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Economic Evaluation

Epidemiology, Real-World Treatment, and Economic Burden of Waldenström Macroglobulinemia: A Comprehensive Analysis Based on Anonymized Claims Data Between 2010 and 2022

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ABSTRACT

Objectives: This study aimed to provide evidence on the epidemiology, real-world treatment patterns, overall survival, and economic burden of Waldenström macroglobulinemia (WM).

Methods: A retrospective analysis of an anonymized large German claims database from January 1, 2010, to June 30, 2022, identified incident WM cases based on a 12-month diagnosis-free period before the first confirmed WM diagnosis (ICD-10-GM code C88.0). WM diagnosis was validated through at least 2 confirmed outpatient diagnoses in different quarters within 12 months or 1 inpatient diagnosis (further sensitivity scenarios were tested). Treatment patterns were analyzed based on the follow-up period after diagnosis, with line of treatment derived by an algorithm using outpatient prescription/inpatient procedure information. Incremental costs were derived by comparing patients with WM with a propensity-score-matched control group.

Results: A total of 593 incident WM cases were identified (mean age: 72.7 years; 46.5% female). In 2021, standardized cumulative incidence ranged from 1.39 to 1.90 per 100 000 persons (males: 1.98 to 2.60; females: 0.73 to 1.25). Median overall survival was 7.9 years. Nearly 70% of patients initially followed a watch-and-wait approach, with less than one-third starting therapy after 2 years. Rituximab, often combined with bendamustine or unspecified inpatient chemotherapy, was the most common treatment. Recently, ibrutinib has been used more frequently in later lines. Incremental cost analysis showed substantial care costs, mainly driven by medications and inpatient care.

Conclusions: The study indicates an increasing incidence of WM in Germany, associated with significant economic burden, despite the majority of newly diagnosed patients initially adopting a watch-and-wait approach.

Keywords: healthcare costs, healthcare resource utilization, overall survival, real-world treatment, Waldenström macroglobulinemia.

VALUE HEALTH REG ISSUES. 2025; 50:101162

Introduction

Waldenström macroglobulinemia (WM) is a B-lymphocytic neoplasm characterized by accumulation of lymphoplasmacytic lymphoma cells in the bone marrow and secretion of monoclonal immunoglobulin M, often affecting lymph nodes and spleen.[1,2] Although its etiology is largely unknown, genetic and immune factors are likely involved.[3] WM predominantly affects elderly men.[4,5]

Epidemiological data primarily come from national cancer registries, with incidence rates varying by region. The US Surveillance, Epidemiology, and End Results (SEER) database reported an incidence of 0.38 per 100 000 persons from 1988 through 2007, whereas rates in South East England and northern Sweden were higher.[4] An age-adjusted WM incidence of 0.55 per 100 000 people in South East England from 1999 through 2001 was reported based on Thames Cancer Registry data.[6] Using data from the Swedish and Northern Lymphoma Registry (2000-2012), the age-adjusted incidence rates for WM in the northern counties Norrbotten and Västerbotten were calculated to be 1.75 and 1.48 per 100 000 persons per year, respectively.[7]

The clinical course of WM is diverse; although many patients do not need treatment at incident diagnosis, most will eventually require systemic treatment.[8] Newer treatments, such as monoclonal antibodies and proteasome inhibitors, have improved therapy options, although their impact on clinical outcomes remains unclear. Some studies suggest improved survival trends, but the evidence is mixed,[8-12] and most investigations do not yet cover the post-Bruton tyrosine kinase era.

This analysis aims to provide WM epidemiological evidence in Germany using a large administrative statutory health insurance

(SHI) database. Currently, nearly 90% of the German population is insured by SHI funds.[13] The SHI contains claims-based data on inpatient and outpatient medical care. These data, originally collected for administrative purposes, offer great research potential and have been increasingly used in the last decades for real-world evidence studies.[14,15] One main advantage of the German claims data is the broad coverage of different healthcare settings, including inpatient care, outpatient specialists, and general practitioners.

Using information from different settings, this study primarily aimed to describe WM epidemiology in Germany, including incidence, prevalence, patient characteristics, and mortality. Furthermore, the analysis sought to describe treatment patterns in routine clinical practice and assess the WM-associated economic burden in the German healthcare setting.

Methods

Data Source

This retrospective study analyzed anonymized claims data between January 1, 2010, and June 30, 2022, from the regional German SHI fund AOK PLUS for approximately 3.4 million individuals (~4% of the German population) from the federal states Saxony and Thuringia. Although the data set is regionally confined, AOK PLUS is part of the larger AOK system, which insures approximately 40% of the German SHI population. The age and sex distribution of the AOK PLUS-insured population is broadly comparable to the overall SHI population (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162).

German claims data provide information on patient demographics (age, sex, date of death) and detailed reimbursement claims on inpatient and outpatient care, including pharmaceutical treatments and therapeutic devices. Inpatient care data included date of admission and discharge, diagnostic and therapeutic procedures (per "Operationen-und Prozedurenschlüssel" operation and procedure coding),[16] the main hospitalization diagnosis, and further primary and secondary diagnoses. Outpatient care data included diagnostic and therapeutic procedures per the German Uniform Valuation Scheme,[17] diagnoses from outpatient physicians, and the type of treating physician (per "Arztgruppenschlüssel" physician code). Inpatient and outpatient diagnoses were coded according to the German Modification of the International Classification of Diseases, Tenth Revision (ICD-10-GM). Data on outpatient prescriptions of reimbursed drugs include prescription date, the type of prescribing physician, and the pharmaceutical reference number of the prescriptions (linked to information on the Anatomical Therapeutic Chemical classification code[18]), defined daily dose, packaging size, strength, and drug formulation.

Assessment of WM Incidence

Incident WM cases were those with a diagnosis-free period of ≥12 months before the first confirmed WM diagnosis (ICD-10-GM: C88.0). Patients who were not continuously insured by the sickness fund in that 12-month prediagnosis period were excluded from the analysis (see Appendix Fig. 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162) to prevent incident case misclassification. A 12-month washout period was selected to balance accurately identifying incident cases with reducing exclusion of individuals due to lack of continuous insurance coverage.[19]

In a base-case scenario, a diagnosis was considered justified if ≥2 confirmed outpatient WM diagnoses by any physicians in 2 different quarters within 12 months or ≥1 inpatient WM diagnosis were identified. To verify the base-case scenario, 4 sensitivity scenarios were applied: (1) only outpatient diagnoses made by a hematologist or oncologist were considered; (2) ≥3 outpatient diagnoses in 3 different quarters were required; (3) identification of ≥3 outpatient diagnoses by a hematologist or oncologist in 3 different quarters within 12 months or ≥1 inpatient WM diagnosis was required; and (4) base-case scenario cases only counted if ≥1 bone marrow biopsy claim was observed.

For each scenario, cumulative incidence for each calendar year (2011-2021) was assessed. For each year, patients meeting incident diagnosis criteria in the respective year were counted. This count was related to the number of non-WM insured (individuals under risk) at the beginning of the respective year. Finally, crude incidence rates were stratified by age and sex and applied to the age and sex distribution of the German SHI population (reference population, based on the KM-6 statistic[20]) to calculate age- and sex- standardized incidence rates.

Assessment of WM Prevalence

Point prevalence was calculated by relating the number of prevalent WM cases to the total number of insured individuals on June 30 of the respective calendar year. Consequently, the prevalent WM cohort considered all living individuals insured by the sickness fund on June 30 of the respective calendar year with ≥2 confirmed outpatient diagnoses (ICD-10-GM: C88.0) in 2 different quarters within 12 months or ≥1 inpatient diagnosis between January 1, 2010, and June 30 of the respective year. Rates were standardized to the German SHI population (KM-6 statistic[20]).

Patient Characteristics

Characteristics of identified incident and prevalent cases were descriptively analyzed. Variables referring to the respective index date or the 12-month preindex period included age, sex, Charlson Comorbidity Index (CCI; see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162[21]) comorbidities, and further comorbidities of interest beyond the CCI. For categorical variables, the number and percentage of patients for each category were reported. For continuous variables, summary statistics, including mean and standard deviation (SD), were reported.

Development of Overall Survival

Overall survival (OS) was analyzed for newly diagnosed patients. Incident patients were followed from the date of incident WM diagnosis and additionally, from the start of treatment (separately by different lines of treatment [LOTs]) to death or end of data availability (censoring at the date of withdrawal from the insurance or June 30, 2022). The time to all-cause death was estimated by the Kaplan-Meier (KM) method.

Real-World Treatment

Real-world treatment patterns were described for incident patients with WM based on the patient-individual follow-up period after first diagnosis.

WM-related pharmacological treatments were identified using inpatient procedures and outpatient prescriptions (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162).

Because LOTs were not explicitly captured in the data set, an algorithm based on prescription/procedure dates was implemented to classify treatment sequences. The algorithm was

Table 1. Overview of patient characteristics.

Characteristics	Incident patients with WM	Prevalent cases being alive and insured on January 1, 2021
N	593	426
Follow-up in months, mean (SD)	44.62 (35.62)	12.0 (0.0)
Age in years, mean (SD) | median	72.70 (11.75) | 75	74.54 (12.24) | 77
Female sex, *n* (%)	376 (46.54)	215 (50.47)
CCI, mean (SD) | median	4.26 (3.38) | 4	4.63 (3.51) | 4
Comorbidities, *n* (%)		
Atrial fibrillation (ICD-10-GM code: I48)	90 (15.18)	79 (18.54)
Other cardiac arrhythmia (ICD-10-GM code: I49)	66 (11.13)	58 (13.62)
Congestive heart failure (ICD-10-GM codes: I11, I50)	172 (29.05)	155 (36.38)
Cerebrovascular disease (ICD-10-GM codes: G45, G46, I60-I69)	103 (17.37)	77 (18.08)
Hypertension (ICD-10-GM code: I10)	429 (72.34)	307 (72.07)
Coronary artery disease (ICD-10-GM code: I20-I25)	154 (25.97)	99 (23.24)
Acute or chronic kidney disease (ICD-10-GM codes: N17-N19)	151 (25.46)	135 (31.69)
Diabetes type I and II (ICD-10-GM codes: E10, E11)	167 (28.16)	115 (27.00)
Cytopenia (ICD-10-GM codes: D46, D61, D63, D69)	61 (10.29)	69 (16.20)
Hepatic disease (ICD-10-GM codes: B18, K70-K77)	92 (15.51)	71 (16.67)
Pulmonary disease (ICD-10-GM codes: J00-J99)	218 (36.76)	212 (49.77)

CCI indicates Charlson Comorbidity Index; ICD, International Classification of Diseases; SD, standard deviation; WM, Waldenström macroglobulinemia.

developed in accordance with previous oncology research based on German claims data and discussed with clinical experts within a feasibility analysis.[22] The first prescription of an agent or application of an agent in an inpatient setting after the incident WM diagnosis was considered the start of the first LOT (1LOT). Any outpatient or inpatient registration of agents used to treat WM within 30 days of starting a LOT was considered part of combination therapy. Any new agent prescribed/applied >30 days after initiating a LOT was defined as the start of a new LOT. A LOT was assumed discontinued at the start of a new LOT, or in case of a treatment gap of >90 days, whichever came first. Patients who did not start treatment within 3 months from the incident diagnosis were considered to be on a watch-and-wait approach.

The time from incident diagnosis to treatment initiation was evaluated by KM analysis. Furthermore, the time to a subsequent LOT was analyzed using KM estimations. Observations were censored in cases of death, end of insurance coverage, or end of study period (June 30, 2022). The most frequent treatments per LOT were described using descriptive statistics.

WM-Associated Incremental Economic Burden

A cross-sectional analysis of the most recently observable calendar year (2021) based on the prevalent WM cohort and a matched control group was performed to derive WM-associated incremental healthcare resource utilization (HCRU)/costs. The control group included individuals continuously insured for ≥12 months before January 1, 2021, without WM diagnosis. Nearest-neighbor propensity score matching (PSM) was used to control for known covariates between control and WM groups. Covariate selection was based on baseline patient characteristics (Table 1), selected according to (1) availability within the database and (2) relevance to WM outcomes as determined through guidance of clinical experts. Statistically significant variables in the logistic regression model used for propensity score estimation were retained. The final covariate set included age, sex, CCI (excluding the WM-specific ICD-10-GM code C88.0 to avoid conflating the comorbidity burden), prior history of cytopenia (ICD-10-GM: D46, D61, D63, D69), prior history of pancytopenia (ICD-10-GM: D61.0, D61.1), and level of care. Each patient with WM was matched to the closest control using 1:1 nearest-neighbor matching.

For both the WM prevalent cohort and the matched controls, data on hospitalizations, outpatient visits, outpatient prescriptions, rehabilitation, and days of work absence were collected between January 1, 2021, and the date of death, insurance withdrawal, or December 31, 2021, whichever came first (HCRU/costs variable details presented in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162). The mean differences of the HCRU and cost parameters per observed patient-year between the matched patients with WM and the non-WM controls were calculated.[23]

General Considerations

In all analyses, P values $< .05$ were considered statistically significant. Statistical analyses were performed using Microsoft SQL Server 2014 (Microsoft Corporation, Redmond, WA), STATA/MP 14 (StataCorp LLC, College Station, TX), and Microsoft Excel.

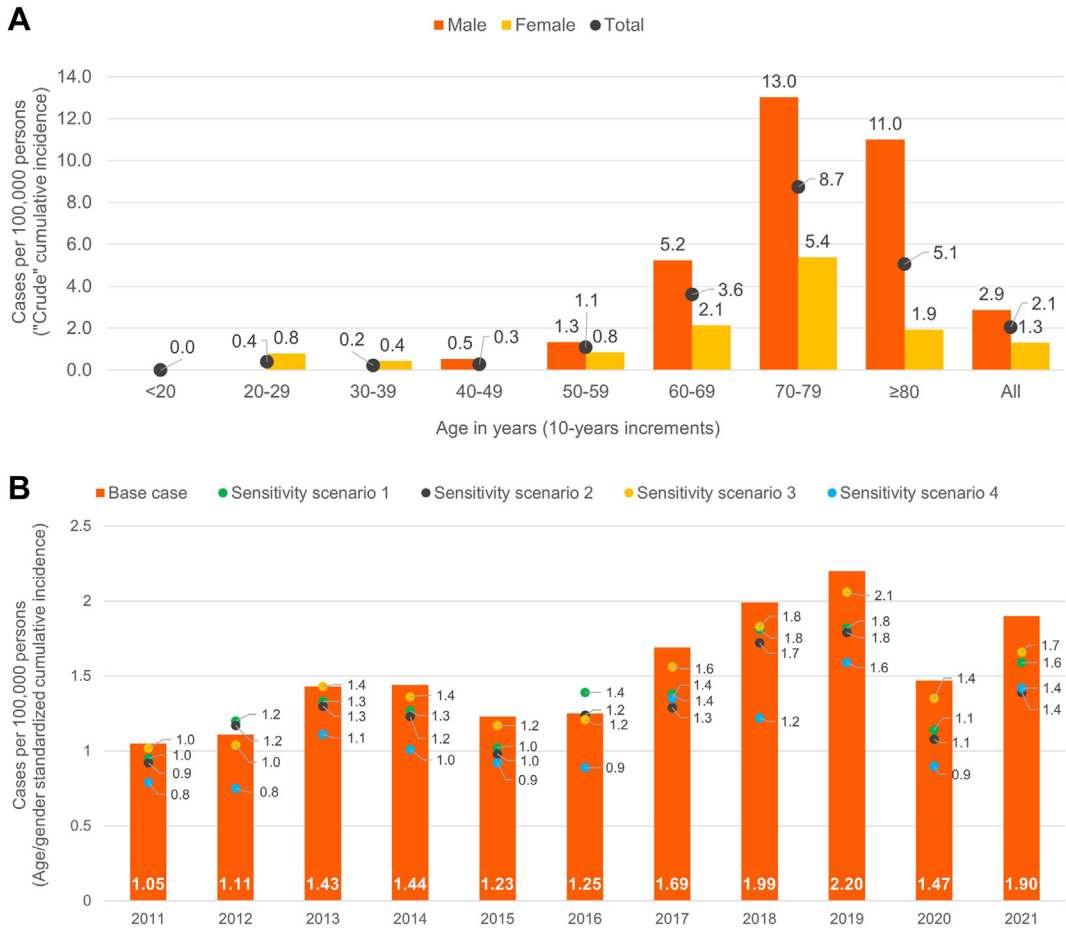
Results

Patient Characteristics

In total, 593 patients were included in the incident WM cohort (base-case scenario; see Appendix Fig. 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162). Mean age at diagnosis was 72.7 years (SD = 11.8), and 46.5% were female (Table 1). Mean CCI based on diagnoses within 12 months before incident WM diagnosis was 3.9 (SD = 3.1). Hypertension (72.3%), pulmonary disease (36.8%), congestive heart failure (29.1%), and diabetes mellitus (28.2%) were the most common comorbidities.

Overall, 426 patients who were living and insured on January 1, 2021, were included in the prevalent cohort. Patients were slightly older (mean age, 74.5 years), had a higher mean CCI (4.6), and more were female (50.5%) than in the incident cohort (Table 1).

Figure 1. (A) Crude cumulative incidence in 2021 by age and sex. (B) Age-/sex-standardized cumulative incidence applying different diagnosis criteria by calendar year.



Incidence of WM

In 2021, the crude cumulative incidence peaked at ages of 70 to 79 years, with 8.7 cases per 100 000 persons (male-to-female ratio: 2.4; Fig. 1A).

The age- and sex-standardized annual incidence increased from 1.05 to 1.90 cases per 100 000 persons from 2011 to 2021 and peaked at 2.20 in 2019 (base case; Fig. 1B). This trend persisted when more restrictive diagnosis criteria were applied (Fig. 1B; Scenario 1-4). Applying the most conservative criteria (Scenario 4), the standardized cumulative WM incidence was 0.79 per 100 000 people in 2011, increased to 1.42 in 2021, and peaked at 1.59 in 2019.

Prevalence of WM

Consistent with increasing incidence, prevalence increased over time. The age- and sex-standardized point prevalence increased from 3.69 cases per 100 000 persons in 2011 to 12.26 in 2021 (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162). The highest increases relative to the preceding year were observed in 2013 (24.3%), 2014 (27.2%), and 2012 (18.6%).

OS

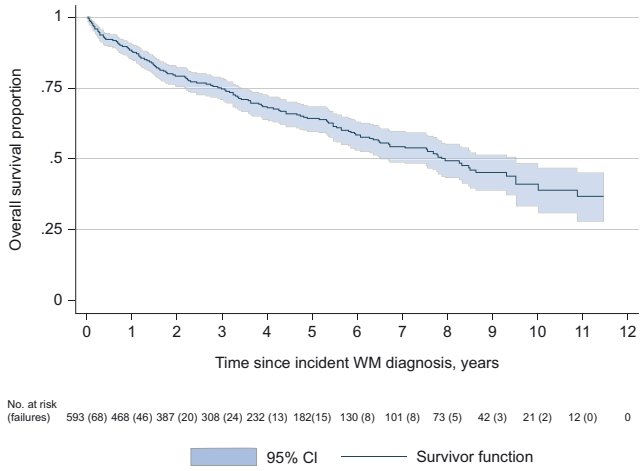
The median time to all-cause death after incident WM diagnosis was 7.9 years (95% CI 6.7-9.5). The survival proportions after 1, 2, and 5 years were 87.2% (95% CI 84.2-89.7), 77.8% (95% CI 74.0-81.0), and 63.7% (95% CI 59.0-68.1), respectively (Fig. 2). The median time to all-cause death following the initiation of 1LOT, 2LOT, and 3LOT was 6.4 years (95% CI 4.4-not reached [NR]), 5.0 years (95% CI 3.3-NR), and 4.4 years (95% CI 3.0-NR), respectively (see Appendix Fig. 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162).

Real-World Treatment

Mean follow-up time for patients with WM was 45.73 months (SD = 35.61). During follow-up, 242 incident patients initiated WM-related treatment. Fifty-two patients (8.77%) started treatment on the day of incident diagnosis. Patients received initial treatment relatively soon after diagnosis, with a quarter of patients starting WM-related therapy within 1.91 months (95% CI 1.38-2.99 months) of incident diagnosis (see Appendix Fig. 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162). However, most patients were initially on the watch-and-wait approach (n = 414, 69.81%) and did not start 1LOT within 3 months from incident diagnosis. After the first percentile, the proportion of treated patients increased slowly over time, reaching the median time to treatment initiation at 91.56 months (95% CI 56.88 months-NR; see Appendix Fig. 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162).

Of 242 patients who initiated 1LOT, 83 (34.30%) initiated 2LOT during follow-up, with 26.03% (95% CI 20.65%-32.63%) having

Figure 2. Kaplan-Meier curve for the overall survival of patients with WM after incident diagnosis.



CI indicates confidence interval; WM, Waldenström macroglobulinemia.

initiated the next LOT within 12 months. Thirty-seven patients (15.29%) initiated 3LOT during the study follow-up period.

In 1LOT, rituximab plus an unspecified inpatient chemotherapeutic treatment (initiated 1LOT between 2011-2017: n = 29, 26.13%; initiated 1LOT between 2018-2022: n = 42, 32.06%) and rituximab plus bendamustine (2011-2017: n = 24, 21.62%; 2018-2022: n = 31, 23.66%) were the most frequently observed regimens (Fig. 3). Rituximab monotherapy was observed in 8.11% (n = 9) and 3.82% (n = 5) of patients who initiated 1LOT from 2011 through 2017, and 2018 through 2022, respectively. Ibrutinib was observed in 5.34% (n = 7) of patients who initiated 1LOT after 2017.

From 2011 through 2017, rituximab, bendamustine, and unspecified inpatient chemotherapy were the most commonly observed 2LOT/3LOT options (as monotherapy or combination therapy), and ibrutinib was the most frequent from 2018 through 2022 (2LOT: n = 16, 34.78%; 3LOT: n = 11, 47.83%). Other agents, such as bortezomib or cyclophosphamide, were rarely seen, especially in recent years (Fig. 3).

WM-Associated Incremental Economic Burden

After PSM, standardized differences between the prevalent WM and control groups for all covariates were considerably smaller (see Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162). Covariates were effectively balanced after matching, with a median standardized difference of 0.2% across covariates (see Appendix Fig. 6 and Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162).

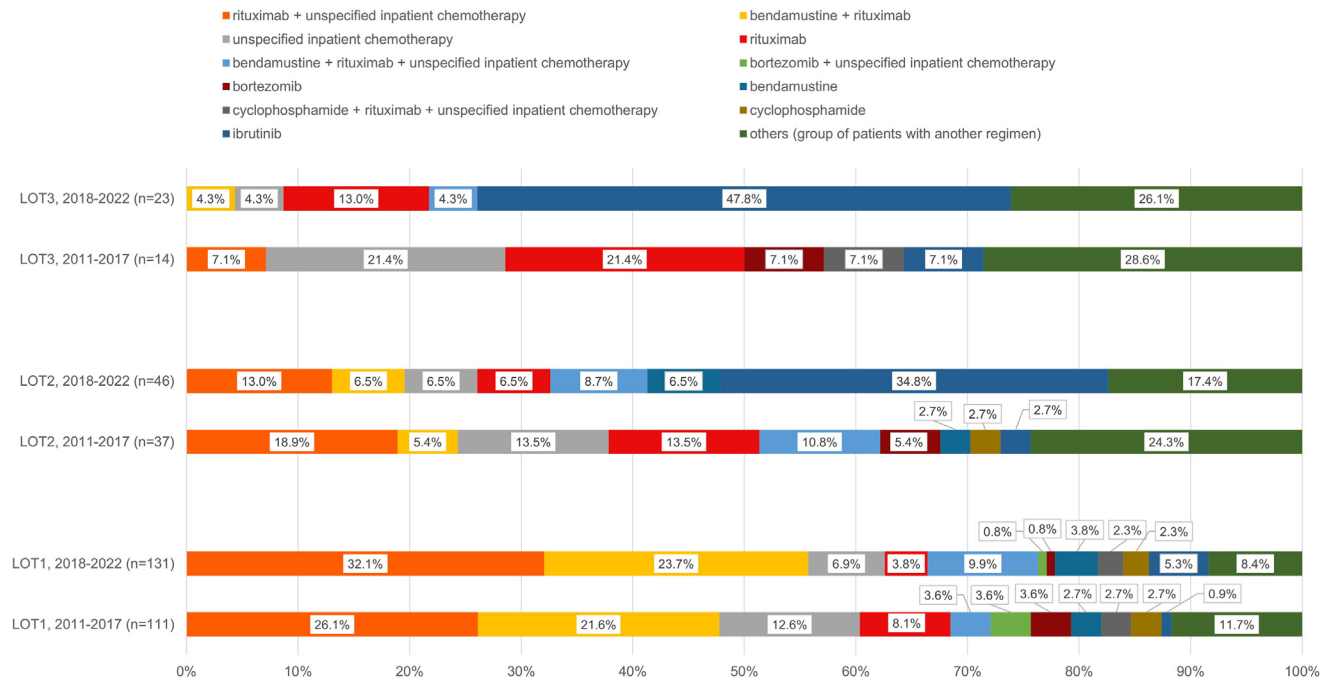
The WM cohort had a significantly higher number of outpatient visits (incremental utilization: Δ = 6.50, $P < .001$) and hospitalizations (Δ = 0.25, P = .007) versus their non-WM matches (see Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162). Incremental utilization of inpatient rehabilitation (covered by the SHI) and medical aids or remedies did not significantly differ between groups. Prescription-related costs were considerably higher in the WM group (7050.81 € versus 2721.13 €; $P < .001$). The total WM-associated incremental costs per observed patient-year were 5750.50 € (see Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101162), primarily driven by hospitalizations and outpatient drugs.

Discussion

Summary of Key Findings

By integrating claims data from a large German SHI provider, this study adds valuable real-world evidence to the limited body of WM research. Here, we found a standardized cumulative WM incidence ranging from 1.39 to 1.90 per 100 000 persons in 2021,

Figure 3. Most frequently observed treatments by LOT and by the time of treatment initiation.



LOT indicates line of treatment.

depending on the diagnostic criteria applied (males: 2.9; females: 1.3 under the base scenario). These rates are notably higher than those reported in older studies from the United States and Europe. Although variations in healthcare systems, population demographics, and study methodologies may explain discrepancies between our findings and prior studies, the higher incidence observed in our study may reflect enhanced diagnostic capabilities, such as next-generation sequencing, increased WM awareness among healthcare providers, and the evolving treatment landscape.

This study confirmed a higher incidence and prevalence of WM in males than females. Furthermore, the peak incidence rate in the 75- to 79-year age group and the mean diagnosis age of 73 years are similar to previous studies.[4-7,24-26]

Regarding treatment patterns, this study highlights the dominance of rituximab-based regimens and the growing use of novel agents such as ibrutinib. These findings are consistent with studies in other regions, although variations in treatment accessibility and regulatory approval timelines may explain uptake differences. The economic burden for patients with WM in this study was substantial, primarily driven by outpatient medications and hospitalizations.

Comparison With Existing Research

Most previous studies investigating WM incidence are United States based. A SEER database analysis of the years 1988 through 2007 revealed an age-adjusted WM incidence of 0.38 per 100 000 persons in the United States.[4] Similarly, Groves et al[27] reported incidence rates of 0.34/100 000 in males and 0.17/100 000 in females, utilizing 11 population-based cancer registries in the United States. Another US study based on Mayo Clinic and Olmsted Medical Group medical records from 1961 through 2010 reported an incidence rate of 0.57 per 100 000 per year.[5] A study in South East England between 1999 and 2001 using Thames Cancer Registry data reported a similar WM incidence, with an age-adjusted incidence of 0.55 per 100 000 people.[6] A Korean analysis using government National Health Insurance data also reported lower WM incidence than our study. However, Jeong et al[24] observed an increasing trend in WM incidence. Differences in ethnicity and geographic variations need to be considered when comparing study results.[4,25] Additionally, most studies identified may be outdated.

Another study utilizing German sickness fund data based on 1 771 217 beneficiaries in 2012 reported a WM prevalence of 0.006%, which is similar to our study findings.[26]

In this study, the median time to all-cause death after incident WM diagnosis was 7.9 years, with a 5-year survival proportion of 63.7%. Apart from the Korean study by Jeong et al,[24] which reported a median OS of 4.5 years, the findings of this analysis are consistent with previous studies. A SEER data-based analysis of 3175 incident patients with WM investigating OS differences between different ethnicities found a median OS of 5.6 years for Hispanic patients and 6.8 years for White patients.[28] Another SEER data-based study including 5784 patients with WM concluded that OS improved over time.[8] Adjusting for age, sex, race, histology, site of involvement, and registry, a median OS of 6 years for those diagnosed between 1991 and 2000 was reported, whereas the estimated median OS for patients diagnosed between 2001 and 2010 was 8 years. This trend was not confirmed in this German analysis.

In this study, nearly 70% of incident patients with WM initially followed a watch-and-wait approach. After 2 years, less than one-third began therapy, highlighting the disease's indolent nature. Many patients had comorbidities before starting treatment: about 1 in 8 had atrial fibrillation, 72% had hypertension, and 25% had kidney disease. This suggests that dose-intense chemotherapy or Bruton tyrosine kinase inhibitors with known cardiotoxicity may be unsuitable, necessitating treatment tailored to individual comorbidities.

Among those who began therapy during follow-up, rituximab plus bendamustine or unspecified inpatient chemotherapy was the most common systemic treatment across lines. After 2015, ibrutinib became prominent in 2LOT and 3LOT. Incremental cost analysis attributed a significant cost of care (5750.50 €) to WM, primarily driven by outpatient prescriptions and inpatient care. Existing literature on real-world treatment of WM is sparse and varied. A 2012 German study showed rituximab alone or in combination as the leading treatment (75.9%), whereas 48.3% had bendamustine prescriptions.[26,29] Another German study from 2009 through 2017 using tumor registry lymphatic neoplasm data highlighted bendamustine-based therapies as the most common 1LOT (85%), mostly combined with rituximab, and also prevalent in 2LOT (31%).[30] Rituximab-based therapies were also common in the current study.

A US study using Veterans Health Administration data from 2006 through 2019 showed rituximab monotherapy as the most common 1LOT.[31] Bendamustine plus rituximab, bortezomib plus dexamethasone plus rituximab, and dexamethasone plus cyclophosphamide plus rituximab were also frequent. Ibrutinib use increased after approval, aligning with current study findings.[31]

Treatment pattern comparisons across studies are challenging because of varying study periods and the introduction of new therapies. For example, Olszewski et al[29] showed that between 1994 and 2013, rituximab monotherapy use increased rapidly after 1999, with bendamustine and bortezomib use rising later.

Limitations

This study used German SHI administrative data, with limitations typical of retrospective claims data studies. First, the database did not differentiate between incident and prevalent diagnoses, and a 12-month diagnosis-free period was used to define incident cases. Although this approach is commonly applied in claims-based research, it may not exclude patients who were previously diagnosed but remained on a watch-and-wait approach before reentering the healthcare system, potentially leading to overestimated incidence rates. A sensitivity analysis using a longer 24-month washout period confirmed the robustness of the results, suggesting that this limitation had minimal impact on the overall findings.

Despite these limitations, the 12-month period represents a balance between capturing newly diagnosed cases and maintaining a sufficiently large sample.

Another limitation is the lack of clinical data, preventing a detailed description of diagnosis reliability and consideration of patient-individual treatment factors. WM diagnoses typically involve clinical and laboratory evaluations, including detection of serum monoclonal immunoglobulin M protein, bone marrow biopsy demonstrating lymphoplasmacytic infiltration, and genetic or imaging studies per International Workshop on WM consensus criteria.[1] However, these clinical data are not captured in claims databases, limiting our ability to fully assess diagnosis reliability or confirm diagnostic guideline adherence. Nevertheless, a notable strength of this study is the availability of a WM-specific ICD-10-GM code (C88.0), alongside a flag in the data indicating a "confirmed" diagnosis. Although the confirmation flag adds reliability, it does not specify whether the diagnosis strictly follows consensus criteria. To address this limitation, we applied robust validation criteria, including at ≥2 confirmed outpatient

diagnoses in different quarters within 12 months or ≥1 inpatient diagnosis. Sensitivity analyses were conducted to strengthen findings by incorporating additional criteria, such as claims for bone marrow biopsy and restricting diagnoses to specialists (eg, hematologists or oncologists).

Furthermore, LOTs were not explicitly captured, necessitating an algorithm to classify treatment episodes. Although systemic agents for WM were uniquely identified, not all agents could be identified because older treatments were generally reimbursed under a general Operationen-und Prozedurenschlüssel code for inpatient chemotherapy/immunotherapy.

The study used regional AOK PLUS claims data, which might limit generalizability to all of Germany. However, previous studies using AOK PLUS data confirmed its utility in understanding disease economic burdens.[22,32] Additionally, the data used in this study included only individuals insured under the SHI system, which covers approximately 90% of the German population. The remaining 10% were primarily privately insured individuals, who may have higher incomes and may exhibit different HCRU patterns. Although this study provides robust evidence on the epidemiology and economic burden of WM within the SHI population, potential minor differences between SHI and private insurance populations should be considered when interpreting the results.

In the incremental cost analysis, although PSM is widely used in observational studies, it is limited by the assumption that all relevant confounders are observable and accurately measured. Unmeasured confounders may still introduce bias, which prevents interpretation of incremental costs as strictly causal in the absence of WM. Furthermore, PSM may reduce precision and does not address potential residual confounding. Alternative approaches to validate and compare results, such as regression adjustment or inverse probability weighting, could provide complementary insights but were not used to maintain methodological consistency. Additionally, the distributional characteristics of cost data are often skewed because of a small proportion of very high-cost patients. Although this analysis used mean cost estimates to describe the incremental economic burden, this approach may obscure the influence of cost variability and outliers. Future studies may consider generalized linear models or quantile regression to better account for inherent skewness and provide a more nuanced understanding of cost distributions.

Lastly, this study analyzed OS based on all-cause mortality because cause-of-death information was unavailable in the claims data. As a result, the survival analysis reflects the broader impact of WM on patient outcomes but does not allow for the interpretation of WM's direct impact on survival. Additionally, sample sizes were insufficient for meaningful OS analysis across specific treatment regimens. Given recent emergence of novel therapies, further studies with larger cohorts and detailed treatment data are needed to evaluate the impact of individual treatment options comprehensively.

Conclusions

Findings of this study indicate a considerable increase in the incidence of WM in Germany, with an incidence peak in males aged 75 to 79 years. With a 5-year survival rate of 64%, the prognosis of German patients with WM is reasonable and may continue to improve with treatment advances. Further research is needed to investigate geographical, environmental, and genetic factors influencing the incidence and mortality in WM.

Although most patients followed a watch-and-wait approach after incident WM diagnosis, a considerable disease burden was shown. The WM-associated incremental costs were >5000 euros per patient-year and were driven mainly by outpatient drug prescriptions and hospitalizations. In patients treated for WM, rituximab, bendamustine, and general inpatient chemotherapies were most common. However, after ibrutinib approval, the number of patients initiating ibrutinib monotherapy increased, particularly in later LOTs, and the landscape will further change with the introduction of new agents currently in development.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2025.101162.

Article and Author Information

Accepted for Publication: May 26, 2025

Published Online: xxxx

doi: https://doi.org/10.1016/j.vhri.2025.101162

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Authorship Confirmation: All authors certify that they meet the ICMJE criteria for authorship.

Author Contributions: *Concept and design:* Buske, Bahar, Tang, Müller
Acquisition of data: Müller
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Drafting of the manuscript: Müller
Critical revision of the paper for important intellectual content: Buske, Herold, Bahar, Yang, Tang, Müller, Hess
Obtaining funding: Bahar, Yang, Tang
Administrative, technical, or logistic support: Müller
Supervision: Buske, Bahar

Funding/Support: This work was supported by BeOne Medicines Ltd, Basel, Switzerland.

Role of the Funder/Sponsor: BeOne Medicines employees are authors of this publication and were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgment: The authors extend their heartfelt gratitude to Angelika Imhof and Katharina Vinz for their invaluable support during the development of this manuscript. Their insights and constructive feedback significantly contributed to the refinement of the research and were essential to the successful completion of this work.

Ethical Approval: Because the study addressed a retrospective anonymized data set, no ethical review was needed. However, the study protocol was reviewed by a scientific steering committee and the data owner (statutory health insurance, AOK PLUS). The work on the data set conformed to all social security data protection requirements.

Patient Consent: In Germany, the use of statutory health insurance claims data for scientific research is regulated by the Code of Social Law (§ 75 SGB X). As the responsible authority, the involved sickness fund approved the use of the data for the purpose of this study. Informed consent was not required by law because the study was based on anonymized data.

Data Availability: All data needed to evaluate the conclusions in the paper are present in the main text and/or the Supplemental Materials.

On request, and subject to certain criteria, conditions, and exceptions, BeOne Medicines Ltd will provide access to individual de-identified participant data from BeOne-sponsored global interventional clinical studies conducted (1) for indications that have been approved based on the BeOne data sharing policy or (2) in programs that have been terminated. BeOne shares data only when permitted by applicable data privacy and security laws and regulations, shares when it is feasible to do so without compromising the privacy of the study participants and other considerations. Data requests may be submitted to ClinicalTrials@beonemed.com.

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