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Survival Trends in Waldenström Macroglobulinemia and Comparison of Outcomes with the General US Population

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Article

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Abstract

Therapeutic options for Waldenström macroglobulinemia (WM) have expanded but improvements in overall-survival (OS) are difficult to interpret due to competing non–WM mortality. We conducted a large single-center retrospective study of 1,020 patients with WM to evaluate survival trends. Patients were stratified by era of active WM diagnosis using a two-era model (1996–2005 and post-2005) and a four-era model (pre-2001, 2001–2007, 2008–2013, and post-2013). OS did not differ significantly across eras in the overall cohort ($p = 0.64$ and $p = 0.86$ for the two- and four-era models). However, among patients aged < 65 years at the time of active WM diagnosis in the 2-era model, OS improved in the post-2006 era (median 18.8 vs 14.1 years, $p = 0.018$). Cause-specific-survival (CSS) improved across all eras, increasing from 15.6 years in 1996–2005 to 18.9 years post-2006 ($p < 0.0001$), and from 13.7 years pre-2001 to not reached in later periods in the four-era model ($p < 0.0001$). Competing-risk-analysis (CRA) demonstrated a reduction in WM-related mortality over time ($p < 0.001$). However, excess mortality persisted, with a standardized mortality ratio (SMR) of 2.79 ($p < 0.001$) among patients < 65 years compared with a matched U.S. population. Our findings highlight improvements in WM-specific survival, while gains in OS are observed in younger patients.

Introduction

Waldenström macroglobulinemia (WM) is a rare, indolent B-cell lymphoproliferative disorder characterized by bone marrow infiltration with at least 10% lymphoplasmacytic cells and the presence of a circulating IgM monoclonal gammopathy.[1, 2] The clinical course of WM is variable, with many patients remaining asymptomatic for prolonged periods, while others develop disease-related complications including anemia, symptomatic hyper viscosity, peripheral neuropathy, systemic light/heavy chain amyloidosis (AL/ALH), and organ dysfunction that necessitate therapy.[3–5] As a result, treatment is typically reserved for patients with symptomatic or otherwise clinically significant disease, often referred to as active disease (AD).

The therapeutic landscape of WM has evolved substantially over the past several decades. Earlier treatment strategies relied largely on alkylating agents and nucleoside analogs, whereas the incorporation of rituximab-based regimens represented a major advance in disease control.[2, 6] More recently, the introduction of Bruton tyrosine kinase inhibitors (BTKi) has further expanded available treatment options, particularly in the relapsed and refractory settings.[7–10] Despite these advances, WM remains incurable, and patients frequently experience multiple lines of therapy over the course of their disease.[11, 12]

Population-based and institutional studies have suggested improvements in survival for patients with WM over time; however, interpretation of these findings is complicated by the contribution of non–WM-related mortality.[13, 14] As WM predominantly affects older individuals with a median age of close to 70 years at presentation, and as such overall survival may not fully capture disease-specific outcomes, cause-specific survival analyses that account for competing risks is essential to more accurately assess

WM-related mortality trends.[15] Moreover, relatively few large cohorts have examined temporal trends in WM outcomes using both traditional survival methods and competing risk approaches across multiple treatment eras.

To address these gaps, we conducted a large single-center retrospective study of patients with WM diagnosed over more than two decades at a tertiary referral center. By stratifying patients according to the era of active disease diagnosis and applying both overall (OS) and cause-specific survival (CSS) analyses along with competing risk analyses (CRA), we sought to evaluate temporal changes in survival while accounting for age, disease-related factors, and evolving treatment patterns. Our objective was to characterize long-term survival trends in WM and to assess whether improvements in disease-specific outcomes have occurred across successive diagnostic eras.

Methods

This study was conducted in accordance with the Declaration of Helsinki, and all methods were performed in accordance with the relevant guidelines and regulations. The Mayo Clinic Institutional Review Board Approval was obtained for conducting the study. Individual informed consent was obtained per institutional requirements and guidelines.

Consecutively seen patients with active WM between 01/01/1996 and 12/31/2018 were included in the study. Patients were grouped into time periods in which active WM was diagnosed. An analysis comparing characteristics and survival between time periods between 1996–2005 and those diagnosed in 2006 or later as well as pre-2001, 2001–2007, 2008–2012, and those diagnosed in 2013 or later was done. The selected time periods were defined to reflect major therapeutic eras in WM. The 1996–2005 vs post-2006 comparison captures the transition to routine rituximab use, while the four-era analysis further delineates periods corresponding to early rituximab adoption, adoption of bendamustine-rituximab and similar chemoimmunotherapy regimens as well as the introduction of BTK inhibitors.[16] Categorical variables were compared using the Chi-square test or Fisher's exact test. OS and CSS were evaluated using the Kaplan–Meier method with group comparisons by log-rank test. For CSS, deaths attributable to causes other than WM were treated as censored events. In cases where the cause of death was unknown, but WM was in remission at the time of death, the death was considered non-WM related. Competing risk analysis was performed to account for non–disease-related deaths. Deaths resulting from WM progression, histologic transformation, AL/ALH, or complications related to WM-directed therapy including therapy-related myeloid neoplasms, were considered WM-related. Deaths from other causes were treated as competing events and patients who were alive at last follow-up were censored. Multivariable Cox proportional hazards regression was used to evaluate factors associated with CSS, treating non–WM-related deaths as censored events. Excess mortality in the WM cohort was evaluated by calculating the Standardized Mortality Ratio (SMR), defined as the ratio of observed deaths to the number of deaths expected in an age, sex, and calendar year–matched U.S. population life tables from the Human Mortality Database. Statistical analysis was performed using BlueSky LLC and Rstudio 2025.09.2.

Results

Patient Characteristics

The study included a total of 1,020 patients with a median age of 66.24 years at time of diagnosis of active WM. Six hundred and thirty-five (62.25%) patients were males and 952 patients (93.33%) identified as Caucasian. The median follow up from time of diagnosis for the entire cohort was 13.1 years (95% CI 12.76–13.7) and the median overall survival was 11.4 years (95% CI 10.57–12.23). At the follow-up cutoff of October 1st, 2025, 561 (55%) of patients had died and the cause of death was known for 467 (83.2%) patients (supplementary Table 1).

Patients were stratified by era of active WM diagnosis using two complementary approaches: a 2-era model comparing 1996–2005 with post-2005, and a four-era model comparing pre-2001, 2001–2007, 2008–2013, and post-2013. Median follow-up measured 20.5 and 11.3 years for the 1996–2005 and post-2006 cohorts, respectively, and 21.3, 20.0, 13.1, and 9.2 years for the pre-2001, 2001–2007, 2008–2013, and post-2013 cohorts. Baseline characteristics by treatment era are summarized in Table 1 using the two-era model. Patients treated in more recent eras were older at the time of active WM diagnosis, with the proportion aged ≥ 65 years increasing over time (44% pre-2001 to 56% post-2013, $p < 0.01$) and median age rising from 64.3 to 66.7 years ($p < 0.01$). Other baseline disease features were comparable across eras, including anemia, thrombocytopenia, $MYD88^{L265P}$ genotype, IPSS-WM risk category, rates of AL/ALH and histologic transformation rates. Frontline treatment patterns evolved, with rituximab use increasing from 15% pre-2001 to over 70% after 2008, and BTK inhibitor therapy expectedly emerging exclusively in the post-2013 era. Treatment patterns are outlined in Supplementary Fig. 1.

Table 1
Baseline clinical and disease characteristics of the entire cohort according to the two-era model

Median age (range)	**1991–2005**	**Post 2006**	**P-value**
	64.0 (31.6–89.6)	**66.5 (36.2–95.4)**	**< 0.01**
Age ≥ 65 years (%)	162/330 (49.1%)	386/690 (55.9%)	0.03
Lactate dehydrogenase > ULN (%)	12/106 (11%)	44/249 (18%)	0.16
Hemoglobin ≤ 11.5g/dL (%)	154/207 (74%)	345/501 (69%)	0.15
Platelet count ≤ 10^{9}/L (%)	24/164 (15%)	54/429 (13%)	0.58
$MYD88^{L265P}$ Mutation	38/52 (73%)	214/285 (75%)	0.88
IPSS-WM High Risk (%)	31/69 (44.9%)	98/259 (37.8%)	0.43
AL Amyloidosis at any point (%)	20/304 (7%)	50/685 (7%)	0.59
Histological transformation	22/330 (7%)	24/690 (4%)	0.56

Abbreviations: ULN, upper limit of normal; IgM, immunoglobulin M; IPSS-WM, International Prognostic Scoring System for Waldenström Macroglobulinemia; BTK, Bruton tyrosine kinase.

Overall Survival Analysis

OS was first analyzed using the two-era model and was comparable between patients diagnosed in 1996–2005 and those diagnosed post-2006, with median OS of 10.9 years (95% CI 9.8–12.1) and 11.9 years (95% CI 10.6–13.5), respectively (p = 0.64; Fig. 1A). The corresponding 10-year OS rates were 53.9% (95% CI 48.6–59.2%) and 57.7% (95% CI 53.2–62.3%). While OS did not improve across these time periods, SMR demonstrated a reduction in the post-2006 era [SMR 1.75 (95% CI: 1.56–1.95)] compared to the 1996–2005 era [SMR 1.99 (1.75–2.25), Supplementary Fig. 2].

Using the four-era stratification, the median OS was 9.9 years (95% CI 8.9–11.6) for the pre-2001 cohort, 12.0 years (95% CI 10.8–13.6) for 2001–2007, 11.7 years (95% CI 10.2–13.6) for 2008–2013 and not reached for post-2013 cohort (p = 0.86, Supplementary Fig. 3A). The 10-year OS rates were 48.9% (95% CI 40.8–57.5%), 59.8% (95% CI 53.1–66.3%), 56.2% (95% CI 50.5–61.8%) and 58.1 (95% CI 51.8–65.7%) respectively.

As age emerged as a dominant factor, the entire cohort was stratified by age and OS was re-examined. Among patients aged ≥ 65 years, OS did not differ significantly in the 2-era model (p = 0.42; Fig. 1B). When further divided into four eras, OS among patients aged ≥ 65 years remained unchanged (p = 0.7). Patients aged < 65 years at time of active WM diagnosis were then analyzed separately. In the two-era model, OS was significantly improved in the post-2006 cohort compared with those diagnosed between 1996–2005, with median OS of 18.8 versus 14.1 years (p = 0.018; Fig. 1C). The corresponding 10-year OS

rates were 63.1% (95% CI, 56.1%–70.1%) in the 1996–2005 era and 75.2% (95% CI, 69.9%–80.8%) in the post-2006 era. When stratified using the four-era model, OS among patients aged < 65 years did not differ significantly across diagnostic periods (p = 0.24). We then calculated the SMR by age group to determine the excess mortality in younger (< 65 years) and older patient groups (≥ 65 years). Compared with the age, sex, and calendar year–matched general population, the SMR was 2.79 (95% CI 2.41–3.21; p < 0.001, Fig. 2) among patients aged < 65 years and 1.57 (95% CI: 1.4–1.73; p < 0.0001) among those aged ≥ 65 years.

On univariable Cox regression analysis, increasing age (HR 1.06, 95% CI 1.05–1.07; p < 0.001), amyloidosis at any time (HR 2.24, 95% CI 1.69–2.99; p < 0.001), and histologic transformation (HR 1.58, 95% CI 1.12–2.22; p = 0.01) were associated with inferior overall survival. IgM level and diagnostic era were not significantly associated with survival.

On multivariable Cox regression analysis, increasing age at active disease (HR 1.09, 95% CI 1.05–1.12, p < 0.001) and the presence of AL/ALH at any time point during the disease course (HR 20.9, 95% CI 3.8-122.7, p < 0.001) remained associated with inferior survival. Histologic transformation demonstrated a trend towards worse survival (HR 2.53, 95% CI 0.90–7.12, p = 0.08).

Cause-Specific Survival Analysis

The CSS was subsequently analyzed and demonstrated a significant improvement across successive diagnostic time periods. In the two-era model, patients diagnosed post-2006 had superior CSS compared with those diagnosed between 1996–2005 (18.9 vs 15.6 years, p < 0.0001, Fig. 3A). The corresponding 10-year CSS rates were 65.4% (95% CI 59.2–70.1%) and 77.7% (95% CI 73.8–81.9%) respectively. Similar findings were observed using the four-era stratification. Median CSS improved from 13.7 years in the pre-2001 cohort to 18.9 years in the 2001–2007 cohort, while median CSS was not reached in the 2008–2013 and post-2013 cohorts (p < 0.0001; Supplementary Fig. 3B). The 10-year CSS rates increased progressively across eras: 61.8% (95% CI 52.4–70.5%) for pre-2001, 69.4% (95% CI 64.1–76.5%) for 2001–2007, 74.3% (95% CI 69.4–79.1%) for 2008–2013, and 82.7% (95% CI 77.5–88.6%) for post-2013.

Among patients aged ≥ 65 years, CSS improved significantly in the post-2006 era compared with 1996–2005, with a median CSS of 18.9 years versus 11.2 years, respectively (p = 0.0028; Fig. 3B). The 10-year CSS for this age group increased from 57.8% (95% CI, 50.2%–66.7%) in 1991–2005 to 71.2% (95% CI, 65.7%–77.1%) in the post-2006 cohort. When further stratified into four eras, CSS improved progressively across successive time periods (p = 0.0046; Supplementary Fig. 3C). Median CSS was 11.0 years in the pre-2001 cohort and 13.2 years in 2001–2007 and was not reached in the 2008–2012 and post-2013 cohorts. Similarly, 10-year CSS rates increased over time, from 55.6% (95% CI, 43%–69%) in the pre-2001 group to 62.5% (95% CI, 53.8%–72.7%) in 2001–2007, 68.6% (95% CI, 61.5%–76.6%) in 2008–2012, and 76.1% (95% CI, 67.7%–85.5%) in the post-2013 cohort. Among patients aged < 65 years at the time of active WM diagnosis, CSS was significantly improved in the two-era model (p = 0.0031; Fig. 3C), with median CSS not reached in either group. The 10-year CSS increased from 71.9% (95% CI,

65.9%–79.0%) pre-2006 to 82.7% (95% CI, 78.1%–87.7%) in the post-2006 cohort. In the four-era model, CSS improved significantly (p = 0.0061; Supplementary Fig. 3D), with a median CSS of 18.9 years in the pre-2001 cohort and not reached in the subsequent three eras. The 10-year CSS rates increased progressively across eras: 66.4% (95% CI, 55.6%–79.2%) pre-2001, 75.8% (95% CI, 68.3%–84.0%) in 2001–2007, 78.8% (95% CI, 72.1%–86.1%) in 2008–2012, and 88.5% (95% CI, 82.3%–95.2%) in the post-2013 cohort.

On multivariable Cox proportional hazards analysis, increasing age at active disease was independently associated with worse CSS (HR 1.07 per year, 95% CI 1.01–1.12; p = 0.01). IgM levels at time of active WM diagnosis and transformed disease status were not independently associated with survival after adjustment for age.

Competing Risk Analysis

CRA was performed to evaluate cause-specific mortality, treating non–WM death as a competing event. In the two-era model, the cumulative incidence of WM-related death differed significantly between groups, with lower disease-specific mortality observed among patients diagnosed in 2006 onwards (p < 0.001; Figs. 4A & 4B). The 10-year cumulative incidence of WM-specific death was 32.4% (95% CI 28.9–38.1%) for the 1991–2005 cohort compared with 21.5% (95% CI 18.8–24.5%) for the post-2006 cohort. In the four-era model, the cumulative incidence of WM-related death also differed significantly across diagnostic periods (p < 0.001; Supplemental Figs. 4A & 4B). The 10-year cumulative incidence of WM-specific death was 37.1% (95% CI 29.6–46.5%) in the pre-2001 cohort, 28.2% (95% CI 23.0-34.6%) in the 2001–2007 cohort, 24.8% (95% CI 20.5–29.9%) in the 2008–2013 cohort, and 17.0 (95% CI 12.7–22.8%) in the post-2013 cohort. Among patients aged ≥ 65 years, CRA demonstrated lower disease-specific mortality among patients diagnosed in 2006 onwards (p < 0.001). The 10-year cumulative incidence of WM-specific death declined from 37.7% (95% CI, 30.9%–46.1%) in 1996–2005 to 25.1% (95% CI, 20.8%–30.2%) in the post-2006 era.

When further stratified into four eras, CRA revealed the cumulative incidence of WM-related death also differed significantly across successive diagnostic periods (p < 0.001). The 10-year cumulative incidence of WM-specific death decreased progressively across eras, from 37.1% (95% CI, 29.6%–46.5%) in the pre-2001 cohort to 28.2% (95% CI, 23.0%–34.6%) in 2001–2007, 24.8% (95% CI, 20.5%–29.9%) in 2008–2013, and 17.0% (95% CI, 12.7%–22.8%) in the post-2013 cohort. Patients aged < 65 years were then examined separately. The cumulative incidence of WM-related death also differed significantly across successive diagnostic periods (p = 0.007). The 10-year cumulative incidence of WM-specific death declined from 27.2% (95% CI, 21.2%–34.9%) in the pre-2006 era to 17.8% (95% CI, 13.6%–23.2%) in the post-2006 era. In the four-era model, CRA demonstrated a significant decline in the cumulative incidence of WM-related death across successive diagnostic periods (p = 0.007). The 10-year cumulative incidence of WM- related deaths decreased from 33.1% (95% CI, 23.3%–46.9%) in the pre-2001 cohort to 24.8% (95% CI, 18.1%–33.8%) in 2001–2007, 21.4% (95% CI, 15.5%–29.5%) in 2008–2013, and 11.3% (95% CI, 6.4%–19.8%) in the post-2013 cohort.

Discussion

In this large single-center retrospective cohort spanning more than two decades, we evaluated temporal trends in survival among patients with WM diagnosed with active disease, using both OS and CSS analyses that accounted for competing risks. Our findings demonstrate a significant improvement in WM-specific survival across successive diagnostic eras. These results highlight the importance of cause-specific and competing risk analyses when interpreting long-term outcomes in WM, a disease that predominantly affects older individuals and is associated with substantial non–disease-related mortality[17].

Although prior studies have suggested improvements in OS over time, interpretation has been limited by the confounding effects of age and competing causes of death. In our cohort, OS did not differ significantly across diagnostic eras despite clear temporal shifts in treatment patterns, including increased use of rituximab-based regimens and the emergence of BTK inhibitors in more recent years. In contrast, CSS improved significantly in later eras, a finding that persisted across multiple temporal stratifications and was confirmed using competing risk analyses. These observations suggest that advances in WM management may have preferentially reduced WM-related mortality, even as overall mortality remains unchanged.

While the OS remained largely unchanged during the different treatment eras, we observed a noticeable improvement in the survival among patients 65 years or younger at the diagnosis of WM in the newer treatment era. Yet, when comparing the mortality with an age-, sex- and calendar-matched US general population cohort, the mortality risk was significantly higher in the younger population, highlighting the need for ongoing improvement in therapies especially in patients with an expected longer lifespan from the diagnosis of WM. The lack of an improvement on OS in older patients may reflect the higher risk of non–WM-related mortality in older patients, which could negate the survival gains associated with therapeutic advances in WM. Differences in treatment tolerance, reduced dose intensity, and potential variations in disease biology in older patients may also contribute to the absence of similar improvements in this group. Older age at the time of active disease diagnosis was independently associated with inferior survival outcomes, and patients aged 65 years or older experienced significantly worse OS and WM-specific survival compared with younger patients consistent with previously published literature [11].

Age emerged as a dominant determinant of both OS and CSS in our study. Improvements in overall survival across successive diagnostic eras were observed when the analysis was limited to patients younger than 65 years at the time of active WM, but not among those aged ≥ 65 years.

Our study has several strengths. The large cohort size, long duration of follow-up, and availability of cause-of-death data allowed for robust evaluation of WM-specific outcomes. Several limitations merit consideration. This was a single-center retrospective study conducted at a tertiary referral center, which limits generalizability. In addition, cause of death was not available for all patients, although competing risk analyses were restricted to cases with known attribution.

In conclusion, this study demonstrates a significant improvement in WM-specific survival across successive treatment eras, while OS improvement was restricted to a younger cohort in the more recent treatment eras. Despite the improvement in the OS in younger patients and the indolent nature of this disease, the burden of WM in these patients persists with a nearly 2.8-fold higher risk of mortality compared to the general population. These findings underscore the need for continued development of novel therapeutics in WM.

Declarations

*The data in this manuscript will be presented as a Poster Abstract at the 2026 Annual EHA Meeting.

Conflict of Interest Statement

The authors declare no conflicts of interest relevant to this manuscript.

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Authorship Contributions

MAK, GG, JPA and SZ contributed to data collection, statistical analysis, data interpretation, and drafting of the manuscript. SZ and JPA conceived and designed the study. MAG, SK, RLK, JP, TMH, RSG, JC, NA, GT, FB, AD, CAT, WG, GSN, DD, EM, PTG, SD, JN RW, TEW, SVR, SMA and PK critically reviewed the manuscript, suggested edits, and all authors approved the final version of the manuscript draft for submission.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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18. Tabke and Figure Legends

Figures

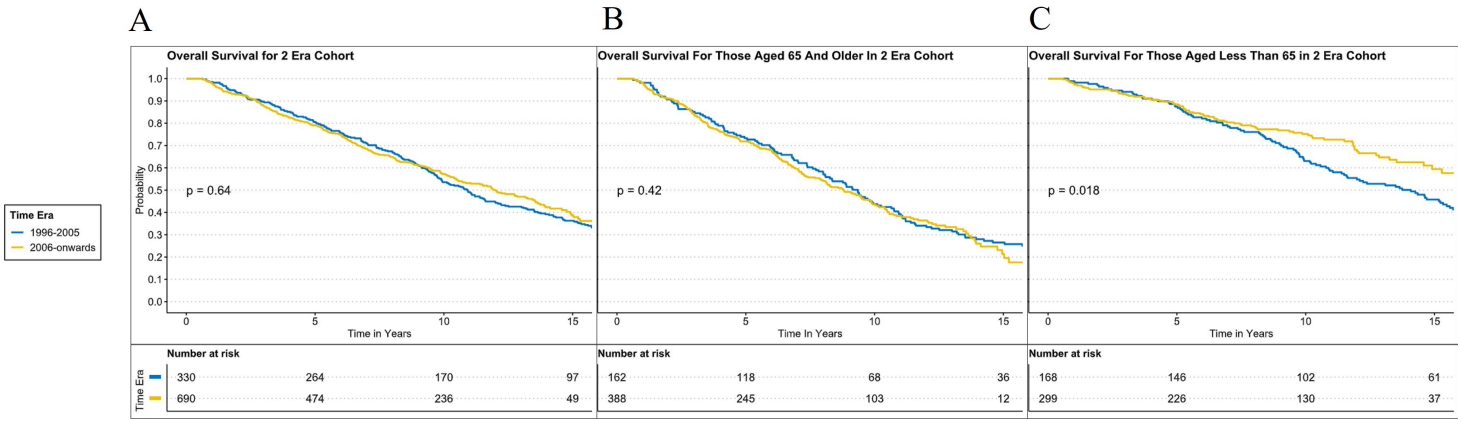

Figure 1

A. Overall survival (OS) for the entire cohort by diagnostic era (two-era model): Kaplan–Meier curves demonstrating OS stratified by diagnostic era (1996–2005 vs post-2006). Survival distributions were compared using the log-rank test, and numbers at risk are shown below the x-axis.

B. Overall survival (OS) among patients aged ≥65 years by diagnostic era (two-era model): Kaplan–Meier curves demonstrating OS among patients aged 65 years and older stratified by diagnostic era (1996–2005 vs post-2006). Survival distributions were compared using the log-rank test, and numbers at risk are shown below the x-axis.

C. Overall survival (OS) among patients aged <65 years by diagnostic era (two-era model): Kaplan–Meier curves demonstrating OS among patients younger than 65 years stratified by diagnostic era (1996–2005 vs post-2006). Survival distributions were compared using the log-rank test, and numbers at risk are shown below the x-axis.

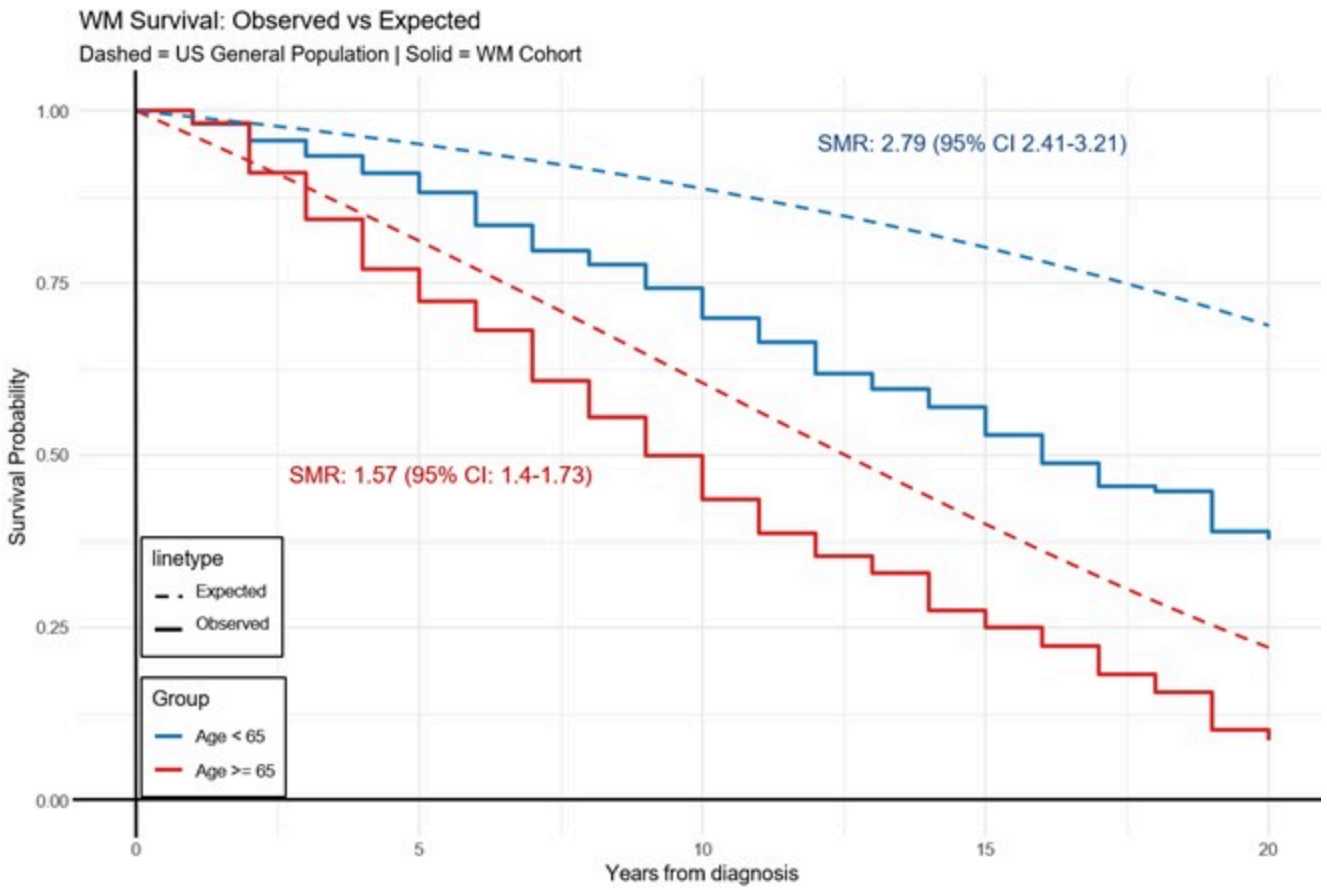

Figure 2

Standardized mortality ratios (SMR) by age group. Observed survival in the WM cohort (solid lines) compared with expected survival from an age-, sex-, and calendar year–matched US general population (dashed lines), stratified by age group (<65 years; blue lines vs ≥65 years; red lines).

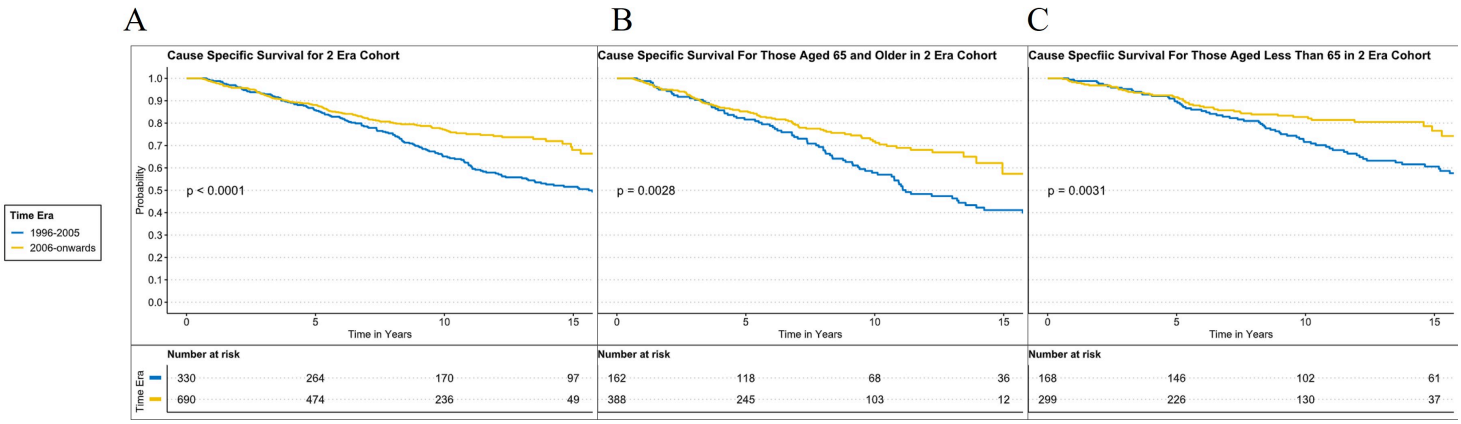

Figure 3

A. Cause-specific survival (CSS) for the entire cohort by diagnostic era (two-era model). Kaplan–Meier curves demonstrating CSS stratified by diagnostic era (1996–2005 vs post-2006). Deaths unrelated to

Waldenström macroglobulinemia (WM) were censored. Survival distributions were compared using the log-rank test, and numbers at risk are shown below the x-axis.

B. Cause-specific survival (CSS) among patients aged ≥ 65 years by diagnostic era (two-era model). Kaplan–Meier curves demonstrating CSS stratified by diagnostic era (1996–2005 vs post-2006) among patients aged ≥65 years. Deaths unrelated to Waldenström macroglobulinemia (WM) were censored. Survival distributions were compared using the log-rank test, and numbers at risk are shown below the x-axis.

C. Cause-specific survival (CSS) among patients aged < 65 years by diagnostic era (two-era model): Kaplan–Meier curves demonstrating CSS stratified by diagnostic era (1996–2005 vs post-2006) among patients aged <65 years. Deaths unrelated to WM were censored. Survival distributions were compared using the log-rank test, and numbers at risk are shown below the x-axis.

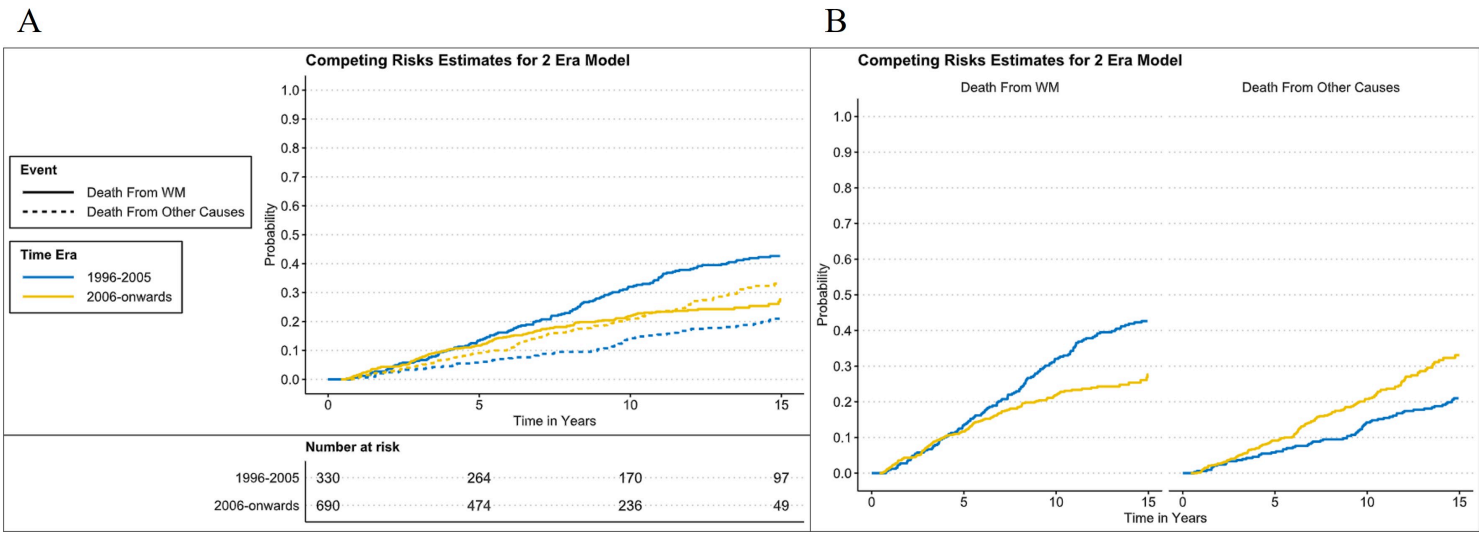

Figure 4

A. Cumulative incidence of cause-specific death by diagnostic era (two-era model). Cumulative incidence curves demonstrating WM–related death (solid lines) and death from other causes (dashed lines), stratified by diagnostic era (1996–2005 vs post-2006). Non–WM-related deaths were treated as competing events.

B. Competing risks estimates of cause-specific death by diagnostic era (two-era model). Cumulative incidence curves for WM–related death (left panel) and death from other causes (right panel), stratified by diagnostic era (1996–2005 vs post-2006). Non–WM-related deaths were treated as competing events. Numbers at risk are shown below the x-axis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFiguresandTables.docx