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ORIGINAL PAPER

Late recurrence of lymphoid malignancies after initial treatment for Hodgkin lymphoma – A study from the Danish Lymphoma Registry

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Summary

We analysed a large cohort of Hodgkin lymphoma (HL) patients in order to characterize: (1) the pattern of late recurrence of lymphoid malignancies (LR) after initial treatment for HL over a 35-year period; (2) the clinicopathological parameters influencing the risk of LR; and (3) the outcome of patients experiencing LR. We reviewed data of 3350 HL patients diagnosed in Denmark between 1982 and 2018 and registered in the Danish National Lymphoma Registry (LYFO). LR was defined as a recurrence of lymphoid malignancy at least five years after initial diagnosis. LR occurred in 58 patients, with a cumulative incidence at 10, 15 and 20 years of 2.7%, 4.0% and 5.4% respectively. LR was more frequently observed in patients with nodular lymphocyte-predominant HL (NLPHL) [hazard ratio (HR) 4.5; 95% confidence interval (CI): 2.4–8.4, $p < 0.001$]. In classical HL (cHL) patients, older age and lymphocytopenia were risk factors for LR with HRs of 1.04 per additional year (95% CI: 1.02–1.06) and 5.6 (95% CI: 2.7–11.5) respectively. Mixed cellularity histological subtype was a risk factor for LR, but only in females, with a HR of 5.4 (95% CI: 1.4–20.4, $p = 0.014$). In contrast to what was observed in NLPHL, LR in cHL was associated with an almost threefold increased risk of death compared with patients in continuous complete remission. Approximately one fifth (22.4%) of patients with LR experienced a second relapse.

KEYWORDS
early relapse, Hodgkin lymphoma, late relapse, overall survival, risk factors

Peter Kamper and Francesco d'Amore share last authorship.

INTRODUCTION

The treatment of Hodgkin lymphoma (HL) has improved over the past three decades. While the overall outcome for younger patients with HL is excellent, that for elderly patients is more modest. Rates for complete remission (CR) after first-line treatment range from 75% to over 90% depending on age, stage and treatment regimen.[1–3]

In recent years, the main therapeutic focus with regard to treatment of HL has been to reduce the risk of treatment toxicity. However, reduction in treatment toxicity is a goal that should be achieved without compromising the favourable outcome or increasing the risk of disease recurrence.

Considering the whole age spectrum of the HL patient population, approximately 20%–30% of patients will experience relapse after CR, even after accurate disease staging and optimal treatment strategies. Among those patients that experience a relapse, most will do so within the first 1–2 years with a good chance of achieving a second CR.[4–6] A smaller subset of patients experience relapse beyond the first two years of follow-up.

There is no consensus definition for late relapse, either in lymphoid malignancies in general, or specifically in HL. Earlier studies have chosen a cut-off for late relapse at two,[7] three,[6,8,9] four[10] or five[4,5,11–15] years after initial diagnosis, or after completion of first-line treatment. In the most recent literature, the cut-off for LR has been five years with an incidence of 3%–5.6%.[13,15,16]

While the International Prognostic Score (IPS) and interim-positron emission topography/computed topography (PET/CT)-scan are used for risk stratification and treatment guidance, no predictive factors for late relapse have yet been identified.[4,7,9,10,13,15]

Late relapse is also poorly characterized with regard to clinical characteristics, underlying biology and therapeutic approaches. While most studies have shown that the prognosis of late relapse is better than that of early relapses (ER), whether it is worse than that of patients in continued first complete remission (cCR) is still debated.[11,13,15]

The aim of the present study was to characterize the frequency, clinical characteristics and outcome associated with late recurrence of lymphoid malignacies (LR) in a cohort of Hodgkin patients treated at tertiary centres in Denmark.

METHODS

Patients

The Danish National Lymphoma Registry (LYFO) was established in 1982 covering West Denmark. In 2000 the database became nationwide and has subsequently registered all lymphoma patients diagnosed at Danish hospitals.[17,18] The database prospectively collects clinical and pathological data from diagnosis until death or end of follow-up, whichever comes first. High registry completeness is ensured by routine cross-reference of the registry with the Danish National Patient Registry and the Danish Pathology Registry.[18] Relapse data were also cross-linked manually with the Danish Pathology Registry to ensure data completeness, and for patients with LR and ER, additional relapses were obtained by review of individual patient pathology reports in the Danish Pathology Registry.[19,20] Our study included all newly diagnosed HL patients recorded in the LYFO registry between January 1982 and December 2018. Inclusion criteria of the study, i.e.: (1) a biopsy-proven HL diagnosis; (2) age 15 years or older at initial diagnosis; (3) achievement of a CR/complete remission unconfirmed (CRu) (including CR PET^-/CT^-, CR PET^-/CT^+) after first-line treatment; and (4) no discordant lymphoma (Figure 1). Patients in CR after five years (cCR), and patients who experienced a relapse within five years of initial diagnosis ('early relapse'; ER) served as comparator subcohorts. Relapse was defined as occurrence of any lymphoma type after initial CR of HL.

All patients were staged according to the Ann Arbor staging system.[21,22] Patients were followed from the date of lymphoma diagnosis until death, end of study (November 2019) or censoring date at end of follow-up, whichever occurred first. Baseline clinicopathological characteristics, information on treatment regimens, and follow-up data were obtained through the LYFO registry.

The study was approved by the regional ethical board of the Central Denmark Region (record no. 1–10–72-118-19), the Danish Data Protection Agency (record no. 1–16–02-212-19) and performed in accordance with the Helsinki Declaration.

Statistical analysis

The cumulative incidence function (CIF) of LR in patients observed to be free from relapse at least five years after initial diagnosis was estimated by the Aalen–Johansen method by accounting for death without preceding relapse as the competing event and compared among various subgroups. Distributional differences of clinical characteristics and treatment outcome between groups were analysed using Pearson's χ^2 test. Follow-up time was estimated as the median of the observed time elapsed from diagnosis to death, end of study period, or date of last follow-up, whichever occurred first. Overall survival (OS) from time of diagnosis and time of first relapse (OSr) to death from any cause, end of study period, or date of last follow-up, whichever occurred first, were estimated by the Kaplan–Meier method. The proportionality was validated by log–log plots. LR was modelled as a time-dependent covariate in survival analysis between LR and cCR patients. Survival outcomes were compared between patients with LR and patients in cCR alive at at least five years from initial diagnosis using multivariate Cox proportional regression models. To account for possible confounding factors we adjusted for age (continuous variable), sex, Ann Arbor stage and time period of initial diagnosis. Progression-free survival was analysed from date of first relapse (PFSr) to either date of subsequent

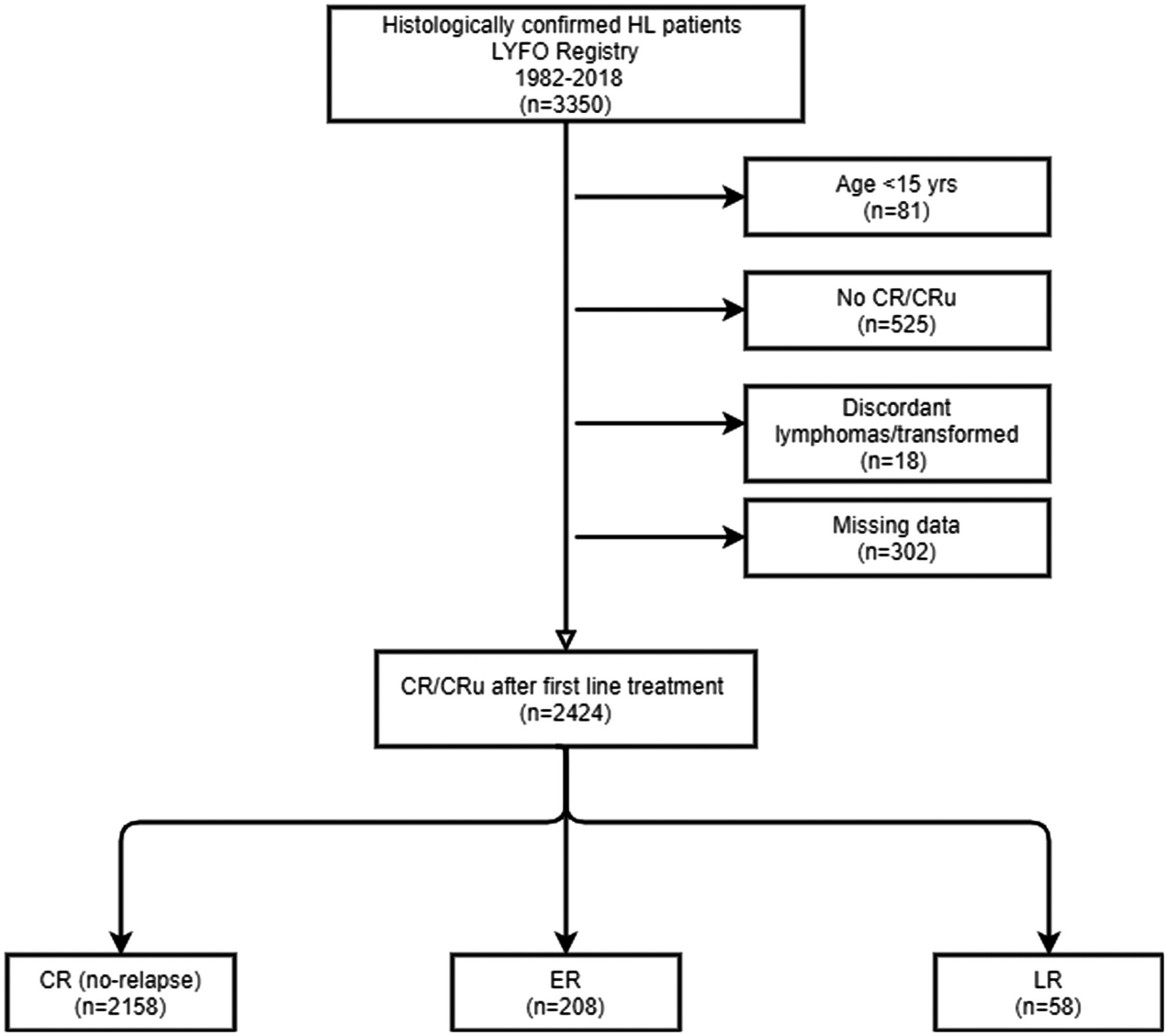

FIGURE 1 Consort diagram illustrating the identification of the study cohort. CR, complete remission; CRu, complete remission unconfirmed; ER, early relapse; LR, late relapse; LYFO, Danish lymphoma registry

relapse or death of any cause or censored, if neither subsequent relapse nor death had occurred, to the date of last follow-up. Relative differences at five and 10 years after first relapse to death (OSr) or next lymphoma reoccurrence (PFSr) were compared between LR and ER and computed using the pseudovalues approach,[23] because of non-proportionality in OSr and PFSr. To account for possible confounding factors we adjusted for age (continuous variable) at time of relapse, sex, Ann Arbor stage and time period of initial diagnosis. For late relapse as the primary event of interest, the independent prognostic value of predefined clinically relevant biomarkers and factors showing a crude association with $p < 0.1$ and proportional hazards between groups were tested in a multivariate Cox regression model. Data were entered into a REDCap database hosted at Aarhus University.[24,25] All p values were two-sided and values were regarded statistically significant if $p < 0.05$. All statistical analyses were performed using Stata software version 17.0 (StataCorp LLC., College Station, TX, USA).

RESULTS

We identified 3350 patients from the LYFO registry diagnosed with HL between January 1982 and December 2018. Figure 1 shows a consort diagram illustrating the establishment of the study cohort. Of the initial 3350 patients, 81 were younger than 15 years of age at diagnosis, 302 had missing data (e.g., no available treatment or no response evaluation data), and 18 had a discordant or transformed lymphoma. In addition, 525 (15.7%) patients did not attain a CR after first-line treatment. After first-line treatment, a CR was obtained in 2424 patients. Of these, 2158 had no reported relapse over the observation period of the study. Among patients obtaining a CR, 266 (11%) experienced a relapse. Of all relapses, 208 (78.2%) occurred less

than five years from initial diagnosis (ER) and 58 (21.8%) at five years or later (LR). The median follow-up time of the entire cohort was 9.4 years (range 0.3–25.5 years).

Patient demographics and clinicopathological features at initial diagnosis

Patients experiencing a LR had a median age of 45 years (range 16–77) at initial diagnosis, while the median age in the ER group was also 45 years (range 15–91). At initial diagnosis 55% of LR and 51% of ER were early stage (Ann Arbor stage I–II, $p = 0.615$). The absolute frequency of histologic subtypes among ER and LR patients reflected the general frequency of histological subtypes in the overall cohort, i.e. cHL nodular sclerosis (NS) type was the most frequently recorded histology (61% among ER and 41% among LR patients), followed by cHL mixed cellularity (MC; ER 19%, LR 31%) and NLPHL (ER 4%, LR 24%). However, looking at relative frequencies, NLPHL was the histologic subtype unequivocally displaying the highest occurrence of LR (see the subsection *Risk factors* below). The male:female ratio was 1.4 and 3.5 for ER and LR respectively, and 1.4 for CR patients. The difference in gender was statistically significant between LR and ER ($p = 0.006$) and LR versus CR ($p = 0.004$). Detailed baseline clinical, paraclinical and treatment characteristics of the subcohorts are shown in Table 1 and Tables S1 and S2. In LR, 19.6% of all relapses were with another lymphoma type than HL; the corresponding number among ER relapses was 9.9% (Table 2).

NLPHL patients with LR were younger than their cHL counterparts (median age 40 vs 50 years at initial diagnosis), while their median age did not differ from patients in CR (40 vs 41 years).

Incidence of LR

The CIF of LR in patients observed to be free from relapse at least five years after initial diagnosis was 2.7% (95% CI: 1.9%–3.6%) at 10 years, 4.0% (3.0%–5.2%) at 15 years, and 5.4% (4.0%–7.2%) at 20 years (Figure 2A). LR was more common in older (≥60 years) patients than younger patients, with CIF values at 10 years after initial diagnosis of 7.0% (4.1%–10.8%) vs 1.9% (1.2%–2.8%), at at 15 years, 8.9% (5.5%–13.4%) vs 3.0% (2.1%–4.2%) (Figure 2B). A trend was observed towards higher LR incidence in patients diagnosed in the decades before 2000 (Figure 2C). NLPHL histology correlated with an increased frequency of LR compared with that in cHL (Figure 2D). The cumulative incidence of late relapse in patients relapsing with a cHL histology is shown in Figure S1.

Clinicopathological features of LR patients

A total of 58 patients relapsed late. The median time to relapse was 8.5 (5.0–18.9) years. Histology data from relapse biopsies were available for 56 LR patients (Table 2). Data were missing in two cases. The median age at relapse was 55 years for LR and 47 years for ER patients.

Overall, patients with LR, more frequently than ER patients, relapsed with another histology than HL (20% vs 10%, $p = 0.018$) (Table 2). A total of 13 (22.4%) LR patients experienced a second relapse compared with 57 (27.4%) of the ER patients.

LR patients with cHL histology at initial diagnosis

Thirty-one of 44 patients with primary cHL relapsed as cHL. In seven of these relapses, a subtype switch occurred from NS to MC (three patients) and to lymphocyte-rich (LyR; one patient) and from MC to NS (two patients) and MC to LyR (one patient). One relapsed with NLPHL histology, six as diffuse large B-cell lymphoma (DLBCL), three with a low-grade B-cell lymphoma and one with a composite lymphoma (cHL/angioimmunoblastic T-cell lymphoma). Histology at relapse was missing in two cHL patients. As first-line treatment, 35 of the 44 cHL LR patients from our study cohort received adriamycin, bleomycin, vinblastine, dacarbazine (ABVD)-like therapy, one patient bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP), two patients mechlorethamine, oncovin, procarbazine, prednisone (MOPP) and two patients radiotherapy only. Four patients received chlorambucil, vinblastine, procarbazine, prednisolone (LVPP), cyclophosphamide, mitoxantrone, oncovin, prednisone (CNOP) or oncovin, etoposide, prednisone, doxorubicin (OEPA).

In patients diagnosed from 2000 onward, relapse treatment and evaluation data were available.

Among cHL patients relapsing late with a cHL histology, 93% received chemotherapy at relapse compared with 90% of patients experiencing an ER (Table 3). The majority of patients relapsing with a cHL histology received ifosfamide, carboplatin, etoposide (ICE)/dexamethasone, high-dose cytarabine, platinol (DHA) (64% of LR and 65% of ER) as rescue therapy. There was no difference in frequency of autologous stem-cell transplantation between LR and ER patients relapsing with a cHL histology (60% vs 63%; $p = 0.831$).

Fifteen of the 31 cHL LR patients had available records of response evaluation after relapse treatment. Nine (60%) achieved a second CR, one (6.5%) had stable disease, four (27%) progressed, and one patient (3%) died before evaluation.

LR patients with NLPHL histology at initial diagnosis

Among the 14 primary NLPHL patients 13 relapsed with NLPHL and one transformed to DLBCL. As first-line treatment, five of the 14 LR NLPHL patients in our study received ABVD-like therapy, two patients MOPP or LVPP, and seven patients radiotherapy only. Interestingly, all NLPHL patients, who developed LR were treated in the pre-rituximab era and, therefore, did not receive antibody as part of the first-line

TABLE 1 Baseline clinicopathological characteristics of the HL study cohort

Characteristics	All patients[a] (*n* = 2424) No. of patients (%)	Early relapse (*n* = 208) No. of patients (%)	Late relapse (*n* = 58) No. of patients (%)	Non-relapse (*n* = 2158) No. of patients (%)
Median age, years (range)	38 (15–93)	45 (15–91)	45 (16–77)	38 (15–93)
Median follow-up, years (range)[b]	9.4 (0.3–25.5)	7.2 (0.7–25.5)	16.0 (5.8–24.3)	9.4 (0.3–24.7)
Age (*n* = 2424)				
<45 years	1424 (58.8)	103 (49.5)	29 (50.0)	1292 (59.9)
≥45 years	472 (19.5)	40 (19.2)	10 (17.2)	422 (19.6)
≥60 years	299 (12.3)	35 (16.8)	15 (25.9)	249 (11.5)
≥70 years	185 (7.6)	22 (10.6)	4 (6.9)	159 (7.4)
≥80 years	44 (1.8)	8 (3.9)	0 (0.0)	36 (1.6)
Sex (*n* = 2424)				
Male	1428 (58.9)	120 (57.7)	45 (77.6)	1263 (58.5)
Female	996 (41.1)	88 (42.3)	13 (22.4)	895 (41.5)
IPS (*n* = 2178)				
0–3	1922 (88.3)	148 (83.2)	41 (85.4)	1733 (88.8)
>3	256 (11.7)	30 (16.8)	7 (14.6)	219 (11.2)
Histology, all subtypes (*n* = 2424)				
NS	1332 (55.0)	126 /60.6)	24 (41.4)	1182 (54.8)
MC	499 (20.6)	39 (18.8)	18 (31.0)	442 (20.5)
LD	19 (0.8)	1 (0.5)	0 (0.0)	18 (0.8)
LR	115 (4.7)	9 (4.3)	1 (1.7)	105 (4.9)
cHL, NOS	304 (12.5)	24 (11.5)	1 (1.7)	279 (12.9)
NLPHL	155 (6.4)	9 (4.3)	14 (24.2)	132 (6.1)
B-symptoms (*n* = 2389)				
No	1352 (56.6)	100 (48.5)	33 (57.9)	1219 (57.3)
Yes	1037 (43.4)	106 (51.5)	24 (42.1)	907 (42.7)
Ann Arbor (*n* = 2424)				
I + II	1499 (61.8)	107 (51.4)	32 (55.2)	1360 (63.0)
III + IV	925 (38.2)	101 (48.6)	26 (44.8)	798 (37.0)
Bulk (*n* = 1626)				
No	1437 (88.4)	85 (85.0)	19 (95.0)	1333 (88.5)
Yes	189 (11.6)	15 (15.0)	1 (5.0)	173 (11.5)
Treatment modality (*n* = 2417)				
ABVD and/or COPP	1867 (77.2)	150 (72.8)	40 (69.0)	1677 (77.9)
BEACOPP	173 (7.2)	7 (3.4)	1 (1.7)	165 (7.7)
MOPP	118 (4.9)	12 (5.8)	3 (5.2)	103 (4.8)
Radiotherapy alone	160 (6.6)	23 (11.2)	9 (15.5)	128 (5.9)
Chemotherapy, other	99 (4.1)	14 (6.8)	5 (8.6)	80 (3.7)
Time period — year of diagnosis (*n* = 2424)				
Before 2000	481 (19.8)	66 (31.7)	26 (44.8)	389 (18.0)
2000–2014	1943 (80.2)	142 (68.3)	32 (55.2)	1769 (82.0)
Haemoglobin <6.5 mmol/l (*n* = 2373)				
No	2090 (88.1)	168 (83.6)	47 (88.7)	1875 (88.5)
Yes	283 (11.9)	33 (16.4)	6 (11.3)	244 (11.5)

TABLE 1 (Continued)

Characteristics	All patients[a] (n = 2424) No. of patients (%)	Early relapse (n = 208) No. of patients (%)	Late relapse (n = 58) No. of patients (%)	Non-relapse (n = 2158) No. of patients (%)
Leucocytes ≥15 × 10^9/l (n = 2371)				
No	2119 (89.4)	170 (85.0)	48 (90.6)	1901 (89.8)
Yes	252 (10.6)	30 (15.0)	5 (9.4)	217 (10.2)
Lymphocytes <0.6 × 10^9/l (n = 1754)				
No	2166 (93.0)	171 (89.1)	40 (76.9)	1955 (93.8)
Yes	162 (7.0)	21 (10.9)	12 (23.1)	129 (6.2)

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; CMT, combined modality treatment; COPP, cyclophosphamide, oncovin, procarbazine, prednisone; CR, complete remission; ER, early relapse; IPS, international prognostic score; LD, lymphocyte-depleted cHL; LR, late recurrence; LyR, lymphocyte rich cHL; MC, mixed cellularity cHL; MOPP, mechlorethamine, oncovin, procarbazine, prednisone; NOS, not otherwise specified; NLPHL, nodular lymphocyte-predominant HL; NS, nodular sclerosis.

[a]All patients obtaining a CR and in remission six month after first-line treatment of HL. Patients with primary refractory disease not included.

[b]The median of the observed follow-up time.

TABLE 2 Histology of LR patients at first diagnosis and at the time of late relapse

Histology at diagnosis	Histology at first relapse: cHL Number (%)	NLPHL Number (%)	Non-HL[a] Number (%)	Composite lymphoma[b] Number (%)	Missing Number (%)
Patients who later experience a LR (n = 58)					
cHL (n = 44)	31 (70.5)	1 (2.3)	9 (20.5)	1 (2.3)	2 (4.5)
NLPHL (n = 14)	0 (0.0)	13 (92.9)	1 (7.1)	0 (0.0)	0 (0.0)
Patients who later experience an ER (n = 208)					
cHL (n = 198)	153 (77.2)	1 (0.5)	17 (8.6)	1 (0.5)	26 (13.1)
NLPHL (n = 10)	2 (20.0)	8 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: cHL, classical Hodgkin lymphoma; ER, early relapse; LR, late recurrence; NLPHL, nodular lymphocyte-predominant HL.

[a]Diffuse large B-cell lymphoma (DLBCL); T-cell lymphoma; marginal zone lymphoma; low-grade B-cell lymphoma, not otherwise specified; lymphoplasmacytic lymphoma; follicular lymphoma (FL).

[b]Composite lymphoma: cHL/T-cell lymphoma; cHL/DLBCL and FL/DLBCL.

treatment. Among the 33 NLPHL patients who received rituximab as part of their first-line anti-neoplastic regimen, none experienced an ER nor a LR. Seven NLPHL LR patients had available records of response evaluation after relapse treatment and all seven patients achieved a second CR.

Risk factors

We compared characteristics of patients with LR to patients in sustained CR (cCR) for five or more years from initial diagnosis. Among LR patients, NLPHL histology was relatively more frequent than cHL histology, HR 4.4 (95% CI: 2.4–8.0, $p < 0.001$). This was confirmed in multivariate Cox proportional hazard regression analysis (HR 5.1; 95% CI: 2.7–9.5, $p < 0.001$). The frequency of LR within the NLPHL subgroup was 9%, as compared with 1.9% among cHL patients. Among cHL patients the frequency of LR was 3.6% in cHL–MC, 1.8% in cHL–NS and 0.5% in all the other histological cHL subtypes taken together (Table 1).

Among cHL patients, multivariate Cox regression analysis identified age and male sex as risk factors for LR with a HR of 1.04 per additional year (95% CI: 1.02–1.06) and 2.28 (95% CI: 1.12–4.62) (Table 4). Interestingly, the presence of low lymphocyte levels at diagnosis was a strong independent risk factor for LR, with a HR of 5.55 (95% CI: 2.68–11.48, $p < 0.001$). Another interesting finding was the overrepresentation of MC histology among females developing LR (HR 5.36; 95% CI: 1.41–20.4), while the same subtype was not overrepresented in female patients with ER. Conversely, among males, the frequency of MC histology was not significantly different between those who developed LR and those who did not. Overall, MC histology was more frequently observed in males than females (27% vs 15%; $p < 0.001$). In addition, an initial diagnosis in the period 2000–2014 seems to minimize the risk of LR (HR 0.49; 95% CI: 0.27–0.89, $p = 0.020$), and also the risk of ER (HR 0.50; 95% CI: 0.37–0.67, $p < 0.001$).

There was no significant association between performance status score (WHO), bulky disease, and initial treatment regimen, such as ABVD/ABVD-like versus BEACOPP. Combined modality treatment regimens (chemotherapy combined with radiotherapy) had a crude HR of 0.46 (0.25–0.85) on the risk of LR, but this was not significant in a multivariate analysis ($p = 0.45$).

When analyses were confined to NLPHL patients, no correlation to the aforementioned factors was evident.

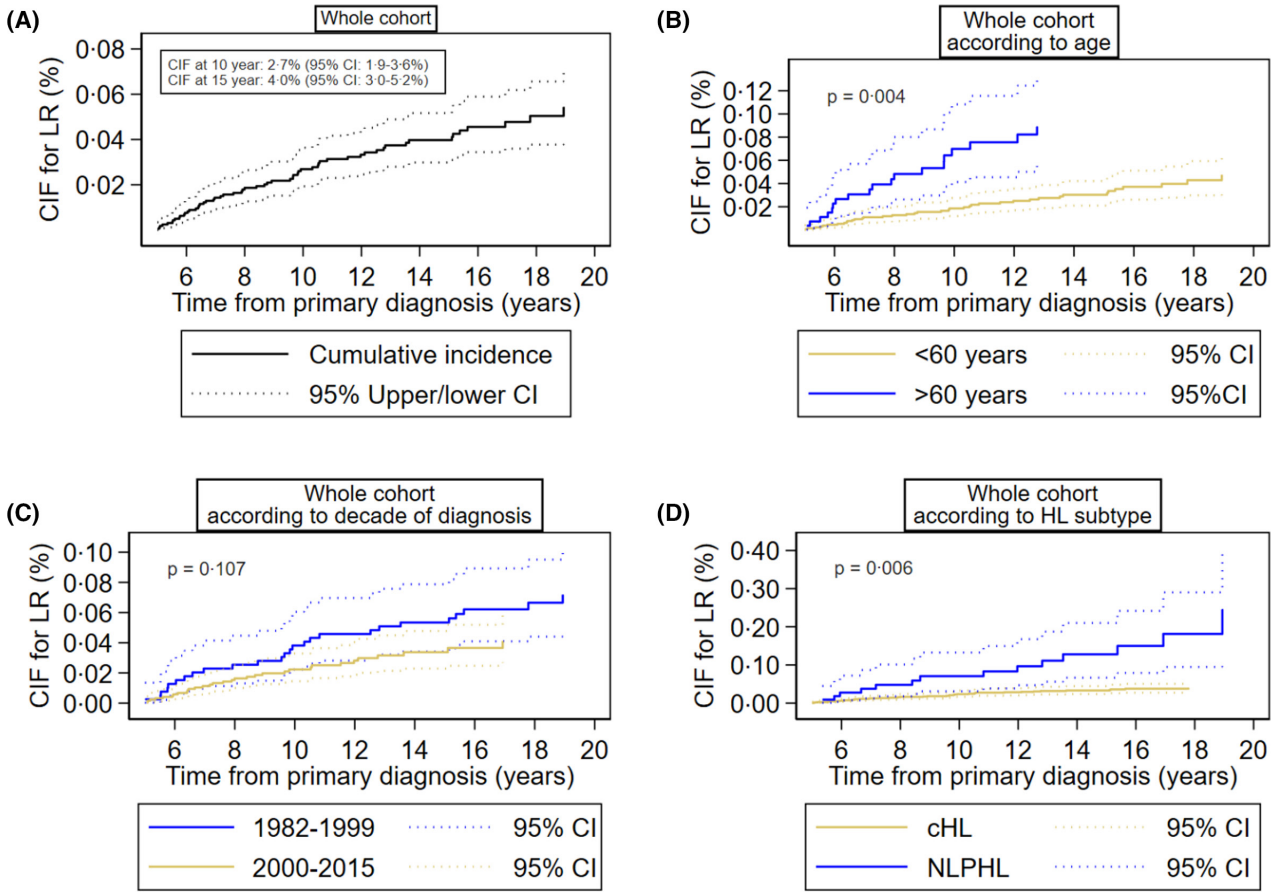

FIGURE 2 Cumulative incidence of LR in patients observed to be relapse free at least five years after initial HL diagnosis. (A) Overall CIF of LR in the entire study cohort; (B) cumulative incidence according to age; (C) time period of primary diagnosis; and (D) according to primary histology. CIF: Cumulative incidence function. LR: Late relapse. CI: Confidence interval [Colour figure can be viewed at wileyonlinelibrary.com]

Survival

Overall survival among LR cHL patients was inferior compared with patients in continued CR at least five years after initial diagnosis (Figure 3A). The median observation time for survival was 12.8 (5–25) years. The 10-year OS values from initial diagnosis for the LR and cCR groups were 51% (95% CI: 25%–71%) versus 93% (95% CI: 92%–94%) respectively, and at 15 years 35% (95% CI: 17%–54%) versus 86% (95% CI: 83%–88%). The HR was 2.69 (95% CI: 1.70–4.24, $p < 0.001$) when accounting for differences in age, sex, Ann Arbor stage, and time period of initial diagnosis.

In contrast, when analysing NLPHL patients no difference in OS was observed between the two groups (Figure 3B) with a 10-year OS for LR patients of 86% (33%–98%) versus 94% (87%–97%) for cCR patients (HR: 3.67; 95% CI: 0.93–14.47, $p = 0.063$).

As illustrated in Figure 4A, OSr of cHL patients with LR was not significantly different from that inpatients with ER. The adjusted absolute difference in OS after first relapse between LR and ER at five and 10 years were 6 percent points (95% CI: −10%; 22%, $p = 0.430$) and 1 per5cent point (95% CI: −15%; 16%, $p = 0.942$). Similar results were observed for PFSr (Figure 4B) with adjusted absolute differences at five and 10 years of 8 percent points (95% CI: −9%; 26%, $p = 0.339$) and − 2 percent points (95% CI: −18%; 15%, $p = 0.835$).

In NLPHL, OSr for patients with LR and ER had an adjusted difference of 32 percent points (95% CI: 1%; 63%, $p = 0.043$) after five years, but no differences were observed after either two or 10 years after relapse (Figure 3C). However, NLPHL LR patients had a better PFSr than ER patients, both at two and five years after relapse [absolute difference of 39 percent points (95% CI: 12%; 66%, $p = 0.005$) and 42 percent points (95% CI: 9%; 74%, $p = 0.011$)] (Figure 4D).

In LR patients, the only parameter influencing OSr and PFSr was age at relapse, with HRs of 1.06 per additional year (95% CI: 1.03–1.09, $p < 0.001$) and 1.03 (95% CI: 1.01–1.06, $p = 0.009$) respectively (Table 5). In our data, neither histology at relapse nor time period of initial diagnosis influenced OSr or PFSr.

DISCUSSION

We present a large nationwide study cohort of 2424 HL patients, who achieved a CR upon first-line treatment, in which LR accounted for approximately a fifth of all relapses. In accordance with previous studies, the cumulative incidence

TABLE 3 Clinical characteristics at time of relapse of patients experiencing either a late or early relapse

	Early relapse (n = 208)			Late relapse (n = 58)		
	Histology at relapse[a]			Histology at relapse[a]		
	cHL (n = 155)	NLPHL (n = 9)	Non-HL (n = 18)	cHL (n = 31)	NLPHL (n = 14)	Non-HL (n = 11)
Characteristics	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Median age at first relapse, years (range)	45 (18–88)	38 (19–69)	59 (17–78)	54 (22–86)	49 (36–75)	67 (30–85)
Median time to first relapse (years)	1.8 (0.6–4.9)	3.1 (1.4–4.7)	1.6 (0.7–4.2)	7.0 (5.0–15.1)	9.8 (5.4–18.9)	9.7 (5.6–16.9)
Chemotherapy at relapse						
Yes	95 (89.6)	5 (71.4)	10 (66.6)	14 (93.3)	4 (66.6)	7 (77.8)
No	11 (10.4)	2 (28.6)	5 (33.3)	1 (6.7)	2 (33.3)	2 (22.2)
Type of chemotherapy at relapse						
ABVD or COPP	5 (5.3)	5 (100.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)
BEACOPP	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CHOP-like	2 (2.1)	0 (0.0)	5 50.0)	3 (21.4)	0 (0.0)	6 (85.7)
ICE	26 (27.7)	0 (0.0)	3(30.0)	4 (28.6)	1 (25.0)	0 (0.0)
DHAP	35 (37.2)	0 (0.0)	1 (10.0)	5 (35.7)	0 (0.0)	0 (0.0)
Other radiotherapy	25 (26.6)	0 (0.0)	1 (10.0)	2 (14.3)	0 (0.0)	1 (14.3)
Yes	23 (23.4)	1 (14.3)	5 (38.5)	2 (13.3)	4 (66.7)	6 (75.0)
No	75 (76.5)	7 (85.7)	8 (61.5)	13 (86.7)	2 (33.3)	2 (25.0)
Autologous SCT						
Yes	66 (62.9)	0 (0.0)	4 (26.7)	9 (60.0)	1	0 (0.0)
No	39 (37.1)	7 (100.0)	11 (73.3)	6 (40.0)	6	10 (100.0)
Second relapse						
Yes	46 (29.7)	7(77.8)	5 (27.8)	9 (29.0)	3 (21.4)	1 (9.1)
No	109 (70.3)	2 (21.8)	13 (72.2)	22 (71.0)	11 (78.6)	10 (90.9)

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; cHL, classical Hodgkin lymphoma; CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; DHAP, dexamethasone, high-dose cytarabine, platinol; ER, early relapse; ICE, iposphamide, carboplatin, etoposide; LR, late recurrence; NLPHL, nodular lymphocyte-predominant HL; NOS, not otherwise specified; SCT, stem-cell transplantation.

[a]Relapse histology unknown in two LR patients and 26 ER patients.

continued to rise even 15 years after initial diagnosis and no plateau was reached. This was applicable for both cHL and NLPHL. The cumulative incidence of LR was 4.0% at 15 years, which is comparable to values reported in earlier studies.[11,13,15] In our study we included all late recurrences of lymphoid malignancies after an initial HL diagnosis. This is in contrast to the aforementioned studies which only included relapses with a HL relapse histology. A direct comparison between the incidence in our study and in the others is therefore not possible. Lymphoid malignancy recurrences continue to arise in HL patients even many years after an initial HL diagnosis.

The German Hodgkin Study Group reported a standardized incidence ratio for HL reoccurrence of almost 85-fold, which indicates that LR–HL is probably not a *de novo* disease event.[13] In our study, 70% of cHL and 93% of NLPHL patients relapsed with the same histology, supporting the hypothesis that the relapse had some kind of clonal relationship to the original tumour. We identified some patients with LR to have relapsed with a different, and sometimes more indolent, histology than HL. At other times, the relapse was with another aggressive lymphoma type, e.g. DLBCL. This could reflect the presence of a pre-existing unrecognized indolent component, a misbalanced host immune system, or it may represent a *de novo* or secondary treatment-induced malignancy.

No effective predictive tool has yet been established to identify patients at risk of LR. In line with previous observations,[26,27] patients with NLPHL histology were at highest risk of LR (four- to fivefold) compared with cHL patients. Most NLPHL patients in our study relapsed with the same histology or occasionally with a DLBCL. Given the rather consistent expression of mature B-cell markers (CD20, CD79A) in the tumour cell population in NLPHL, and that this tumour is generally regarded as a B-cell lymphoma, this behaviour is more reminiscent of an indolent B-cell disorder than of HL.[28,29]

Our study also identified a clear sex-related difference in the risk of developing LR among patients with cHL. Male patients seemed to be at a higher risk of developing LR than

TABLE 4 Risk factors for LR in cHL patients observed to be relapse free more than five years from first diagnosis

	Univariate analysis of LR		Multivariate analysis of LR[a]	
Risk factor	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age (continuous)	1.04 (1.02–1.05)	<0.001	1.04 (1.02–1.06)	<0.001
Age				
<45 years	ref.		ref.	
45–60 years	1.78 (0.80–3.98)	0.160		
>60 years	5.06 (2.59–9.89)	<0.001	5.17 (2.63–10.14)	<0.001
Male sex	2.63(1.30–5.32)	0.014	2.50 (1.24–5.07)	0.011
Ann Arbor Stage III–IV	2.01 (1.11–3.64)	0.020	1.77 (0.98–3.21)	ns
MC histology	2.58 (1.41–4.70)	0.002	1.91 (1.03–3.55)	0.041
MC subtype in males	1.79 (0.90–3.53)	0.100	1.55 (0.77–3.09)	ns
MC subtype in females	5.48 (1.54–19.47)	0.009	5.36 (1.41–20-41)	0.014
IPS score 4–7	2.64 (1.16–6.03)	0.021	1.35 (0.56–3.27)	ns
B-symptoms	1.27 (0.70–2.29)	0.436		
Lymphocytes $<0.6\times10^9$/l	5.45 (2.73–10.87)	<0.001	5.55(2.68–11.48)	<0.001
Decade of initial diagnosis after year 2000	0.54 (0.30–1.00)	0.051	0.49 (0.27–0.89)	0.020

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; IPS, International Prognostic Score; LR, late recurrence; MC, mixed cellularity classical Hodgkin lymphoma (cHL); ns, statistically not significant.

[a]Adjusted for age (continuous), sex, Ann Arbor stage, and decade of initial diagnosis.

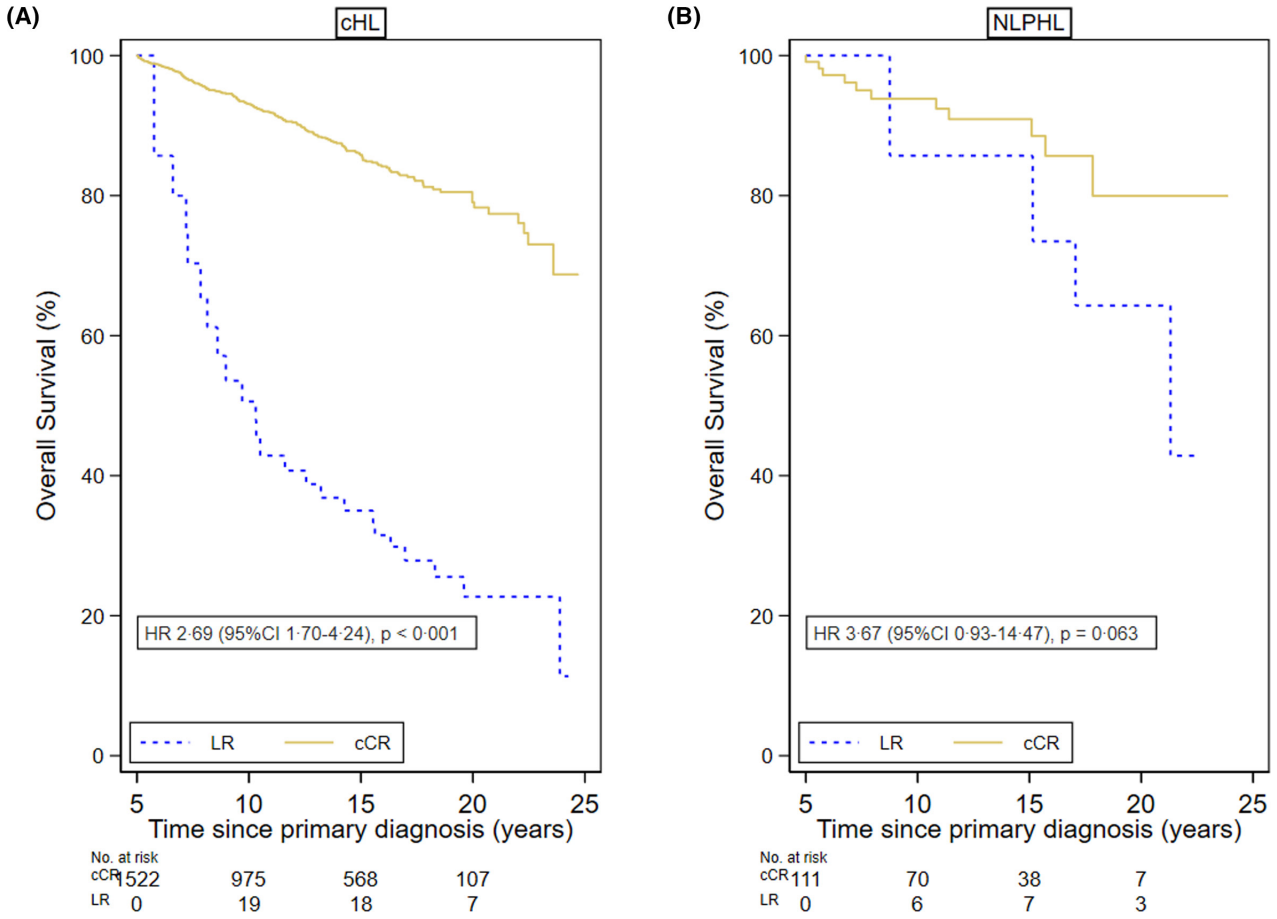

FIGURE 3 Overall survival in patients with late relapse (LR) or in continued complete remission (cCR) in: (A) classical Hodgkin lymphoma (cHL); and (B) nodular lymphocyte-predominant HL (NLPHL). CI, confidence interval; HR, hazard ratio [Colour figure can be viewed at wileyonlinelibrary.com]

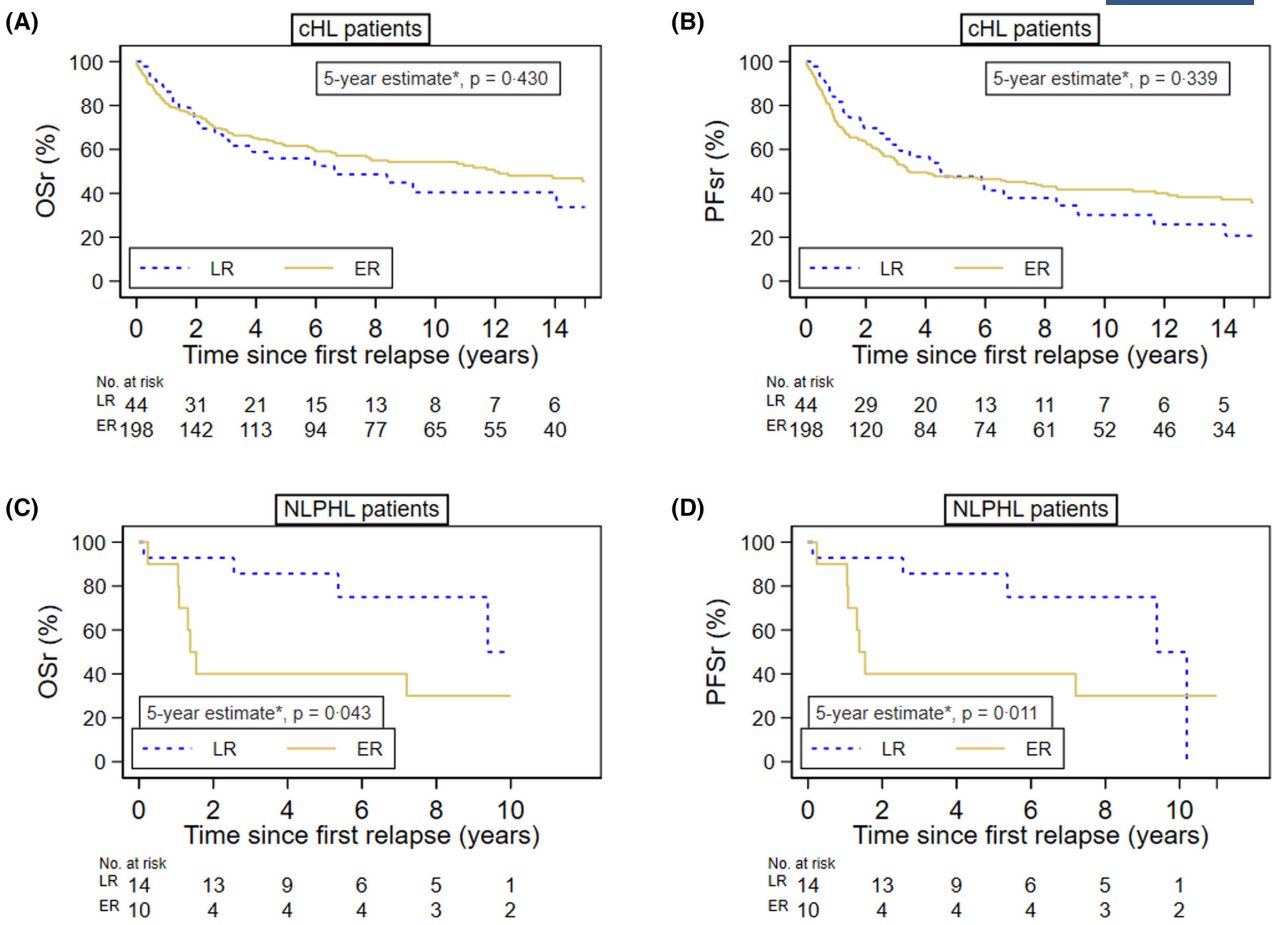

FIGURE 4 (A) Overall survival after first relapse (OSr) in cHL. (B) Second progression-free survival (PFSr) in cHL patients. (C) OSr in NLPHL patients. (D) PFSr in NLPHL. cHL, classical Hodgkin lymphoma; ER, early relapse; LR, late relapse; NLPHL, nodular lymphocyte-predominant HL; *, five-year estimate obtained from multivariate regression analysis using pseudovalues [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Risk factors of overall survival and progression-free survival after first relapse for patients with late relapse

	Overall survival after 1. Relapse (OSr)[a]		Progression-free survival after 1. Relapse (PFSr)[a]	
Risk factor	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age at first relapse, years	1.06 (1.03–1.09)	<0.001	1.03 (1.01–1.06)	0.009
Sex: Male vs female	2.26 (0.66–7.77)	ns	0.84 (0.35–2.01)	ns
Primary histology: NLPHL vs cHL	0.64 (0.20–2.09)	ns	0.56 (0.20–1.58)	ns
Ann Arbor stage at initial diagnosis: I–II vs III–IV	2.20 (0.96–5.05)	ns	1.55 (0.75–3.23)	ns
Decade of initial diagnosis after year 2000 vs before 2000	0.60 (0.25–1.46)	ns	0.92 (0.42–2.00)	ns

Abbreviations: CI, confidence interval; HR: hazard ratio; cHL: classical Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant HL.
[a]Multivariate Cox regression analysis: adjustment for age at relapse, sex, Ann Arbor stage at initial diagnosis and decade of primary diagnosis.

females. Interestingly, female patients with cHL of MC subtype had a fivefold increased risk of developing LR compared with their male counterparts. This is a novel observation, not found in previous reports. Vassilakopolos et al.[30] reported non-NS histologies to be a risk factor for LR, but provided no further subtype information and did not identify gender-associated differences. Most reports found no increased risk of LR related to specific cHL subtypes.[15] The number of events in the MC subtype is small and a definitive conclusion cannot be drawn at present. This finding warrants further confirmation in larger patient cohorts.

With rare exceptions,[15] most studies found increasing age to be an independent risk factor for LR.[10,12,13,30] This observation could reflect the fact that older patients receive less intensive front-line treatment and/or have a senescent, altered host immune system including different tumour

micro-environmental features. It could also just reflect the fact that people as a consequence of increasing age are at risk of developing new lymphomas as they get older.

In accordance with a previous report,[13] we found inferior OS in cHL patients with LR compared with patients in cCR. In the present study, cHL experiencing LR had an almost threefold increased risk of death compared with patients in cCR.[4,7,9–11,15] A number of previous studies on LR in HL do not report significant differences in OS between LR and cCR patients. One should interpret these results cautiously, since they often do not differentiate between cHL and NLPHL, a circumstance which could account for the observed discrepancies. In fact, in all studies where NLPHL was excluded, LR was associated with inferior survival. Clinicians should be aware of this increased mortality when decisions on second-line treatment are made.

In our study, OSr and PFSr of cHL patients with LR did not differ significantly from those of patients with ER. This is in contrast with some previous reports, where OSr and PFSr after LR were better than after ER.[10,13,15] The reason for this difference is unclear, but may depend on the demographic composition of the study cohorts, both at diagnosis and at relapse. In our cohort, the median age at relapse in the LR group was much older than in the ER group, reflecting a real-world-like study cohort in line with the population-based nature of the lymphoma registry. Other study cohorts are derived from clinical trials and may therefore be more selective in terms of demographic parameters such as age and comorbidities.

A potential limitation of this study is its retrospective nature, but a prospective clinical study with the aim of evaluating the incidence of LR does not seem feasible. The study period stretches over 35 years resulting in differences in diagnostic criteria, follow-up procedures, including diagnostic imaging methods, and standard treatment regimens. This could account for the reduced risk of LR in the most recent time period. The number of LR events in the study is small, which poses a limitation to the correlation analyses done in the study. Especially in the NLPHL subgroup the small number of events could explain the lack of correlation with any risk factors for the development of LR. The strength of the present study derives from the completeness and data quality of the LYFO registry, and the broadness of the patient population spectrum reflecting (compared with a clinical trial cohort) the real-world distribution of the disease in the general population. Another strength of the study is the cross-linkage at the individual level with the Danish Pathology Registry to ensure data completeness and to obtain histology reports on first and secondary relapses. Potential immortal-time bias was reduced by starting the comparison between the LR and cCR group at five years after initial diagnosis. The risk of overestimating survival in the LR group were reduced by modelling LR as a time-dependent covariate.

In summary, our study results improve our knowledge of the occurrence, clinical behaviour and outcome for LR in HL patients of all histological subtypes. They illustrate clear prognostic differences between LR occurring in NLPHL patients, with unaffected overall outcome, and LR occurring in cHL, in which it was predictive of a poorer prognosis. Further studies looking into the biology behind LR are warranted to identify factors related to e.g. tumour cells, their cellular micro-environment and host features, which may help to predict the risk of LR and improve follow-up strategies in HL.

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CONFLICT OF INTERESTS

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Maja Dam Andersen, Francesco d'Amore, Lena Modvig and Peter Kamper designed the study. Maja Dam Andersen, Lena Modvig, Stephen Hamilton-Dutoit, Ilse Christiansen, Jacob Haaber Christensen, Rasmus Bo Dahl-Sørensen, Danny Stoltenberg and Peter Kamper collected the clinical data. Maja Dam Andersen, Maja Vase and Lena Modvig analysed the data. Maja Dam Andersen, Peter Kamper and Francesco d'Amore interpreted the results. Maja Dam Andersen and Francesco d'Amore provided financial support. Maja Dam Andersen, Francesco d'Amore and Peter Kamper drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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