

Survival Outcomes in Waldenström Macroglobulinemia Relative to the U.S. General Population Across Modern Treatment Eras

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Background: Improvements in the therapeutic landscape of Waldenström macroglobulinemia (WM) have improved disease control. However, because WM predominantly affects older adults, interpretation of overall survival (OS) is confounded by competing non-WM-related mortality. Furthermore, the extent to which survival in patients with WM approaches that of the general U.S. population remains poorly characterized. We evaluated temporal survival trends in WM and quantified excess mortality compared with an age-, sex-, and calendar year-matched U.S. population.

Methods: We performed a retrospective single-center study of 1,020 consecutive patients with active WM diagnosed between 1996 and 2018. Patients were stratified according to the era of active disease diagnosis into two eras (1996–2005 vs. post-2006) reflecting major therapeutic advances. OS and cause-specific survival (CSS) were estimated using Kaplan–Meier methods. Competing risk analyses evaluated WM-related mortality while accounting for non-WM-related deaths. Excess mortality relative to the U.S. general population was assessed using standardized mortality ratios (SMRs) derived from Human Mortality Database life tables matched for age, sex, and calendar year.

Results: The cohort had a median age of 66.2 years and a median follow-up of 13.1 years. Although therapeutic strategies evolved substantially over time, including increased rituximab use and the introduction of BTKi therapy, OS for the overall cohort did not differ significantly across treatment eras (median 10.9 vs. 11.9 years, $P=0.64$). Among patients younger than 65 years, however, OS improved significantly in the post-2006 era, increasing from 14.1 to 18.8 years ($P=0.018$), whereas no significant improvement was observed among patients aged ≥ 65 years.

In contrast, WM-specific outcomes improved consistently across successive treatment eras. Median CSS increased from 15.6 years in patients diagnosed during 1996–2005 to 18.9 years in those diagnosed after 2006 ($p<0.0001$); 10-year CSS improved from 65.4%

to 77.7%. Competing risk analyses confirmed a significant reduction in WM-related mortality over time, with the 10-year cumulative incidence of WM-specific death decreasing from 32.4% (95% CI 28.9–38.1%) to 21.5% (95% CI 18.8–24.5%) in the two-era analysis ($P<0.001$).

Despite these encouraging improvements, patients with WM continued to experience substantially higher mortality than the matched U.S. general population. Overall excess mortality declined modestly across treatment eras (SMR 1.99 vs. 1.75), but remained significantly elevated (**Figure 1**). Notably, younger patients experienced the greatest relative excess mortality, with an SMR of 2.79 (95% CI, 2.41–3.21; $P<0.001$), indicating nearly a threefold higher risk of death compared with similarly aged individuals in the general population. In contrast, patients aged ≥ 65 years had a lower, though still significantly elevated, SMR of 1.57 (95% CI, 1.40–1.73; $P<0.001$), **Figure 2**.

Conclusions: Modern therapies have significantly reduced WM-related mortality and substantially improved cause-specific survival across successive treatment eras. However, patients with WM continue to experience significantly higher mortality than the age-, sex-, and calendar year–matched U.S. population, particularly among those diagnosed before age 65. These findings highlight that, despite therapeutic advances, a considerable survival gap persists and underscore the continued need for more effective treatment strategies capable of normalizing life expectancy in patients with WM.

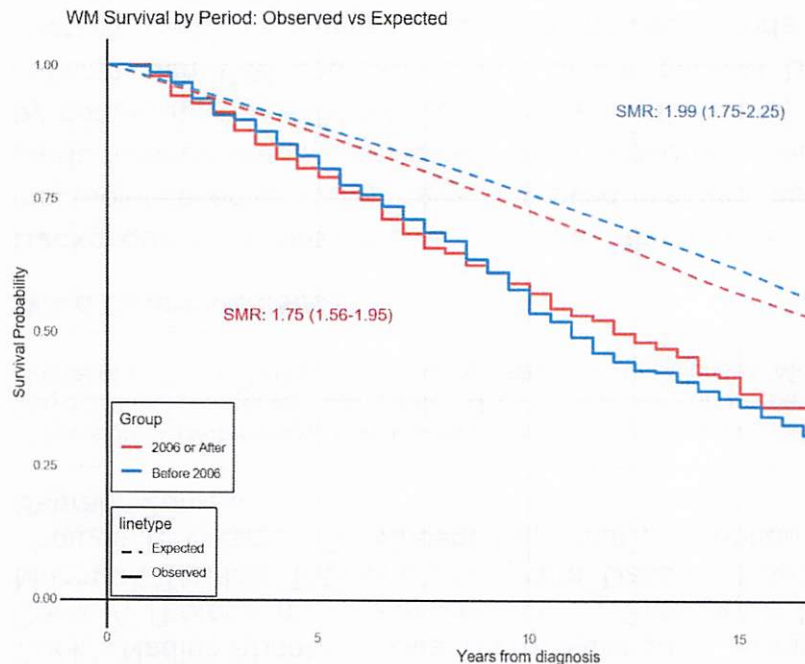


Figure 1. Observed overall survival for patients with active WM compared to expected survival of the age-, sex- and calendar year-matched general US population demonstrates a modest reduction in standardized mortality rates (SMR) in the more recent cohort.

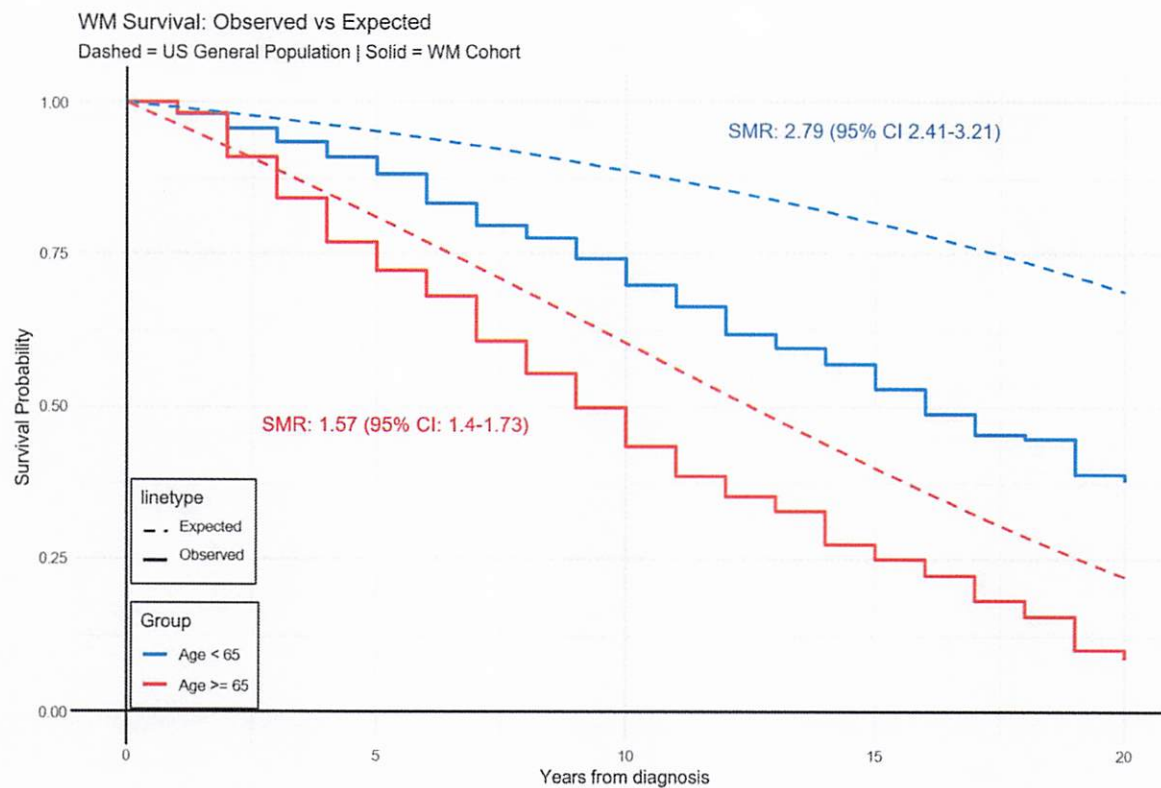


Figure 2. Standardized mortality ratios (SMR) by age group (<65 years and ≥65 years) for patients with active WM compared to expected survival of the age-, sex- and calendar year-matched general US population demonstrates the higher mortality burden in younger patients.

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