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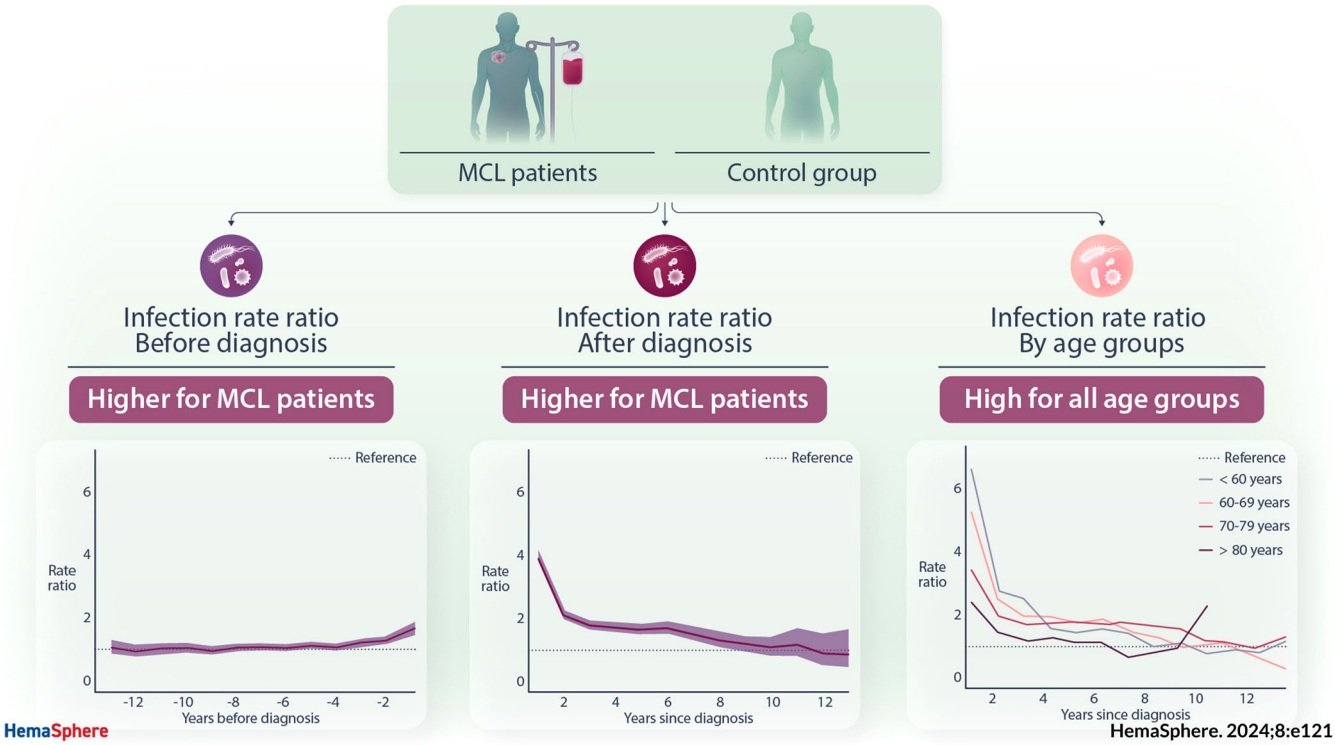
Graphical Abstract



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Abstract

Advancements in treatments have significantly improved the prognosis for mantle cell lymphoma (MCL), and there is a growing population of survivors with an increased susceptibility to infections. We assessed the incidence of infections by clinical characteristics and treatment both before and after MCL diagnosis in Sweden. Patients with a diagnosis of MCL ≥ 18 years between 2007 and 2019 were included, along with up to 10 matched comparators. Infectious disease diagnosis and anti-infective drug dispensation were identified by the National Patient and the Prescribed Drug Registers, respectively. Patients and comparators were followed from the diagnosis/matching date until death, emigration, or June 30, 2020. Overall, 1559 patients and 15,571 comparators were followed for a median duration of 2.9 and 5 years, respectively. The infection rate among patients was twofold higher, RRadj = 2.14 (2.01–2.27), contrasted to the comparator group. There was a notable rise in infection rates already 4 years before MCL diagnosis, which reached a fourfold increase in the first year after diagnosis and persisted significantly increased for an additional 8 years. Among patients, 69% (n = 1080) experienced at least one infection during the first year of follow-up. Influenza, pneumonia, other bacterial infections, urinary tract infections, and acute upper respiratory infections were the most frequent. Notably, MCL remained to be the primary leading cause of death among patients (57%, n = 467/817). Infections as the main cause of death were rare (2.6%, n = 21). Our study highlights the importance of thoroughly assessing infectious morbidity when appraising new treatments. Further investigations are warranted to explore strategies for reducing infectious disease burden.

INTRODUCTION

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma. Recent decades have, through the introduction of new treatment concepts, shown an improvement in MCL-specific survival, something that has been awaited for a long time. However, these advancements have led to a growing population of MCL survivors who face both the risk of disease relapses and long-term side effects of treatments. Patients also have a cumulative immunosuppressive state due to the underlying lymphoma and, with that, an elevated risk of infections. We therefore hypothesized that infections are a significant cause of morbidity in MCL patients,[1] attributed to a complex interplay between the disease itself, antineoplastic treatments, age-related issues, and disease complications.[2–5]

Patients with MCL exhibit immune deficiencies involving various immune system components, such as B, dendritic, T, and natural killer cells.[3–5] While the precise mechanisms besides treatment-induced immunosuppression contributing to infection risk remain unclear, hypogammaglobulinemia is well characterized and found to be associated with infection risk.[3,5] Additionally, the advanced age of MCL patients, with a median age at diagnosis above 70 years of age, and their age-related physiological declines and comorbid conditions further elevate infection risks.

Despite extensive research on the burden of infections in lymphoma,[6–8] no study has specifically assessed infections in MCL patients, rendering this field largely unexplored. This study aims to investigate the incidence of infections and the causes of death from infections among survivors of MCL compared to the general

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population in Sweden, focusing on age, sex, and calendar-year-matched comparators. By disentangling the excess burden associated with MCL and its treatment, this research seeks to understand the epidemiology and risk factors for infections in MCL survivors using linkages between several nationwide complete register-based data, crucial for optimizing posttreatment care and improving quality of life.

MATERIALS AND METHODS

Participants

We undertook an observational study using population-based registers. We identified and included all individuals aged ≥18 years diagnosed with MCL between 2007 and 2019 in Sweden. These individuals were registered in the Swedish Cancer Register (SCR) and the Swedish Lymphoma Register (SLR). The SLR, a nationwide quality-of-care registry, has been operational since the year 2000,[9] covering approximately 95% of all lymphoma cases compared to the SCR.[10,11] Information regarding clinical characteristics at the time of diagnosis (such as age, sex, performance status, Ann Arbor stage, histology (blastoid/pleomorphic versus classic), Ki67, and prognostic factors required for calculating the MCL International Prognostic Index (MIPI[12]), as well as details about initial treatments and relapses for each participant, were collected from the SLR.[9]

For each patient, seven to 10 comparators from the Total Population Register were selected. These comparators were paired on their year of birth, sex, and the year of diagnosis, and they also had to be alive and lymphoma-free at the diagnosis date of the corresponding patient. The entire cohort of patients and their respective comparators was subsequently linked to the Swedish National Patient Register (NPR), encompassing both the Inpatient and Outpatient registers. This extensive register, spanning hospitalizations from 1987 and specialized outpatient care from 2001, was utilized to collect all infection events until June 30, 2020. Similarly, the National Prescribed Drug Register (PDR), a national healthcare register established in July 2005 that contains data on all pharmaceuticals dispensed to the whole population in Sweden, was used to pinpoint all prescriptions of anti-infective medications. Data regarding the highest attained education level and marital status were procured from the comprehensive national database, the Longitudinal Integrated Database for Health Insurance and Labor Market Studies. To retrieve information regarding the date and cause of death for all participants, the Swedish Cause of Death Register (COD) was consulted.

Incident infectious diseases

Any newly diagnosed infectious disease occurring during follow-up was identified through linkage with the NPR using the International Classification of Disease–10th version (ICD10) codes (Supporting Information S1: Table S1), and all anti-infective drug dispensation was identified from the PDR using the Anatomical Therapeutic Chemical code (ATC), excluding vaccines and prophylactic treatments for patients and comparators (Supporting Information S1: Table S2). To prevent an overestimation of infection rates, the study retrieved the date of diagnosis for any newly diagnosed infection or prescribed drug, and only the initial occurrence of an infection or prescribed drug within a given month was considered. Any additional infections or prescribed drugs documented in that same month were disregarded.

Likewise, we identified all infectious disease and anti-infective drug dispensation available from the NPR and the PDR until the MCL diagnosis date to investigate the infection rates before the MCL diagnosis or matching date (for comparators). Each participant was followed from the diagnosis/matching date until death, emigration, or June 30, 2020, whichever came first.

Cause of death

We assessed infectious disease-related death, as well as death from MCL, cancers other than MCL, and other causes of death in patients through a linkage with the COD register. For each participant who died during follow-up, the leading cause of death was identified. In patients dying from MCL, we also investigated the contributing causes of death from infections. Since the detailed causes of death were only exhaustive until December 31, 2019 due to data unavailability at the time of linkage, the end of follow-up was defined as the time from entry until death, emigration, or December 31, 2019, whichever came first for the cause of death assessment.

Statistical analysis

Background sociodemographic data and comorbidities were summarized and compared between patients and comparators using chi-square tests when applicable. For a given participant, all infections that occurred during the follow-up were considered. Thus, a participant was still at risk of a new infection after developing a first infectious disease or being prescribed an anti-infective drug (after at least 30 days). The time axis was the time since diagnosis.

A Poisson regression model was used to estimate the population level averaged infection rate ratio (RR) in patients contrasted with comparators while adjusting for sex, age, and year at diagnosis (or matching), Charlson comorbidity index, and a time-dependent variable indicating the number of previous infections (if any) accounting for the patients' background risk in the recurrent events model. The follow-up time was split into time bands of 1 year for each participant and was further adjusted for in the models. This allows the background rate in the Poisson model to be constant only within a year. Infection rates (IR) were estimated as the total number of events over the total number of person-years reported as IR per person-year. The models included a binary variable reflecting the status of exposure (patients versus comparators).

To investigate if the RR differed across subgroups in age categories, sex, comorbidity, education level, marital status, family history of lymphoma, and year since diagnosis, models with interactions between the exposure and each of these variables were created. The models were reparametrized to directly estimate the effect of the exposure in each stratum of the given variables and likelihood ratio tests were used to test for interaction between the exposure and the specific variable.

To account for nonindependent observations (multiple events per subject), repeated events were accounted for using a robust sandwich estimator for the covariance matrix for the coefficient estimates in the regression models.[13,14]

For the analyses of temporal trends of infections, the follow-up was restricted to 2 years after diagnosis/matching; we included interaction terms between case/comparator status and the calendar year of diagnosis to estimate the RR of infections, comparing cases to comparators for each point of the calendar year and then summarized the trends graphically.

To assess the effects of different first-line treatments on the occurrence of infections, subcohorts of patients undergoing the specified treatments with their respective comparators were defined. The clinical characteristics of patients were evaluated as predictors of infections among the MCL patients only, but otherwise, the same modeling approach was used as described above. To assess possible

surveillance bias due to patients visiting healthcare services more frequently following the MCL diagnosis, we conducted sensitivity analyses in which the follow-up started 2 years from the MCL diagnosis/matching date.

Stata version 15 (StataCorp. 2017, Stata Statistical Software: Release 15; StataCorp LLC.) was used for data preprocessing, and all statistical analyses were performed using R software.[15]

Ethics

The study has been approved by the Regional Board of the Ethical Committee in Stockholm, Sweden (2007/1335-31/4, 2010/1624-32), the ethical committee in Lund, Dnr 2012/212, and the ethical committee in Uppsala, Dnr 2016/178.

RESULTS

Description of the study population

The study included 1559 patients and 15,571 comparators followed for a median duration of 2.9 and 5 years, respectively. The median age at MCL diagnosis/matching was 72 years (range 22–97). Patients more often presented with comorbid disease and a positive family history of lymphoma than comparators. Renal diseases, other malignancies, pulmonary disease, and peptic ulcer were the most common comorbidities (Table 1 and Supporting Information S1: Table S3).

Infection rates

Among patients, 85.2% ($n = 1329$) developed infections over the follow-up period, of whom 1080 individuals (69.3%) experienced at least one infection during the first year, resulting in a total of 6245 infections (Tables 1 and 2). The IR of infections in patients was 1.05 (1.03–1.08) per person and year versus 0.38 (0.38–0.38) in comparators (Table 2). Overall, the infection rate among patients was twofold higher than for comparators, with an adjusted rate ratio (RRadj) of 2.14 (2.01–2.27). The increased rate was observed across all patient characteristics, including age, sex, comorbidities, and family history of lymphoma (Table 2).

We observed a significantly increased infection rate during the last 4 years preceding the diagnosis of MCL (Figure 1A). Following MCL diagnosis, infections were four times more frequent in patients than comparators in the first year, and this higher infection rate persisted for up to 8 years after diagnosis (Figure 1B). Furthermore, the youngest patients had a higher infection rate after MCL diagnosis than elderly patients (Figure 1C).

In general, the infection rate ratio in the first 2 years after MCL diagnosis remained constantly increased for all infections combined and bacterial infections (Figure 2) and patients in all first-line treatment categories (Nordic-MCL2 [Rituximab [R] and cyclophosphamide, doxorubicin, vincristine and prednisone [CHOP], alternating with R-cytarabine followed by an autologous stem cell transplantation [ASCT]], R-Bendamustine, R-CHOP, R-CHOP/Cytarabine) showed two-to-four times higher infection rate relative to their comparators (Supporting Information S1: Table S4). Patients receiving ibrutinib in first line observed higher rate of bacterial (RRadj = 3.51 (2.15–5.71)) and other infections (RRadj = 11.97 (4.56–31.41)), and those receiving lenalidomide observed RRadj = 8.53 (2.42–30.05) for viral infections and RRadj = 2.39 (1.30–4.38) for other infections contrasted to comparators. Viral infection rates were higher in patients treated in the first line with cytarabine and Nordic-MCL2, whereas other infection rates were higher in Nordic-MCL2 and R-CHOP/Cytarabine-treated patients (Supporting Information S1: Table S5).

Considering specific types of infections, influenza and pneumonia, other bacterial infections, other infections of the urinary system, acute upper respiratory infections, and mycoses were the most frequent (Supporting Information S1: Figure S1). Influenza and

TABLE 1 Characteristics of mantle cell lymphoma (MCL) patients diagnosed in Sweden in 2007–2019 and matched general population comparators.

	MCL patients *N* (Col %)	Comparators *N* (Col %)	*p* Value
Overall	1559	15,571	
Median age at MCL diagnosis/matching (range)	72 (22–97)	72 (21–97)	
Total person-years	5925.6	85,711.4	
Median follow-up in years (range)	2.9 (0–13.5)	5.0 (0–13.5)	
Total subjects with infection (%)	1329 (85.2)	9598 (61.6)	
Total subjects with infection within the first year	1080	3921	
% among subjects with infection	81.3%	40.9%	
% among all subjects	69.3%	25.2%	
Age categories at diagnosis/matching			
<60	214 (13.7%)	2142 (13.8%)	
60–69	452 (29.0%)	4553 (29.2%)	
70–79	507 (32.5%)	5052 (32.4%)	
≥80	386 (24.8%)	3824 (24.6%)	0.99
Sex			
Female	430 (27.6%)	4294 (27.6%)	
Male	1129 (72.4%)	11,277 (72.4%)	0.99
Year of diagnosis/matching			
2007–2009	292 (18.7%)	2917 (18.7%)	
2010–2014	630 (40.4%)	6290 (40.4%)	
2015–2019	637 (40.9%)	6364 (40.9%)	0.99
Charlson comorbidity index[a]			
0	723 (46.4%)	8432 (54.2%)	
1	480 (30.8%)	4226 (27.1%)	
≥2	356 (22.8%)	2913 (18.7%)	<0.01
Highest achieved education level			
≤9	532 (34.1%)	5697 (36.6%)	
10–12	633 (40.6%)	6008 (38.6%)	
≥13	385 (24.7%)	3669 (23.6%)	
Missing	9 (0.6%)	197 (1.3%)	0.02
Marital status			
Not married	605 (38.8%)	6588 (42.3%)	
Married	950 (60.9%)	8937 (57.4%)	
Missing	4 (0.3%)	46 (0.3%)	0.01
Family history of lymphoma			
No	1474 (94.5%)	14,943 (96.0%)	
Yes	85 (5.5%)	628 (4.0%)	<0.01

[a]Details on the different types of comorbidities are in Supporting Information S1: Table S3.

TABLE 2 Total number of infections, infection rate (IR), and infection rate ratio (RR) with 95% confidence interval (CI) in mantle cell lymphoma (MCL) patients diagnosed in Sweden in 2007–2019 versus matched general population comparators.

	MCL patients (*N* = 1559)		Comparators (*N* = 15,571)			
	Events	IR (95% CI) per person-year	Events	IR (95% CI) per person-year	RR_{adj} (95% CI)[a]	*p*[*]
Overall	6245	1.05 (1.03–1.08)	32,633	0.38 (0.38–0.38)	2.14 (2.01–2.27)	
Age categories at diagnosis/matching						
<60	1131	0.94 (0.88–0.99)	3591	0.25 (0.24–0.26)	2.47 (2.20–2.78)	
60–69	2451	1.13 (1.08–1.17)	9387	0.32 (0.32–0.33)	2.33 (2.12–2.55)	
70–79	1886	1.06 (1.01–1.11)	11,632	0.42 (0.42–0.43)	2.06 (1.89–2.24)	
≥80	777	1.01 (0.94–1.08)	8023	0.53 (0.52–0.54)	1.63 (1.48–1.79)	<0.01
Sex						
Female	1735	1.08 (1.03–1.13)	10,859	0.45 (0.45–0.46)	1.92 (1.72–2.13)	
Male	4510	1.04 (1.01–1.08)	21,774	0.35 (0.35–0.36)	2.24 (2.10–2.38)	<0.01
Charlson comorbidity index						
0	3163	0.96 (0.93–1.00)	14,852	0.28 (0.28–0.29)	2.54 (2.36–2.73)	
1	1926	1.09 (1.04–1.14)	9566	0.44 (0.43–0.45)	1.92 (1.76–2.10)	
≥2	1156	1.33 (1.25–1.41)	8215	0.70 (0.69–0.72)	1.71 (1.54–1.91)	<0.01
Highest achieved education level						
≤9	1905	1.11 (1.06–1.16)	12,387	0.40 (0.40–0.41)	2.10 (1.91–2.30)	
10–12	2530	1.03 (0.99–1.07)	12,220	0.36 (0.36–0.37)	2.21 (2.04–2.39)	
≥13	1788	1.04 (0.99–1.09)	7651	0.37 (0.37–0.38)	2.08 (1.90–2.27)	<0.01
Missing	22	0.77 (0.48–1.16)	375	0.42 (0.38–0.46)	-	
Marital status						
Not married	2102	1.03 (0.99–1.08)	13,481	0.40 (0.39–0.41)	2.03 (1.87–2.20)	
Married	4122	1.06 (1.03–1.10)	19,090	0.37 (0.36–0.37)	2.19 (2.04–2.36)	<0.01
Missing	21	1.50 (0.93–2.29)	62	0.23 (0.17–0.29)	-	
Family history of lymphoma						
No	5772	1.04 (1.02–1.07)	31,320	0.38 (0.38–0.39)	2.12 (1.99–2.26)	
Yes	473	1.20 (1.09–1.31)	1313	0.36 (0.34–0.38)	2.36 (2.04–2.73)	<0.01
Years since diagnosis/matching						
≤1	2248	1.64 (1.58 – 1.71)	5701	0.38 (0.37–0.39)	3.98 (3.76–4.21)	
2–5	2835	0.90 (0.86–0.93)	16,705	0.38 (0.37–0.39)	1.86 (1.75–1.99)	
6–10	1074	0.86 (0.81–0.91)	8988	0.38 (0.38–0.39)	1.48 (1.29–1.69)	
>10	88	0.62 (0.49–0.76)	1239	0.38 (0.36–0.40)	0.98 (0.63–1.53)	<0.01

Abbreviations: IR, unadjusted incidence rate; RRadj, rate ratio (and 95% confidence interval [CI]) mutually adjusted for sex, age, year at diagnosis (or matching), comorbidity index, year since diagnosis, and a time-dependent variable indicating the number of previous infections.

[a]Comparators are the reference group.

[*]*p*-Value for interaction.

pneumonia dominated in absolute numbers (407 events) in patients, with a clearly elevated rate ratio RRadj = 3.84 (3.26–4.51). Similarly, the rate ratio of other bacterial infections, RRadj = 5.49 (4.57–6.60), and urinary tract infections, RRadj = 1.49 (1.19–1.87), were also significantly increased (Figure 3). Other infectious diseases, RRadj = 8.19 (6.08–11.04), mycoses, RRadj = 7.78 (5.71–10.61), and upper respiratory infections, RRadj = 6.35 (4.84–8.33) were presented with the highest rate ratios in patients (Figure 3). We observed a very high-rate ratio of immunodeficiency with predominantly antibody defects (hypogammaglobulinemia, *n* = 21 events) relative to comparators, RRadj = 147.21 (32.75–661.62).

As expected within the patient group, patients with a Charlson comorbidity index of 1 or ≥2 (compared to those with scores of 0), blastoid or pleomorphic subtype (vs. classic), high proliferation (High [Ki67 ≥ 30%], vs. low [Ki67 < 30%]), and patients who had experienced relapses (both 1st or 2nd and ≥3 relapses, as opposed to those who had never relapsed) all presented with a higher risk of infections. Other factors associated with a higher rate of infections included first-line treatment with chemoimmunotherapy and treatment with ibrutinib (Table 3). In the sensitivity analyses where the follow-up started 2 years from the MCL diagnosis/matching date (excluding first-line treatment years), the overall infection rate remained twofold increased among the patients with RRadj = 1.96 (1.84–2.09) (Supporting Information S1: Table S6) relative to the comparators. In a subgroup analysis, starting the follow-up 2 years after the first treatment start, patients who underwent a second-line treatment were censored at the date of the second-line treatment start. Thus, all patients (*N* = 374) and their comparators (*N* = 3502) in this subgroup

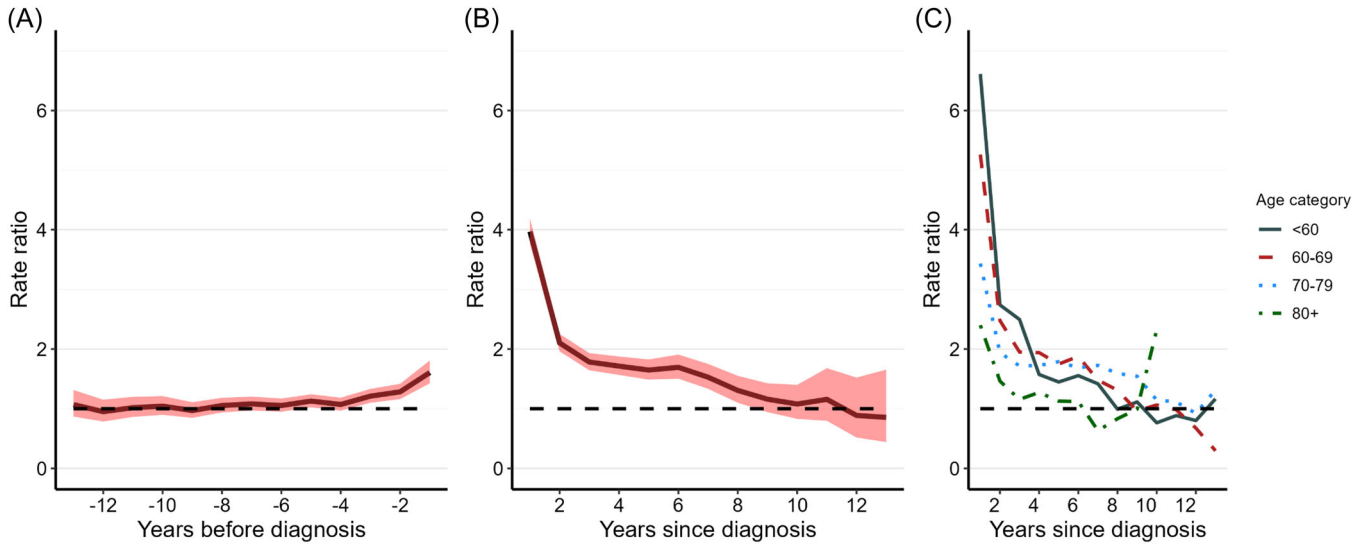

FIGURE 1 Overall time-varying rate ratio (RRadj) with 95% confidence interval of infections over time before (A), since mantle cell lymphoma (MCL) diagnosis/matching (B), and since MCL diagnosis/matching stratified by age group at diagnosis (C) in MCL patients diagnosed in Sweden in 2007–2019 contrasted with matched population comparators. The dashed horizontal line represents the null value (meaning RR = 1). The RRadj in B and C were adjusted for sex, age, year at diagnosis (or matching), comorbidity index, year since diagnosis, and a time-dependent variable indicating the number of previous infections. The RRadj in (A) was adjusted for sex, year since follow-up start, and a time-dependent variable indicating the number of previous infections.

analysis were followed from 2 years posttreatment initiation until the second-line treatment start, death, emigration, or June 30, 2020, whichever comes first. It was observed that the infection rate ratio remained high for 5 years after the 2-year exclusion period from the first-line treatment start (Supporting Information S1: Figure S2), indicating prolonged susceptibility following first-line treatment. Considering infections that required hospitalization as a surrogate for infection severity using the inpatient register, patients experienced a fivefold increased risk of severe infections versus comparators, RRadj = 4.89 (4.29–5.57).

Causes of death

Notably, MCL remained the primary leading cause of death among patients, accounting for 467 out of 817 patient deaths (57%). This was followed by other cancers (23.5%, $n = 192$ deaths [excluding MCL]), other causes of death (17%, $n = 137$ deaths, predominantly cardiovascular-related deaths), and infections (2.6%, $n = 21$ deaths). In the comparator group, the leading causes were deaths due to other causes (69%, $N = 2566$), followed by death due to other cancers (excluding MCL, 25%, $N = 926$), and death due to infections (6%, $N = 225$). The infection-related mortality rate among patients was 3.54 (2.19–5.42) per 1000 person-years against 2.63 (2.29–2.99) per 1000 person-years in the comparator group. Relapsed patients mostly died from MCL (Supporting Information S1: Table S7). The mortality rates remained markedly high during the first 5 years following MCL diagnosis for all causes and decreased over time (Figure 4). Among patients who died from MCL as the primary cause of death, 25.5% ($n = 119$) also had a concomitant infection reported as a secondary cause of death.

DISCUSSION

In this comprehensive population-based investigation, we observed an elevated infection rate among MCL patients already 4 years before the MCL diagnosis. This increased risk continued until 8 years after diagnosis. Notably, this infection rate ratio was consistently high across all primary treatment modalities. Patients with preexisting comorbidities, relapses, those undergoing treatment of any kind, and particularly those treated with ibrutinib as a first-line therapy experienced an elevated infection rate versus comparators. The most frequent localization included infections affecting the renal and respiratory systems. However, MCL continued to be the primary cause of mortality (57%) within this specific patient cohort, although concomitant infections were seen as a secondary cause of death in 26% of all patients who died from MCL.

Infections remain a severe health issue in patients burdened by malignant B-cell lymphomas. However, only a few prior investigations exist. In a recent study involving diffuse large B-cell lymphoma patients, infection-related outpatient visits were twofold higher than in the general population. Additionally, the incidence rate ratio (IRR) for inpatient bed days for infections was 1.49 (1.38–1.61), and this increase persisted for up to a 10-year follow-up period.[16] In another recent study that included a partially overlapping population, MCL patients exhibited higher rates of infection-related outpatient visits and hospitalizations than comparators.[1] These findings align with the results obtained in our report, indicating a consistent pattern of increased infection-related healthcare utilization in MCL patients but without details of specific infections and treatments as presented in our study.

In the context of hematological malignancies in general, the findings of the current study also align with those previously reported for myeloproliferative neoplasms[17] and multiple myeloma (MM) patients.[6,18,19] In a study involving 479 MM patients followed over 12 years, 65% developed at least one infection, primarily of bacterial origin. Infections were strongly associated with high disease burden, relapsed disease, and high-dose chemotherapy treatment.[19] Moreover, a study on 9253 MM patients reported an increased risk of developing any infection, bacterial infections, and viral infections with hazard ratios of 7.1 (6.8–7.4), 7.1 (6.8–7.4), and 10.0 (8.9–11.4), respectively.[18] These observations bear similarities to our current findings as MCL and MM are quite comparable and share nearly

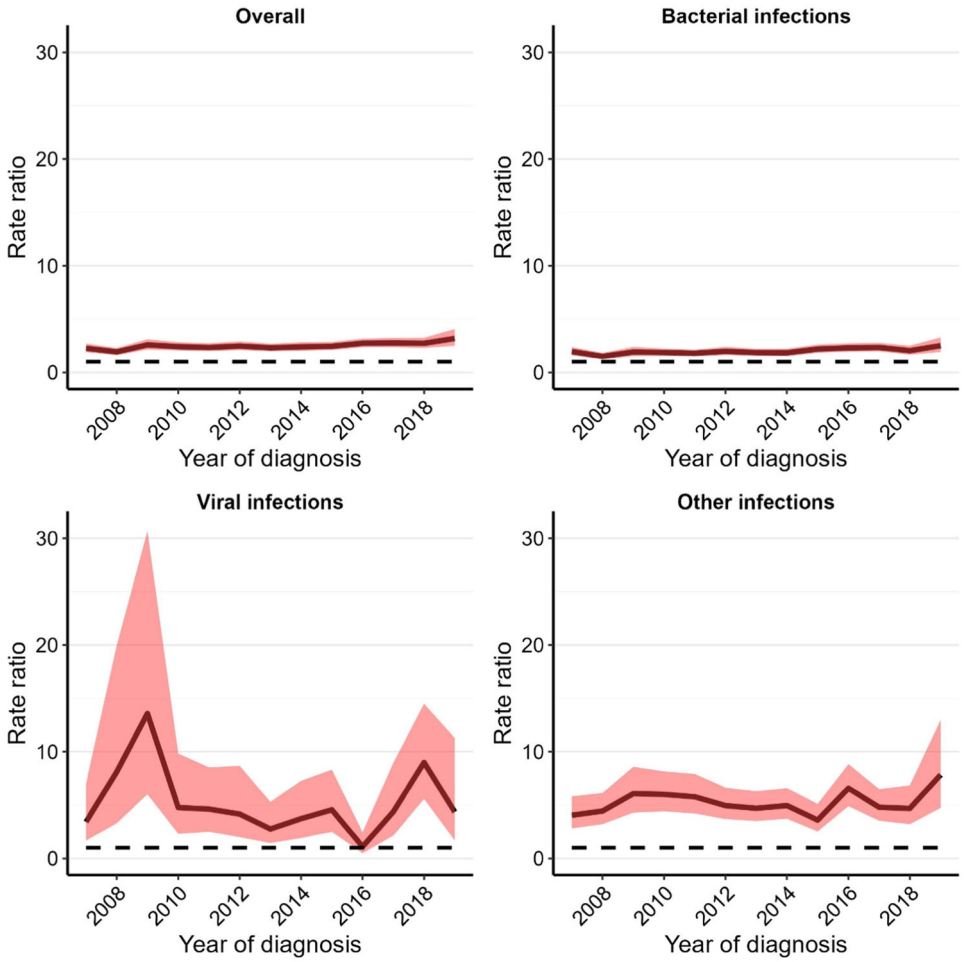

FIGURE 2 First 2-year infection rate ratio trend (RRadj) with 95% confidence interval over calendar time (years of diagnosis) in mantle cell lymphoma (MCL) patients diagnosed in Sweden in 2007–2019 relative to matched population comparators, overall and stratified by type of infection. The dashed horizontal line represents the null value (meaning RR = 1). Other infections indicate all infections that are of nonbacterial and nonviral origin. The RRadj were adjusted for sex, age, year at diagnosis (or matching), comorbidity index, year since diagnosis, and a time-dependent variable indicating the number of previous infections.

identical treatment strategies, including immunochemotherapy, ASCT, and supportive care for patients.

In our study, infection rates in patients were increased several years before the diagnosis of MCL, indicating potential shared disease factors, both genetic and environmental. Also, 80% of MCL patients present with advanced disease stage III or IV at diagnosis, suggesting an extended phase of subclinical development preceding the diagnosis. Infections might manifest as an early sign of incipient MCL, given that MCL is known to impair various immune cells, although this impact has not been extensively explored.

There is a common understanding that rituximab maintenance leads to an elevated incidence of infections. In the recent calendar period, rituximab maintenance is prescribed for 3 years in younger patients and for 2 years in the elderly. However, as previously documented,[9] only a minority of patients ($n = 137$; 11.9%) initiated post-remission maintenance with rituximab in our study.

Prior to the rituximab era, the mean survival of all MCL patients was only 3–5 years.[20] Adding the anti-CD20 antibody rituximab, high-dose cytarabine, and ASCT to the front-line treatment protocol has improved outcomes.[21] The introduction of Bruton tyrosine kinase inhibitors both in the first line in trials[22] and routine at relapse and the introduction of CAR-T cell therapy[23] at relapse has further advanced the prognosis. The fourfold increase in infection rates observed during the initial years following MCL diagnosis suggests a combination of disease and treatment-related effects. It is challenging to separate the impact of treatment from the disease itself when both contribute to a weakened immune response, making patients more susceptible to infections. For example, both rituximab and chemotherapy are known to lower serum immunoglobulin levels and neutrophil counts.[3,24] Bendamustine plus rituximab in the first line showed a lower infection rate than R-CHOP treatment in MCL patients.[25] However, adding ibrutinib to rituximab—bendamustine in elderly MCL patients—followed by ibrutinib plus rituximab maintenance, has led to a long-term higher incidence of infections, particularly pneumonia.[26] In relapsed or refractory MCL patients, Ibrutinib was reported to induce more infections, particularly upper respiratory tract infections.[27] However, limited data are available regarding the immune recovery dynamics following immunochemotherapy. It is clear that we add more and more treatments and novel agents to try to improve the prognosis for MCL patients, and this will likely lead to an even larger problem with infections in the future. The findings of ibrutinib-treated patients showing a high risk of infections also demonstrate that novel agents are not safer from an infection risk perspective than conventional chemotherapy.

Regarding mechanisms for infections, it is known that patients with B-cell lymphoma undergoing CHOP-based chemotherapy with

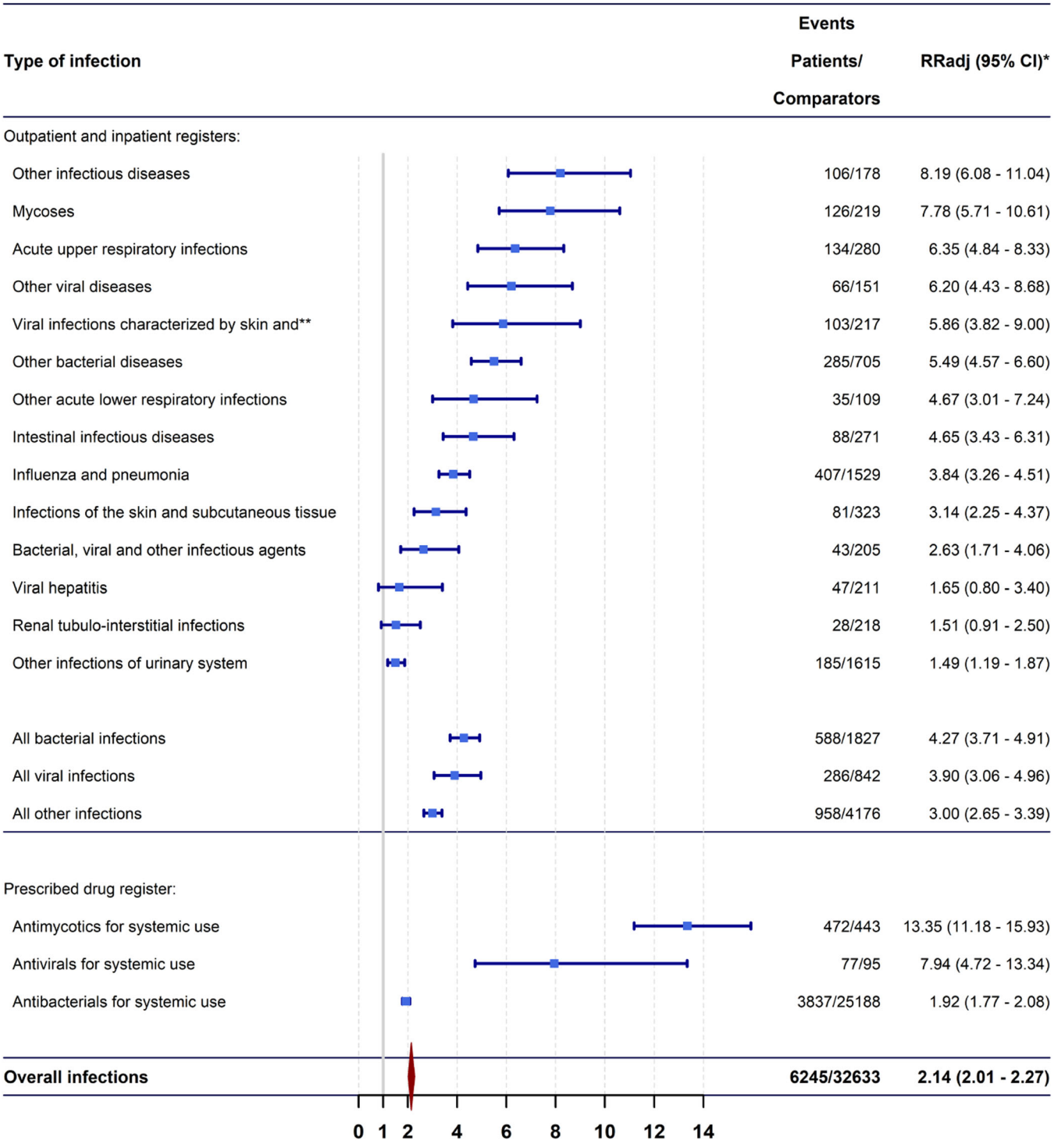

FIGURE 3 Rate ratios (RRadj) with 95% confidence intervals (CI) of different types of infections in mantle cell lymphoma (MCL) patients diagnosed in Sweden in 2007–2019 compared with general population comparators. RRadj were adjusted for age at diagnosis, sex, calendar year, Charlson comorbidity index, year since diagnosis, and a time-dependent variable indicating the number of previous infections. The vertical solid line indicates the null value (meaning RR = 1). *Comparators group is the reference. **Viral infections characterized by skin and mucous membrane lesions. Excluding prophylactic treatment drugs, ATC code J01EE01 (Trimethoprim/sulfamethoxazole), J01EA01 (Trimethoprim), J05AB01 (Aciclovir), and J05AB11 (Valaciclovir) from the Prescribed Drug Register. Very high-rate ratio for Immunodeficiency with predominantly antibody defects (ICD10 D80.1-D80.6), events: 21/2 (patients/comparators), RRadj = 147.21 (32.75–661.62).

rituximab have a significant depletion of CD19+/CD20+, CD4+, CD3+, CD8+, and CD56+ cells during treatment. A high risk of infections caused by a cellular immune deficiency in bendamustine-treated patients, mainly due to decreased CD4+ cell counts, has also been reported.[28] The addition of ibrutinib to chemotherapy as a back-bone significantly increased the risk of infections in clinical trials.[22,26] It takes approximately 1 year for B cells and 2 years for T cells to recover to their pretreatment levels.[3] Rituximab is known to induce secondary

TABLE 3 Description and rate ratio (RRadj) with 95% confidence interval (CI) of infections according to clinical characteristics and treatment categories among mantle cell lymphoma (MCL) patients diagnosed in Sweden in 2007–2019. (continued on next page)

	Patients	Total events	Rate (95% CI) per 100 person-years	RRadj (95% CI)[a]
Stage				
Ann Arbor I	86	337	0.78 (0.70–0.87)	1.0 (reference)
Ann Arbor II	145	621	0.97 (0.89–1.04)	1.09 (0.92–1.29)
Ann Arbor III	177	762	0.98 (0.91–1.05)	1.06 (0.89–1.25)
Ann Arbor IV	1080	4397	1.11 (1.08–1.15)	1.17 (1.01–1.35)
Missing	71	128	1.02 (0.85–1.21)	1.07 (0.84–1.37)
Charlson comorbidity index				
0	723	3163	0.96 (0.93–1.00)	1.0 (reference)
1	480	1926	1.09 (1.04–1.14)	1.09 (1.01–1.17)
≥2	356	1156	1.33 (1.25–1.41)	1.24 (1.14–1.36)
MIPI				
Low risk (<5.7)	191	1072	0.95 (0.89–1.00)	1.0 (reference)
Intermediate risk (5.7–6.1)	448	2328	1.10 (1.06–1.15)	1.09 (0.97–1.21)
High risk (>6.1)	742	2179	1.10 (1.05–1.15)	1.11 (0.98–1.25)
Missing	178	666	0.95 (0.88–1.03)	1.00 (0.87–1.15)
Histologic subtype				
Classic	249	1100	0.91 (0.85–0.96)	1.0 (reference)
Blastoid or pleomorphic	149	601	1.22 (1.12–1.32)	1.29 (1.13–1.46)
Missing	1161	4544	1.08 (1.05–1.11)	1.13 (1.04–1.24)
KI67 - proliferation				
Low (<30%)	196	1002	1.04 (0.97–1.10)	1.0 (reference)
High (≥30%)	226	1015	1.20 (1.12–1.27)	1.13 (1.01–1.26)
Missing	1137	4228	1.03 (1.00–1.06)	0.99 (0.91–1.08)
Relapse[b]				
Never	982	3135	0.97 (0.93–1.00)	1.0 (reference)
1–2	564	2781	1.18 (1.14–1.23)	1.22 (1.14–1.30)
≥3	13	329	1.01 (0.90–1.12)	1.17 (1.01–1.37)
Primary treatment				
Immunochemotherapy				
No treatment	82	292	0.68 (0.60–0.76)	1.0 (reference)
Yes (any immunochemotherapy given)	1251	5502	1.10 (1.07–1.13)	1.30 (1.12–1.51)
Missing	226	451	0.95 (0.86–1.04)	1.10 (0.91–1.32)
Radiotherapy				
No	1225	5370	1.09 (1.06–1.12)	1.0 (reference)
Yes	101	396	0.77 (0.70–0.85)	0.83 (0.73–0.94)
Missing	233	479	0.95 (0.87–1.04)	0.84 (0.74–0.95)
Treatment consolidation				
Non-ASCT	1020	3842	1.03 (1.00–1.07)	1.0 (reference)
ASCT	299	1959	1.09 (1.04–1.14)	1.00 (0.92–1.09)
Missing	240	444	1.08 (0.99–1.19)	0.87 (0.78–0.98)
Type of chemotherapy treatment				
Nordic-MCL2	291	1705	1.14 (1.09–1.20)	1.0 (reference)
Chlorambucil	93	290	1.14 (1.01–1.28)	1.05 (0.89–1.23)
Cytarabine	17	65	0.99 (0.77–1.27)	0.98 (0.71–1.36)
FC	15	76	1.10 (0.87–1.38)	0.95 (0.72–1.26)

TABLE 3 (Continued)

	Patients	Total events	Rate (95% CI) per 100 person-years	RRadj (95% CI)[a]
R-Bendamustine	439	1576	1.06 (1.00–1.11)	0.94 (0.84–1.04)
R-CHOP	181	721	1.19 (1.10–1.28)	1.00 (0.89–1.12)
R-CHOP/Cytarabine	154	887	1.03 (0.96–1.10)	0.92 (0.83–1.02)
Missing	331	819	0.83 (0.77–0.89)	0.79 (0.70–0.88)
Other	38	106	1.14 (0.94–1.38)	1.03 (0.81–1.32)
Lenalidomide				
No	1266	5560	1.05 (1.02–1.08)	1.0 (reference)
Yes	16	97	1.05 (0.85–1.29)	1.05 (0.78–1.40)
Missing	277	588	1.12 (1.03–1.21)	0.89 (0.80–0.98)
Ibrutinib				
No	1273	5609	1.04 (1.02–1.07)	1.0 (reference)
Yes	14	68	1.74 (1.35–2.20)	1.56 (1.21–2.01)
Missing	272	568	1.11 (1.02–1.20)	0.88 (0.80–0.98)

Abbreviations: ASCT, autologous stem cell transplant; FC, fludarabine, cyclophosphamide; (R-)CHOP, (Rituximab-) Cyclophosphamide, doxorubicin, vincristine, prednisone.
[a]Rate ratio (RRadj) adjusted for sex, age, year at diagnosis (or matching), comorbidity index, year since diagnosis, and a time-dependent variable indicating the number of previous infections.
[b]Relapse, A time-dependent variable.

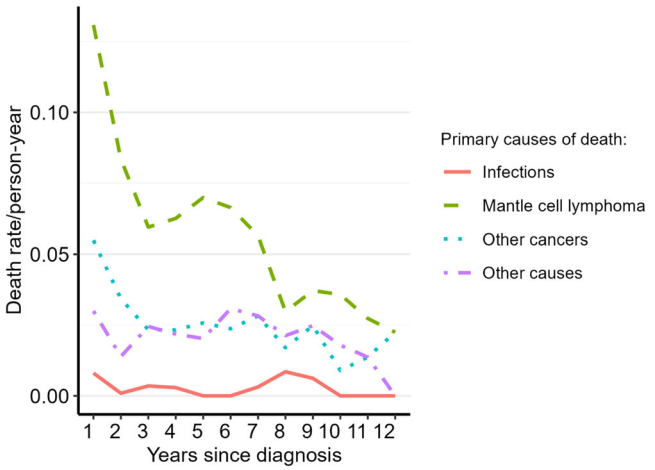

FIGURE 4 Death rate per person-year over year since diagnosis in mantle cell lymphoma (MCL) patients diagnosed in Sweden in 2007–2019 according to different leading causes of death recorded from 2007 to 2019.

hypogammaglobulinemia, and the number of rituximab injections during maintenance after ASCT in young MCL patients was correlated with infections and hypogammaglobulinemia.[29] It is worth noting that a connection between ibrutinib treatment and the development of infectious complications has also been reported.[30] In a phase II registration trial of ibrutinib, the most common infections were observed in the upper respiratory and urinary tract.[31] These observations underscore the possibility that the aggressive treatment required for long-term remission of MCL contributes to the elevated infection risks in this patient population, potentially affecting the quality of life for these individuals.

In contrast to prior studies highlighting infections as the primary cause of death in MM[18,32] and chronic lymphocytic leukemia patients,[33,34] our findings show that 57% of patients primarily succumbed to recurrent MCL, with infections serving as a secondary cause of death in 26% of these cases. In our study, infections as the primary cause of death were relatively rare (2.6%) compared to deaths due to other malignancies (23.5%) or other causes (17%, with cardiovascular-related deaths dominating). These observations also highlight that despite the elevated rate of infections seen in MCL, advancements in treatment and the quality of care provided to these patients have mitigated the mortality associated with infectious diseases.

To our knowledge, this is the most extensive study investigating infection rates in MCL patients compared to the general population. We have reviewed all medical records with trained research nurses, so the treatment and relapse variables are updated for all patients.[9] As MCL predominantly affects the elderly, with a median age at diagnosis above 70 years, the presence of comorbidities that also heighten susceptibility to infections is a challenge. By comparing MCL patients to age, sex, and year-matched comparators, it becomes possible to separate the increased infection rate attributable to MCL and its treatment from the expected risk faced by an elderly population with comorbidities. However, despite the matching strategy, the comparators group does not entirely mirror the patient group, as matching was not conducted on clinical variables. Consequently, renal diseases, peptic ulcers, malignancies, chronic obstructive pulmonary diseases, and dementia emerged as more prevalent among patients than comparators. While it is essential to notice that the comorbidity index encompasses the entirety of participants' lifespans when available, implying that reported comorbidities could have manifested at any point before the diagnosis of MCL or matching date, we cannot discount the possibility of a screening effect resulting in an increased diagnosis of comorbid diseases in the months preceding MCL diagnosis, and that remains a potential contributing factor warranting further consideration.

The infection rate ratios from our study might be overestimated due to surveillance bias, particularly during the initial years following diagnosis, since MCL patients will visit hospitals more often and thus report more infections than comparators. Additionally, primary care physicians might refer patients earlier, or patients could promptly contact their hospital doctor to seek medical assistance, particularly for

less severe conditions. To address this issue, we excluded successive diagnoses or drug prescriptions occurring within a 30-day window and all treatments mainly used with a prophylactic intention. We furthermore conducted sensitivity analyses starting follow-up 2 years after diagnosis/matching. However, the results should still be interpreted with this limitation in mind. Also, since our study relied on registry data, no laboratory tests were available for infectious disease confirmation or further documentation of infection types. Additionally, we could not assess the severity of the infections, so we used infections leading to hospitalization as a surrogate for severe infections.

Finally, as the treatment landscape for MCL evolves with the transition to novel targeted drugs and improved survival rates, the risk of infections remains a significant limitation to the benefits derived from advanced treatments. Increased awareness of these risks among clinicians and effective communication of these risks to patients will be of paramount importance. Furthermore, prophylactic treatment with immunoglobulin replacement therapy for preventing infections[35] could possibly reduce the posttreatment infection risk. However, this has to be proven in clinical trials.

CONCLUSION

MCL patients face an elevated rate of infections both prior to and for several years following MCL diagnosis and treatment. The intensive therapy needed to achieve long-term remissions along with the underlying disease contributes significantly to the increased infection rates. Infections remain a prominent cause of morbidity in MCL patients, even though their impact on mortality is still overshadowed by MCL-related mortality. The findings highlight the importance of thoroughly assessing morbidity related to infectious diseases when appraising new treatments. Consequently, further investigations are warranted to explore strategies for reducing the burden of infectious diseases and/or sequencing of treatments.

AUTHOR CONTRIBUTIONS

Ingrid Glimelius, Kossi D. Abalo, Sara Ekberg, Karin E. Smedby, Mats Jerkeman, and Simon Pahnke designed the study. Kossi D. Abalo and Sara Ekberg independently performed and reviewed the statistical analyses. Therese M. L. Andersson critically reviewed the statistical methods. Kossi D. Abalo and Ingrid Glimelius wrote the paper. All authors interpreted the data, provided input for the manuscript, and approved the final version.

CONFLICT OF INTEREST STATEMENT

Mats Jerkeman received honoraria from Abbvie, AstraZeneca, BMS, Kite/Gilead, Pierre Fabre, Roche, Sobi, and Takeda and research support from Abbvie, AstraZeneca, BMS, and Roche. Ingrid Glimelius received research support from Takeda and participated in educational sessions arranged by Janssen Cilag, Abbvie, and Kite Gilead. Karin E. Smedby received honoraria from Incyte and Celgene, and research support from Janssen Cilag. The other authors have no relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY STATEMENT

Our study's data comes from nationwide registers, as detailed in the methods section. Access to this data is subject to national data protection laws, but it can be obtained from the authors with permission from the Swedish Authority for Privacy Protection. Interested researchers can contact the corresponding author (KDA, kossi.dovene.abalo@ki.se) or the principal investigator (IG, ingrid.glimelius@igp.uu.se) for collaborative research projects, provided they do not overlap with ongoing projects. The statistical analysis plan is also accessible to anyone.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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