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Age, anthracycline and mortality in 28,000 classic Hodgkin lymphoma patients: cohort study of a complete population

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Abstract

Classic Hodgkin lymphoma (CHL) has an excellent prognosis in younger patients but outcomes are poorer in those aged ≥ 60 years at diagnosis. We used routinely collected English data to assess baseline characteristics, survival and treatment approaches in 28 175 patients with CHL registered between 1997 and 2020 with a particular focus on 1 958 patients aged 60 to 79 years at diagnosis with known first-line chemotherapy regimens. Mortality rates (all causes, lymphoma-specific and other causes) were calculated first without and then with adjustment for available characteristics to identify factors associated with survival.

Survival outcomes for younger patients were better than older ($p < 0.001$) and lymphoma-specific mortality for all patients < 80 years at diagnosis has improved in recent calendar years ($p < 0.001$). Fewer comorbidities and better performance status were associated with better lymphoma-specific survival in older patients ($p < 0.001$). Chemotherapeutic approaches in those aged 60-79 years at diagnosis were heterogenous and the most common regimens, in order, were ABVD, AVD, ChIVPP, VEPEMB, CHOP and single-agent treatments. Lymphoma-specific mortality rates varied substantially between these regimens even following adjustment for known characteristics ($p < 0.001$), with ABVD and AVD having better outcomes than other regimens. Anthracycline use was strongly associated with increased lymphoma-specific survival ($p < 0.001$) and geographical regions where fewer patients were prescribed anthracycline had poorer lymphoma-specific survival ($p = 0.002$).

The findings from this large dataset clearly indicate the importance of anthracycline prescription where possible for older CHL patients, with use of ABVD/AVD preferred over CHOP or VEPEMB. Patients should be carefully optimised prior to commencement of chemotherapy.

Introduction

Hodgkin's Disease, first described in 1832¹ and now known as classic Hodgkin lymphoma (CHL), has a bimodal age distribution with the majority of patients presenting as teenagers or younger adults.²⁻⁴ Initially CHL was uniformly fatal, but its prognosis was transformed with the introduction first of radiotherapy in the 1940s and then of chemotherapy in the 1960s. Currently, over 90% of younger adults are cured of their disease.⁵ However, for the roughly 20% of patients presenting when aged ≥ 60 years (hereafter referred to as "older" patients), survival is below that of their younger counterparts, with cure achieved for only around 60%.⁶

Some possible reasons for the age-related survival differences are known. Disease biology differs, with rarer histological subtypes such as lymphocyte-depleted and mixed cellularity more common among older patients.⁶ Reactivation of infection with Epstein Barr virus also sometimes occurs in the setting of immunosenescence, and is associated with poorer prognosis in older patients with nodular sclerosis histologic subtype.⁷ Older patients are more likely to have medical co-morbidities that may limit the deliverable intensity of treatments and contribute to higher treatment-related mortality.⁸ There are higher levels of toxicity from treatment including infection, cytopenias, cardiac and pulmonary toxicity associated with the standard first-line chemotherapy agent bleomycin.⁹⁻¹² Finally, treatment pathways for younger patients are clearly defined whereas there is scant official guidance on treatment choices for older patients. Thus, treatments used are variable, perhaps partly due to the complexities inherent in managing these patients.

Despite these postulated reasons, there is much that is not known regarding the patterns and determinants of mortality among older patients with CHL. Therefore, we have used data from the English population-based cancer registry to conduct the largest cohort study to date of older CHL patients with defined first-line chemotherapy treatment and documented their mortality from all causes, from lymphoma, and from other causes, according to age and other factors.

Methods

Study population

All patients registered in England from 1st January 1997 to 31st December 2020 with lymphoma were identified using the National Disease Registration Service (NDRS).¹³ Eligible patients with histologically confirmed CHL (excluding nodular lymphocyte-predominant Hodgkin lymphoma) diagnosed at ages 18-89 years were identified (Table S1, Figure S1).

The data received included date of diagnosis, age at diagnosis, sex, ethnicity, geographical region, quintiles of the index of multiple deprivation (IMD)¹⁴, stage, comorbidity index¹⁵, histological subtype, date of death and underlying cause of death up to 30th June 2023. Detailed data on chemotherapy administration started from 1st January 2012¹⁶, with performance status at the time of chemotherapy administration¹⁷ and information on radiotherapy use¹⁸ also recorded.

Objectives

The objectives of the analysis of the whole cohort were to describe survival and mortality by age at diagnosis and year of diagnosis. The objective of the analysis of the first-line chemotherapy sub-cohort was to examine survival and mortality by first-line chemotherapy regimen and baseline patient characteristics.

Statistical methods

Patients entered the study on their date of CHL diagnosis and were followed until the earliest of death or 30th June 2023. Causes of death were coded according to international classification of disease-10. Lymphoma-specific mortality was defined as death due to any lymphoma subtype. Analyses were performed for overall mortality, lymphoma-specific mortality and other cause mortality.

The distribution of patient characteristics in different age groups was compared using the chi-squared test for heterogeneity. Survival of the whole cohort was assessed using the Kaplan-Meier method and significance tests for differences between the groups conducted using the log-rank test. Relative survival, comparing the study population to the general population, was calculated from national life tables stratified by single calendar year, single year of age and sex.

For the first-line chemotherapy sub-cohort, five-year survival was assessed using both crude and adjusted mortality rates. Poisson regression was used to estimate average adjusted mortality rates according to age, sex, stage, comorbidity score, performance status, years since diagnosis, geographic region, IMD and histological subtype with rates according to each variable adjusted for all the others, and tests for trend or heterogeneity between groups used the likelihood ratio test.

To assess the relationship between anthracycline use and mortality, the percentage of patients receiving first-line anthracycline chemotherapy (i.e. containing doxorubicin or mitoxantrone) in each geographical region was calculated using logistic regression, first with no adjustment and then with adjustment for all the variables listed above apart from geographical region. Average mortality rates adjusted for the same variables were then calculated and a test for trend in the rate with increasing use of anthracycline in the region was carried out. This analysis was then repeated following inclusion of anthracycline use by the individual patient in the adjustment.

This study was approved by the South Central - Oxford B Research Ethics Committee (19/S/0227). Individual participants' informed consent was not required. Analyses were performed using Stata V.18.5 and R V.4.4.3. Further methodological information is given in Supplementary Methods.

Results

Survival analysis of the whole cohort

The whole cohort included 28 175 patients of whom 90.5% were followed until either death or 5 years after diagnosis. 45.8% of patients were aged 18-39 years at diagnosis, 25.6% aged 40-59, 23.3% aged 60-79 and 5.4% aged 80-89 (Table 1). Older patients (≥ 60) were more likely to come from a less deprived area, present with advanced stage (3 or 4) disease, have co-morbidities and have histological subtypes other than nodular sclerosis ($p < 0.001$ in all cases).

The mortality rates for lymphoma, all other causes and all causes were highest in the first year following diagnosis for all age-groups except those aged 18-39, for whom the rates were highest in the second year (Figure 1, Table S2). Lymphoma was the predominant cause of death in all age groups and mortality from other causes was also increased (Table S3). Survival in younger patients was close to that of the general population, but for older patients relative survival was much poorer (Figure 2, Table S4).

5-year lymphoma-specific survival (LSS) improved with later calendar year of diagnosis for those aged 60-79 ($p < 0.001$; 1997-2004: 59.5% [95% confidence interval: 57.0-62.0], 2012-

2020: 70.0% [68.3-71.8]) (Figure 3). There was a smaller absolute improvement for younger patients ($p<0.001$ for ages 18-59), while for those aged 80-89 there was no improvement ($p=0.11$; Figure S2). Survival from other causes improved most among older age groups (60-79: $p=0.01$, 80-89: $p<0.001$).

Description of the first-line chemotherapy sub-cohort

A total of 8 345 patients had a record of first-line chemotherapy delivered during 2012-2020 (Table 1). 47.8% of patients were aged 18-39 at diagnosis, 24.6% aged 40-59, 23.5% aged 60-79 and 4.1% aged 80-89. This sub-cohort included 76.7% of those in the whole cohort who were diagnosed aged 18-39, 70.6% of those aged 40-59, 66.6% of those aged 60-79 and 42.4% of those aged 80-89 (Table S5).

Chemotherapy regimens were grouped as follows for analysis: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), AVD (ABVD with omission of bleomycin), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), VEPEMB (vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide), ChIVPP (chlorambucil, vinblastine, procarbazine, prednisolone), single-agent, or other. In patients aged 18-59, ABVD predominated as the first-line treatment regimen (86.5%) but there was much greater heterogeneity of treatment delivered to patients aged 60-89 (Table 1, Figure S3). ABVD remained the most common regimen delivered to patients aged 60-69 (69.2%) but beyond that its use declined with increasing age (70-79: 29.0%, 80-89: 5.3%). The use of anthracyclines of any type as part of a first-line regimen also declined with age (Figure S4), as did the use of bleomycin (Figure S5). Use of ChIVPP was highest in the oldest patients (60-69: 6.5%, 70-79: 27.1%, 80-89: 45.6%). Single-agent regimens delivered to patients aged 60-89 comprised vinblastine ($n=25$, 1.1% of total), brentuximab vedotin ($n=21$ [including the UK-run BREVITY trial], 0.9%), chlorambucil ($n=17$, 0.7%) and gemcitabine ($n=2$, 0.1%) (Figure S6). Use of first-line radical dose radiotherapy varied little with age among patients receiving chemotherapy given with curative intent (ABVD, AVD, CHOP or VEPEMB) (24.2%, 22.0% and 24.2% respectively, Figure S7).

Factors associated with mortality

After adjustment of each factor for all the other recorded factors, the lymphoma-specific mortality rate among those aged 60-79 at diagnosis increased with increasing age, stage, comorbidity score, and performance status ($p<0.001$ in all cases), and it decreased with increasing years since diagnosis ($p<0.001$) (Figure 4). This shows that these factors were all independently associated with lymphoma mortality in this group. In patients aged 60-79 at diagnosis, the lymphoma-specific mortality rate was particularly high in patients aged 75-79, patients with comorbidity score 2+ or performance status 2+ and during the first year following diagnosis. For younger patients, trends were mostly similar, but they often did not reach statistical significance and in every case the absolute difference in the mortality rate across the levels of each factor was much larger in those aged 60-79 than in those aged 18-39 or 40-59 (Figures 4 and S8). There was no significant variation in lymphoma-specific mortality with histological subtype in any age-group.

For patients aged 60-79 the lymphoma mortality rate was highest where chemotherapy was commenced within four weeks of diagnosis but after that it did not vary up to 12 weeks from diagnosis (Figure S9).

In patients aged 60-79, mortality from causes other than lymphoma increased with increasing age at diagnosis, comorbidity score and performance status, and also with male sex and stage III/IV disease, but for all these factors the variation across the categories was much smaller than the corresponding variation in mortality from lymphoma (Figure S10). Patterns of mortality

from all causes were similar to that from lymphoma, except that mortality was higher in males than females (Figure S11).

Choice of first-line treatment and survival in patients aged 60-79

For patients aged 60-79, there was substantial variability between the crude rates for overall mortality, lymphoma-specific mortality, and mortality from other causes according to the first-line chemotherapy regimen delivered ($p<0.001$ for all three endpoints) (Figure 5). The five-year LSS in the six groups was: ABVD 83.8% (81.9-85.6), AVD 80.4% (77.4-83.0), CHOP 67.6% (61.6-72.9), VEPEMB 70.4% (65.2-74.9), ChIVPP 46.1% (41.8-50.3) and single-agent treatment 16.5% (10.5-23.7).

Comparison of baseline characteristics for the groups receiving different first-line regimens showed that patients receiving ABVD were likely to be younger and have a better performance status and lower comorbidity score (Table S6). Patients in receipt of AVD, CHOP, VEPEMB and ChIVPP were more likely to be older (all $p\leq 0.002$) and patients in receipt of ChIVPP and single-agent treatments were more likely to have a poorer performance status at commencement of chemotherapy ($p\leq 0.001$). There was also variation between the geographical regions of England in the proportion of patients receiving each chemotherapy regimen ($p<0.001$ for every regimen), and a shift over calendar year, with AVD more commonly chosen in 2016-20 than in 2012-15 while ABVD and single-agent regimens were less commonly chosen ($p<0.001$).

Following adjustment for the known characteristics of the cohort, the lymphoma-specific mortality rate still varied substantially between the different regimens; rates for patients receiving ABVD and patients receiving AVD were identical (Figures 6 and S12) but patients receiving VEPEMB or CHOP had higher mortality. Patients receiving an anthracycline-containing regimen had substantially better 5-year adjusted LSS than those who received an anthracycline-free regimen (79.7% [77.7-81.5] versus 59.8% [56.0-63.4]), $p<0.001$; Figure S13). Patients in receipt of multi-agent regimens had significantly greater adjusted 5-year LSS than those in receipt of single-agent treatments ($p<0.001$; Figure S14) and, although ChIVPP is a multiagent regimen, patients receiving it had markedly higher mortality than other multiagent regimens (Figure 6).

68.6% of patients completed chemotherapy as planned. Between 27% and 48% of patients in receipt of non-ABVD regimens required upfront modification of treatment for comorbidities at baseline compared with only 19% for patients in receipt of ABVD (Table S7). Between 18% and 26% of patients required dose reduction of chemotherapy during treatment, with the highest rates for ChIVPP.

Information regarding dose reduction was available for 80.2% of patients who received an anthracycline-containing regimen and dose reduction of chemotherapy was required for 18.6% of them. Despite this, there was no decrement to adjusted LSS following adjustment for baseline characteristics ($p=0.8$; Figure S15). With follow-up starting from 3 months after diagnosis to exclude those with early mortality following chemotherapy commencement, a slight but non-significant reduction in adjusted overall survival (OS) was seen in the 15.3% who required early cessation of chemotherapy ($p=0.07$; Figure S16).

Where radical doses of radiotherapy were delivered to patients receiving curative approaches to chemotherapy (defined for this purpose as ABVD, AVD, CHOP or VEPEMB) this was associated with improved adjusted OS ($p<0.001$), LSS ($p=0.004$), and other cause survival ($p=0.006$) compared to those not in receipt of such radiotherapy, with rates adjusted for factors including stage (Figure S17).

Regional variation in anthracycline prescription

Most patients (>95%) aged 18-39 or 40-59 received anthracycline in first-line CHL treatment irrespective of the geographical region in which they lived (Figures S18 and S19). However, for patients aged 60-79, there was substantial variation between the nine English regions in the choice of chemotherapy regimen, and the crude percentages of patients aged 60-79 receiving anthracycline-based chemotherapy varied by 18.7% between the region with highest (90.1%) and lowest (71.4%) anthracycline use (Figure 7). Following adjustment of these percentages for baseline characteristics within each region, a range of 21.7% remained between the highest (90.7%) and lowest (69.0%) regions. There was also a highly significant association between regional anthracycline use and lymphoma-specific mortality in patients aged 60-79, varying from 50.91 per 1000 person years in the region with the highest anthracycline use to 83.3 per 1000 person years in the region with the lowest anthracycline use ($p=0.002$ for trend, LSS mortality rate ratio lowest use versus highest use: 1.6). When anthracycline use by individual patients was added into the model, this trend was much less pronounced and was no longer statistically significant ($p=0.1$).

In contrast to the lymphoma-specific mortality, there was no significant trend in non-lymphoma mortality for patients aged 60-79 at diagnosis, and no significant trends in either lymphoma-specific or non-lymphoma mortality among patients age 18-39 or 40-59 years at diagnosis (Figures S18 and S19).

Patients aged 80-89 at diagnosis

A total of 340 patients aged 80-89 at diagnosis were in the first-line chemotherapy sub-cohort and three-quarters of them had performance status of 1 or above (Table 1). ChIVPP was the most common regimen delivered (45.6%, Table 1). Receipt of anthracycline was associated with better adjusted LSS (5-year LSS 61.3% [54.5-67.5] with anthracycline use versus 32.1% (25.5-38.7) without, $p<0.001$; Figure S20).

Discussion

We have presented a population-based study of cause-specific mortality in over 28 000 CHL patients diagnosed in England during 1997 to 2020. We have demonstrated that lymphoma-specific survival has improved with calendar year of diagnosis for those aged 60-79, although it still lags behind that of younger patients. We have focussed on the nearly 2000 older patients aged 60-79 diagnosed during 2012 to 2020 with documented modern chemotherapy and observed that, for those receiving ABVD or AVD, both the lymphoma-specific mortality rate and the mortality rate from all causes is lower than among those receiving other regimens. Within this group, those living in geographical regions where a greater proportion of the first-line chemotherapy included an anthracycline had lower lymphoma-specific mortality.

Older CHL patients remain a challenging group for clinicians to manage due to physiological differences compared with younger patients and a lack of official guidance regarding management, especially where there are multiple comorbidities and a perceived lack of fitness for intensive chemotherapy. Several recent studies have described baseline characteristics of older CHL patients and examined factors affecting choices of treatment and survival (Table S8).^{6, 8, 10, 11, 19-33} Patient and disease-related factors associated with better survival in these studies have included younger age at diagnosis, female sex, better socioeconomic status, absence of mixed cellularity histology, early stage CHL, better performance status and fewer comorbidities. Treatment with anthracycline-containing regimens and particularly ABVD-like treatments have been associated with improved survival but these are given to the youngest fittest patients. A number of predictive scores have been developed to predict survival at baseline in all older patients and those treated intensively.^{26, 31, 33} Our findings are broadly in

line with those of these previous studies, except that we did not find better lymphoma-specific survival in females, nor any variation in survival between patients with different histological subtypes.

Among patients aged <60 and given first-line chemotherapy, the overwhelming majority of patients received ABVD, but at older ages a substantial proportion received other regimens, ABVD being used in the youngest and fittest older patients. Following adjustment for comorbid factors, the lymphoma-specific mortality rate was identical in patients receiving ABVD or AVD, but higher for those receiving VEPEMB or CHOP and higher still for those receiving ChIVPP or single-agent regimens (which may be expected, as they are often used with palliative intent). Analysis of chemotherapy choices over calendar period demonstrated that the regimens at either end of the spectrum of tolerability—ABVD and single-agent regimens—were favoured more in the earlier diagnostic period, suggesting an evolving appreciation for the greater efficacy of multi-agent regimens for older patients and a move away from use of bleomycin in older patients.

The strong negative effect on lymphoma-specific mortality of increasing age—even within the age-band 60-79— was striking, as was the effect of poor performance status and comorbidities, underscoring the importance of adequate management of these factors at diagnosis. Beyond the first four weeks following CHL diagnosis there was no association between increased waiting time from diagnosis to commencement of treatment and increased lymphoma-specific mortality. This may suggest that, whilst the aim should always be prompt initiation of chemotherapy, taking some time to optimise medical comorbidities and performance status prior to chemotherapy in older patients may not be detrimental, unless they require urgent treatment. This aligns with similar studies in CHL showing no association with delayed time to treatment and reduced survival in matched populations^{34, 35}; similarly in a study of patients with diffuse large B cell lymphoma shorter time to treatment was associated with adverse clinical factors and significantly reduced 2-year event-free survival, which could reflect the difficulty with clinical trial enrolment of patients who are very unwell at diagnosis and may lead to bias in clinical trial reporting³⁶.

For patients in receipt of anthracycline-based treatment there was no association between dose reduction during treatment and increased mortality after adjustment for baseline characteristics, suggesting that appropriate treatment modification based on patient fitness is a suitable approach. For patients who had early cessation of chemotherapy, overall mortality was slightly but not significantly higher than for those who did not, suggesting that completing chemotherapy with dose modification where appropriate may be preferable to fully stopping treatment.

Radical doses of radiotherapy combined with curative approaches to first-line chemotherapy was associated with improved adjusted survival. Although this is likely substantially explained by strong selection bias, radiotherapy is well known to improve local disease control in CHL and some of this effect may be causative. This highlights the importance of utilising this usually well-tolerated treatment modality for standard indications in older CHL patients where there is less concern over late effects, a common reason for radiotherapy omission in younger patients.

Our finding that among older patients there is wide variation between the different geographical regions of England in the proportion of first-line chemotherapy prescriptions that include anthracyclines was unexpected. It underscores the lack of standardisation of chemotherapeutic approaches for older CHL patients and the paucity of guidance available for management of this patient group, and variation in the resulting mortality associated with this variation may be considered as a natural experiment.³⁷

A strength of this study is the size and completeness of the whole cohort, covering the entire population of England, allowing derivation of statistically meaningful results from 'real world' data that are therefore directly applicable to clinical practice. Only one larger contemporary series of older CHL patients has been reported⁶ but this did not examine the effect of differing first-line chemotherapy regimens on survival and mortality rates, making the current study the largest exploration of this important factor.

There are however some limitations to this study. The analyses are limited to variables that are routinely collected by the NDRS and it was not possible to analyse progression-free survival as data on recurrence is not collected. There were also missing data in other variables analysed in the first-line chemotherapy sub-cohort (performance status=19.6%, stage=8.8%, histological subtype=2.3%). Registration of underlying cause of death followed World Health Organization guidelines but may be subject to inaccuracies by reporting clinicians.³⁸ Information on chemotherapy was available for only two-thirds of the patients diagnosed during 2012 to 2020 at ages 60-79, reflecting gradual roll-out of national data collection, meaning that the groups in receipt of differing regimens or anthracycline-based treatment are not complete. As this is an observational study it is not possible to fully out-rule confounding in our adjusted analyses; however, in the analysis of lymphoma mortality rates following anthracycline-containing regimens (ABVD, AVD, VEPEMB and CHOP) there is not a substantial difference between the crude and adjusted mortality rates as shown in Figures 5 and 6, suggesting an absence of significant residual confounding. Similarly, although we cannot conclude firmly that the observed differences between the lymphoma mortality in the different regions is due to the different levels of anthracycline prescription, the strong correlation between the lymphoma-specific mortality rate and the regional use of anthracyclines does suggest a causal link between increased anthracycline use and improved survival.

Novel therapies have been successfully incorporated into the first-line management of CHL and the therapeutic landscape is moving away from the chemotherapeutic approaches described in our cohort. Brentuximab vedotin (BV) combined with AVD as a chemotherapy backbone has been evaluated against ABVD in advanced stage CHL in the ECHELON-1 randomised controlled trial (RCT) with demonstration of similar efficacy and less pulmonary toxicity³⁹ and is approved for use in many territories including the United Kingdom as of April 2025. Modulation of the immune microenvironment as a therapeutic strategy is attractive in older CHL patients who have distinct immunological signatures in comparison to younger patients⁴⁰ and this has been evaluated in the SWOG S1826 RCT which compared AVD in combination with the checkpoint inhibitor (CPI) nivolumab versus BV-AVD.⁴¹ A pre-specified subgroup analysis showed a superior 2-year OS of 96% in older N+AVD-treated CHL patients.⁴² This approach will likely define the new standard of care for older CHL management if universally reimbursed.

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Patient Characteristics	Whole Cohort (n=28,175)				Sub-Cohort (n=8345) First-Line Chemotherapy			
	18-39y	40-59y	60-79y	80-89y	18-39y	40-59y	60-79y	80-89y
Total	12911 (100%)	7200 (100%)	6555 (100%)	1509 (100%)	3993 (100%)	2054 (100%)	1958 (100%)	340 (100%)
Year of diagnosis	p<0.001				-			
1997-2004	3937 (30.5)	2046 (28.4)	1667 (25.4)	295 (19.6)	-	-	-	-
2005-2011	3770 (29.2)	2244 (31.2)	1948 (29.7)	411 (27.2)	-	-	-	-
2012-2020	5204 (40.3)	2910 (40.4)	2940 (44.9)	803 (53.2)	3993 (100.0)	2054 (100.0)	1958 (100.0)	340 (100.0)
Sex	p<0.001				p<0.001			
Male	6805 (52.7)	4551 (63.2)	3737 (57.0)	704 (46.7)	2063 (51.7)	1289 (62.8)	1133 (57.9)	173 (50.9)
Female	6106 (47.3)	2649 (36.8)	2818 (43.0)	805 (53.3)	1930 (48.3)	765 (37.2)	825 (42.1)	167 (49.1)
Ethnicity	p<0.001				p<0.001			
White	10236 (79.3)	5924 (82.3)	5672 (86.5)	1333 (88.3)	3066 (76.8)	1655 (80.6)	1718 (87.8)	322 (94.7)
Black	340 (2.6)	259 (3.6)	94 (1.4)	8 (0.5)	107 (2.7)	92 (4.5)	32 (1.6)	<5 (<1)
Asian	930 (7.2)	76 (1.1)	272 (4.1)	34 (2.2)	360 (9.0)	131 (6.4)	108 (5.5)	10 (2.9)
Unknown/ other	1405 (10.9)	631 (8.8)	517 (7.9)	134 (8.9)	460 (11.5)	176 (8.6)	100 (5.1)	7 (2.1)
Geographical region	p<0.001				p<0.001			
East Midlands	1128 (8.7)	702 (9.8)	572 (8.7)	139 (9.2)	384 (9.6)	240 (11.7)	206 (10.5)	34 (10.0)
East of England	1517 (11.8)	845 (11.7)	801 (12.2)	208 (13.7)	453 (11.3)	234 (11.4)	235 (12.0)	42 (12.4)
London	2392 (18.5)	1105 (15.4)	786 (12.0)	170 (11.3)	770 (19.3)	318 (15.5)	206 (10.5)	42 (12.4)
North East	589 (4.6)	342 (4.8)	349 (5.3)	65 (4.3)	174 (4.4)	100 (4.9)	109 (5.6)	18 (5.3)
North West	1561 (12.1)	887 (12.3)	830 (12.7)	171 (11.3)	477 (12.0)	232 (11.3)	245 (12.5)	43 (12.7)
South East	2080 (16.1)	1210 (16.8)	1067 (16.3)	277 (18.4)	633 (15.9)	325 (15.8)	321 (16.4)	52 (15.3)
South West	1182 (9.2)	720 (10.0)	732 (11.2)	182 (12.1)	391 (9.8)	231 (11.3)	237 (12.1)	37 (10.9)
West Midlands	1297 (10.1)	722 (10.0)	705 (10.8)	141 (9.3)	342 (8.6)	187 (9.1)	177 (9.0)	32 (9.4)
Yorks/Humber	1165 (9.0)	667 (9.3)	713 (10.9)	156 (10.3)	369 (9.2)	187 (9.1)	222 (11.3)	40 (11.8)
Index of multiple deprivation	p<0.001				p<0.001			
1- most deprived	2734 (21.2)	1497 (20.8)	1145 (17.5)	201 (13.3)	828 (20.7)	483 (23.5)	350 (17.9)	43 (12.7)
2	2708 (21.0)	1465 (20.4)	1213 (18.5)	281 (18.6)	860 (21.5)	403 (19.6)	357 (18.2)	67 (19.7)
3	2684 (20.8)	1422 (19.8)	1496 (22.8)	311 (20.6)	842 (21.1)	413 (20.1)	424 (21.7)	67 (19.7)
4	2442 (18.9)	1434 (19.9)	1362 (20.8)	376 (24.9)	748 (18.7)	387 (18.8)	404 (20.6)	79 (23.2)
5- least deprived	2343 (18.2)	1382 (19.2)	1339 (20.4)	340 (22.5)	715 (17.9)	368 (17.9)	423 (21.6)	84 (24.7)
Stage	p<0.001				p<0.001			
1	811 (11.7)	658 (17.3)	615 (17.3)	118 (15.0)	252 (7.0)	231 (12.2)	211 (11.8)	22 (7.3)
2	3278 (47.4)	1322 (34.7)	837 (23.6)	194 (24.7)	1701 (46.9)	650 (34.4)	414 (23.1)	65 (21.7)
3	1154 (16.7)	743 (19.5)	894 (25.2)	257 (32.7)	610 (16.8)	380 (20.1)	488 (27.2)	109 (36.3)
4	1672 (24.2)	1082 (28.4)	1201 (33.9)	218 (27.7)	1062 (29.2)	631 (33.4)	681 (38.0)	104 (34.7)
Unknown	5996 (-)	3395 (-)	3008 (-)	722 (-)	368 (-)	162 (-)	164 (-)	40 (-)
Comorbidity index	p<0.001				p<0.001			
0	8069 (95.0)	4227 (87.0)	3172 (68.4)	676 (58.7)	3771 (94.5)	1756 (85.5)	1313 (67.1)	197 (57.9)
1	338 (4.0)	374 (7.7)	707 (15.2)	208 (18.1)	186 (4.7)	184 (9.0)	311 (15.9)	59 (17.4)
2	48 (0.6)	156 (3.2)	404 (8.7)	128 (11.1)	25 (0.6)	73 (3.6)	187 (9.6)	48 (14.1)
3+	35 (0.4)	102 (2.1)	354 (7.6)	140 (12.2)	10 (0.3)	41 (2.0)	147 (7.5)	36 (10.6)
Unknown	4421 (-)	2341 (-)	1918 (-)	357 (-)	<5 (-)	-	-	-
Histological subtype	p<0.001				p<0.001			
Nodular sclerosis	7929 (61.4)	3274 (45.5)	2236 (34.1)	455 (30.2)	2140 (53.6)	766 (37.3)	578 (29.5)	88 (25.9)
Mixed cellularity	1383 (10.7)	1152 (16.0)	1317 (20.1)	262 (17.4)	408 (10.2)	311 (15.1)	326 (16.7)	47 (13.8)
Lymphocyte-rich	412 (3.2)	413 (5.7)	291 (4.4)	45 (3.0)	91 (2.3)	120 (5.8)	87 (4.4)	9 (2.7)
Lymphocyte-depleted	42 (0.3)	51 (0.7)	75 (1.1)	26 (1.7)	7 (0.2)	8 (0.4)	15 (0.8)	<5 (<1)
Other	3145 (24.4)	2310 (32.1)	2636 (40.2)	721 (47.8)	1347 (33.7)	849 (41.3)	952 (48.6)	193 (56.8)
Performance status	-				p<0.001			
0	-	-	-	-	2507 (76.9)	1116 (67.5)	661 (43.2)	64 (24.2)
1	-	-	-	-	662 (20.3)	435 (26.3)	601 (39.5)	114 (43.2)
2+	-	-	-	-	90 (2.8)	103 (6.2)	269 (17.6)	86 (32.6)
Unknown	-	-	-	-	734 (-)	400 (-)	427 (-)	76 (-)
First-line chemotherapy	-				p<0.001			
ABVD	-	-	-	-	3462 (86.7)	1768 (86.1)	998 (51.0)	18 (5.3)
AVD	-	-	-	-	121 (3.0)	118 (5.7)	323 (16.5)	47 (13.8)
CHOP	-	-	-	-	25 (0.6)	25 (1.2)	96 (4.9)	22 (6.5)
VEPEMB	-	-	-	-	-	<5 (<1)	129 (6.6)	33 (9.7)
ChlVPP	-	-	-	-	5 (0.1)	23 (1.1)	310 (15.8)	155 (45.6)
Single-agent	-	-	-	-	<5 (<1)	<5 (<1)	33 (1.7)	32 (9.4)
Other	-	-	-	-	379 (9.5)	113 (5.5)	69 (3.5)	33 (9.7)
Radiotherapy	-				p<0.001			
First-line curative	-	-	-	-	837 (21.0)	522 (25.4)	420 (21.5)	56 (16.5)
Palliative	-	-	-	-	141 (3.5)	59 (2.9)	121 (6.2)	18 (5.3)
Not given	-	-	-	-	3015 (75.5)	1473 (71.7)	1417 (72.4)	266 (78.2)
Status by 5 years follow-up								
Alive	10739 (83.2)	5525 (76.7)	2997 (45.7)	236 (15.6)	2579 (64.6)	1278 (62.2)	826 (42.2)	68 (20.0)
Censored at <5 years follow up	1433 (11.1)	681 (9.5)	508 (7.7)	63 (4.2)	1312 (32.9)	607 (29.6)	453 (23.1)	46 (13.5)
Died in year 1	161 (1.2)	444 (6.2)	1735 (26.5)	795 (52.7)	20 (0.5)	66 (3.2)	321 (16.4)	122 (35.9)
Died in years 2-5	578 (4.5)	550 (7.6)	1315 (20.1)	415 (27.5)	82 (2.1)	103 (5.0)	358 (18.3)	104 (30.6)

Table 1: Characteristics of the whole cohort and first-line chemotherapy sub-cohort.

Chemotherapy, radiotherapy and performance status were recorded only from 1st January 2012.

p-values are for heterogeneity between categories.

y= age at diagnosis (years). Yorks/Humber= Yorkshire and the Humber. ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD without bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide. ChIVPP= chlorambucil, vinblastine, procarbazine, prednisolone.

Percentages relate to % of patients.

Figure legends

Figure 1: Overall, lymphoma-specific and other cause annual mortality rates (left panel) and survival (right panel) by age at diagnosis for the whole cohort.

See Table S2 for numbers at risk, numbers of deaths and mortality rates.

Vertical lines and shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between categories of age at diagnosis.

y= age at diagnosis (years).

Figure 2: Relative survival for the whole cohort and first-line chemotherapy sub-cohort by age at diagnosis.

See Table S3 for numbers at risk.

p-values are for heterogeneity between categories of calendar year.

y= age at diagnosis (years).

Figure 3: Overall, lymphoma-specific and other cause survival by year of diagnosis for the whole cohort by age at diagnosis.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between categories of calendar year.

y= age at diagnosis (years).

Figure 4: Adjusted lymphoma-specific mortality rates per 1000 person-years by patient and lymphoma characteristics for patients aged 40-59 and 60-79 years at diagnosis in the first-line chemotherapy sub-cohort.

Each characteristic is adjusted for all the others using Poisson regression. Age is adjusted for in 5-year intervals from 40-59 and 60-79. *p*-values are for trend except for region and histological subtype where they are for heterogeneity.

See Figure S8 for adjusted lymphoma-specific mortality in patients aged 18-39 years at diagnosis and Figures S10 and S11 for adjusted all-cause and adjusted other cause mortality in patients aged 18-39, 40-59 and 60-79 years at diagnosis respectively.

y= age at diagnosis (years). M= male. F= female. Yorks/Humber= Yorkshire and the Humber. IMD= index of multiple deprivation. NOS= not otherwise specified.

Figure 5: Overall, lymphoma-specific and other cause crude mortality rates and survival in patients aged 60-79 years at diagnosis by receipt of the six most common first-line chemotherapy regimens in the first-line chemotherapy sub-cohort.

Patients with no recorded cause of death are included in the deaths from all causes, but not in the lymphoma or the non-lymphoma deaths.

Patients not in receipt of one of the six most common first-line chemotherapy regimen groupings delivered to older patients are excluded.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD without bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide. ChIVPP= chlorambucil, vinblastine, procarbazine, prednisolone.

Figure 6: Adjusted overall, lymphoma-specific and other cause mortality rates and survival in patients aged 60-79 years at diagnosis by receipt of the six most common first-line chemotherapy regimens in the first-line chemotherapy sub-cohort.

Patients with no recorded cause of death are included in the deaths from all causes, but not in the lymphoma or the non-lymphoma deaths. Patients not in receipt of one of the six most common first-line chemotherapy regimen groupings delivered to older patients are excluded.

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression. Age is adjusted for in 5-year intervals from 60-79.

The shaded areas represent 95% confidence intervals. *p*-values are for heterogeneity between groups.

ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD without bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide. ChIVPP= chlorambucil, vinblastine, procarbazine, prednisolone.

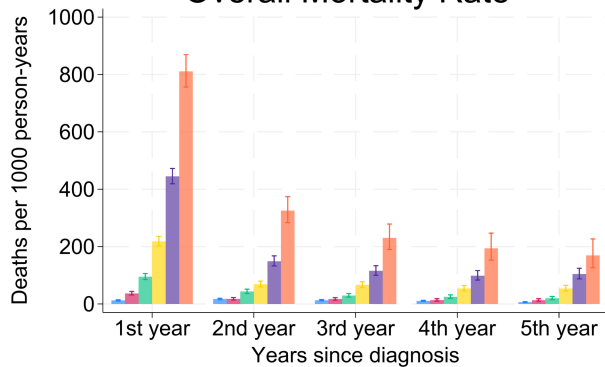
Figure 7: Regional variation in anthracycline use and adjusted lymphoma-specific and other cause mortality rates in first-line chemotherapy sub-cohort in patients aged 60-79 years at diagnosis.

Panel A shows the unadjusted and adjusted percentages of patients receiving anthracycline by region with adjustment for age, sex, stage, comorbidity status, performance status, deprivation index and histological subtype by logistic regression. Panel B shows mortality rates adjusted for age, sex, stage, comorbidity score, performance status, year since diagnosis, deprivation index and histological subtype using Poisson regression, with regions ordered from highest regional level of adjusted anthracycline use to lowest. Panel C shows the same mortality rates but including adjustment for receipt of anthracycline on an individual patient basis.

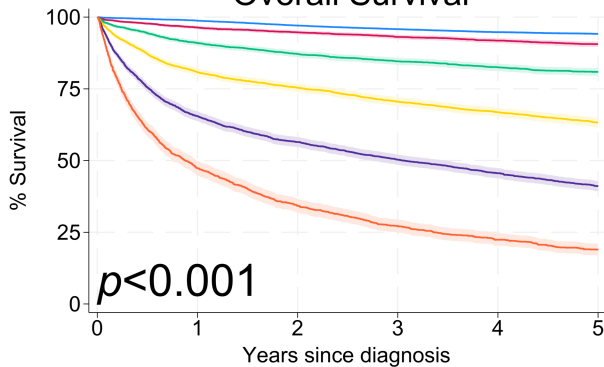
Age is adjusted for in 5-year intervals from 60-79. *p*-values are for trend.

Yorks/Humber= Yorkshire and the Humber.

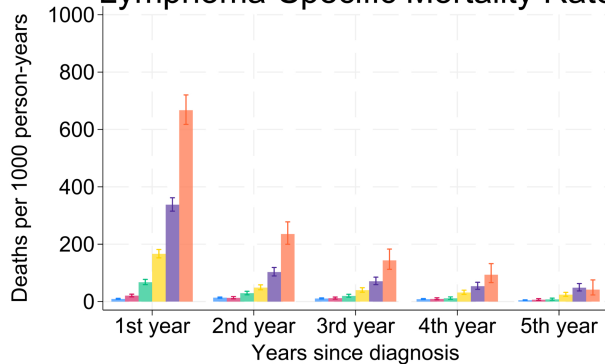
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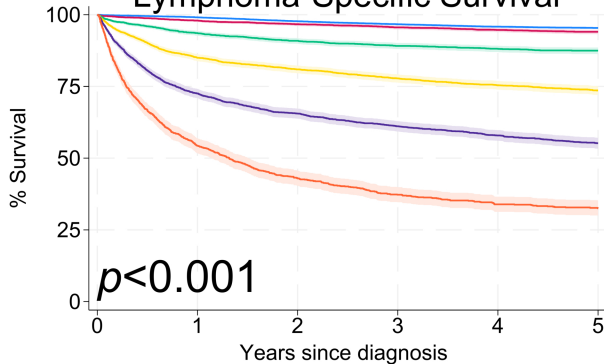
Overall Survival



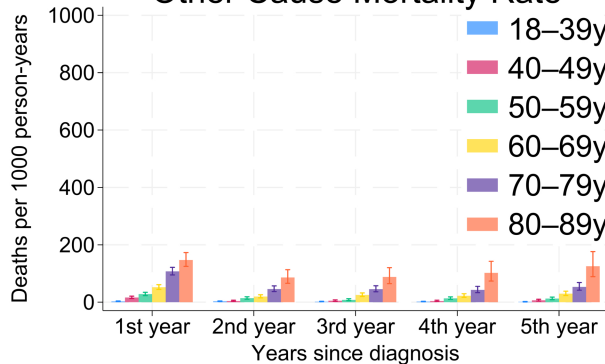
Lymphoma-Specific Mortality Rate



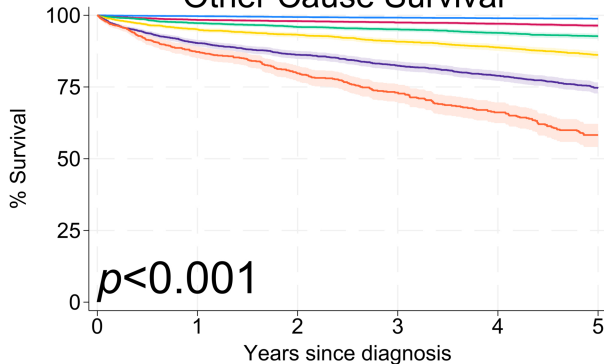
Lymphoma-Specific Survival



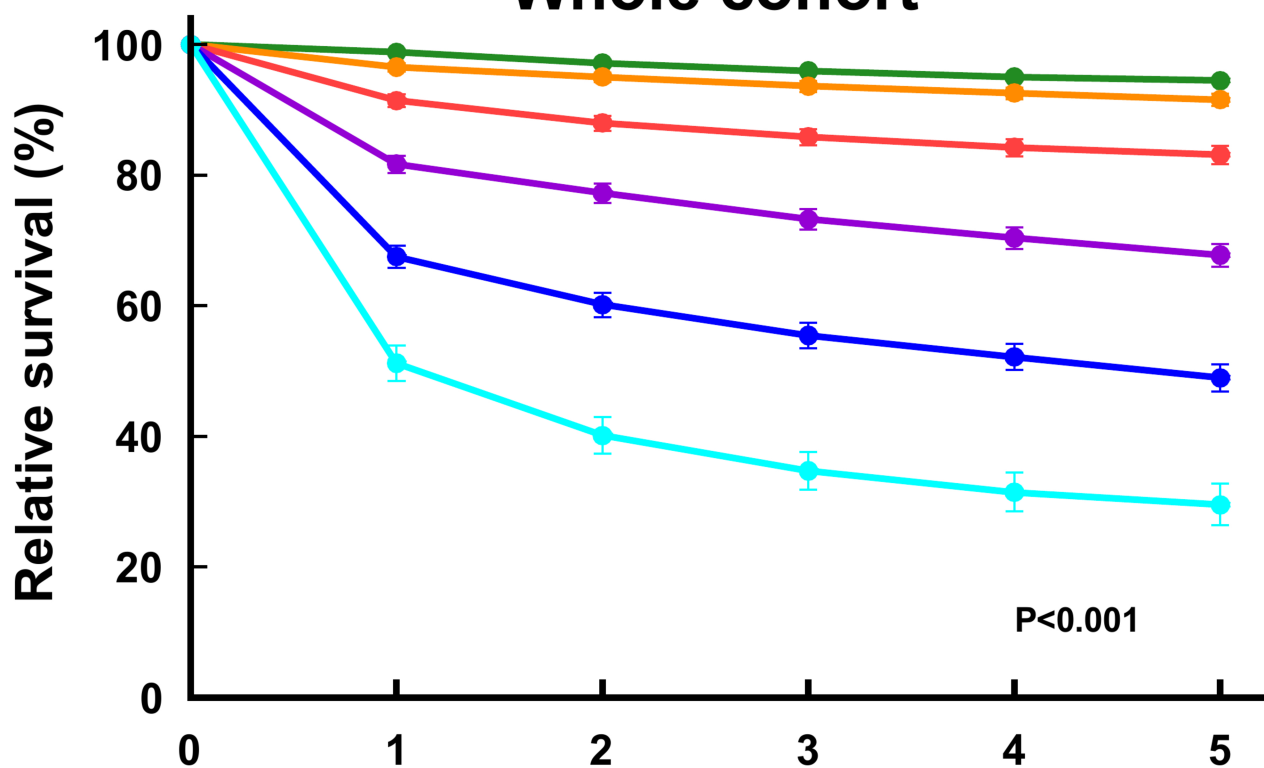
Other Cause Mortality Rate



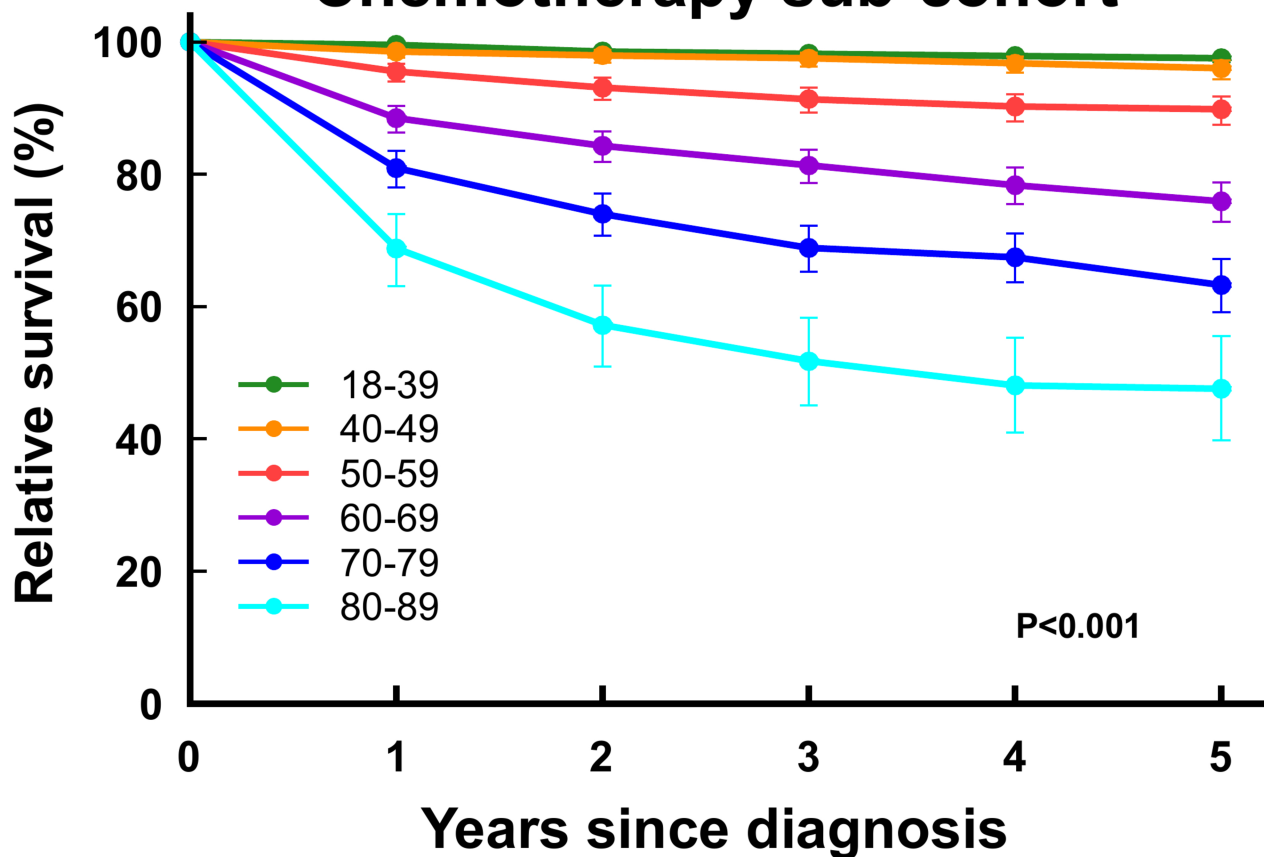
Other Cause Survival

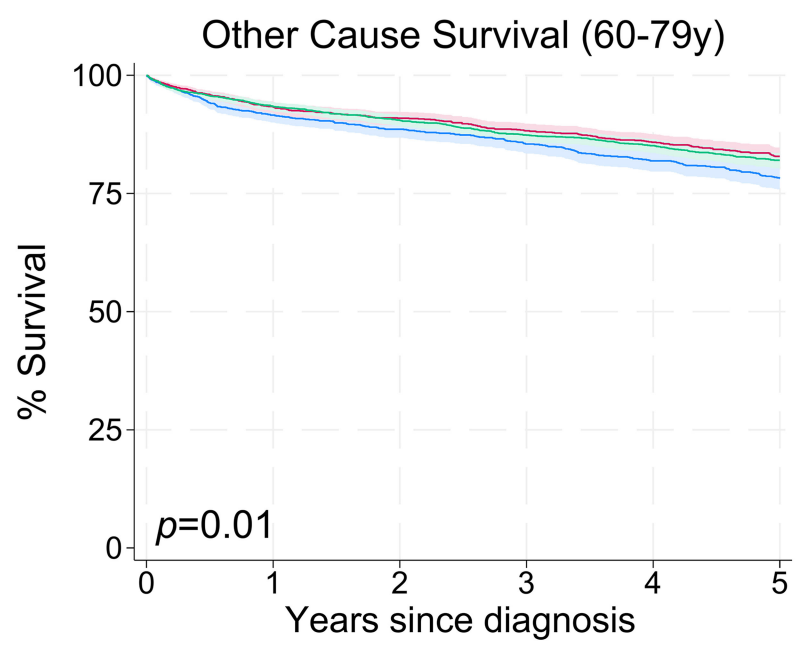
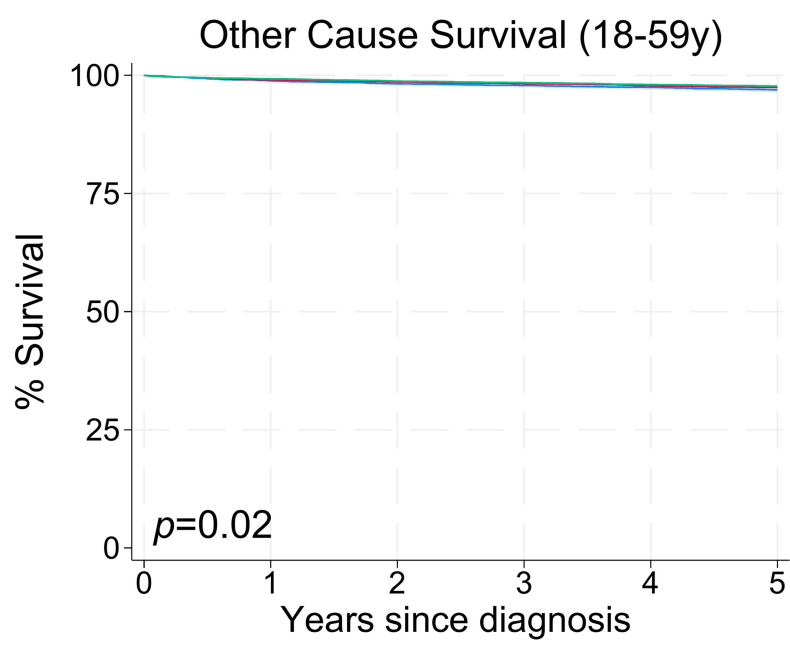
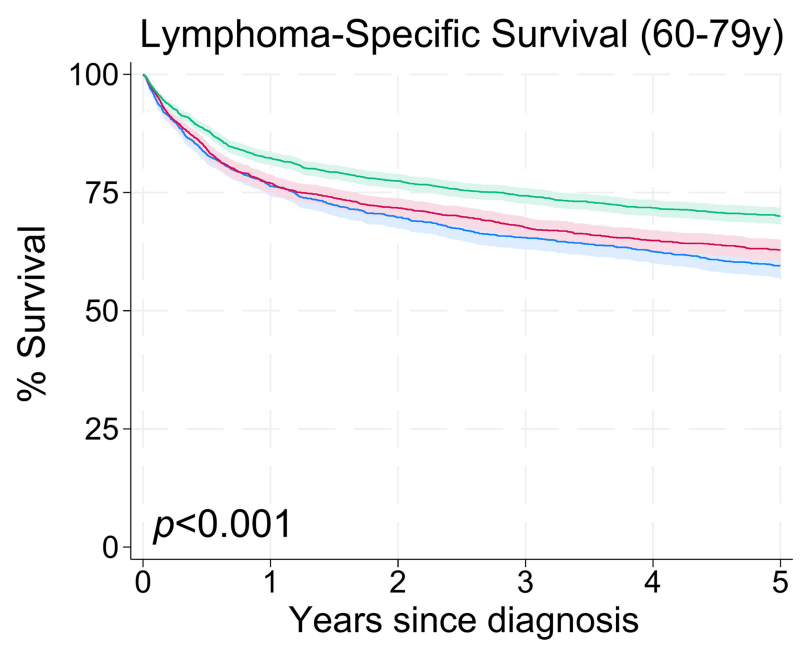
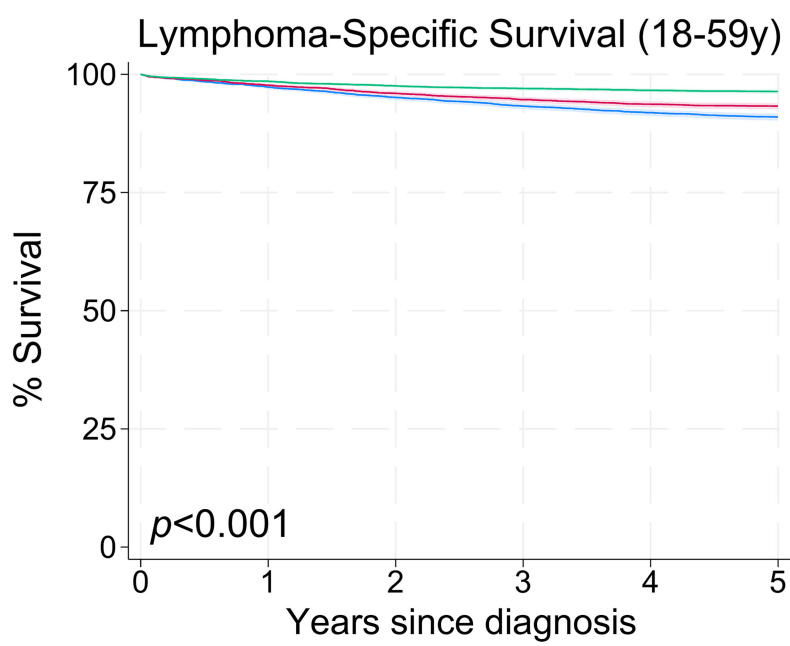
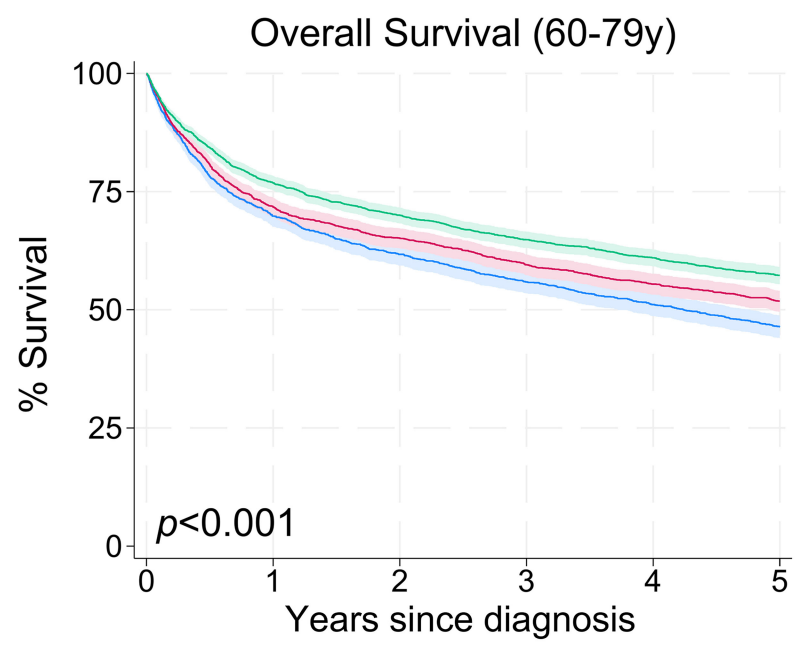
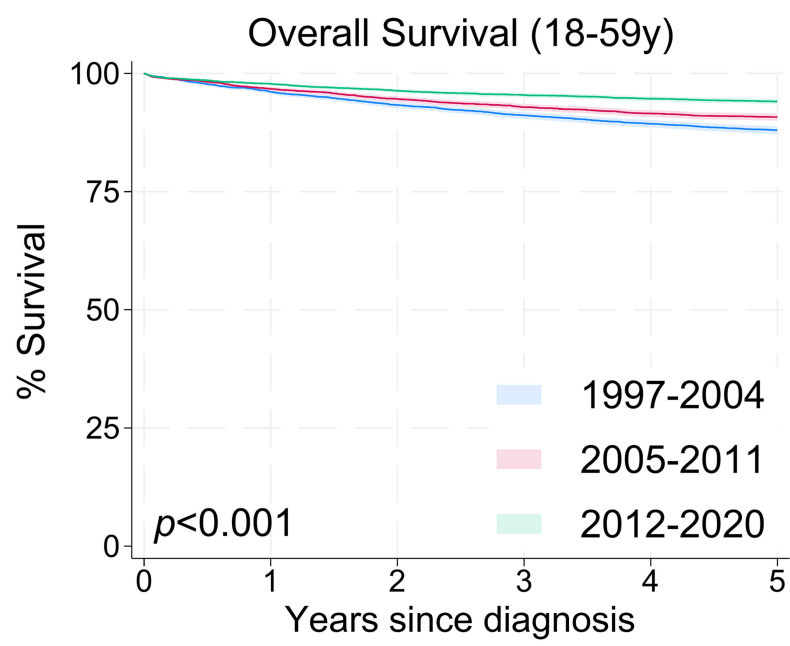


Whole cohort



Chemotherapy sub-cohort





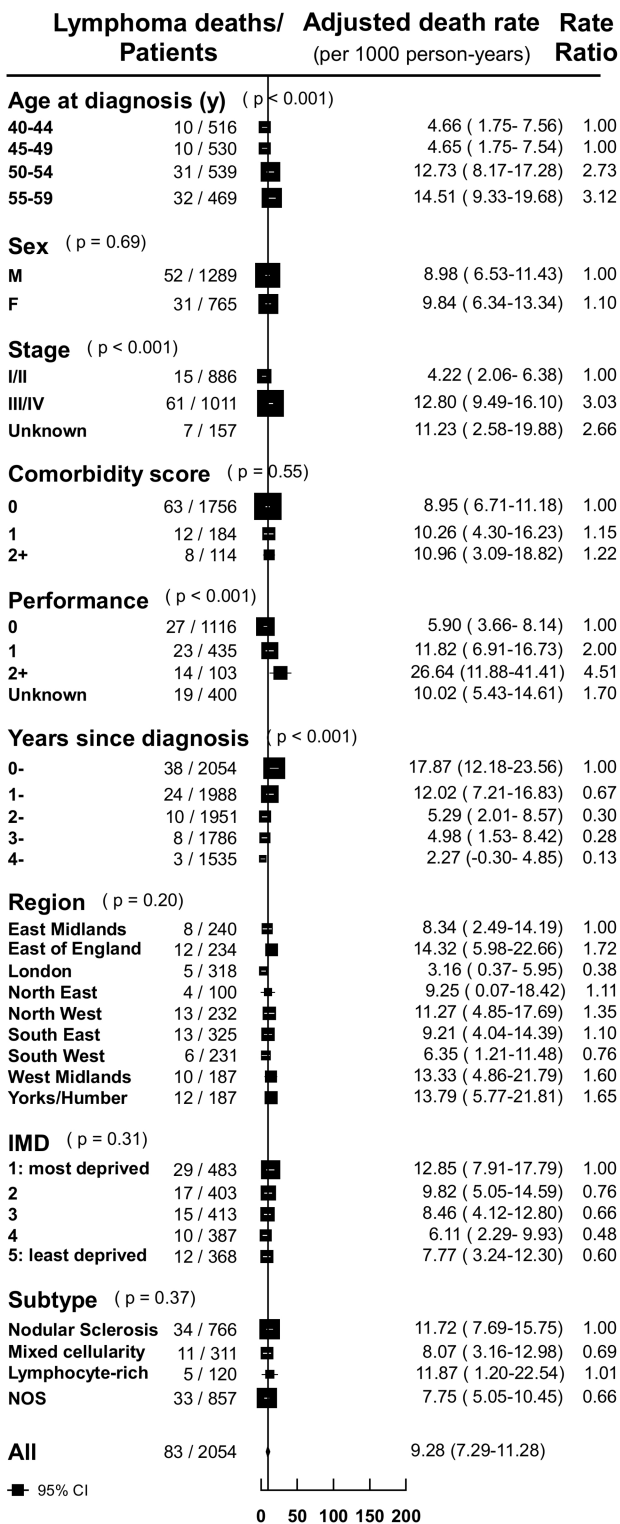
Number at risk

1997-2004	5983	5751	5584	5452	5347	5266
2005-2011	6014	5819	5689	5586	5505	5459
2012-2020	8114	7936	7818	7302	6394	5539

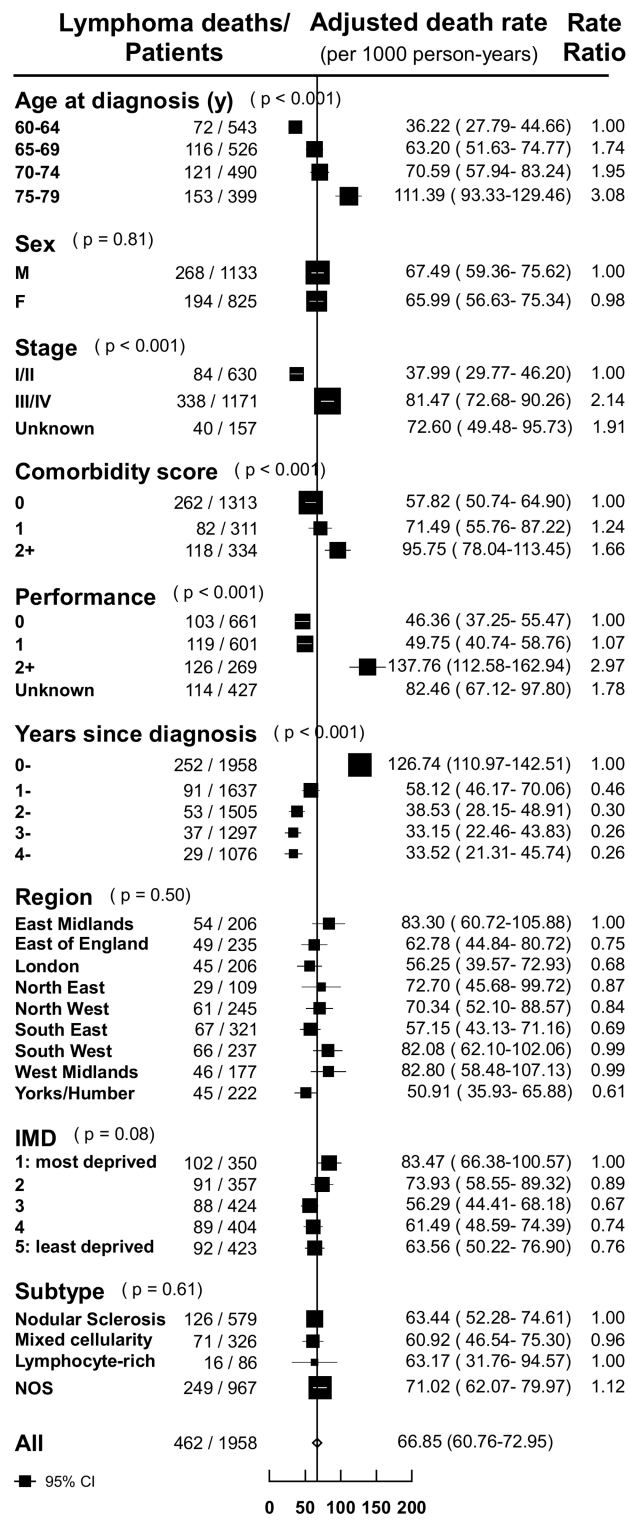
Number at risk

1997-2004	1667	1164	1029	932	852	774
2005-2011	1948	1397	1269	1160	1080	1010
2012-2020	2940	2259	2058	1792	1509	1213

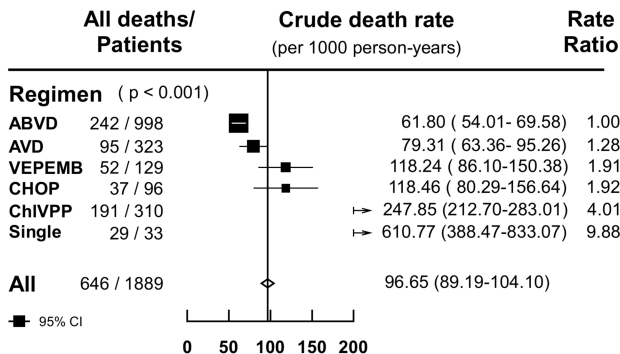
Age 40-59y



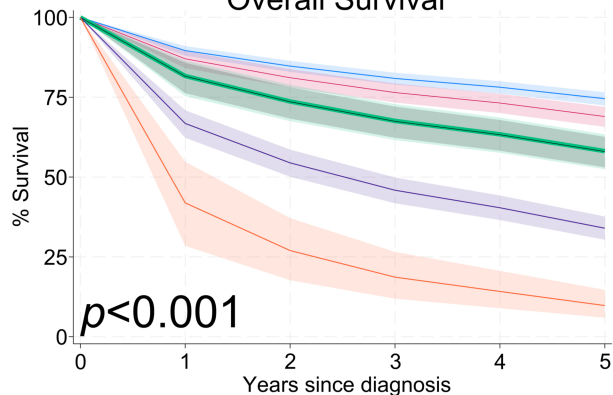
Age 60-79y



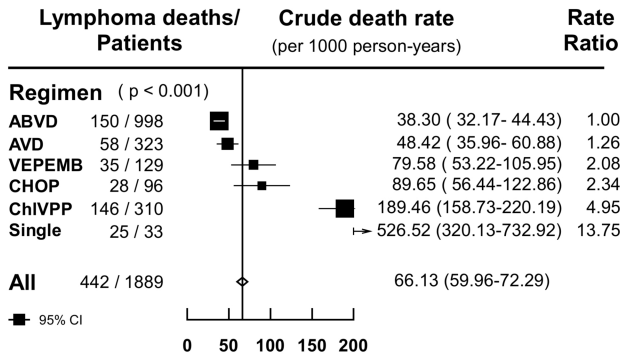
All-Cause Mortality



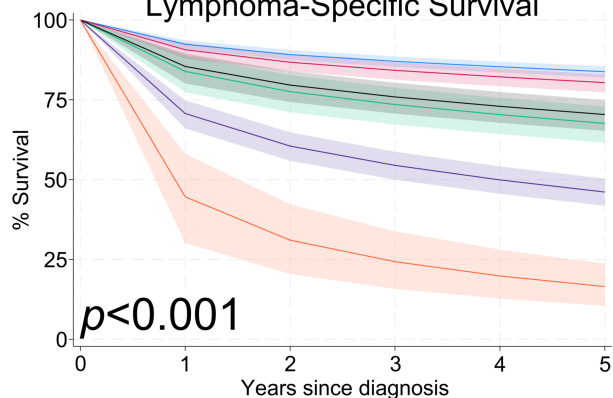
Overall Survival



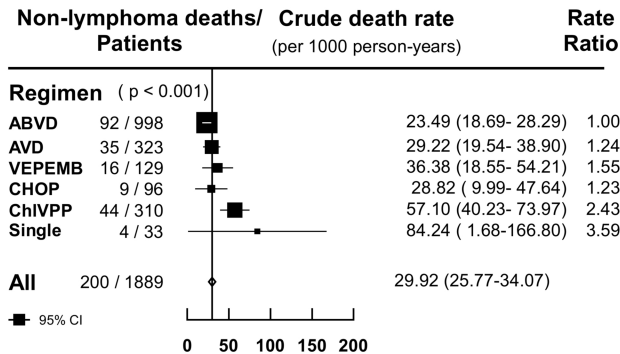
Lymphoma-Specific Mortality



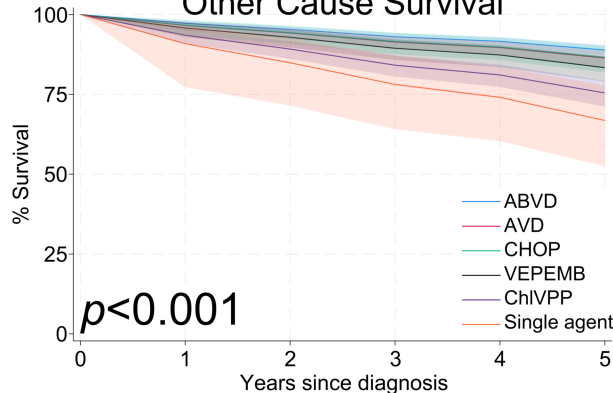
Lymphoma-Specific Survival



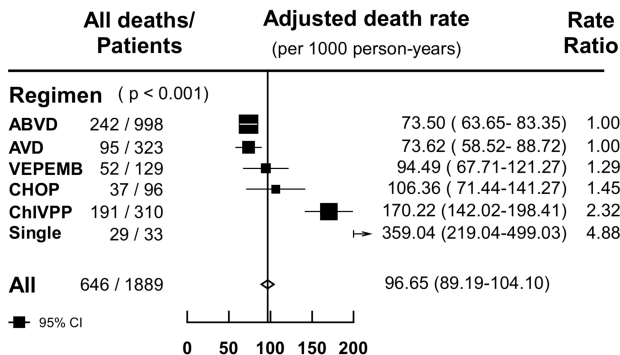
Other Cause Mortality



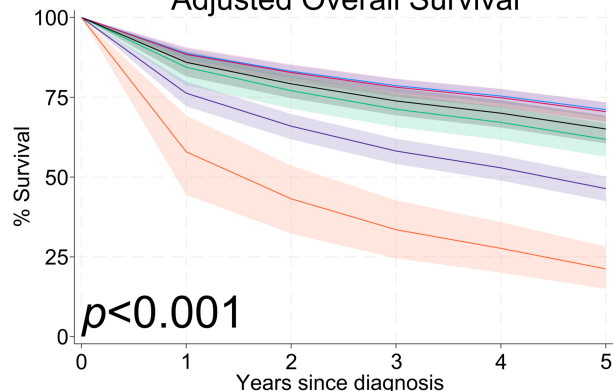
Other Cause Survival



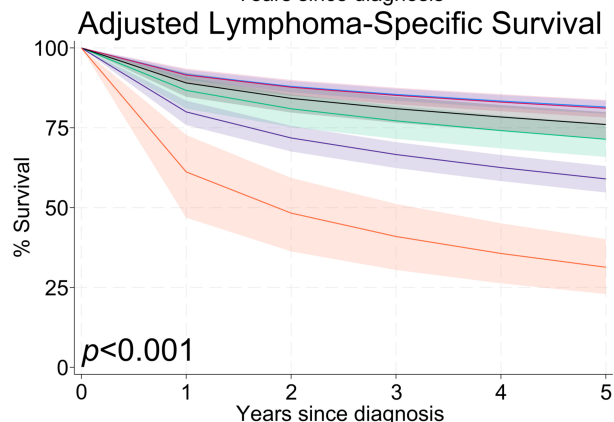
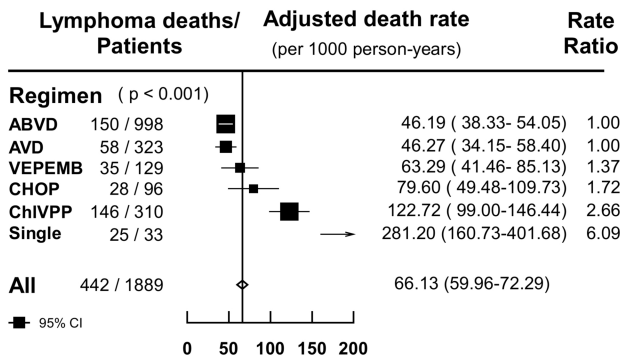
Adjusted All-Cause Mortality



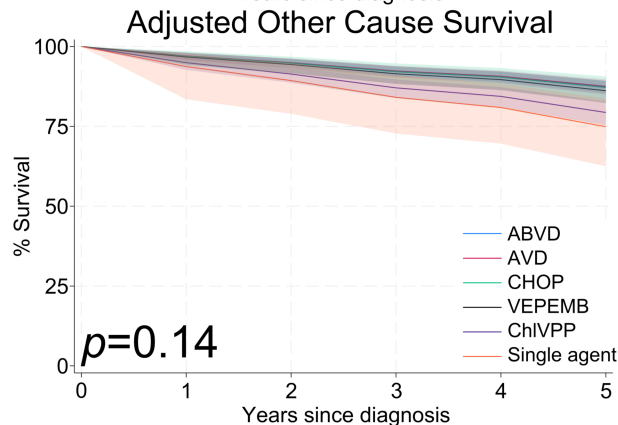
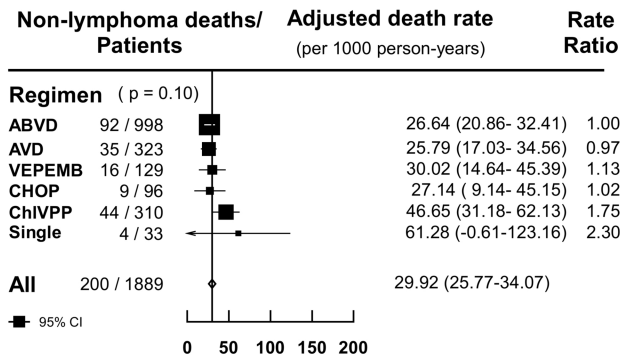
Adjusted Overall Survival



Adjusted Lymphoma-Specific Mortality



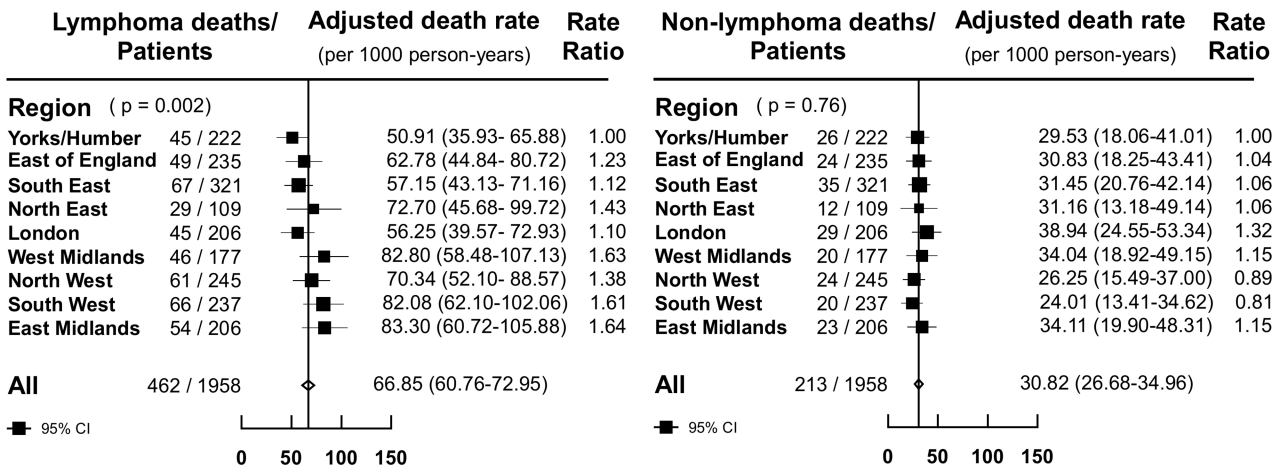
Adjusted Other Cause Mortality



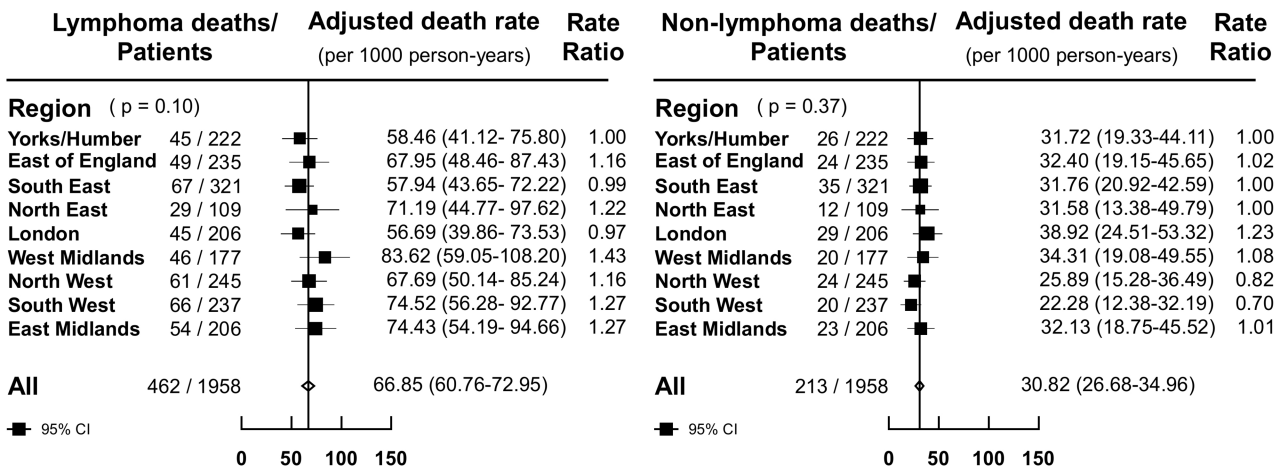
A Anthracycline use by region ordered from highest to lowest adjusted %

Region	Anthracycline use/ Total	% Use Unadjusted	% Use Adjusted
Yorks/Humber	200/222	90.1	90.7
East of England	205/235	87.2	86.3
South East	269/321	83.8	83.1
North East	85/109	78.0	81.1
London	162/206	78.6	80.3
West Midlands	141/177	79.7	77.6
North West	182/245	74.3	75.0
South West	172/237	72.6	72.6
East Midlands	147/206	71.4	69.0

B Adjusted mortality rates ordered by adjusted regional use of anthracycline



C Panel B with additional adjustment for anthracycline use by individual patient



Age, anthracycline and mortality in 28,000 classic Hodgkin lymphoma patients: cohort study of a complete population

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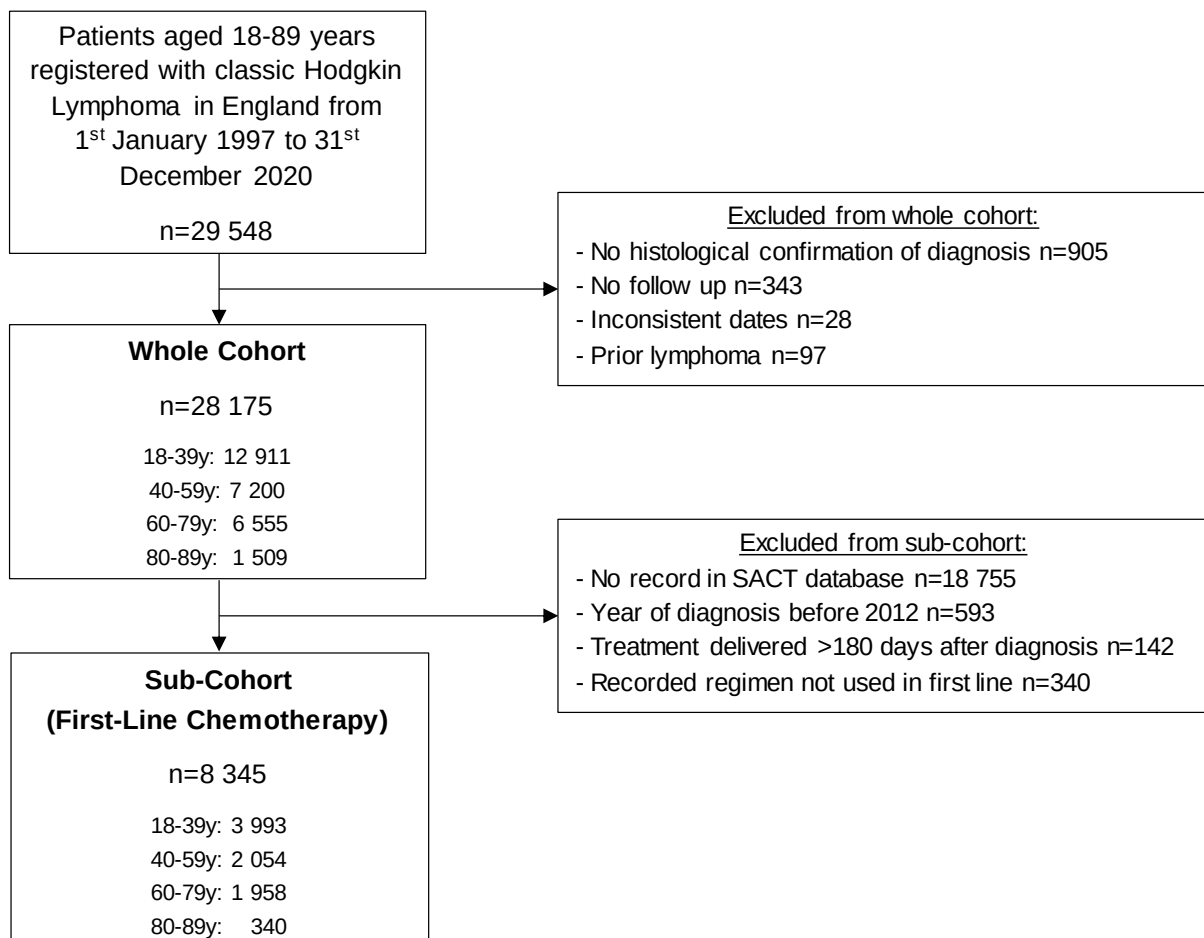
Table S1: Combinations of ICD-10 and ICD-morphology codes used to identify patients with classic Hodgkin Lymphoma in the dataset.

ICD= International Classification of Diseases.

ICD 10 codes	Morphology ICD codes
C770	9653
C813	9653
C819	9653
C813	9654
C813	9655
C814	8000
C819	9650
C770	9651
C773	9651
C810	9651
C814	9651
C810	9657
C814	9657
C810	9658
C814	9658
C770	9652
C812	9652
C819	9652
C859	9590
C811	9650
C819	9650
C109	9656
C760	9656
C770	9656
C771	9656
C774	9656
C778	9656
C779	9656
C811	9656
C810	9657
C811	9657
C811	9663
C819	9663
C811	9664
C811	9665
C811	9666
C811	9667
C819	Absent
C817	8000
C819	8000
C859	9590
C770	9650
C771	9650
C819	9650
C859	9650
C817	9661
C817	9662
C819	9669

Figure S1: Flow chart for derivation of the study cohort.

y= age at diagnosis (years). SACT= Systemic Anti-Cancer Therapy.



Supplementary Methods

Whole cohort

All patients registered in England from 1st January 1997 to 31st December 2020 with lymphoma were identified from combinations of international classification of diseases (ICD)-10 and ICD-morphology codes (Table S1). Patients with no histological confirmation of their diagnosis, no follow-up, inconsistent dates recorded or a prior lymphoma diagnosis were then excluded (Figure S1).

First-line chemotherapy sub-cohort

Patients receiving first-line chemotherapy were identified through the Systemic Anti-Cancer Therapy (SACT) data set. SACT data collection commenced in England in 2012. In its first year of operation, only 29% of patients registered as diagnosed with classic Hodgkin Lymphoma (CHL) were included in the database, suggesting incomplete reporting (Table S5). However, the percentage of patients included increased year by year and, by 2020, 86% of CHL patients were included, suggesting a high level of coverage, although probably still not complete.

To identify patients receiving first-line chemotherapy in the SACT database, all those with chemotherapy delivered >180 days following the date of CHL diagnosis were excluded, as were all those with chemotherapy known not to be used in the first line (i.e., clear salvage regimens or chemotherapy never used for CHL).

Patients in the first-line chemotherapy sub-cohort who received radical radiotherapy were identified as those receiving radiotherapy within a year of CHL diagnosis with a dose and fractionation consistent with curative intent.

Censoring

Patients remaining alive at 5 years after diagnosis were censored, as most CHL patients without relapse would be considered cured at this point.

Deaths due to causes other than lymphoma were censored for lymphoma-specific mortality analysis. Deaths due to lymphoma or unknown cause were censored for other cause mortality analysis.

Relative survival and standardised mortality ratios (Figure 2, Table S3 and S4)

Observed numbers of deaths were tabulated according to age at diagnosis, time since diagnosis and cause of death. The corresponding expected number of deaths and standardised mortality ratios by age at diagnosis and time since diagnosis were calculated from national mortality rates obtained from the Office for National Statistics stratified by single calendar year, five-year age groups, sex and quintiles of the index of multiple deprivation (IMD). Relative survival was estimated using the Ederer II estimator.¹

Factors associated with percentage of patients receiving different chemotherapy regimens (Table S6)

The factors associated with percentage of patients receiving the different chemotherapy regimens were assessed by multinomial logistic regression.

Poisson regression, average adjusted mortality rates and adjusted survival curves (Figure 4, Figures 6-7, Figures S8-S20)

For the first line chemotherapy sub-cohort, information was available for a number of different patient characteristics or factors. Poisson regression was used to estimate the effect of each factor adjusted for the confounding effect of other factors. Patients were entered into the study on their date of CHL diagnosis and were followed until the earliest of death or 30th June 2023. The length of time between these two dates was the patient's contribution to the person-years at risk. Contributions to the person years at risk from all patients in the study were combined and then tabulated simultaneously by all the factors shown in Table S6, using the categories shown, as well as by chemotherapy regimen and years since diagnosis in single years. Deaths occurring to patients who were contributing to the person-years at risk were also tabulated in the same way.

Poisson regression models were then fitted either to the entire sub-cohort or to subsections of it, for example, patients whose age at diagnosis lay in a certain range, with the number of deaths as the dependent variable and all the factors of interest as independent multiplicative variables. All factors were parameterised as categorical variables using the categories described in the paragraph above. The number of person-years associated with each combination of factors was also included as an independent variable with coefficient constrained to be one. These models provided estimates of the mortality rate ratios as they varied over the levels of one factor after adjusting for the other factors included in the model.

To obtain average adjusted annual mortality rates (rather than rate ratios) for each level of every factor that were directly comparable with each other, a factor of interest was chosen. A Poisson regression model with the factor of interest and also all the other factors to be included in the adjustment was fitted. Then, for each level of the factor of interest, its marginal effect was obtained.² This was done by assuming that all the data had that particular level of the factor of interest and averaging the rates over all the combinations of the remaining factors that appeared in the data. All these rates were then averaged, weighting each one by the proportion of the total person-years associated with it. This process was repeated for each level of every factor of interest.

Survival curves were calculated as follows. If $\hat{\lambda}_i$ denotes the average annual mortality rate for the i^{th} year since diagnosis (calculated as in the paragraph above), and $\hat{\sigma}_i^2$ denotes the variance of $\hat{\lambda}_i$, then the cumulative rate up to the end of year 5, and its corresponding variance, were calculated as:

$$\hat{\Lambda} = \sum_{j=1}^5 \hat{\lambda}_j, \quad \text{var}(\hat{\Lambda}) = \sum_{j=1}^5 \hat{\sigma}_j^2.$$

The cumulative rates (point estimates and 95% confidence limits) were then transformed into the survival curves using the formula, $\hat{P} = \exp(-\hat{\Lambda})$.

References

1. Dickman PW, Coviello E. Estimating and modeling relative survival. The Stata Journal. 2015;15:186–215.
2. Mize TD, Bing H. Inequality and Total Effect Summary Measures for Nominal and Ordinal Variables. Sociological Science. 2025;12:115-157.

Table S2: Number of patients per age category at diagnosis with annual overall, lymphoma-specific and other cause mortality rates and percentage survival by time since diagnosis in the whole cohort (n=28 175).

Numbers correspond to the mortality rate and survival plots by age at diagnosis presented in figure 1.

y= age at diagnosis (years). CI= confidence interval.

Age Category at Diagnosis	Time since diagnosis (years)	Number of patients at risk at start of time period	Total deaths during time interval	Overall mortality rate per 1000 person years (95% CI)	% overall survival at end of time period (95% CI)	Lymphoma deaths during time interval	Lymphoma-specific mortality rate per 1000 person years (95% CI)	% lymphoma-specific survival at end of time period (95% CI)	Other cause deaths during time interval	Other cause mortality rate per 1000 person years (95% CI)	% other cause survival at end of time period (95% CI)
18-39y	0 - 1	12 911	161	12.6 (10.6-14.5)	98.8 (98.6-98.9)	120	9.4 (7.7-11.0)	99.1 (98.9-99.2)	38	3.0 (2.0-3.9)	99.7 (99.6-99.8)
	1 - 2	12 750	219	17.3 (15.0-19.6)	97.1 (96.8-97.3)	173	13.7 (11.6-15.7)	97.7 (97.5-98.0)	40	3.2 (2.2-4.1)	99.4 (99.2-99.5)
	2 - 3	12 531	162	13.1 (11.1-15.1)	95.8 (95.4-96.1)	134	10.8 (9.0-12.7)	96.7 (96.4-97.0)	25	2.0 (1.2-2.8)	99.2 (99.0-99.3)
	3 - 4	12 080	127	10.8 (9.0-12.7)	94.7 (94.4-95.1)	102	8.7 (7.0-10.4)	95.8 (95.5-96.2)	25	2.1 (1.3-3.0)	99.0 (98.8-99.1)
	4 - 5	11 356	70	6.3 (4.9-7.8)	94.2 (93.7-94.6)	52	4.7 (3.4-6.0)	95.4 (95.0-95.7)	16	1.4 (0.7-2.2)	98.8 (98.6-99.0)
40-49y	0 - 1	3 786	137	37.0 (30.8-43.2)	96.4 (95.7-96.9)	77	20.8 (16.2-25.4)	98.0 (97.4-98.4)	60	16.2 (12.1-20.3)	98.4 (98.0-98.8)
	1 - 2	3 649	64	17.7 (13.4-22.0)	94.7 (93.9-95.4)	47	13.0 (9.3-16.7)	96.7 (96.1-97.2)	16	4.4 (2.3-6.6)	98.0 (97.5-98.4)
	2 - 3	3 585	61	17.2 (12.9-21.6)	93.1 (92.2-93.8)	41	11.6 (8.0-15.1)	95.6 (94.9-96.2)	18	5.1 (2.7-7.4)	97.5 (96.9-97.9)
	3 - 4	3 443	46	13.7 (9.7-17.6)	91.8 (90.9-92.6)	31	9.2 (6.0-12.5)	94.7 (93.9-95.4)	14	4.2 (1.9-6.3)	97.1 (96.5-97.6)
	4 - 5	3 274	43	13.5 (9.5-17.6)	90.6 (89.6-91.5)	22	6.9 (4.0-9.8)	94.0 (93.2-94.8)	21	6.6 (3.8-9.4)	96.4 (95.8-97.0)
50-59y	0 - 1	3 414	307	95.1 (84.5-105.8)	91.0 (90.0-91.9)	216	66.9 (58.0-75.9)	93.5 (92.7-94.4)	90	27.9 (22.1-33.7)	97.3 (96.7-97.8)
	1 - 2	3 107	132	43.4 (36.0-50.9)	87.1 (86.0-88.2)	89	29.3 (23.2-35.4)	90.9 (89.9-91.8)	43	14.2 (9.9-18.4)	95.9 (95.2-96.5)
	2 - 3	2 975	86	29.5 (23.3-35.8)	84.6 (83.4-85.8)	57	19.6 (14.5-24.6)	89.1 (88.0-90.2)	24	8.2 (4.9-11.5)	95.1 (94.3-95.8)
	3 - 4	2 817	68	25.0 (19.1-31.0)	82.5 (81.2-83.8)	31	11.4 (7.4-15.4)	88.1 (87.0-89.2)	36	13.2 (8.9-17.6)	93.9 (93.0-94.7)
	4 - 5	2 616	50	19.9 (14.4-25.5)	80.9 (79.5-82.2)	19	7.6 (4.2-11.0)	87.5 (86.3-88.6)	31	12.4 (8.0-16.7)	92.7 (91.7-93.6)
60-69y	0 - 1	3 461	666	218.5 (201.9-235.1)	80.8 (79.4-82.0)	507	166.4 (151.9-180.8)	85.0 (83.7-86.1)	158	51.8 (43.8-59.9)	95.1 (94.3-95.8)
	1 - 2	2 795	186	69.1 (59.1-79.0)	75.4 (73.9-76.8)	132	49.0 (40.7-57.4)	80.9 (79.6-82.2)	53	19.7 (14.4-25.0)	93.2 (92.3-94.1)
	2 - 3	2 609	167	66.5 (56.4-76.6)	70.5 (69.0-72.0)	99	39.4 (31.7-47.2)	77.8 (76.3-79.2)	66	26.3 (20.0-32.6)	90.8 (89.7-91.8)
	3 - 4	2 376	122	54.0 (44.4-63.5)	66.8 (65.2-68.4)	71	31.4 (24.1-38.7)	75.4 (73.9-76.8)	50	22.1 (16.0-28.2)	88.8 (87.6-89.9)
	4 - 5	2 145	110	54.1 (44.0-64.2)	63.3 (61.7-64.9)	49	24.1 (17.4-30.9)	73.6 (72.0-75.1)	60	29.5 (22.1-37.0)	86.2 (84.9-87.5)
70-79y	0 - 1	3 094	1 069	444.8 (418.1-471.5)	65.5 (63.7-67.1)	810	337.0 (313.8-360.3)	72.6 (70.9-74.1)	257	106.9 (93.9-120.0)	90.3 (89.1-91.4)
	1 - 2	2 025	278	149.1 (131.6-166.6)	56.5 (54.7-58.2)	192	103.0 (88.4-117.5)	65.6 (63.8-67.3)	85	45.6 (35.9-55.3)	86.3 (84.8-87.6)
	2 - 3	1 747	189	115.7 (99.2-132.2)	50.3 (48.5-52.1)	115	70.4 (57.5-83.2)	61.1 (59.3-62.9)	74	45.3 (35.0-55.6)	82.4 (80.8-83.9)
	3 - 4	1 508	139	98.6 (82.2-114.9)	45.6 (43.8-47.3)	76	53.9 (41.8-66.0)	57.9 (56.1-59.7)	61	43.2 (32.4-54.1)	78.9 (77.1-80.6)
	4 - 5	1 296	124	104.5 (86.1-122.9)	41.1 (39.3-42.8)	57	48.0 (35.6-60.5)	55.2 (53.3-57.1)	65	54.8 (41.5-68.1)	74.7 (72.7-76.6)
80-89y	0 - 1	1 509	795	810.7 (754.4-867.1)	47.3 (44.8-49.8)	651	663.9 (612.9-714.9)	54.3 (51.7-56.9)	143	145.8 (121.9-169.7)	87.2 (85.1-89.1)
	1 - 2	714	198	325.6 (280.2-370.9)	34.2 (31.8-36.6)	145	238.4 (199.6-277.2)	42.9 (40.3-45.6)	53	87.2 (63.7-110.6)	80.0 (76.9-82.3)
	2 - 3	516	105	230.2 (186.2-274.2)	27.2 (25.0-29.5)	65	142.5 (107.8-177.1)	37.2 (34.7-39.9)	40	87.7 (60.5-114.9)	73.1 (69.8-76.1)
	3 - 4	394	67	194.2 (147.7-240.7)	22.4 (20.3-24.6)	32	92.7 (60.6-124.9)	33.9 (31.3-36.6)	35	101.4 (67.8-135.0)	66.2 (62.4-69.6)

	4 - 5	297	45	169.3 (119.8-218.8)	18.9 (17.0-21.0)	11	41.4 (16.9-65.8)	32.5 (29.9-35.2)	34	127.9 (84.8-170.9)	58.3 (54.1-62.2)
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Table S3: Excess deaths in the whole cohort and first-line chemotherapy sub-cohort by age at diagnosis and cause of death.

Numbers correspond to the mortality rate and survival plots by age at diagnosis presented in figure 2.

Obs= observed. Exp= expected. SMR= standardised mortality ratio. CI= confidence interval.

For unknown cause of death, the national rates are not available so cannot be estimated.

Cause of death	18-39		40-59		60-79	
	Obs/exp	SMR (95% CI)	Obs/exp	SMR (95% CI)	Obs/exp	SMR (95% CI)
Whole cohort <1 year since diagnosis						
Lymphoma	121/ -	-	296/ -	-	1335/ -	-
All non-lymphoma deaths	37/ 0.1	588.6 (414.4, 811.3)	147/ 0.8	192.6 (162.8, 226.4)	397/ 15.3	26.0 (23.5, 28.7)
Infection	8/ <0.01	5062.1 (2185.5, 9974.4)	35/ <0.01	3534.1 (2461.6, 4915.1)	21/ 0.1	152.1 (94.2, 232.6)
Other haematological cancer	1/ <0.01	1149.9 (29.1, 6406.6)	6/ <0.1	540.9 (198.5, 1177.4)	12/ 0.3	39.4 (20.4, 68.8)
Other cancer	1/ <0.01	139.6 (3.5, 777.7)	9/ 0.3	35.3 (16.1, 67.0)	47/ 4.9	9.6 (7.0, 12.8)
Cardiac	2/ <0.01	416.3 (50.4, 1503.7)	21/ 0.2	126.0 (78.0, 192.6)	103/ 3.4	29.9 (24.4, 36.3)
Respiratory	3/ <0.01	1771.3 (365.3, 5176.4)	13/ <0.1	520.5 (277.2, 890.1)	41/ 0.8	50.2 (36.1, 68.2)
Other	22/ <0.1	470.6 (294.9, 712.5)	63/ 0.3	213.3 (163.9, 272.9)	173/ 5.7	30.6 (26.2, 35.5)
Unknown	3/ -	-	1/ -	-	3/ -	-
<i>Overall</i>	<i>158/ 0.1</i>	<i>2457.7 (2089.4, 2872.2)</i>	<i>443/ 0.8</i>	<i>557.7 (507.0, 612.2)</i>	<i>1732/ 15.9</i>	<i>109.0 (103.9, 114.3)</i>
Whole cohort 2-5 years since diagnosis						
Lymphoma	465/ -	-	342/ -	-	807/ -	-
All non-lymphoma deaths	102/ 40.1	2.5 (2.1, 3.1)	198/ 116.8	1.7 (1.5, 1.9)	498/ 439.1	1.1 (1.0, 1.2)
Infection	8/ 0.7	10.9 (4.7, 21.4)	13/ 1.5	8.9 (4.7, 15.2)	8/ 4.1	1.9 (0.8, 3.8)
Other haematological cancer	5/ 0.6	8.6 (2.8, 20.1)	10/ 1.8	5.6 (2.7, 10.3)	41/ 9.0	4.5 (3.3, 6.1)
Other cancer	13/ 5.9	2.2 (1.2, 3.8)	54/ 39.2	1.4 (1.0, 1.8)	151/ 141.8	1.1 (0.9, 1.2)
Cardiac	18/ 3.2	5.7 (3.4, 9.0)	40/ 22.9	1.7 (1.3, 2.4)	102/ 90.7	1.1 (0.9, 1.4)
Respiratory	13/ 1.2	11.2 (6.0, 19.2)	9/ 4.6	1.9 (0.9, 3.7)	33/ 26.2	1.3 (0.9, 1.8)
Other	45/ 28.6	1.6 (1.1, 2.1)	72/ 46.8	1.5 (1.2, 1.9)	163/ 167.2	1.0 (0.8, 1.1)
Unknown	11/ -	-	10/ -	-	10/ -	-
<i>Overall</i>	<i>567/ 41.0</i>	<i>13.8 (12.7, 15.0)</i>	<i>540/ 121.1</i>	<i>4.5 (4.1, 4.9)</i>	<i>1305/ 456.5</i>	<i>2.9 (2.7, 3.0)</i>
Sub-cohort <1 year since diagnosis						
Lymphoma	13/ -	-	38/ -	-	253/ -	-
All non-lymphoma deaths	7/ <0.01	1132.2 (455.2, 2332.9)	27/ 0.1	219.2 (144.4, 318.9)	67/ 3.3	20.3 (15.7, 25.8)
Infection	0/ <0.01	0.0 (0.0, 57941.7)	8/ <0.01	4611.4 (1990.9, 9086.3)	4/ <0.1	123.9 (33.8, 317.3)
Other haematological cancer	0/ <0.01	0.0 (0.0, 44908.0)	1/ <0.01	665.1 (16.8, 3705.4)	1/ 0.1	14.0 (0.4, 78.3)
Other cancer	0/ <0.01	0.0 (0.0, 5762.2)	0/ <0.1	0.0 (0.0, 92.3)	5/ 1.1	4.5 (1.4, 10.4)
Cardiac	0/ <0.01	0.0 (0.0, 9257.7)	2/ <0.1	88.4 (10.7, 319.3)	18/ 0.6	30.6 (18.2, 48.4)
Respiratory	1/ <0.01	5652.9 (143.0, 31496.2)	3/ <0.01	628.3 (129.6, 1836.1)	7/ 0.2	36.1 (14.5, 74.4)
Other	6/ <0.01	1244.5 (456.7, 2708.8)	13/ 0.1	247.3 (131.7, 422.8)	32/ 1.3	24.8 (17.0, 35.0)
Unknown	0/ -	-	1/ -	-	1/ -	-
<i>Overall</i>	<i>20/ <0.01</i>	<i>3172.6 (1937.9, 4899.9)</i>	<i>65/ 0.1</i>	<i>512.0 (395.1, 652.6)</i>	<i>320/ 3.4</i>	<i>93.7 (83.7, 104.6)</i>
Sub-cohort 2-5 years since diagnosis						
Lymphoma	55/ -	-	45/ -	-	211/ -	-
All non-lymphoma deaths	25/ 10.6	2.4 (1.5, 3.5)	54/ 32.5	1.7 (1.2, 2.2)	144/ 131.2	1.1 (0.9, 1.3)
Infection	3/ 0.1	24.2 (5.0, 70.7)	4/ 0.4	10.3 (2.8, 26.4)	3/ 1.2	2.4 (0.5, 7.0)
Other haematological cancer	0/ 0.1	0.0 (0.0, 26.9)	1/ 0.4	2.3 (0.1, 12.8)	16/ 2.9	5.6 (3.2, 9.1)
Other cancer	1/ 1.6	0.6 (0.0, 3.6)	13/ 10.0	1.3 (0.7, 2.2)	34/ 43.3	0.8 (0.5, 1.1)
Cardiac	3/ 0.8	3.8 (0.8, 11.2)	10/ 5.7	1.7 (0.8, 3.2)	35/ 22.2	1.6 (1.1, 2.2)
Respiratory	5/ 0.4	11.4 (3.7, 26.5)	6/ 2.0	2.9 (1.1, 6.4)	14/ 10.6	1.3 (0.7, 2.2)
Other	13/ 7.5	1.7 (0.9, 3.0)	20/ 13.9	1.4 (0.9, 2.2)	42/ 51.0	0.8 (0.6, 1.1)
Unknown	2/ -	-	4/ -	-	3/ -	-
<i>Overall</i>	<i>80/ 10.7</i>	<i>7.5 (5.9, 9.3)</i>	<i>99/ 33.4</i>	<i>3.0 (2.4, 3.6)</i>	<i>355/ 135.7</i>	<i>2.6 (2.4, 2.9)</i>

Table S4: Relative survival estimates for the whole cohort and first-line chemotherapy sub-cohort by age at diagnosis.

y= age at diagnosis (years).

Age at diagnosis	Years since diagnosis				
	0-1	1-2	2-3	3-4	4-5
18-39y:	98.8 (98.6-99.0)	97.2 (96.9-97.5)	96.0 (95.6-96.3)	95.0 (94.6-95.4)	94.5 (94.1-94.9)
40-49y:	96.6 (95.9-97.1)	95.1 (94.3-95.7)	93.6 (92.8-94.4)	92.6 (91.6-93.4)	91.6 (90.6-92.5)
50-59y:	91.4 (90.4-92.4)	88.0 (86.8-89.1)	85.9 (84.6-87.1)	84.3 (82.9-85.5)	83.1 (81.7-84.5)
60-69y:	81.7 (80.3-83.0)	77.3 (75.7-78.7)	73.2 (71.6-74.8)	70.4 (68.7-72.0)	67.8 (66.0-69.5)
70-79y:	67.5 (65.8-69.2)	60.2 (58.3-62.0)	55.4 (53.5-57.4)	52.2 (50.1-54.2)	49.0 (46.9-51.1)
80-89y:	51.2 (48.4-53.9)	40.1 (37.3-42.9)	34.7 (31.8-37.6)	31.4 (28.5-34.5)	29.5 (26.4-32.7)

Age at diagnosis	Years since diagnosis				
	0-1	1-2	2-3	3-4	4-5
18-39y:	99.6 (99.3-99.7)	98.6 (98.1-98.9)	98.2 (97.7-98.6)	97.9 (97.4-98.3)	97.6 (97.0-98.0)
40-49y:	98.6 (97.6-99.2)	98.0 (96.9-98.8)	97.5 (96.2-98.4)	96.7 (95.3-97.8)	96.0 (94.4-97.2)
50-59y:	95.5 (94.0-96.7)	93.1 (91.2-94.6)	91.4 (89.3-93.1)	90.2 (88.0-92.1)	89.8 (87.5-91.8)
60-69y:	88.5 (86.3-90.3)	84.3 (81.8-86.5)	81.3 (78.6-83.7)	78.4 (75.5-81.0)	75.9 (72.8-78.8)
70-79y:	80.9 (78.0-83.5)	74.0 (70.7-77.1)	68.9 (65.3-72.2)	67.5 (63.7-71.1)	63.3 (59.2-67.2)
80-89y:	68.8 (63.0-74.0)	57.2 (50.9-63.2)	51.7 (45.1-58.3)	48.1 (41.0-55.3)	47.6 (39.8-55.5)

Figure S2: Overall, lymphoma-specific and other cause survival by year of diagnosis for patients in the whole cohort aged 80-89 years at diagnosis.

The shaded areas represent 95% confidence intervals.

p -values are for heterogeneity between categories of calendar year.

y= age at diagnosis (years).

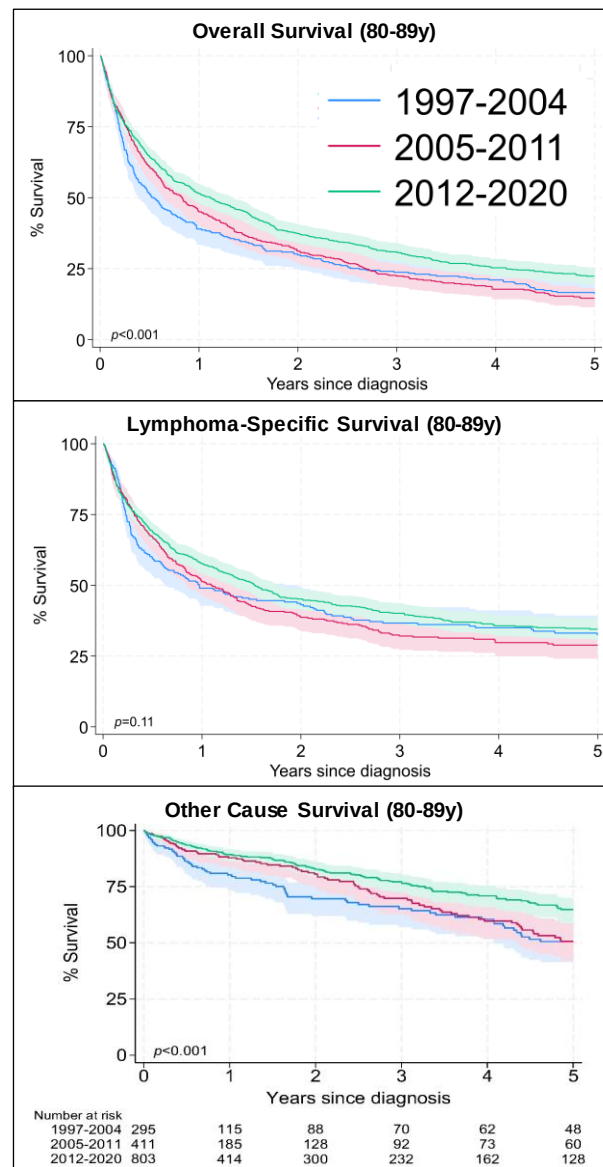


Table S5: Numbers of patients in the first-line chemotherapy sub-cohort recorded as receiving chemotherapy as a proportion of the whole cohort by calendar year and age at diagnosis.

SACT= systemic anti-cancer therapy. y= age at diagnosis (years).

	Number of patients with chemotherapy records in SACT / number of patients in whole cohort (%)				
	18-39 y	40-59 y	60-79 y	80-89 y	All
2012	188/527 (35.7)	88/369 (23.8)	90/311 (28.9)	7/79 (8.9)	373/1286 (29.0)
2013	289/531 (54.4)	163/323 (50.5)	148/309 (47.9)	24/86 (27.9)	624/1249 (50.0)
2014	408/584 (69.9)	209/328 (63.7)	210/360 (58.3)	40/109 (36.7)	867/1381 (62.8)
2015	456/591 (77.2)	253/345 (73.3)	236/350 (67.4)	28/83 (33.7)	973/1369 (71.1)
2016	477/575 (83.0)	261/305 (85.6)	240/325 (73.8)	38/84 (45.2)	1016/1289 (78.8)
2017	572/647 (88.4)	273/319 (85.6)	257/329 (78.1)	48/83 (57.8)	1150/1378 (83.5)
2018	505/555 (91.0)	270/303 (89.1)	275/348 (79.0)	58/95 (61.1)	1108/1301 (85.2)
2019	535/590 (90.7)	268/311 (86.2)	264/317 (83.3)	56/97 (57.7)	1123/1315 (85.4)
2020	563/606 (92.9)	269/305 (88.2)	238/292 (81.5)	41/86 (47.7)	1111/1289 (86.2)
All	3993/5206 (76.7)	2054/2908 (70.6)	1958/2941 (66.6)	340/802 (42.4)	8345/11,857 (70.4)

	Number of patients with chemotherapy records in SACT / number of patients in whole cohort (%)				
	60-64 y	65-69 y	70-74 y	75-79 y	All
2012	36/87 (41.4)	21/82 (25.6)	21/80 (26.2)	12/62 (19.4)	90/311 (28.9)
2013	39/82 (47.6)	43/83 (51.8)	30/62 (48.4)	36/82 (43.9)	148/309 (47.9)
2014	71/89 (79.8)	63/107 (58.9)	44/85 (51.8)	32/79 (40.5)	210/360 (58.3)
2015	59/87 (67.8)	67/94 (71.3)	61/89 (68.5)	49/80 (61.2)	236/350 (67.4)
2016	67/85 (78.8)	64/80 (80.0)	55/77 (71.4)	54/83 (65.1)	240/325 (73.8)
2017	60/74 (81.1)	67/83 (80.7)	68/89 (76.4)	62/83 (74.7)	257/329 (78.1)
2018	72/85 (84.7)	72/89 (80.9)	69/89 (77.5)	62/85 (72.9)	275/348 (79.0)
2019	65/69 (94.2)	65/78 (83.3)	83/100 (83.0)	51/70 (72.9)	264/317 (83.3)
2020	74/84 (88.1)	64/71 (90.1)	59/69 (85.5)	41/68 (60.3)	238/292 (81.5)
All	543/742 (73.2)	526/767 (68.6)	490/740 (66.2)	399/692 (57.7)	1958/2941 (66.6)

Figure S3: Proportion of patients receiving different first-line chemotherapy regimens in the first-line chemotherapy sub-cohort by age at diagnosis.

y= age at diagnosis (years). ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD without bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide. ChIVPP= chlorambucil, vinblastine, procarbazine, prednisolone.

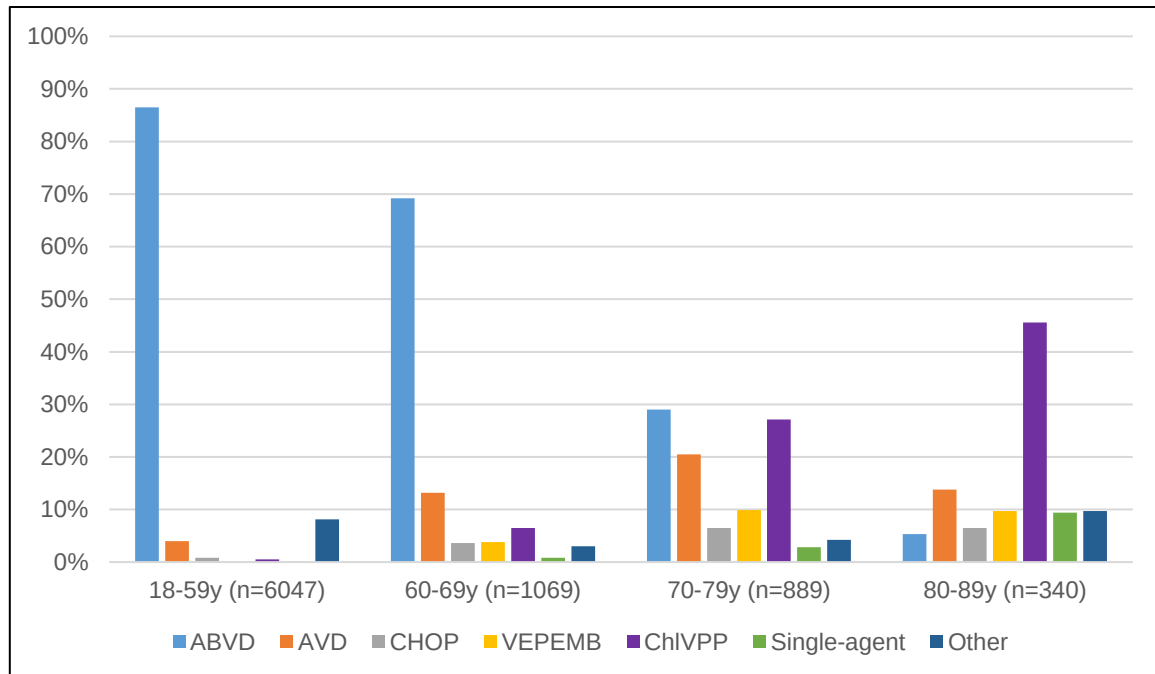


Figure S4: Proportion of patients receiving anthracycline-containing chemotherapy regimens in the first-line chemotherapy sub-cohort by age at diagnosis.

y= age at diagnosis (years).

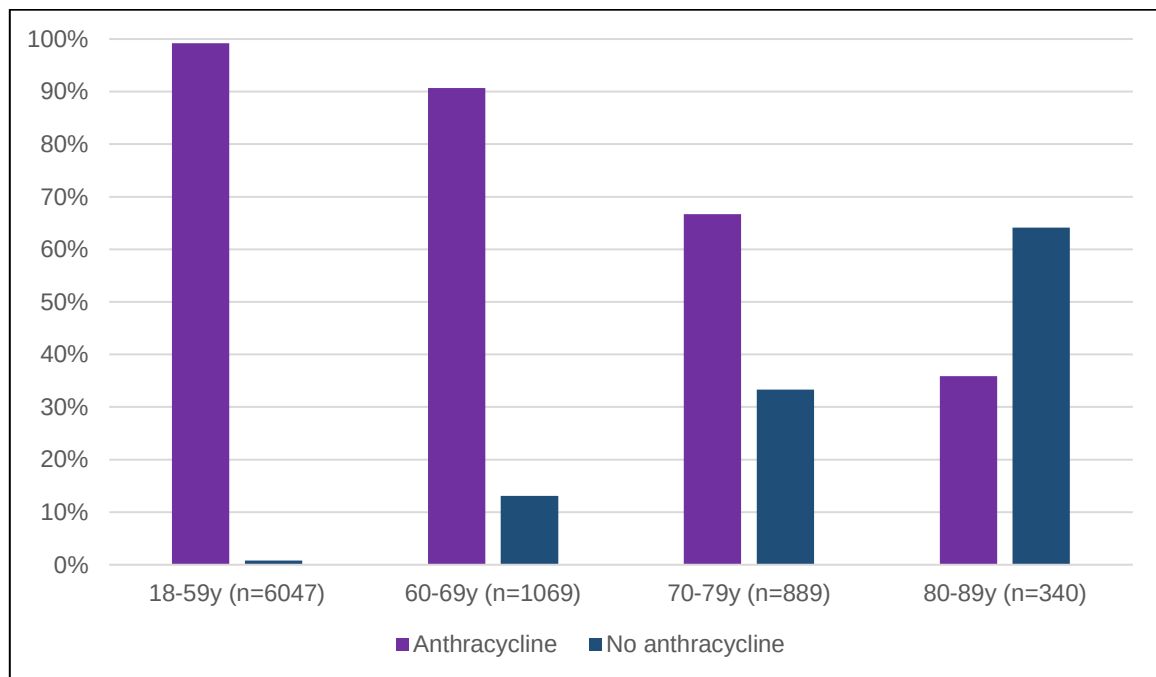


Figure S5: Proportion of patients receiving bleomycin-containing chemotherapy regimens in the first-line chemotherapy sub-cohort by age at diagnosis.

y= age at diagnosis (years).

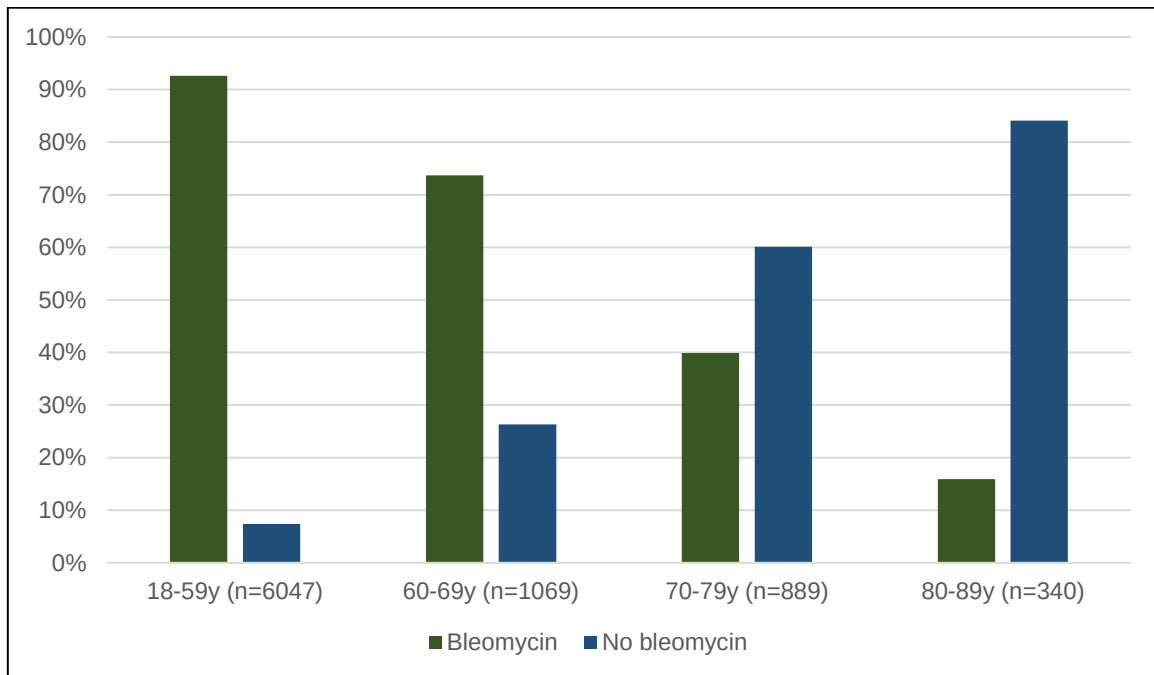


Figure S6: Single-agent chemotherapy regimens delivered in the first-line chemotherapy sub-cohort by age at diagnosis.

y= age at diagnosis (years).

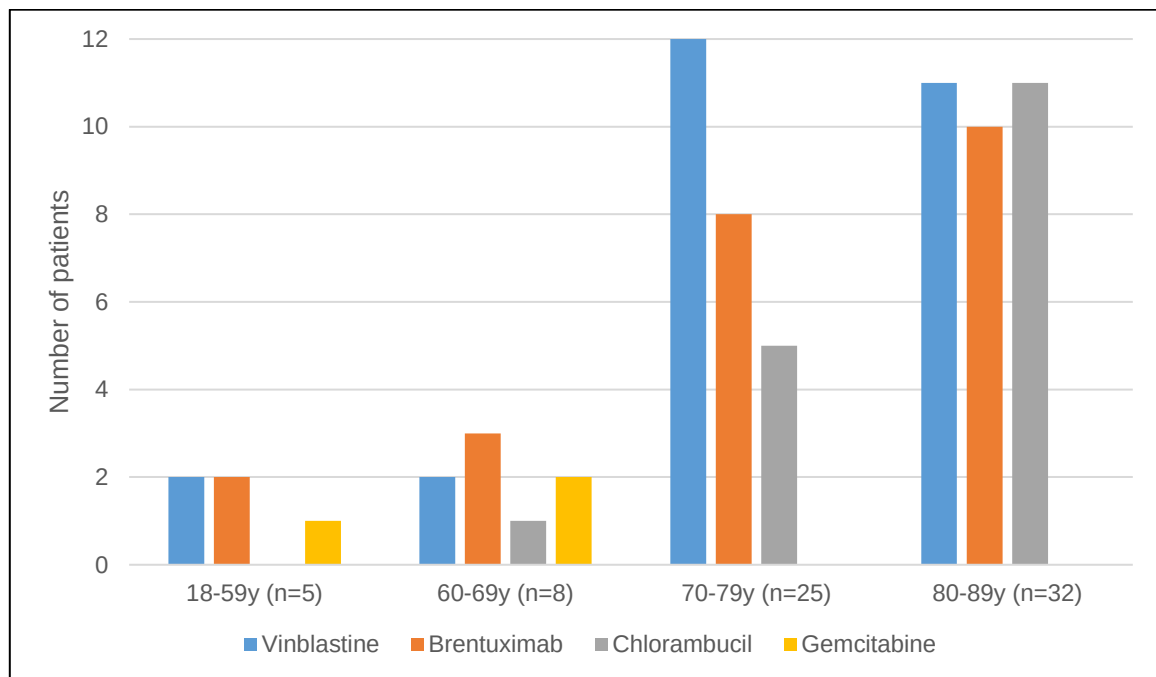


Figure S7: Proportion of patients receiving radical doses of radiotherapy with curative approaches to first-line chemotherapy in the first-line chemotherapy sub-cohort by age at diagnosis.

Curative approaches to first-line chemotherapy included ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), AVD (ABVD without bleomycin), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) and VEPEMB (vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide).

y= age at diagnosis (years).

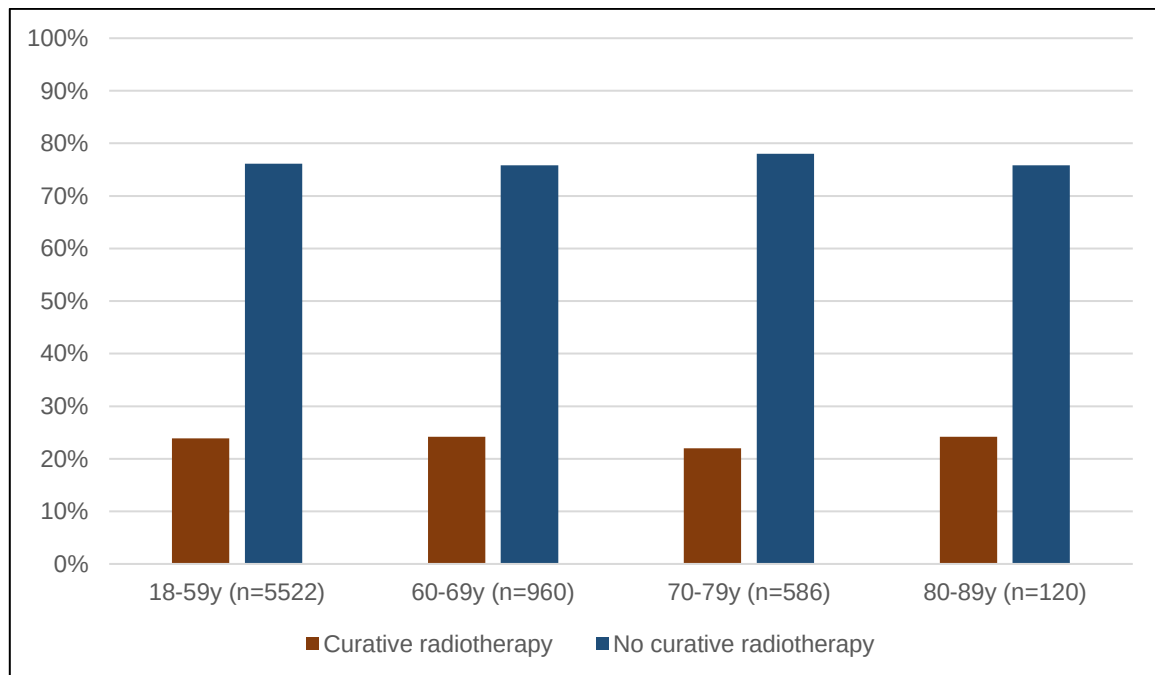


Figure S8: Adjusted lymphoma-specific mortality rates per 1000 person-years by patient and lymphoma characteristics for patients aged 18-39 years at diagnosis in the first-line chemotherapy sub-cohort.

Each characteristic is adjusted for all the others using Poisson regression. *p*-values are for trend except for region and histological subtype where they are for heterogeneity.

y= age at diagnosis (years). M= male. F= female. Yorks/Humber= Yorkshire and the Humber. IMD= index of multiple deprivation. NOS= not otherwise specified.

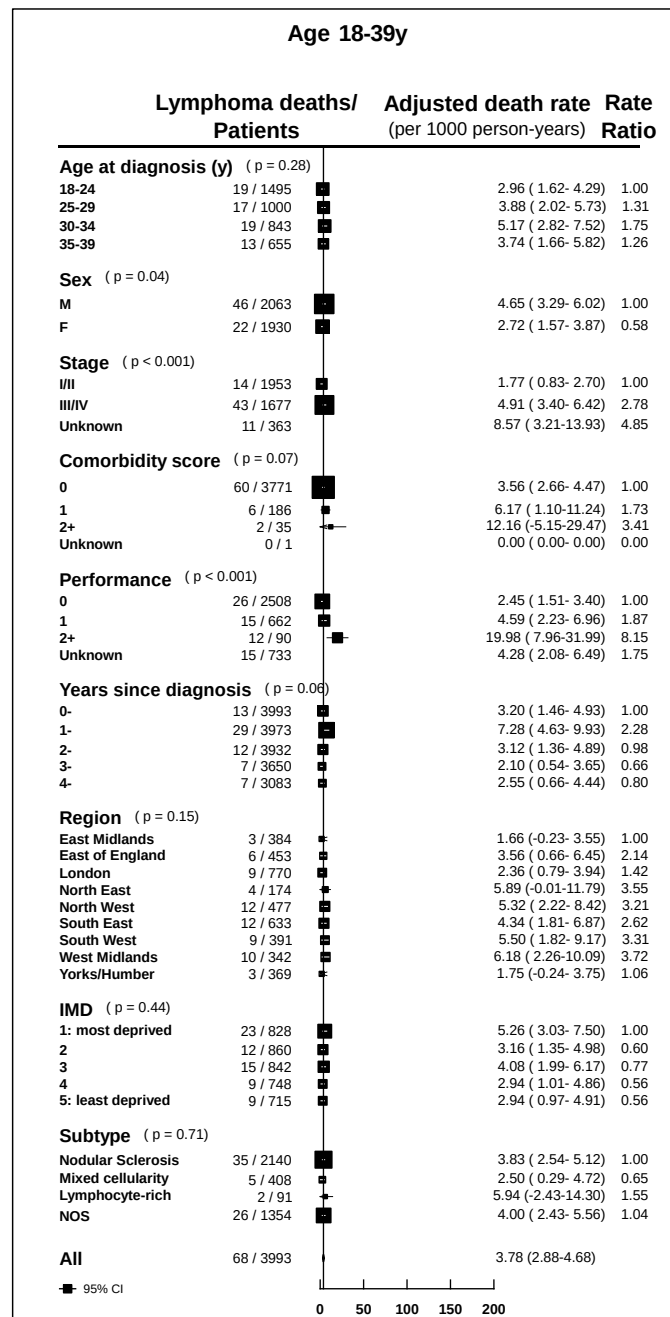


Figure S9: Adjusted all-cause, lymphoma-specific and other cause mortality rates per 1000 person-years by time from diagnosis to commencement of chemotherapy in patients aged 18-39, 40-59 and 60-79 years at diagnosis in the first-line chemotherapy sub-cohort.

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index, chemotherapy regimen and histological subtype by Poisson regression.

p-values are for trend.

y= age at diagnosis (years).

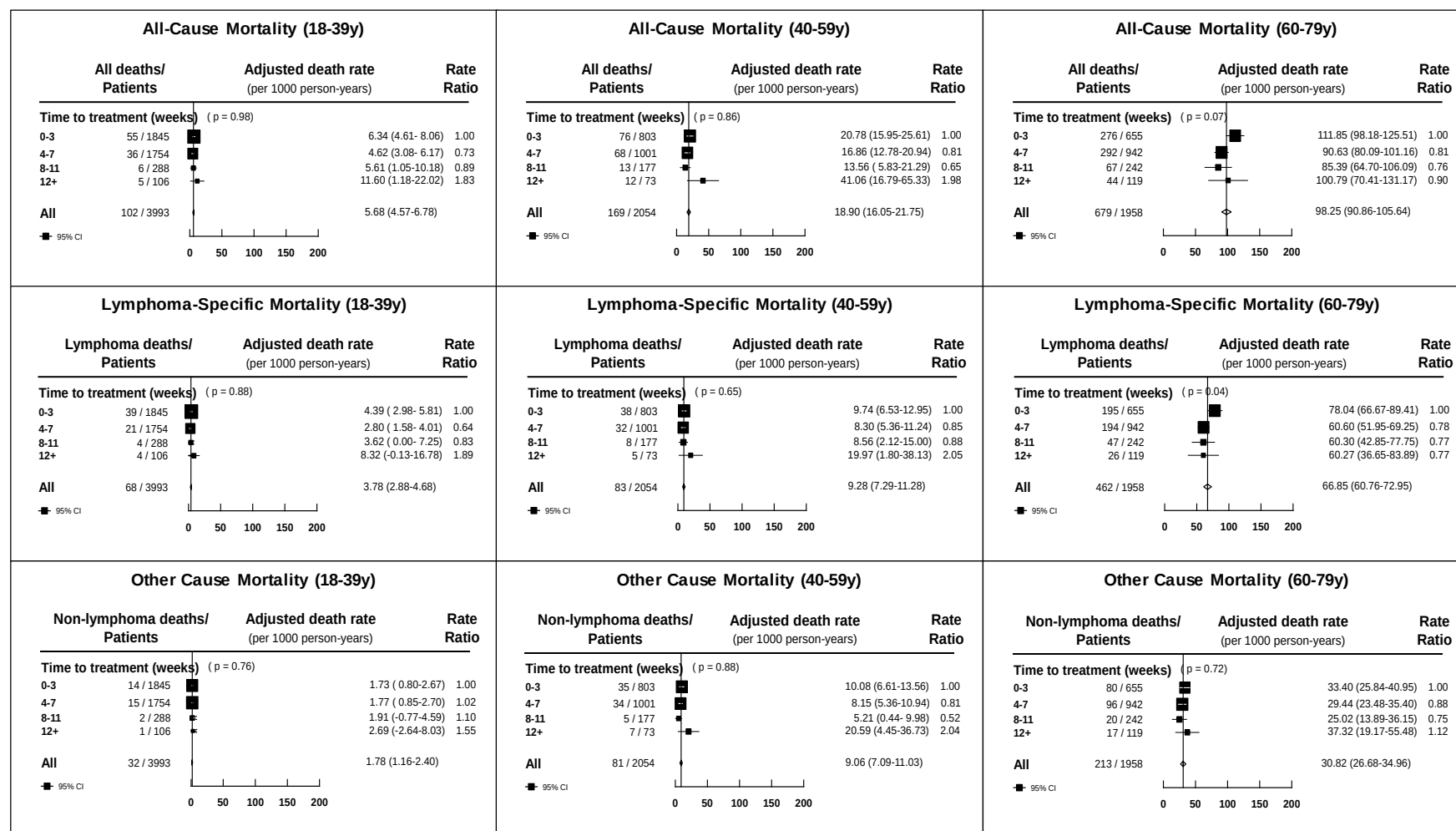


Figure S10: Adjusted other cause mortality rates per 1000 person-years by patient and lymphoma characteristics for patients aged 18-39, 40-59 and 60-79 years at diagnosis in the first-line chemotherapy sub-cohort.

Each characteristic is adjusted for all the others using Poisson regression. *p*-values are for trend except for region and histological subtype where they are for heterogeneity.

y= age at diagnosis (years). M=male. F=female. Yorks/Humber= Yorkshire and the Humber. IMD= index of multiple deprivation. NOS= not otherwise specified.

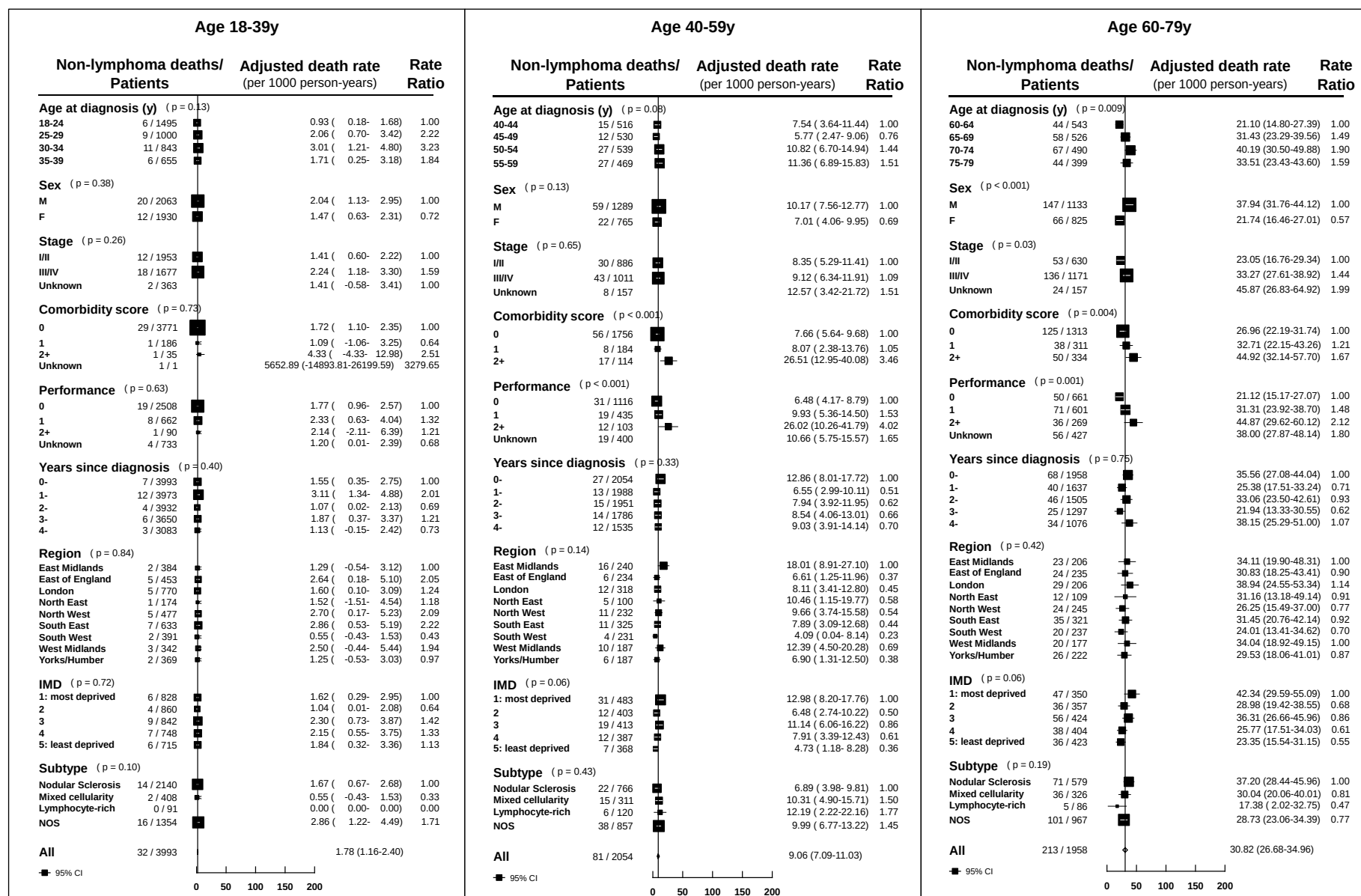


Figure S11: Adjusted all-cause mortality rates per 1000 person-years by patient and lymphoma characteristics for patients aged 18-39, 40-59 and 60-79 years at diagnosis in the first-line chemotherapy sub-cohort.

Each characteristic is adjusted for all the others using Poisson regression. *p*-values are for trend except for region and histological subtype where they are for heterogeneity.

y= years. M=male. F=female. Yorks/Humber= Yorkshire and the Humber. IMD= index of multiple deprivation. NOS= not otherwise specified.

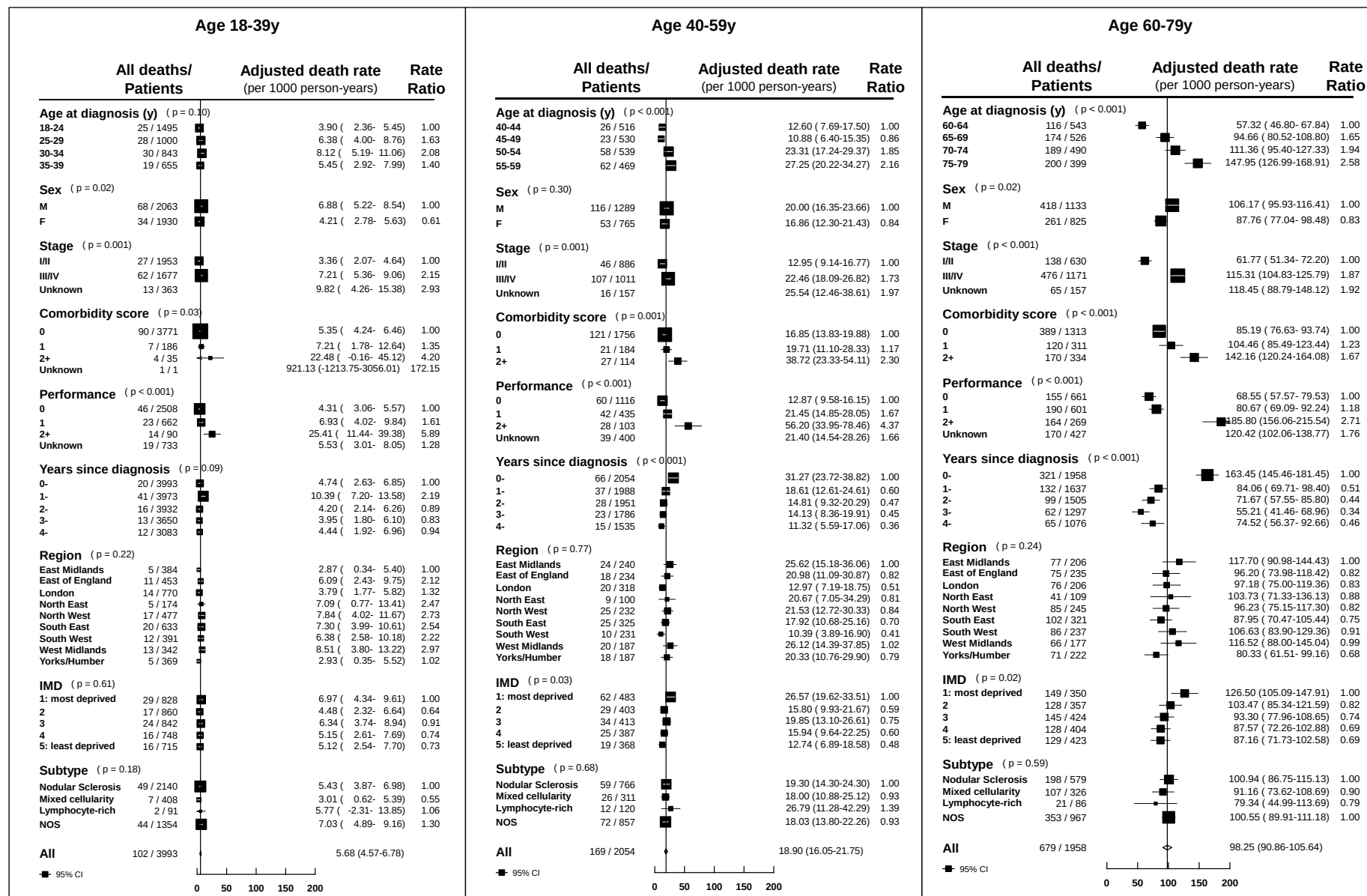


Table S6: Percentages of patients aged 60-79 years at diagnosis receiving different first-line chemotherapy regimen by baseline factors.

Factors associated with percentage of patients receiving different first-line chemotherapy regimens were assessed by multinomial logistic regression.

Patients not in receipt of the six most common first-line chemotherapy regimen groupings were excluded (n=69). Unknown values were excluded for *p* value calculation.

p-values are for heterogeneity with respect to patient characteristics within each chemotherapy regimen.

M= male. F= female. ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD with omission of bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide. ChIVPP= chlorambucil, vinblastine, procarbazine, prednisolone. Yorks/ Humber= Yorkshire and the Humber. NOS= not otherwise specified.

Characteristics	ABVD n=998	AVD n=323	CHOP n=96	VEPEMB n=129	ChIVPP n=310	Single-agent n=33
Age						
60-64	74%	11%	2%	2%	6%	1%
65-69	61%	16%	5%	6%	8%	1%
70-74	39%	20%	7%	9%	20%	2%
75-79	20%	21%	6%	9%	32%	4%
	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> =0.002	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.001
Sex						
M	51%	17%	5%	7%	15%	2%
F	52%	15%	5%	7%	17%	2%
	<i>p</i> =0.61	<i>p</i> =0.27	<i>p</i> =0.90	<i>p</i> =0.91	<i>p</i> =0.41	<i>p</i> =0.46
Stage						
Limited (I - II)	56%	17%	4%	6%	16%	1%
Advanced (III - IV)	50%	16%	5%	7%	16%	3%
Unknown	43%	22%	6%	9%	16%	1%
	<i>p</i> =0.03	<i>p</i> =0.70	<i>p</i> =0.10	<i>p</i> =0.42	<i>p</i> =0.67	<i>p</i> =0.003
Performance status						
0	59%	17%	6%	4%	10%	1%
1	49%	20%	5%	8%	15%	1%
2+	37%	12%	4%	6%	30%	3%
Unknown	49%	15%	4%	9%	14%	3%
	<i>p</i> <0.001	<i>p</i> =0.01	<i>p</i> =0.71	<i>p</i> =0.02	<i>p</i> <0.001	<i>p</i> =0.001
Comorbidity index						
0	54%	16%	5%	6%	14%	2%
1	49%	16%	6%	6%	17%	1%
2+	40%	18%	5%	8%	20%	2%
	<i>p</i> <0.001	<i>p</i> =0.59	<i>p</i> =0.51	<i>p</i> =0.26	<i>p</i> =0.02	<i>p</i> =0.60
Year of diagnosis						
2012-15	56%	12%	4%	6%	14%	3%
2016-20	48%	19%	5%	7%	17%	1%
	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> =0.001	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.001
Region						
East Midlands	38%	11%	9%	9%	22%	9%
East of England	51%	28%	5%	2%	11%	1%
London	52%	16%	6%	6%	16%	2%
North East	36%	18%	3%	2%	6%	2%
North West	50%	12%	5%	8%	22%	1%
South East	53%	21%	8%	2%	16%	<1%
South West	47%	16%	2%	7%	20%	<1%
West Midlands	53%	17%	4%	4%	19%	1%
Yorks / Humber	71%	10%	1%	10%	7%	1%
	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.001

Index of multiple deprivation						
1 (most deprived)	44%	19%	7%	5%	20%	3%
2	52%	16%	5%	5%	18%	2%
3	49%	18%	4%	8%	16%	1%
4	52%	15%	6%	9%	14%	1%
5 (least deprived)	57%	15%	4%	7%	12%	2%
	$p=0.001$	$p=0.41$	$p=0.25$	$p=0.08$	$p=0.01$	$p=0.41$
Histological subtype						
Nodular Sclerosis	51%	17%	4%	7%	15%	2%
Mixed cellularity	56%	15%	3%	5%	18%	3%
Lymphocyte-rich	55%	16%	7%	4%	13%	-
Other / NOS	49%	17%	6%	7%	16%	2%
	$p=0.28$	$p=0.64$	$p=0.13$	$p=0.51$	$p=0.42$	$p=0.37$

Figure S12: Adjusted overall, lymphoma-specific and other cause survival for patients in the first-line chemotherapy sub-cohort aged 60-79 years at diagnosis by use of ABVD versus AVD (n=998 ABVD, n=323 AVD).

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

A(B)VD= doxorubicin, (bleomycin,) vinblastine, dacarbazine.

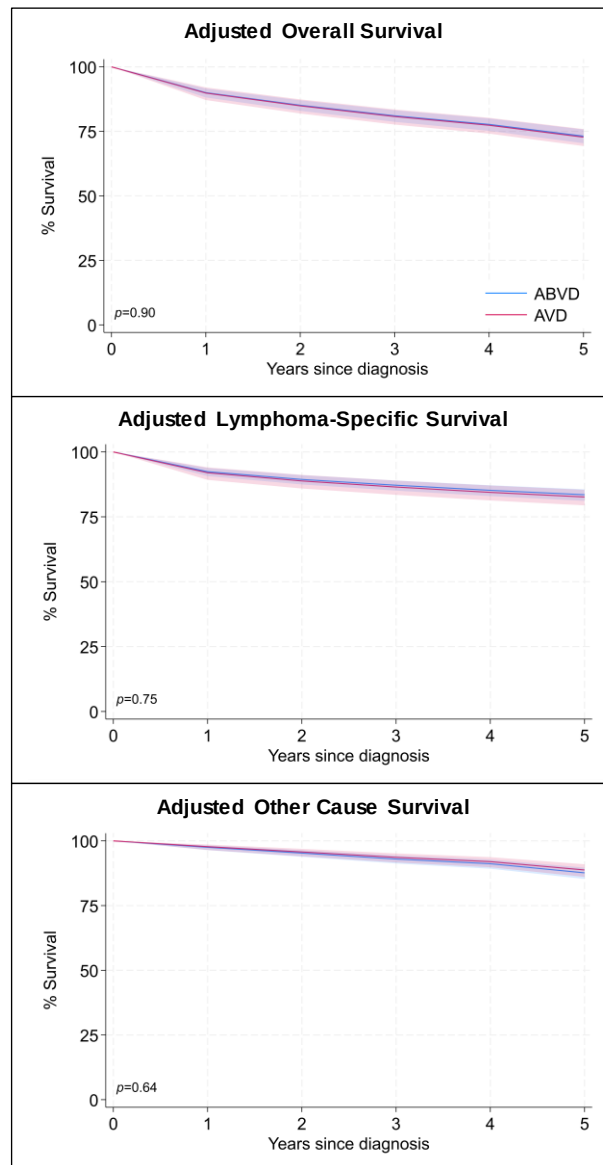


Figure S13: Adjusted overall, lymphoma-specific and other cause survival for patients in the first-line chemotherapy sub-cohort aged 60-79 years at diagnosis by anthracycline use (n=1563 anthracycline, n=395 no anthracycline).

Anthracycline use was defined as delivery of at least one dose of doxorubicin or mitoxantrone. Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

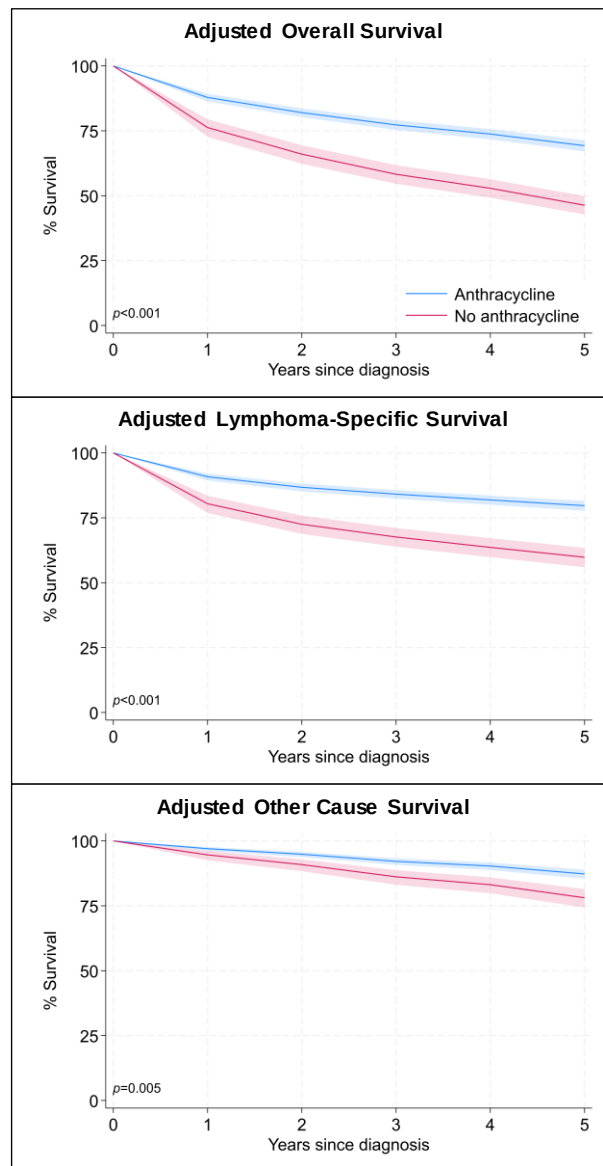


Figure S14: Adjusted overall, lymphoma-specific and other cause survival for patients in the first-line chemotherapy sub-cohort aged 60-79 years at diagnosis by use of multi-agent versus single-agent chemotherapy (n=1925 multi-agent, n=33 single-agent).

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

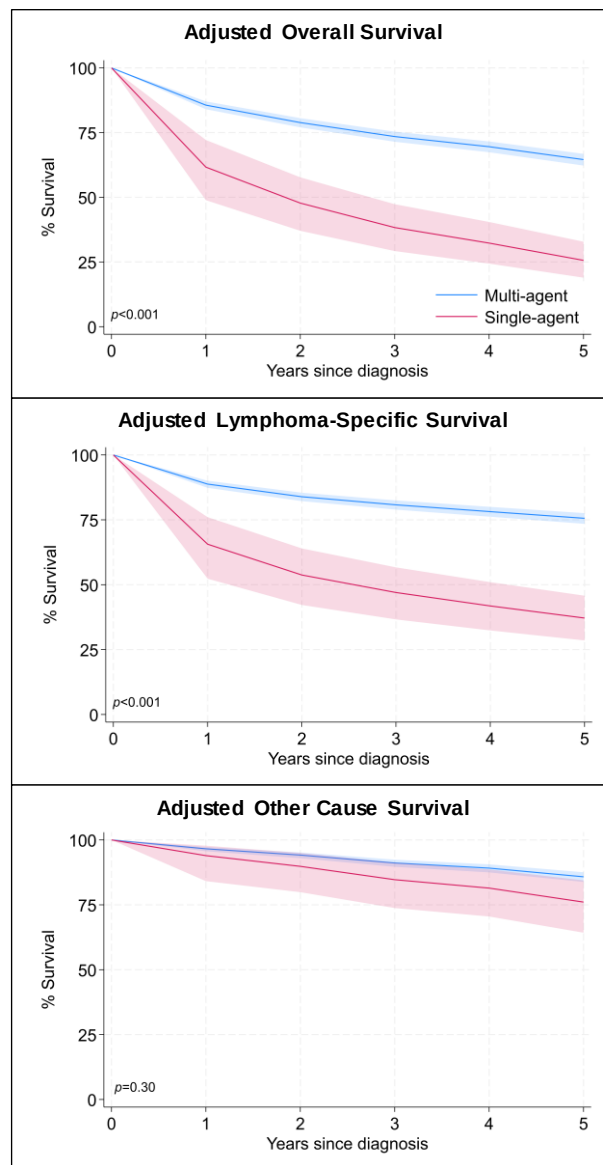


Table S7: Treatment-related factors associated with patients aged 60-79 years at diagnosis receiving different first-line chemotherapy regimens in the first-line chemotherapy sub-cohort.

Patients not in receipt of the six most common first-line chemotherapy regimen groupings were excluded (n=69).

Missing data: comorbidity adjustment at baseline= 18.2% (n=344), dose reduction during treatment= 20.0% (n=378), early cessation= 33.8% (n=639).

ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD with omission of bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. ChlVPP= chlorambucil, vinblastine, procarbazine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide.

Treatment-related factors	ABVD n=998	AVD n=323	CHOP n=96	VEPEMB n=129	ChlVPP n=310	Single-agent n=33
Modification for comorbidity at baseline	19%	28%	33%	30%	27%	48%
Dose reduction during treatment	18%	22%	19%	21%	26%	21%
Early cessation of treatment	15%	16%	20%	19%	12%	11%
Curative radiotherapy	23%	26%	19%	21%	15%	3%

Figure S15: Adjusted overall, lymphoma-specific and other cause survival in patients aged 60-79 years at diagnosis in receipt of anthracycline-containing first-line chemotherapy by record of dose reduction in the first-line chemotherapy sub-cohort (n=1021 with no dose reduction, n=233 with dose reduction).

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression.

Patients with missing data for dose reduction are excluded (n=309).

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

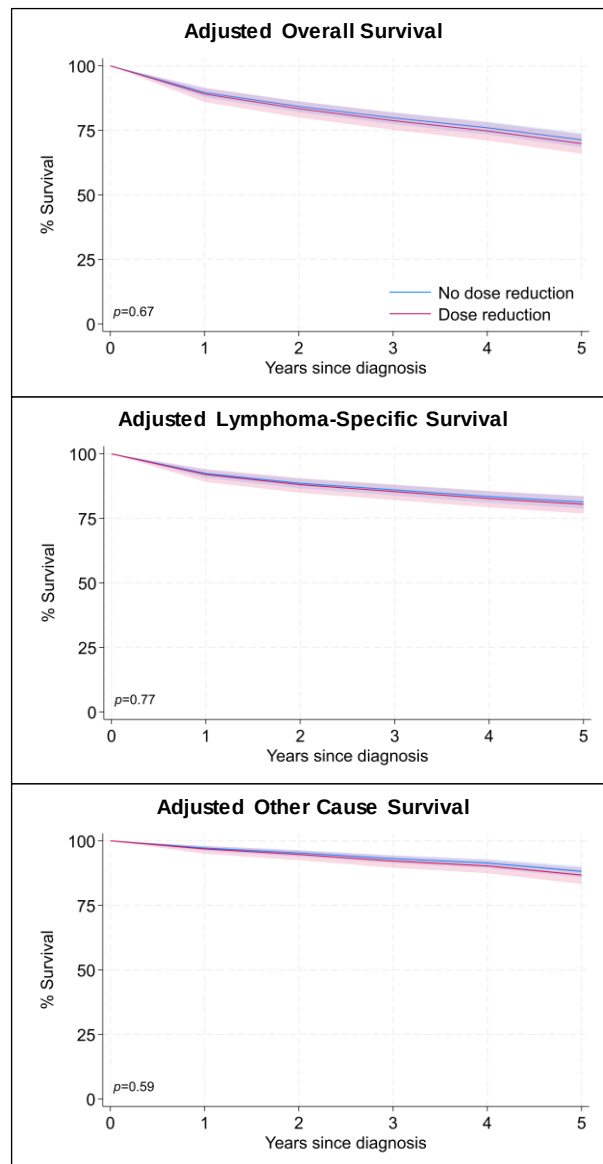


Figure S16: Adjusted overall, lymphoma-specific and other cause survival in patients aged 60-79 years at diagnosis in receipt of anthracycline-containing first-line chemotherapy by record of early cessation in the first-line chemotherapy sub-cohort (n=806 without early cessation, n=146 with early cessation).

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression.

Patients with missing data for early cessation (n=537) are excluded. Follow up commenced at 3 months following diagnosis to exclude those with early mortality following chemotherapy commencement (n=74 excluded).

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

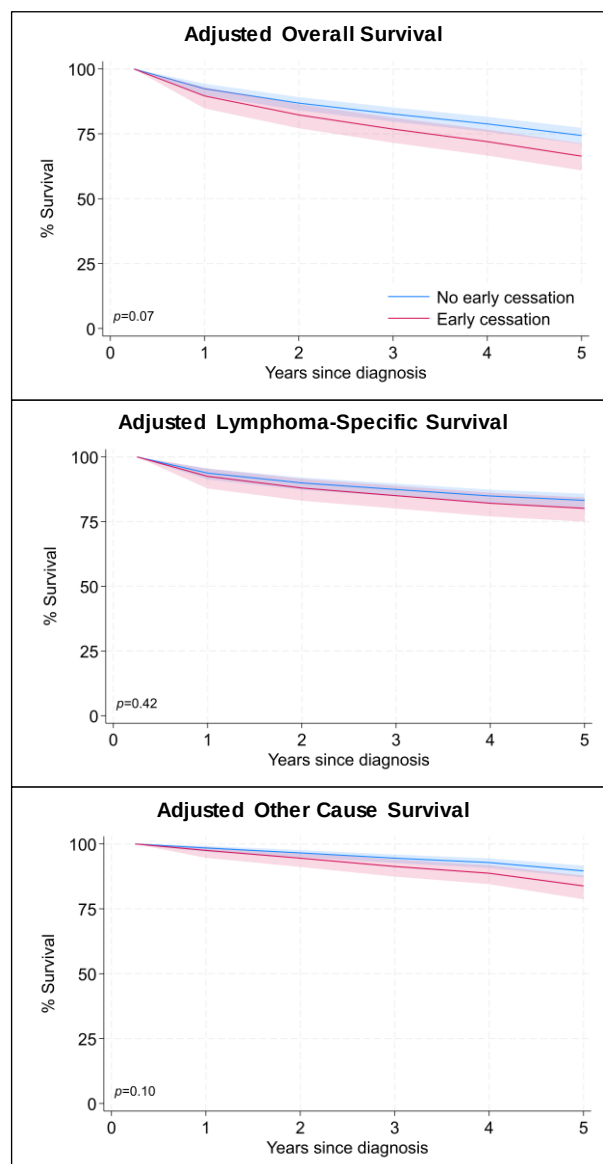


Figure S17: Adjusted overall, lymphoma-specific and other cause survival by use of radical doses of radiotherapy in patients aged 60-79 years at diagnosis receiving curative approaches to first-line chemotherapy in the first-line chemotherapy sub-cohort (n=1546 in receipt of ABVD, AVD, CHOP or VEPEMB with n=361 in receipt of curative radiotherapy and n=1185 not in receipt).

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index, histological subtype and chemotherapy subtype by Poisson regression.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. AVD= ABVD without bleomycin. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. VEPEMB= vinblastine, cyclophosphamide, procarbazine, mitoxantrone, bleomycin, etoposide.

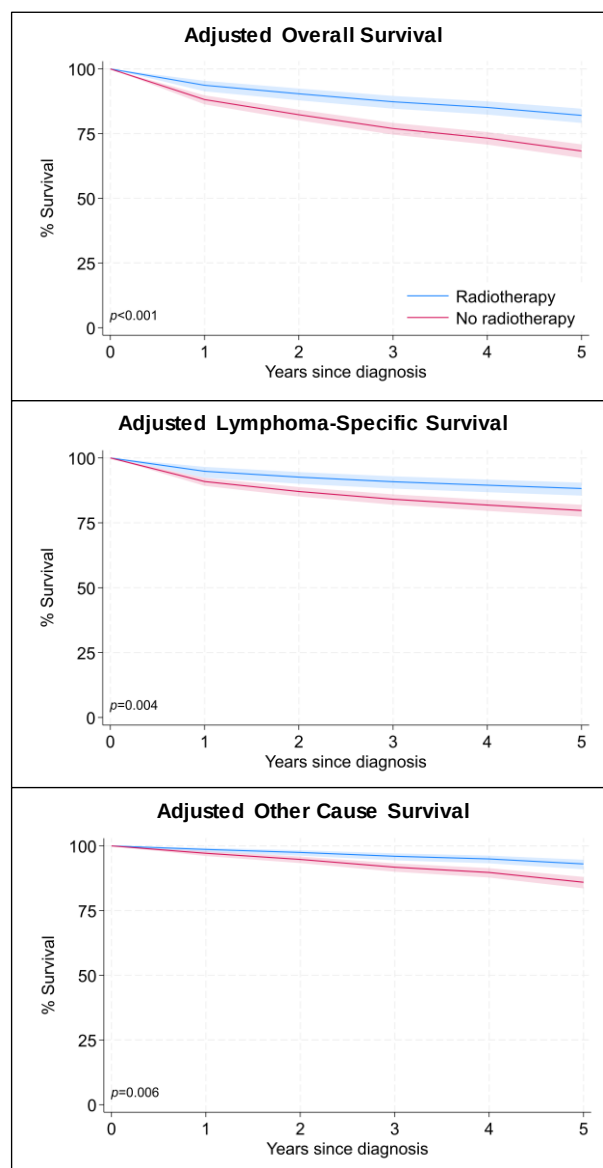


Figure S18: Regional variation in anthracycline use and adjusted lymphoma-specific and other cause mortality rates in the first-line chemotherapy sub-cohort in patients aged 18-39 years at diagnosis.

Panel A shows the unadjusted and adjusted percentages of patients receiving anthracycline by region with adjustment for age, sex, stage, comorbidity status, performance status, deprivation index and histological subtype by logistic regression. Panel B shows mortality rates adjusted for age, sex, stage, comorbidity score, performance status, year since diagnosis, deprivation index and histological subtype using Poisson regression, with regions ordered as in panel A of Figure 6. Panel C shows the same mortality rates but including adjustment for receipt of anthracycline.

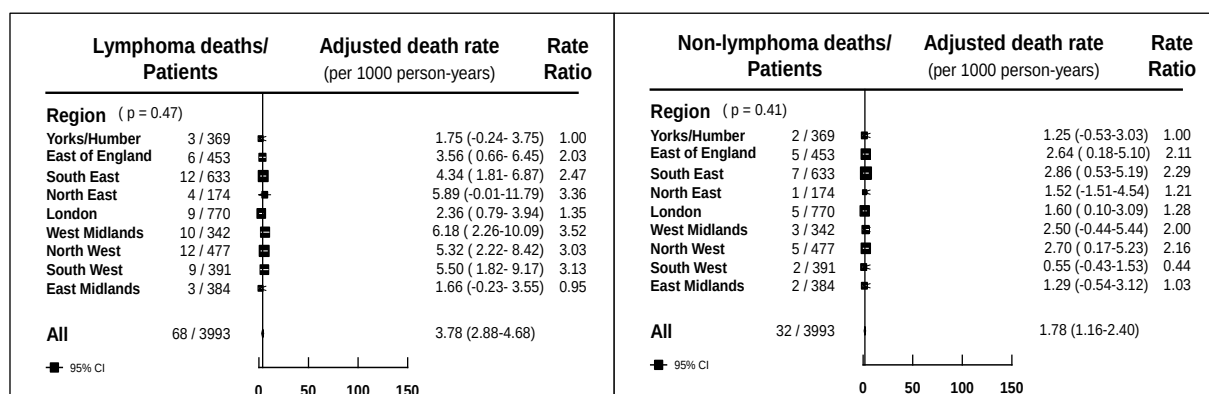
p-values are for trend.

Yorks/Humber= Yorkshire and the Humber.

A Anthracycline use by region ordered from highest to lowest adjusted %

Region	Anthracycline Use/Total	% Use Unadjusted	% Use Adjusted
Yorks/Humber	368/369	99.7	99.6
East of England	453/453	100.0	100.0
South East	627/633	99.1	98.9
North East	174/174	100.0	100.0
London	766/770	99.5	99.4
West Midlands	339/342	99.1	99.0
North West	477/477	100.0	100.0
South West	391/391	100.0	100.0
East Midlands	384/384	100.0	100.0

B Adjusted mortality rates ordered by adjusted regional use of anthracycline



C Panel B with additional adjustment for anthracycline use by individual patient

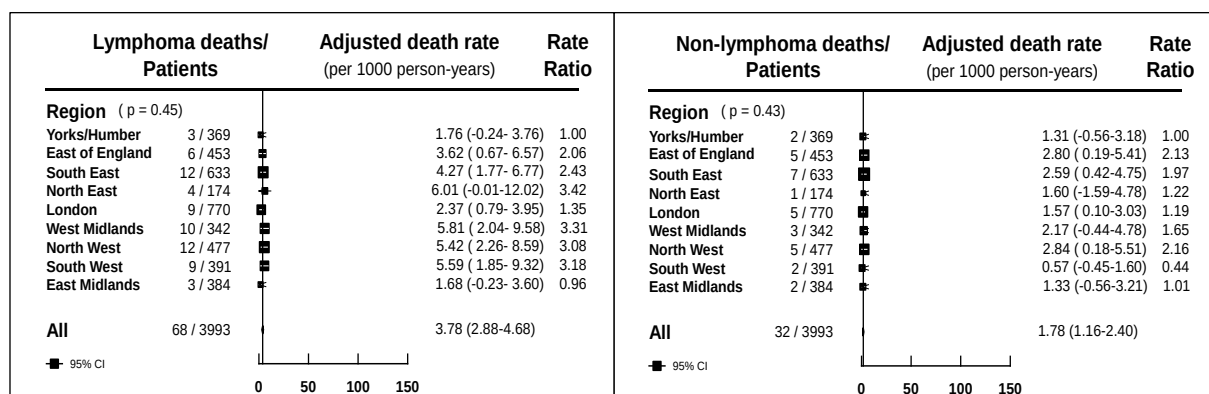


Figure S19: Regional variation in anthracycline use and adjusted lymphoma-specific and other cause mortality rates in the first-line chemotherapy sub-cohort in patients aged 40-59 years at diagnosis.

Panel A shows the unadjusted and adjusted percentages of patients receiving anthracycline by region with adjustment for age, sex, stage, comorbidity status, performance status, deprivation index and histological subtype by logistic regression. Panel B shows mortality rates adjusted for age, sex, stage, comorbidity score, performance status, year since diagnosis, deprivation index and histological subtype using Poisson regression, with regions ordered as in panel A of Figure 6. Panel C shows the same mortality rates but including adjustment for receipt of anthracycline.

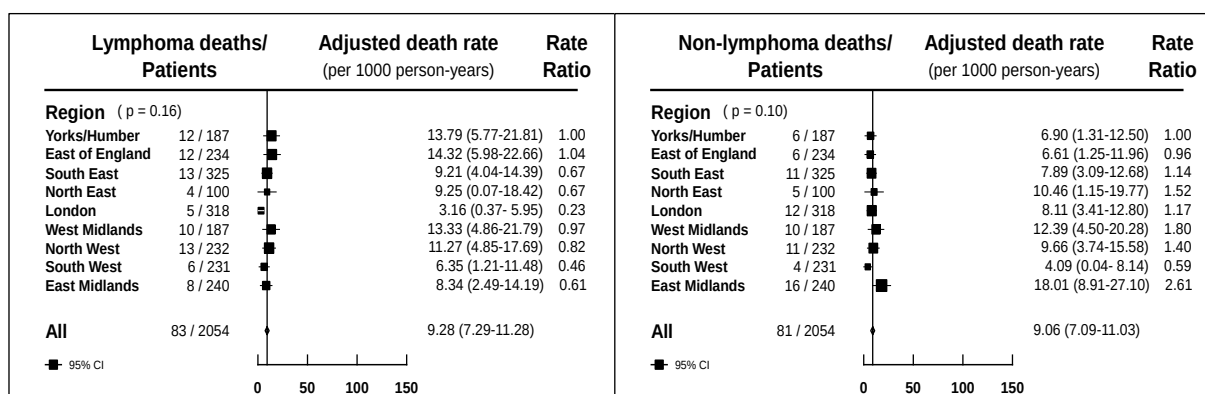
p-values are for trend.

Yorks/Humber= Yorkshire and the Humber.

A Anthracycline use by region ordered from highest to lowest adjusted %

Region	Anthracycline Use/Total	% Use Unadjusted	% Use Adjusted
Yorks/Humber	186/187	99.5	99.6
East of England	233/234	99.6	99.4
South East	321/325	98.8	98.8
North East	97/100	97.0	96.7
London	315/318	99.0	99.1
West Midlands	185/187	98.9	98.9
North West	226/232	97.4	97.7
South West	227/231	98.3	98.1
East Midlands	230/240	95.8	95.3

B Adjusted mortality rates ordered by adjusted regional use of anthracycline



C Panel B with additional adjustment for anthracycline use by individual patient

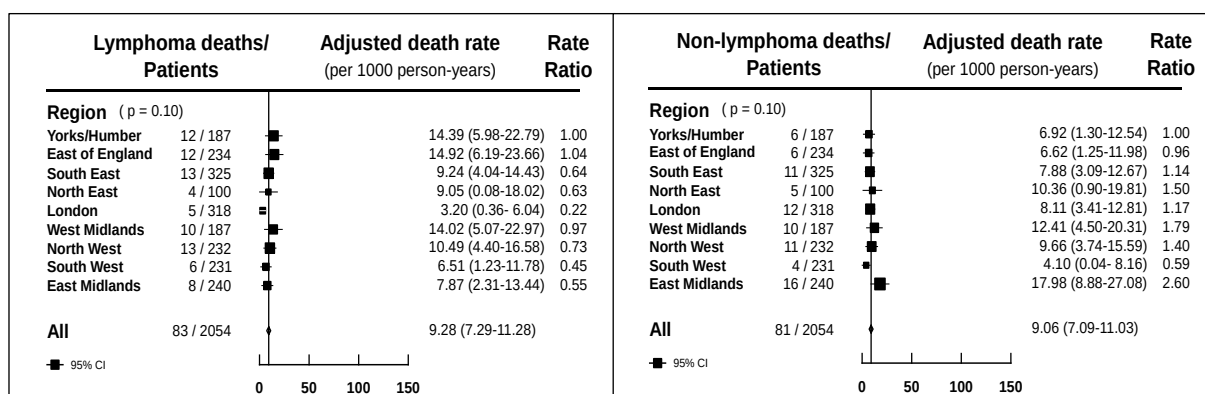


Figure S20: Adjusted overall, lymphoma-specific and other cause survival in patients aged 80-89 years at diagnosis by anthracycline use in the first-line chemotherapy sub-cohort (n=122 in receipt of anthracycline, n=218 not in receipt of anthracycline).

Adjustments made for age, sex, stage, comorbidity score, performance status, year since diagnosis, geographical region, deprivation index and histological subtype by Poisson regression.

The shaded areas represent 95% confidence intervals.

p-values are for heterogeneity between groups.

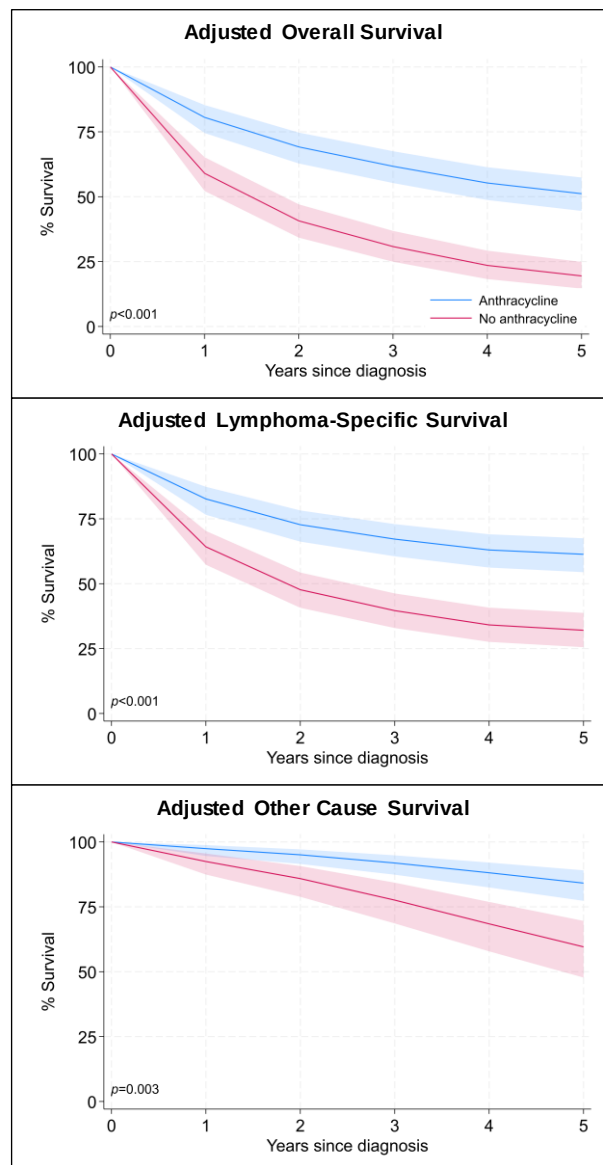


Table S8: Findings of previous analyses of older patients with CHL published in calendar period 2015 to 2026, with a focus on factors associated with improved survival.

y= age at diagnosis (years). OS= overall survival. CHL= classic Hodgkin lymphoma. RS= relative survival. ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine. EFS= event-free survival. SEER= Surveillance, Epidemiology and End Results. LSS= lymphoma-specific survival. IPS= international prognostic score. PFS= progression-free survival. ADL= activities of daily living. CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone. FFP= freedom from progression. NLPHL= nodular lymphocyte-predominant Hodgkin lymphoma. BMI= body mass index.

First author, year of publication	Type of study	Cohort description	Calendar period of diagnoses	Choice of end-point	Factors associated with improved survival/ reduced mortality	Other key findings
Bishton 2015	Registry analysis- Nottingham-sire Lymphoma Registry	≥60y n=208	1973-2012	OS	More recent year of diagnosis Younger age at diagnosis Female sex	-
Goyal 2017	Registry analysis- National Cancer Database	≥60y n=3795 Early stage CHL only	2004-2012	OS	Combined modality treatment More recent year of diagnosis No comorbidities Female sex Non-white ethnicity Higher income	-
Bjorkholm 2018	Registry analysis- Swedish Cancer and Lymphoma Registry	All ages n=7997 45% ≥50y	1973-2014 cancer registry, 2000-2013 lymphoma registry	RS	More recent year of diagnosis for ≥70y Younger age at diagnosis Female sex	-
Major 2019	Registry analysis- National Cancer Database	All ages n=46,261 24% ≥60y	2004-2013	OS RS	Younger age at diagnosis Female sex Treatment at academic/ research facility Fewer comorbidities Early stage CHL No B-symptoms Absence of mixed cellularity histology Chemotherapy use Radiotherapy use (just early stage)	<u>Factors associated with likelihood of delivery of therapy</u> Younger age Fewer comorbidities Absence of extranodal disease Absence of lymphocyte-rich/ -depleted histologies Advanced stage CHL Treatment at academic/ research facility
Wrobel 2019	Retrospective cohort study	>50y n=385	2001-2013	OS EFS	<u>Early stage CHL</u> Younger age Better performance status	-

		Treated with ABVD/ ABVD-like regimens			<u>Advanced stage CHL</u> Younger age Fewer comorbidities Absence of cardiovascular disease Absence of mixed cellularity/ lymphocyte-depleted histology Absence of bulky disease (just OS) Better performance status (just EFS) Absence of extranodal disease	
Rodday 2019-treatment choice analysis Rodday 2021-mortality analysis	Registry analysis- SEER-Medicare	≥65y n=2825 for treatment choice analysis n=2686 for mortality analysis	1999-2014 for treatment choice analysis 2000-2013 for mortality analysis	Treatment choice Lymphoma-specific mortality Other cause mortality	Full chemotherapy regimens Younger age Absence of frailty Married Fewer comorbidities Absence of cardiac comorbidities Absence of lymphocyte depleted histology Absence of B symptoms Female gender (just early stage CHL and other cause mortality) Absence of prior cancer (just early stage CHL and other cause mortality) Stage I>II and III>IV (just lymphoma-specific mortality)	<u>Factors associated with choice of treatment</u> Partial > full regimens: frailty, cardiovascular disease, advanced stage CHL, less recent year of diagnosis Single > full regimens: older age at diagnosis, frailty, cardiovascular disease, prior cancer, lymphocyte-rich histology, advanced stage CHL, less recent year of diagnosis, lack of B symptoms No treatment > full regimens: older age at diagnosis, frailty, cardiovascular disease, lymphocyte-depleted histology, advanced stage CHL, B symptoms, less recent year of diagnosis
Thomas 2021	Registry analysis- Veterans Affairs Central Cancer Registry	All ages n=847 40% ≥60y Treated with bleomycin and doxorubicin-containing chemotherapy regimens	2002-2013	Development of bleomycin pulmonary toxicity	Younger age at diagnosis Fewer comorbidities	<u>Factors associated with development of bleomycin pulmonary toxicity</u> Older age History of smoking Higher level of comorbidities
Galli 2020	Retrospective cohort study	≥60y n=76	1999-2018	OS LSS Other cause survival	Younger age at diagnosis (just OS) Lack of severe comorbidity (OS, other cause survival) Fewer comorbidities (just OS) Better IPS score (OS, LSS)	-

					Anthracycline treatment (OS, LSS)	
Sykorova 2020	Retrospective cohort study	≥60y n=182	1995-2016	OS PFS	Higher albumin Higher lymphocyte count Absence of leukocytosis Anthracycline treatment Younger age at diagnosis (just OS) Absence of anaemia (just OS) Female gender (just OS) Better performance status (just OS) Few comorbidities (just OS)	-
Orellana- Noia 2021	Retrospective cohort study	≥60y n=244	2010-2018	OS PFS Competing risks analysis of LSS	ABVD-like treatment Absence of impairment of ADL (just OS, PFS) Absence of geriatric syndrome at baseline (just OS) Fewer comorbidities (just OS) Advanced stage CHL (just PFS)	<u>Factors associated with likelihood of ABVD-like therapy</u> Younger age Presence of B symptoms Better performance status Absence of geriatric syndrome at baseline Fewer comorbidities
Kumar 2021	Registry analysis- SEER- Medicare	≥65y n=813 development cohort, n=502 validation cohort Treated with full regimens of chemotherapy	2000-2013	OS	Fewer comorbidities Younger age at diagnosis Absence of B symptoms Early stage CHL Lack of disability (<i>not included in the model for the validation cohort</i>)	-
Wahlin 2021	Registry analysis- Swedish Lymphoma Registry	All ages n=2347 29% >60y	2000-2014	OS RS	Receipt of ABVD (in comparison to CHOP) Early stage CHL Better performance status More recent year of diagnosis (just OS) Younger age at diagnosis (just OS) Nodular sclerosis histology (just OS) Female gender (just OS) Absence of B symptoms (just OS) Lower IPS (just OS)	-
Cheng 2022	Registry analysis- BC Cancer Lymphoid Cancer database	≥60y n=744	1961-2019	OS PFS LSS	Better performance status Nodular sclerosis histology Younger age at diagnosis More recent year of diagnosis (just OS, LSS) Early stage CHL (just OS, LSS)	-

					Receipt of ABVD (just OS, PFS) <u>Advanced stage CHL</u> Lack of anaemia (just OS, PFS) Lack of leukocytosis (just OS, PFS) Higher lymphocyte count (just OS, PFS) Stage IV (in comparison to III) (just OS, PFS) Lower IPS (just PFS)	
Goh 2023	Combined registry analysis- Lymphoma and Related Diseases Registry- and retrospective cohort study	>60y n=195	2011-2020	OS PFS	Anthracycline treatment Better performance status Non-smoking status Lack of poly-pharmacy Bleomycin treatment Normal albumin levels Fewer comorbidities (just PFS) ABVD-like treatment (just PFS)	<u>Factors associated with unplanned hospitalisation in first-line treatment</u> Worse performance status Anthracycline treatment
Goveia 2023	Registry analysis- Brazilian Prospective HL Registry	≥60y n=136	2009-2018	OS PFS	Younger age at diagnosis Early stage CHL Better socio-economic status	-
Lia 2023	Registry analysis- Cancer Registry of Norway	≥60y n=492 Includes NLPHL	2000-2015	OS LSS	Full chemotherapy regimens Younger age at diagnosis (just OS) Early stage (just OS)	<u>Cause of death analysis</u> Increased risk of death from other haematological malignancies, dementia and cardiovascular disease than non-CHL controls
Shah 2023	Registry analysis- SEER-18	≥60y n=4957	2000-2015	OS LSS	Non-Hispanic White ethnicity Younger age at diagnosis (just OS) Female gender (just OS) Early stage CHL (just OS) Married (just OS) Chemotherapy treatment (just OS) More recent year of diagnosis	-
Mehtap 2024	Retrospective cohort study	≥60y n=178 derivation cohort, n=108 validation cohort	2004-2020	Early death (within 12 months) OS	Female gender Higher albumin levels Better performance status Early stage CHL (just OS- <i>not included in the model for the validation cohort</i>)	-
Lia 2025	Registry analysis- Cancer Registry of	≥60y n=279 training cohort, n=792 validation cohort	2000-2015	OS PFS	Younger age at diagnosis Better performance status Fewer comorbidities	-

	Norway + Swedish Lymphoma Register	Treated with anthracycline			<u>Variables not included in model for validation cohort:</u> Early stage CHL Lack of dependency of ADLs Higher BMI Lack of B symptoms Higher dose intensity of anthracycline Lymphocyte-rich / - depleted histology	
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