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ORIGINAL PAPER

Survival of patients with mantle cell lymphoma in the rituximab era: Retrospective binational analysis between 2000 and 2020

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Summary

Mantle cell lymphoma (MCL) is a rare peripheral B-cell lymphoma characterised by eventual relapse and progression towards a more aggressive disease biology. With the introduction of rituximab- and cytarabine-based immunochemotherapy regimens, the prognosis of the disease has changed dramatically over the last two decades. To assess the real-world survival of patients with MCL, we used a population-based cohort of 564 patients with MCL who were diagnosed and treated between 2000 and 2020. Patient data were collected from seven Finnish treatment centres and one Spanish treatment centre. For the entire patient population, we report a 2-year overall survival (OS) rate of 77%, a 5-year OS of 58%, and a 10-year OS of 32%. The estimated median OS was 80 months after diagnosis. MCL is associated with increased mortality across the entire patient population. Additionally, we assessed the survival of patients after MCL relapse with the aim of establishing a cut-off point of prognostic significance. Based on our statistical analysis of survival after the first relapse, disease progression within 24 months of the initial diagnosis should be considered as a strong indicator of poor prognosis.

KEYWORDS
lymphoma, mantle cell lymphoma, POD, real-world data, survival

INTRODUCTION

Mantle cell lymphoma (MCL) is a rare subtype of peripheral B-cell lymphoma originating from mantle-zone B cells of the lymph node. It is characterised by the overexpression of cyclin D1, which is associated with the t(11;14)(q13;q32). Patients diagnosed with MCL are typically over 60 years of age, and approximately two out of three are male.[1] In Finland, the annual incidence of MCL in 2019 was 110 cases, with 79 cases in men and 31 in women.[2]

According to the WHO classification, MCL is categorised into four main subgroups. The nodal subtype comprises 80%–90% of MCL cases and can be further categorised into conventional, pleomorphic, and blastoid variants of differing morphologies. The remaining 10%–20% of cases represent the leukaemic non-nodal subtype, which is a more indolent type with improved prognosis. Several prognostic markers have been suggested for assessing the prognosis of patients with newly diagnosed MCL. The MCL international prognostic index (MIPI) and tumour cell proliferation rate, measured by Ki-67 immunohistochemistry, are used as independent prognostic tools that guide treatment decisions for patients eligible for chemoimmunotherapy.[1] Furthermore, the testing for *SOX-11* has enabled reliable identification of the subset of patients that can be safely monitored for years before initiating treatment, as the lack of *SOX-11* overexpression generally implies an indolent subtype of the disease.[3] Finally, after active treatment, the presence of minimal residual disease is associated with inferior progression-free survival (PFS) and overall survival (OS).[4]

Mantle cell lymphoma has been associated with poor survival outcomes. Before the introduction of the monoclonal CD20 antibody rituximab in the late 1990s, the median first-line OS of patients with MCL was 2–3 years.[5,6] The introduction of rituximab, a high-dose (HD) cytarabine, and autologous stem cell transplantation-based regimens into clinical practice has enabled considerable improvement in patient survival. For example, in the Nordic MCL2 trial, the 10-year survival was 58%.[7] In the early reports from the Nordic MCL trials, the survival curve appeared to reach a plateau, suggesting that some patients could be cured of the disease.[8] However, during long-term follow-up, further late relapses were detected.[7,9] Despite the significant advances in both diagnostics and treatment, MCL remains an incurable disease that is characterised by inevitable relapses, shortened periods of remission, and progression towards a more aggressive morphology.[1]

The treatment guidelines for MCL are based on clinical trials including participants who are often younger and healthier than real-world patients with better access to treatment. Moreover, as MCL mostly affects the elderly population, a significant proportion of patients are not eligible for intensive treatment protocols. To the best of our knowledge, information on real-life survival outcomes of patients with MCL using existing treatments is limited, and there is scarce understanding about survival after the first relapse. In this large, retrospective binational analysis, we aimed to explore the real-life survival outcomes of patients with MCL diagnosed and treated in the era of rituximab and HD therapy with autologous stem cell transplantation (ASCT). We also aimed to explore survival patterns after first-line treatment and establish a prognostic cut-off point for early relapse.

METHODS

Data collection

The data collection for this retrospective registry study was approved by the Finnish Social and Health Data Permit Authority in September 2020 (THL/2791/14.02.00). Data were collected between September 2020 and February 2022. The following eight Finnish hospitals and one Spanish hospital participated in the study: Kuopio, Oulu, Tampere, and Turku University Hospitals and Central Hospitals in Jyväskylä; Joensuu (North Karelia); Mikkeli; and Germans Trias i Pujol Hospital in Badalona, Spain.

The medical records of patients with MCL were reviewed for basic patient information, diagnostic information related to MCL, parameters for calculating MIPI, and extensive records of relapses and treatment lines received. In total, 564 patients with a histologically confirmed MCL diagnosis between 2000 and 2020, who had completed first-line treatment by June 2021, were included in the study. Of these, 523 were from Finland and 41 were from Spain. The population coverage for the Finnish and Spanish hospitals participating in the study was 3.3 million and 700 000 patients, respectively.

Statistical analysis

Descriptive and exploratory statistics were reported from the collected data and demographic variables. The MIPI score was calculated for all patients with sufficient information available from the medical records, which comprised 455 patients. OS was calculated from the date of diagnosis to the last follow-up date for patients that were alive at the time of the data collection, and from the date of diagnosis to the date of death from any cause for patients that had died prior the data collection. For disease-specific survival (DSS), the end-points considered were similarly the last follow-up date for living patients, and the date of death from MCL for patients that had died. Age- and sex-standardised net survival (NS) was calculated using background population data from Finland and Spain. Survival after the first and second relapse was calculated from the date of relapse to the last follow-up date for living patients, and to the date of death for patients that had died. In estimating MCL-specific mortality, death from MCL was considered as an event of interest and death from any other cause was considered to be a competing event. When calculating the cumulative incidence of other-cause

mortality, death from any other cause was considered an event of interest and death from MCL was considered a competing event.

Progression of disease (POD) after first-line treatment was calculated at 12-month intervals up to 5 years from the date of diagnosis (POD12 to POD61+) to identify a prognostic cut-off point for early progression of disease. All survival, POD24, and excess hazards were estimated using the multidimensional penalised spline model.[10] A log-rank test was performed to assess the statistical significance of factors affecting survival. Pearson's chi-squared test was used to assess the statistical significance of the prognostic factors.

Statistical analysis was conducted using IBM SPSS Statistics version 27.0 (IBM Corp, Armonk, NY, USA) and R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). A P value less than 0.05 was considered significant.

RESULTS

Patient characteristics and treatment

In our study population, 411 (72.9%) of patients were male and 153 (27.1%) were female. Median age at diagnosis was 70 years (range: 27–92 years). Most of the patients presented with advanced stage IV disease (65.2%) and were considered high-risk based on MIPI. For all the patients included in the study, a diagnosis of MCL that was confirmed by a pathologist was required; however, in 389 patients (70.0%) we were unable to obtain further details on the histological subtype. Therefore, the histological subtype was excluded from the survival analysis. The patient characteristics are summarised in Table 1. Patterns of relapse, survival, and treatment lines are illustrated in a flow chart (Figure 1). Patient characteristics by treatment era are available in Table S1.

Chemotherapy was administered to 517 (91.7%) patients. Rituximab was administered to a total of 489 (86.7%) patients as first-line treatment, and a total of 161 (28.6%) patients underwent maintenance rituximab therapy after the first-line treatment. Table 2 summarises the use of chemotherapy, rituximab, and rituximab maintenance therapy.

The treatments administered were classified into five main subcategories as follows: MCL2-like treatments comprising the Nordic MCL regimen and equivalent therapies aimed at ASCT, the Finnish elderly regimen (MCL-FI), the CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone)-like regimens, and bendamustine. All patients undergoing other treatment regimens or more than one type of first-line treatment were classified as "other". The treatment categories and number of patients undergoing each treatment are described in Table 3.

None of the patients in this study population underwent targeted therapy as the first-line treatment, and the use of targeted therapies was generally limited during the entire follow-up period. Later treatment lines combined, ibrutinib, bortezomib and lenalidomide was given to a total of 35, 24 and four respective patients.

TABLE 1 Patient characteristics

Variable	No (564)
Age (median)	70
Age (range)	27–92
<65	192 (34.0%)
65–74	183 (32.5%)
≥75	189 (33.5%)
Sex	
Female	153 (27.1%)
Male	411 (72.9%)
Stage	
I	29 (5.1%)
II	43 (7.6%)
III	92 (16.3%)
IV	368 (65.3%)
Missing	32 (5.7%)
MIPI	
Low	57 (10.1%)
Intermediate	156 (27.7%)
High	240 (42.5%)
Missing	111 (19.7%)
LDH	
Normal	272 (48.2%)
Elevated	237 (42.0%)
Missing	55 (9.8%)
WBC count	
Normal	289 (51.2%)
Elevated	222 (39.4%)
Missing	53 (9.4%)
B symptoms	
No	307 (54.5%)
Yes	210 (37.2%)
Missing	47 (8.3%)

Abbreviations: LDH, lactate dehydrogenase; MIPI, mantle cell lymphoma international prognostic index; WBC, white blood cell.

Survival after MCL diagnosis

Figure 2 shows the survival times and patterns observed in our study. For the entire patient population, we report a 2-year OS of 77%, a 5-year OS of 58% and a 10-year OS of 32%. The estimated median OS was 80 months [95% confidence interval (CI): 68.9–91.1]. NS rates at 2, 5 and 10 years were 82% (95% CI: 78.1–85.5), 66% (95% CI: 60.0–70.5), and 50% (95% CI: 42.6–56.9), respectively. DSS rates were slightly lower than the NS rates at

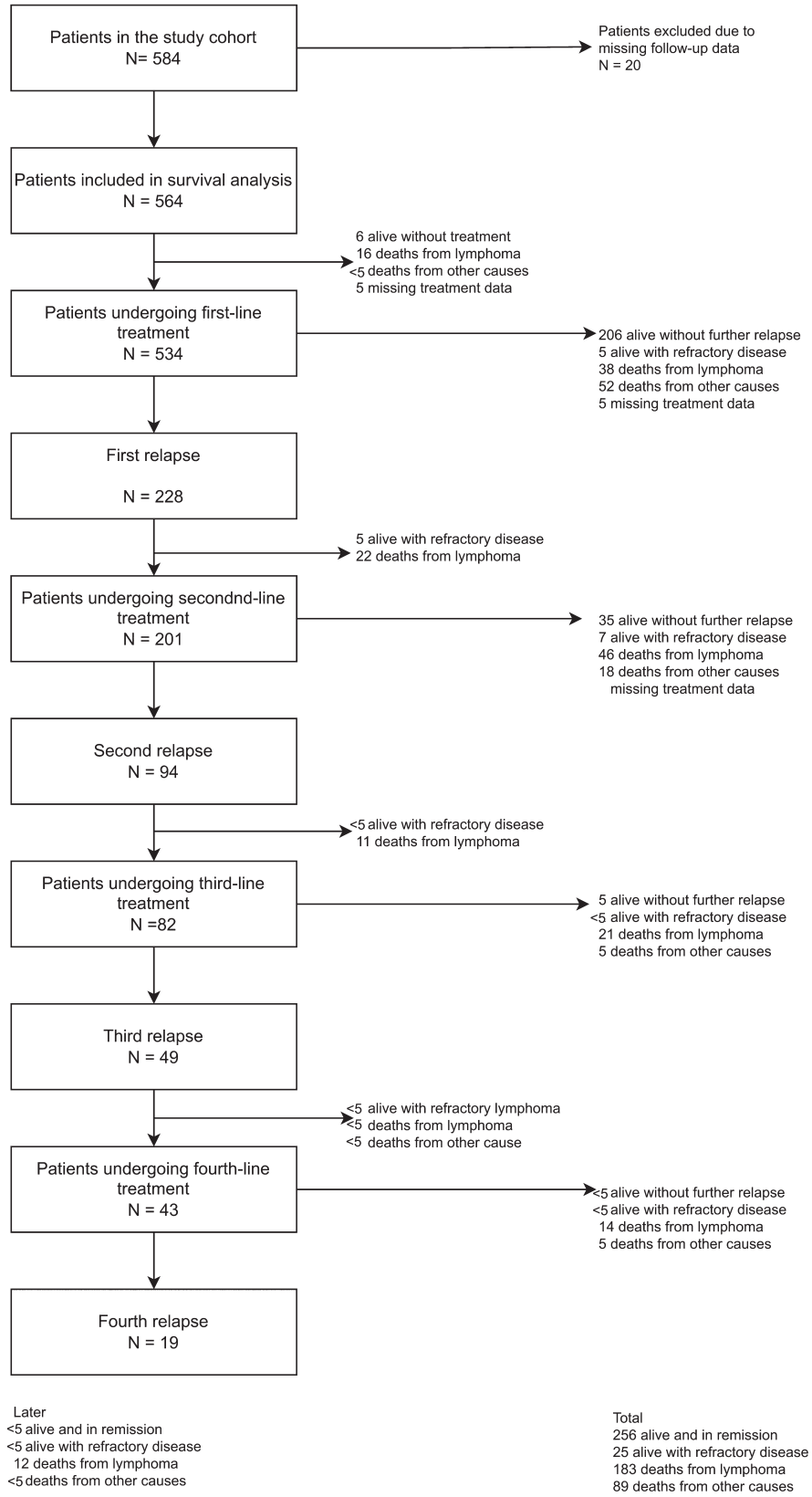

FIGURE 1 Flow chart of the patterns of relapse, survival, and treatment lines

84%, 68%, and 47% at the respective time points. The estimated median DSS was 115 months (95% CI: 97.0–133.0). Survival is shown in Figure 2A. Excess mortality (Figure 2B) from MCL was observed during the entire 10-year follow-up period, and the cumulative incidence (C) of MCL deaths was 45% (95% CI: 39.6–50.4). The risk of death from MCL (Figure 2D) was greater

during years 0–2 after diagnosis and from year 6 onwards. Kaplan-Meier analysis illustrating the OS and DSS are provided in supplementary file (Figures S1 and S2).

Survival after the first and second relapse

The OS and DSS rates after the first and second relapses are shown in Figure 3. The median OS and DSS were 18 (CI 95%: 13.0–23.0) and 27 (CI 95%:17.3–36.7) months, respectively, after the first relapse (Figure 3A), and seven (CI 95%: 3.5–10.5) and 15 months (CI 95%: 8.5–21.5), respectively, after the second relapse (Figure 3B). Kaplan-Meier analysis on OS and DSS after first and second relapse are available in supplementary file (Figures S3–S6).

TABLE 2 The administration of chemotherapy, rituximab and ASCT

Total patients undergoing chemotherapy (chemo vs. no chemo)	517
Total patients treated with rituximab and first-line chemotherapy	489
Total patients undergoing maintenance rituximab after first-line treatment[a]	161
MCL2-like	70 (43.5%)
MCL-FI	23 (14.3%)
CHOP-like	15 (9.3%)
Bendamustine	10 (6.2%)
Other[b]	43 (26.7%)
Total patients treated with maintenance rituximab after ASCT	36

Abbreviations: ASCT, autologous stem cell transplantation; CHOP, rituximab cyclophosphamide doxorubicine vincristine and prednisone; MCL, mantle cell lymphoma.

[a]Ten patients discontinued the maintenance treatment prematurely because of adverse effects.

[b]To ensure patient anonymity and privacy, populations of less than five patients were included in the 'Other' category.

Effect of age in MCL survival

The prognostic effects of age and patterns of excess mortality in our study population are shown in Figure 4. For patients under 65 years of age, the estimated median OS was 125 months (CI 95%: 156.4–93.6), and the DSS was 171 months (CI 95%: 218.5–123.5). The 2-year OS was 92%, 5-year OS was 75%, and 10-year OS was 54%. The estimated median OS was 93 months (CI 95%: 106.3–79.7), and the DSS was 117 months (CI 95%: 139.1–94.9) for patients aged between 65 and 74 years, and the 2-, 5- and 10-year OS were 80%, 65%, and 27%, respectively. For patients aged 75 years or older, the estimated median OS was 37 months (CI 95%: 42.5–31.5), and the DSS was 54 months (CI 95%: 73.0–35.0). In this age group, the two-, five- and 10-year survivals were 60%, 33%, and 11%, respectively (Figure 4A,C,E). Excess mortality over the follow-up period was observed regardless of the age group (Figure 4B,D,F). Kaplan-Meier analysis on OS and DSS by age groups is available in supplementary file (Figures S7 and S8).

Prognostic effect of early relapse

Early relapse within 24 months of completing first-line treatment was associated with statistically significant worse

TABLE 3 Overview of first line chemotherapies

Treatment name	Example regimen	No (564)
MCL2-like[a]	3 × R-maxi-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone) *alternating* 3 × R- HD-Arac (rituximab, high-dose cytarabine) + 1 × HD-BEAM (carmustine, etoposide, cytarabine, melphalan) + ASCT	221
MCL-FI	4 × R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone) *alternating* 4 × R-fludarabine-Arac (rituximab, fludarabine, cytarabine) + 2 × CHOP (cyclophosphamide, doxorubicine, vincristine and prednisone) + rituximab maintenance therapy up to 2 years	39
CHOP-like	6 × cyclophosphamide, doxorubicine, vincristine and prednisone often in combination with rituximab	55
Bendamustine	6 × bendamustine often in combination with rituximab	60
Other[b]	Including R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-BAC (rituximab, bendamustine, cytaraine), AraC (single cytarabine) Patients receiving more than one type of treatment (MCL2 de-escalated to R-CHOP, etc.) Patients receiving treatment not otherwise specified.	146
Radiation only		11
Total patients undergoing chemotherapy (chemo vs. no chemo)		517

Abbreviations: MCL, mantle cell lymphoma; rhyperCVAD/MA, rituximab cyclophosphamide vincristine doxorubicin and dexamethasone alternated with high-dose methotrexate and cytarabine.

[a]Eleven Spanish patients treated with rhyperCVAD/MA instead of MCL2 were included in this category.

[b]To ensure patient anonymity and privacy, populations of less than five patients were included in the 'Other' category.

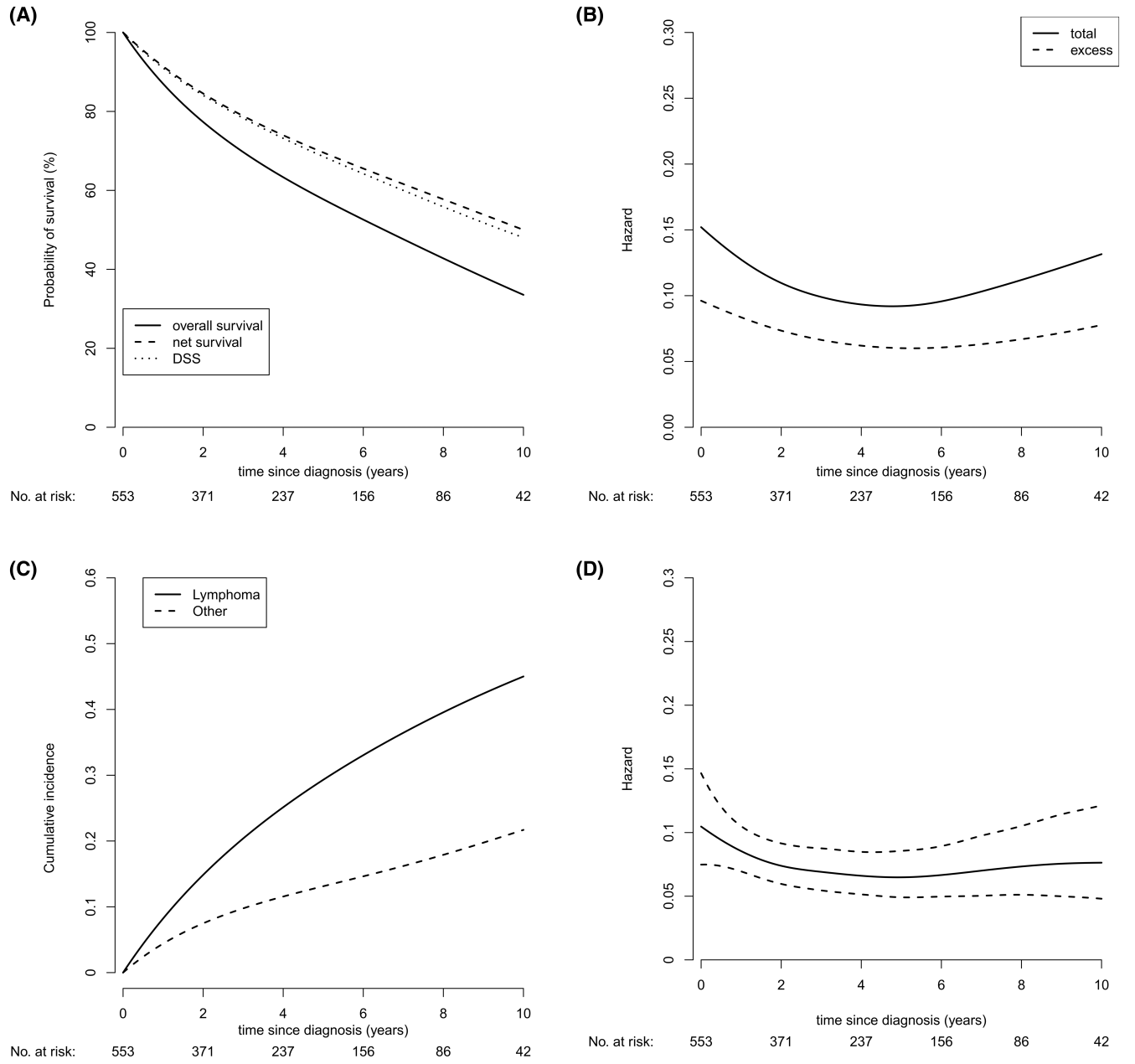

FIGURE 2 Survival (A), excess mortality (B), cumulative incidence of mantle cell lymphoma (MCL) deaths (C) and risk of death from MCL (D) for the entire patient population. DSS, disease-specific survival

survival compared to later relapse (OS 7 vs. 41 months; 95% CI: 3.0–11.0 vs. 29.1–52.9; $p < 0.05$). Figure 5 shows the difference in survival between patients who relapsed within or after 24 months from initial MCL diagnosis. Kaplan-Meier analysis on the effect of early relapse is available in supplementary file (Figures S9 and S10).

Survival by treatment era

When assessing the OS and DSS according to specified dates of treatment (2000–2005, 2006–2010, 2011–2015, and 2016–2020), we could not identify any correlation between a specified time period and the OS. A very modest ($p = 0.043$) correlation was seen between the treatment era and the DSS; however, this effect is likely explained by the younger median age of patients diagnosed and treated between 2000 and 2005 (Table S1, Figures S11–S13).

Survival by treatment centre or nation

To investigate possible differences in OS and DSS between the treatment centres, we compared the survival rates between each treatment centre and in all Finnish treatment centres combined with the Spanish treatment centre. No significant differences in the OS or DSS were observed in either analysis (Figures S14–S16).

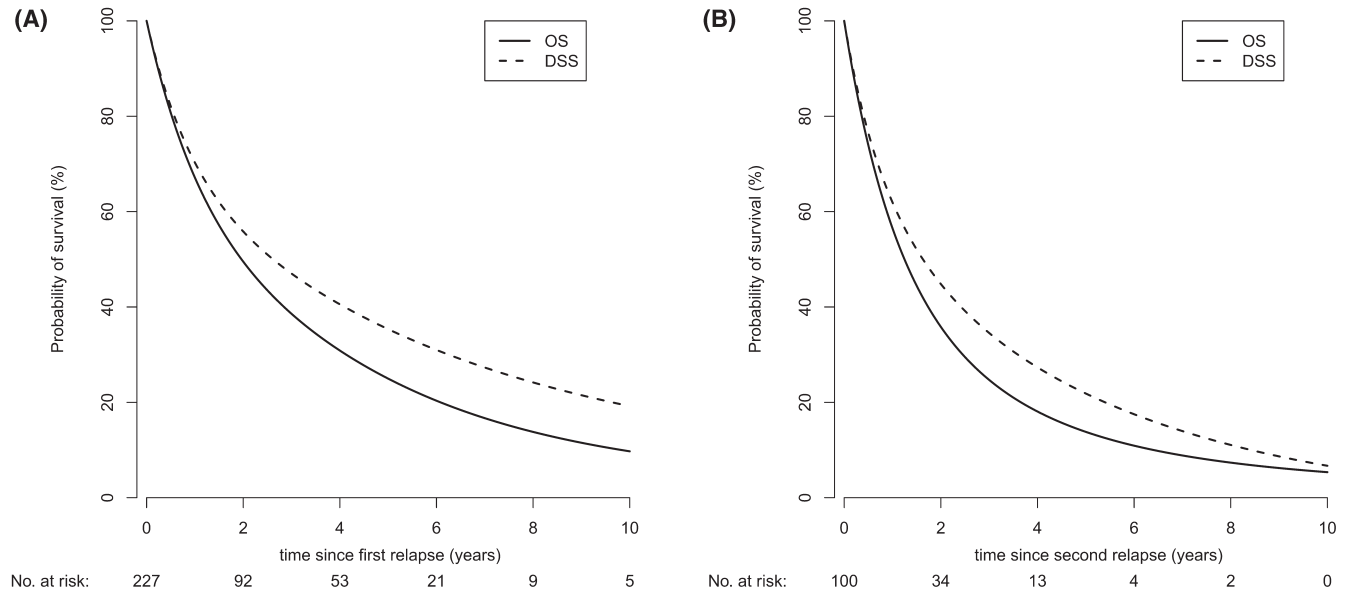

FIGURE 3 Survival after the first (A) and second (B) relapse of mantle cell lymphoma (MCL). DSS, disease-specific survival; OS, overall survival

DISCUSSION

We analysed the survival of 564 real-world patients with MCL diagnosed between 2000 and 2020. We report a 2-year OS of 77%, a 5-year OS of 58% and a 10-year OS of 32%. The estimated median OS was 80 months.

MCL has been associated with poor survival outcomes, frequent relapses, and a tendency to relapse with more aggressive disease biology. Before the introduction of the monoclonal CD20 antibody rituximab in the late 1990s, OS was generally only 2–3 years.[5,6] With the present induction regimens including rituximab, HD cytarabine, and HD chemotherapy + ASCT, which are currently considered the gold standard for MCL treatment, the prognosis of MCL has greatly improved and excellent treatment results have been reported in several clinical trials. However, these trials typically exclude patients who are above 65 years of age and have comorbidities or a poor performance status (WHO PS > 2).

Several international guidelines recommend immunochemotherapy for patients diagnosed with advanced disease with a non-indolent subtype.[11–14] While the exact treatment protocols vary by region, the treatment algorithms for young and fit patients generally consist of an induction immunochemotherapy involving rituximab and cytarabine and consolidation treatment with an autologous stem cell transplant. In Finland, patients aged younger than 65 (–75) years with good performance status (WHO PS 0–1) generally undergo treatment according to the Nordic MCL regimen (MCL2) as the first-line treatment. This includes six rounds of alternating maxi-R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) and HD cytarabine, followed by consolidative HD therapy and ASCT. The Spanish treatment guidelines also suggest a cytarabine-based induction followed by consolidation therapy with ASCT for the treatment of young, transplant-eligible patients with MCL.[15] The most frequently used approach in this group of Spanish patients (n = 10) was rhyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternated with MA (HD methotrexate and cytarabine).

The optimal treatment for non-transplant-eligible patients remains unclear. For chemotherapy-naïve patients presenting with indolent MCL, the combination of rituximab and bendamustine (R-B) appears to be superior to R-CHOP.[16] However, a randomised European trial of elderly patients with MCL comparing R-CHOP and R-FC (rituximab, fludarabine, cyclophosphamide), followed by rituximab maintenance therapy, found excellent results in the R-CHOP arm, with median OS and PFS of 9.8 and 5.4 years, respectively.[17]

In more recent studies, several maintenance regimes have yielded promising results in treating the elderly population with MCL, especially in terms of PFS. The results of the MCL R2 Elderly Clinical Trial observed a PFS of 5.1 years for patients that received rituximab and lenalidomide maintenance therapy, compared to a PFS of 3 years for patients receiving only maintenance rituximab.[18] Similarly, the phase III SHINE study reported a PFS of 6.7 years for chemotherapy-naïve patients that received maintenance ibrutinib treatment combined with the R-B regimen and maintenance rituximab.[19]

Both R-B and R-CHOP are commonly used in Finnish centres, particularly in elderly patients who are unable to tolerate more intensive regimens. In Spanish treatment centres, the most common treatment approaches for the elderly patient population are VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) or R-B, followed by rituximab maintenance therapy if remission has been achieved with induction.[15]

Cytarabine-based immunochemotherapies are also a viable option for elderly patients, and a recent study by

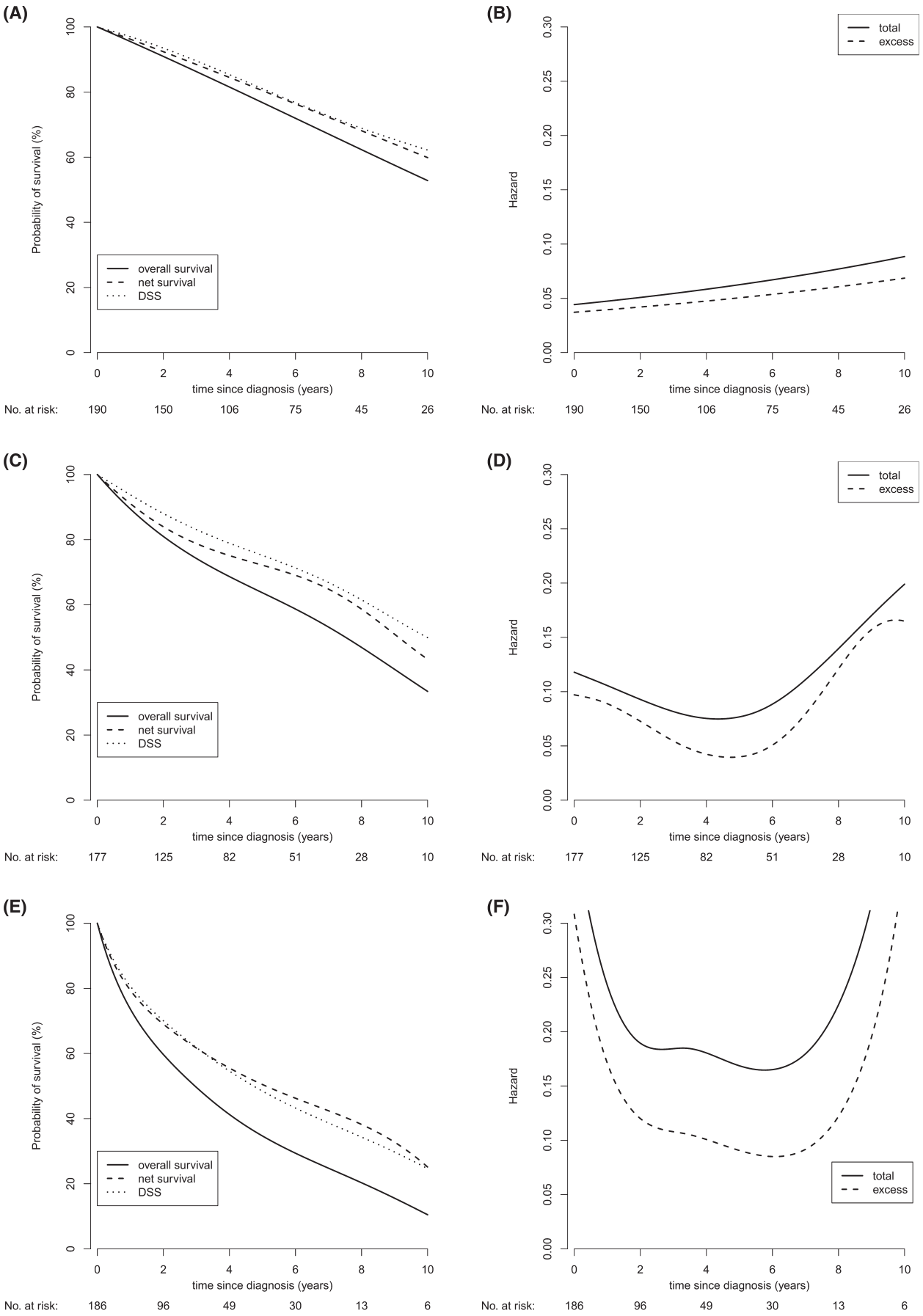

FIGURE 4 Survivals (A, C, E) and excess mortality (B, D,F) according to age groups (≥75 years). DSS, disease-specific survival

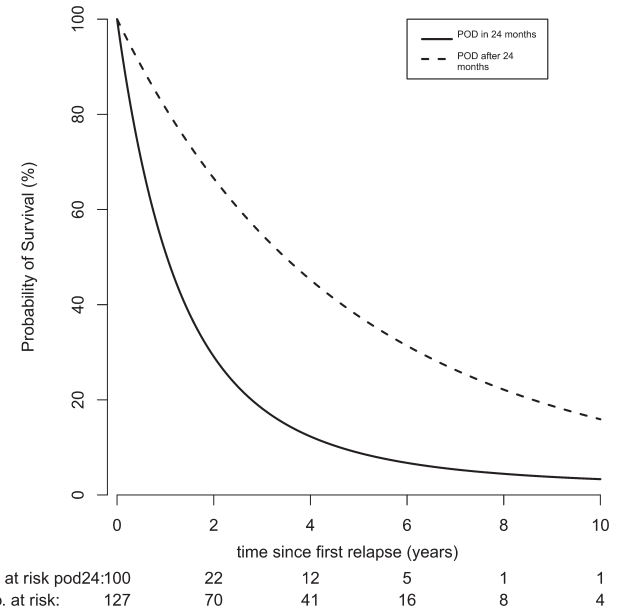

FIGURE 5 Overall survival after first relapse. Patients relapsing within 24 months of first-line treatment versus patients relapsing after 24 months. POD, progression of disease

Ratnasingam et al.[20] found evidence of their superiority over R-CHOP-type regimens. Between 2004 and 2010, several Finnish centres recruited eligible elderly non-transplant patients over 65 years of age in the MCL-FI trial. The treatment protocol in this trial consisted of ten rounds of alternating R-CHOP and R-AraC (rituximab and cytarabine), with eight doses of rituximab and 2 years of maintenance rituximab therapy. The trial demonstrated a promising outcome, with a PFS of 70% and OS of 72% at 4 years of follow-up.[21] After the recruitment period of the original study, this regimen has remained in use in several Finnish centres.

Retrospective analyses assessing the long-term survival of patients with MCL are limited and mostly involve patients treated prior to the introduction of rituximab. A population-based study from Denmark reported a median disease free survival (DFS) of 15 months and a median OS of 30 months for a cohort of 105 patients with MCL diagnosed between 1992 and 2000.[5] In a recent retrospective Surveillance, Epidemiology, and End Results (SEER)-based analysis of patients with MCL under 65 years of age, Wu et al.[22] observed an increase in median OS from 67 to 107 months between patient groups treated between 1995 and 2000 and between 2001 and 2012 for the entire cohort.

We found that the survival of patients with MCL has improved significantly compared to that in the pre-rituximab era. Particularly in patients under 65 years of age, OS and DSS were consistent with the results observed in clinical trials.[7–9] However, even in patients aged 75 years or older, the survival observed clearly exceeded the average pre-rituximab OS of 2–3 years. This indicates that advances in the treatment of MCL also benefit elderly patients who are considered ineligible for the most intense treatment regimens.

Excess mortality due to MCL was observed across the entire patient population. Interestingly, the occurrence of mortality was not similarly distributed among all the age groups. During the follow-up period, a linear increase in excess mortality was observed in patients under 65 years. Patients in the older age groups displayed a two-peaked curve with most MCL-related excess mortality occurring during the years 0–2 and 6–8 of follow-up. The difference is likely due to the more effective treatments implemented for the youngest age group, resulting in a longer remission period and a more gradual excess mortality curve. A longer follow-up time could reveal a similar increase in patients younger than 65 years.

In contrast to the findings of Wu et al.,[22] we could not identify any correlation between the treatment era and patient survival when assessing the data at 5-year intervals. There are several possible explanations for this observation. In our dataset, most patients underwent rituximab and cytarabine-based chemotherapy as the first-line treatment, which have been shown to improve patient survival.[7–9,20–21] However, only a small number of young patients in our study population treated according to the MCL2-equivalent regimen and with consolidative ASCT underwent maintenance with rituximab. Therefore, the survival figures may not reflect a possible future survival benefit of rituximab maintenance therapy in patients under 65 years. Another possible explanation as to why no improvement in survival was observed during the study period was the limited use of targeted treatments due to their high cost and strict compensation policies. For example, ibrutinib is reimbursed by Finnish social insurance only as the fourth-line therapy.[23]

The survival of patients with MCL who relapsed after modern immunochemotherapy regimens has recently been addressed in two independent studies. In a recent study involving patients initially treated in the Nordic MCL2 and MCL3 trials, Eskelund et al.[9] report a median OS of 22 months after the first relapse and a median OS of 11, 8, and 6 months after the subsequent second, third, and fourth relapses, respectively. The MANTLE-FIRST study, which involved a total of 606 younger patients with relapsed and refractory MCL, reported an OS of 36 months after the first relapse.[24]

We analysed survival rates after the first and second relapse events. The median OS was 18 months after the first relapse and 7 months after the second. The duration of survival was influenced by the duration of remission after the first-line treatment. For patients who relapsed within 24 months of diagnosis, the median OS was 7 versus 41 months among patients experiencing a later relapse ($p < 0.05$). Similar to results from other cohorts on MCL and follicular lymphoma,[25,26] our results suggest that relapse within 24 months of diagnosis is associated with poor prognosis.

The strength of this study is that it is a large real-world binational dataset collected from high-quality electronic patient records. To the best of our knowledge, this is the first retrospective, population-based study of MCL survival involving such data. This study contributes to ongoing efforts to further

improve the survival of patients with MCL and aims to initiate discussion on the introduction of more effective therapies. Although rituximab and immunochemotherapy have yielded excellent results, we did not observe any improvement in terms of patient survival during the last 20 years.

Our study has some limitations. As we were unable to collect information on histological subtypes and other prognostic markers such as the Ki-67% proliferation index, we could not evaluate their effect on survival. Furthermore, the treatment of patients included in our dataset is likely to have been guided by pathologist-verified gross diagnosis of MCL, patient characteristics, and the clinical experience of physicians prescribing treatment. This may have led to overtreatment of patients in whom a diagnosis was made in the early days of our study, particularly in patients with indolent-type MCL.

Finally, all findings presented here represent a patient cohort diagnosed and treated between 2000 and 2020. Novel therapeutic approaches, such as targeted treatments, chimeric antigen receptor T-cell therapy, and longer maintenance rituximab therapy, are likely to improve the survival of patients with newly diagnosed MCL.

This retrospective population-based study found that MCL prognosis has considerably improved with the introduction of rituximab, cytarabine-based chemotherapy, and consolidative ASCT. However, despite current treatment, the disease remains incurable and is associated with excess mortality across all age groups. Our results indicate that there was no improvement in survival over the past 20 years, highlighting the need for further research and the introduction of new treatments. Similar to other cohorts, we report an unfavourable prognosis for patients experiencing early relapse <24 months after diagnosis.

AUTHOR CONTRIBUTIONS

Minna Harmanen: research design, data collection, data analysis, writing. Mika Hujo: data analysis and figure preparation. Reijo Sund: data analysis. Outi Kuittinen: research design, funding, data analysis, writing. Aino Rönkä: research design, funding, data analysis, writing. Marc Sorigue: data collection, data analysis, writing, Madiha Khan, Roosa Prusila, Tuula Klaavuniemi, Esa Kari, Esa Jantunen, Kaisa Sunela, Aino Rajamäki, Erika Alanne, Hanne Kuitunen, Juan-Manuel Sancho, Arja Jukkola: data collection. All authors have read and approved the manuscript.

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CONFLICT OF INTEREST

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

Due to privacy and ethical concerns, the datasets generated and used for this study cannot be made available. Documentation on data collection process and dataset are available from the corresponding author on reasonable request. Background population data from Finland and Spain used for the statistical analysis are publicly available at Human Mortality Database (http://mortality.org).

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SUPPORTING INFORMATION

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

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