Received: 24 June 2024 | Revised: 13 November 2024 | Accepted: 2 December 2024

DOI: 10.1002/jha2.1070

eJHaem

British Society for Haematology

RESEARCH ARTICLE

The long-term risk of immune-related conditions in survivors of diffuse large B-cell lymphoma: A Danish nationwide registry study

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Abstract

Background: There is limited knowledge of the long-term effects on the immune system after treatment for diffuse large B-cell lymphoma (DLBCL).

Methods: This study included DLBCL patients from the Danish Lymphoma Registry who obtained complete remission (CR) after (R)-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)-like immunochemotherapy. Each R^+ CHOP-like treated patient was matched to five comparators from the Danish background population and furthermore compared to R^- CHOP-like treated patients. Incidence rate

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ratios (IRRs) and risk differences (RDs) were calculated for a wide range of infections, autoimmune conditions, and immune deficiencies (AC-IDs) combined and by subtypes.

Results: R^+ CHOP-like treated patients had a higher risk of infections overall (IRR 1.5, 95% confidence interval [CI] 1.4–1.7: 10-year RD 5.0%, 95% CI 2.2%–7.8%) and for a majority of the subtypes than matched comparators. Likewise, they had a higher risk of AC-IDs overall (IRR 1.4, 95% CI 1.1–1.7; RD 0.8%, 95% CI 0.7%–2.2%) than matched comparators, however only of clinical relevance for three subtypes; autoimmune diseases of the endocrine system, sarcoidosis and immune deficiencies. The addition of rituximab to CHOP-like therapy did not alter the incidence rates (IR) of infections overall (IRR 1.1, 95% CI 0.9–1.3) or AC-IDs overall (IRR 0.8, 95% CI 0.5–1.3) compared to CHOP-like therapy alone, although the IR for respiratory infections was significantly elevated (IRR 1.5, 95% CI 1.1–2.1). However, an increased use of IVIG treatment was observed among R^+ CHOP survivors.

Conclusion: R-CHOP-like treated patients face an increased risk of infections and AC-IDs overall compared with the background population. The risk of infections and AC-IDs did not change overall after the addition of rituximab to CHOP, however, an increased risk of respiratory infections is notable. These findings could highlight the need for expanded vigilance and prophylaxis strategies.

KEYWORDS
autoimmune conditions, diffuse large B-cell lymphoma, immune deficiencies, immunochemotherapy, infections

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent type of non-Hodgkin lymphoma (NHL), with a prevalence of 43.3 per 100.000 population within 10 years from diagnosis in the United Kingdom [1]. With the addition of rituximab to standard first-line CHOP or CHOEP (cyclophosphamide, doxorubicin, vincristine, prednisolone ± etoposide) chemotherapy (collectively called R-CHOP-like therapy), remission rates are ≥75% and 5-year survival rates > 65% [2–7]. For patients in complete remission (CR) after first-line R-CHOP-like therapy, the five-year relapse risk is approximately 20% with the majority of relapses occurring within the first 24 months after the end of therapy. DLBCL patients without relapse in the first 2 years after CR face a low risk of relapse. With a median age of 65 years at diagnosis, patients with DLBCL in durable remission have a long expected residual lifetime [8–10]. Therefore, focus on health problems that arise after treatment of DLBCL is critical in order to improve survivorship [8].

Immunological dysfunction is speculated to be a key element in the pathogenesis of at least some cases of DLBCL. For example, several subtypes of autoimmune conditions are recognized as risk factors for the development of DLBCL, just as an increased risk for DLBCL is known among HIV-infected people with or without AIDS. Possible explanations for the lymphomagenesis mechanism behind these associations are chronic immune stimulation, immunological disturbances, and immunosuppressive therapy [11–13]. In addition, immunochemotherapy used in the treatment of DLBCL can lead to reduced levels of adequate immune cells (particularly B-cells) for up to 1–2 years after treatment leading to hypogammaglobulinemia in a substantial number of patients [14–18]. If and when the immune system is fully recovered after treatment of DLBCL is largely unknown.

A recent study by Shree et al. found that survivors of DLBCL have elevated risks of several immune-related conditions, including various types of infections as well as autoimmune conditions and immune deficiencies (AC-IDs), suggesting more persistent immune dysregulation [19]. As clinical trials do not typically capture long-term immune-related adverse events, observational studies are critical in order to achieve important knowledge about the patient trajectories after treatment of DLBCL in a longer perspective [8].

The present nationwide registry-based cohort study investigated the risk of developing infections and AC-IDs among Danish DLBCL patients in CR after R-CHOP-like therapy. The risks were compared to those observed in a matched Danish background population and to patients with DLBCL treated without rituximab. Furthermore, the risk of hypogammaglobulinemia after R-CHOP-like therapy was assessed using treatment with intravenous immunoglobulin (IVIG) as a surrogate and compared to that of the matched Danish background population.

2 | METHODS

2.1 | Study population

The Danish National Lymphoma Registry (LYFO), which includes ~95% of lymphoma cases treated at Danish haematology departments since its establishment in the year 2000, was used to identify patients with DLBCL diagnosed in the period 2000–2018 [20]. All patients were included unless they fulfilled one or more of the following exclusion criteria: 1) age ≤18 years at diagnosis, 2) receiving < 3 or > 8 cycles of (R)-CHOP-like therapy, 3) not responding with CR or CR unconfirmed (CRu) after (R)-CHOP-like therapy within a year of diagnosis according to positron emission tomography (PET)-based or computer tomography (CT)-based response criteria [21, 22], 4) dead, relapsed or emigrated within 90 days from date of response evaluation, 5) occurrence of discordant/composite lymphoma or Richters' transformation at the time of DLCBL diagnosis and 6) diagnosed with human immunodeficiency virus (HIV) or any of the AC-IDs before 90 days after response evaluation. Using these criteria, a DLBCL cohort in CR/CRu after (R)-CHOP-like therapy and alive and relapse-free at least 90 days after response evaluation without prior AC-ID was established to study incident AC-IDs and infections after treatment of DLBCL.

Patients were grouped according to whether they received first-line CHOP-like therapy with or without rituximab (Figure S1). For clarification purposes, DLBCL survivors treated with rituximab in addition to CHOP-like therapy will be labelled "R^+ CHOP survivors" while those treated without rituximab in addition to CHOP-like therapy will be labelled "R^- CHOP survivors".

The R^+ CHOP group was matched to a background population selected from the Danish Civil Registration System using five comparators from the Danish background population for every R^+ CHOP patient [23]. The comparators had to fulfil the following inclusion criteria: 1) same-sex and birth year as the index R^+ CHOP survivor, 2) no prior diagnosis of lymphoma, 3) alive and reside in Denmark at the inclusion date for the particular R^+ CHOP survivor, 4) no previous diagnosis of HIV or any of the AC-IDs before the inclusion date, and 5) same Charlson comorbidity index (CCI) score 180 days before the date of DLBCL-diagnosis for the index R^+ CHOP survivor [24]. Using the Danish National Patient Registry (DNPR) [25] and the Danish National Prescription Registry [26] the CCI score for a specific individual is calculated at a specific time-point based on the occurrence of 19 selected conditions (and weighted according to severity) prior to that time-point as a cumulative score using corresponding ICD10-codes and Anatomical Therapeutic Chemical (ATC) codes respectively [27]. This approach has been previously validated [28].

2.2 | Detection of immune-related conditions

Immune-related conditions were identified by searching the DNPR for specific International Classification of Diseases 10th revision (ICD-10) codes of the specific immune-related conditions. DNPR covers all visits to public hospitals in Denmark since 1977, private hospitals and private outpatient speciality clinics since 2003 [25]. Guided by previous studies on immune-related conditions we categorized ICD-10 codes as either infections or AC-IDs. These were further divided into 13 groups of infections and 11 groups of AC-IDs (Tables S1 and S2). Only infections requiring hospitalizations and AC-IDs requiring outpatient clinical visits and/or hospitalizations were identified; visits to the emergency room were excluded in both cases. To reduce the risk of counting the same infection multiple times, new hospitalizations for infections registered within 28 days of a previous infection were not included. For the rheumatological diseases (rheumatoid arthritis [RA], axial spondylarthritis [AxSpA], psoriatic arthritis [PsA], systemic lupus erythematosus [SLE], Sjögren's syndrome, dermato/polymyositis, systemic sclerosis, giant cell arteritis, polymyalgia rheumatica and small vessel vasculitis) a validation procedure requiring at least two registrations within a 2-year period in DNPR were required, as inspired by Ibfelt et al. [29]. The first time receiving IVIG treatment after the index was identified in the DNPR using the treatment code BOHJ10.

2.3 | Follow-up

Follow-up was measured from the inclusion date corresponding to 90 days after the date of response evaluation until the occurrence of either relapse (among DLBCL survivors), new lymphoma diagnosis (among comparators), death, or censoring (10 years after the inclusion date, administrative censoring on December 31, 2018, or on date of emigration) whichever comes first. In analyses investigating the incidence rate of AC-IDs, follow-up was terminated at the date of the first AC-ID diagnosis, whereas analyses investigating the incidence rate of infections included all infections observed within the follow-up period in a recurrent events setup.

2.4 | Statistical analyses

The Kaplan-Meier estimator was used to estimate overall survival (OS) and progression-free survival (PFS). Poisson regression including person-time as an offset on a logarithmic scale was used to estimate incidence rates (IR) and incidence rate ratios (IRRs) for the occurrence of specific infections and AC-IDs per 1000 person-years (pyrs). To assess the dynamic impact of DLBCL treatment on the occurrence of infections and AC-IDs, rematching with the background population was done after two and five years in CR for survivors. IRs and IRRs were calculated in the respective time periods 0–2, 2–5, 5–10 and 0–10 years after inclusion. Furthermore, Poisson regression was also used to estimate IRs and IRRs of infections and AC-IDs between R^+ CHOP survivors and R^- CHOP survivors; both crude (univariate) and adjusted (multivariate). The latter was adjusted for age (continuous), Ann Arbor stage (I-II vs. III-IV), performance score (0-1 vs. 2–4), extranodal involvement (yes vs. no), and level of lactate dehydrogenase (LDH) (normal vs. elevated).

The Aalen-Johansen estimator was used to estimate cumulative risks for specific infections or AC-IDs; with relapse (among DLBCL survivors), later lymphoma diagnosis (among matched comparators) and death as competing events. In order to test for risk differences (RD) at the time-point of 10 years after the index between R^+ CHOP survivors and matched comparators, pseudo-observations for the cumulative incidence (based on the Aalen-Johansen estimator) were used as described in Kragh Andersen and Pohar Perme [30]. Also, the Aalen-Johansen estimator was used to estimate the cumulative risk of IVIG treatment after inclusion, and Gray's test was used to test for differences between R^+ CHOP survivors and matched comparators during the entire follow-up.

Finally, statistical analyses within subtypes of infections or AC-IDs were only performed if at least 5 different individuals in total between the groups being compared experienced events within their given follow-up periods.

The study was registered in the North Denmark Region (ID number 2021–253).

3 | RESULTS

3.1 | Patient characteristics

A total of 2,347 R^+ CHOP survivors (90.1% CHOP and 9.9% CHOEP) were identified (Table 1).

The median follow-up was 74 months for R^+ CHOP survivors and 76 months for the matched comparators. For R^+ CHOP survivors the 5-year PFS was 73% (95% CI, 71%–75%) and the 5-year OS was 81% (95% CI, 80%–83%) compared to a 5-year OS of 89% (95% CI, 88%–89%) for the matched comparators (Figures S2 and S3).

3.2 | Hospitalizations due to infections

Among R^+ CHOP survivors, the IR of any type of infection during the 10-year follow-up period was 79.6/1000 person-years (pyrs), which was significantly higher than the rate among matched comparators (IR 51.8/1000 pyrs, IRR 1.5 (95% CI, 1.4–1.7)) (Table S3). The 10-year cumulative risk of a first infection requiring hospital admission was 32.0% among R^+ CHOP survivors and 27.0% among matched comparators, leading to a 10-year RD of 5.0% (95% CI, 2.2%–7.8%) (Table S3). These results were consistent across the majority of the infection rates according to baseline clinical characteristics as presented in Table S3.

The rate of infections in R^+ CHOP survivors was significantly higher than that of the matched comparators for all considered infection types, except cardiac infections, genitourinary infections and sexually transmitted diseases (excluding HIV), with the significant IRRs ranging from 1.3 for gastrointestinal, abdominal, spleen and hepatic infections to 3.2 for eye and ear infections (Table S5). The 10-year RD was significant for only three out of 11 types of infections, with RDs ranging from 2.7% (95% CI, 1.3%–4.1%) for skin and musculoskeletal infections to 3.4% (95% CI, 1.1%–5.6%) for respiratory/chest infections (Table S5 and Figure S4).

The IRR for infections overall was 2.1 (95% CI, 1.8–2.3) in the period 0–2 years, 1.4 (95% CI, 1.2–1.6) in the period 2–5 years and 1.4 (95% CI, 1.2–1.6) in the period 5–10 years after inclusion. For nine out of 11 of the considered infection types, the IRR was greatest in the period 0–2 years after inclusion (Figure 1). Beyond 5 years after the inclusion of R^+ CHOP survivors, the IRs were still significantly elevated for six out of the 11 types of infections considered (Figure 1).

3.3 | Hospitalizations and outpatient clinical visits due to autoimmune conditions or immune deficiencies

The IR of the AC-IDs (all subtypes included) was higher among R^+ CHOP survivors (8.1/1000 pyrs) compared to the matched comparators (6.0/1000 pyrs), leading to a significant IRR of 1.4 (95% CI, 1.1–1.7) (Table S4). The 10-year cumulative risk of the AC-IDs (all subtypes included) was 6.0% among R^+ CHOP survivors and 5.2% among matched comparators with a non-significant 10-year RD of 0.8% (95% CI, 0.7%–2.2%) (Table S4). AC-ID rates according to baseline clinical characteristics are presented in Table S4, a lot of which yielded statistically significant elevated IRRs, but not RDs.

The IRs of specific types of AC-IDs were generally low, as only autoimmune diseases of the endocrine system and gastrointestinal and renal conditions yielded an IR > 1/1000 pyrs in both groups of R^+ CHOP survivors and matched comparators (Table S6). For only three out of 11 of the AC-ID subtypes, the IRRs calculated for the whole 10-year follow-up period were statistically significant, these being autoimmune diseases of the endocrine system with an IRR of 1.6 (95% CI, 1.1–2.3), sarcoidosis with an IRR of 6.5 (95% CI, 2.6–16.0) and specific immune deficiencies with an IRR of 4.2 (95% CI, 1.3–13.1) (Table S6). R^+ CHOP survivors had a significantly increased 10-year cumulative risk of sarcoidosis (RD 0.4%, 95% CI 0.1%–0.7%) while RDs for all other subtypes were not significant (Figure S5 and Table S6).

Furthermore, the IRR of AC-IDs (all subtypes included) was 1.4 (95% CI, 0.9–2.0) in the period 0–2 years, 1.8 (95% CI, 1.3–2.6) in the period 2–5 years and 1.7 (95% CI, 1.2–2.5) in the period 5–10 years after inclusion. When looking at these time intervals within subtypes of AC-IDs, most IRRs were not significantly elevated in the R^+ CHOP group, except for the aforementioned subtypes of sarcoidosis (interval 0–2 and 2–5 years), specific immune deficiencies (5–10 years) and autoimmune diseases of the endocrine system (5–10 years) (Figure 2).

3.4 | The effect of rituximab included in the CHOP regimen

In addition to the 2,347 R^+ CHOP survivors, 358 R^- CHOP survivors (84.6% CHOP and 15.4% CHOEP) were identified (Table 1). Compared to the R^+ CHOP survivors, the group of R^- CHOP survivors were slightly younger (median age, 59 vs. 66) and had fewer high-risk

TABLE 1 Demographical and clinical characteristics of DLBCL survivors and comparators. Subgroups with unknown information are explicitly shown.

Characteristic	DLBCL (R^+ CHOP), $N = 2347$	Comparator, $N = 11{,}735$	DLBCL (R^- CHOP), $N = 358$
Age, median (range)	66 (18–92)	66 (18–93)	59 (19–89)
Sex, *n* (%)			
Female	1002 (42.7%)	5010 (42.7%)	167 (46.6%)
Male	1345 (57.3%)	6725 (57.3%)	191 (53.4%)
Charlson comorbidity index, *n* (%)			
0	1521 (64.8%)	7605 (64.8%)	252 (70.4%)
1	452 (19.3%)	2260 (19.3%)	68 (19.0%)
2	243 (10.4%)	1215 (10.4%)	28 (7.8%)
>2	131 (5.6%)	655 (5.6%)	10 (2.8%)
Ann Arbor stage, *n* (%)			
I-II/unknown	1068 (45.5%)	…	228 (63.7%)
III-IV	1279 (54.5%)	…	130 (36.3%)
Performance score, *n* (%)			
0–1	2108 (90.0%)	…	322 (89.9%)
2–4	233 (10.0%)	…	36 (10.1%)
Unknown	6	…	0
Chemotherapy, *n* (%)			
CHOEP	232 (9.9%)	…	55 (15.4%)
CHOP	2115 (90.1%)	…	303 (84.6%)
Cycles, *n* (%)			
3–5	462 (19.7%)	…	123 (34.4%)
6	1460 (62.2%)	…	129 (36.0%)
7–8	425 (18.1%)	…	106 (29.6%)
Extranodal involvement, *n* (%)			
No	998 (42.5%)	…	181 (50.6%)
Yes	1349 (57.5%)	…	177 (49.4%)
Elevated LDH, *n* (%)			
Normal	1217 (53.0%)	…	215 (63.4%)
Elevated	1079 (47.0%)	…	124 (36.6%)
Unknown	51	…	19
B symptoms, *n* (%)			
No	1464 (63.4%)	…	247 (70.0%)
Yes	844 (36.6%)	…	106 (30.0%)
Unknown	39	…	5
Radiotherapy, *n* (%)			
No	1503 (64.0%)	…	153 (42.7%)
Yes	844 (36.0%)	…	205 (57.3%)

Abbreviations: CHOP (CHOEP), Cyclophosphamide, doxorubicin, vincristine, prednisolone (and etoposide); DLBCL, Diffuse large B-cell lymphoma; LDH, Lactate dehydrogenase.

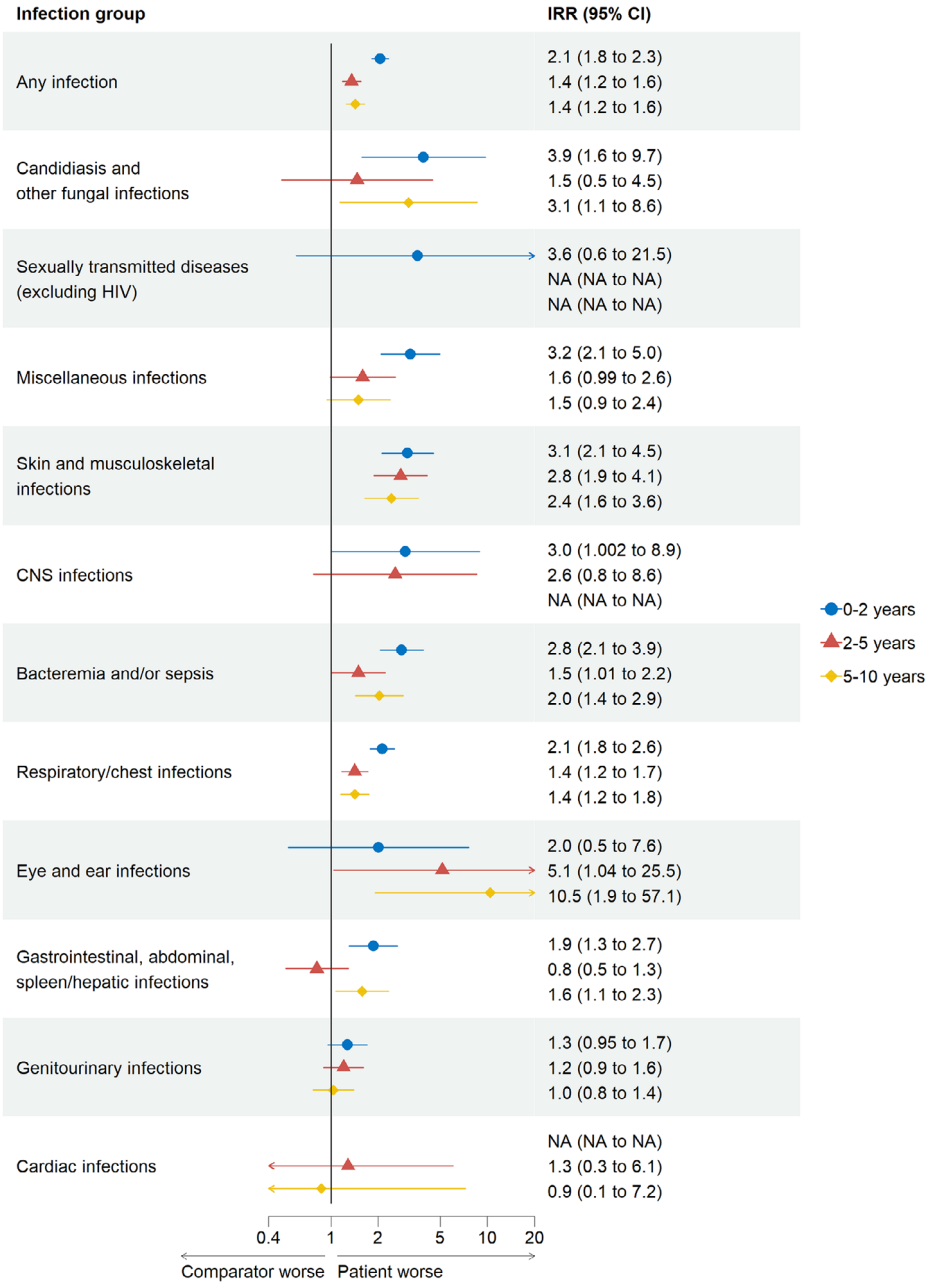

FIGURE 1 IRR estimates for R^+ CHOP survivors and matched comparators according to specific infection types over three different time spans (0-2, 2–5 and 5–10 years). An IRR > 1 corresponds to higher incidence rates among DLBCL survivors compared to matched comparators. Missing IRR estimates are marked as NAs in the figure and are due to missing incidences of infections in the corresponding time periods. CI, Confidence interval; CNS, Central nervous system; DLBCL, Diffuse large B-cell lymphoma; IRR, Incidence rate ratio; NA, Not Available; R^+ CHOP, Rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone (± etoposide).

features such as Ann Arbor stage III-IV (36.3% vs. 54.5%), extranodal involvement (49.4% vs. 57.5%), elevated LDH (36.6% vs. 47.0%), and B-symptoms (30.0% vs. 36.6%) (Table 1). Median follow-up for R^- CHOP survivors was 120 months, and the 5-year OS was 78% (95% CI, 74%–83%) compared to a 5-year PFS of 65% (95% CI, 61%–71%) (Figures S2 and S3).

The crude IR of any infection for R^- CHOP survivors during the 10-year period was 56.7/1000 pyrs. The corresponding crude IRR against R^+ CHOP survivors of 1.4 (95% CI, 1.2–1.7) showed a significantly increased rate of infections associated with rituximab use. However, when adjusting for possible confounders, the IRR became non-significant at 1.1 (95% CI, 0.9–1.3). This was consistent in each time period 0–2 years (adjusted IRR 1.4, 95% CI 0.99–2.1), 2–5 years (adjusted IRR 1.2, 95% CI 0.8–1.8) and 5–10 years (adjusted IRR 0.8, 95% CI 0.6–1.04) after index, although there was a trend toward higher incidence rates among R^+ CHOP survivors in the initial period that equalized over time. In general, the adjusted IRR showed significant differences in respiratory/chest infections (IRR 1.5, 95% CI 1.1–2.1),

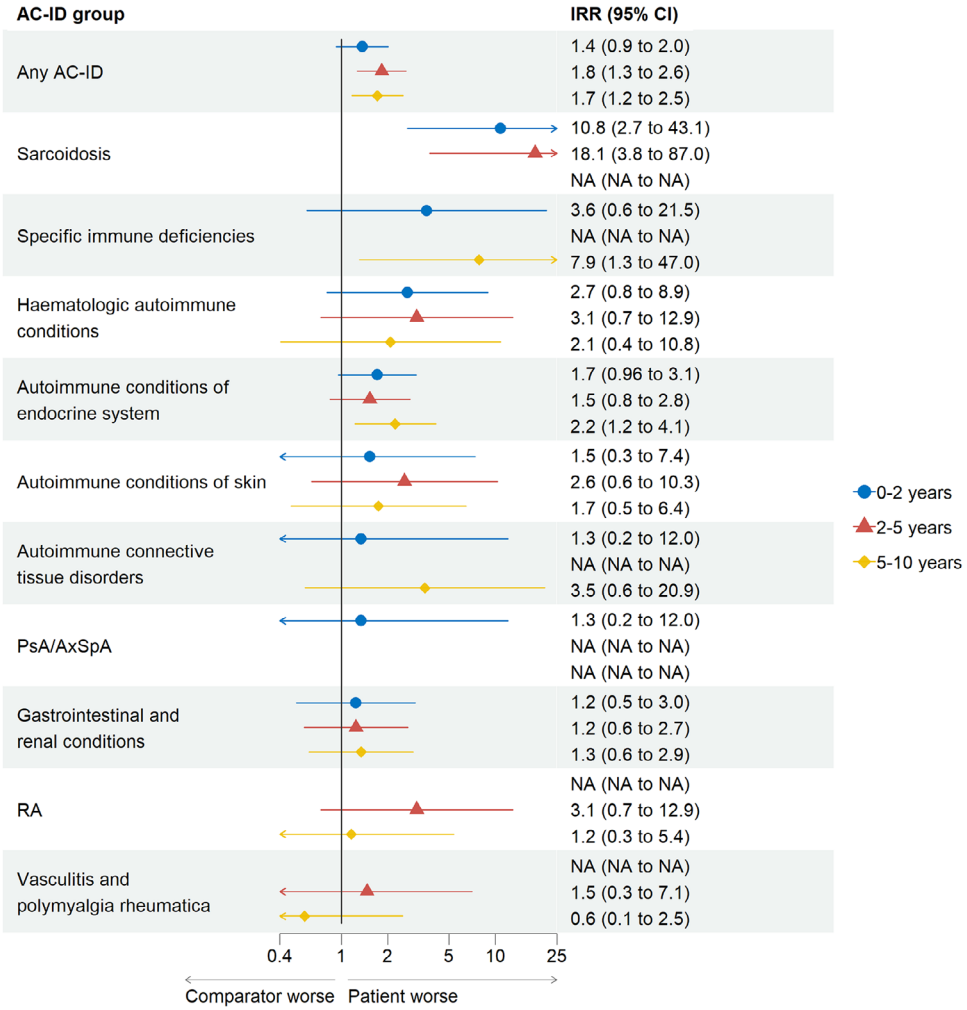

FIGURE 2 IRR estimates for R^+ CHOP survivors and matched comparators according to specific autoimmune conditions over three different time spans (0-2, 2–5 and 5–10 years). An IRR > 1 corresponds to higher incidence rates among DLBCL survivors compared to matched comparators. Missing IRR estimates are marked as NAs in the figure and are due to too few incidences of AC-IDs in the corresponding time periods. The x-axis is shown on a logarithmic scale. AC-ID, Autoimmune condition or immune deficiency; axSpA, Axial spondyloarthritis; CI, Confidence interval; DLBCL, Diffuse large B-cell lymphoma; IRR, Incidence rate ratio; PsA, Psoriatic arthritis; R^+ CHOP, Rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone (± etoposide); RA, Rheumatoid arthritis.

gastrointestinal, abdominal, spleen and hepatic infections (IRR 0.6, 95% CI 0.4–0.96), and genitourinary infections (IRR 0.6, 95% CI 0.4–0.9); with the latter two subtypes observed less frequently in R^+ CHOP survivors (Figure 3).

The crude IR of AC-IDs (all subtypes included) for R^- CHOP survivors during the 10-year period was 9.0/1000 pyrs, yielding a non-significant crude IRR of 0.9 (95% CI, 0.6–1.5) against R^+ CHOP survivors. The adjusted IRR was non-significant at 0.8 (95% CI, 0.5–1.3). Also, there were no significant differences between R^+ CHOP survivors and R^- CHOP survivors for AC-ID subtypes (Figure 4).

3.5 | The requirement for IVIG treatment

R^+ CHOP survivors had a significantly elevated cumulative risk of IVIG treatment compared to matched comparators ($p < 0.01$) during the entire follow-up (Figure S6), and more specifically the 10-year cumulative risks of receiving IVIG treatment were 1.6% (95% CI, 1.0%–2.2%) and 0.2% (95% CI, 0.1%–0.3%), respectively, in the groups of R^+ CHOP survivors and matched comparators. Also, no R^- CHOP survivors received IVIG treatment after inclusion during the 10-year follow-up period.

4 | DISCUSSION

4.1 | Infections among DLBCL survivors

This study found an increased risk of infections requiring hospitalization overall among R^+ CHOP survivors compared to the background population. The increased risk was seen for a plethora of infections, including respiratory/chest infections, bacteremia and/or sepsis,

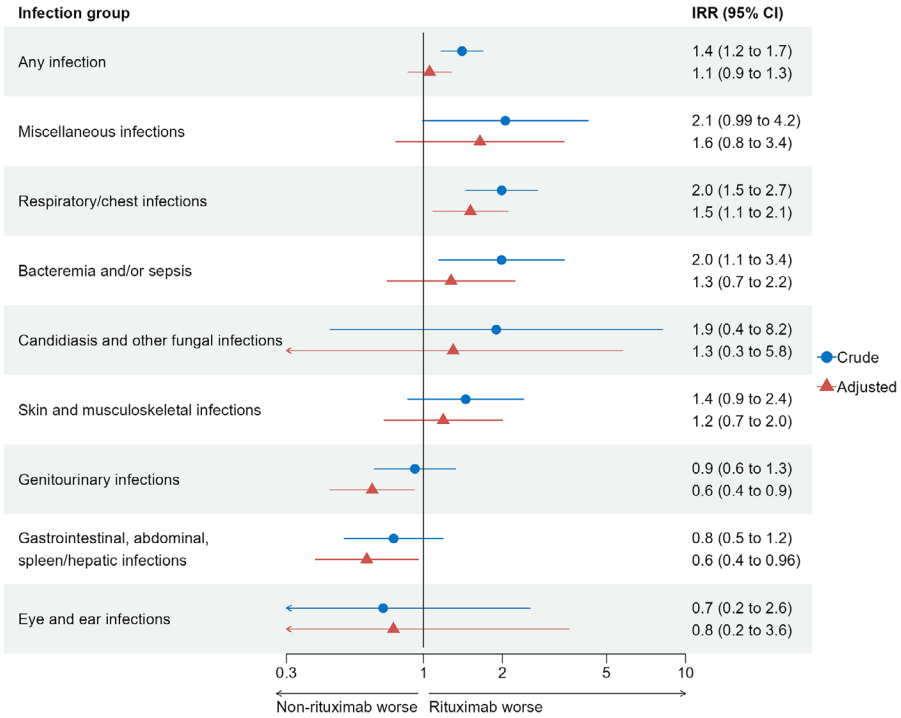

FIGURE 3 IRR estimates between R^+ CHOP survivors and R^- CHOP survivors according to specific infection groups; a mixture of crude and adjusted estimates with corresponding 95% CIs. An IRR > 1 corresponds to higher incidence rates among R^+ CHOP survivors compared to R^- CHOP survivors. The x-axis is shown on a logarithmic scale. CI, Confidence interval; IRR, Incidence rate ratio; R^+ CHOP, Rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone (± etoposide); R^- CHOP, Cyclophosphamide, doxorubicin, vincristine, prednisolone (± etoposide) without rituximab.

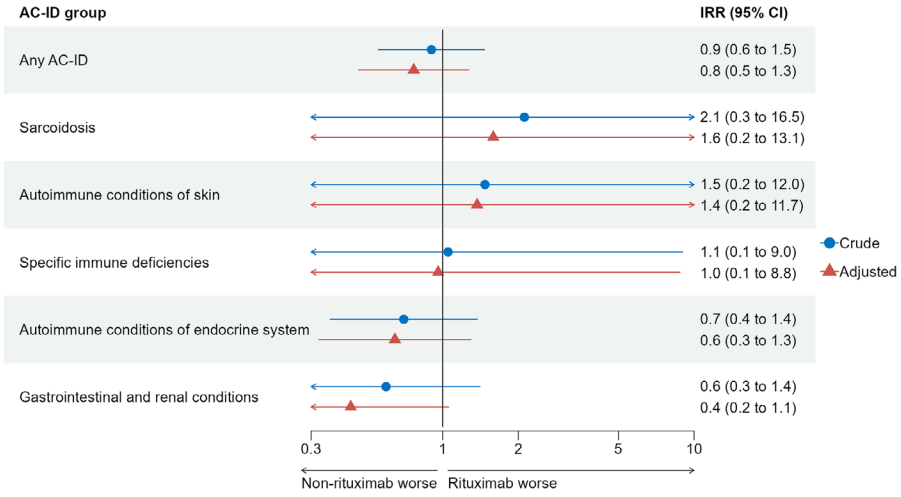

FIGURE 4 IRR estimates between R^+ CHOP survivors and R^- CHOP survivors according to specific AC-ID groups; a mixture of crude and adjusted estimates with corresponding 95% CIs. An IRR > 1 corresponds to higher incidence rates among R^+ CHOP survivors compared to R^- CHOP survivors. The x-axis is shown on a logarithmic scale. AC-ID, Autoimmune condition or immune deficiency; CI, Confidence interval; IRR, Incidence rate ratio; R^+ CHOP, Rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone (± etoposide); R^- CHOP, Cyclophosphamide, doxorubicin, vincristine, prednisolone (± etoposide) without rituximab.

CNS infections, eye and ear infections, gastrointestinal, abdominal, spleen/hepatic infections, candidiasis and other fungal infections, skin and musculoskeletal infections, and other miscellaneous infections. Since a high proportion of these specific types of infections are relatively common in the Danish population, the risk of being exposed to these infections is higher for R^+ CHOP survivors compared to the background population in contrast to the rarer types of infections like cardiac infections and sexually transmitted diseases. Likewise, the risk of sexually transmitted diseases may be more associated with a certain sexual risk behaviour rather than immunosuppression. Urinary

tract infections were insignificant among DLBCL survivors in our study, which may be explained by the fact that these types of infections are most often managed in general practice. Persisting immunosuppression is known to be most significant in the first years after treatment [17, 31], which most likely explains the higher rate of infections among R^+ CHOP survivors within the first 2 years after complete remission in our study. However, an increased overall rate was also seen > 5 years after the completion of successful first-line treatment. The heightened risk of infections makes it relevant to speculate if preventive measures should be more in focus, for example, increased patient education about infectious prevention, symptom awareness and encouragement to vaccination against the most common infections (i.e. coronavirus disease 2019 [COVID-19], influenza virus, Haemophilus influenzae and streptococcus pneumonia in Denmark).

The risk of infections associated with the use of rituximab has been well-documented in the early pivotal rituximab studies comparing R^+ CHOP to R^- CHOP [3, 6, 32]. These studies demonstrated that the addition of rituximab significantly improves survival but also increases the incidence of febrile neutropenia, bacterial pneumonia, and viral reactivations such as herpes zoster. These trials highlight the trade-off between improved clinical outcomes and increased toxicity, especially in immunocompromised and elderly patients. Nevertheless, with improved survival, an increase in infection risk would be acceptable in most situations. While it is well established that rituximab causes detectable biochemical changes in the immune system such as neutropenia and hypogammaglobulinemia, and should set the stage for higher susceptibility and severity of infections, newer studies focusing on R^+ CHOP versus R^- CHOP regimens predominantly conclude that there is not a significant difference in overall infection rates, making it less clinically relevant when used additionally to chemotherapy than one might assume [18, 33–38].

In the present study, the R^+ CHOP survivors showed an increased rate only for respiratory/chest infections relative to R^- CHOP survivors. This is a particularly interesting finding given that rituximab leads to a reduced response to vaccinations (for example vaccinations targeting COVID, influenza and pneumococcus; the most frequently given vaccinations among the adult population in Denmark) due to its B-cell depleting mechanism and the likely lower vaccine effectiveness in the R^+ CHOP group may explain this finding. To better reduce the risk of respiratory infections in DLBCL survivors, future studies should investigate in particular which specific subtypes of respiratory infections they are most susceptible to.

4.2 | AC-IDs among DLBCL survivors

This study found a higher incidence of AC-IDs in R^+ CHOP survivors compared to the background population. However, the absolute risk of an AC-ID was low in general, and the RD of 0.8% was small and not statistically significant nor clinically meaningful. As AC-IDs are generally very infrequent, the present study has limited power to detect small differences for rare subtypes of AC-IDs. This absence of clear, clinically relevant AC-ID associations is informative and reassuring to patients and clinicians. Worth mentioning, however, is a significant link between DLBCL and sarcoidosis, which may be explained by the sarcoidosis-lymphoma syndrome defined by Brincker et al. [39]. The sarcoidosis-lymphoma syndrome stated a 5.5-times higher risk of lymphoma after sarcoidosis compared to the general population but since then sarcoidosis after lymphoma has been reported as well. Like in our study, London et al. reported an incidence of sarcoidosis at a median interval of 18 months after lymphoma diagnosis (non-Hodgkin or Hodgkin). The lymphoma diagnosis was in complete response at the onset of sarcoidosis among 92% [40]. Furthermore, the observed increased risk of immune deficiencies among R^+ CHOP survivors is likely explained by the long-lasting impact on the immune system from the use of immunochemotherapy and is likely iatrogenic in nature. Although the diagnosis code (ICD10, D80) of hypogammaglobulinemia was rarely registered in DNPR, there is an increased use of IVIG treatment among R^+ CHOP survivors compared to the background population, with IVIG serving as a surrogate measurement for hypogammaglobulinemia. Since the DLBCL diagnosis code encompasses complications related to DLBCL, the increased use of IVIG treatment among R^+ CHOP survivors indicates that these patients are likely diagnosed with hypogammaglobulinemia. Registration of IVIG treatment was not seen for R^- CHOP survivors, which suggests that rituximab is the cause of hypogammaglobulinemia because of its B-cell depleting mechanism. However, increased awareness of hypogammaglobulinemia could also be an explanation for the increased use of IVIG treatment in recent times.

Rituximab is a part of the standard treatment for several of the AC-IDs included in the present study, and so R-CHOP-like therapy could protect against some of these diseases by diminishing both the symptoms and progression. Despite this, the present study did not show a significantly reduced IR for AC-IDs among R^+ CHOP survivors, neither overall nor in any of the considered AC-IDs groups compared to R^- CHOP survivors (Figure 4). This may be explained by the absence of specific AC-ID analyses on the rheumatic disease subtypes RA, SLE, Sjögren's syndrome and other autoimmune connective tissue disorders and vasculitis and polymyalgia rheumatica from this analysis due to too few events by each disease subtype. Importantly, these are some of the autoimmune conditions actively treated with rituximab [41–43]. In a sensitivity analysis, we collected the subtypes of RA, PsA/AxSpA, sarcoidosis, autoimmune connective tissue disorders, and vasculitis and polymyalgia rheumatica in a single group of inflammatory rheumatic conditions, but again we found no significant differences in IRs between R^+ CHOP survivors and R^- CHOP survivors.

4.3 | Further perspective

Several studies have investigated the risk of infection-related hospital admissions in patients with DLBCL [44–46]. The most common types of infections seen in patients with DLBCL were infections of the respiratory system, febrile neutropenia, skin and soft tissue infections and bloodstream infections, which corresponds to the findings in our study. However, in contrast to our study, these studies do not estimate the risk relative to a general population (nor other patient groups) and differ by including patients with ongoing treatment because

of active disease. To the best of our knowledge, the study of Shree et al. is the first to investigate the risk of long-term immune-related conditions among DLBCL survivors [19]. The study found significantly increased IRs of a plethora of immune-related conditions among DLBCL survivors, with the most prominent being humoral deficiency (IRRs 5.7–11.9), fungal pneumonia (IRRs 4.2–5.7), viral pneumonia (IRRs 3.8–4.9), and autoimmune hemolytic anaemia (IRRs 4.9–9.1) even after 5–10 years of survivorship. Results from the present study are largely consistent with the findings of Shree et al. (2020), as it also found significantly higher risks 5–10 years after inclusion for six out of 11 of the infection subtypes and 2 out of 10 of the AC-ID subtypes among R^+ CHOP survivors (Figures 1 and 2). The striking finding of an increased humoral deficiency among DLBCL survivors was explained by Shree et al. by the addition of rituximab since there were significant differences in the IRRs of DLBCL survivors in the pre- and post-rituximab periode respectively compared to other cancer types. This represents the only finding in the study of Shree et al. where rituximab appeared to have an impact on the risk for immune-related conditions. This aligns with a significantly higher need for IVIG treatment among R^+ CHOP survivors in our study, although our study could not showcase further major implications of rituximab either.

Shree et al. used other non-haematological cancer survivors as a comparator group, whereas this study used the Danish background population, likely healthier and less exposed to chemotherapy, reducing confounding and thus isolating the actual effect of DLBCL and treatment hereof. Intuitively, this would lead to larger differences between R^+ CHOP survivors and the background population compared to the differences between R^+ CHOP survivors and other cancer survivors. Differences in methodology, such as the inclusion of relapse cases and smaller categorization of infection subtypes, may explain why Shree et al. reported higher IRRs (up to 11.9) compared to 4.2 in this study.

4.4 | Strengths and limitations

The primary strengths of this study include the use of high-quality registry data with long follow-up and nationwide coverage in a country with equal and free access to healthcare for all citizens. Furthermore, the ability to match five comparators from the entire Danish background population to each R^+ CHOP survivor on sex, age, and CCI enables a comparison between these two groups with limited confounding. Likewise, age, sex, Ann Arbor stage, LDH level, extranodal involvement, and performance score for R^+ CHOP survivors and R^- CHOP survivors were also adjusted to overcome possible confounding factors such as disease severity. The exclusion of DBCL patients and comparators with pre-existing autoimmune conditions and HIV allowed us to isolate the effect of DLBCL and the treatment thereof on the incidence of new-onset AC-IDs. In order to minimize the risk of including erroneous diagnoses that might have been mistakenly classified as new conditions, this study implemented a validation procedure to confirm the inclusion of rheumatological diagnoses [29]. Lastly, when using clinical databases and national registers there is an inherent risk of wrong or missing registrations of diseases; however, most of the registers used in this study have been validated in previous studies showing relatively high accuracies [20, 25].

A primary limitation of this study is that DNPR only captures visits to public and private hospitals meaning infections and AC-IDs managed by general practitioners were not included. While AC-IDs would rarely be managed by general practitioners, handling of infections is common. This may bias the true associations of risk of infections among R^+ CHOP survivors and comparators since it is likely that general practitioners might be more inclined to refer recently cured DLBCL to a hospital. The inclusion of prescriptions of anti-infectives could have captured events from general practice [26]. However, such prescriptions were not included in the present study, as DLBCL survivors in Denmark often receive orally administered antibiotics directly from haematology departments, which would not be captured by this registry. Additionally, this study cannot exclude the probability that R^+ CHOP survivors have acquired a different health-seeking behaviour than the background population, which makes them seek medical care more frequently, simultaneously with better access to health care as they continue to be followed by a Danish haematology department for up to 5 years after CR. Therefore, some degree of surveillance bias could occur when comparing patients with DLBCL to the general population.

Furthermore, due to a limited number of events and hence a low statistical power of the results, risk estimates could not be calculated or reported within certain infection- and AC-ID subtypes. Finally, the differences in conclusions based on IRR and RD results for some of the analyses might be driven by the fact that many of the diagnoses analyzed in this study were quite rare, resulting in possibly small absolute 10-year RDs but higher relative differences on an IRR-scale; especially regarding outcomes of certain AC-ID subtypes.

This study was limited in its aim of uncovering whether the risks of infections and AC-IDs could be attributed to the underlying immune constitution predisposing the patients to lymphoma, DLBCL or the subsequent treatment. An analysis which examines preexisting AC-IDs and the frequency of infections prior to DLBCL diagnosis and treatment may be informative and should be considered in future studies. The lack of extrapolated data on hypogammaglobulinemia (IgG levels) from IVIG prescription was an additional limitation. Furthermore, a comparison of patients with DLBCL to patients with other malignancies would add information about the impact of DLBCL and the treatment thereof relative to the impact of other more common cancers treated with CD20-depleting therapies. In this study, DLBCL survivors were censored at relapse to examine the effect of the usual first-line treatment and DLBCL itself exclusively. However, an increased risk for malignancies among DLBCL survivors [47] provides the incitement to investigate if the occurrence of secondary primary malignancies (and subsequent immunosuppressing chemotherapy) contributed to a higher risk of infections and AC-IDs in the follow-up period.

5 | CONCLUSION

R^+ CHOP survivors, especially within the first 2 years after treatment, face an increased rate and excess risk of infections overall, and for

many subtypes, compared with the background population. While the incidence rate of AC-IDs overall was increased compared to the background population, the majority of the subtypes did not contribute to this finding except for autoimmune diseases of the endocrine system, immune deficiencies and sarcoidosis, where only the latter showed an increased absolute risk in R^+ CHOP survivors after 10 years. The inclusion of rituximab in CHOP-like therapy for DLCBL did not affect the overall risk of immune-related conditions, although the risk of respiratory infections was increased after rituximab exposure and more patients received IVIG after rituximab exposure. Overall, vigilance and prophylaxis strategies concerning infections seem relevant, but there should be no concern for AC-ID in general after successful treatment for DLBCL with R-CHOP.

AUTHOR CONTRIBUTIONS

Laura Schou Pedersen, Nadja Nørholm Klausen, Emilis Danielsen Bacevičius, Lasse Hjort Jakobsen and Tarec Christoffer El-Galaly initiated and designed the study. Lasse Hjort Jakobsen acquired data. Lasse Hjort Jakobsen and Jonas Faartoft Jensen did the statistical analysis. Laura Schou Pedersen, Nadja Nørholm Klausen, Emilis Danielsen Bacevičius, Jonas Faartoft Jensen and Lasse Hjort Jakobsen made the first manuscript draft. All authors interpreted the data, drafted and reviewed the manuscript, and approved the final manuscript.

We would like to acknowledge all who contributed to the Danish Lymphoma Registry (LYFO) and the Danish Clinical Quality Program (RKKP).

CONFLICT OF INTEREST STATEMENT

LHJ: Honoraria from Roche; TSL: Consultancy Roche, Gilead, BMS and Novartis. Research support Genentech; MRC: Consultancy Abbvie, Janssen and Genmab; LWED: Research contract with BMS and Abbvie outside the present work (payment to Department); JMJ: Consultancy Abbvie, Gilead/Kite, Roche, Incyte, SOBI, Caribou Bioscience and Celgene/BMS; The rest of the authors declare no conflict of interest.

FUNDING INFORMATION

TCEG received funding from the Danish Cancer Society.

DATA AVAILABILITY STATEMENT

The statistical analyses in this study were conducted in R (version 4.2.2) and SAS (version 9.4). Data from this study is not available due to personally identifiable information.

ETHICS STATEMENT

The study was performed in accordance with the ethical principles of the Declaration of Helsinki. In Denmark, registry-based research does not require approval from the Danish National Research Ethics Committee.

PATIENT CONSENT STATEMENT

Not applicable to this study based on Danish registers.

CLINICAL TRIAL REGISTRATION

Not applicable to this study based on Danish registers.

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SUPPORTING INFORMATION

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

How to cite this article: Pedersen LS, Klausen NN, Jensen JF, Bacevičius ED, Brown P, Mészáros Jørgensen J, et al. The long-term risk of immune-related conditions in survivors of diffuse large B-cell lymphoma: A Danish nationwide registry study. eJHaem. 2025;6:e1070.
https://doi.org/10.1002/jha2.1070