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

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## Abstract

Older patients with classical Hodgkin lymphoma (cHL) have lower tolerance and inferior outcomes after standard chemotherapy regimens. To identify patient-derived indicators of frailty associated with outcome, we retrospectively analyzed patient and disease characteristics, treatment and outcome in a Norwegian population-based cohort of older (≥60 years) patients with cHL diagnosed 2000-2015. We included 279 patients (median age 69 years, range 60-90) treated with curative intent, defined as any typical cHL regimen with ≥50% standard doxorubicin dose in the first cycle. In this Norwegian cohort, treatment-related mortality was 8%, median progression-free survival (PFS) and overall survival (OS) were 7.1 years (95% confidence interval [CI]: 5.0-9.3) and 8.7 years (95% CI: 7.0-10.4), respectively. Multivariable analyses identified patient-derived prognostic factors working independently of stage, histology, and International Prognostic Score. We derived a frailty index ranging from 0-3 with one point each for age ≥70 years, Eastern Cooperative Oncology Group status ≥2, and a Cumulative Illness Rating Scale in Geriatrics score ≥8. Patients were categorized as fit (score 0, 34% of patients), unfit (score 1-2, 60%), and frail (score 3, 7%), with 5-year PFS of 74%, 49%, and 11%, and 5-year OS of 86%, 52%, and 22%, respectively. The proposed frailty score was validated in an external cohort of 792 similarly selected patients from the Swedish Lymphoma Register, where comorbidities were scored based on the Charlson comorbidity index (0-2 *vs*. 3 or higher). In this comprehensive study, we develop a frailty score for elderly cHL patients to inform clinical decisions and prospective trials evaluating selective therapies for older patients.

## Introduction

Despite considerable progress in the treatment of classical Hodgkin lymphoma (cHL) over the last decades, the management of patients with increasing age remains a challenge.[1-3] Compared to younger patients, differences related both to aging itself and lymphoma biology may account for the inferior outcome. Only 20-30% of patients with cHL are over the age of 60 at diagnosis and, historically, these patients have rarely been included in clinical trials.[4] With the recognition of the unmet need of this group, there is now considerable interest in studies specifically aimed at older cHL patients.

There is no consensus as to the optimal chemotherapy for elderly patients with cHL. Most recommendations include anthracycline-based combination regimens, given with or without radiotherapy according to disease extent, as for younger patients.[5-7] Physiological decline with age and underlying comorbidities can result in inter-individual variation in frailty and age-related vulnerability to adverse health outcomes.[3,8,9] For older cHL patients, this may lead to higher and often unpredictable toxicity when administering chemotherapy regimens developed for younger patients. Consequently, dose reductions and loss of tumor control, reduced quality of life, and higher treatment-related mortality may follow. Improved management of older cHL patients needs to address the greater heterogeneity of patients' health status. There are also differences in disease biology and clinical presentation, such as a higher proportion of older patients with adverse histological subtypes, B symptoms, advanced stage, and Epstein Barr Virus positivity in older *versus* younger patients with CHL.[3,7] Over the last decade, novel drugs have been introduced into first-line treatment of younger patients with cHL, primarily brentuximab vedotin (BV) and the checkpoint inhibitors nivolumab and pembrolizumab.[10,11] For older patents included in the SWOG1826 trial, nivolumab with doxorubicin, vinblastine and dacarbazine (N-AVD) showed promising tolerability and effect, as have combinations of BV with other anthracycline-containing backbones.[12-14] These studies, however, included presumably fit older patients. In patients unsuitable for traditional combination chemotherapy, novel agents alone or in combinations without anthracyclines have also been promising, such as the combination of BV and dacarbazine.[15-20] With these innovations becoming more readily available for first-line treatment, we need to better understand which patients will tolerate the traditional anthracycline-based combinations.

Despite the increasing interest in implementing frailty assessment and management in oncology services in general, no standard approaches have been developed for older cHL patients.[21,22] However, geriatric assessment (GA), evaluating somatic, functional and social health domains, has been explored in hematologic malignancies and several screening tools have been proposed for outcome prediction and tailoring of treatment.[8] Several groups have developed GA tools in older patients with diffuse large B-cell lymphoma (DLBCL), where age, level of comorbidities, and functional independence together may predict outcome independently of known disease-derived risk factors.[23,24] Isaksen *et al.*[25] also showed that patients above a certain level of frailty may not benefit from anthracycline-based therapy at full dose.

There is considerable interest in developing similar tools for GA in cHL.[7] However, cHL is a rare disease in older patients compared to DLBCL, so proposed GA scoring systems are mostly derived from smaller patient cohorts and few of them are validated in independent or even prospective cohorts, a limitation relevant also to combinations of novel drugs. To this end, we here use population-based Scandinavian patient cohorts treated with still relevant standard anthracycline-based regimens, often used as the backbone for combinations with newly introduced drugs, to generate and validate a simplified frailty index tool applicable to older cHL patients.

# Methods

## Study design

We performed a retrospective population-based cohort study in patients diagnosed with cHL at age ≥60 years in Norway 2000-2015 (*Online Supplementary Figure S1*).[26] Patients were identified through Cancer Registry of Norway (CRN) and verified by review of original histology reports. Patients alive at study start were given the possibility to refuse to participate (*Online Supplementary Methods*).

We focused on cHL patients with curative-intent treatment consisting of standard anthracycline-containing regimens used for HL with ≥50% of full dose doxorubicin in the first cycle. We excluded patients with composite lymphomas or nodular lymphocyte predominant HL (NLPHL), patients treated with a palliative intent or with anthracycline-free chemotherapy or extended-field irradiation as primary treatment.

From the Swedish Lymphoma Register (SLR),[27] we included an external validation cohort consisting of similar patients aged ≥60 years diagnosed with cHL 2000-2015 (*Online Supplementary Methods* and *Online Supplementary Figure S2*). The study was approved by the Regional Committee for Medical Research Ethics South East Norway (REK 2016/1202).

## Norwegian analysis cohort

Patient-related variables from time of diagnosis included age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS),[28] body mass index (BMI) and smoking habits. Comorbidity was determined by Cumulative Illness Rating Score for Geriatrics (CIRS-G)[29] and dependency of help according to Katz Index of Independence in Activities of Daily Living (ADL).[30] For the latter two parameters, status of the patient before start of lymphoma symptoms was assessed from prior medical records and consideration of the subsequent impact of lymphoma on organ function and self-reliance was minimized as much as possible.

Diagnostic procedures and curative treatment of patients aged ≥60 years followed national guidelines. We recorded histological subtype and disease extent based on computed tomography (CT) scans and bone marrow biopsy, B symptoms, bulky disease (lesion ≥10 cm in largest diameter on CT scans), and relevant blood tests. Patients were grouped according to clinical risk as having limited disease (stage I-IIA) with or without risk factors or advanced disease (stage III-IVB), the latter with assignment of International Prognostic Score (IPS). In brief, treatment was risk-adapted with 2-4 cycles of chemotherapy followed by involved

site radiotherapy for limited disease, and 6 cycles of chemotherapy for advanced disease (*Online Supplementary Methods*).[31]

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 pre-planned number of cycles. Patients with treatment-related mortality (TRM) were excluded from the analysis of total doxorubicin doses.

Tumor response was documented according to Cheson *et al.*[32] TRM was defined as death of any cause during or within three months after treatment not clearly due to cHL (*Online Supplementary Methods*).

### Swedish validation cohort

Swedish guidelines for diagnostic work-up of older cHL patients and treatment are based on anthracycline-containing regimens in line with Norwegian recommendations. Comorbidities were scored with Charlson Comorbidity Index (CCI) based on diagnoses retrieved from the Swedish National Patient Register.[33] The CCI cutoff in analysis was 0-2 *versus* ≥3, and matched the percentile distribution of CIRS-G scores in the Norwegian cohort (*Online Supplementary Methods*).

## Results

### Patients in the training cohort

Of the 279 patients in the Norwegian cohort, the median age was 69 years (range 60-90) (*Online Supplementary Tables S1, S2*). Nodular sclerosis was the most common histology (45%), and the proportion of mixed cellularity was 17%. Presence of B symptoms (49%) or advanced stage disease (68%) was common. Overall, most patients were independent in ADL (85%) and had ECOG PS of 0-1 (77%). Median BMI was 25.2 kg/m$^2$ and median CIRS-G was 6 (range 0-23).

For treatment, cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) was the most often used (79%), followed by doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (19%). The majority (86%) received a doxorubicin dose of ≥80% in the first cycle. Of the 258 (93%) patients evaluable for dose intensity of the full treatment (excluding 21 patients with TRM), median total doxorubicin dose was 100% (range 8-100%) and 73% had a total relative dose ≥80%. Ninety percent of patients with limited disease and 20% with advanced disease were irradiated as part of primary treatment.

### Outcome

Among the 279 patients, 21 (8%) died from TRM and 74% achieved complete response (CR). TRM was 9.4% in ABVD treated patients compared to 6.8% after CHOP. According to age, TRM was 5.8% in patients aged 60-69 years at diagnosis, 6.9% in those aged 70-79 years, and 20% in those ≥80 years of age. Response rates and TRM according to clinical risk group are detailed in *Online Supplementary Table S3* and *Online Supplementary Figure S3*. With a median follow-up for surviving patients of 9.4 years (range 4.7-21.5) in the whole cohort, median PFS was 7.1 years (95% confidence interval [CI]: 5.0-9.3), and OS was 8.7 years (95% CI: 7.0-10.4). Outcome was better in patients with limited disease (median PFS: 12.2 years; 95% CI: 10.3-14.0; median OS: 13.0 years; 95% CI: 11.3-14.6) compared to advanced disease (median PFS: 4.1 years, 95% CI: 2.4-5.8; median OS: 5.9 years, 95% CI: 4.4-7.5) (*Online Supplementary Figure S4*).

### Predictive variables for outcome

In all 279 patients, we first explored both host- and disease-derived variables for their association with PFS and OS (Table 1). In univariate analysis, host-derived variables were associated with PFS and OS were age, ECOG PS, dependency in ADL, BMI, and CIRS-G score. A higher BMI was associated with better outcomes, but few patients (3%) had BMI ≥35 kg/m$^2$. For age, BMI and CIRS-G results are shown for dichotomized variables (<70 years *vs.* ≥70, BMI <26 kg/m$^2$ *vs.* ≥26, CIRS-G score <8 *vs.* ≥8), but results were also significant when used as continuous variables. Among disease-related variables, histological subtype, stage, presence of B symptoms and clinical risk group, showed significant associations with both PFS and OS. Dose intensities of doxorubicin in the first cycle and total treatment were significantly associated with both PFS and OS.

In multivariable analysis of all patients, the patient-related variables of age, ECOG PS and CIRS-G retained significant association with PFS, as did the disease-related parameters, histological subtype and clinical risk group. Similar results were found with CIRS-G, age and BMI as continuous variables (*Online Supplementary Table S4*). Treatment was not included in the multivariable analysis, as only variables present at start of treatment (i.e., those that guide treatment decisions) would be of interest when developing a geriatric prediction model. For OS, once again, age and CIRS-G were associated with outcome, but the association was no longer significant for ECOG PS.

Separate analyses of patients with limited and advanced disease were carried out despite lower numbers of patients in these subgroups (*Online Supplementary Table S5*). For both groups, the patient-related variables of age, CIRS-G and ECOG PS were numerically associated with PFS and OS, but with smaller numbers of patients; not all of these retained independent significance in the multivariable analysis. In patients with advanced disease, multivariable models confirmed IPS to be prognostic in terms of PFS and OS. Dose intensity of doxorubicin in the first cycle was significantly associated with PFS and OS in both subgroups, as was relative doxorubicin dose for total treatment in patients with advanced disease.

### Development of the frailty score

Based on results of multivariable analysis for PFS, we de-

**Table 1.** Univariate and multivariable Cox regression analysis for progression-free and overall survival up until 5 years for all patients.

| Characteristic (N) | 5-year progression-free survival | | | | 5-year overall survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariable analysis | | Univariate analysis | | Multivariable analysis | |
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| **Patient-related variables** | | | | | | | | |
| Age at diagnosis, years | | <0.001* | | 0.012* | | <0.001* | | 0.002* |
| <70 (149) | Ref | | | | | | | |
| ≥70 (130) | 2.1 (1.5-3.0) | | 1.7 (1.1-2.5) | | 2.6 (1.8-3.9) | | 2.1 (1.3-3.2) | |
| Sex | | 0.52 | | 0.17 | | 0.39 | | 0.11 |
| Female (128) | Ref | | | | | | | |
| Male (151) | 1.1 (0.8-1.6) | | 1.3 (0.9-1.9) | | 1.2 (0.8-1.7) | | 1.4 (0.9-2.1) | |
| ECOG PS | | <0.001* | | 0.037* | | <0.001* | | 0.16 |
| 0-1 (214) | Ref | | | | | | | |
| ≥ 2 (62) | 3.0 (2.0-4.3) | | 1.6 (1.0-2.5) | | 3.0 (2.0-4.4) | | 1.4 (0.9-2.3) | |
| ADL | | 0.040* | | 0.55 | | 0.027* | | 0.65 |
| Independent (237) | Ref | | | | | | | |
| Dependent (37) | 1.6 (1.0-2.6) | | 1.2 (0.7-2.0) | | 1.7 (1.1-2.8) | | 1.1 (0.6-2.0) | |
| BMI/kg/m$^{-2}$ | | 0.029* | | 0.14 | | 0.050* | | 0.21 |
| <26 (164) | Ref | | | | | | | |
| ≥26 (100) | 0.6 (0.4-1.0) | | 0.7 (0.5-1.1) | | 0.7 (0.4-1.0) | | 0.7 (0.5-1.2) | |
| CIRS-G | | 0.004* | | 0.007* | | <0.001* | | <0.001* |
| <8 (188) | Ref | | | | | | | |
| ≥8 (87) | 1.7 (1.2-2.4) | | 1.7 (1.2-2.5) | | 2.3 (1.5-3.3) | | 2.3 (1.5-3.6) | |
| Smoking | | 0.19 | | | | 0.10 | | |
| No (111) | Ref | | | | | | | |
| Yes, current/past (142) | 1.3 (0.9-1.9) | | | 1.4 (0.9-2.1) | | | | |
| **Disease-related variables** | | | | | | | | |
| Histology | | <0.001* | | 0.014* | | <0.001* | | 0.005* |
| Nodular sclerosis (126) | Ref | | | | | | | |
| Mixed cellularity (48) | 0.9 (0.5-1.5) | 0.71 | 0.8 (0.5-1.4) | 0.53 | 0.9 (0.5-1.7) | 0.81 | 0.9 (0.5-1.7) | 0.75 |
| Lymphocyte-rich (30) | 0.2 (0.1-0.7) | 0.006* | 0.2 (0.1-0.7) | 0.009* | 0.3 (0.1-0.9) | 0.032* | 0.3 (0.1-1.0) | 0.042* |
| Lymphocyte-depleted/ cHL NOS (75) | 1.7 (1.1-2.5) | 0.011* | 1.3 (0.9-2.0) | 0.19 | 2.0 (1.3-3.1) | 0.001* | 1.7 (1.1-2.8) | 0.018* |
| Stage (Ann Arbor) | | <0.001* | | | | <0.001* | | |
| I (48) | Ref | | | | | | | |
| II (68) | 1.6 (0.8-3.4) | 0.21 | | | 1.4 (0.6-3.1) | 0.43 | | |
| III (92) | 2.8 (1.4-5.5) | 0.004* | | | 2.4 (1.2-5.0) | 0.018* | | |
| IV (71) | 5.5 (2.8-10.8) | <0.001* | | | 4.8 (2.3-9.8) | <0.001* | | |
| B symptoms | | <0.001* | | | | <0.001* | | |
| Absent (143) | Ref | | | | | | | |
| Present (136) | 1.9 (1.3-2.7) | | | | 2.3 (1.6-3.4) | | | |
| Risk groups | | <0.001* | | 0.003* | | <0.001* | | 0.006* |
| Limited disease (90) | Ref | | | | | | | |
| Advanced disease (189) | 2.9 (1.8-4.5) | | 2.2 (1.3-3.6) | | 2.9 (1.7-4.8) | | 2.2 (1.2-3.9) | |
| **Treatment-related variables** | | | | | | | | |
| Doxorubicin dose 1 cycle | | <0.001* | | | | <0.001* | | |
| 50-79% (40) | Ref | | | | | | | |
| ≥80% (239) | 0.3 (0.2-0.5) | | | | 0.3 (0.2-0.5) | | | |
| Total doxorubicin dose | | 0.004* | | | | 0.001* | | |
| ≥80% (188) | Ref | | | | | | | |
| 50-79% (45) | 1.9 (1.2-3.0) | 0.006* | | | 2.1 (1.3-3.5) | | | |
| ≤49% (25) | 2.1 (1.2-3.8) | 0.015* | | | 2.4 (1.3-4.5) | 0.006* | | |

Numbers (N) may not add up to the total in each group; N is given for valid cases only. Univariate and multivariable Cox regression analysis was performed for progression-free and overall survival right-truncated at 5 years. **P* values <5% significance threshold. Sex was included in the multivariable model although *P* values were 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. ADL: activity of daily living; BMI: body mass index; CI: confidence interval; cHL NOS: classical Hodgkin lymphoma not otherwise specified; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; ECOG PS: performance status by Eastern Cooperative Oncology Group; HR: hazard ratio; Ref: reference.

veloped a frailty index ranging from 0-3, with one point each for age ≥70 years, ECOG PS ≥2, and CIRS-G score ≥8 (Table 2 and *Online Supplementary Table S6*). The cut-off for fit (0), unfit (1-2), and frail (3) were based on distribution of the score and the predictive value in Kaplan-Meier curves for 5-year PFS and OS. In the total cohort, we were able to assign a frailty score in 272 of the 279 patients: 92 (34%) fit, 162 (60%) unfit, and 18 (7%) frail. For fit patients, median PFS and OS were not reached, and 5-year PFS and OS were 74% (95% CI: 65-83%) and 86% (95% CI: 79-93%), respectively (Figure 1). Compared to fit patients, unfit and frail patients had a significantly shorter median PFS of 4.8 years (95% CI: 3.3-7.4, *P*<0.001) and 0.5 years (95% CI: 0.3-2.0, *P*<0.001), respectively. For unfit patients, 5-year PFS was 49% (95% CI: 42-58%) and OS 52% (95% CI: 45-61%). For frail patients, 5-year PFS and OS estimates were 11% (95% CI: 3-41%) and 22% (95% CI: 9-53%), respectively. Comparing PFS in fit *versus* frail patients in the total cohort showed a hazard ratio (HR) of 7.9 (95% CI: 4.2-14.9, *P*<0.001). Results were numerically similar for patients with limited and advanced disease separately, but there were only 2 frail patients with limited disease.

In terms of PFS, the frailty score remained significant (*P*<0.001) in CHOP-treated patients (HR 2.8 and 8.4 in unfit and frail patients compared to fit). Only 53 fit or unfit patients and no frail patients were treated with ABVD, reflecting a tendency to select ABVD for younger and healthier patients, and here the frailty index was not significantly associated with PFS.

Internal validation showed C-indices of 0.69 for PFS and 0.70 for OS.

Treatment-related mortality varied by frailty group with 1%, 9%, and 22% in fit, unfit, and frail patients, respectively. CR rates were 85%, 73%, and 28% in the three groups (*Online Supplementary Figure S5*).

## Treatment intensity by frailty group

For fit patients, nearly all received full dose doxorubicin in the first cycle (Figure 2). For unfit patients, ≥80% dose of doxorubicin in the first cycle was associated with better 5-year PFS and OS than initial doses <80%. For frail patients, both groups were small and had generally poor outcome, but there was no clear benefit of giving an initial higher dose of doxorubicin. For the dose intensity of doxorubicin in the total treatment, there was no clear difference in outcomes for the fit and unfit patients when comparing dose levels ≥50%, but outcome appeared inferior with doses <50% (*Online Supplementary Figure S6*). For frail patients, there seemed to be no benefit associated with higher total doses of doxorubicin, but the numbers in each group were low.

## External validation of the frailty score

The Swedish validation cohort consisted of 792 patients (*Online Supplementary Table S7*). Details of the regimen used were known for approximately half of the patients (47%). Age, ECOG PS, and comorbidities expressed by CCI were independently associated with PFS and OS, shown with a distribution-based similar cut-off for CCI as for CIRS-G in the Norwegian cohort. (See *Online Supplementary Table S8*; data for CCI as a continuous variable are not shown.) We were able to assign a frailty score in 783 of the 792 patients, 255 (33%) fit, 505 (65%) unfit, and 23 (3%) frail patients. For fit patients, median PFS and OS were not reached and 5-year PFS and OS were 75% (95% CI: 69-80%) and 76% (95% CI: 67-83%), respectively. Corresponding figures for 5-year PFS and OS were 37% (95% CI: 33-41%) and 53% (95% CI: 44-61%) for unfit patients, and 4% (95% CI: 0-24%) and 0% (95% CI: 0-69%) for frail patients, respectively (Figure 3 and *Online Supplementary Table S9*). Comparing PFS in fit and frail patients in the external cohort resulted in a HR of 9.5 (95% CI: 5.8-15.5, *P*<0.001).

Sensitivity analysis of 273 patients with full treatment details showed similar results, but there were few frail patients in this model (*Online Supplementary Table S10* and *Online Supplementary Figure S7*). Although the tendency to treat unfit or frail patients with CHOP instead of ABVD was more pronounced in the Swedish patients, the frailty index performed similarly in ABVD-treated patients (N=156, HR for PFS unfit *vs*. frail 1.8, 95% CI: 0.90-3.43, *P*=0.096) as in the full cohort. No frail patients were treated with ABVD.

**Table 2.** Cox regression analysis of frailty score on 5-year progression-free survival and overall survival.

| Frailty score | Frailty group (N) | 5-year PFS | | 5-year OS | |
|---|---|---|---|---|---|
| | | Univariate analysis | | Univariate analysis | |
| | | HR (95% CI) | *P* | HR (95% CI) | *P* |
| 0 | Fit (92) | Ref | | Ref | |
| 1-2 | Unfit (162) | 2.3 (1.5-3.6) | <0.001* | 4.2 (2.3-7.6) | <0.001* |
| 3 | Frail (18) | 7.9 (4.2-14.9) | <0.001* | 10.8 (5.0-23.0) | <0.001* |

Numbers (N) may not add up 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 (PFS) and overall survival (OS) right-truncated at 5 years. **P* values <5% significance threshold. CI: confidence interval; HR: hazard ratio; Ref: reference.

# Discussion

In this retrospective population-based analysis of elderly patients with cHL, scoring of prior comorbidities together with age and performance status at diagnosis allowed prediction of outcome in terms of PFS, OS, and TRM. We used CIRS-G to develop the frailty index in the Norwegian study cohort excluding organ dysfunction due to lymphoma. We were able to validate the scoring system in an independent registry cohort from Sweden using CCI based on pre-existing conditions extracted from registries. The CCI performed similarly to CIRS-G both with a distribution-based cut-off for relevant disease burden and as a continuous variable. All patients were treated with contemporary anthracycline-based regimens, but full treatment details were available only for a subset of patients in the validation cohort, in which the index performed similarly. This simplified frailty index carries prognostic information independently of factors related to biology and extent of the disease, which are cornerstones in risk prediction in younger patients with cHL. Anthracycline-based regimens are still relevant today as combination partners for novel agents, such as N-AVD or BrECADD, and the frailty index will need to be validated in larger real-world cohorts treated accordingly.[10,12,13]

Detailed GA in older patients with cHL as a basis for therapeutic decisions is not routine practice.[7] Recently, there has been increased focus on assessing frailty in older patients with malignancy to allow better tailoring of treatment, and possibly improve quality of life and increase survival.[22] ASCO

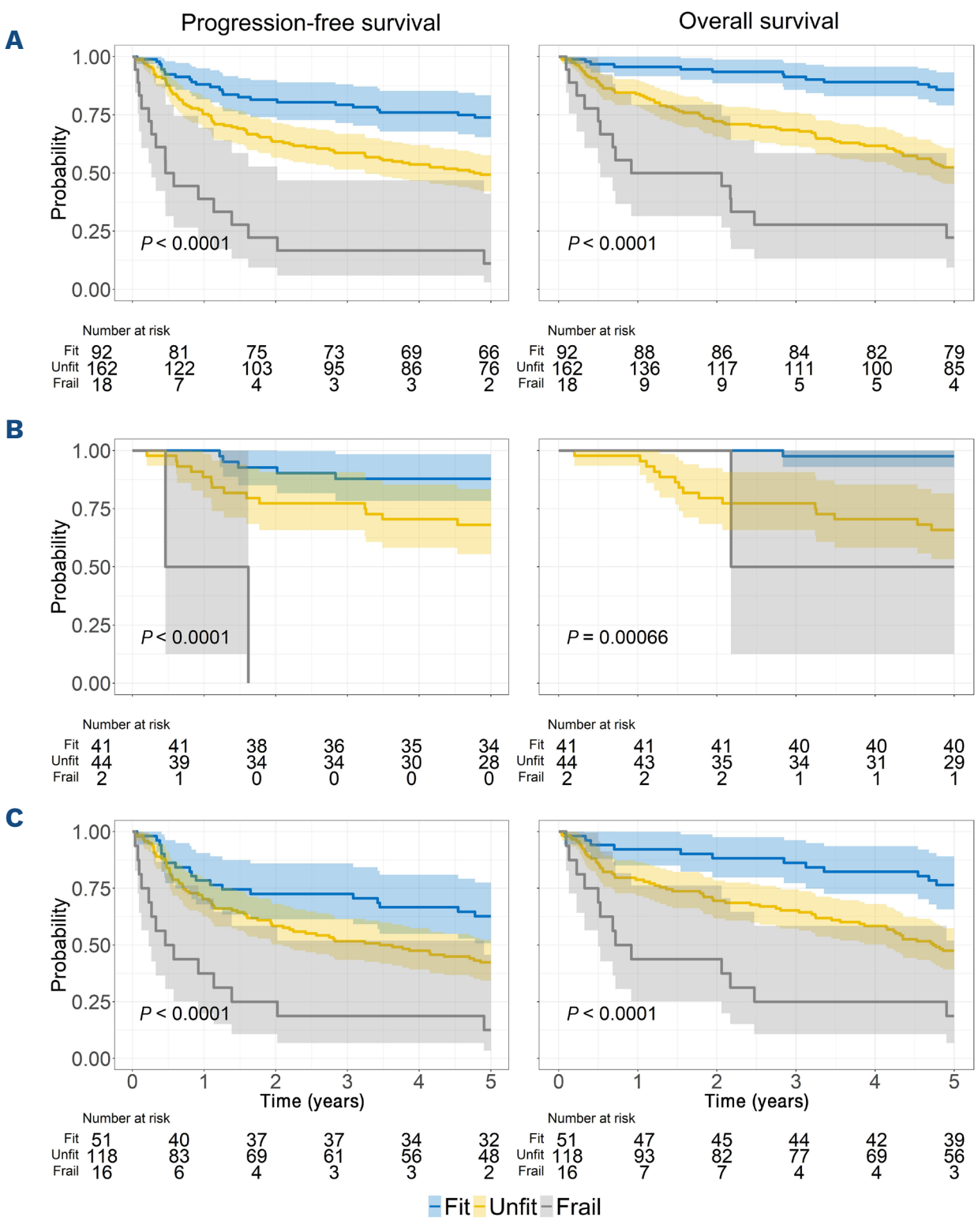


**Figure 1. Progression-free and overall survival up until 5 years according to frailty groups.** (A) All patients. (B) Patients with limited disease. (C) Patients with advanced disease.

2018 Guidelines for Geriatric Oncology suggested vulnerabilities should be assessed on a minimum level as function, comorbidity, falls, depression, cognition, and nutrition.[21] As the presence of lymphoma may reversibly impact on many of these aspects of health, we retrospectively aimed to assess comorbidities and functional level prior to the lymphoma diagnosis, using CIRS-G (which includes depression and cognitive function) and ADL. We used ECOG PS and BMI from the time of diagnosis, as data prior to the onset of lymphoma were lacking in most patients.

With our frailty score, patients were not classified as frail based on age alone, and patients ≥70 years could still belong to the unfit group with a rather favorable 5-year PFS. On the other hand, the outcome for patients classified as frail was disappointing even when treated with doxorubicin-containing regimens. The 2-year PFS in this subgroup was below 20% and clearly identifies patients in highest need of improved therapies. However, only 7% of the Norwegian cohort belonged to this group, probably reflecting our original selection of patients treated with an attempt to cure.

One strength of the present study is the availability of large national data registries with detailed information available from different health records. Our simple frailty index is valuable, as no validated scoring system for frailty of elderly cHL patients is available to date, and results from other retrospective studies are conflicting regarding impact of age, comorbidities, and functional independence.[34-40] For instance, in their retrospective multicenter study, Orellana-Noia *et al.*[38] evaluated 244 cHL patients aged ≥60 years

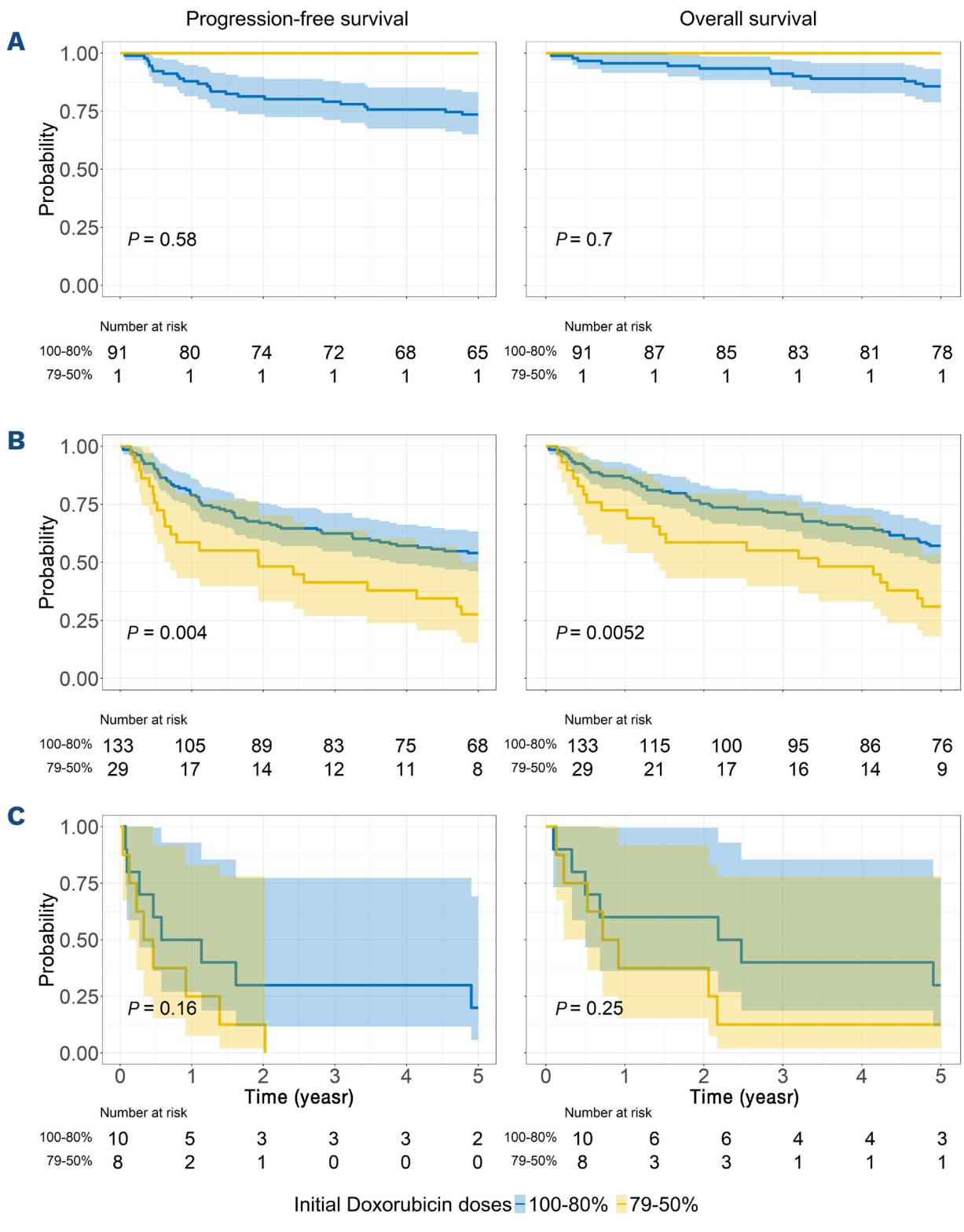


**Figure 2. Progression-free and overall survival up until 5 years of patients according to frailty score and initial dose of doxorubicin.** (A) Fit, (B) unfit and (C) frail patients.

across 10 US medical centers. Their study design, sample size, and included population were comparable to ours. However, in their final analysis for PFS and OS, only dependency in ADL retained independent prognostic value; other host- or disease-related variables, including disease extent, age, and CIRS-G did not. In the Shield study, dependency in ADL, IPS and ECOG PS were associated with the likelihood of achieving CR, but with CR at the end of treatment included in multivariable models for PFS and OS, these variables were not predictive on their own.[36] Prospective data of GA is available from three recent phase II trials of novel regimens designed for elderly cHL patients. In their study of brentuximab vedotin (BV) sequential with AVD, Evens *et al.*[39] found dependency in instrumental ADL to be associated with prognosis in multivariable analysis, and in the recent LYSA study on bendamustin, doxorubicin, vinblastine and prednisone the number of medications taken for reasons other than cHL was the only item of GA independently associated with outcome.[40] Torka *et al.*[41] reported no correlations between baseline geriatric impairments and outcomes in 37 patients treated with N-AVD. These discrepancies may result from a different selection of patients, the mostly retrospective study design, and discrepancies in understanding how to assess a patient's health status prior to the onset of lymphoma. We specifically aimed to assess comorbidities and dependency based on the original medical records or registry data, so as not to interfere with disease symptoms. This represents a fun-

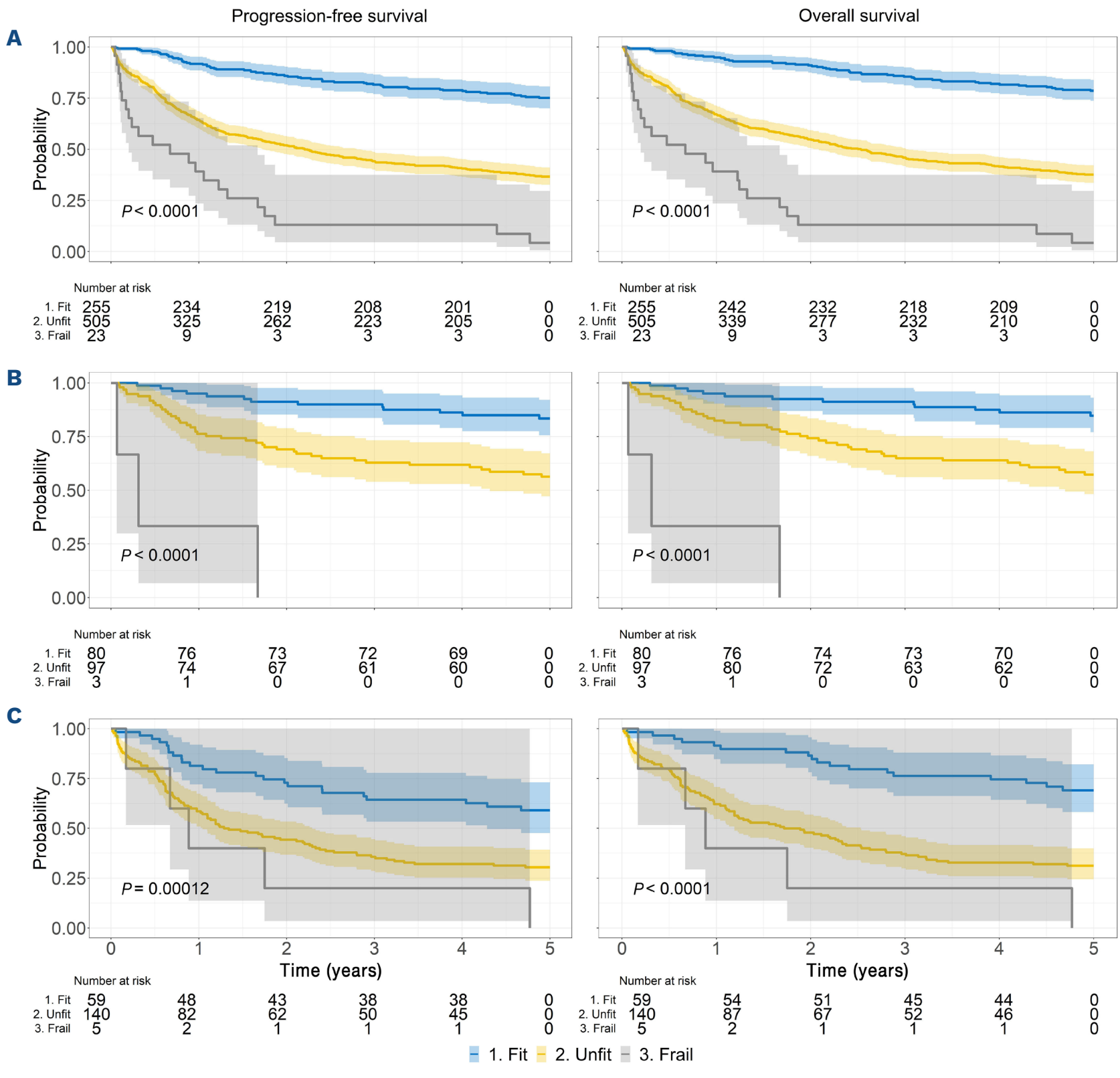


**Figure 3. Progression-free and overall survival up until 5 years according to frailty groups in the external validation cohort.** (A) All patients. (B) Patients with limited disease. (C) Patients with advanced disease (C).

damental difference in assessing the same factors based on patient status when admitted for lymphoma.

There are no established recommendations for treatment of older patients with cHL.[7] Anthracyclines are likely important, but the optimal dose and combination partners, including eventual use of novel drugs, have not been firmly established.[7,9,34,42] In our data, the outcome of unfit patients is significantly better with higher doses of doxorubicin in the first cycle, mostly in CHOP or ABVD. Total doses below <50% doxorubicin seem associated with poorer outcome for both fit and unfit patients. SEER registry data have also shown that patients selected to receive dose-intense chemotherapy have better 1-year survival, but choice of dose intensity is likely affected by underlying fitness.[43,4] Although this is not possible to prove without a randomized trial, our results support the hypothesis that dose of doxorubicin is important for the healthier older patients. Since several novel regimens tested in older patients are based on similar anthracycline-containing backbones, our frailty score may be valuable also in these settings, but larger high-quality data sets are lacking.[12,13] Whether anthracyclines are beneficial in frail patients remains unclear in our data. In a recent subanalysis of our national cHL cohort, the outcome of those treated with palliative intent, either defined as treatment with less than 50% doxorubicin in the first cycle or a declared palliative intent, was similar to the frail cohort of the present analysis and without a clear benefit of adding anthracyclines. These frail patients will probably benefit from other new first-line therapies, possibly also based on BV or checkpoint inhibitors.[15-17,19,20]

Besides its focus on development of a scoring system for GA, our study gives insights into contributions of disease biology to outcome. As reported previously, nodular sclerosis and mixed cellularity were the most common histological subtypes.[8,35,38,43] In multivariable analysis, lymphocyte-rich histology was associated with better PFS and OS, as recently shown also by Rodday *et al.*[43] Patients with limited stages, commonly treated also with consolidation radiotherapy, did better than patients with advanced stages, and for older patients with advanced disease, the IPS was predictor of outcome.[5,45] This underscores the importance of considering both patient- and disease-related parameters prior to treatment.

We acknowledge limitations in our data. Firstly, the retrospective design comes with the risk of missing or inaccurate data, especially connected to retrospectively assessing CIRS-G or ADL. Secondly, we focus on an earlier period, ending accrual with patients diagnosed in 2015. Most patients in both cohorts were treated with CHOP, selecting only the younger or less frail patients for ABVD. This may limit the representability compared to current treatment options, but the index performed similarly in ABVD-treated Swedish patients and novel agents have still not been introduced into first-line treatment in many countries. Also, the most promising novel combinations for curative treatment of older cHL patients still contain doxorubicin in doses comparable to the regimens used in our registry cohort.[12,13] Thirdly, due to limited availability of larger real-world cohorts, we had to accept the use of different comorbidity scoring in the two cohorts, but conducted sub-analyses to show that CIRS-G and CCI perform similarly in their respective cohorts. Lastly, despite being the largest population-based study with detailed patient data available, and with validation in an independent registry cohort, our proposed frailty index needs further validation in prospective studies. To this end, we plan a prospective registry study in Scandinavia. We also acknowledge that frailty is not a static measure and may change during therapy. Therefore, lead-in treatment with targeted agents alone prior to choice of first-line regimen, and continuous GA with tailoring of intensity may be optimal, concepts that were not assessed in our study.

In conclusion, we present a frailty score that predicts 5-year PFS and OS in elderly patients with cHL treated with doxorubicin-based contemporary combination regimens independent of disease-related risk factors. The external validation demonstrated the generalization of the frailty index using either CIRS-G or CCI. These patient-related parameters provide important knowledge to help tailor treatment strategies for older patients. An online calculator for assessment of the frailty score is available at Lymphomapredictor.rn.dk.

## Disclosures

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## Contributions

*KL, RRKJ and AF are responsible for study concept and design. KL, BLW, NÖ, ØF, UMF, HB, IBB and AF are responsible for data collection and assembly. KL, RRKJ, DM, PW and AF are responsible for data analysis and interpretation. KL, RRKF, DM, PW and AF created the figures and tables. SB and AF supervised the study. KL and AF wrote the manuscript. All authors helped write the manuscript, and reviewed and approved the final version for publication.*

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## Data-sharing statement

*The data of this study are available from the corresponding author upon reasonable request.*

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