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Clinical characteristics and outcomes among 2347 patients aged ≥85 years with major lymphoma subtypes: a Nordic Lymphoma Group study

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Summary

There is a lack of data regarding treatment and prognosis for the growing group of oldest old patients with lymphoma. Therefore, we studied 2347 patients aged ≥85 years from the Danish and Swedish lymphoma registers 2000–2016 (Denmark) and 2007–2013 (Sweden). Outcome was assessed using relative survival (RS). The 2-year RS overall for patients with aggressive lymphomas was 38% [95% confidence interval (CI) 35–42%], of whom 845 (66%) patients received active treatment (chemotherapy, radiotherapy, immunotherapy, other). For aggressive lymphomas, not receiving active treatment was associated with an inferior 2-year RS of 12% (95% CI 9–17%) compared to 49% (95% CI 45–53%) for patients who received active treatment (excess mortality rate ratio 2·84, 95% CI 2·3–3·5; $P < 0·0001$). For patients with indolent lymphoma, the 2-year RS was 77% (95% CI 72–82%). Here, 383 (46%) patients received active treatment at diagnosis, but did not have better 2-year RS (75%, 95% CI 67–81%) compared to those who did not receive active treatment (83%, 95% CI 74–89%). We conclude that outcomes for the oldest old patients with lymphoma are encouraging for several subtypes and that active treatment is associated with improved outcome amongst the oldest old patients with aggressive lymphomas, indicating that age itself should not be a contraindication to treatment.

Keywords: lymphoma, oldest old, treatment, survival, elderly.

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Introduction

According to data from the United States Census Bureau the world population aged >80 years has tripled from 1980 to 2010. This increase is projected to continue, particularly in the oldest group aged >85 years.[1] As the incidence of most lymphoma subtypes increases with age, the population of old patients with lymphoma is also expected to grow.[2,3] Improvements in cancer survival in recent decades have primarily been achieved for the younger patient groups and population-based studies have consistently reported worse outcomes in older populations with cancer.[2,4–6] This may be due to an increased risk of treatment-related morbidity and mortality, but also to suboptimal management of the oldest old patients with cancer, due to fear of imposing undue toxicity.

Comorbidities, frailty, and old age per se largely preclude inclusion of the very old in clinical trials.[7] In the absence of large randomised trials, the treatment of older patients is informed mainly by single-arm trials and observational studies, and therefore optimal treatment strategies for old patients remain poorly defined.[3,8,9] Further, the management of old patients with lymphoma is complicated by a greater burden of comorbidity, physical/mental deconditioning and a potential increase in treatment-associated complications due to age-related differences in pharmacokinetics and increased organ dysfunction.[10,11]

Lymphomas are generally highly chemosensitive and can be cured even when occurring at advanced age, if managed optimally.[12,13] Moreover, with increased life expectancy and better health amongst older persons, the general perception of the oldest old as being too frail for curative therapy may be outdated. With a rise in incidence and prevalence of lymphoma in an increasingly ageing population, more knowledge regarding disease course, treatment and prognosis for the oldest old patients with lymphoma is warranted. Therefore, we aimed to characterise the population of very old (aged ≥85 years) patients with lymphoma with regard to distribution of lymphoma subtypes and characteristics, treatment patterns and relative survival (RS) using data from two population-based national lymphoma registers.

Patients and Methods

Data sources and study population

This study was performed within the collaborative framework of the Nordic Lymphoma Group, with participation of the Swedish and Danish Lymphoma Groups and their population-based registers. The Danish National Lymphoma Register (LYFO) was initiated in 1982 and from 2000 coverage was nationwide. In a recent validation study, LYFO demonstrated a high degree of both completeness (95%) and correctness of entered variables with the Danish Cancer Register and medical records used as reference.[14,15] The Swedish Lymphoma Register (SLR) was established in 2000 and since 2007 includes detailed data regarding active treatment, treatment type and response. Compared to the Swedish Cancer Register, to which all cancer diagnoses are registered by law, the coverage of the SLR is ~95% of all lymphoma cases diagnosed in Sweden.[16]

The study population included all patients aged ≥85 years diagnosed with any type of lymphoma from 1 January 2000 to 31 December 2016 for Danish patients and from 1 January 2007 to 31 December 2013 for Swedish patients. Diagnoses were made according to current World Health Organization (WHO) classification pathology guidelines.[17,18] Patients were followed from diagnosis until death, emigration, or end of follow-up (11 April 2015 for Swedish patients, 21 September 2019 for Danish patients), whichever occurred first. The study was approved by the Regional Boards of the Ethics Committees in Stockholm (2015/2028-31/2, 2019-01446) and Southern Denmark (8/44586).

Patients were stratified according to aggressive and indolent subtypes, as well as main lymphoma subtype according to the WHO classification.[19] Aggressive lymphomas encompassed diffuse large B-cell lymphoma (DLBCL), T-cell lymphomas (TCL; excluding primarily cutaneous variants), Hodgkin lymphoma (HL), mantle cell lymphoma (MCL) and other aggressive lymphomas [Burkitt lymphoma, primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, aggressive lymphoma not otherwise specified (NOS)]. Indolent lymphomas encompassed follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) including Morbus Waldenström, and other indolent subtypes (hairy cell leukaemia, cutaneous T-cell lymphoma and indolent lymphoma NOS). A proportion of patients only had a recorded diagnosis of lymphoma NOS and could not be further subclassified. The cohort was linked to the Swedish and Danish Patient Registers [20,21] to collect information on comorbid disease occurring 10 years prior to lymphoma. Comorbidity was measured according to the Charlson Comorbidity Index (CCI), as previously described.[22,23] Active treatment was defined as chemotherapy, radiotherapy (RT), immunotherapy or other (surgery, splenectomy, ultraviolet B/topical treatment or antibiotics). No active treatment included management with watch-and-wait and best supportive care including steroids only.

Statistical methods

Relative survival was used as a measure of net survival and was estimated as the ratio of the observed all-cause survival to the expected survival in an age-, sex-, country- and calendar-period-matched population (assumed lymphoma free). The Pohar Perme method was used to calculate expected survival in the matched Danish and Swedish general populations using data obtained via the Human Mortality Database (www.mortality.org). RS is a measure of total (both direct and indirect) excess mortality associated with a lymphoma diagnosis, with the advantage of not having to rely on

classification of cause of death.[24] Results are presented in cumulative RS graphs and as 2-year RS estimates with 95% confidence intervals (CIs). Additionally, we used multivariable flexible parametric models to estimate excess mortality rate ratios (EMRRs). These models were fitted on the log cumulative excess hazard scale and used restricted cubic splines to model the baseline excess hazard function.[25] All models were fitted using five degrees-of-freedom for the baseline excess hazard. Variables included in the multivariable model were age (assuming a linear effect), sex, CCI (categorised into scores of 0, 1 or ≥2), WHO Performance Status (PS), Ann Arbor stage, country and active treatment. Proportional hazards were assessed graphically through Martingale residuals and tested formally using likelihood ratio tests for interactions between the covariates and the spline representing the time scale. Time-varying effects were allowed for age, WHO PS and country. Separate analyses were performed for individual lymphoma subtypes and aggressive *versus* indolent lymphomas. Statistical analyses were performed with STATA software, version 15 (StataCorp., College Station, TX, USA).

Results

Patient characteristics and treatment

A total of 2347 consecutive patients aged ≥85 years with any lymphoma subtype were identified during the study period. Of these, 1159 were Danish and 1188 were Swedish, constituting 6% and 9% of all Danish and Swedish patients diagnosed with a lymphoma during the study period respectively. Overall, 1283 (55%) had an aggressive lymphoma subtype, 835 (36%) an indolent subtype and 229 (10%) had a lymphoma NOS (Table I). DLBCL was the most commonly occurring subtype (n = 924, 39%). Patients with a lymphoma NOS diagnosis more often presented with a CCI of >1 and were less likely to receive active treatment.

Table I. Distribution of lymphoma subtypes in 2347 patients aged ≥85 years at lymphoma diagnosis in Denmark and Sweden.

Lymphoma subtype	*N* (%)
Aggressive subtypes	All: 1283
Diffuse large B-cell lymphoma	924 (39)
T-cell lymphoma	103 (4)
Hodgkin lymphoma	65 (3)
Mantle cell lymphoma	138 (6)
Aggressive other	53 (2)
Indolent subtypes	All: 835
Follicular lymphoma	201 (9)
Marginal zone lymphoma	153 (6)
Lymphoplasmacytic lymphoma including Morbus Waldenström	237 (10)
Indolent other	244 (10)
Lymphoma not otherwise specified	229 (10)

The median (range) age in the study population was 87 (85–105) years, with 579 (25%) patients aged ≥90 years. Most patients were women, 1329 (57%). In the whole cohort, 990 (42%) had a CCI of 0, 541 (23%) had CCI of 1 and 816 (35%) had a CCI of ≥2; with a similar distribution amongst aggressive and indolent lymphoma subtypes (Table II). Patient characteristics differed by country regarding proportion of patients with comorbidity (a larger proportion of Danish patients had no comorbidity, 48% vs 36%), but were otherwise similar (Table S1).

Treatment information was available for 2034 (87%) patients, of whom 1319 (65%) received active treatment and 715 (35%) did not. Patient characteristics for the 313 (13%) patients with missing treatment data were similar to those who received no active treatment (data not shown).

Aggressive lymphomas

Among patients with aggressive lymphomas, 845 (66%) received active treatment (Table III), most often chemotherapy (n = 628, 74%). Patients who received active treatment more often presented with WHO PS 0–1, Stage I–II, CCI 0 and age-adjusted International Prognostic Index (aaIPI) 0–1, compared to those who did not receive active treatment (Table II). The most commonly administered regimen was CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), and 340 (40%) patients started standard therapy defined as either CHOP or CEOP (cyclophosphamide, epirubicin, vincristine, prednisone; 76% with rituximab) (Table S2). Among patients treated with rituximab-CHOP (R-CHOP), 143 (43%) only completed one to three cycles. RT was given to 231 (27%) patients, of whom 86 (10%) received RT in combination with chemotherapy and 145 (17%) as monotherapy (Table S2).

The 2-year RS for patients with aggressive lymphoma subtypes was 38% [95% confidence interval (CI) 35–42%]. For those who received active treatment, the 2-year RS was 49% (95% CI 45–53%) with a plateau of RS of 44% at 5 years. For those without active treatment, the 2-year RS was 12% (95% CI 9–17%), with the highest excess mortality within the first 3 months (3-month RS: 24% for patients who did not receive treatment; Fig 1A). Excess mortality in a multivariable model was close to threefold increased among patients who did not receive active treatment compared to those who did ($EMRR_{adj}$ 2·84, 95% CI 2·3–3·5; $P < 0·0001$). The RS rates for individual subtypes are presented in Fig 2. Especially for patients with DLBCL, active treatment was associated with improved outcome [2-year RS 51% (95% CI 46–56%) vs. 10% (95% CI 7–15%)]. Further, with standard treatment (R-CHOP or R-CEOP, n = 340) the 2-year RS was 64% (95% CI 60–73%) whereas with low-intensive systemic therapies [cyclophosphamide, oncovin, prednisone (COP) or single-agent chemotherapy], RT or immunotherapy only, 2-year RS was 40% (95% CI 34–47%).

Table II. Characteristics of lymphoma patients aged ≥85 years at diagnosis in Denmark and Sweden, overall and stratified by aggressive *versus* indolent lymphoma subtype and active *versus* no treatment.

		Aggressive subtypes*			Indolent subtypes*		
Characteristic	Whole cohort	All patients	Active treatment†	No treatment†	All patients	Active treatment†	No treatment†
N (%)	2347 (100)	1283 (61)	845 (66)	284 (22)	835 (39)	383 (46)	333 (40)
Age, years, median (range)	87 (85–105)	87 (85–105)	87 (85–101)	88 (85–105)	87 (85–100)	87 (85–100)	87 (85–99)
Sex, *n* (%)							
Male	1018 (43)	560 (44)	374 (44)	110 (39)	378 (45)	167 (44)	160 (48)
Female	1329 (57)	723 (56)	471 (56)	174 (61)	457 (55)	216 (56)	173 (52)
WHO PS, *n* (%)							
0–1	1535 (65)	740 (58)	580 (69)	93 (33)	655 (79)	307 (80)	252 (76)
2–4	742 (32)	505 (39)	253 (30)	175 (62)	155 (19)	68 (18)	71 (21)
Missing	70 (3)	38 (3)	12 (1)	16 (6)	25 (2)	8 (2)	10 (3)
Ann Arbor Stage, *n* (%)							
I–II	697 (30)	462 (36)	359 (43)	67 (24)	185 (22)	100 (26)	63 (19)
III–IV	1275 (54)	612 (48)	407 (48)	132 (46)	538 (65)	247 (65)	225 (68)
Missing	375 (16)	209 (16)	79 (9)	85 (30)	112 (13)	36 (9)	45 (13)
aaIPI, *n* (%)							
0	381 (16)	225 (18)	186 (22)	25 (9)	127 (15)	43 (13)	43 (13)
1	683 (29)	302 (23)	240 (28)	36 (13)	315 (38)	136 (41)	136 (41)
2	488 (21)	269 (21)	199 (24)	43 (15)	181 (22)	60 (18)	60 (18)
3	220 (9)	169 (13)	93 (11)	55 (19)	23 (3)	10 (3)	10 (3)
Missing	575 (25)	318 (25)	127 (15)	125 (44)	189 (22)	83 (25)	83 (25)
CCI score, *n* (%)							
0	990 (42)	543 (42)	391 (46)	98 (35)	363 (43)	141 (42)	141 (42)
1	541 (23)	303 (24)	188 (22)	74 (26)	186 (22)	77 (23)	77 (23)
>1	816 (35)	437 (34)	266 (31)	112 (39)	286 (34)	115 (35)	115 (35)
Active treatment, *n* (%)							
Yes	1319 (56)	845 (66)			383 (46)		
No	715 (31)	284 (22)			333 (40)		
Missing	313 (13)	154 (12)			119 (14)		

aaIPI, age-adjusted International Prognostic Index; CCI, Charlson Comorbidity Index; WHO PS, World Health Organization Performance Status.
*Patients with a lymphoma NOS diagnosis not included in either subdivision.
†Patients with missing treatment data not included.

Prognostic factors associated with inferior outcomes in a multivariable analysis were age, female sex, WHO PS 2–4, Stage III–IV disease, presence of B symptoms and CCI score of >1 (Table S3). There were no significant differences by sex in distribution of prognostic factors or treatment, except for a lower proportion of female patients with aggressive lymphomas who started standard treatment (23%) compared to male patients (30%) (data not shown). Outcomes were similar by calendar period (2000–2008 vs. 2009–2016, Figure S1a).

Indolent lymphomas

Among patients with indolent lymphomas, 46% received active treatment. These patients more often had Stage I–II disease and a lower aaIPI score, but otherwise baseline characteristics were similar to those who did not receive active treatment, including CCI score (Table II). For patients managed with active treatment, 234 (61%) received chemotherapy, most often chlorambucil (n = 155, 66%). In all, 58 (15%) patients received RT as monotherapy (Table III). The use of RT was most predominant among lower stages, with 47% and 29% of patients with Stage I and II receiving RT. The proportion of patients treated with immunotherapy alone was 14% (Table S2).

The 2-year RS for patients with indolent lymphomas was 77% (95% CI 72–82%) overall, 83% (95% CI 74–89%) for those who did not receive treatment and 75% (95% CI 67–81%) for those who did (Fig 1B) ($EMRR_{adj}$ 0·68, 95% CI 0·4–1·1; P = 0·14). Administration of active treatment was not associated with improved RS for any of the individual indolent subtypes, and overall RS rates were encouraging for all indolent subtypes (2-year RS >70%, RS for individual subtypes are presented in Fig 2).

Prognostic factors associated with adverse outcomes in a multivariable analysis were WHO PS 2–4 and presence of B symptoms (Table S3). Outcome improved during the study period, with a 2-year RS of 82% (95% CI 76–87%) for

Table III. Distribution of primary treatment among patients who have received any active treatment, and stratified by indolent *versus* aggressive lymphoma subtypes.

Treatment	Patients who received active treatment n = 1319 (56% of all patients)	Aggressive subtypes* n = 845 (66% of all patients with aggressive lymphoma)	Indolent subtypes† n = 383 (46% of all patients with indolent lymphomas)
Chemotherapy (±RT)	921 (70)†	628 (74)†	234 (61)
Chemotherapy no RT	818 (62)	531 (63)	232 (61)
Chemotherapy + RT	92 (7)	86 (10)	2 (0)
RT only	221 (17)	145 (17)	58 (15)
Immunotherapy only	90 (7)	25 (3)	54 (14)
Other treatment only	19 (1)	10 (1)	8 (2)
Unknown treatment	68 (5)	37 (4)	29 (8)

RT, radiotherapy. Other treatment = surgery, splenectomy, ultraviolet B/topical treatment, antibiotics.
*Patients with lymphoma NOS diagnosis not included in either subdivision.
†11 patients with missing RT data.

patients diagnosed 2009–2016, compared to 66% (95% CI 57–74%) 2000–2008 (Figure S1b).

Discussion

We present real-world data on a large, consecutive cohort of the oldest old patients (aged ≥85 years) with lymphoma, providing important information for both patients and treating clinicians. We demonstrate that administration of active treatment significantly reduced the excess mortality associated with aggressive lymphomas amongst the very old. This indicates that age in itself should not be a contraindication for treatment and that efforts to identify patients who will benefit from treatment and increase treatment tolerability for the oldest old patients with lymphoma are warranted. Further, we demonstrate encouraging RS for indolent lymphomas overall, both among actively treated and other patients.

For aggressive lymphomas, administration of active treatment was associated with a 2-year RS of 49% and a 5-year RS of 44%, demonstrating that intensive, curative treatment is both feasible and tolerable for a proportion of the oldest old patients with lymphoma. Active treatment was especially beneficial for patients with DLBCL receiving standard treatment with an encouraging 2-year RS of 64%. However, this result needs to be interpreted with caution due to the inherent risk of confounding by indication and the selection of fit patients for standard intensive treatment. Data regarding dose reductions were not available, but it is likely that the majority of patients in the present study received attenuated regimens. Non-completion of treatment was also common, with 43% of patients receiving R-CHOP only completing one to three cycles, although a proportion of these may be pre-planned due to limited-stage disease. Nonetheless, it is evident that these reduced chemotherapy protocols have the potential to achieve cure for a proportion of old patients. Overall, our outcomes are comparable with those from Peyrade *et al.*[12] who found that the attenuated R-mini-CHOP regimen may enable remission, cure and/or good palliation without intolerable toxicity, and a few other reports.[26,27]

The improved survival seen for patients with aggressive lymphomas who received active treatment calls for better tools to evaluate treatment eligibility in the oldest old, to avoid diagnostic delay and to identify regimens with high tolerability. Currently, there are no perfect methods to do this as both the well-validated Complete Geriatric Assessment (CGA) and Q8-questionnarie have the inherent risk of interpreting lymphoma-associated symptoms as frailty,[3,7,28] although a prognostic score integrating the CGA, IPI and haemoglobin value has demonstrated prognostic significance.[29] Further, more liberal use of RT and supportive drugs, such as granulocyte-colony stimulating factors, optimisation of general health and involvement of family caregivers could potentially increase the number of patients eligible for active treatment.[3] Prior studies have reported improved survival rates with pre-planned dose reductions among patients aged ≥85 years.[30,31] Also, pre-phase treatment with steroids has been shown to improve physical status and enable treatment of older patients.[32] The field of novel targeted drugs is also very promising in this context.[28,33] Likewise, it is clear from our subtype-specific RS results that older patients diagnosed with TCL, other aggressive lymphomas, MCL and HL have a relatively poor prognosis regardless of whether they receive treatment or not, indicating a need for novel treatment strategies.[34,35]

For indolent subtypes, active treatment was not associated with a reduction in excess mortality. As not all indolent lymphomas require treatment this finding is plausible, as lymphomas selected for a watch-and-wait strategy are likely associated with better prognosis. Also, the lack of association between treatment and improved survival for patients with indolent subtypes strengthens the notion that the primary

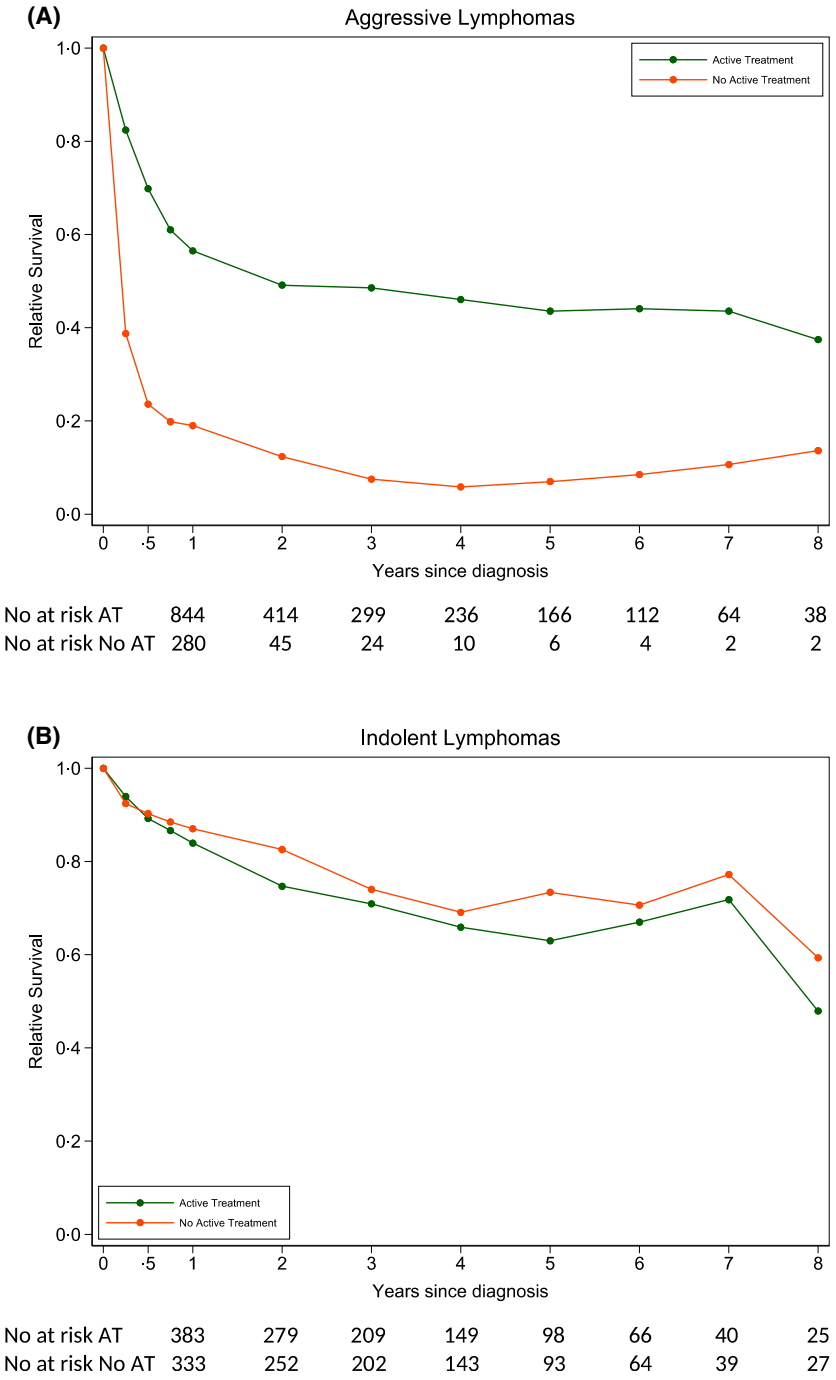

Fig 1. Cumulative relative survival stratified by active treatment (AT) yes/no for patients with (A) aggressive and (B) indolent lymphoma subtypes with number at risk presented below the graph. [Colour figure can be viewed at wile yonlinelibrary.com]

indication for treatment among older patients with indolent lymphomas should be relief of symptoms. Only a few studies have evaluated the outcome among very old patients with indolent lymphomas and there is no consensus on standard treatment.[8,9,36] Thus, the encouraging RS rates for old patients with indolent lymphoma demonstrated in our present study provides important clinical information both for clinicians who manage older patients with lymphoma and for the patients and their relatives.

In our present study, the comorbid burden among patients with indolent lymphoma did not differ by treatment, and comorbidity did not impact excess mortality. In contrast, among aggressive subtypes, patients who received active treatment had less comorbidity. Interestingly, as previously demonstrated by our group, comorbid patients with DLBCL and male patients with MCL treated with curative intent did not have inferior lymphoma-specific outcome compared to non-comorbid patients with DLBCL and MCL.[22,37] Hence,

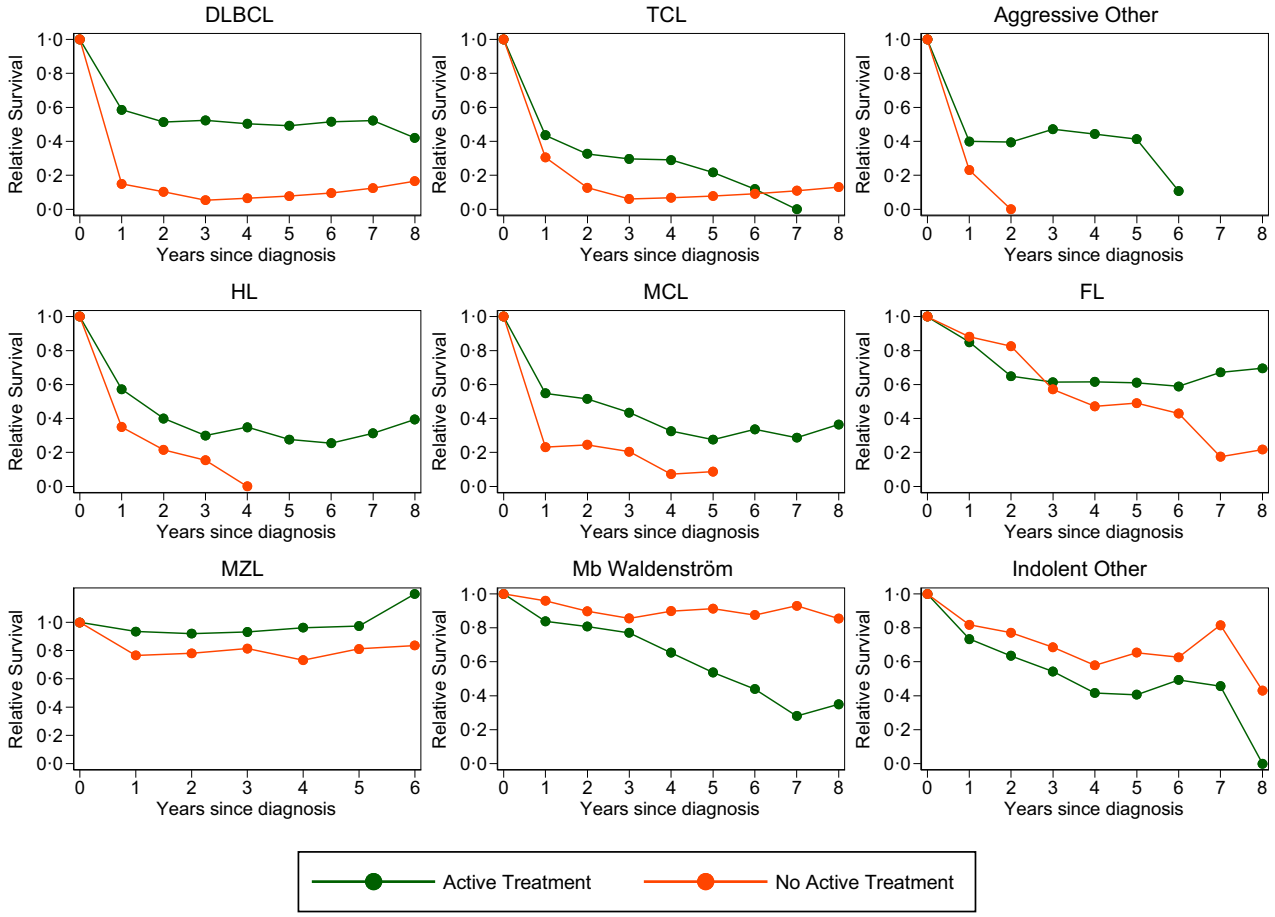

Fig 2. Cumulative relative survival (RS) stratified by individual subtypes and by active treatment yes/no, with RS rates listed below:Diffuse large B-cell lymphoma (DLBCL): 2-year RS overall: 41% (95% CI 37–45%), for active treatment: 51% (95% CI 46–56%), for no treatment: 10% (95% CI 7–15%).T-cell lymphoma (TCL): 2-year RS overall: 26% (95% CI 17–36%), for active treatment: 33% (95% CI 20–46%), for no treatment: 13% (95% CI 3–30%).Aggressive other: 2-year RS overall: 17% (95% CI 8–29%), for active treatment: 40% (95% CI 17–62%), for no treatment: 0% (95% CI 0–0%).Hodgkin lymphoma (HL): 2-year RS overall: 32% (95% CI 19–45%), for active treatment: 40% (95% CI 21–58%), for no treatment: 22% (95% CI 6–43%).Mantle cell lymphoma (MCL): 2-year RS overall: 41% (95% CI 31–51%), for active treatment: 52% (95% CI 38–64%), for no treatment: 25% (95% CI 11–40%).Follicular lymphoma (FL): 2-year RS overall: 68% (95% CI 58–77%), for active treatment: 65% (95% CI 51–76%), for no treatment: 61% (95% CI 59–93%).Marginal zone lymphoma (MZL): 2-year RS overall: 86% (95% CI 72–93%), for active treatment: 92% (95% CI 64–98%), for no treatment: 78% (95% CI 52–91%).Morbus Waldenström (Mb Waldenström): 2-year RS overall: 87% (95% CI 76–93%), for active treatment: 81% (95% CI 62–91%), for no treatment: 90% (95% CI 69–97%).Indolent other: 2-year RS overall: 71% (95% CI 61–78%), for active treatment: 63% (95% CI 48–76%), for no treatment: 77% (95% CI 61–87%). [Colour figure can be viewed at wileyonlinelibrary.com]

the mere presence of comorbidity should not determine treatment choice, although treatment may need to be adapted in the presence of some comorbidities. Further, we noticed that a large proportion of our patients did not have any prior comorbidity, according to the CCI classification. This may indicate that the very old lymphoma population, particularly patients with asymptomatic indolent lymphomas, constitutes a selected group of comparatively healthy older patients, fit enough to undergo diagnostic evaluation. Regarding the distribution of other clinical characteristics they were similar in our present study to what has previously been reported for older patients with lymphoma.[8,38,39] This also applies to prognostic factors, although for patients with indolent lymphomas only the presence of B symptoms and WHO PS score remained significant.

Distribution of lymphoma subtypes in the present study was largely similar to that of the general lymphoma population.[40] However, there was a lower frequency of FL, MZL and HL cases in our population, whereas patients with 'lymphoma NOS' were more numerous. This may also be indicative of a lower diagnostic intensity, especially among potentially asymptomatic indolent lymphomas, among the very old.

In the present study, we provide valuable data regarding clinical characteristics and prognosis of the largely unstudied, but steadily growing group of lymphoma patients aged

≥85 years in Denmark and Sweden. The use of population-based data provides a unique cohort capturing >95% of all lymphoma cases. Our present report of RS also represents a strength, as mortality due to other causes is prevalent in this age group. The high mortality in this age group inevitably also limits the number of patients left in later years of follow-up, despite the relatively large study population at diagnosis. Thus, the RS for later time period after diagnosis needs to be interpreted with caution due to small numbers. Other limitations include the lack of data regarding toxicity and frailty assessment. Although the use of relative survival captures excess mortality caused both directly and indirectly by the cancer through for example intolerable toxicity of treatment, the lack of toxicity data, dose reductions, and other patient-level data preclude us from further deducing associations between patient characteristics, treatment administration and tolerability.

To conclude, we demonstrate encouraging RS rates for very old patients diagnosed with lymphoma, for several subtypes, and show that active treatment improves RS for old patients with aggressive lymphomas, DLBCL in particular. Thus, age itself should not constitute a contraindication to treatment. For patients with indolent lymphomas, treatment was not associated with reduced excess mortality, wherefore treatment for indolent subtypes should probably be reserved for symptomatic patients. Prospective studies to determine relevant factors to identify patients who will tolerate and benefit from treatment among the oldest old patients with lymphoma are warranted.

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Conflict of interest

Authors report no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient characteristics stratified by country.

Table S2. Treatments administered among patients who received active treatment, stratified for indolent *versus* aggressive subtypes.

Table S3. Main effect excess mortality rate ratios (EMRRs) and 95% confidence intervals (CIs) associated with clinical prognostic factors among patients aged ≥85 years diagnosed with indolent or aggressive lymphoma subtypes.

Fig S1. Cumulative relative survival stratified by calendar period (2000–2008 vs. 2009–2016) and (A) aggressive and (B) indolent lymphoma subtypes.

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