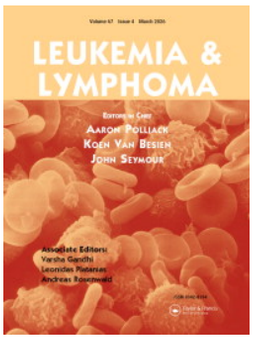

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Survival in mantle cell lymphoma patients burdened by a second primary malignancy

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ABSTRACT

Second primary malignancies (SPMs) increasingly affect mantle cell lymphoma (MCL) survivors. In nationwide Danish and Swedish cohorts (2000–2020), we evaluated overall survival among MCL patients with SPMs versus matched non-lymphoma individuals with comparable malignancies and MCL patients without SPMs, respectively. Of 3094 MCL survivors, 19% in Denmark and 15% in Sweden developed an SPM, with a median of three years from MCL diagnosis to first SPM. MCL patients with SPMs had about double the mortality risk compared with non-lymphoma counterparts (pooled HR 2.1, 95% confidence interval (CI) 1.3–3.5), and worse survival than MCL patients without SPMs (pooled HR 1.6, 95% CI 1.4–1.9). In Swedish MCL patients with SPMs, deaths were attributed to subsequent hematologic malignancies (9%), solid cancers (14%), primary MCL (23%), non-cancer causes (11%), with 40% still alive. Development of SPMs in MCL is associated with substantially higher mortality, supporting long-term surveillance and proactive management of late complications.

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MCL; second primary malignancy; survival

Introduction

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of B-cell lymphoma. The disease is incurable for most patients and relapses are common; however, recent progress in treatment strategies has significantly improved prognosis [1,2]. With these advances, there is a growing population of MCL survivors at risk of late effects from multiple lines of treatment [3].

One of the most concerning late effects in lymphoma patients is the development of second primary malignancies (SPMs) [4,5]. SPMs are new, distinct types of cancer that occur in patients who have previously been diagnosed with another primary cancer. SPMs are well described in lymphoma patients: non-Hodgkin lymphoma (NHL) patients have a 40% increased rate of solid SPMs, including non-melanoma skin cancers, and a fivefold increased rate of myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML) compared to the general population [6]. Recent large-scale studies in Sweden and Denmark demonstrated an elevated risk of SPMs among MCL survivors [4,5]. In

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Denmark, high-dose chemotherapy and autologous stem cell transplant were linked to increased risks of non-melanoma skin cancers and MDS-AML, but not solid cancers [4]. In Sweden, MCL patients had a 60% higher overall rate of developing any SPM compared to the general population. Particularly, advanced age at MCL diagnosis, male sex, family history of lymphoma, and rituximab–bendamustine treatment (versus the Nordic protocol treatment) were associated with increased SPM risk [5].

The development of SPMs can be attributed to various factors including genetic predisposition, environmental exposures, lifestyle factors, treatments given for the primary lymphoma [5], including chemo- and radiotherapy [7], and clonal hematopoiesis [8]. In addition, immune dysregulation intrinsic to the lymphoma itself as described in chronic lymphocytic leukemia (CLL) [9], older age at first treatment and male sex are risk factors for developing SPMs in NHL [10]. MDS-AML was seen primarily in those older than 60 years, while the development of solid SPMs appears to be associated with male gender [10,11].

Although the risk of SPM in lymphoma patients is increasingly well-documented [4–6,12], the survival after SPMs remains largely understudied. In this context, we hypothesized three key outcomes. First, the presence of SPMs reduces the survival in MCL patients compared to those without SPM. Second, MCL patients with SPMs experience worse survival than individuals with a similar primary malignancy and third, patients with a SPM have a higher risk of dying from MCL due to difficulties in tolerating treatments or impaired health status.

The objectives of this study were to determine whether the diagnosis of SPM affects survival in MCL patients and to compare survival for patients with SPMs secondary to MCL to patients with same malignancy type but without prior lymphoma. Additionally, we sought to identify potential factors that may contribute to variations in survival.

Materials and methods

Study populations

All patients diagnosed with MCL between 2000 and 2020 in Denmark and 2000–2017 in Sweden and aged ≥18 years at diagnosis were identified from the Danish National Lymphoma Registry and the Swedish Cancer Registry, respectively. In Sweden, information on clinical characteristics and treatment data were retrieved from the Swedish Lymphoma Register (SLR) [13]. Furthermore, clinical information and treatment data were collected with more granularity for Swedish patients from 2007 onwards in a nationwide medical record review [14]. Swedish patients were linked to the Swedish Patient Register, which tracks hospitalizations and specialist visits, to gather data on comorbid diseases occurring within 10 years prior to MCL diagnosis. Comorbidities were assessed using the Charlson comorbidity index (CCI) until six months prior to the first diagnosis of MCL. Additional information on highest attained education level and emigrations was obtained from national databases, and the Swedish Cause of Death Register provided dates and causes of death for all individuals. Similarly, in Denmark, data were sourced from the Danish Lymphoma Registry to gather treatment, clinicopathological information, death, and treatment outcomes, while SPMs were obtained from the Danish Cancer Registry. Finally, the Danish National Patient Register, which contains data on all in- and outpatient contacts in Denmark, was utilized to assess comorbidities, and the Danish Education Register to assess educational levels [15,16]. In both countries, reporting any cancer diagnosis to the national board registries is mandatory by law, with nearly complete coverage.

For comparison of MCL patients with and without SPM, the study population included all patients described above. The follow-up period started from the date of MCL diagnosis and continued until death, emigration, or the end of the study period, which was 31 December 2021 in Denmark and 31 December 2019 in Sweden.

To compare MCL patients who developed SPM to individuals from the general population with a primary malignancy, we included all MCL patients who developed at least one SPM during follow-up. These patients were then matched with individuals from the general population (comparators) who had a similar primary malignancy as the SPM of the index patient but without a history of lymphoma. Matching was performed without replacement in a 1:5 ratio on birth year, sex, malignancy type (using the International Classification of Diseases (ICD-10) codes), calendar year of SPM, and stage of the SPM/primary malignancy when diagnosed. Both patients and comparators were followed from the diagnosis of the SPM (or the malignancy for comparators) until end of follow-up.

Malignancies definition

SPM was defined as the first malignancy occurring at any time during follow-up after the MCL diagnosis. Among the comparators, malignancies were identified as the first malignancy diagnosed and recorded in the cancer registers using the ICD-10 codes. Certain malignancies were excluded as SPMs due to the high risk of

misclassifications of the initial MCL, including non-follicular lymphoma, unspecified types of NHL, CLL, malignant immunoproliferative diseases, mature T/NK cell lymphoma, and secondary unspecified malignant neoplasms of lymph nodes. SPMs and primary malignancies were stratified into hematologic (including MDS-AML) and solid cancers. Subgroup analyses were performed grouping malignancies in MDS-AML, solid cancers, and non-melanoma skin cancers.

Statistical analysis

All statistical analyses were conducted separately in each country following the same standardized statistical analysis plan. Median follow-up was estimated using the reverse Kaplan–Meier estimator. All-cause mortality was compared between MCL patients diagnosed with SPM and those without, considering SPM as a time-dependent exposure. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models, adjusted for age, sex, year of MCL diagnosis, CCI, educational level, MCL International Prognostic Index (MIPI [17]), and stage. In the Swedish data models, interactions between the time-dependent 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.

Overall survival (OS) was compared between MCL patients with SPM and the matched comparators from the general population. Multivariable all-cause mortality HRs were calculated with adjustments for age, sex, year of SPM/malignancy, and stage of SPM/malignancy.

The country-level HRs were combined to estimate pooled hazard ratios (pHRs) using the inverse variance weighted method with a random effect [18,19]. We quantified the between-country variability in the pHR by estimating the *I*-square (I^2, expressed as a percentage) quantifying the proportion of total variation in the estimated effects that are due to heterogeneity.

The proportion of patients with a history of cancer and their causes of death were descriptively summarized as trajectories evaluating the relationships between different stages and quantifying the flows from one stage to another in the Swedish data. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) [20].

Ethical considerations

The study was 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. In Denmark, the study was registered in the North Denmark Region (F2024-001). Ethical approval is not needed in Denmark for retrospective studies on registry data. All data were pseudonymized.

Results

MCL patients with and without SPM

A total of 1255 and 1839 MCL patients were included in Denmark and Sweden, respectively. The median ages at MCL diagnosis were 70 years in Denmark and 71 years in Sweden. Among the included patients, 234 (19%) in Denmark and 283 (15%) in Sweden developed at least one SPM. The median time from MCL diagnosis to SPM was three years (IQR: 1–6 years) in both countries. Patients with and without SPM were comparable regarding age at MCL diagnosis, sex, year of diagnosis, and educational level (Table 1). Considering SPM as time-dependent exposure, OS was significantly decreased in MCL patients with SPM (pHR = 1.6, 95% CI: 1.4–1.9; Denmark adjusted HR = 1.7, 95% CI: 1.4–2.0; Sweden adjusted HR = 1.6, 95% CI: 1.4–1.9), with no heterogeneity between countries (I^2 = 0). In both countries, there was increased mortality for patients with hematological SPMs. In Sweden, the adjusted HR among all hematological SPMs was 8.3 (95% CI: 4.9–13.9), while in Denmark, the only observed hematological SPMs were MDS-AML, with adjusted HR of 2.3 (95% CI 1.2–4.6). Patients with non-melanoma skin SPMs had a higher risk (adjusted HR = 1.5, 95% CI: 1.2–2.0), and those with other solid SPMs had double (adjusted HR = 2.1, 95% CI: 1.6–2.8) the mortality risk compared to patients without SPMs. The high mortality rate was observed across all variable strata, and in particular, a decreasing trend was observed for those with increasing age at MCL diagnosis, high MIPI, and advanced stage (Figure 1).

Using the Swedish cohort, we investigated whether SPM occurrence influenced MCL-specific mortality; we modeled SPM diagnosis as a time-dependent exposure and considered MCL-specific death as the event, adjusting for age, sex, calendar year, education level, MIPI score, CCI, and disease stage at MCL diagnosis. During the follow-up period, 65 MCL-related deaths occurred among 283 patients who developed SPM, compared with 634 MCL-related deaths among 1556 patients without SPM. We observed a slightly higher MCL-specific death rate in patients with SPM versus without SPM (crude HR = 1.33, 95% CI: 1.02 -1.73) that turned non-statistically significant (adjusted HR = 1.24, 95% CI: 0.95–1.62) after accounting for confounders.

Table 1. Baseline characteristics at mantle cell lymphoma (MCL) diagnosis describing MCL patients with and without second primary malignancy (SPM), followed from MCL diagnosis in Denmark (2000–2020) and Sweden (2000–2017).

		Denmark, *N* (col%)		Sweden, *N* (col%)	
		MCL without SPM	MCL and SPM	MCL without SPM	MCL and SPM
Overall		1021	234	1556	283
Age of MCL diagnosis, years, median (Q25–Q75)		70 (62–77)	70 (63–76)	72 (64.3–79.6)	71 (65.0–77.3)
Time since MCL diagnosis, years, median (Q25–Q75)		–	3.1 (1.4–6.0)	–	3.1 (1.1–5.7)
Age at MCL diagnosis	<60	194 (19.0)	37 (15.8)	253 (16.3)	37 (13.1)
	60–69	308 (30.2)	76 (32.5)	428 (27.5)	88 (31.1)
	70–79	321 (31.4)	89 (38.0)	504 (32.4)	113 (39.9)
	80+	198 (19.4)	32 (13.7)	371 (23.8)	45 (15.9)
Sex	Female	337 (33.0)	68 (29.1)	445 (28.6)	70 (24.7)
	Male	684 (67.0)	166 (70.9)	1111 (71.4)	213 (75.3)
Year of MCL diagnosis	2000–2004	80 (8.8)	30 (13.6)	324 (20.8)	47 (16.6)
	2005–2009	181 (19.8)	55 (25.0)	352 (22.6)	84 (29.7)
	2010–2014	265 (29.0)	68 (30.9)	524 (33.7)	106 (37.5)
	2015–end[a]	388 (42.5)	67 (30.5)	356 (22.9)	46 (16.3)
Highest achieved education level	≤9 years	338 (37.0)	68 (30.9)	600 (39.1)	102 (36.4)
	10–12 years	426 (46.6)	104 (47.3)	588 (38.4)	109 (39.0)
	≥13 years	150 (16.4)	48 (21.8)	345 (22.5)	69 (24.6)
	Missing	107	14	23	3
Charlson comorbidity index	0	576 (56.4)	144 (61.5)	775 (49.8)	151 (53.4)
	1	185 (18.1)	47 (20.1)	449 (28.9)	89 (31.4)
	2+	260 (25.5)	43 (18.4)	332 (21.3)	43 (15.2)
MIPI	High risk (≥6.2)	141 (14.3)	24 (10.6)	555 (35.7)	84 (29.7)
	Intermediate risk (5.7–6.1)	276 (27.9)	93 (41.0)	306 (66.4)	78 (78.8)
	Low risk (<5.7)	571 (57.8)	110 (48.5)	155 (33.6)	21 (21.2)
	Missing	33	7	540	100
Stage Ann Arbor	Ann Arbor I–II	98 (9.6)	27 (11.5)	238 (16.0)	44 (16.1)
	Ann Arbor III–IV	923 (90.4)	207 (88.5)	1253 (84.0)	230 (83.9)
	Missing			65	9
Radiotherapy	No	969 (94.9)	215 (91.9)	939 (90.4)	189 (91.7)
	Yes	52 (5.1)	19 (8.1)	100 (9.6)	17 (8.3)
	Missing			517	77
Chemo-immunotherapy	No	166 (16.3)	28 (12.0)	60 (5.1)	10 (4.4)
	Yes	855 (83.7)	206 (88.0)	1107 (94.9)	219 (95.6)
	Missing			389	54

[a]31 December 2020 in Denmark and 31 December 2017 in Sweden.

MCL patients with SPM compared to matched comparators with a similar primary malignancy

All 234 MCL patients with SPM in Denmark were successfully matched with 1170 comparators, while 265 patients were matched with 870 comparators in Sweden (Table 2). The median age at SPM was 74 (IQR: 68–79) years in Denmark and 76 (IQR: 70–81) years in Sweden. In both countries, the median follow-up for patients with SPM and comparators with cancer was approximately five years (Table 2). The most common SPMs were non-melanoma skin cancer, malignancies of male genital organs (including prostate), gastrointestinal, and respiratory tract. In total, 17 out of 499 patients developed secondary MDS-AML, accounting for 3.4% of all SPMs in both countries (Supplementary Table S1).

Stage at SPM/malignancy diagnosis was only available for solid malignancies. In Denmark, 75.2% of the solid SPMs for MCL patients were diagnosed at a localized stage, 5.6% at localized metastasis, and 3.4% with distant metastasis. In Sweden, these proportions were 68.3%, 7.9%, and 5.7%, respectively (Table 2). MCL patients had lower OS in Denmark and Sweden compared to the matched general population for all SPM types, including solid SPMs (Figure 2). In Denmark, the median OS for all types of SPMs was 4.3 years for MCL patients versus 8.2 years for comparators. The median OS for solid SPMs (excluding non-melanoma skin cancer) was 3.2 years in MCL patients versus 5.5 years for comparators. In Sweden, the median OS for all SPMs was 2.7 years for MCL patients versus 8.6 years for comparators. The median OS for solid SPMs (excluding non-melanoma skin cancer) was 4.0 years for MCL patients versus 10.9 years for comparators (Table 3). In Denmark, the median OS for MCL patients with MDS-AML as SPM from the time of MDS-AML was 10.1 months compared to 19.9 months in the comparator group. In Sweden, MCL patients with MDS-AML as SPM had a median OS of 4.4 months, with median OS not reached for comparators. Relative to comparators, SPMs in MCL patients were associated with increased mortality (pHR = 2.1, 95% CI 1.3–3.5, I^2 = 91.3%). This elevated risk was also observed for solid cancers excluding non-melanoma skin cancer (pHR = 1.7, 95% CI 1.1–2.7, I^2 = 82.4%), for non-melanoma skin cancer

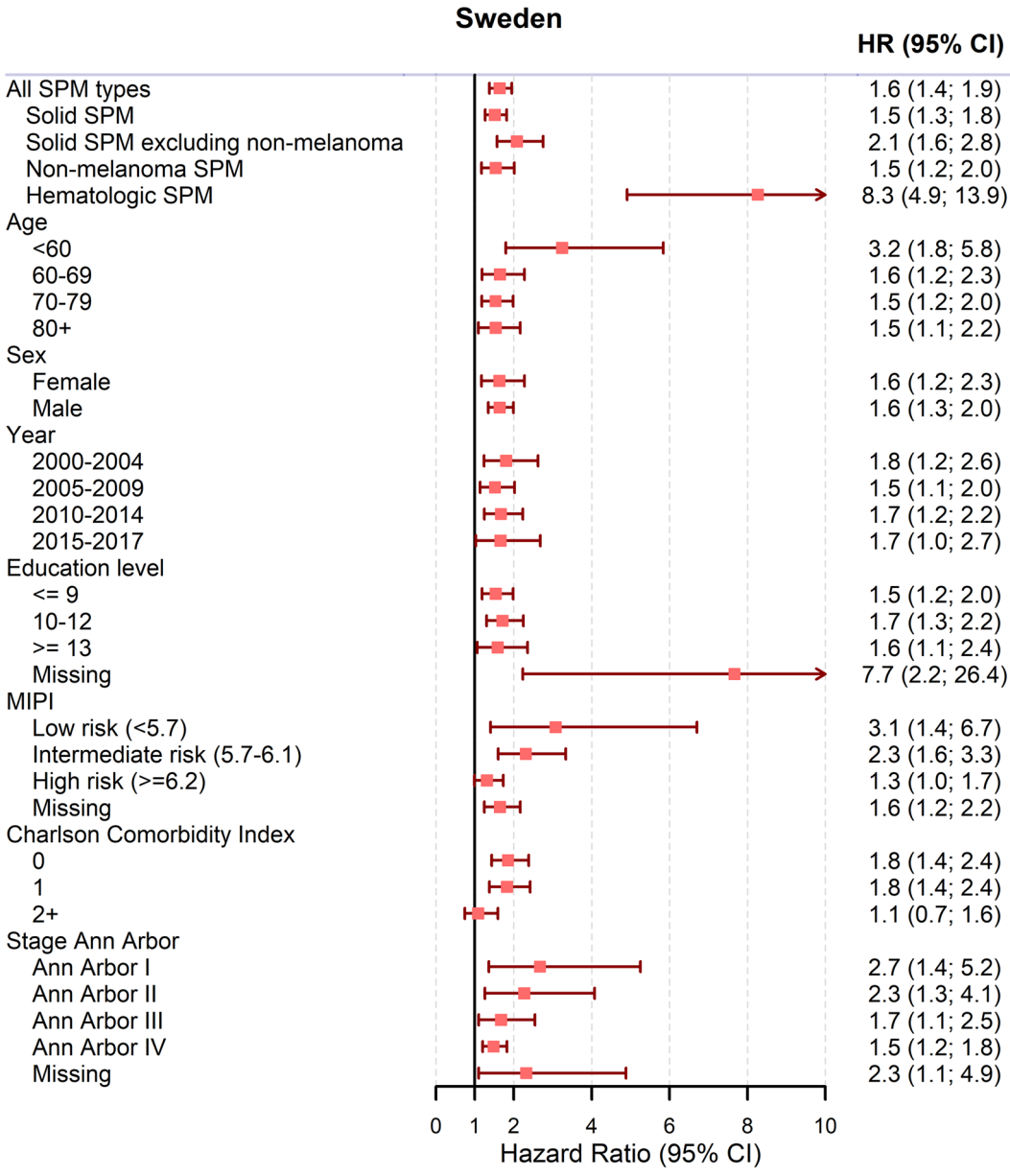

Figure 1. Adjusted all-cause mortality hazard ratios (HR) in Sweden, with 95% confidence intervals (95% CIs), comparing mantle cell lymphoma (MCL) patients with a second primary malignancy (SPM) versus those without SPM. The analysis is conducted overall, by type of SPM, and introducing interactions between age, sex, year, education level, MIPI, Charlson comorbidity index, and stage at MCL diagnosis and the time-dependent exposure SPM.

(pHR = 3.0, 95% CI 2.3–4.1, I^2 = 39.6%), and for hematological SPMs (pHR = 2.4, 95% CI 1.3–4.5, I^2 = 0%) (Figure 3).

Next, we investigated specific causes of death in the Swedish cohort. Among the 169 (60%) patients with MCL and SPM who died during follow-up, 26 (9%) died from hematological malignancies (excluding MCL), 39 (14%) from solid cancers, 65 (23%) from their underlying MCL, and 32 (11%) from cancer-unrelated causes (Figure 4). Among MCL patients with SPMs, eight (2.8%) had a history of cancer prior to their MCL diagnosis, while 275 (97.2%) did not (Figure 4). Among MCL patients with skin SPMs, 36 (47%) died from MCL and only five (6.5%) died from the skin cancer. For MCL patients with either a solid SPMs or a hematologic SPMs, the primary cause of death was the solid cancer (38 out of 89, 43%) and the hematological malignancy (11 out of 20, 55%), respectively (Supplementary Table S2). The higher mortality in MCL SPM patients was consistent across sex, age, and year of SPM diagnosis (Figure S1). MCL patients diagnosed with distant metastasis SPMs had especially increased mortality compared to comparators (pHR = 4.0, 95% CI: 2.3–7.1, I^2 = 0, Figure S1).

Table 2. Baseline characteristics of MCL patients with second primary malignancy (SPM) and general population comparators without history of lymphoma at inclusion (date of SPM for MCL patients and date of first malignancy for the matched comparators) in Denmark and in Sweden.

		Denmark		Sweden	
		Matched comparators without lymphoma (%)	MCL patients with SPM (%)	Matched comparators without lymphoma (%)	MCL patients with SPM (%)
Overall, *N*		1170	234	870	265
Age, years, median (Q25–Q75)		74 (68–79)	74 (68–79)	76 (72–81)	76 (70–81)
Follow-up, years, median (95% CI)[a]		5.1 (4.7–5.4)	4.8 (4.0–5.9)	4.5 (4.1–5.2)	4.6 (3.7–6.7)
Time since MCL diagnosis, years, median (Q25–Q75)		–	3.1 (1.4–6.0)	–	2.8 (1.1–5.6)
Age at SPM/malignancy	<60	82 (7.0)	16 (6.8)	26 (3.0)	12 (4.5)
	60–69	253 (21.6)	49 (20.9)	118 (13.6)	53 (20.0)
	70–79	560 (47.9)	116 (49.6)	445 (51.1)	127 (47.9)
	≥80	275 (23.5)	53 (22.6)	281 (32.3)	73 (27.5)
Sex	Female	340 (29.1)	68 (29.1)	198 (22.8)	65 (24.5)
	Male	830 (70.9)	166 (70.9)	672 (77.2)	200 (75.5)
Year of SPM/malignancy diagnosis	2000–2004	39 (3.3)	8 (3.4)	31 (3.6)	11 (4.2)
	2005–2009	132 (11.3)	26 (11.1)	124 (14.3)	41 (15.5)
	2010–2014	287 (24.5)	58 (24.8)	237 (27.2)	72 (27.2)
	2015–end[a]	712 (60.9)	142 (60.7)	478 (54.9)	141 (53.2)
SPM/malignancy stage at diagnosis	Localized	908 (77.6)	176 (75.2)	691 (79.4)	181 (68.3)
	Local metastasis	75 (6.4)	13 (5.6)	40 (4.6)	21 (7.9)
	Distant metastasis	49 (4.2)	8 (3.4)	35 (4.0)	15 (5.7)
	Not applied or missing	104 (8.9)	26 (11.1)	103 (11.8)	46 (17.4)
	Unmeasured	34 (2.9)	11 (4.7)	1 (0.1)	2 (0.8)

MCL: mantle cell lymphoma; Q25–Q75: distribution quantiles 25% and 75%.
[a]Median follow-up in year from a reversed Kaplan–Meier's estimate.

Sensitivity analyses were conducted where different exclusion periods were applied, considering only SPM occurring after one, two, and five years after the MCL diagnosis to allow for different treatment intervention effects prior to the SPM diagnosis. These analyses were conducted using only the Swedish cohort, and results were aligned with the main finding of excess risk of death in MCL SPM patients relative to comparators (Supplementary Table S3).

Discussion

In this two-nationwide population-based study, we investigated the previously unexplored impact of SPMs on survival in MCL patients, and the effect of a prior MCL on survival following the SPM. MCL patients who developed SPMs showed a particularly poor survival, compared to both MCL patients without SPMs and matched comparators with similar malignancies but no history of lymphoma. An increased all-cause mortality was observed across all SPM types. MCL patients with SPMs had a twofold higher mortality than non-lymphoma comparators with a similar malignancy.

The median OS for MCL patients is approximately five years from diagnosis [14]. While MCL is considered incurable, some patients achieve prolonged remission following first-line chemoimmunotherapy. However, many require multiple lines of treatment, increasing their exposure to alkylating agents and radiation, which heightens their susceptibility to SPMs. The lower survival rates observed in MCL patients with SPMs, compared to those without SPMs may reflect the combined impact of aggressive treatments, the compromised immune system, the potential of clonal evolution due to chemotherapy [8], and the risk of dying from the SPM. Notably, while there is higher mortality among MCL patients with non-melanoma skin cancer compared with the general population, further investigation indicated that MCL itself was the primary cause of death in 47% of these cases, with only 6.5% due to skin cancers. Therefore, the increased mortality observed in non-melanoma skin cancers is likely driven by the underlying lymphoma rather than by skin cancer itself.

In general, only a handful of studies regarding SPM survival in lymphoma patients have previously been reported and findings suggest poorer OS rates. For instance, in classical Hodgkin lymphoma (cHL), OS is worse for cHL patients with SPMs after 11 years of follow-up and developing SPM is an independent adverse prognostic factor [21]. Although MCL is a non-curable disease, the burden of SPM is as frequent as in the highly curable subtype of cHL [22,23]. A worse OS among HL patients with second primary head and neck cancer [24], breast [25], and lung cancer [26] has previously been described. However, we acknowledge that HL and MCL patient populations differ significantly in terms of age at diagnosis,

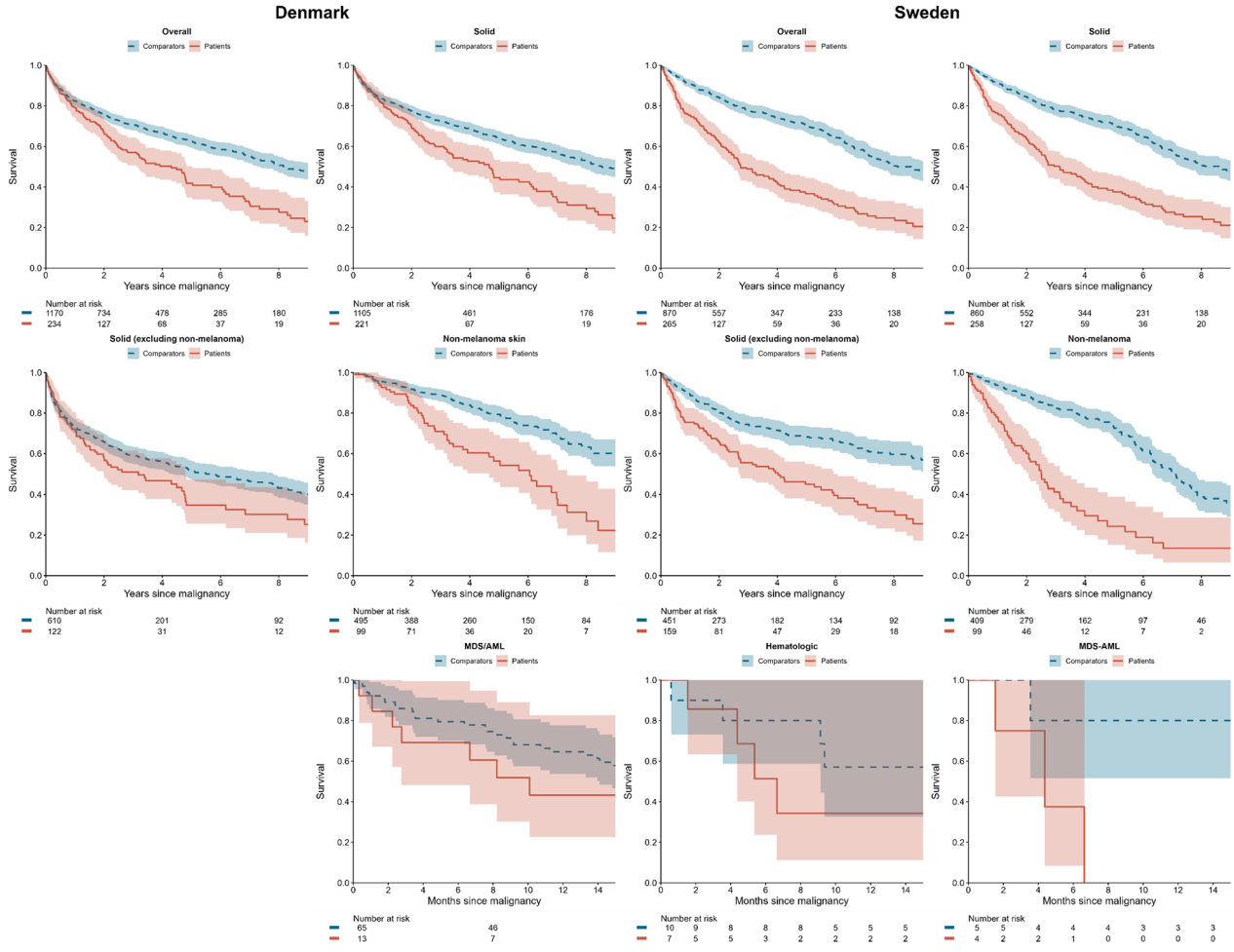

Figure 2. Overall survival with 95% confidence interval after diagnosis of second primary malignancy (SPM) in MCL patients (red, solid line) and after first malignancy for the matched background population comparators (blue, dashed line) without a history of lymphoma, in Denmark (left panel) and in Sweden (right panel). Time on the *x*-axis is measured in years except for MDS-AML or hematologic SPMs where *x*-axis is measured in months. Hematologic: includes four MDS-AML and three others hematologic in Sweden.

Table 3. Overall survival at different time points after diagnosis of second primary malignancy (SPM) in MCL patients and after first malignancy for the matched background population (comparators) without a history of lymphoma in Denmark and in Sweden.

	Denmark					
	Overall		Solid including non-melanoma skin		Solid excluding non-melanoma skin	
Overall survival at:	MCL patients with SPM	Matched comparators without lymphoma	MCL patients with SPM	Matched comparators without lymphoma	MCL patients with SPM	Matched comparators without lymphoma
2 years, % (95% CI)	66.6 (60.3–72.9)	75.8 (73.3–78.3)	69.5 (63.1–75.8)	77.6 (75.0–80.1)	57.6 (48.4–66.8)	65.8 (61.9–69.7)
5 years, % (95% CI)	41.8 (34.2–49.5)	62.5 (59.4–65.7)	44.6 (36.7–52.6)	64.3 (61.1–67.5)	34.7 (24.1–45.4)	51.7 (47.2–56.3)
8 years, % (95% CI)	29.1 (20.8–37.4)	51.0 (47.1–54.8)	31.1 (22.3–39.8)	52.5 (48.6–56.5)	30.2 (19.3–41.2)	43.1 (38.0–48.2)
Median survival (years)	4.3 (3.1–5.0)	8.2 (7.3–9.7)	4.7 (3.3–6.1)	8.6 (7.8–9.9)	3.2 (2.0–4.8)	5.5 (4.4–7.8)
			Sweden			
2 years, % (95% CI)	62.1 (56.2–68.5)	84.1 (81.5–86.7)	63.7 (57.9–70.2)	84.4 (81.8–87.0)	65.9 (58.6–74.0)	80.4 (76.6–84.4)
5 years, % (95% CI)	36.7 (30.2–44.4)	70.1 (66.6–73.9)	37.6 (31.1–45.6)	70.4 (66.9–74.2)	44.9 (36.7–54.9)	68.3 (63.5–73.5)
8 years, % (95% CI)	24.7 (18.5–33.1)	50.4 (45.8–55.5)	25.4 (19.0–33.9)	50.5 (45.9–55.6)	31.7 (23.3–43.1)	59.7 (54.1–65.9)
Median survival (years)	2.7 (2.4–4.0)	8.6 (7.3–10.0)	3.1 (2.5–4.0)	8.6 (7.3–10.0)	4.0 (2.7–6.1)	10.9 (9.3–13.1)

radiotherapy exposure, and treatment lines received, making a direct comparison of SPM burden and outcomes less optimal.

There are also a few studies on NHL [27,28] and chronic myeloid leukemia [29] survivors where decreased survival were shown for those who developed SPMs. Smeland

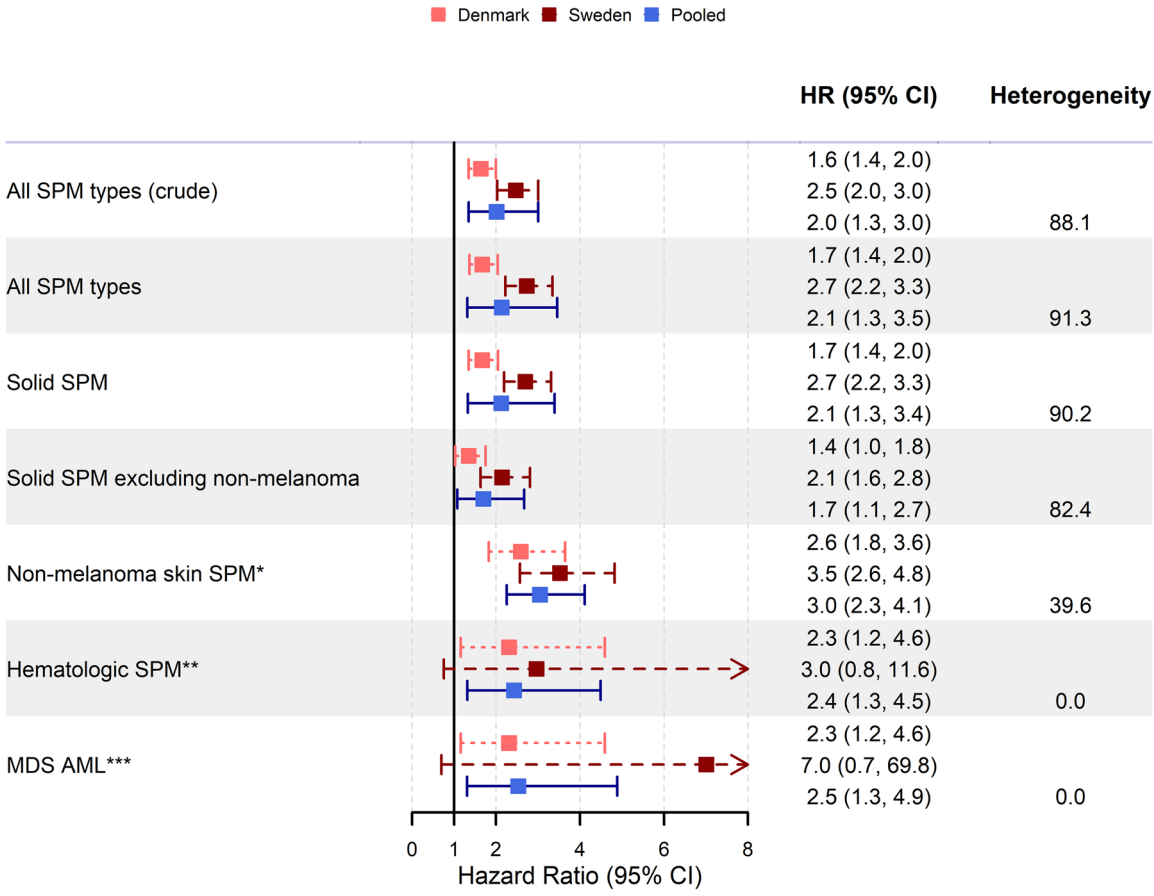

Figure 3. Crude and adjusted all-cause mortality hazard ratio (HR) and pooled hazard ratios (for both countries) with 95% confidence interval after diagnosis of second primary malignancy (SPM) in MCL patients versus after first malignancy for the background population (comparators) without a history of lymphoma in Denmark and Sweden. HR adjusted for age, sex, and year of SPM in Denmark; age, sex, year of SPM, and SPM/malignancy stage at diagnosis in Sweden. *Non-melanoma skin SPM model adjusted for sex, year, and SPM/malignancy stage at diagnosis (for Sweden). **Hematologic SPM model adjusted for age, sex, and year at SPM/malignancy diagnosis (for Sweden). ***Crude (non-adjusted) HR for MDS AML (for Sweden), due to too few events Heterogeneity: between country heterogeneity reported as I^2 (%).

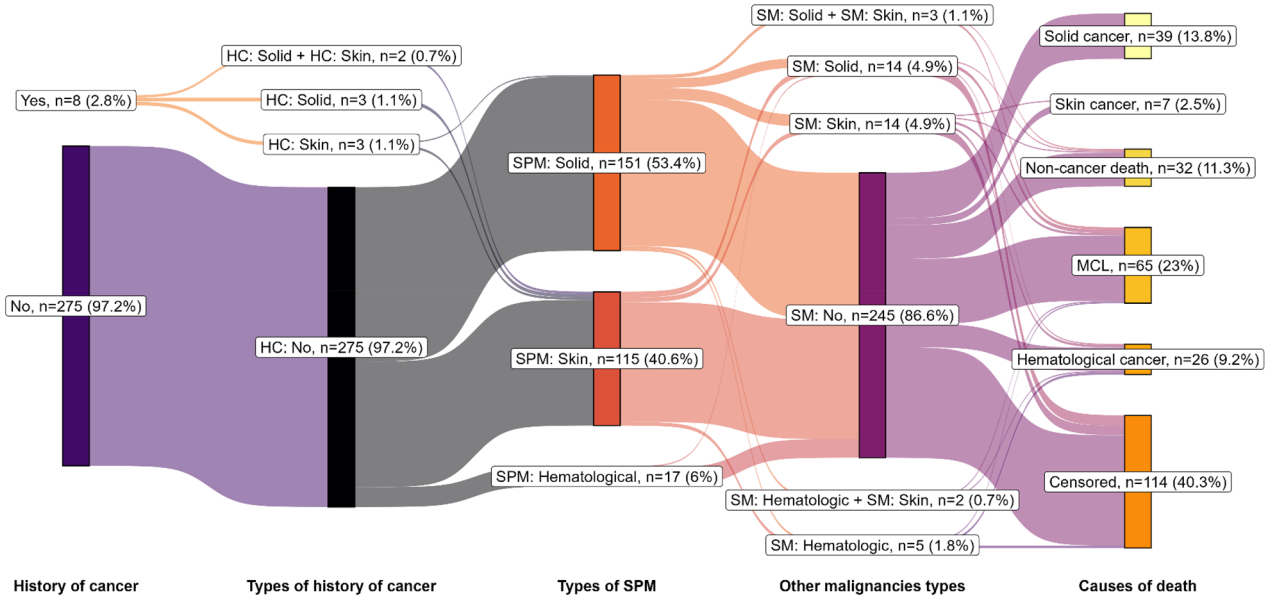

Figure 4. Trajectories in history of cancer (HC) and types of HC, type of second primary malignancy (SPM), other secondary malignancies (SM), and cancer causes of death in mantle cell lymphoma (MCL) patients with SPM in Sweden. The 'Censored, n = 114 (40.3%)' group refers to patients with no death record available, meaning they are supposed to be alive at the time of the last linkage.

et al. found that SPMs accounted for 7% of deaths among NHL patients receiving high-dose therapy and autologous transplant, which made it the second most prevalent cause of death [30]. Among patients with CLL and follicular lymphoma who developed SPMs, studies have reported higher cancer-related mortality ratios (standardized mortality ratios (SMRs) ranging from 2 to 54) compared to cancer-related mortality in the general population [31–33]. However, it is important to note that these findings may have been overestimated, as their comparisons were made to the general population. In contrast, our study compared MCL patients with versus without SPMs, as well as to individuals from the general population who had the same type of cancer as the SPM.

In the specific context of MCL, our study is the first to report a reduced survival rate in patients with SPMs. Secondary MDS-AML in MCL patients was especially associated with exceedingly poor survival, with median OS of only 4.4 months and 10.1 months in Sweden and Denmark, respectively. The difference between the countries in OS after MDS-AML could reflect differences in the types of MDS discovered; although, secondary MDS-AML generally has a poor prognosis. Numerical differences may also be explained by the small number of patients with this type of SPM and the MCL disease status at the time of MDS-AML may also impact the prognosis. Furthermore, secondary MDS-AML typically presents with high-risk cytogenetic abnormalities, whereas a substantial proportion of de novo MDS-AML cases in the comparator population may have lower-risk disease.

Given the rarity of MCL, we deemed it appropriate to compare MCL patients with SPM to non-lymphoma comparators, by balancing the two groups on age, sex, year, SPM types, and stage using matching. Our findings revealed a twofold higher risk of mortality in the MCL SPM group, furthermore, distant metastasis at the time of SPM diagnosis was associated with the poorest survival, independent of age, sex, or year of diagnosis, highlighting the significant morbidity burden of MCL on post-SPM survival.

One limitation of our study was the lack of data on whether the observed SPMs were treated and when the SPMs occurred in relation to MCL treatments. To address potential biases related to timing of SPM and MCL treatment lines, we performed sensitivity analyses applying different exclusion periods based on typical MCL treatment trajectories [14]. Exclusion windows of 1, 2, and 5 years were selected to reflect the completion of first-line therapy, the occurrence of disease progression, and response to treatment, respectively. Across all analyses, the increased mortality risk associated with SPMs remained consistent, supporting the robustness of our findings regardless of when SPMs occurred or variations in prior treatments. However, we emphasize that this approach does not fully account for the impact of specific treatment lines or intensity on SPM development. Future studies that incorporate detailed information on treatment regimens, number of therapy lines, and cumulative doses are needed to more accurately evaluate the effects of treatment type on the risk of SPMs in MCL patients. Furthermore, elderly patients, who already have a reduced life expectancy, may be receiving palliative care, making the diagnosis of a SPM less impactful on survival. Interpretation is also challenged by limitations in the causes of death data; in Denmark, the Danish causes of death register is not suitable for an in-depth analysis in this context, while in Sweden, where cause of death is often reported, the validity of death records for patients with multiple cancers can be questionable.

To our knowledge, this study represents the largest and most comprehensive investigation into survival in MCL patients with SPMs, comparing them to both MCL patients without SPMs and to non-lymphoma matched comparators.

These findings also have broader implications for other lymphoma patients. Conducting similar analyses in patients with indolent lymphomas, which are typically treatable but not curable and with many long-term survivors at risk of SPM, would moreover provide valuable insights.

Conclusions

MCL patients with SPMs experience significantly worse survival compared to MCL patients without SPMs, and when compared to matched comparators from the general population with similar malignancies without lymphoma. This emphasizes that the occurrence of SPM is a severe outcome in MCL patients, contributing to mortality from both SPM and MCL, and underscores the need for further studies on optimal management of these challenging clinical scenarios. Finally, our study highlights the value of real-world data in understanding rare diseases and suggests future investigations to explore similar patterns in other cancer subtypes.

Author contributions

KDA, TT, IG, TCE, JB, SE, KES, MJ, PB, TSL, KG, and SP designed the study. KDA, TT, and JB independently performed and reviewed the statistical analyses. SE critically reviewed the statistical methods. KDA, IG, and TT wrote the paper. All authors interpreted the data, provided input for the manuscript, and approved the final version.

Disclosure statement

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Data availability statement

Our study's data come from nationwide registers, as detailed in 'Materials and methods' section. Access to this data is subject to national data protection laws, but it can be obtained from the Swedish and Danish Authorities following granted applications to Privacy Protection and the respective ethical boards. Interested researchers can contact the principal investigator (IG, ingrid.glimelius@igp.uu.se) for collaborative research projects (Sweden) or Tarec El-Galaly (tarec.galaly@clin.au.dk) (Denmark), provided they do not overlap with ongoing projects. The statistical analysis plan is accessible to anyone.

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