The Shifting Cause-of-Death Landscape in Multiple Myeloma During the Daratumumab Era: A Race- and Sex-Stratified Competing Risk Analysis of 91,768 SEER Patients

Jahanzeb Akhtar MBBS1, Muhammad Rafay Rafique MBBS2, Ghulam Shah Khan MBBS3, Abdullah Akram MBBS2, Mahnoor Khalid MBBS4, Shammas Muzammil MBBS5, Salman Masood MBBS3, Aatiqa Altaf MBBS3
1Central Park Medical College, Lahore, Pakistan. 2Nawaz Sharfi Medical College, Gujrat, Pakistan. 3Federal Medical College, Islamabad, Pakistan. 4University of Health Sciences, Lahore, Pakistan. 5Shifa Tameer-e-Millat University, Islamabad, Pakistan

BACKGROUND

Survival in multiple myeloma (MM) has improved substantially with successive novel therapies, particularly daratumumab after 2015. As myeloma-specific mortality declines, non-myeloma causes of death assume proportionally greater significance. Whether these shifts differ by race/ethnicity or sex in the contemporary immunotherapy era remains uncharacterized.

METHODS

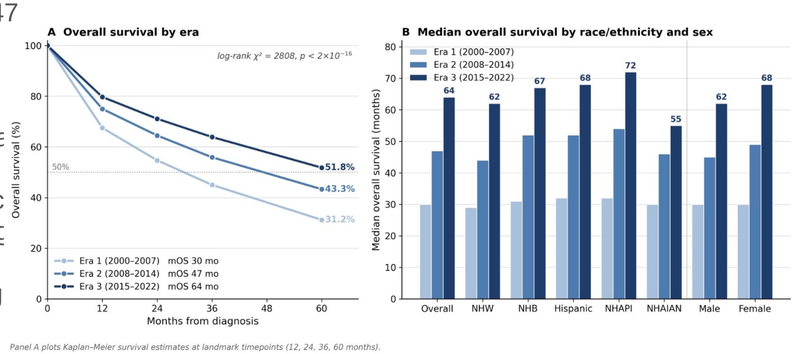
We identified 91,768 patients with plasma cell myeloma (ICD-O-3: 9732/3) diagnosed 2000–2022 from SEER-22, stratified into Era 1 (2000–2007), Era 2 (2008–2014), and Era 3 (2015–2022). Cause of death was classified as myeloma-specific, cardiovascular, infectious, renal, pulmonary, or other non-myeloma. Cumulative incidence functions were estimated with Gray's test for between-era comparisons. Multivariable Fine-Gray subdistribution hazard models were fitted for each cause-specific outcome, adjusting for era, race/ethnicity, sex, age, income quintile, marital status, and rurality. Race × era and sex × era interactions were evaluated. Overall survival was estimated by Kaplan-Meier with log-rank testing.

DISCUSSION

One in three MM deaths in the daratumumab era is now non-myeloma in origin. NHB patients demonstrate the greatest myeloma survival gains yet bear the highest non-myeloma competing mortality burden, implicating cardiovascular and infectious causes as emerging drivers of racial survival disparities. Cardiovascular risk management and infection prophylaxis should be integrated into MM survivorship care, with urgency for racially and socioeconomically vulnerable populations.

RESULTS

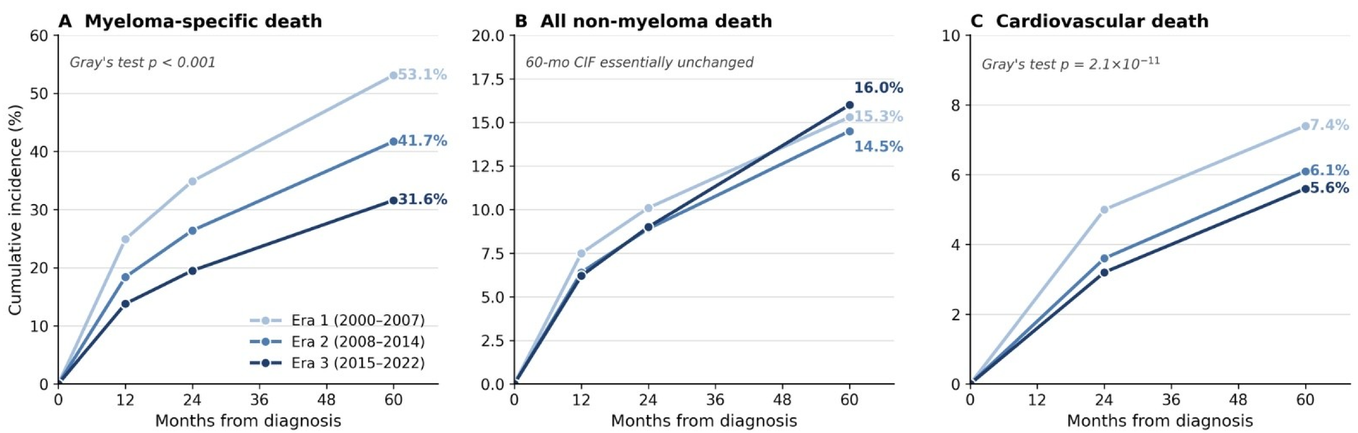
Non-myeloma deaths rose monotonically: 24.6% (Era 1) → 28.7% (Era 2) → 33.5% (Era 3; p<0.001), while myeloma-attributed deaths declined from 75.4% to 66.5%. Median overall survival improved from 30 to 47 to 64 months ($p<2\times10^{-16}$). Each era independently predicted lower myeloma-specific mortality (Era 3: SHR 0.45, 95% CI 0.443–0.465, p<0.001). Non-Hispanic Black (NHB) patients showed the largest era-related myeloma mortality reduction (Era 3 SHR 0.414) and longer median survival than Non-Hispanic White patients in Era 3 (67 vs. 62 months), confirming deepening of the Black survival paradox. Cardiovascular disease remained the second leading cause of death across all eras, with NHB patients carrying a 33% higher cardiovascular subdistribution hazard (SHR 1.33, 95% CI 1.252–1.417, p<0.001) and the largest absolute rise in non-myeloma deaths (28.0%→39.5%; Δ+11.5 pp). Infectious mortality remained elevated in NHB patients (SHR 1.30, p<0.001) and the lowest income quintile (SHR 1.59, p<0.001).



Panel A plots Kaplan–Meier survival estimates at landmark timepoints (12, 24, 36, 60 months).

Figure 2: Overall survival by era, race/ethnicity, and sex

Cumulative incidence of death by cause and era (Fine–Gray, competing risks)



Values are cumulative incidence estimates at landmark timepoints (12, 24, 60 months); lines connect landmarks.

Figure 1: Cumulative incidence of death by cause and era