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RESEARCH ARTICLE

Congestive heart failure after anthracycline-containing treatment for Hodgkin lymphoma: A Swedish matched cohort study

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Abstract

Introduction: Congestive heart failure (CHF) is a known complication after anthracyclines and radiotherapy for classical Hodgkin lymphoma (cHL). Contemporary cHL treatment may be associated with less risk because radiotherapy use and techniques have changed substantially over time.

Methods: In this study, Swedish cHL patients diagnosed in 2000–2018, and treated with adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine (ABVD) or bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), were matched 1:10 to the general population on birth year and sex to investigate relative rates and cumulative risks of CHF.

Results: A total of 1994 cHL patients were included, with a median age of 34 years. The median follow-up was 8.1 years. The CHF rate was higher for patients versus comparators (adjusted hazard ratio [HR] = 3.02, 95% confidence interval [CI]: 2.26–4.02). Patients treated with ≤200 mg/m^2 of anthracyclines had HR of 2.89

(95% CI: 1.51–3.47) versus 3.91 (95% CI: 2.72–5.60) for >200 mg/m^2. Treatment with ABVD was associated with a significantly higher CHF rate (adjusted HR = 3.25, 95% CI: 2.31–4.23), while BEACOPP was not (adjusted HR = 1.95, 95% CI: 0.91–4.16). The increase in relative rates translated to the absolute scale, with an increased risk persisting up to 18 years for low cumulative doses.

Conclusion: These findings highlight that cHL survivors still face a substantial excess risk of CHF in the modern treatment era and that focus on cardiovascular health remains relevant.

1 | BACKGROUND

Patients with classical Hodgkin lymphoma (cHL) have an excellent 5-year survival of around 80%–95% depending on the stage and risk classification [1, 2]. With the bimodal peak incidence in age groups 18–30 and around 50 years, the residual life expectancy is very long after successful treatment of cHL [3, 4]. The favorable prognosis of cHL is attributed to the use of multiagent chemotherapy and radiotherapy, which can be associated with overlapping late toxicities, one of them being congestive heart failure (CHF) [5]. The risk of CHF is explained by the use of mediastinal radiotherapy and/or anthracycline-containing chemotherapy such as current worldwide standard treatments like ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) and BEACOPP (bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, vincristine, procarbazine, and prednisone) [6–9]. Whereas multiagent chemotherapy remains a critical component of cHL treatment regardless of stage, the use of radiotherapy has changed substantially in past decades with the implementation of fluorodeoxyglucose-positron emission tomography (FDG-PET)-guided treatment leading to less and smaller radiation fields. Radiotherapy is now predominantly used in patients with limited-stage disease as only a minority of patients with advanced-stage disease have FDG-PET-positive residual lesions after chemotherapy [8, 10]. Concerning anthracyclines, the use of doxorubicin remains unchanged in the standard first-line treatments (50 mg/m^2 per cycle of ABVD and 25 mg/m^2 for BEACOPP) and is also included in the most recently developed first-line chemotherapy regimens such as BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, Adriamycin [doxorubicin], dacarbazine, and dexamethasone), A+AVD (brentuximab vedotin, Adriamycin [doxorubicin], vinblastine, and dacarbazine), and N-AVD (nivolumab, Adriamycin [doxorubicin], vinblastine, and dacarbazine) [11–13].

Nimwegen et al. showed that treatment with anthracyclines in patients with cHL increased the risk of CHF 3-fold, independent of concomitant radiotherapy, compared with patients treated with chemotherapy without anthracyclines, based on data from patients treated between 1965 to 1995 [6]. More recent data based on Danish registers showed a dose-response relationship between the cumulative dose of anthracyclines and the risk of CHF in patients with non-Hodgkin lymphoma, with a hazard ratio (HR) of 6.8 for patients treated with six cycles of R-CHOP(-like) treatment using lymphoma patients treated without anthracyclines as reference [14]. As CHF is also a common disease in the background population, investigating the CHF incidence associated with anthracycline use for cHL relative to the expected incidence in the general population is critical to understanding the potential absolute CHF reduction that would be achievable with less cardiotoxic therapies. However, these contrasts are not well studied. Furthermore, the decrease in the use of mediastinal radiotherapy warrants a re-examination of the risk of CHF in nationwide cohorts of real-world patients with cHL treated in a modern era.

In this nationwide Swedish matched cohort study, the risk of CHF after contemporary cHL treatment was investigated and compared to the incidence observed in matched comparators. Furthermore, risk factors associated with CHF among the patients with cHL were investigated.

2 | METHODS

2.1 | Data sources and study population

This cohort study included all newly diagnosed cHL patients aged 18–80 who were treated with ABVD or BEACOPP during 2000–2018 and registered in the Swedish Lymphoma Register (SLR). The SLR was initiated in 2000 and contains detailed information on diagnosis, baseline clinicopathological values, treatment regimens, response evaluations, and information on relapse. SLR has a high coverage of 95% using data from the Swedish Cancer Register as a reference [15, 16]. The SLR does not contain explicit information on doses of chemotherapy, but estimated doses were calculated from treatment regimens and the number of treatment cycles with the assumption of full doses in every cycle. The date of the end of first-line chemotherapy was in most cases registered by the treating physician, but for those patients with a missing date ($n = 73$), the end of treatment was calculated by the known length of the combination of treatment regimen and the number of treatment cycles. Patients treated with AVD were categorized in the ABVD group ($n = 48$), escalated BEACOPP was categorized as BEACOPP ($n = 66$), and patients treated with both ABVD and BEACOPP were allocated to the BEACOPP group ($n = 46$).

Using the identification number unique to all Swedish residents, patients with cHL were linked to other national registers [17]. The

Swedish Cancer Register, initiated in 1958, was used to ensure only the first ever cHL diagnosis for each patient was included [18]. The Swedish Total Population Register was used for matching each cHL patient in a 1:10 ratio based on sex and birth year to population comparators. The matched comparators had to be alive, residing in Sweden, and free from cHL on the matching date (from this point referred to as the inclusion date).

CHF diagnoses and comorbidities were identified in the Swedish National Patient Register using the International Classification of Diseases 10th and 9th revision (ICD-10 and ICD-9) codes (see Table S1 for all codes). This register contains data on all inpatient hospital contacts (with national coverage since 1987) and all outpatient hospital contacts (since 2001) [19]. In addition to the ICD-codes, diabetes mellitus was also identified by Anatomical Therapeutic Chemical Classification System codes for prescriptions of insulin and blood glucose-lowering drugs. The first hospital contact where CHF was the main or secondary diagnosis following study inclusion was considered an event. Comorbidities considered included hypertension, thyroid diseases, hyperlipidemia, renal diseases, diabetes mellitus, atrial fibrillation, and acute myocardial infarction and were defined as any hospital contact with a main or secondary diagnoses codes of comorbidity in 10 years prior to inclusion (see Table S1 for specific codes).

Dates of death were retrieved from the National Swedish Cause of Death Register, and dates of first emigration after inclusion date from the Swedish Total Population Register [17, 20]. Educational level was obtained from the Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies, defined as the highest achieved educational level at the time of inclusion [21], and categorized as low (≤9 years), intermediate (10–12 years), and high (≥13 years).

Patients with cHL ($n = 12$) and comparators ($n = 415$) who had any diagnosis of CHF within the previous ten years before the inclusion date were excluded, as only incident events were of interest. Additionally, missing information on treatment (number of cycles or dates) for the cHL patients was an exclusion criterion ($n = 25$). Due to the exclusion criteria for comparators, some cHL patients had less than ten comparators.

2.2 | Statistical analysis

Patients were followed from the end of first-line lymphoma treatment until an event of CHF, death from all causes, or censoring (emigration from Sweden or end of the study period, December 31, 2019), whichever came first. The underlying timescale for all analyses was time since the end of first-line treatment. Cause-specific HRs with associated 95% confidence intervals (CIs) for CHF, comparing patients to matched comparators, were estimated using flexible parametric survival models (FPMs) with two degrees of freedom (df) for the baseline cumulative hazard rate [22]. Both univariable and multivariable models were applied, with the latter adjusted for the following confounders: sex, age, and calendar year of inclusion (the latter two assuming non-linear effects using restricted cubic splines with three df), highest achieved education, and previous comorbidities (hypertension, thyroid disease, hyperlipidemia, renal disease, diabetes mellitus, atrial fibrillation, and acute myocardial infarction). Additional models are described in Statistical Appendix S1. Among the cHL patients, separate unadjusted and adjusted (for age and sex) FPMs were applied to assess potential clinical risk factors. The choice of df was determined based on the Akaike information criterion.

Non-parametric estimates of the cause-specific cumulative incidence (CIF) of CHF were estimated by patient/comparator status using the Aalen-Johansen estimator, with death before CHF as a competing event. Additionally, FPMs were used to calculate cause-specific CIFs for CHF. These are described in detail in Statistical Appendix S2. All CIs (non-parametric and model-based) were calculated using the delta method.

All analyses were conducted in Stata (StataCorp. Stata Statistical Software: Release 18; StataCorp LLC.) using the packages merlin and multistate [23, 24]. The study was approved by the Swedish Ethical Review Authority (no. 2019-00242).

3 | RESULTS

Among the 1994 cHL patients treated with ABVD or BEACOPP and 19713 matched comparators, 61 (3.1%) and 225 (1.1%), respectively, experienced CHF during follow-up (Table 1). The number and proportion of patients and comparators who died during follow-up were 169 (8.5%) and 587 (3.0%), respectively. The median age at inclusion was 34 years for patients (interquartile range [IQR]: 25–51) and comparators (IQR: 25–50). Among the patients, 8.7% had CCI ≥ 2 at diagnosis and 35% had a high educational level. The corresponding proportions for comparators were 5.1% and 34%.

Most cHL patients had advanced-stage disease (57%), non-bulky disease (79%), and absence of B-symptoms (55%) (Table 2). A total of 1,642 (82%) were treated with ABVD (including 48 with AVD) and 352 (18%) were primarily treated with BEACOPP (including 66 with escalated BEACOPP and 46 with both ABVD and BEACOPP). With an estimated mean cumulative anthracycline dose of 237 mg/m^2 (standard deviation 93.6), a total of 271 patients (14%) were treated with ≤100 mg/m^2 anthracycline, 726 (36%) with 101–200 mg/m^2, 635 (32%) with 201–300 mg/m^2, and 362 (18%) with > 300 mg/m^2.

The median follow-up was 8.1 years (range: 0.0–19.7). Based on the adjusted model, the CHF-specific HR was 3.02 (95% CI: 2.26–4.02) when comparing all cHL patients to matched comparators (Table 3). When relaxing the PH assumption, the time-dependent HR decreased over time, from a 7-fold rate initially after the end of treatment to 2-fold after 14 years and onward until the end of follow-up (Figure S1).

When contrasting patients to comparators by cumulative dose of anthracyclines received, both patients exposed to ≤200 mg/m^2 and >200 mg/m^2 had a significantly higher CHF rate than comparators when assuming proportional hazards (adjusted HR = 2.89, 95% CI: 1.51–3.47, for ≤200 mg/m^2 and HR = 3.91, 95% CI: 2.72–4.72 for >200 mg/m^2) (Table 3). Relaxing the PH assumption showed that patients treated with less anthracycline experienced an increased CHF rate relative to the comparators for the first 13 years after the end

TABLE 1 Frequencies and percentages of characteristics for patients with classical Hodgkin lymphoma (cHL) and comparators.

Characteristic	cHL patients (*N* = 1994) *n* (col %)	Comparators (*N* = 19713) *n* (col %)
CHF event during follow-up		
Yes	61 (3.1)	225 (1.1)
Deceased during follow-up		
Yes	169 (8.5)	587 (3.0)
Sex		
Male	1052 (52.8)	10,391 (52.7)
Female	942 (47.2)	9,322 (47.3)
Age at inclusion (years)		
0–25	515 (25.8)	5,071 (25.7)
26–40	714 (35.8)	7,115 (36.1)
41–60	534 (26.8)	5,263 (26.7)
>60	231 (11.6)	2,264 (11.5)
Median age (IQR)	34 (25–51)	34 (25–50)
Inclusion year		
2000–2006	523 (26.2)	5176 (26.3)
2007–2012	722 (36.2)	7162 (36.3)
2013–2018	749 (37.6)	7375 (37.4)
Highest achieved educational level		
Low (≤9 yrs)	948 (47.5)	9659 (49.0)
Intermediate (10–12 yrs)	319 (16.0)	2984 (15.1)
High (≥13 yrs)	703 (35.3)	6699 (34.0)
Missing	24 (1.2)	371 (1.9)
Thyroid disease		
Yes	27 (1.4)	282 (1.4)
Hyperlipidemia		
Yes	29 (1.5)	261 (1.3)
Renal disease		
Yes	41 (2.1)	236 (1.2)
Hypertension		
Yes	110 (5.5)	767 (3.9)
Diabetes mellitus		
Yes	72 (3.6)	555 (2.8)

Abbreviations: CHF, congestive heart failure.; col, column; IQR, interquartile range; n, number; yrs, years.
Due to rounding, some percentages might not add up to 100.

of treatment, while those treated with a high dose had an elevated relative CHF rate throughout follow-up (Figure 1).

Stratifying patients by Ann Arbor stage showed similar elevated HRs when assuming PH (Table 3). When allowing for HRs to be time-dependent, limited-stage patients experienced a constant significantly elevated CHF rate throughout follow-up. Advanced-stage patients had an almost 8-fold CHF rate in relation to comparators early on, which

TABLE 2 Frequencies and percentages of clinical characteristics for patients with classical Hodgkin lymphoma (cHL).

Characteristic	cHL patients (*N* = 1994) *n* (col %)
Ann Arbor stage	
Limited (IA–IIA)	849 (42.6%)
Advanced (IIB–IVB)	1128 (56.6%)
Missing	17 (0.9%)
Bulky disease	
0	1578 (79.1%)
1	380 (19.1%)
Missing	36 (1.8%)
WHO performance status	
0	1469 (73.7%)
1	425 (21.3%)
2	52 (2.6%)
3	22 (1.1%)
4	6 (0.3%)
Missing	20 (1.0%)
B-symptoms	
0	1095 (54.9%)
1	874 (43.8%)
Missing	25 (1.3%)
Radiotherapy	
0	140 (7.0%)
1	523 (26.2%)
Missing	1331 (66.8%)
Chemotherapy regimen (first line)	
ABVD	1642 (82.3%)
BEACOPP	352 (17.7%)
Number of treatment cycles (first line)	
1	8 (0.4%)
2	254 (12.7%)
3	34 (1.7%)
4	252 (12.6%)
5	30 (1.5%)
6	636 (31.9%)
7	21 (1.1%)
8	276 (13.8%)
Missing	483 (24.2%)
Anthracycline dosage	
≤100 mg	271 (13.6%)
101–200 mg	726 (36.4%)
201–300 mg	635 (31.8%)
>300 mg	362 (18.2%)

(Continues)

TABLE 2 (Continued)

Characteristic	cHL patients (*N* = 1994) *n* (col %)
Anthracycline dosage, dichotomized	
≤200 mg	997 (50.0%)
>200 mg	997 (50.0%)
Mean dose (sd)	237.3 (93.6)

Abbreviations: ABVD, adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, vincristine, procarbazine, and prednisone; cHL, classical Hodgkin lymphoma; col, column; n, number; sd, standard deviation; WHO, World Health Organization.
Due to rounding, some percentages might not add up to 100.

TABLE 3 Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) estimated from flexible parametric proportional hazards models, comparing congestive heart failure (CHF) rates between Hodgkin lymphoma (HL) patients and comparators.

	HR[a] (95% CI)	HR[b] (95% CI)
Matched comparators	1.00	1.00
HL patients	2.84 (2.14–3.77)	3.02 (2.26–4.02)
By cumulative anthracycline dose		
Matched comparators	1.00	1.00
HL patients exposed to ≤200 mg/m2	2.11 (1.39–3.18)	2.89 (1.51–3.47)
HL patients exposed to > 200 mg/m2	3.74 (2.63–5.32)	3.91 (2.72–5.60)
By Ann Arbor stage		
Matched comparators	1.00	1.00
HL patients limited stage (IA–IIA)	2.38 (1.56–3.63)	2.73 (1.79–4.16)
HL patients advanced stage (IIA–IVB)	3.29 (2.32–4.66)	3.31 (2.32–4.72)
By treatment regimen		
Matched comparators	1.00	1.00
ABVD	3.07 (2.28–4.13)	3.25 (2.40–4.39)
BEACOPP	1.79 (0.84–3.80)	1.95 (0.91–4.16)

Abbreviations: ABVD, adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, vincristine, procarbazine, and prednisone; CHF, congestive heart failure; CI, confidence interval; HL, Hodgkin lymphoma; HR, hazard ratio.
[a]Unadjusted.
[b]Adjusted for sex, age, and calendar year of inclusion (modeled using restricted cubic splines), highest achieved education, and previous comorbidities (hypertension, thyroid disease, hyperlipidemia, renal disease, diabetes mellitus, atrial fibrillation, and acute myocardial infarction).

decreased over time and with the 95% CI including unity after 16 years (Figure S2).

Contrasting patients to comparators by treatment regimen (ABVD or BEACOPP), patients treated with ABVD were older (median age 38.8 vs. 36.0), more likely to be female (49.6% vs. 36.4%), and received higher mean cumulative doses of anthracyclines (248 mg/m^2 vs. 188 mg/m^2) (Table S2). When compared with comparators, patients treated with ABVD had a significantly higher CHF rate (adjusted HR = 3.25, 95% CI: 2.40–4.39). Patients treated with BEACOPP had an adjusted HR of 1.95 (95% CI: 0.91–4.16) (Table 3).

Based on non-parametric estimation of cause-specific CIFs, the 5-, 10-, and 15-year cumulative risk of CHF was 1.82% (95% CI: 1.27–2.52), 3.80% (95% CI: 2.85–4.95), and 4.81% (95% CI: 3.61–6.25) for cHL patients, and 0.59% (95% CI: 0.49–0.72), 1.21% (95% CI: 1.03–1.42), and 2.03% (95% CI: 1.73–2.37) for comparators (Figure 2).

The predictions of the cause-specific CIFs for patients and comparators were standardized by calendar year of diagnosis and are given by sex (male/female) and age (30/60 years) in Figure 3 (by anthracycline dose) and Figure 4 (by stage). In the younger age group (30 years), the cumulative risks of CHF were small for both sexes, regardless of stage and anthracycline dose. Among individuals who entered the study at age 60, patients with cHL who received more than 200 mg of anthracyclines had a higher risk of CHF relative to comparators throughout follow-up (male-specific 10-year cumulative risk for high dose and comparators: 19.1% [95% CI: 13.5%–26.2%] and 6.2% [95% CI: 5.1%–7.6%]) (Figure 3, accompanying table: Table S3). 60-year-old patients who received a low anthracycline dose experienced an increased risk during the first 10 years (male-specific 5-year cumulative risk for low dose: 11.9% [95% CI: 8.0%–17.4%]).

When contrasting by stage, the 10-year cumulative risks of CHF for 60-year-old males were 14.6% (95% CI: 10.5%–20.1%) for advanced stage, 16.0% (95% CI: 10.6%–23.3%) for limited stage, and 6.2% (95% CI: 5.1%–7.6%) for comparators, respectively. For 60-year-old females, the 10-year cumulative risks of CHF by stage were 8.1% (95% CI: 5.5%–11.9%) for advanced stage, 8.5% (95% CI: 5.4%–13.1%) for limited stage, and 3.2% (95% CI: 2.4%–4.1%) for comparators (Figure 4, accompanying table: Table S4).

Overall, the cumulative risk of CHF was higher among older (aged 60 at diagnosis) individuals, and the differences between cHL patients and comparators remained throughout follow-up for both males and females (Figure S3).

Baseline features associated with an increased rate of CHF among the cHL patients were male sex (unadjusted HR for females = 0.51, 95% CI: 0.30–0.86), age per 1-year increase (sex-adjusted HR = 1.09, 95% CI: 1.07–1.11), diabetes mellitus (sex- and age-adjusted HR = 2.26, 95% CI: 1.10–4.62), and acute myocardial infarction prior to cHL diagnosis (sex- and age-adjusted HR = 5.56, 95% CI: 1.96–15.8) (Table S5).

4 | DISCUSSION

In this Swedish matched cohort study, cHL patients treated with anthracycline-containing chemotherapy experienced an increased rate

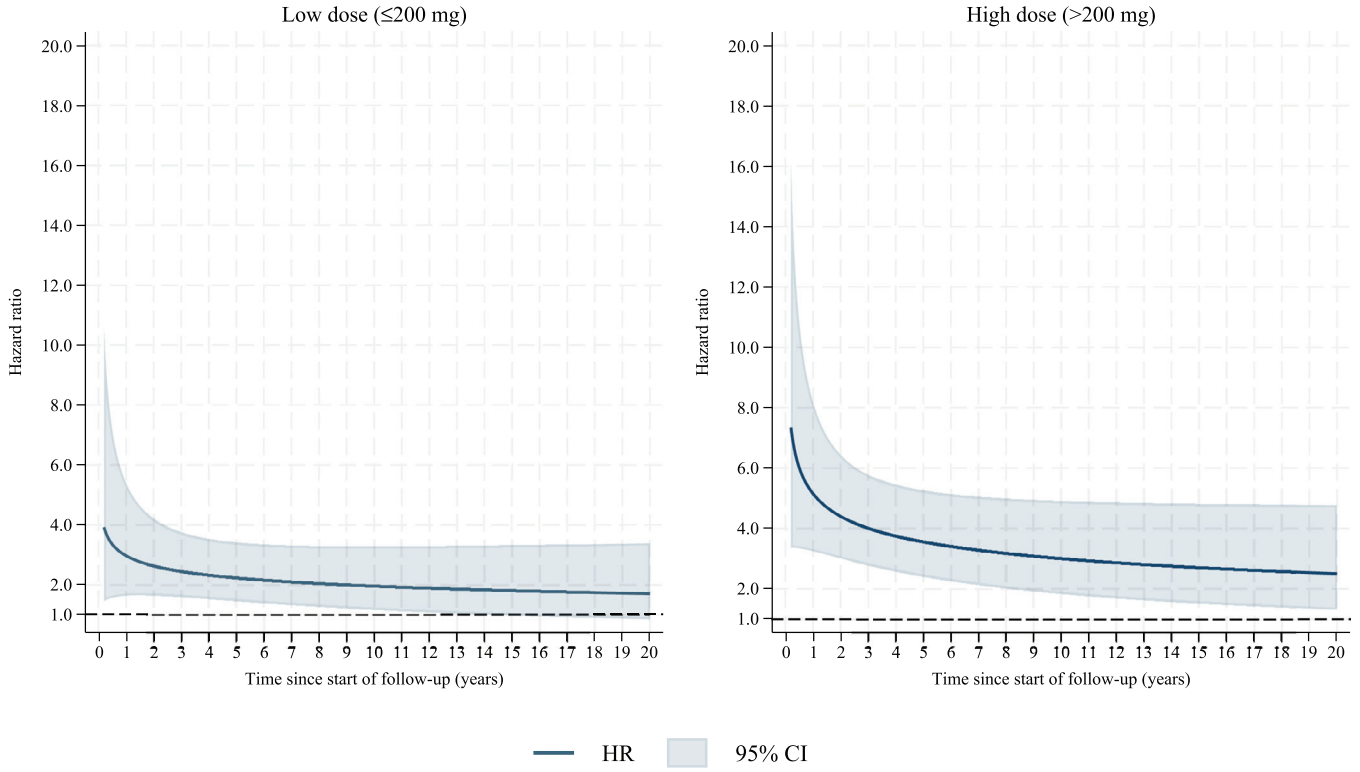

FIGURE 1 Adjusted time-dependent hazard ratios (HRs) with 95% confidence intervals, comparing the cause-specific rate of congestive heart failure between patients with classical Hodgkin lymphoma treated with low (left panel) and high (right panel) cumulative doses of anthracycline to comparators. Adjusted for sex, age, and calendar year of inclusion (the latter two modeled using restricted cubic splines), highest achieved education, and previous comorbidities (hypertension, thyroid disease, hyperlipidemia, renal disease, diabetes mellitus, atrial fibrillation, and acute myocardial infarction).

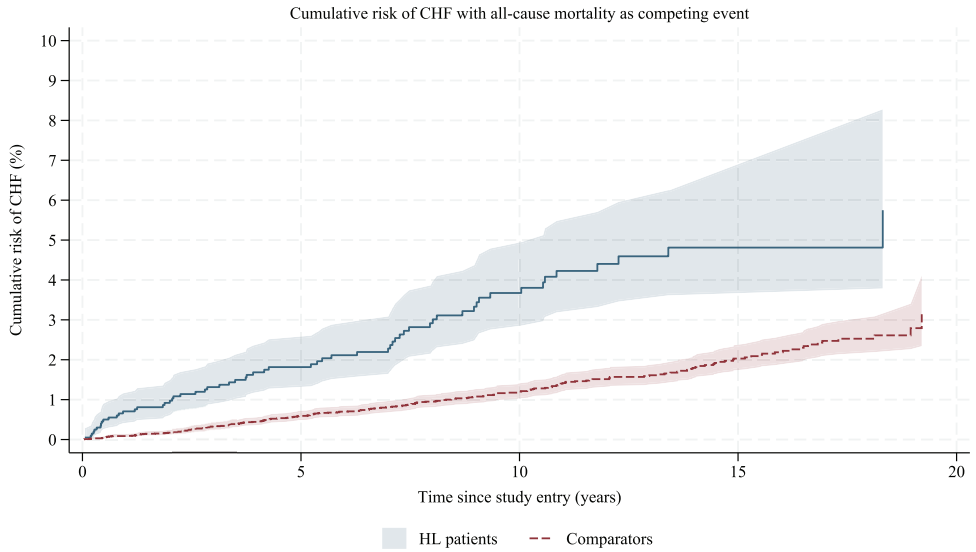

FIGURE 2 Aalen-Johansen estimates of cumulative risk of congestive heart failure (CHF) in percent among patients with classical Hodgkin lymphoma (cHL) and comparators. 95% confidence intervals estimated using the delta method.

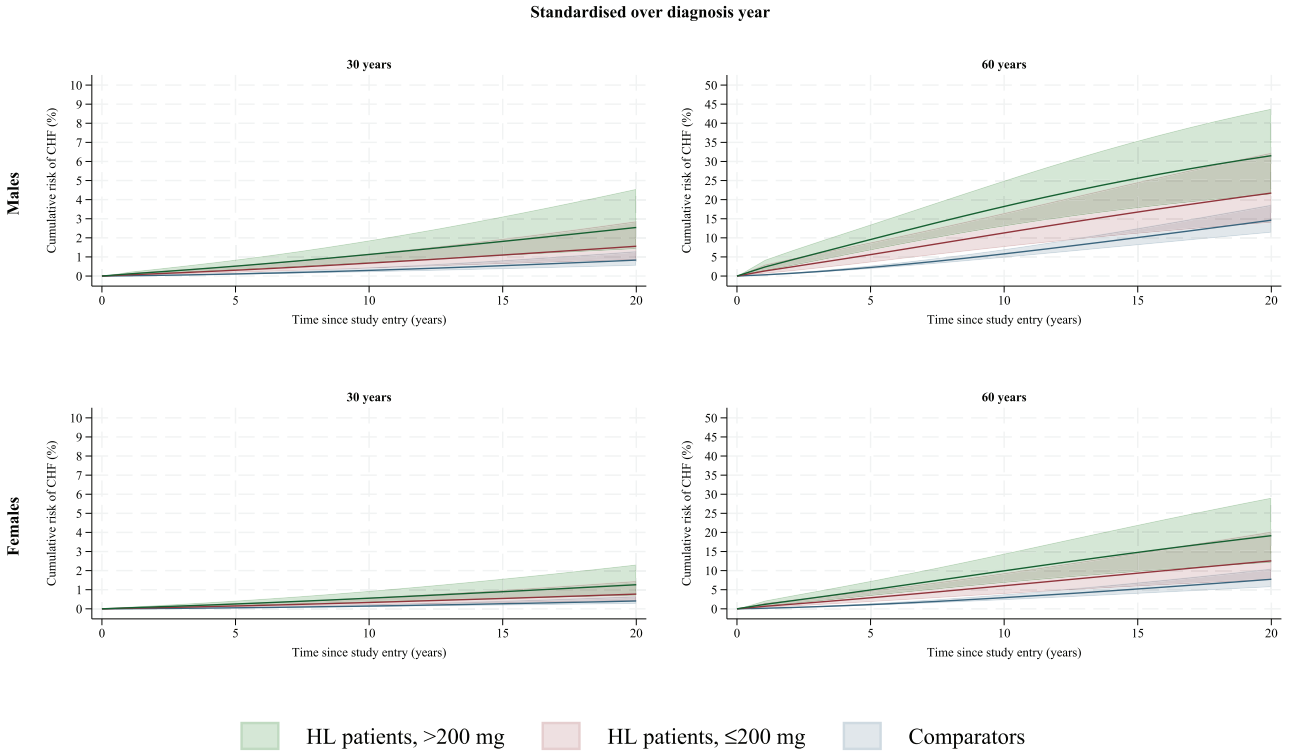

FIGURE 3 Cumulative probability of congestive heart failure (CHF) among males (top panels) and females (bottom panels), aged 30 and 60 years, by anthracycline dose (for patients with classical Hodgkin lymphoma (cHL)). Predicted from a flexible parametric survival model adjusted for sex, age, and diagnosis year at inclusion (the latter two modeled with restricted cubic splines). Standardized over calendar year distribution in the study population. Note the difference in scale on the y-axis between left and right panels. Pointwise 5- and 10-year estimates with 95% confidence intervals (CIs) are given in Table S3.

of new-onset CHF compared to comparators from the general population for more than a decade after the end of treatment. Interestingly, this increased rate was not found when limiting the analysis to patients treated with BEACOPP relative to comparators. An increase in absolute risk was especially notable among patients treated with high cumulative anthracycline doses. The data concerning the duration of time for which cHL patients remained at an increased risk of CHF add valuable information to the existing literature as this information can specify time windows where increased awareness of symptoms consistent with CHF is needed. The dose-response relationship established here is equally important from a treatment strategy perspective when considering dose reductions.

In the last two decades, improved radiotherapy techniques, such as breathing-adapted therapy, intensity-modulated therapy, and involved site or node radiotherapy (ISRT/INRT) have substantially reduced the volume of healthy tissue exposed to radiation [25]. In a simulation study performed by Maraldo et al., INRT reduced radiation to the heart compared to mantle field treatment by a median of 17.3 Gray, which was associated with an estimated lower risk of cardiovascular morbidity by 7.3% points [10]. The reduced use of radiotherapy and better techniques have likely changed the pattern of radiation-induced late toxicities [26, 27]. However, complete omission of radiotherapy is still not possible as the treatment remains a cornerstone in securing durable remissions in cHL. This was seen in the H10 trial, which included an investigation into the feasibility of omitting the use of radiotherapy [28]. The experimental FDG-PET-negative arm where radiotherapy was omitted was closed prematurely because an interim futility analysis identified an increased risk of early relapse [29].

Based on Swedish data, a study by Weibull et al. on temporal trends of treatment-related incidence of diseases of the circulatory system among patients with cHL found that this had declined since the mid-1980s, suggesting that changes to radiotherapy techniques may translate to fewer cases of cardiotoxicity in a population-based setting. Similarly, a Swedish cohort study showed that the mortality from diseases of the circulatory system after treatment for cHL has been declining since the 1980s [30].

Nimwegen et al. refer to their increased risk as a persistently increased risk in their study of cardiovascular disease after cHL treatment with 40 years of follow-up. However, their study only showed that the cumulative incidence was persistently higher. In the present study, the time-dependent relative risk informs on the relative risk over time, compared to a matched background population. This shows that only patients treated with >200 mg/m^2 have a persistently increased risk for CHF (Figure 1), as compared to patients treated with less, who are only at an increased risk for about 13 years. The study by Nimwegen reported a standardized incidence ratio for heart failure of 6.8 (95% CI: 5.9–7.6) compared to age-, sex-, and calendar period-specific observations from the general population, which was higher than the adjusted

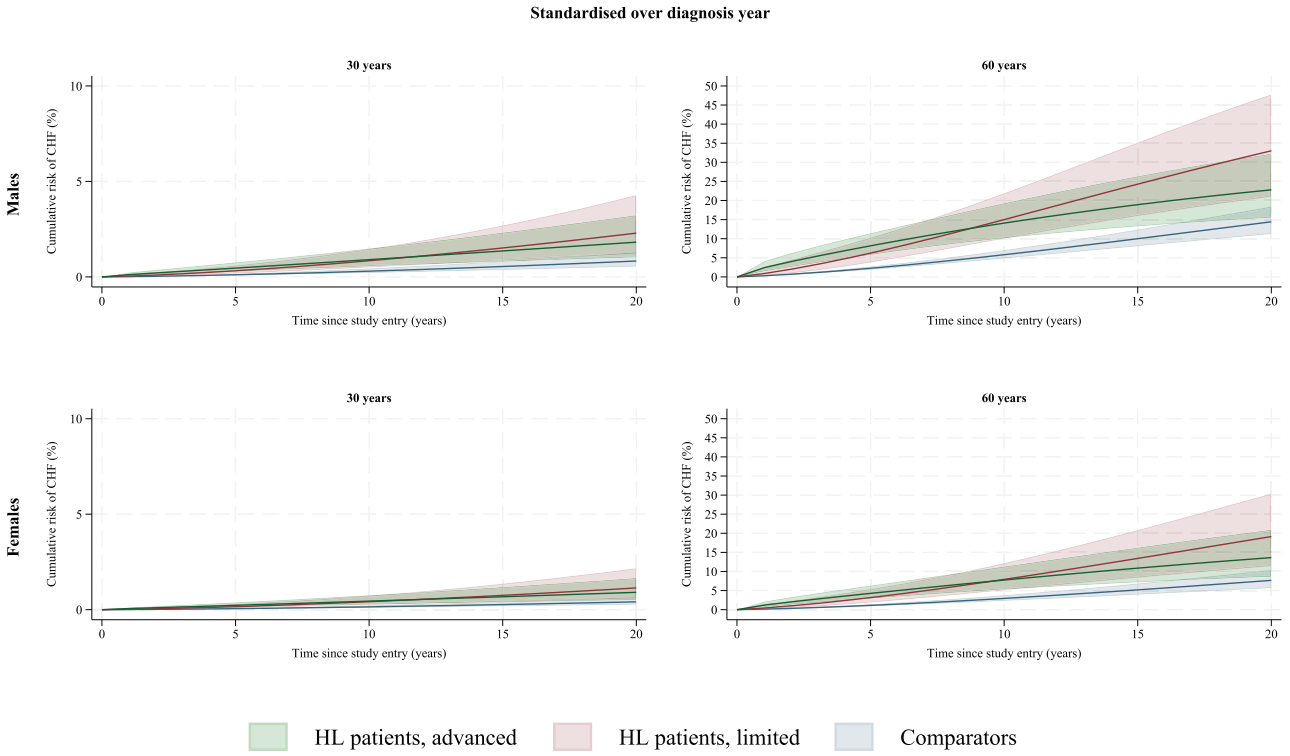

FIGURE 4 Cumulative probability of congestive heart failure (CHF) among males (top panels) and females (bottom panels), aged 30 and 60 years, by stage (for patients with classical Hodgkin lymphoma [cHL]). Predicted from a flexible parametric survival model adjusted for sex, age, and diagnosis year at inclusion (the latter two modeled with restricted cubic splines). Standardized over calendar year distribution in the study population. Note the difference in scale on the y-axis between the left and right panels. Pointwise 5- and 10-year estimates with 95% confidence intervals (CIs) are given in Table S4.

HR of 2.9 presented herein. Compared to the present study, the previously reported standardized incidence ratio of heart failure was expected to be higher, as it was based on cHL patients treated between 1965 and 1995, where the use of radiotherapy differed substantially compared to modern treatment regimens [5].

In a recent study investigating the risk of cardiovascular diseases among patients with lymphoma treated in the modern treatment era, Boddicker et al. found that factors associated with CHF were age, smoking, and anthracycline-containing treatment [31]. Within the present cHL cohort, risk factors were male sex, older age, diabetes mellitus, hypertension (although only borderline significant), and acute myocardial infarction. Age and pre-existing cardiovascular factors, such as hypertension and diabetes mellitus, have been shown to be associated with CHF in survivors of non-Hodgkin lymphoma, and CHF is a known complication of acute myocardial infarction [32, 33]. It is especially noteworthy that the 30-year-old patients had almost negligible risks of CHF independently of disease stage and anthracycline dose, suggesting that younger patients may be less susceptible to the cardiotoxic effects of anthracyclines.

Recent studies suggest that treatment with high-dose chemotherapy and autologous stem cell transplantation increases the risk of CHF independently, adding to the risks associated with first-line treatments [34, 35]. In a previous study by our group, which included patients with cHL, treatment with high-dose chemotherapy was associated with an increased risk of CHF (HR of 2.6) in addition to the risk associated with previous treatment lines that included anthracyclines. The present study did not include information on second-line therapies for cHL such as high-dose chemotherapy and autologous stem cell transplantation. Nevertheless, CHF risks observed in the present study are mainly explained by first-line treatment due to the limited number of relapses in cHL.

In the current study, only patients treated with ABVD had a significantly increased CHF rate relative to comparators. This was in contrast to patients treated with BEACOPP and may be explained by the lower anthracycline dose given per cycle in the two treatment regimens (50 mg/m^2 per cycle of ABVD and 25 mg/m^2 for BEACOPP), thus resulting in a lower cumulative anthracycline dose. In the current study, the mean anthracycline dose in ABVD-treated patients was 248 mg/m^2 while in BEACOPP it was only 188 mg/m^2 (Table S3), which supports this hypothesis.

In the 2022 European Society of Cardiology guidelines on cardio-oncology, baseline echocardiography is recommended for all patients prior to treatment with anthracyclines and within 12 months after completion of treatment. Furthermore, for high-risk patients, echocardiography is recommended at every two treatment cycles and within three months after completing therapy, and for moderate-risk patients, it is recommended after a cumulative dose of ≥250 mg/m^2 of anthracyclines [36]. The present study also found a dose-response relationship

between the estimated dose of anthracyclines and the risk of CHF using a threshold of a cumulative dose of 200 mg/m^2 of anthracyclines. Similar results have been shown by us previously for patients with diffuse large B-cell lymphoma and follicular lymphoma [14]. However, it remains to be shown that intensive screening for CHF leads to better cardiovascular outcomes without compromising cancer survival due to more frequent chemotherapy dose reductions.

The main strength of the present study is the utilization of prospectively collected data from the SLR combined with the national registers allowing for the capture of events with virtually no loss to follow-up. The study, however, had some major limitations related to the identification of events. Events were identified using ICD-9 and ICD-10 codes for CHF, which are only registered for patients with a hospital contact, thus necessitating diagnostic work-up or treatment in a hospital setting. If individuals had more subtle signs of CHF, that is, symptoms managed by their general practitioner, these cases were not captured. This may have led to a risk of systematic false negatives of CHF diagnoses for both patients and the general population. However, patients with cHL may have been more likely to receive a diagnosis of CHF compared to the general population due to the surveillance bias associated with frequent hospital contacts, thus leading to a higher degree of false negative diagnoses for the general population compared to patients with cHL. This bias would overestimate the perceived risks of CHF associated with anthracycline-containing chemotherapy for patients with cHL relative to the general population. Among patients with cHL, the ≤200 mg/m^2 versus >200 mg/m^2 cumulative anthracycline dose stratification may be an inaccurate cutoff due to the large likelihood of CHF diagnoses remaining undiagnosed, which may be unequally distributed between the cutoff values. The final limitation related to the definition of events was the impracticability of adhering to cancer therapy-related cardiovascular toxicity definitions as outlined in the European Society of Cardiology guidelines on cardio-oncology [36]. As such, it was not feasible to categorize the CHF events into a degree of severity, due to the events being based on clinical ICD-codes.

Another major limitation was the missing information on radiotherapy and radiation doses in SLR and the absence of information about radiation fields. Therefore, this study cannot address cardiovascular risks associated with contemporary radiotherapy against the mediastinum. The registers also did not have any parameters on lifestyle factors such as smoking, sedentary lifestyle, or obesity, but the educational level was added as a proxy for these, as it has been shown to be inversely correlated to these factors [37]. Finally, the anthracycline doses reported were estimated from a number of treatment cycles and treatment regimens, and while there was no missing information on the parameters for the included patients, some patients may have received dose reductions of anthracyclines. This would lead to an underestimation of the perceived risk of CHF associated with treatment with anthracyclines reported in this study. Furthermore, under the assumption that there are more dose reductions in the >200 mg/m^2 group, this would lead to an overestimation of the inferred risk associated with patients treated with >200 mg/m^2 compared to those treated with less.

In conclusion, patients with cHL treated with ABVD in the modern treatment era had an increased risk of CHF relative to comparators from the general population with a dose-response relationship between estimated cumulative anthracycline dose and CHF risk. Factors associated with an increased CHF-specific rate within the cHL cohort were male sex, older age, diabetes mellitus, hypertension, and acute myocardial infarction. Therefore, there should be a low threshold for referring patients with symptoms of CHF to echocardiography, and patients successfully treated for cHL should be educated about the signs and symptoms of CHF as well as given advice on the importance of lifestyle that maintains cardiovascular health.

AUTHOR CONTRIBUTIONS

Joachim Baech, Tarec Christoffer El-Galaly, Ingrid Glimelius, Sandra Eloranta, and Caroline E. Dietrich contributed to the conception and design of the study. Joshua P. Entrop, Ingrid Glimelius, Daniel Molin, and Karin E. Smedby contributed to the acquisition of data. Joachim Baech and Caroline E. Dietrich performed an analysis of the data. Joachim Baech drafted the manuscript. All authors contributed to the interpretation of the results and revised the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this study are available at the National Board of Health and Welfare, Sweden, and Statistics Sweden for investigators with the appropriate approvals, but restrictions apply. However, data can be made available from the authors upon reasonable request for meta-analyses, and with the appropriate approvals of the Swedish Ethical Review Authority (https://etikprovningsmyndigheten.se).

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

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REFERENCES

1. Straus DJ, Długosz-Danecka M, Connors JM, Alekseev S, Illés Á, Picardi M, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021;8(6):e410-21.
2. Engert A, Diehl V, Franklin J, Lohri A, Dörken B, Ludwig WD, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 Years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009;27(27):4548-54.
3. Medeiros LJ, Greiner TC. Hodgkin's disease. Hodgkin's disease Cancer. 1995;75(1 Suppl):357-69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8001007
4. Biccler JL, Glimelius I, Eloranta S, Smeland KB, de Nully Brown P, Jakobsen LH, et al. Relapse risk and loss of lifetime after modern combined modality treatment of young patients with Hodgkin lymphoma: A Nordic lymphoma epidemiology group study. J Clin Oncol. 2019;37(9):703-13.
5. Van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Petersen EJ, Raemaekers JMM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med. 2015;175(6):1007-17. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25915855
6. Van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood. 2017;129(16):2257-65. Available from: http://www.bloodjournal.org/content/bloodjournal/129/16/2257.full.pdf
7. Myrehaug S, Pintilie M, Tsang R, Mackenzie R, Crump M, Chen Z, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. Leuk Lymphoma. 2008;49(8):1486-93. Available from: https://pubmed.ncbi.nlm.nih.gov/18608873/
8. Maraldo M V., Brodin NP, Aznar MC, Vogelius IR, Munck af Rosenschöld P, Petersen PM, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. Ann Oncol. 2013;24(8):2113-18. Available from: https://watermark.silverchair.com/mdt156.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAh8wggIbBgkqhkiG9w0BBwagggIMMIICCAIBADCCAgEGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMu8MiKtT1jKE182V8AgEQgIIB0iFaW8phWb7mq0bf0zCk8KgySanadKzx7wT8b7WXNYVkbPhS
9. Ng AK. Review of the cardiac long-term effects of therapy for Hodgkin lymphoma. Br J Haematol. 2011;154(1):23-31. Available from: https://pubmed.ncbi.nlm.nih.gov/21539537/
10. Maraldo M V., Brodin NP, Vogelius IR, Aznar MC, Munck Af Rosenschold P, Petersen PM, et al. Risk of developing cardiovascular disease after involved node radiotherapy versus mantle field for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2012;83(4):1232-327.
11. Ansell SM, Radford J, Connors JM, Długosz-Danecka M, Kim WS, Gallamini A, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Engl J Med. 2022;387(4):310-20.
12. Borchmann P, Moccia A, Greil R, Hertzberg M, Schaub V, Hüttmann A, et al. Treatment related morbidity in patients with classical Hodgkin lymphoma: results of the ongoing, randomized phase III HD21 trial by the German Hodgkin Study Group. Blood. 2022;140(Supplement 1):771-73. Available from: https://doi.org/10.1182/blood-2022-165917
13. Herrera AF, Leblanc ML, Castellino SM, Li H, Rutherford SC, Evens AM, et al. Plenary Session SWOG S1826, a randomized study of nivolumab (N) -AVD versus brentuximab vedotin (BV)—AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). 2023:3907488.
14. Baech J, Hansen SM, Lund PE, Soegaard P, Brown P N, Haaber J, et al. Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2440 lymphoma patients treated with or without anthracyclines. Br J Haematol. 2018;183(5):717-26. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.15603
15. Abrahamsson A, Dahle N, Jerkeman M. Marked improvement of overall survival in mantle cell lymphoma: a population based study from the Swedish Lymphoma Registry. Leuk Lymphoma. 2011;52(10):1929-35. Available from: https://www.tandfonline.com/doi/abs/10.3109/10428194.2011.587560
16. Årsrapport nationellt kvalitetsregister. Nationella kvalitetsregistret för lymfom. 2020.
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
18. Barlow L, Westergren K, Holmberg L, Tälback M. The completeness of the Swedish Cancer Register—a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.
19. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JLL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Pub Health. 2011;11(1):450. Available from: http://www.biomedcentral.com/1471-2458/11/450
20. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.
21. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37. Available from: https://doi.org/10.1007/s10654-019-00511-8
22. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97.
23. Crowther MJ. merlin—A unified modeling framework for data analysis and methods development in Stata. Stata J. 2020;20(4):763-84. Available from: https://journals.sagepub.com/doi/full/10.1177/1536867X20976311
24. Crowther MJ, Lambert PC. Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Stat Med. 2017;36(29):4719-42. Available from: https://pubmed.ncbi.nlm.nih.gov/28872690/
25. Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89(4):854-62.
26. Lagerlöf I, Fohlin H, Enblad G, Glimelius B, Goldkuhl C, Palma M, et al. Limited, but not eliminated, excess long-term morbidity in stage I-IIA Hodgkin lymphoma treated with doxorubicin, bleomycin, vinblastine, and dacarbazine and limited-field radiotherapy. J Clin Oncol. 2022;40(13):1487-97.
27. Glimelius I, Enblad G, Fohlin H, Fossa A, Goldkuhl C, Gustavsson A, et al. No excess long-term mortality in stage I-IIA Hodgkin lymphoma patients treated with ABVD and limited field radiotherapy. 2020;(October 2019):685-91.
28. Andre MPE, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2017;35(16):1786-96.
29. Raemaekers JMM, André MPE, Federico M, Girinsky T, Oumedaly R, Brusamolino E, et al. Omitting Radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with

an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2014;32(12):1188-94.
30. Eloranta S, Lambert PC, Sjobërg J, Andersson TML, Bjorḱholm M, Dickman PW, et al. Temporal trends in mortality from diseases of the circulatory system after treatment for Hodgkin lymphoma: A population-based cohort study in Sweden (1973 to 2006). J Clin Oncol. 2013;31(11):1435-41.
31. Boddicker NJ, Larson MC, Castellino A, Herrmann J, Inwards DJ, Thanarajasingam G, et al. Anthracycline treatment, cardiovascular risk factors and the cumulative incidence of cardiovascular disease in a cohort of newly diagnosed lymphoma patients from the modern treatment era. Am J Hematol. 2021;96(May):1-10.
32. Salz T, Zabor EC, Brown P N, Dalton SO, Raghunathan NJ, Matasar MJ, et al. Preexisting cardiovascular risk and subsequent heart failure among non-Hodgkin lymphoma survivors. J Clin Oncol. 2017;35(34):3837-43. Available from: https://ascopubs.org/doi/10.1200/JCO.2017.72.4211
33. Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, et al. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail. 2021;8(1):222-37.
34. Murbraech K, Smeland KB, Holte H, Loge JH, Lund MB, Wethal T, et al. Heart failure and asymptomatic left ventricular systolic dysfunction in lymphoma survivors treated with autologous stem-cell transplantation: a national cross-sectional study. J Clin Oncol. 2015;33(24):2683-91.
35. Baech J, Husby S, Trab T, Kragholm K, Brown P, Gørløv JS, et al. Cardiovascular diseases after high-dose chemotherapy and autologous stem cell transplant for lymphoma: A Danish population-based study. Br J Haematol. 2023;204(3):967-75. Available from: https://onlinelibrary.wiley.com/doi/10.1111/bjh.19272
36. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-361. Available from: https://academic.oup.com/eurheartj/article/43/41/4229/6673995
37. Hoeymans N, Smit HA, Verkleij H, Kromhout D. Cardiovascular risk factors in relation to educational level in 36 000 men and women in The Netherlands. Eur Heart J. 1996;17(4):518-25.[CrossRef] PMID: 8733083

SUPPORTING INFORMATION

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

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