease	21 (19%)	23 (30%)	15 (33%)		
Cardiac arrhythmia	14 (12%)	12 (15%)	17 (37%)		
Valve disease, operated	2 (2%)	1 (1%)	4 (9%)		
Pacemaker	3 (3%)	1 (1%)	3 (7%)		
Missing	0	0	0		

NOTE. Boldface indicates significance. Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; CCI: Charlson comorbidity index. *Further described in supplemental methods. Fisher's exact test was used to compare all categorical variables.

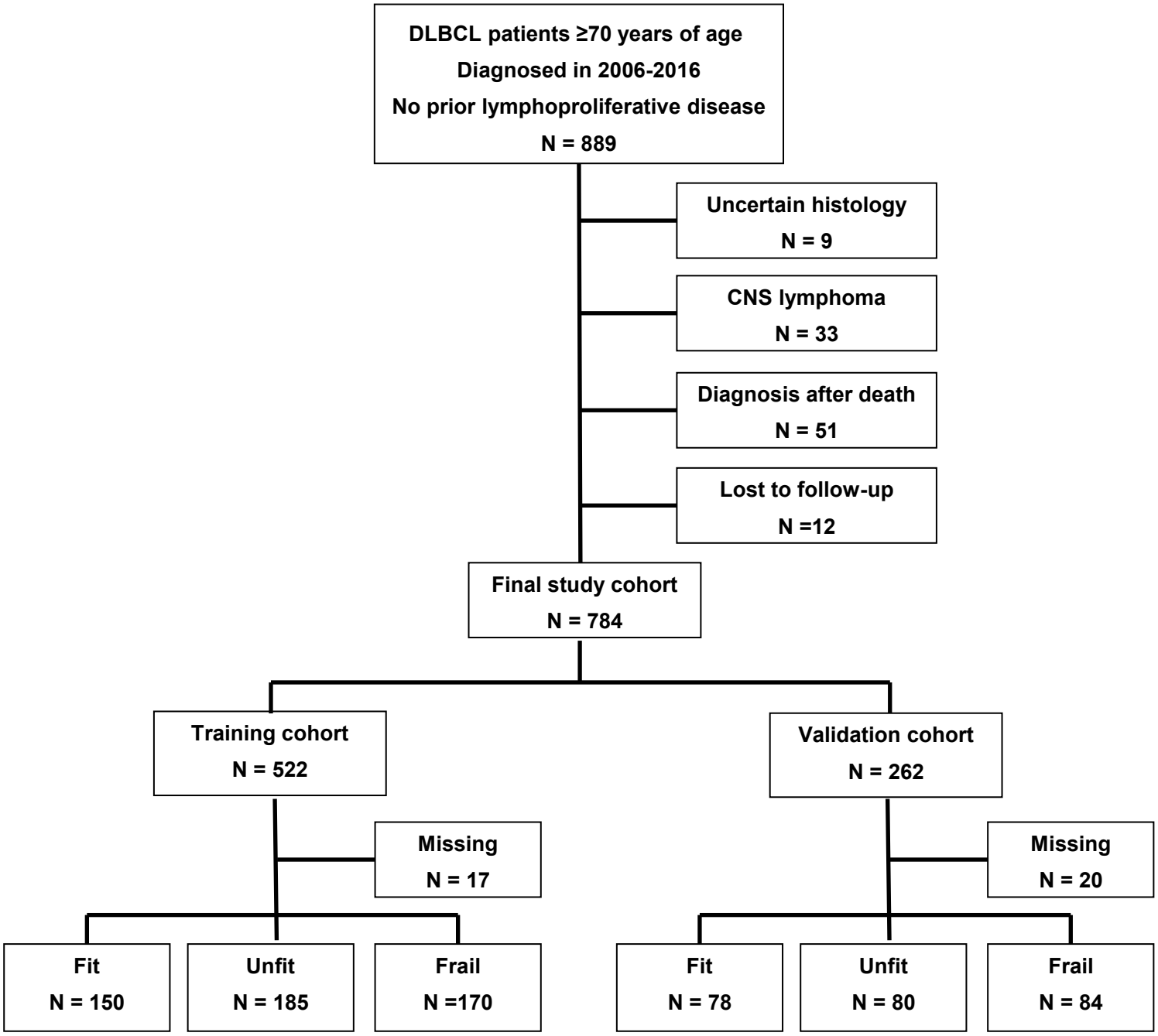
Supplemental Table 7. Patient baseline characteristics for frail patients that received R-CHOP vs an anthracycline-free regimen

Characteristics	R-CHOP, N=63 (%)	Anthracycline-free, N=81 (%)	*P*
Age, years			
Median (range)	78 (70-91)	84 (70-92)	**<0.001**
70-74 years	16 (25%)	7 (9%)	
75-79 years	21 (33%)	14 (17%)	
80-84 years	16 (25%)	24 (30%)	
≥85 years	10 (16%)	36 (44%)	
Sex			0.615
Female	33 (52%)	38 (47%)	
Male	30 (48%)	43 (53%)	
Stage (Ann Arbor)			0.720
I-II	22 (35%)	25 (31%)	
III-IV	41 (65%)	56 (69%)	
Missing	0	0	
ECOG PS			0.200
0-1	15 (24%)	12 (15%)	
≥ 2	47 (76%)	67 (85%)	
Missing	1	2	
IPI-score			0.498
Low-intermediate (1-2)	12 (21%)	12 (16%)	
High-intermediate (3-5)	45 (79%)	64 (84%)	
Missing	6	5	
CCI			0.545
Score 0-1	29 (46%)	32 (40%)	
Score 2	11 (17%)	12 (15%)	
Score ≥3	23 (37%)	37 (46%)	
Missing	0	0	
GNRI			0.294
Absent/Low	8 (13%)	17 (24%)	
Moderate	29 (48%)	29 (41%)	
Severe	24 (39%)	25 (35%)	
Missing	2	10	
Heart disease*			**<0.001**
No	37 (59%)	24 (30%)	
Yes	26 (41%)	57 (70%)	
Heart failure	7 (11%)	32 (40%)	**<0.001**
Coronary artery disease	15 (24%)	36 (44%)	
Cardiac arrhythmia	14 (22%)	35 (43%)	
Valve disease, operated	1 (2%)	5 (6%)	

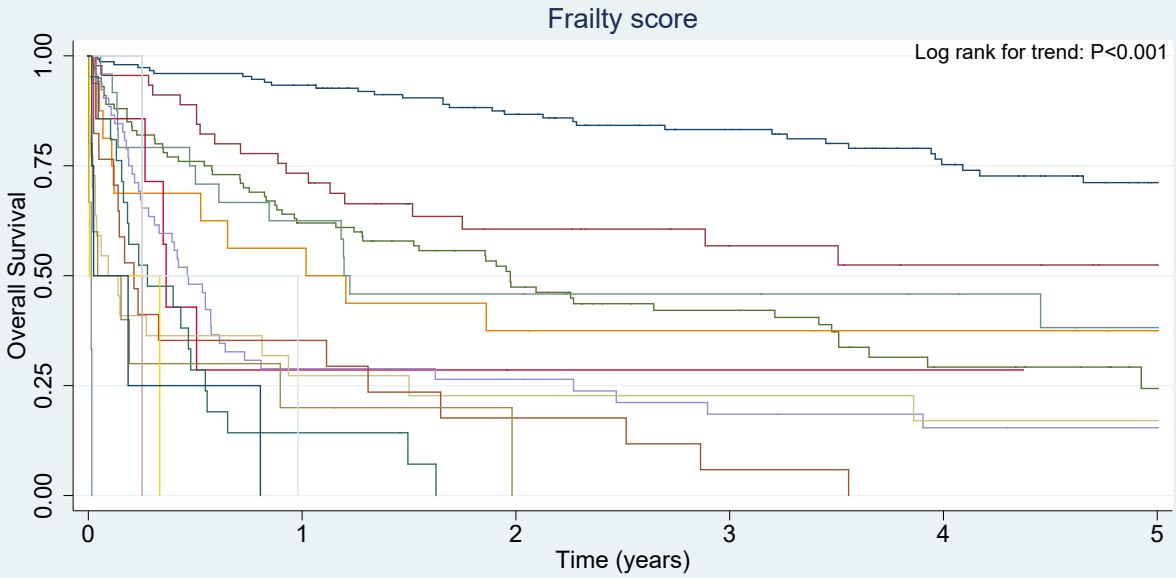
Pacemaker	2 (3%)	4 (5%)
Missing	0	0

NOTE. Boldface indicates significance. Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; CCI: Charlson comorbidity index; GNRI, Geriatric Nutritional Risk Index. *Further described in supplemental methods. Fisher's exact test was used to compare all categorical variables.

Supplemental Figure 1. Flow chart.



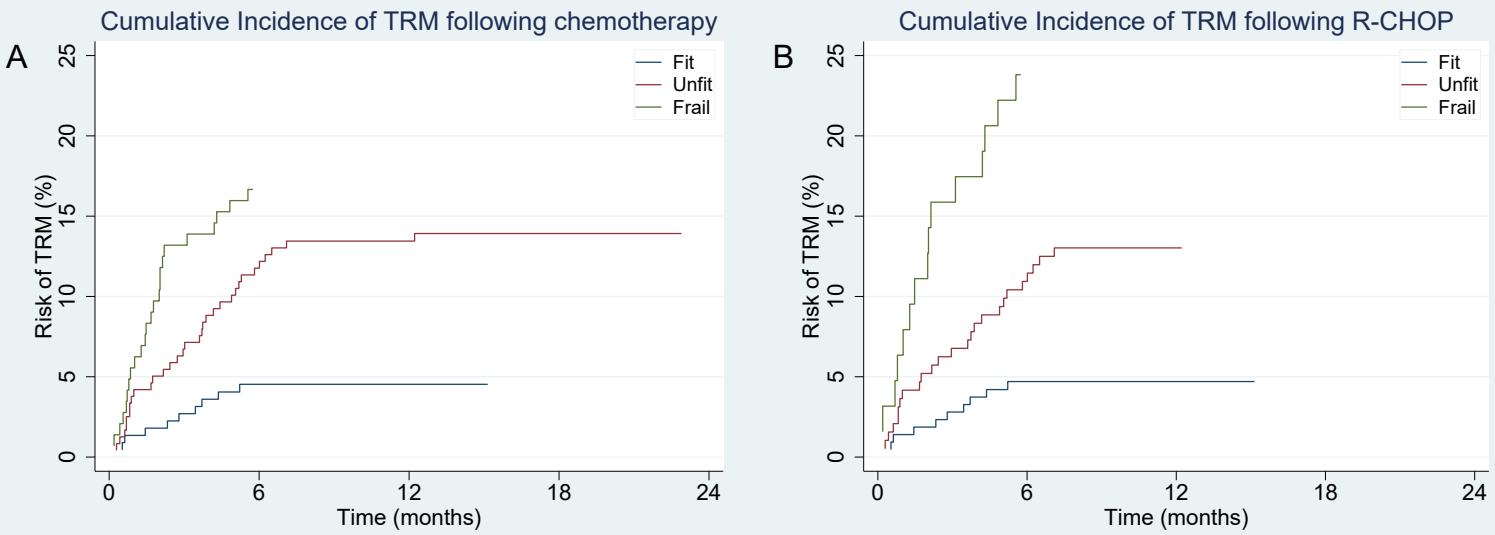
Supplemental Figure 2. Overall survival for patients with frailty score 1 to 20 in the training cohort.



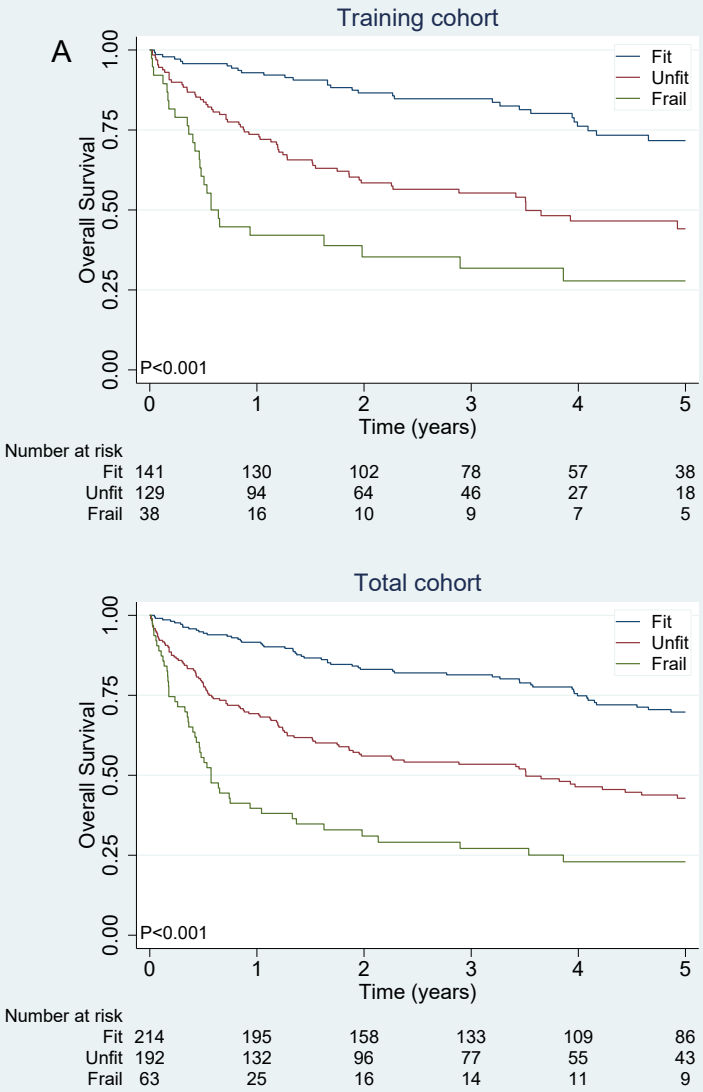
Number at risk

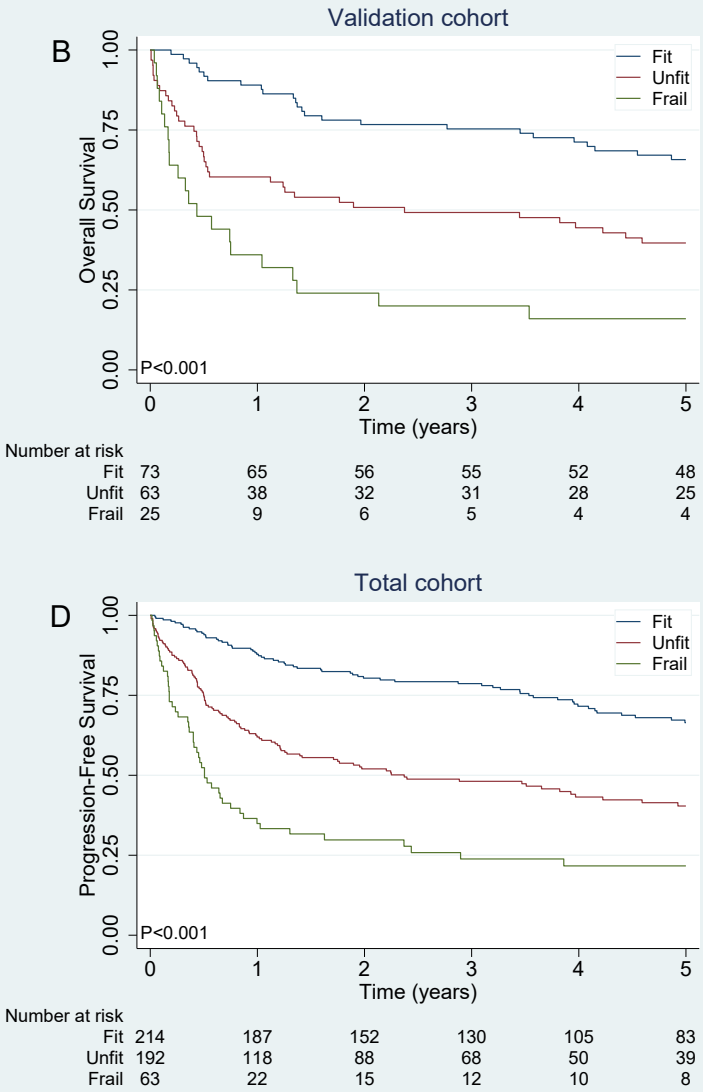
Score 1	150	139	110	83	61	42
Score 1.5	45	33	20	13	10	7
Score 2	100	61	40	28	12	5
Score 2.5	16	9	6	5	4	3
Score 3	24	15	11	9	7	4
Score 3.75	7	2	1	1	1	0
Score 4	52	14	11	7	5	4
Score 5	22	6	5	5	3	3
Score 6	17	6	3	1	0	0
Score 7.5	3	0	0	0	0	0
Score 8	21	3	0	0	0	0
Score 10	10	2	0	0	0	0
Score 12	1	0	0	0	0	0
Score 15	2	0	0	0	0	0
Score 16	2	0	0	0	0	0
Score 20	4	0	0	0	0	0

Supplemental Figure 3. Cumulative incidence of treatment-related mortality (TRM) for fit, unfit and frail patients in the total cohort **(A)** following chemotherapy, and **(B)** following R-CHOP.

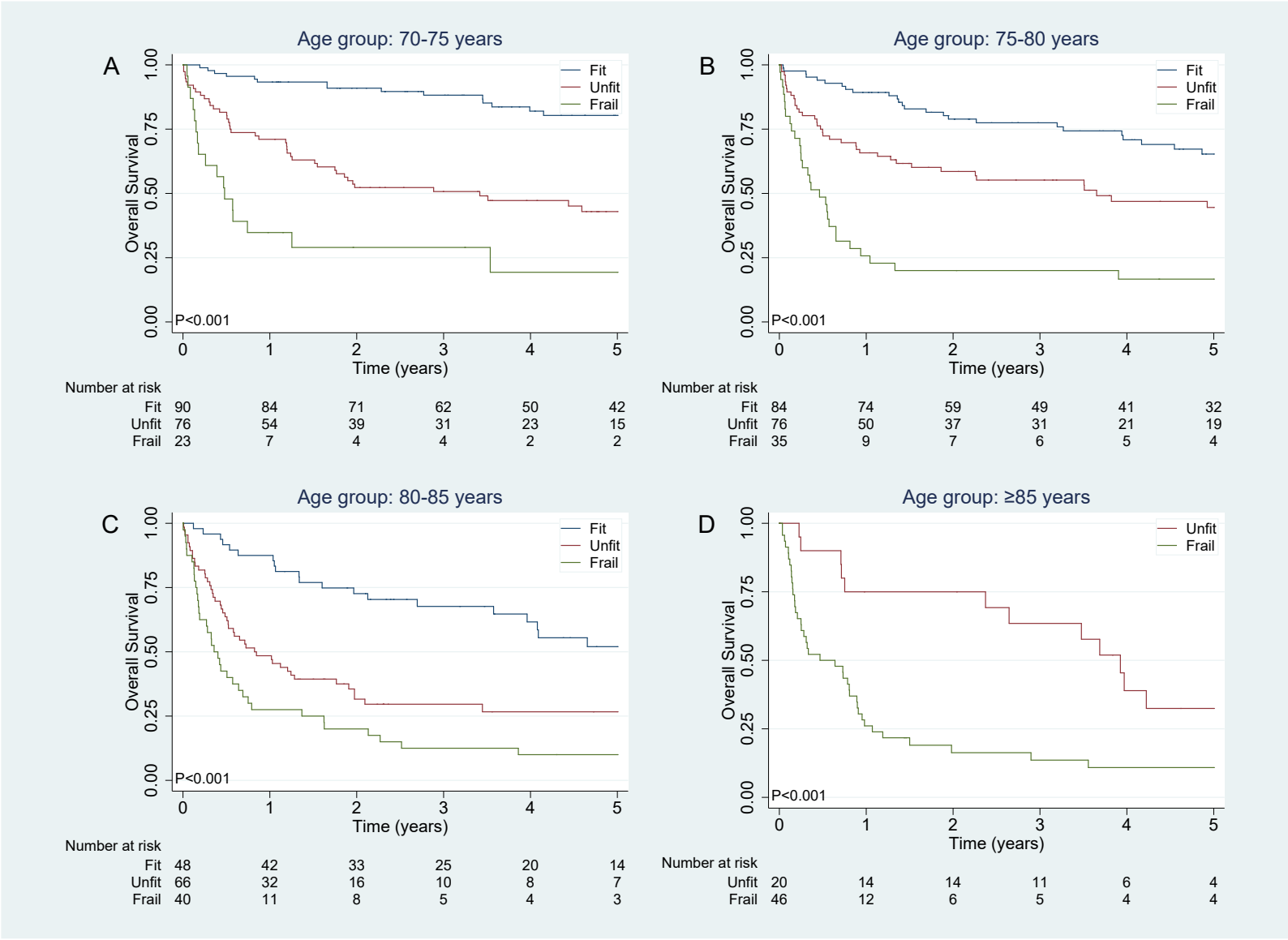


Supplemental Figure 4. Survival by frailty group for patients that received R-CHOP. Overall survival by frailty group in the **(A)** training cohort, **(B)** validation cohort and **(C)** total cohort. **(D)** Progression-free survival by frailty group in the total cohort.

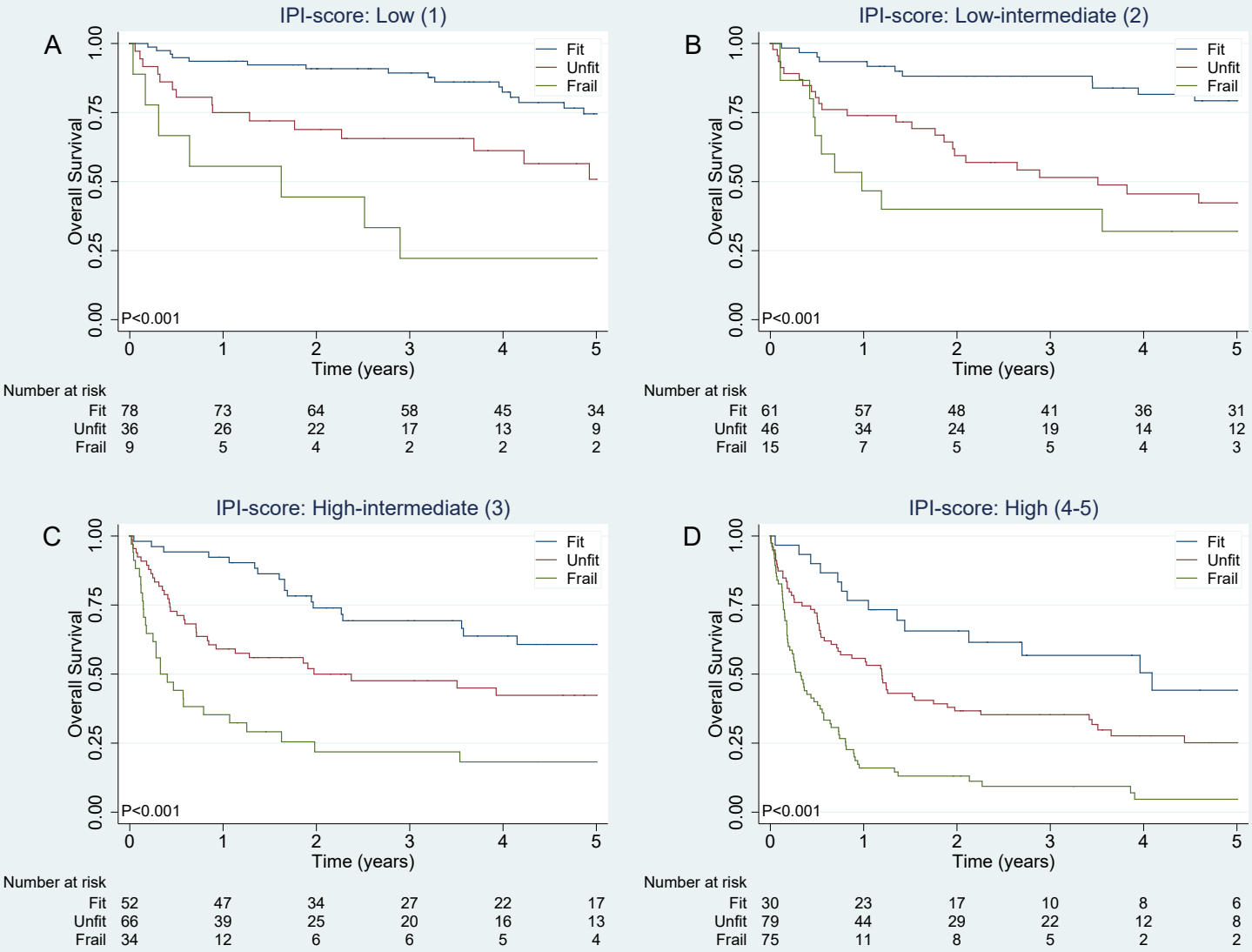




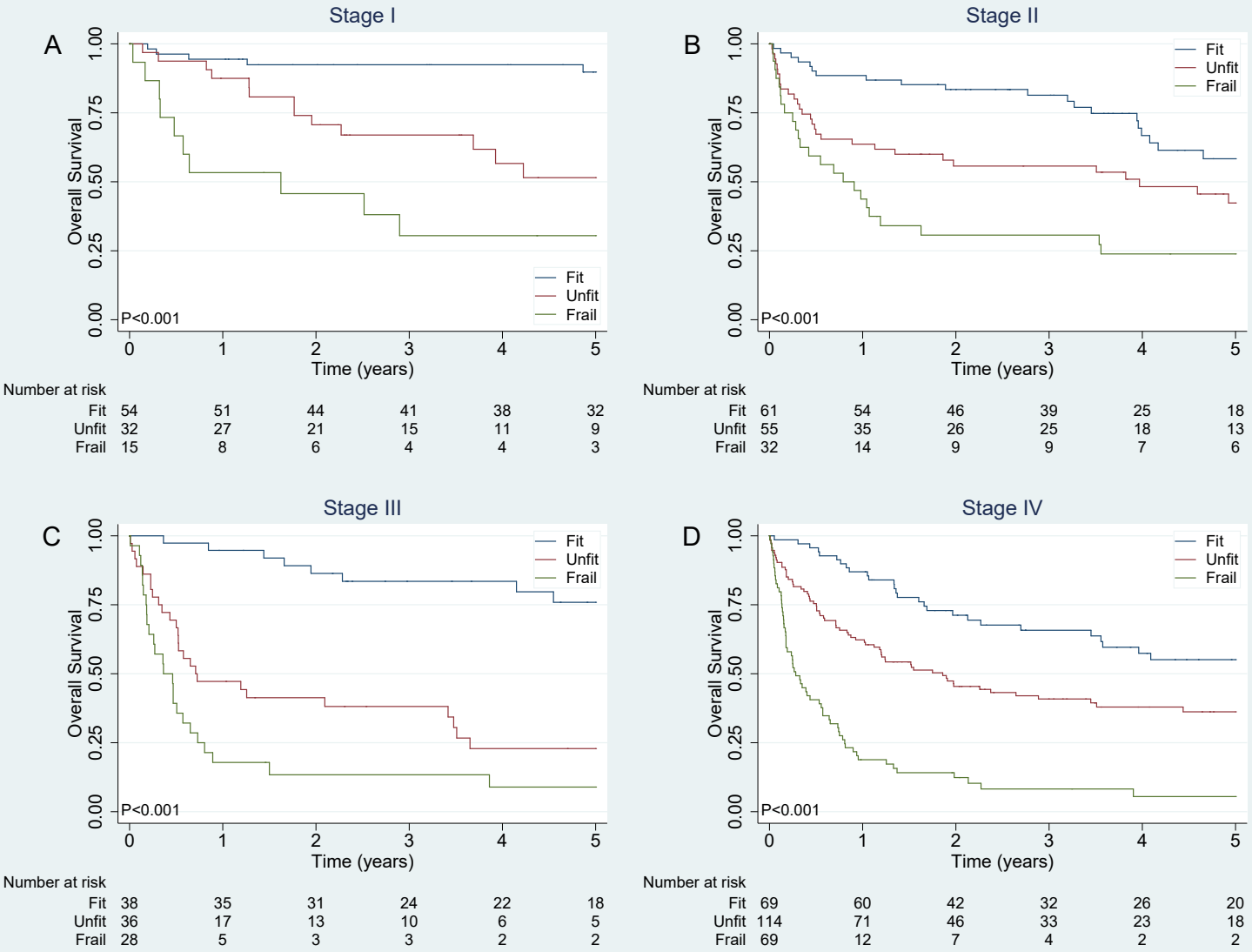
Supplemental Figure 5. Overall survival for fit, unfit and frail patients that received chemotherapy, stratified by age group.



Supplemental Figure 6. Overall survival for fit, unfit and frail patients that received chemotherapy, stratified by IPI-score.



Supplemental Figure 7. Overall survival for fit, unfit and frail patients that received chemotherapy, stratified by stage.



Supplemental Figure 8. **(A)** Overall survival and **(B)** progression-free survival for unfit patients receiving R-CHOP>80%, R-CHOP 70-80% and R-CHOP<70% dosage.