

Characteristics and Outcomes of Finnish Patients with Waldenström Macroglobulinemia—A Real-World Study

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Abstract

In this nationwide retrospective real-world evidence (RWE) study, we report the incidence, prevalence, patient characteristics, comorbidities, overall survival, causes of deaths and healthcare resource utilization (HCRU) of all Finnish patients diagnosed with Waldenström macroglobulinemia during 2007-2021. The median overall survival (mOS) for all WM patients during the entire study period was 7.3 years and an improvement in the OS was observed over time.

Introduction: Waldenström macroglobulinemia (WM) is a rare, slow-growing B-cell lymphoma characterized by the proliferation of lymphoplasmacytic cells in the bone marrow. WM has been difficult to diagnose and treat. However, recent advances in diagnostics, including the discovery of MYD88 and CXCR4 mutations, and in treatment, including targeted, patient-tolerable therapeutic options in often elderly patients, have together improved the clinical outcomes. **Methods:** In this nationwide retrospective real-world evidence (RWE) study, we report the incidence, prevalence, patient characteristics, comorbidities, overall survival, causes of deaths and healthcare resource utilization (HCRU) of all Finnish patients diagnosed with WM during 2007-2021. **Results:** The mean incidence was 0.49, age standardized incidence 0.23 and prevalence (in 2021) 3.7 per 100,000 people. The median overall survival (mOS) for all WM patients during the entire study period was 7.3 years. An improvement in the OS was observed over time (2007-2014 vs. 2015-2021 cohorts). Infections along with WM itself were a major cause of death among WM patients. **Conclusions:** To our knowledge, this is the first RWE study of WM patients in Finland.

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Introduction

Waldenström macroglobulinemia (WM) is a chronic B-cell lymphoma characterized by the proliferation of lymphoplasmacytic cells in the bone marrow and presence of monoclonal IgM immunoglobulins in the serum.^{1,2} WM is approximately two-fold more commonly diagnosed in men than women, and the median age at diagnosis is approximately 70 years.^{2,3} In the United States, an age-adjusted incidence of 0.38 per 100,000 population (0.54 for males and 0.27 for females), with an increase from 0.03 in <50 years olds to 2.85 in ≥80 years old, has been reported.³ European studies have reported slightly higher rates of WM with an overall

age-adjusted incidence of 0.55 per 100,000 population (0.73 for males and 0.42 for females) in the United Kingdom and 0.99 per 100,000 population in Sweden.⁴

The histopathological diagnosis of WM is lymphoplasmacytic lymphoma (LPL) confirmed by a bone marrow biopsy together with an increased production and secretion of monoclonal IgM immunoglobulins in the serum.⁵⁻⁷ These can lead to a number of complications including hyperviscosity, amyloidosis, cryoglobulinemia and autoimmune-related problems.^{2,5} The diagnosis of WM is often difficult, however, some of the recent discoveries can help to differentiate WM from other B-cell disorders. Notably, an activating L265P mutation in the *MYD88* gene is very common in WM, and occurs in over 90% of the patients.⁸ Moreover, mutations in the *CXCR4* gene are seen in approximately 30% of the patients.^{9,10}

While the newly diagnosed patients often remain asymptomatic for years and do not require treatment, when the disease progresses, most patients are treated with systemic therapies.^{7,11-16} The choice of therapy depends on the clinical manifestation of

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the disease and IPSSWM (International Prognostic Scoring System for WM) risk category that is based on 5 covariates including age, levels of hemoglobin, monoclonal IgM immunoglobulin and b2-microglobulin, and platelet counts.^{5,13,17} The development of new therapies has revolutionized the treatment of WM. According to the 11th international workshop on Waldenström's macroglobulinemia (IWWM-11), chemoimmunotherapies, including dexamethasone-cyclophosphamide-rituximab and bendamustine-rituximab regimens are currently the recommended front-line treatment in most WM patients.¹⁸ Bruton tyrosine kinase inhibitors (BTKi) are recommended for patients with significant comorbidities or frailty, but also in younger patients who may suffer from the long-term effects of chemotherapy.¹⁸ For patients with relapsed or refractory WM, treatment depends on the choice of treatment in the first line, and can for example consist of chemoimmunotherapy, proteasome inhibitor combination, BTKi, anti-CD20 or BCL-2 inhibitor therapy.¹⁹ The treatment guidelines for WM in Finland follow the international guidelines.²⁰

WM is a disease of the elderly. As frail and often elderly patients are typically not included in clinical trials, real-world evidence (RWE) studies are required to understand the patient population, current treatment practices and outcomes. Here, in this nationwide retrospective RWE study, we have utilized the healthcare registries of Finland and studied the patient characteristics, outcomes and healthcare resource utilization (HCRU) of all Finnish WM patients diagnosed between 2007 and 2021. To our knowledge, this is the first RWE study of WM patients in Finland.

Materials and Methods

Data Sources and Cohort Formation

This non-interventional, retrospective registry-based study utilized existing data generated as part of normal clinical care, treatment and follow-up of patients diagnosed with WM nationwide during 2007-2021. A preliminary cohort was identified from the Cancer Registry and for the identified cohort data were collected from four nationwide registries (see Supplemental Methods for more details of the collected data).

The study cohort included all adult patients diagnosed with WM, that is, ICD-10 code C88.0 recorded in specialized care and classified to have WM based on pathology sample, that is, ICD-O-3 morphology code 9761 recorded at the Cancer Registry, between January 1, 2007 and December 31, 2021. It is important to note that neither patients who had received WM diagnosis (9761) by a pathologist, but no WM diagnosis (C88.0) by an oncologist, nor patients who had received LPL diagnosis (9671) by the pathologist, even if they had received WM diagnosis (C88.0) by an oncologist, were included in the cohort.

An age, sex, and home municipality matched controls (1:3) without lymphomas were also collected. Patients were followed from the diagnosis date recorded at Cancer Registry, defined as index date, until death or end of study (EOS; December 31, 2022), whichever came first. Thus, all patients had a minimum of 1 year of possible follow-up. For the controls, the index date was set as the index date of the corresponding case. The cohorts were stratified by the index year (2007-2014 vs. 2015-2021).

Treatment Modalities

Inpatient medication data are not available nationwide in Finland and therefore, we approximated the treatment modalities using data on reimbursement numbers, reimbursed drug purchases, and contacts to specialized care. Patients were considered to have an IV episode if they had at least 4 outpatient hematology or oncology visits within 14 weeks and WM as the main diagnosis. The criteria for the IV-therapy episodes were determined to include all possible rituximab or bendamustine treatments. Patients were considered to start a treatment at first reimbursed drug purchase for WM or at the start of first IV episode, whichever came first. See Supplemental Methods for details on the used reimbursement numbers and specialty and procedure codes.

Statistical Analyses

The annual incidence and prevalence were estimated by dividing the number of incident cases per year and number of prevalent patients alive at the end of the year by the size of the background population at the end of the given year, respectively. Age-adjusted incidence was estimated using WHO-world weights. Ninety-five percent confidence intervals (CIs) were estimated using Poisson regression and the presence of monotonic trend was tested using the Mann-Kendall trend test.

Co-diagnoses were summarized and Charlson comorbidity index (CCI)²¹ was defined using specialized care diagnosis data from 5 years prior to index. The difference between strata was tested using the Kruskal-Wallis test for continuous variables and a chi-squared/Fisher's exact test for categorical variables.

Overall survival (OS) was assessed using the Kaplan-Meier fit and Cox proportional-hazards model as time from the index until death (event) or EOS (censoring event). The Cox model included age at index as continuous covariate and sex, CCI and diagnosis year as categorical covariates. Time to treatment was analyzed using a competing risk model as the time from index to the start of treatment (event), death (competing risk), or EOS (censoring). The median time was reported from the event free survival. The immediate causes of death were analyzed up to the end of 2021 due to data availability constraints.

In the analysis of all-cause HCRU, only patients diagnosed in 2011 or later were included, as primary care data were available only from 2011 onwards. The costs (other than outpatient medications) were determined based on the publicly available unit costs of the healthcare in Finland in 2017.²² The unit costs include the average cost of procedures, operations, laboratory examinations, inpatient medications, and overheads related to the visit, and are estimated separately for each specialty field and contact type. The costs of outpatient medications were provided in the data by the Finnish Social Insurance Institution (SII) as list prices. The unit costs and the outpatient medication costs were scaled to 2022 prices using the price index of public healthcare expenditure. The accumulation of healthcare contacts and corresponding costs were estimated using a mean cumulative function per patient.

To protect identity of patients as required by the Finnish law, all patient numbers below 5 were censored and reported as $n < 5$. All analyses were performed with R version 4.0.5.

Table 1 Clinical Characteristics of the WM Patients Diagnosed in Finland During 2007-2021

		Overall	2007-2014	2015-2021	P
		N = 399	N = 198	N = 201	
Age at diagnosis (years; median [IQR])		72.8 [64.7, 80.8]	74.1 [64.1, 82.0]	72.2 [64.9, 79.5]	.485
Follow-up time (months; median [IQR])		50.5 [21.7, 89.0]	74.3 [19.0, 125.3]	44.6 [22.6, 63.3]	<.001
Sex, N(%)	Female	162 (40.6)	87 (43.9)	75 (37.3)	.213
	Male	237 (59.4)	111 (56.1)	126 (62.7)	
Charlson's comorbidity index (CCI), N(%) ^a	0	238 (59.6)	119 (60.1)	119 (59.2)	.421
	1	35 (8.8)	16 (8.1)	19 (9.5)	
	2	92 (23.1)	50 (25.3)	42 (20.9)	
	3+	34 (8.5)	13 (6.6)	21 (10.4)	
University hospital area of home municipality, N(%) ^b	Helsinki	147 (37.0)	73 (37.1)	74 (37.0)	.945
	Kuopio	45 (11.3)	20 (10.2)	25 (12.5)	
	Oulu	49 (12.3)	26 (13.2)	23 (11.5)	
	Tampere	77 (19.4)	38 (19.3)	39 (19.5)	
	Turku	79 (19.9)	40 (20.3)	39 (19.5)	

Abbreviation: IQR = interquartile range.

^a 5 y prior to diagnosis considered.

^b For 0.5% of patients, data of home municipality was missing.

Results

Incidence and Prevalence

The mean incidence of WM was 0.49 per 100,000 (0.39 in female and 0.59 in male) and age standardized incidence 0.23 per 100,000 (0.16 in female and 0.31 in male; Figure 1A and B). Monotonic trends were not observed either in the annual incidence ($P = .843$) or in the age-standardized incidence ($P = .621$). WM was diagnosed mainly within the elderly population and the highest incidence was found in the age group of 80-84 years old (Figure 1C). The prevalence of WM in 2021 was 3.7 per 100,000 people.

Patient Characteristics

The study cohort consisted of all WM patients diagnosed in Finland during 2007-2021. The patient characteristics at diagnosis are presented in Table 1. The total number of WM patients in the study cohort was 399, the median age at diagnosis was 72.8 years and the median length of follow-up was 4.2 years. WM was found to affect more men, with 59.4% of all WM patients during the study period being male. Most of the patients had a CCI of 0 at diagnosis, but also a notable proportion, 31.6% of patients, had a CCI of ≥ 2 . To examine the possible changes in the characteristics and outcomes over time, we stratified the patient population into early and late cohorts based on the diagnosis year. In the early cohort of 2007-2014 there were 198, and in the late cohort of 2015-2021 there were 201 WM patients diagnosed. No significant differences in the baseline characteristics between the two cohorts were observed. The proportion of WM diagnoses among men was higher in the late than in the early cohort (62.7% vs. 56.1%); however, this difference was not statistically significant.

Co-diagnoses

Essential (primary) hypertension (ICD-10: I10) was the most common co-diagnosis among WM patients at the baseline (Supplemental Table 1). Unsurprisingly, given the clinical course

of WM, patients often presented with anemia at diagnosis. When comparing the two time windows, hypertension was more common in patients diagnosed in the late cohort compared to those diagnosed in the early cohort (28.9% vs. 17.1%, $P = .010$). Other neoplasms (of which 91% was monoclonal gammopathy of unknown significance; MGUS) were more common in the early cohort compared to the late cohort (26.4% vs. 17.5%, $P = .042$). The relatively high number of MGUS diagnoses likely reflects the clinical nature of the disease, wherein MGUS may develop to WM (Supplemental Figure 1A). The higher frequency of MGUS diagnoses observed in the earlier cohort may be attributed to the lower use of bone marrow biopsies during that period. In contrast, the more frequent use of bone marrow biopsies in the later cohort may have facilitated earlier and more definitive diagnosis of WM. The rest of the top 20 co-diagnoses were observed at similar frequencies in both time windows.

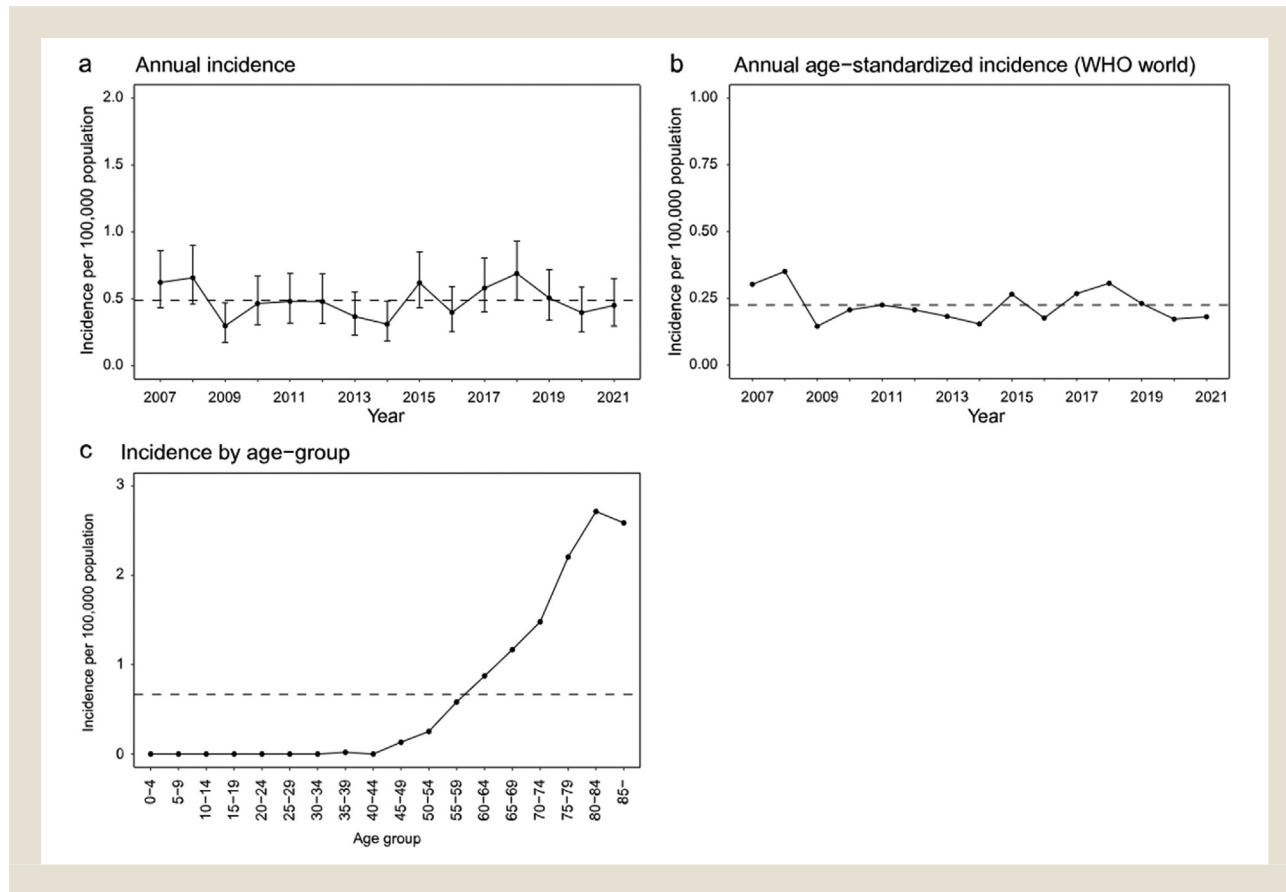
Interestingly, we observed also a relatively high number of multiple myeloma (MM) diagnoses (C90) among the WM patients. This prompted us to look in detail at the relative occurrence of MM and WM diagnoses (Supplemental Figure 1B). Indeed, we found that most of the MM diagnoses were recorded before the WM diagnosis, indicating an initial misdiagnosis of MM.

Survival

The median OS (mOS) for all WM patients during the entire study period was 7.3 years (Figure 2A). This was significantly lower to the age-, sex-, and home municipality-matched controls who had an mOS of 12.8 years (log rank $P < .001$). To assess the possible changes in survival over time, we studied the OS in 2 time periods based on the year of diagnosis. The mOS of WM patients in the early cohort was 6.2 years while the mOS was not reached in the late cohort (Figure 2B; log rank $P = .071$). No change in the OS of the matched controls was observed over time (Figure 2C; log rank $P = .894$). In the Cox proportional-hazards model, we observed an

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Figure 1 Incidence of WM in Finland during 2007-2021. (A) Annual, (B) age standardized, and (C) age-group specific incidence. The dotted line indicates the average incidence over time.



improvement in the OS of WM patients over time when adjusted by age, sex and CCI (Figure 2D). The hazard ratio (HR) for patients diagnosed in the late cohort compared to the patients diagnosed in the early cohort was 0.72 (95% CI, 0.53-0.98, $P = .035$) indicating a 28% reduced hazard of death among the late cohort compared to the early cohort. Additionally, older age and higher CCI were associated with poorer survival.

Treatment

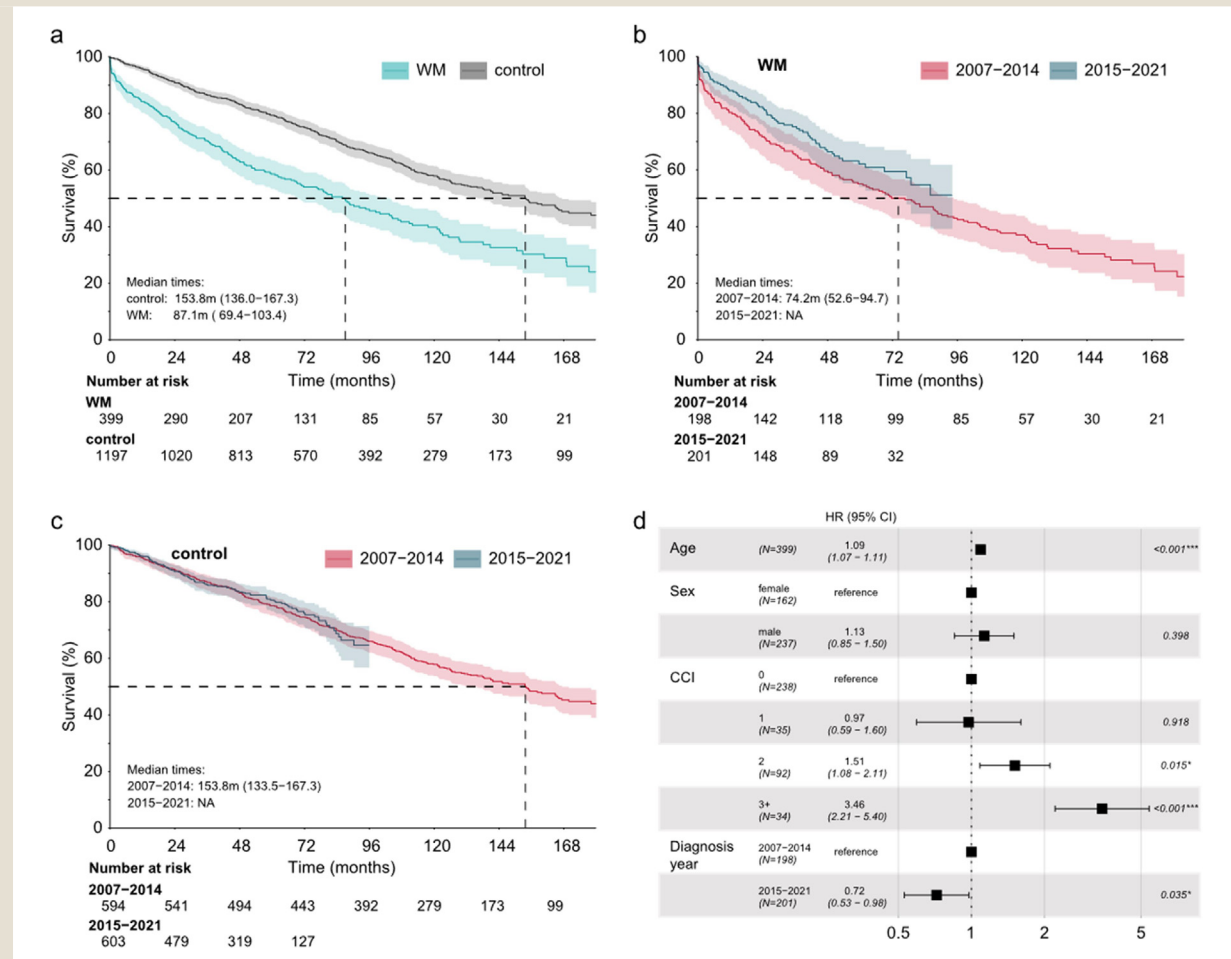
While the hospital administered medication data were not available in this study, we utilized data on reimbursed medications, procedures and the approximated intravenous (IV) therapy episodes to estimate the proportion of treated WM patients. About 53.6% of patients received IV therapy and 36.6% had at least one reimbursed drug purchase for WM during the follow-up (Supplemental Table 2). When combining these 2 variables, a total of 239 patients (59.9%) received treatment during the follow-up, with the highest treatment initiation rate occurring during the first few months after the diagnosis (Figure 3A). At 3 months, 31.8% (95% CI, 27.6-36.7) of patients had started treatment, after which the treatment initiation rate was gradual. Also, a notable proportion of patients died before starting any treatment for WM (at 10-year time point

26.6%, 95% CI, 22.2-31.7). Median event-free survival (mEFS; that is, alive and treatment not yet started) was 8.1 months (95% CI, 5.5-13.8). Only 10 patients (2.5%) had plasmapheresis during the follow-up. The median age at the start of treatment was 71.5 years (IQR: 64.4-78.9) and 40.2% were female. Most treated WM patients did not have any major comorbidities (CCI being 0 for 60.7%). The median OS from the start of the treatment was 87.7 months (95% CI, 66.2-97.3; Figure 3B).

Causes of Death

We also looked in detail to the immediate causes of death recorded among WM patients. A total of 194 WM patients died during 2007-2021. WM (27.3%) and infection (25.8%) were the most commonly recorded immediate causes of death, followed by cardiovascular disease (15.5%), solid cancer (7.2%), other hematologic cancers (4.1%) and diffuse large B-cell lymphoma (DLBCL) (3.6%) (Figure 4A). With the notable number of DLBCL recorded as an immediate cause of death among WM patients, we examined in detail the number and timing of DLBCL and WM diagnoses (Figure 4B). DLBCL diagnoses were mainly recorded at the end of the follow-up, suggesting a transformation of the disease. In total, DLBCL diagnosis was recorded for 23 patients (5.8%).

Figure 2 The overall survival of WM patients and their matched controls in Finland. (A) The OS of all WM patients diagnosed in 2007-2021 and their matched controls. (B) The OS of WM patients and (C) their matched controls with index in 2007-2014 and 2015-2021. (D) The Cox proportional-hazards model for survival in WM patients.



Healthcare Resource Utilization

All-cause HCRU was measured by the events (N) and costs (€) of primary care contacts, specialized care outpatient contacts, emergency room (ER) visits, and inpatient days, as well as outpatient medications. Most of the events for WM patients came from primary care contacts throughout the follow-up (Figure 5A, Supplemental Table 3). During the first 4 years after the diagnosis, the number of inpatient days was highest compared to the rest of the follow-up time. In line with this, the inpatient days formed a large part of the costs during the first 4 years (Figure 5B, Supplemental Table 3). While the number of events and costs due to inpatient days decreased during the follow-up, the number of events and costs due to both primary care and specialized care outpatient contacts remained relatively constant during the entire follow-up time. Interestingly, while the number of outpatient medication events remained the same over time, the costs were higher during the end of the follow-up when compared to the first years after diagnosis.

Discussion

This retrospective nationwide RWE study investigated the characteristics, comorbidities, outcomes, causes of deaths and HCRU of the 399 Finnish patients diagnosed with WM during 2007-2021. To our knowledge, this is the first RWE study of WM patients in Finland. As clinical trials on WM are very limited, RWE studies are invaluable in understanding the patient population and outcomes in this small patient group.

While WM is still an incurable cancer, we report an improvement in the survival of WM patients in Finland. The mOS was 6.2 years in the early cohort of 2007-2014 and not reached in the late cohort of 2015-2021. Importantly, the Cox proportional-hazards model, adjusted by age, sex and CCI, showed a 28% reduction in the hazard of death in the late cohort when compared to the early cohort. The mOS of all WM patients during the study period was 7.3 years, while it was 12.8 years for the matched controls. The mOS observed in this study was slightly poorer compared to other reports. A US study on WM patients diagnosed between 1991 and 2010 reported

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Figure 3 (A) Event-free survival (EFS) of all WM patients analyzed with competing risk model (red curve representing the probability of death and grey curve the probability of starting treatment). The median EFS from WM diagnosis was 8.1 months (95% CI, 5.5-13.8). (B) Overall survival (OS) of treated WM patients. The median OS from the start of treatment was 87.7 months (95% CI, 66.2-97.3).

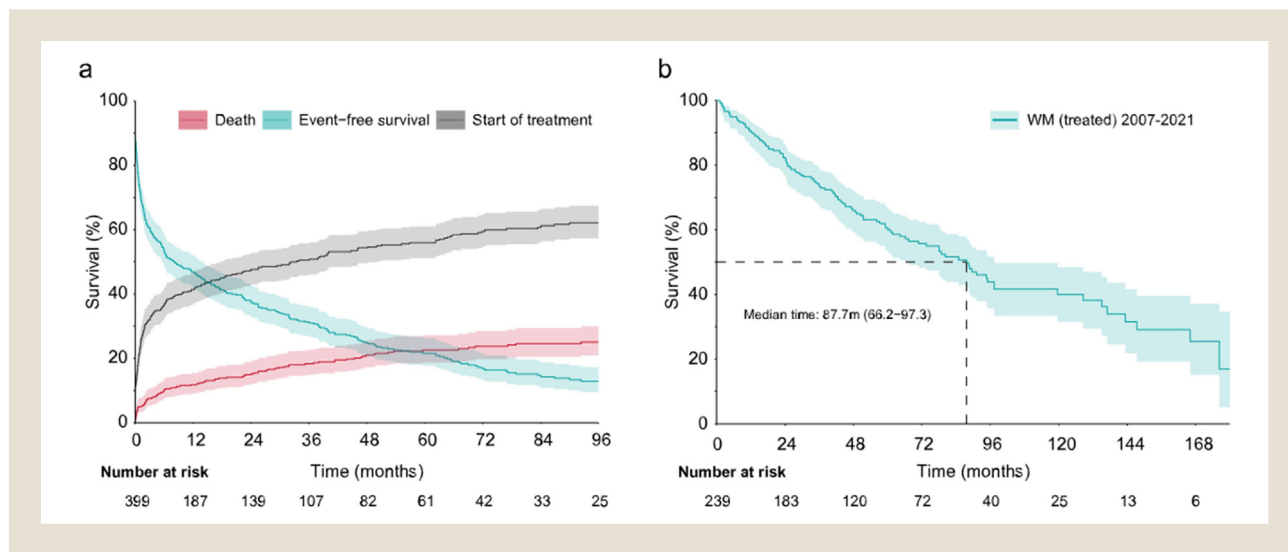
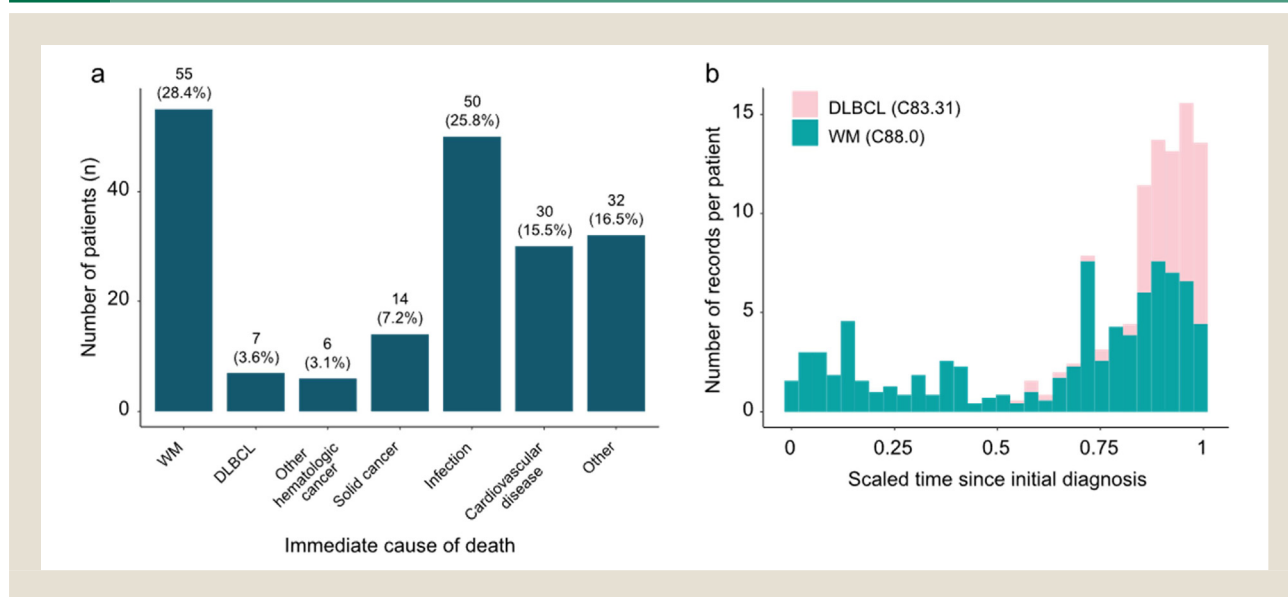


Figure 4 Causes of death. (A) The immediate causes of death recorded in WM patients during 2007-2021 in Finland. (B) The number of WM and DLBCL diagnoses per patient as a function of scaled time since initial diagnosis of WM (among those with DLBCL as immediate cause of death, $n = 7$).



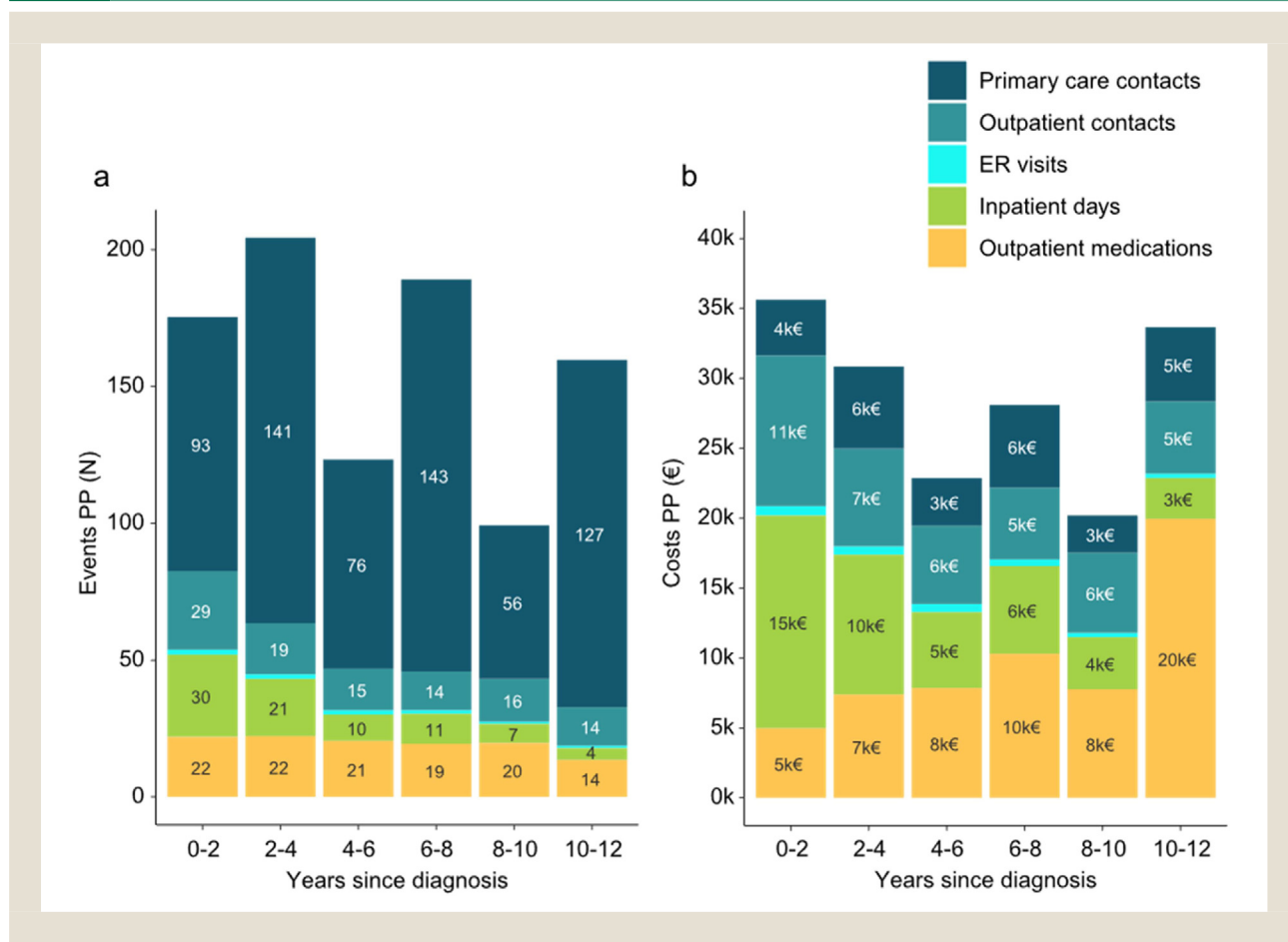
an mOS of 7 years for the entire study period, with a statistically significant improvement from 6 years in 1991-2000 to 8.2 years in 2001-2010.²³ Similarly, in Sweden, an 8 year mOS was reported in WM patients diagnosed between 2000 and 2014.²⁴

Although the inpatient medication data were not available for this study, we estimated the proportion of patients receiving treatment based on the reimbursement and specialized care data. We found that 60% (239/399) of patients received therapy during the follow-up. At 3 months, 32% of patients had started the treatment, which

is in line with a Swedish RWE study, where 30% (297/981) of WM patients were reported to receive therapy 0-3 months after the initial diagnosis.²⁴

We report an age standardized incidence of 0.23 per 100,000 population in Finland (adjusted to WHO world standard population). This is lower than in the US and UK, where an age adjusted incidences of 0.38 and 0.55 per 100,000 population, respectively, have been reported.^{3,4} A Swedish study reported an age-adjusted incidence of 1.15 per 100,000 persons.²⁴ The differences between

Figure 5 Healthcare resource utilization in WM patients. All-cause HCRU by (A) the number of events per patient (PP) and by (B) the costs PP as primary care contacts, specialized care outpatient contacts, emergency room (ER) visits, inpatient days, and outpatient medications.



the observations in this study and the Swedish study are likely because LPL patients without diagnosis by an oncologist were not included in our study. It is also important to note that the studies in the US, UK, and Sweden utilized the US and European standard populations when adjusting the incidence by age. Therefore, the age-standardized incidences of these studies are not fully comparable with our study. We report a higher incidence among men (0.59 in men vs. 0.39 in women). A higher incidence among men has been previously reported also in the US (0.54 in men vs. 0.27 in women) and in the UK (0.73 in men and 0.42 in women).^{3,4} The incidence of WM was observed to gradually increase after the age of 45 and the highest incidence was found in the age group of 80-84 years old. The median age at diagnosis was 72.8 years, which is in line with previous reports.^{3,23-26}

40.4% of the WM patients had a CCI ≥ 1 at diagnosis and no notable differences were observed between the early and late cohorts. In Sweden, a CCI ≥ 1 has been reported in 48% of the WM patients²⁷ while in a German RWE study, 29.1% of the WM patients were found to have a CCI ≥ 1 .²⁸ It is possible that there are notable differences between countries in the recording practices that may again affect the comorbidity index. Of the

baseline co-diagnoses, hypertension (ICD-10: I10) was the most common. This can be largely attributed to the high median age of the patient population. Interestingly, hypertension was significantly more common among the late cohort than the early cohort.

The observation that many WM patients had several MM diagnoses prior to WM diagnosis (most probably being a misdiagnosis of MM) highlights the importance of developing diagnostic accuracy to recognize and differentiate WM from other lymphoproliferative diseases, and to ensure appropriate treatment for the patients. Moreover, we report the diagnosis of DLBCL in 5.8% of WM patients. A US study from 2000 to 2014 reported a 2.4% 10-year cumulative transformation incidence.²⁹ While the transformation to DLBCL remains rare, it has been associated with inferior survival,³⁰ and was recorded as the immediate cause of death in 3.6% of the patients in this study.

Finally, we analyzed HCRU among WM patients. The majority of HCRU events came from primary care contacts, while the cause of costs changed during the follow-up with inpatient days forming a large part of the costs in the beginning of the follow-up and outpatient medications towards the end of the follow-up. The high number of inpatient days observed during the first years after

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diagnosis might be due to the often poor condition of the patients at diagnosis. Supporting this, the rate of treatment initiation was highest during the first few months after diagnosis, whereas the later treatment initiations and the associated increase in the HCRU may appear less pronounced due to averaging across patients. The introduction of targeted therapies during the later years of the study period may have contributed to the increased costs of outpatient medications towards the end of the follow-up.

Study Strengths and Limitations

Finland has universal healthcare primarily funded by taxation. All permanent residents in Finland, regardless of their financial situation, are entitled to the same level of public healthcare and thus the real-world data (RWD) in national registries are not skewed in terms of selection criteria. However, this study is subject to limitations generally related to registry-based RWE studies. The data reflect the everyday clinical coding practices and thus may be nonstandardized and incomplete and is subject to missing data or differing coding practices.

The Cancer Registry is based on pathology samples and statements, which may sometimes be erroneous. This is especially true in hematology with often complex diagnostic criteria. In this study, we required a WM diagnosis in specialized care on top of the record of WM in Cancer Registry. Only 11 patients (<3%) did not have a diagnosis of WM recorded at specialized care and thus were excluded, emphasizing that the impact of possible erroneous records from the Cancer Registry is minimal. However, we were not able to cross-validate the cohort, that is, how many patients had diagnosis recorded at the specialized care but no records in the Cancer Registry because of the lack of bone marrow biopsy. Moreover, instead of the bone marrow biopsy, diagnoses have been sometimes made by only bone marrow aspirates, which are not recorded in the Cancer Registry. Therefore, there may be an underestimation in the cohort sizes and thus incidence of WM in the study.

Additionally, inpatient medication, laboratory and pathology data were not available in Finland nationwide at the time of the data application and thus, these data were not collected for this study. Thus, the treatment modalities and the analysis of the EFS rely only on the reimbursed medication purchases, performed procedures and contacts to specialized care, and therefore, deeper analysis of the treatment patterns and outcomes, such as time to next treatment, and any analysis of the laboratory values and genetics were not possible to include in this study. Also, the lack of inpatient medication data may have induced some inaccuracy in the estimation of the initiation date of the treatment. Last, the medication costs were calculated using the list prices and may not reflect the actual costs that may have been lower due to special agreements between the pharmaceutical companies and the Finnish authorities.

Clinical Practice Points

- Clinical trials on WM are very limited and thus RWE studies are invaluable in understanding the patient population and outcomes in this small patient group.
- We report an improvement in the survival of WM patients in Finland during 2007–2021.

- We found that 60% of WM patients received therapy during the follow-up.
- We found that many WM patients had several MM diagnoses prior to WM diagnosis (most probably being a misdiagnosis of MM) highlighting the importance of developing diagnostic accuracy to recognize and differentiate WM from other lymphoproliferative diseases, and to ensure appropriate treatment for the patients.

Disclosure

Medaffcon provided support for planning the study, analyzing the data and interpretation of the results, drafting the manuscript, and medical writing. EM is employed by Johnson & Johnson. JV and EH are employees of Medaffcon Oy. PA has received honoraria from BeiGene, Celgene, GlaxoSmithKline, Johnson & Johnson, Menarini, Oncopeptides, Pfizer, Sanofi, Takeda.

CRedit authorship contribution statement

Eleonora Mäkelä: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Johanna Viikula:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Essi Havula:** Writing – review & editing, Writing – original draft, Validation, Project administration, Conceptualization. **Pekka Anttila:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

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Consent

According to the Finnish Act on Secondary use of health and social data (552/2019), no patient consent was required.

Ethics Statement

The study was approved by The Finnish Social and Health Data Permit Authority Findata (data permit number THL/6570/14.02.00/2021 findata-rems-2021/694).

Data Availability Statement

This study is based on the secondary use of healthcare register data. Only the registry personnel had full access to patient data. The single-level data cannot be shared. Only the registry holders have the authority to grant rights to third parties for data usage in accordance with the Act on Secondary Use of Health and Social Data.

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Supplementary information

Supplementary methods

Cohort formation and data collection. Data on specialized and primary care was collected from the Care Register for Healthcare, data on reimbursed medication purchases from the Social Insurance Institution (SII), causes of death from the Statistics Finland, and demographics and controls from the Digital and Population Services Agency (DVV). Controls were not allowed to have diagnosis of follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, WM, or chronic lymphatic leukemia at any time point.

Treatment modalities. Reimbursement numbers 117, and 390 and 1512 were considered in the analysis of the reimbursed drug purchases. The reimbursement number 117 is used for leukemias, other malignant blood and bone marrow diseases, and malignant lymphoid diseases. Only the following drug purchases with reimbursement number 117 were considered: chlorambucil, cyclophosphamide, dexamethasone, etoposide, fludarabine, methotrexate, methylprednisolone, and predniso(lo)ne. Reimbursement number 390 and 1512 were used for ibrutinib. When identifying the IV episodes, specialty code 10 was considered to correspond to hematology and specialty code 65 to oncology. Patients receiving plasmapheresis were retrieved from the procedures (procedure code WW400).

Causes of death

The immediate death causes were grouped based on ICD-10 codes as follows:

- WM: C88.0 and C83.0
- Diffuse large cell B-cell lymphoma (DLBCL): C83.3
- Other hematologic cancer: C81-C96
- Solid cancer: rest of the codes starting with C
- Infection: codes starting with A, B, and J, and N10, N30, and U07.1
- Cardiovascular disease: codes starting with I
- Other: all the rest

HCRU

The following ATC codes were included in the analysis of the reimbursed outpatient medications: A02, A10, B01, B03, C, J, H02, L, M05, N.

Sanity checks. As some patients died of DLBCL, we checked the diagnosis records of WM (ICD-10: C88.0) and on DLBCL (ICD-10: C83.31) throughout the follow-up for these patients, to assess if a true transformation of WM to DLBCL had taken place, or a possible misdiagnosis. The follow-up of each patient was scaled to 1 and a histogram of the WM and DLBCL diagnosis records was plotted as a function of time representing an average patient who died of DLBCL. Similar analysis was performed for patients with a record of multiple myeloma (ICD-10: C90) or monoclonal gammopathy diagnosis (MGUS, ICD-10: D47.2) in the baseline (5 years prior to index), to assess whether WM or MM/MGUS was a misdiagnosis. Here, we included both the baseline and the follow-up data on the WM and MM/MGUS diagnosis records and for each patient, scaled both the baseline and follow-up to 1.

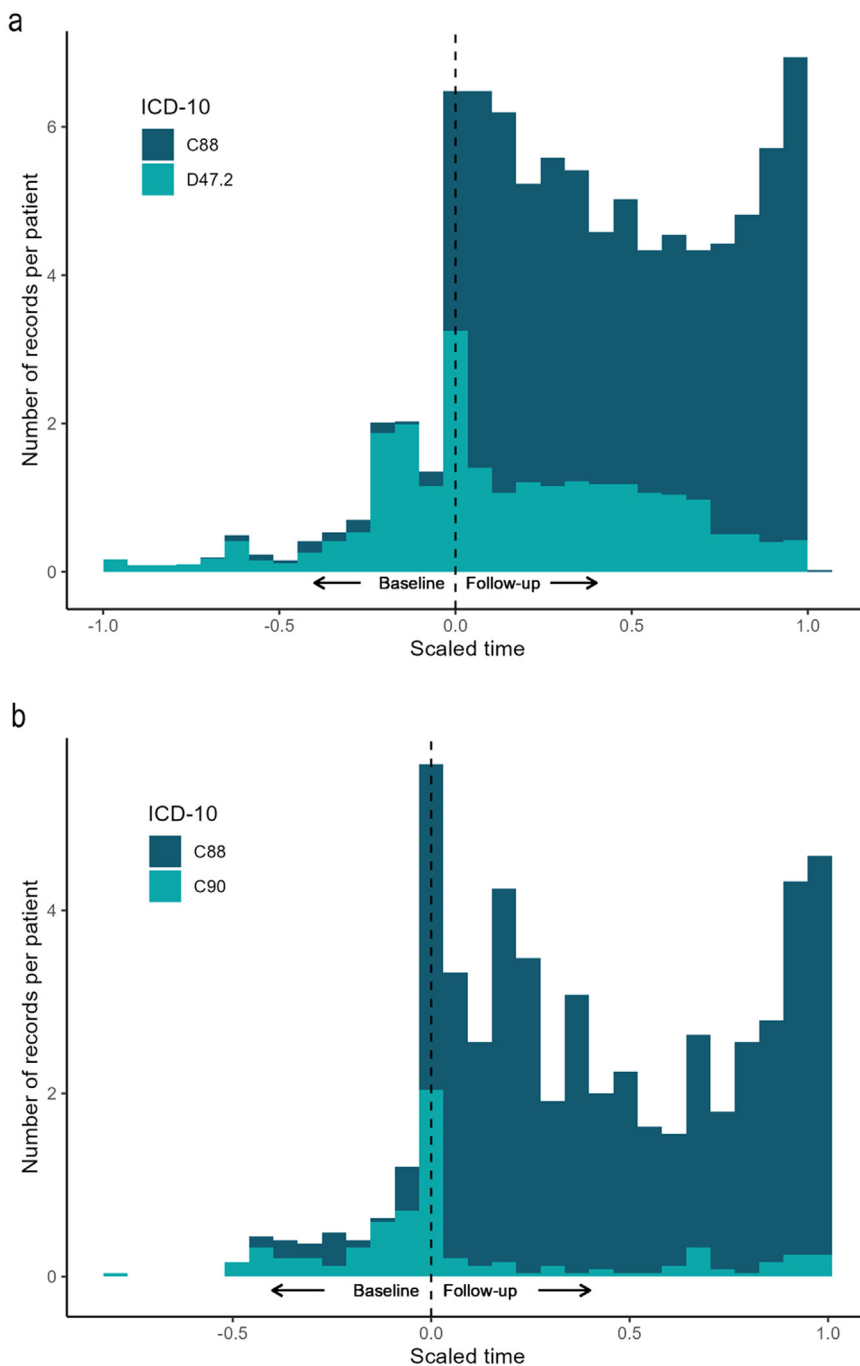
Supplementary Table S1 Top 20 most prevalent co-diagnoses of WM patients recorded at specialty care during the 5 years before WM diagnosis.

ICD-10	Description	Overall n (%)	2007–2014 n (%)	2015–2021 n (%)
I10	Essential (primary) hypertension	89 (23)	33 (17.1)	56 (28.9)
D47*	Other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue	85 (22)	51 (26.4)	34 (17.5)
D64	Other anaemias	83 (21.4)	40 (20.7)	43 (22.2)
H25	Senile cataract	58 (15)	34 (17.6)	24 (12.4)
I48	Atrial fibrillation and flutter	48 (12.4)	25 (13)	23 (11.9)
I25	Chronic ischaemic heart disease	41 (10.6)	23 (11.9)	18 (9.3)
H90	Conductive and sensorineural hearing loss	37 (9.6)	19 (9.8)	18 (9.3)
K57	Diverticular disease of intestine	37 (9.6)	13 (6.7)	24 (12.4)
J18	Pneumonia, organism unspecified	33 (8.5)	15 (7.8)	18 (9.3)
N40	Hyperplasia of prostate	29 (7.5)	12 (6.2)	17 (8.8)
I50	Heart failure	27 (7)	17 (8.8)	10 (5.2)
E78	Disorders of lipoprotein metabolism and other lipidaemias	26 (6.7)	8 (4.1)	18 (9.3)
C90	Multiple myeloma and malignant plasma cell neoplasms	25 (6.5)	14 (7.3)	11 (5.7)
E11	Non-insulin-dependent diabetes mellitus	23 (5.9)	8 (4.1)	15 (7.7)
H40	Glaucoma	20 (5.2)	9 (4.7)	11 (5.7)
I35	Nonrheumatic aortic valve disorders	19 (4.9)	10 (5.2)	9 (4.6)
M17	Gonarthrosis [arthrosis of knee]	19 (4.9)	14 (7.3)	5 (2.6)
D50	Iron deficiency anaemia	18 (4.7)	11 (5.7)	7 (3.6)
G45	Transient cerebral ischaemic attacks and related syndromes	18 (4.7)	7 (3.6)	11 (5.7)
N10	Acute tubulo-interstitial nephritis	18 (4.7)	5 (2.6)	13 (6.7)

* 91% of the D47 diagnoses were D47.2 Monoclonal gammopathy, MGUS

Supplementary Figure S1

Histogram of the average number of ICD-10 records of Waldenström macroglobulinemia (WM, C88) and (a) monoclonal gammopathy (MGUS, D47.2) and (b) multiple myeloma (MM, C90) per patient among those with a record of MGUS (n=77) and MM (n=25) at baseline. To present all patients in one figure, the baseline and follow-up were both scaled to one for each patient, time zero representing the timing of WM diagnosis.



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Supplementary Table S2 Reimbursed medications and procedures during the follow-up.

Variable, n (%)	Overall n=399	Stratification by diagnosis year	
		2007-2014 n=198	2015-2021 n=201
Any treatment ¹	239 (59.9)	124 (62.6)	115 (57.2)
Reimbursement for outpatient drug for WM granted	243 (60.9)	125 (63.1)	118 (58.7)
Reimbursed drug purchase ² for WM	146 (36.6)	85 (42.9)	61 (30.3)
Reimbursement for ibrutinib* granted	38 (9.5)	15 (7.6)	23 (11.4)
Reimbursed ibrutinib purchase	31 (7.8)	13 (6.6)	18 (9.0)
IV episode ³	214 (53.6)	111 (56.1)	103 (51.2)

¹ Reimbursed medication purchase for WM and/or IV episode.

² See Supplemental Methods for the detailed list of included drugs.

³ At least 4 visits at hematology or oncology unit within 14 weeks with WM as main diagnosis.

* Reimbursement for ibrutinib started in 02/2018 in Finland.

Supplementary Table S3 HCRU by events (N) and costs (€) per patient.

	Time Interval (Years)	Events PP (N)	Costs PP (€)
Specialized care ER visits	0–2	1,9	686
	2–4	1,7	618
	4–6	1,7	593
	6–8	1,4	474
	8–10	0,9	319
	10–12	0,9	324
	Specialized care inpatient days	0–2	30,0
2–4		20,9	9982
4–6		9,7	5419
6–8		11,0	6273
8–10		7,0	3713
10–12		4,4	2911
Specialized care outpatient contacts		0–2	28,7
	2–4	18,7	6974
	4–6	15,1	5593
	6–8	14,1	5130
	8–10	15,6	5728
	10–12	14,0	5164
	Outpatient medications	0–2	22,0
2–4		22,3	7397
4–6		20,5	7859
6–8		19,5	10308
8–10		19,8	7775
10–12		13,6	19950
Primary care contacts		0–2	92,8
	2–4	140,8	5868
	4–6	76,4	3403
	6–8	143,2	5903
	8–10	56,0	2655
	10–12	126,8	5299