REGULAR ARTICLE

blood advances

Incidence, timing, and prognosis of heart failure after treatment for large B-cell lymphoma in Sweden during 2007-2022

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Key Points

- Patients with LBCL had a sustained increased risk of developing nonischemic HF after chemotherapy.
- After HF, LBCL history was associated with a higher all-cause but not cardiovascular mortality than comparators.

Patients with large B-cell lymphoma (LBCL) are at increased risk of heart failure (HF) potentially due to anthracycline-based chemotherapy. However, associations with LBCL treatment intensity, HF subtype, and outcome remain undercharacterized. We conducted a nationwide cohort study of 8453 Swedish patients diagnosed with LBCL (median age 70 years) between 2007 and 2022 and 71 506 matched population comparators without a history of HF. The 5-year cumulative incidence of new-onset HF among patients was 8.1% overall, corresponding to a twofold increased rate, driven mainly by nonischemic HF (hazard ratio [HR]$_{\text{nonischemic}}$, 2.33; 95% confidence interval [CI], 2.16-2.50) and less by ischemic HF (HR$_{\text{ischemic}}$, 1.30; 95% CI, 1.04-1.62). An increased rate of new-onset nonischemic HF remained after 2 years of follow-up (HR, 1.78; 95% CI, 1.60-1.94). Few patients had reduced intensity treatment (4 R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone], n = 84) of whom none developed HF. Patients selected for intensive treatment (eg, R-CHOEP with etoposide or dose-adjustment [R-DA-EPOCH]) were not at higher risk of HF compared with those treated with standard R-CHOP (HR, 0.73; 95% CI, 0.58-0.92), although unmeasured differences in baseline fitness or frailty may have influenced treatment selection. After HF onset, patients with LBCL had consistently higher all-cause (but not cardiovascular) mortality than comparators. Our findings indicate that patients with LBCL face a sustained long-term risk of nonischemic HF, highlighting the importance of survivorship care and vigilant HF symptom screening.

Introduction

Large B-cell lymphoma (LBCL) primarily affects older adults with a median age of >70 years.[1,2] Standard first-line treatment is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or Pola-R-CHP (replacing vincristine with polatuzumab vedotin),[3] but more intensive therapies, for example, adding etoposide or prolonged infusion and dose adjustment (R-CHOEP, R-DA-EPOCH) and/or inclusion of central nervous system (CNS)–penetrating agents, may be relevant in younger patients with high-risk LBCL.[4] Recent Swedish data report a relative survival of 75% across all patients and >80% in younger individuals with high-risk disease.[2]

Submitted 23 September 2025; accepted 25 January 2026; prepublished online on *Blood Advances* First Edition 6 February 2026. https://doi.org/10.1182/bloodadvances.2025018515.

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All research data are maintained by Karolinska Institutet and data cannot be shared publicly due to secrecy agreements made with the authorities that maintain the original data sources.

The full-text version of this article contains a data supplement.

Anthracyclines, a key component of LBCL therapy, carry a risk of heart failure (HF).[5] Although more intensive regimens often include similar doses of doxorubicin as R-CHOP, some (eg, DA-EPOCH) may reduce cardiotoxicity due to the prolonged infusion times.[6] Similar cardiovascular risks have been proposed for R-CHOP and R-CHOEP, suggesting that addition of etoposide per se is not a predictor of HF risk.[7] Furthermore, some patients with low-stage nonbulky LBCL can be treated successfully with shorter-course R-CHOP, which likely reduces cardiotoxicity, but long-term outcomes are still undocumented.[8,9]

Ischemic heart disease is the most common cause of HF in high-income countries,[10] but HF after cancer therapy might represent a different subtype and prognosis. The aims of this study were therefore to estimate the incidence of new-onset HF, overall and by ischemic and nonischemic subtype, and to explore associations between treatment intensity and HF incidence and outcomes among patients with LBCL relative to the general population.

Methods

Setting and study population

This register-based matched cohort study included all patients in Sweden diagnosed at age ≥18 years with LBCL between 2007 and 2022. The patients with LBCL (hereon referred to as patients) were identified in the Swedish Lymphoma Register. For a list of included diagnosis codes, see supplemental Table 1. This register includes clinical information on primary diagnoses of incident lymphomas with national coverage, with low missingness, and high accuracy for most variables.[11] A total of 10 755 patients with LBCL were recorded in the Swedish Lymphoma Register during this period. Of these, we excluded patients with a history of cancer (other than melanoma, nonmelanoma skin cancer and prostate cancer) (n = 1251) and patients without a record of active lymphoma treatment (n = 388), leaving 9116 patients in the cohort.

Ten general population comparators were individually matched to the patients (sampled without replacement) from the Swedish Total Population Register, which covers individuals with legal residence in Sweden for at least 1 year.[12] Matching was performed on age and sex, and the comparators had to be alive and free from any lymphoma at the date of the patient's LBCL diagnosis (index date). After exclusions of previous cancer (same as for the patients, n = 10 003) and exclusions of comparators of patients with history of cancer (n = 12 574) or no active treatment (n = 3339), 81 568 comparators remained in the study population (Figure 1).

Outcome variables

HF was defined using inpatient diagnoses from the National Patient Register according to the International Classification of Diseases (ICD) revisions versions 8 and 10 (ICD-8: 425, 427.0, 427.1, 428 and ICD-10: I110, I130, I132, I255, I42.0, I42.9, I50.0-50.9). For the subgroup analyses, ischemic HF was defined as either a diagnosis of ischemic cardiomyopathy (ICD-10: I255), a diagnosis of acute coronary syndrome (ICD-10: I200 or I21X), or a coronary artery intervention procedure code (indicative of acute myocardial damage as a cause of HF) up to 60 days before the recorded HF diagnosis (Nordic Medico-Statistical Committee procedure codes: FNA, FNB, FNC, FND, FNE, FNG, FNF). HF diagnoses that did not meet the criteria for ischemic HF were considered nonischemic.[13] This definition attempted to capture the 2 temporal pathways by which ischemic heart disease can lead to HF: long-term via chronic coronary artery disease and short-term where acute loss of myocardial tissue serves as the proximate trigger. This approach strived to balance capturing both chronic and acute ischemic contributions while minimizing misclassification from remote events.

Information on date and cause of death were obtained from the National Cause of Death Register. All-cause mortality was defined as any death during follow-up. Cardiovascular disease (CVD) mortality was defined as deaths where the underlying cause of death included diseases of the heart (ICD-10: I00-I09, I11, I13, I20-I51), hypertension without heart disease (ICD-10: I10, I12), cerebrovascular diseases (ICD-10: I60-I69), atherosclerosis (ICD-10: I70), aortic aneurysm and dissection (ICD-10: I71), and other disease of the arteries, arterioles, or capillaries (ICD-10: I72-I78).

Treatment exposure

Two main treatment groups were defined for patients treated with curative intent according to standard of care and high intensity at first line. Standard of care was defined as R-CHOP (without subsequent systemic CNS prophylaxis), and high-intensity treatment was classified as R-CHOP with addition of high-dose methotrexate and/or cytarabine (as CNS prophylaxis), R-CHOEP, or some other intensive regimen such as R-DA-EPOCH, regimens containing methotrexate, for example, R-MPV (rituximab, methotrexate, vincristine, and procarbazine), or R-Hyper-CVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine). Reduced-intensity chemotherapy treatment corresponding to the FLYER protocol was also identified for descriptive purposes because this approach has been gradually introduced in Sweden since 2019 with the aim to reduce toxicity while maintaining treatment efficacy,[8] as supported by the National Clinical Trials Network study S1001.[9] This group of patients was defined as having no bulky disease, low stage (I-II), and Eastern Cooperative Oncology Group scores 0 to 1, aged <80 years at diagnosis, and treated with 4 cycles of R-CHOP group (with or without addition of Rituximab x2). Patients with reduced-intensity treatment (n = 84), nonstandard (eg, bendamustine, COP [cyclophosphamide, vincristine, prednisone], cyclophosphamide, or chlorambucil, n = 287), or missing treatment data (n = 840) were excluded from all analyses where standard and high-intensity treatments were compared (Figure 1).

Confounders

Information about comorbidity history was retrieved from the National Patient Register which includes information on non-primary health care contacts (ie, visits to inpatient and outpatient specialist clinics). Of particular relevance for this study were pre-existing cardiovascular comorbidities, type 1 or 2 diabetes, alcohol-related conditions, chronic obstructive pulmonary disease, and renal failure. A list of the specific diseases considered and their definitions according to the ICD classification and the Anatomical Therapeutic Chemical Codes for dispensed drugs recorded in the National Prescribed Drug Register are provided in supplemental Table 1.

The Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies was used to obtain information on

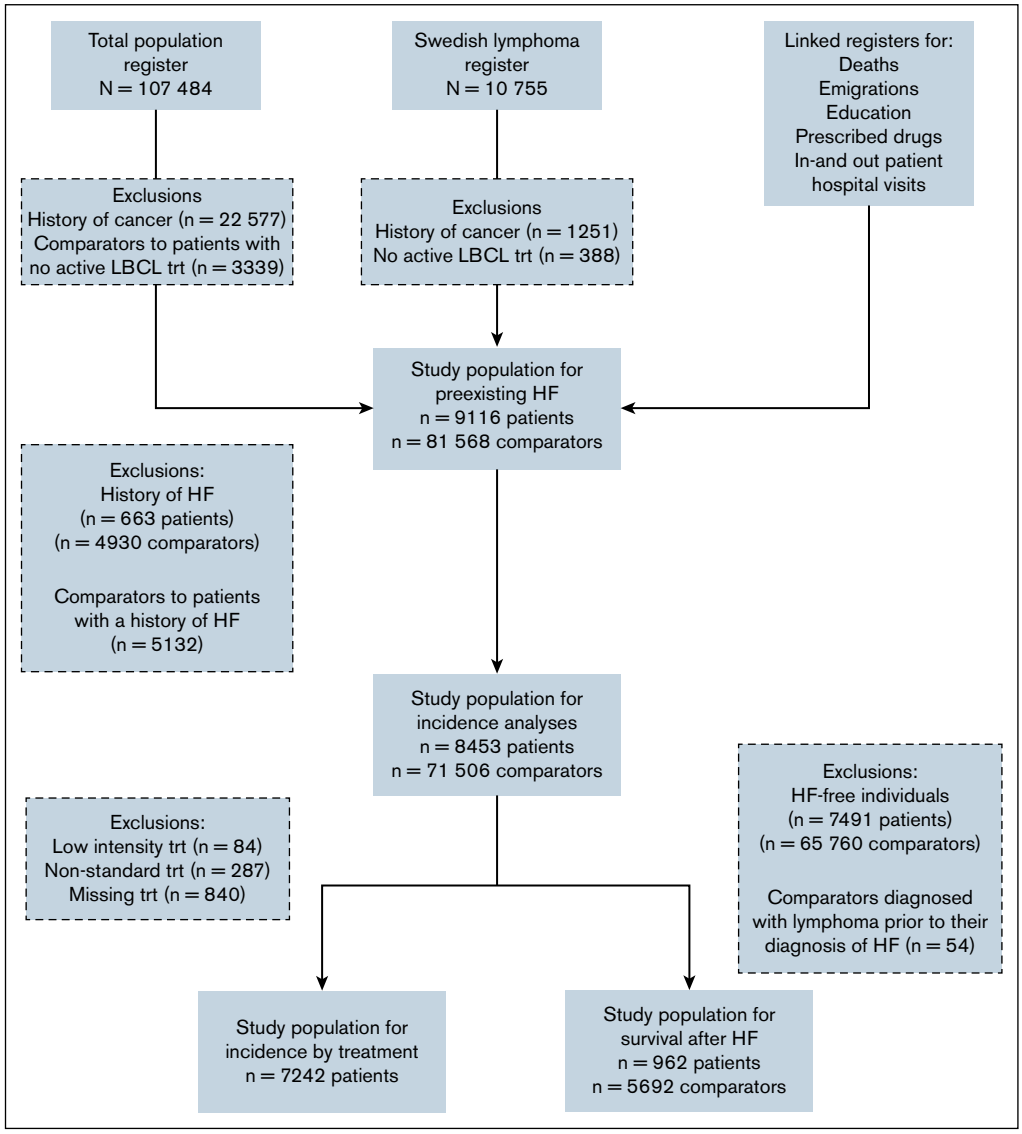


Figure 1. Flowchart illustrating the inclusion and exclusion criteria for studying different aspects of risk and prognosis of HF among patients with LBCL in Sweden diagnosed from 2007 to 2022 and population comparators. trt, treatment.

highest educational level achieved, used as a proxy for socioeconomic status.

Statistical analysis

We conducted 3 sets of analyses, each using different definitions of the study population, to address the objectives of this study: (1) to assess the baseline prevalence of preexisting HF in patients and comparators; (2) to compare the incidence of new-onset HF during follow-up overall, by HF subtype, and by treatment intensity; and (3) to compare all-cause and CVD-specific mortality after a diagnosis of HF by patient/comparator status.

To assess preexisting HF, we analyzed the full matched cohort regardless of availability of treatment data. Odds ratios for preexisting HF were estimated using logistic regression, adjusting for age at diagnosis/matching date, sex, and calendar year.

For studying incidence of new-onset HF, individuals with prior HF were excluded (Figure 1). Follow-up started at the date of lymphoma diagnosis/matching date and continued until the earliest of new-onset HF diagnosis, death, emigration, or administrative censoring (31 December 2023). Comparators diagnosed with any subtype of lymphoma during follow-up were censored at the diagnosis date. The cumulative incidence of HF, overall and by age at diagnosis, was estimated nonparametrically in the presence of competing risks of death and contrasted using Gray's test. Cox proportional hazards models were used to estimate cause-specific hazard ratios (HRs) comparing patients to comparators, adjusting for predefined confounders selected based on their relevance as potential clinical modifiers of lymphoma therapy: age at diagnosis (<60 years, 60-69 years, 70-79 years, ≥80 years), calendar year of diagnosis (2007-2010, 2011-2014, 2015-2018, 2019-2022), sex, education level (low [≤9 years], intermediate [10-12 years],

high [≥13 years]), and relevant cardiovascular comorbidities (yes/no). The proportional hazards assumption was assessed using the Grambsch-Therneau test. Time-dependent HRs were estimated by stratifying follow-up into 0-6 months (acute HF risk) and >6 months postdiagnosis (posttreatment risk) to address that some HF cases might have been preexisting and diagnosed incidentally during the clinical workup. In addition, time-stratified analysis with cutoff at 2 years was performed as this reflects the time when clinical follow-up ends according to Swedish treatment guidelines.

Cox regression was also used to compare HF incidence among patients receiving high-intensity chemoimmunotherapy and those receiving standard R-CHOP. In addition to the variables mentioned previously, this model was further adjusted for LBCL risk group according to the age-adjusted International Prognostic Index (aaIPI), categorized as follows: low risk (aaIPI < 2) or high risk (aaIPI ≥ 2), stratified by age (≤70 years and >70 years). Patients with reduced-intensity treatment were excluded because there were no HF events in this group.

Last, we estimated all-cause and CVD-specific mortality after HF restricting to patients and comparators who developed incident HF (any type) during follow-up. Follow-up began at the date of HF diagnosis and ended at death, emigration, or administrative censoring (31 December 2023), whichever occurred first. For CVD-specific mortality, deaths from other causes were censored. Cox regression models were used to estimate cause-specific HRs, adjusted for age at diagnosis, elapsed time since the index date, calendar year, sex, education level, and history of CVD comorbidities. Effect modification with respect to timing of the HF in relation to the lymphoma diagnosis/matching date (0-0.5 years, 0.5-2 years, 2-5 years, >5 years) was formally addressed using a likelihood ratio test for interaction with case/comparator status.

Individuals with missing data for covariates were retained using indicator variables for missingness. All statistical analyses were conducted using Stata version 18 (StataCorp, 2023).

Results

Among the 9116 patients included in the study population, 966 (10.6%) were diagnosed with new-onset HF during follow-up, most classified as nonischemic (n = 879) (Table 1). A similar pattern was observed for comparators, albeit the number of incident HFs was lower (n = 6463, 7.9%). In both the LBCL and comparator groups, nonischemic HF was most often represented by unspecific HF diagnoses (supplemental Table 3, 96.7% for LBCL and 96.5% for comparators). Dilated cardiomyopathy was the second most common type of nonischemic HF among the patients with LBCL (1.6%), whereas it was hypertensive cardiomyopathy for comparators (1.4%). Approximately 60% of the study population was males, and the median age at matching date was 70 years. A relatively large proportion of both patients and comparators had a history of HF (7.3% of patients and 6.0% of comparators) translating to patients having 20% higher odds of preexisting HF than comparators (odds ratio, 1.20; 95% confidence interval [CI], 1.10-1.31).

During a median follow-up of 6.2 years (interquartile range, 3.1-10.2 years), patients had a more than twofold increased risk for new-onset HF of any type than comparators in the adjusted analysis (HR, 2.16; 95% CI, 2.01-2.31) (Figure 2; supplemental Table 4). The association was stronger during the first 6 months after LBCL diagnosis (HR, 4.67; 95% CI, 3.91-5.48). After the first 6 months, the excess rate of any HF among patients remained

Table 1. Demographic characteristics and baseline medical history of comorbidities for 9116 patients with LBCL diagnosed at age 18 years or above in Sweden from 2007 to 2022 and 81 568 matched population comparators

Characteristic	Patients with LBCL n (%)*	Comparators n (%)*
Total	9116 (10.1)	81 568 (89.9)
HF during follow-up		
Yes	966 (10.6)	6 463 (7.9)
Ischemic HF during follow-up		
Yes	87 (1.0)	946 (1.2)
Nonischemic HF during follow-up		
Yes	879 (9.6)	5 517 (6.8)
Sex		
Male	5431 (59.6)	50 721 (62.2)
Female	3685 (40.4)	30 847 (37.8)
Age at diagnosis†		
<60 years	2193 (24.1)	20 907 (25.6)
60-69 years	2171 (23.8)	19 808 (24.3)
70-79 years	2813 (30.9)	24 636 (30.2)
≥80 years	1939 (21.3)	16 217 (19.9)
Date of lymphoma diagnosis†		
2007-2010	2020 (22.2)	18 361 (22.5)
2011-2014	2232 (24.5)	20 020 (24.5)
2015-2018	2424 (26.6)	21 634 (26.5)
2019-2022	2440 (26.8)	21 553 (26.4)
Highest attained education level		
Low (≤9 years)	2890 (32.1)	25 231 (31.4)
Intermediate (10-12 years)	3672 (40.8)	33 168 (41.3)
High (≥13 years)	2428 (27.0)	21 876 (27.3)
Preexisting HF		
Yes	663 (7.3)	4 930 (6.0)
Preexisting CVD‡		
Yes	2814 (30.8)	23 923 (29.3)
Diabetes		
Yes	1135 (12.5)	9 450 (11.6)
Alcohol-related conditions		
Yes	96 (1.1)	1 179 (1.4)
Chronic obstructive pulmonary disease		
Yes	61 (0.7)	734 (0.9)
Renal failure		
Yes	99 (1.1)	484 (0.6)

Patients and comparators are matched on age and sex, and the comparators had to be alive and lymphoma free at the date of the patient's lymphoma diagnosis.
*Column percentages.
†Matching date for comparators.
‡Distributed across hypertension (91%), atrial fibrillation (15%), heart valve disease (4%), and hyperlipidemia (use of lipid-reducing drugs, 7%).

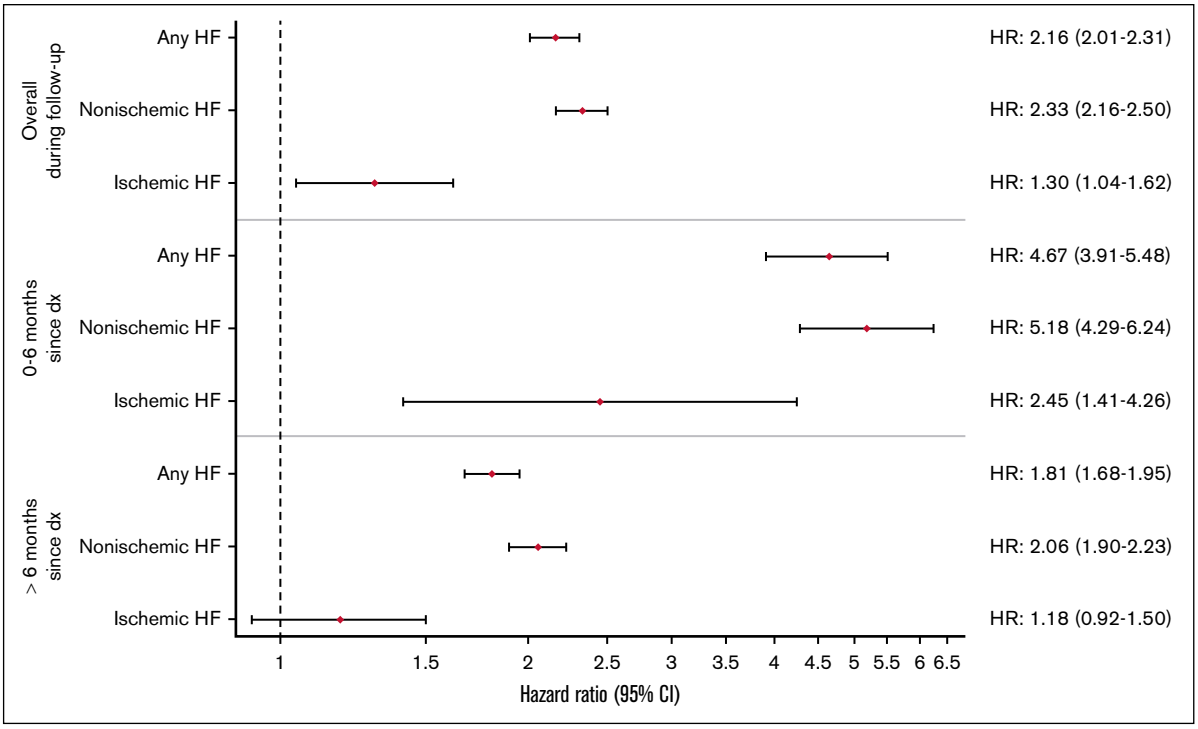


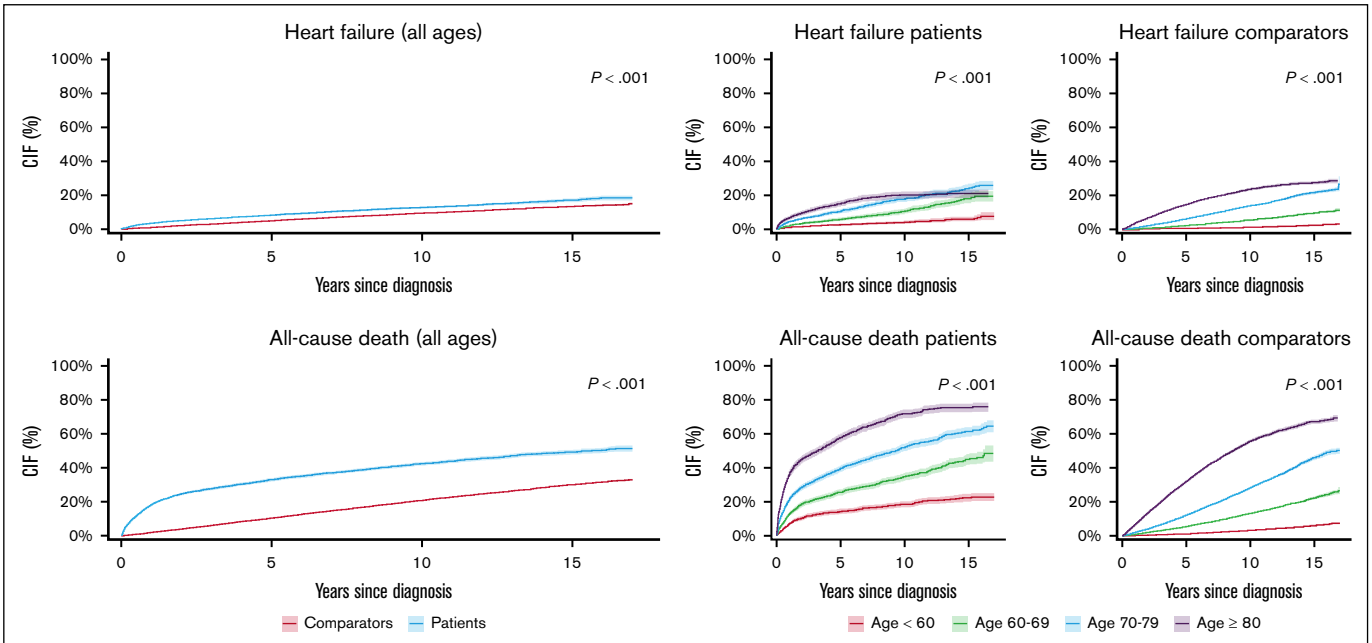
Figure 2. HRs with 95% CIs from Cox regression models comparing the incidence rate of new-onset any HF and by subtype (ischemic and nonischemic) among patients with LBCL (n = 8453) to population comparators (n = 71 506) overall during follow-up and by time period 0 to 6 months and >6 months from diagnosis. Separate models were estimated to allow for nonproportional hazards (0-6 months and after 6 months of follow-up). All HRs were adjusted for sex, age at entry, calendar year of entry, education level, and CVD comorbidity before index date.

close to twofold (HR, 1.81; 95% CI, 1.68-1.95). Importantly, the increased risk of HF remained after 2 years of follow-up, which reflects the clinical follow-up routine of patients with LBCL (HR, 1.78; 95% CI, 1.63-1.95) (supplemental Figure 1).

In terms of absolute risk, this corresponded to a 5-year cumulative incidence of new-onset HF of 8.1% (95% CI, 7.6-8.8) among the patients, compared with 4.9% (95% CI, 4.7-5.1) among the comparators (Figure 3). The 10-year cumulative incidence was 12.7% (95% CI, 11.9-13.6) for patients with LBCL and 9.5% for comparators (95% CI, 9.2-9.8). The largest differences in absolute risk of HF between patients and comparators were found for individuals diagnosed with LBCL at ages <80 years (eg, 5-year risk among patients 70-79 years was 10.7% vs 6.3% among comparators). For individuals aged 80+ years, the absolute risks of HF were similar for patients and comparators (5-year risk patients: 15.0%, 95% CI, 13.3-16.9, comparators: 14.7%, 95% CI, 14.0-15.4).

In terms of HF subtypes, the overall adjusted rate of nonischemic HF for patients vs comparators was more than doubled (HR, 2.33; 95% CI, 2.16-2.50) (Figure 2). For ischemic HF, the corresponding excess rate among patients was 30% (HR, 1.30; 95% CI, 1.04-1.62). When further stratifying the results by follow-up time, we found substantially higher rates of both nonischemic (HR, 5.18; 95% CI, 4.29-6.24) and ischemic HF (HR, 2.45; 95% CI, 1.42-4.26) among patients than comparators during the first 6 months of follow-up. After 6 months of follow-up, the excess risks were attenuated, and although the excess risk for nonischemic HF remained twofold (HR, 2.06; 95% CI, 1.90-2.33), the excess risk of ischemic HF among patients was no longer significant (HR, 1.18; 95% CI, 0.92-1.50) (Figure 2). In a sensitivity analysis applying a broader definition of ischemic HF where history of an ischemic event at any time before HF was considered sufficient to classify the HF as ischemic, the number of patients with ischemic HF increased to 216 (22% of HF events) and to 2166 for comparators (335 of HF events). The overall results were robust to this definition (supplemental Figure 2). Also, in a landmark analysis with start of follow-up at 6-months, the results were consistent yielding HRs of 1.93 (95% CI, 1.79-2.08) for any HF, 1.18 (95% CI, 0.92-1.50) for ischemic HF, and 2.06 (95% CI, 1.90-2.23) for nonischemic HF. Additional adjustment for history of autoimmune disease did not change the results (data not revealed). In an additional analysis, incorporating both inpatient and outpatient HF diagnoses, the broader definition resulted in more exclusions for history of HF at baseline (LBCL: 772 [8.5%], comparators: 5730 [7.0%]) but did not change the main results (supplemental Figure 3).

When focusing on variations in incidence of HF by clinical characteristics and treatment intensity (Table 2), we identified 5297 patients selected for standard treatment and 1945 patients treated with a more intensive chemoimmunotherapy regimen. Patients selected for intensive treatment were younger (49% <60 years vs 19% for standard), less often had CVD comorbidities at baseline (17% for intensive, 28% for standard), and less often had diabetes (8% for intensive, 11% for standard, supplemental Table 5). Overall, 75% of patients achieved complete or partial response to first-line



	Heart failure risk among patients		Heart failure risk among comparators	
	At 5 years (95% CI)	At 10 years (95% CI)	At 5 years (95% CI)	At 10 years (95% CI)
All ages	8.1 (7.6-8.8)	12.7 (11.9-13.6)	4.9 (4.7-5.1)	9.5 (9.2-9.8)
< 60	2.6 (2.0-3.4)	4.1 (3.2-5.1)	0.5 (0.4-0.6)	1.4 (1.2-1.6)
60-69	5.8 (4.8-6.9)	10.7 (9.2-12.3)	2.3 (2.1-2.6)	5.7 (5.3-6.1)
70-79	10.7 (9.4-12.0)	17.8 (16.1-19.7)	6.3 (6.0-6.7)	14.0 (13.4-14.7)
≥ 80	15.0 (13.3-16.9)	20.1 (17.9-22.3)	14.7 (14.0-15.4)	23.8 (22.9-24.7)

	All-cause death risk among patients		All-cause death risk among comparators	
	At 5 years (95% CI)	At 10 years (95% CI)	At 5 years (95% CI)	At 10 years (95% CI)
All ages	33.0 (32.0-34.1)	42.6 (41.4-43.8)	10.4 (10.2-10.7)	21.0 (20.6-21.3)
< 60	14.4 (12.9-15.9)	18.6 (16.8-20.5)	1.2 (1.1-1.4)	3.3 (3.0-3.6)
60-69	25.7 (23.8-27.6)	34.8 (32.5-37.1)	5.5 (5.1-5.8)	13.2 (12.6-13.8)
70-79	39.5 (37.5-41.5)	52.2 (49.8-54.6)	12.3 (11.8-12.8)	28.3 (27.5-29.1)
≥ 80	58.0 (55.4-60.5)	72.0 (69.3-74.5)	31.9 (31.0-32.9)	55.8 (54.7-57.0)

Figure 3. Cumulative incidence of HF, irrespective of subtype, estimated nonparametrically in the presence of the competing risk of all-cause death. The table illustrates point estimates of the CIF at 5 and 10 years after index date (ie, LBCL diagnosis date for patients and matching date for comparators), with 95% CIs. CIF, cumulative incidence functions.

treatment. Intensive treatments were associated with lower rate of HF relative to standard therapy with a confounder adjusted HR of 0.73 (95% CI, 0.58-0.92) for HF of any type and 0.67 (95% CI, 0.53-0.86) for nonischemic HF (Table 3). In a sensitivity analysis with further adjustment for consolidative radiotherapy, the results were robust ($HR_{intensive\ treatment\ vs\ standard}$, 0.74; 95% CI, 0.58-0.92). Likewise, when restricting the population to patients who responded to first-line treatment (n = 6453, 76%), the results remained consistent (HR, $HR_{intensive\ treatment\ vs\ standard}$, 0.73; 95% CI, 0.57-0.93). Starting follow-up at 6 months (proxy for treatment completion) resulted in landmark HRs of 0.70 (95% CI, 0.54-0.91) for any HF, 1.36 (95% CI, 0.69-2.68) for ischemic HF, and 0.64 (95% CI, 0.48-0.84) for nonischemic HF.

Last, among patients and comparators with a new-onset HF during follow-up, we estimated all-cause and CVD-specific mortality rates with follow-up starting at the date of HF diagnosis (Table 4). All-cause mortality was higher among patients with LBCL (HR, 1.16; 95% CI, 1.06-1.26) than comparators. The association was not modified by elapsed time since the lymphoma diagnosis date (*P* for interaction: .548). Conversely, a reduced CVD-specific mortality was observed (HR, 0.81; 95% CI, 0.70-0.94). The reduced CVD-specific mortality was limited to patients who were diagnosed with HF within 2 years of their LBCL diagnosis ($HR_{0\text{-}6\ months}$, 0.48; 95% CI, 0.32-0.72 and $HR_{6\text{-}24\ months}$, 0.72; 95% CI, 0.52-0.98) (*P* for interaction = .002). When broadening the definition of CVD-specific death to include also contributing

Table 2. Clinical characteristics and distribution of new-onset HF during study follow-up for 8453 patients diagnosed with LBCL at age 18 years or above in Sweden between 2007 and 2022

Characteristic	All patients n (%)*	HF during follow-up n (%)*
Total	8453 (100.0)	966 (11.4)
Stage		
Limited (I-II)	2951 (34.9)	338 (35.0)
Advanced (IIB-IVB)	5211 (61.6)	599 (62.0)
Missing	291 (3.4)	29 (3.0)
Elevated serum level of lactate dehydrogenase (S-LD) at diagnosis†		
No	2335 (27.6)	341 (35.3)
Yes	3488 (41.3)	430 (44.5)
Missing	2630 (31.1)	195 (20.2)
World Health Organization performance status		
0 = Normal activity level	3690 (43.7)	404 (41.8)
1 = Symptoms but ambulatory	2894 (34.2)	395 (40.9)
2 = Ambulatory >50%	866 (10.2)	98 (10.1)
3 = Ambulatory <50%	547 (6.5)	50 (5.2)
4 = Bedridden	275 (3.3)	7 (0.7)
Missing	181 (2.1)	12 (1.2)
Age-adjusted risk group		
Low-risk young	1749 (20.7)	150 (15.5)
High-risk young	1626 (19.2)	143 (14.8)
Low-risk old	1296 (15.3)	292 (30.2)
High-risk old	1393 (16.5)	199 (20.6)
Missing	2389 (28.3)	182 (18.8)
Chemoimmunotherapy regimen		
Reduced-intensity treatment (FLYER protocol)	84 (1.0)	0 (0.0)
Standard	5297 (62.7)	764 (79.1)
Intensive	1945 (23.0)	93 (9.6)
Other	287 (3.4)	48 (5.0)
Missing	840 (9.9)	61 (6.3)
Radiotherapy		
No	6831 (80.8)	808 (83.6)
Yes	998 (11.8)	123 (12.7)
Missing	624 (7.4)	35 (3.6)
Treatment response		
Complete/partial remission	5636 (75.3)	817 (84.6)
Stable/progressive disease	547 (7.3)	38 (3.9)
Missing	1304 (17.4)	111 (11.5)

*Column percentages.
†Defined as S-LD >3.5 (age at diagnosis [or matching date] 18-70 years), S-LD >4.3 (age > 70 years).

causes of CVD death, there was no longer a statistically significant difference in CVD-specific mortality compared with the general population comparators (HR, 1.01; 95% CI, 0.91-1.12).

Discussion

In this study, as expected, the LBCL group had a higher incidence of HF, particularly of nonischemic subtype, compared with the general population. This increased risk was most pronounced within the first 6 months of diagnosis but remained close to twofold for nonischemic HF beyond 2 years. The risk of HF was not elevated in patients selected for intensive treatment compared with standard. After an HF diagnosis, patients with LBCL had higher all-cause mortality, which may in part reflect lymphoma-related mortality but lower CVD-specific mortality relative to comparators. Although recent studies have revealed promising outcomes with a reduced-intensity R-CHOP regimen, our study was not powered to evaluate this subgroup.[8,9] Future studies should evaluate the effectiveness and toxicity of the less intensive regimen in real-world settings. Taken together, this extends current understanding of HF risk in LBCL beyond the established link with anthracyclines. By differentiating between HF subtypes, evaluating whether more intensive regimens confer additional risk, and evaluating prognosis after HF, we provide novel insights of real-world outcomes.

Approximately 7% of the patients diagnosed with LBCL had a history of HF, similar to a Danish study of patients aged ≥75 years with diffuse LBCL reporting a slightly higher HF prevalence of 9.2%,[12] which likely reflects an older population. Although baseline HF may reflect shared risk factors between CVD and cancer, a bidirectional relationship with HF itself associated with an increased risk of malignancy, possibly related to chronic inflammation and neurohormonal activation, has also been suggested.[14,15]

The 5-year cumulative incidence of new-onset HF (8.1%) in our cohort was higher than reported previously. For example, Baech et al[16] found a 5.4% risk of HF non-Hodgkin lymphoma patients treated with anthracyclines, though their cohort had a lower median age than ours (64 vs 70 in our study) and was CVD free before lymphoma. Anthracycline-related toxicity is a well-established mechanism for nonischemic HF, which was also the primary driver of HF risk in this study. However, we also observed a marked increase in ischemic HF in the short term. This may reflect overlapping risk factors, such as hypertension,[17,18] diabetes,[17,18] obesity,[19,20] and smoking,[21-23] which are more prevalent in patients with cancer.[24] Our population consisted mostly of patients with diffuse LBCL, but a minority had mediastinal LBCL who may have been treated with mediastinal radiotherapy, which is associated with an increased risk of ischemic heart disease. The lower risk of HF observed among patients selected for intensive treatment, despite adjustment, is unlikely to represent a true protective effect. Rather, it may be a null effect skewed by selection bias or residual confounding by indication.

In the comparator group, ~14% of new-onset HF was classified as ischemic using our time-sensitive definition. This is lower than the 44% ischemic HF reported for Swedish general population comparators in a similarly designed register-based study among patients with rheumatoid arthritis where any history of coronary artery disease was used to define ischemic HF.[13] In a population-based study reporting the epidemiology of HF in Sweden in 2010, 51% had history of ischemic heart disease in registers from primary care, outpatient specialty care, or hospital records.[25] When

Table 3. Adjusted HRs and 95% CIs to contrast the risk of HF overall and by subtype (ischemic and nonischemic) among 7242 Swedish patients diagnosed and treated for LBCL using standard or intensive treatment protocols

	HF any subtype	Ischemic HF	Nonischemic HF
Exposure	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Chemotherapy regimen			
Standard	1.00 (REF)	1.00 (REF)	1.00 (REF)
Intensive	0.73 (0.58-0.92)	1.38 (0.75-2.53)	0.67 (0.53-0.86)
Confounders			
Sex			
Male	1.00 (REF)	1.00 (REF)	1.00 (REF)
Female	0.73 (0.63-0.83)	0.37 (0.22-0.61)	0.77 (0.67- 0.89)
Year of diagnosis (matching date for comparators)			
2007-2010	1.00 (REF)	1.00 (REF)	1.00 (REF)
2011-2014	0.91 (0.76-1.08)	0.50 (0.28-0.89)	0.97 (0.80-1.16)
2015-2018	0.77 (0.63-0.94)	0.48 (0.26-0.89)	0.82 (0.66-1.00)
2019-2022	0.95 (0.70-1.29)	0.49 (0.19-1.30)	1.03 (0.75-1.41)
Age-adjusted risk group*			
Low-risk young	1.00 (REF)	1.00 (REF)	1.00 (REF)
High-risk young	1.33 (1.05-1.69)	1.76 (0.86-3.63)	1.29 (1.01-1.65)
Low-risk old	1.27 (0.98-1.64)	0.56 (0.22-1.38)	1.37 (1.04-1.80)
High-risk old	1.19 (0.91-1.56)	0.89 (0.37-2.17)	1.22 (0.92-1.63)
Missing information	1.01 (0.74-1.39)	0.78 (0.27-2.21)	1.03 (0.75-1.45)
Age at diagnosis			
Additional year	1.06 (1.05-1.07)	1.10 (1.06-1.14)	1.06 (1.05-1.07)
Highest attained education level			
Low (≤9 years)	1.00 (REF)	1.00 (REF)	1.00 (REF)
Intermediate (10-12 years)	0.97 (0.83-1.13)	0.82 (0.49-1.37)	0.99 (0.84-1.16)
High (≥13 years)	0.69 (0.57-0.83)	0.78 (0.43-1.41)	0.67 (0.55-0.83)
Missing information	1.49 (0.90-2.46)	0.94 (0.13-6.95)	1.55 (0.92-2.61)
Preexisting CVD history*			
No	1.00 (REF)	1.00 (REF)	1.00 (REF)
Yes	2.00 (1.75-2.31)	1.74 (1.10-2.75)	2.04 (1.76-2.36)

REF, reference.
*Excluding HF diagnoses as these were already excluded from the study population.

broadening our definition to classify HF events as ischemic if there was any history of ischemic heart disease, the proportion increased to 33% among comparators.

The risk of HF was substantially higher in the early period after lymphoma diagnosis with the HR in the first 6 months more than twice that observed thereafter. This could be related to the clinical workup related to the lymphoma diagnosis and subsequent close monitoring during primary treatment. The weaker association observed beyond 2 years may partly reflect an effective "depletion of susceptibles" in both groups. However, in a prospective study where occurrence of cardiotoxicity was monitored using regular echocardiograms, 98% of cardiac dysfunction events occurred within a year after treatment and most cases were asymptomatic.[26] They proposed that rather than considering early or late cardiotoxicity in 2 different entities, cardiotoxicity represents a continuum, beginning with myocardial injury that evolves into symptomatic HF. Together with our findings, this may support the need for early cardiac surveillance after lymphoma therapy with cardiotoxic agents. In addition, it could suggest that most cases would be captured by routine echocardiograms (ie, not symptom driven) within the first year, possibly preempting the need for long-term follow-up.

The LBCL group had higher all-cause but lower CVD-specific mortality. This may reflect the competing risk of lymphoma-related death and cause-of-death classification. Among patients who developed HF within 2 years of diagnosis when clinical monitoring is typically more intense, it is possible that subclinical or early-stage HF contributes to the observed lower CVD-specific mortality. This is particularly relevant if HF treatment was initiated with the aim to improve HF outcomes[27] because prior studies have revealed that prompt therapy can lead to substantial recovery of cardiac function.[28] However, our results are also sensitive to the definition of CVD-specific death. When adding CVD deaths that were recorded as contributing, rather than underlying, we no

Table 4. All-cause and CVD-specific MRR and 95% CI for new-onset HF comparing patients with LBCL with general population comparators

Exposure	All cause		CVD specific	
	Deaths during follow-up n (%)*	MRR (95% CI)	Deaths during follow-up n (%)*	MRR (95% CI)
History of LBCL				
No (comparator)	3591 (85.2)	1.00 (REF)	1738 (89.6)	1.00 (REF)
Yes (patient)	625 (14.8)	1.16 (1.06-1.26)	201 (10.4)	0.81 (0.70-0.94)
Confounders				
Sex				
Male	2592 (61.4)	1.00 (REF)	1197 (61.7)	1.00 (REF)
Female	1629 (38.6)	0.91 (0.85-0.97)	742 (38.3)	0.84 (0.76-0.92)
Age at index date (lymphoma diagnosis or matching date)				
<60 years	108 (2.6)	1.00 (REF)	38 (2.0)	1.00 (REF)
60-69 years	532 (12.6)	1.58 (1.28-1.95)	197 (10.2)	1.63 (1.15-2.31)
70-79 years	1641 (38.9)	2.70 (2.22-3.30)	715 (36.9)	3.25 (2.34-4.51)
>79 years	1935 (45.9)	4.62 (3.79-5.65)	989 (51.0)	6.72 (4.83-9.35)
Year of diagnosis†				
2007-2010	1733 (41.1)	1.00 (REF)	856 (44.1)	1.00 (REF)
2011-2014	1355 (32.1)	0.97 (0.90-1.04)	620 (32.0)	0.87 (0.78-0.97)
2015-2018	860 (20.4)	0.90 (0.83-0.99)	365 (18.8)	0.73 (0.64-0.83)
2019-2022	268 (6.4)	0.91 (0.79-1.04)	98 (5.1)	0.65 (0.51-0.81)
Years since lymphoma diagnosis†				
0-0.5 years	420 (10.0)	1.00 (REF)	168 (8.7)	1.00 (REF)
0.5-2 years	907 (21.5)	1.05 (0.93-1.18)	418 (21.6)	1.17 (0.96-1.38)
2-5 years	1254 (29.7)	1.05 (0.94-1.18)	600 (30.9)	1.17 (0.98-1.40)
>5 years	1635 (38.8)	1.33 (1.18-1.49)	753 (38.8)	1.45 (1.21-1.74)
Highest attained education level				
Low (≤9 years)	2093 (50.5)	1.00 (REF)	1011 (52.9)	1.00 (REF)
Intermediate (10-12 years)	1460 (35.2)	0.97 (0.90-1.04)	631 (33.0)	0.91 (0.82-1.00)
High (≥13 years)	589 (14.2)	0.86 (0.78-0.94)	268 (14.0)	0.85 (0.74-0.97)
Preexisting CVD history				
No	2028 (48.1)	1.00 (REF)	864 (44.6)	1.00 (REF)
Yes	2188 (51.9)	1.06 (1.00-1.13)	1075 (55.4)	1.22 (1.11-1.34)

MRR, mortality rate ratio; REF, reference.
*Column percentages.
†Matching date for comparators.

longer saw a difference in CVD-specific mortality between patients and comparators.

The key strengths of this study are the large cohort and the novel assessment of HF by subtype and prognosis. Several limitations should be acknowledged. First, we did not have information to investigate the potential confounding effect of smoking, family history, or body mass index. In addition, the COVID-19 pandemic may have introduced changes in health-seeking behavior.[29] A previous Swedish study, however, revealed a short-term drop in diagnoses of indolent lymphomas but not aggressive types (mainly LBCL).[29,30] For the within-patient comparisons, we lacked information on cumulative anthracycline dose to further stratify the group of intensively treated patients. Also, allocation to treatment group is to some extent performed at the discretion of the treating physician, and thus our results may have been subject to confounding by indication. Missing data on risk group classification and education were handled using an indicator for missingness. A complete case analysis nevertheless did not alter our study conclusions. Last, our classification of nonischemic HF was defined based on the absence of ischemia, which may have led to subtype misclassification. This approach has, however, been used previously,[13] and in this study, ischemic HF was further identified via addition of coronary procedure codes. Most ischemic HF cases in our study reflected acute myocardial infarction events, which generally have a high positive predictive value.[31] The nonischemic HFs likely represent a heterogeneous set of etiologies but because most ICD codes used did not imply the underlying etiology (I50*), further meaningful subclassification was not possible. HF events that were managed exclusively in primary or outpatient care are

also missed, potentially underestimating the true incidence. HF events diagnosed in the inpatient setting have previously been validated with a high positive predictive value (>82%) and a low degree of miscoding, whereas the quality of HF records in outpatient care is, to our knowledge, not validated in Sweden.[13,32,33] However, including outpatient records did not meaningfully change the conclusions. Finally, information on follow-up intensity, for example, number of echocardiographic examinations, and clinical data on echocardiographic measures were not available, and thus variation in monitoring practices or underlying disease severity could not be accounted for.

In conclusion, patients with LBCL face an elevated risk of developing HF, particularly of nonischemic origin, both early and long after diagnosis compared with the general population comparators free from lymphoma. Treatment with anthracyclines has been associated with HF after lymphoma in prior studies, and our findings suggest that more intensive chemoimmunotherapy regimens do not appear associated with a further elevation in risk compared with the standard R-CHOP regimen in this observational setting. However, this finding should be interpreted cautiously given the risk of residual confounding with fitter patients being preferentially selected for intensive therapy. Patients with LBCL had higher all-cause but not cardiovascular mortality rates than the comparators which provides evidence that HFs that arise after LBCL may not be of a more aggressive origin. The findings underscore the need for cardiac monitoring regardless of treatment strategy and call for further research into mechanisms beyond chemotherapy intensity that contribute to HF risk in this population.

Acknowledgment

This study was supported by a grant from the Nordic Cancer Union (grant number #A16008).

Authorship

Contribution: S.E., S.J.G., and K.E.S. designed the study; S.E. and F.B. performed the statistical analyses of the data; K.E.S., T.C.E.-G., S.H., S.J.G., and K.K. provided clinical insights into the definitions of study exposures and end points; K.E.S. had the main responsibility for the data acquisition; S.E., S.J.G., and F.B. led the writing process of the manuscript; and all authors provided input on the study design and the statistical analysis plan, and revised and approved the final version of the manuscript.

Conflict-of-interest disclosure: K.E.S. reports honoraria from AbbVie and Incyte. The remaining authors declare no competing financial interests.

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