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Disparities in Multiple Myeloma Mortality Rate Trends by Demographic Status in the USA

SISHIR DODDI[1] and M. HAMMAD RASHID[2]

[1]*Department of Medicine, University of Toledo College of Medicine, Toledo, OH, U.S.A.;*
[2]*Department of Hematology and Oncology, The Toledo Clinic, Toledo, OH, U.S.A.*

Abstract. *Background/Aim: Multiple myeloma (MM) is a hematological malignancy that arises when plasma cells undergo malignant monoclonal proliferation. This study aimed to assess the demographic disparities and temporal trends in the mortality rates of this disease. Patients and Methods: We employed the Center for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) database. Results: We found that for the overall U.S. population, the age-adjusted mortality rate per 1,000,000 (AAMR) decreased from 1999 to 2020. However, rates differed between demographic groups. In addition, we sought to find a significant average annual percent change (AAPC) in mortality rate from 1999 to 2020 for various demographic populations and compared groups to find disparities in mortality rate trend. In 2020, the AAMR due to MM was 38.0 and for women 24.1. The AAPC in AAMR from 1999 to 2020 in men was –1.0% (95%CI=–1.3 to –0.7) and in women was –1.6% (95%CI=–1.6 to –2.3). A significant difference in trend by sex was found, where women had a higher rate of decline. In 2020, the AAMR for the American Indian or Alaska Native (AI/AN) population was 15.0, the Asian American and Pacific Islander (AAPI) had 14.8, the Black and African American population had an AAMR of 55.6 and the White population had an AAMR of 28.1. The AAPC for the AI/AN population was -2.2% (95%CI=–3.5 to –0.9), for the AAPI population it was -0.9% (95%CI=–1.5 to –0.4), the Black and African American population had –1.5% (95%CI=–2.2 to –0.8) and the AAPC for the White population was –1.1% (95%CI=–1.6 to –0.6). A significant difference in trend of decline was found between the AAPI and Black and African American populations and between the AI/AN and Black and African American populations. When assessing the U.S. by states, the mid-southeast U.S. had the greatest density of the states with high AAMRs. Conclusion: These findings suggest which populations are at increased risk for mortality due to multiple myeloma and where we should apply additional resources and research.*

Multiple myeloma (MM) represents 10% of hematological malignancies and arises when plasma cells undergo malignant monoclonal proliferation. This proliferation damages the bone marrow and causes lytic bone lesions, renal failure, anemia, and immunodeficiencies (1). MM may arise from other plasma cell dyscrasias, notably smoldering myeloma and monoclonal gammopathy of undetermined significance (2). The diagnosis of MM requires a 10% or greater presence of malignant plasma cells along with at minimum one characteristic MM finding, which includes hypercalcemia, renal impairment, anemia, and bone lesions (CRAB) (3).

The treatment of MM focuses on suppressing the malignancy to improve quality of life by reducing MM-related comorbidities. Therapies used in MM treatment include proteosome inhibitors, immunomodulatory agents, monoclonal antibodies, and hematopoietic stem cell transplantation. Treatment consists of multiple steps, the first being induction therapy. After induction therapy, candidacy for hematopoietic stem cell transplantation is evaluated and administered if the criteria are met. Once transplantation has occurred, patients are given low-dose antimyeloma treatment for maintenance (4). Lower-intensity regimens followed by maintenance therapy are typically reserved for patients who are not eligible for transplant (3).

Correspondence to: Sishir Doddi, Department of Medicine, University of Toledo College of Medicine, 3000 Arlington Ave, Toledo, OH, U.S.A. Tel: +1 4404978119, e-mail: sishir.doddi@utoledo.edu.

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The impact of MM in the United States population has been investigated previously (5, 6). These studies evaluated the impact of MM using the US surveillance, epidemiology, and end results (SEER) database, which uses cancer diagnosis and prognosis-related information from a select number of states that aim to represent the total US population. To our knowledge, we are the first to utilize the Center for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) database, which relies on mortality and demographic information from death certificates of all individuals in the US, to assess mortality due to MM in the US. With this information, we can investigate and identify disparities in mortality rates by sex, race, age, and by state and region of the US.

Patients and Methods

Dataset. The CDC WONDER was used to access mortality data due to MM (ICD Code 90.0) from 1999 to 2020 (7). The multiple cause-of-death public use record was analyzed using national mortality rate information to identify deaths due to MM or with MM as an underlying cause between 1999 and 2020. Previous studies have used this dataset to analyze trends in cancer mortality (8, 9). Institutional Review Board approval was not required as CDC Wonder comprises public and deidentified data.

Data collection. We queried the dataset to gather mortality data of various demographic groups due to MM from 1999 to 2020. Age-adjusted mortality rate (AAMR) due to MM was collected with information regarding sex, race, age, and state (10). Crude Mortality Rate per 1,000,000 was collected to investigate rates by age groups. Sex was defined as male or female. The race groups were defined as Native American or Alaskan Native (AI/AN), Asian or Pacific Islander (AAPI), Black or African American, and White. The age groups used were 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and 85 or above. Ages below 55 were not included in the analysis as this data set is unreliable due to low mortality counts.

Statistical analysis. The AAMR per 1,000,000 and standard error were calculated for MM-related deaths from 1999 to 2020 in the US. This was used to extract mortality numbers and rates of various groups. The AAMR of a group was determined by dividing the mortality number of a group by the group's total US population for that year (mortality number/total population) and standardizing it to the 2000 US Standard Population. We then used the Joinpoint Regression Program (Joinpoint V 4.9.0.0, National Cancer Institute) to calculate the annual percent change (APC) for each year from 1999 to 2020 (11). APCs and corresponding 95% confidence intervals were calculated using the Grid Search Method (2,2,0), permutation, and parametric test. The Joinpoint Regression Program analyzed APC trends for various groups from 1999 to 2020 (12-15). This program analyzes trends by identifying changes in APC rates with log-linear regression models. Significant temporal trends from 1999 to 2020 were determined for each group and the overall average age adjusted mortality rate (AAPC) from 1999 to 2020 was calculated. Parallel pairwise comparison test was used to determine significant difference in mortality rates between groups. Significance was determined using a 2-tailed *t*-test with significance set at $p<0.05$. A Choropleth map to visualize AAMR by state was generated by R package usmap.

Results

Total population. From 1999 to 2020, 252,452 deaths occurred due to MM or with MM as an underlying cause. The average AAMR in this period was 34.2 per 1,000,000. MM mortality rate decreased between 1999 and 2009 and 2012 and 2020 (Figure 1).

Rates by sex. In 1999, women had a mortality rate of 32.7 per 1,000,000, and in 2020 had a rate of 24.1. In this period, two significant downtrends were found (Figure 1). The overall AAPC from 1999 to 2020 for females was -1.6% (95%CI=–2.3 to –1.0). The 1999 to 2009 time period had an APC of –2.27% (95%CI=–2.6 to –1.9), and the 2012 to 2020 time period had an APC of -1.93% (95%CI=–2.4 to –1.4).

Men had an AAMR of 42.7 per 1,000,000 in 1999 and 38.0 in 2020. There was an overall downtrend of AAMR from 1999 to 2020 in this population with an AAPC of –1% (95%CI=–1.3 to –0.7). From 1999 to 2016 there was a gradual decline with an APC of –0.85% (95%CI=–1 to –0.6). An increased rate of decline was observed from 2016-2020, with an APC of –1.83% (95%CI=–3.4 to –0.3). Parallel pairwise comparison found a significant difference in trend between males and females. For every year in this time period, women had a lower AAMR when compared to men (Figure 1).

Rates by race. From 1999 to 2020, the Black or African American population had the highest AAMR, followed by the White, American Indian or Native American, and Asian American or Pacific Islander populations (Figure 2). From 1999 to 2020 the Black or African American population had an AAPC of –1.5% (95%CI=–2.2 to –0.8). The White population had an AAPC of –1.1% (95%CI=–1.6 to –0.6). The AI/AN population had an AAPC of –2.2% (95%CI=–3.5 to –0.9) and the AAPI population had an AAPC of -0.9% (95%CI=–1.5 to –0.4). Parallel pairwise comparison found a significant difference between the AI/AN and Black population and AAPI and White populations.

When assessing temporal trends, the American Indian or Alaska Native group had a significant downtrend between 1999 and 2012 with an APC of –4.08% (95%CI=–5.7 to –2.5). Between 1999 and 2020, the AAPI population had a significant downtrend of APC –0.89% (95%CI=–1.4 to –0.4). The Black or African American population observed significantly decreased mortality rates between 1999 and 2009 with an APC of –2.04% (95% CI=–2.4 to –1.7) and from 2013 to 2020 with an APC of –2.09% (95% CI =–2.7 to –1.5). The White population had a significant downtrend between 2002 and 2009 with an APC of –2.01% (95% CI=–2.6 to –1.5) and between 2012 to 2020 with an APC of –1.60% (95% CI=–1.9 to –1.3).

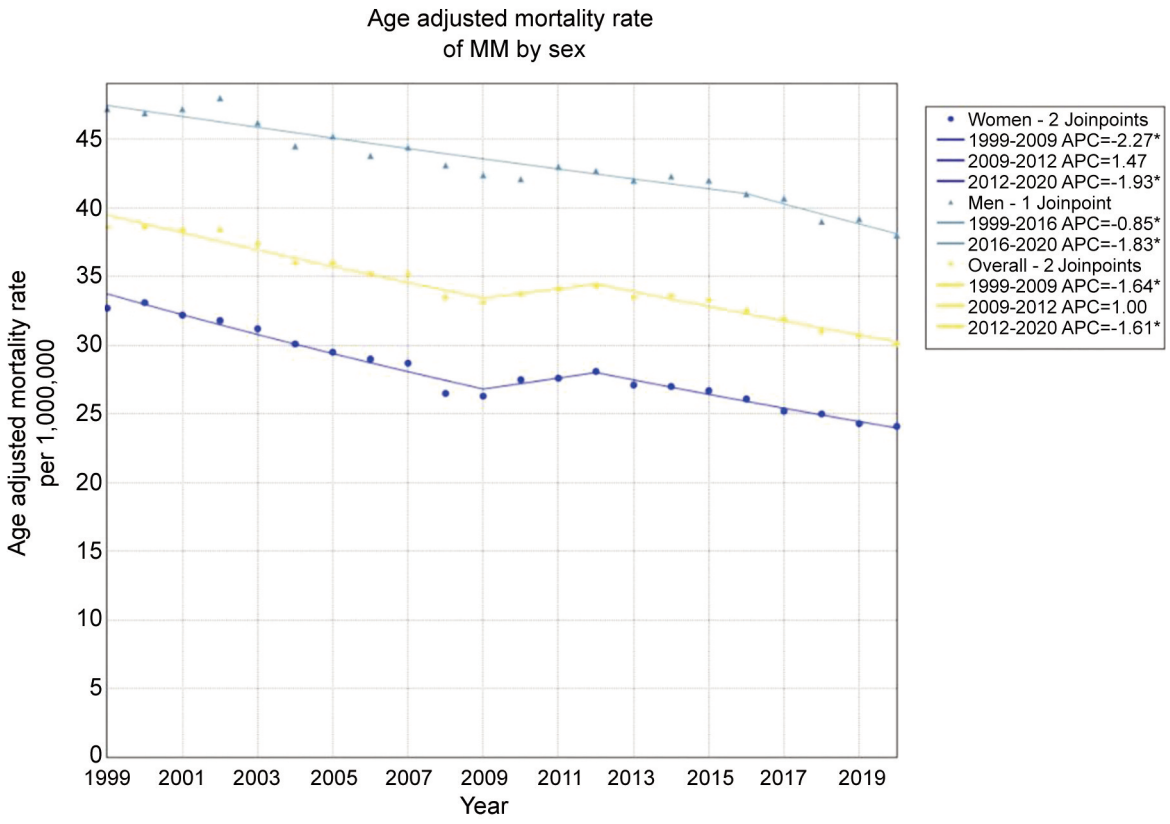

Figure 1. *Age adjusted mortality rate (AAMR) due to multiple myeloma (MM) between 1999 and 2020 according to sex. The graph depicts AAMR per 1,000,000 between 1999 and 2020 separated according to sex with "overall" signifying the entire population. The graph legend provides the annual percent change (APC) if a significant trend was found in a group. *Significant APC.*

Ten year age groups. Between 1999 and 2020, the 85 and over age group had the highest mortality rate, followed by the 75 to 84, 65 to 74, 55 to 64, and 35 to 44 age groups (Figure 3). The 35 to 44 age group had a significant downtrend between 1999 and 2020 with an APC of –2.53% (95%CI=–3.4 to –1.7). Between 1999 and 2020, the 45 to 54 age group also had a significant downtrend with an APC of –1.80% (95%CI=–2.1 to –1.5). The 55 to 64 age group had significantly decreased rates between 1999 and 2020, with an APC of –2.19% (95%CI=–2.4 to –2.0). Similarly, the 65 to 74 age group had a decreasing trend between 1999 to 2020 with an APC of –2.02% (95%CI=–2.2 to –1.8). The 75 to 84 age group had a downtrend between 1999 and 2009 with an APC of –1.03% (95%CI=–1.5 to –0.6), and between 2014 and 2020 with an APC of –2.11% (95%CI=–3.0 to –1.2). Individuals 85 years of age or above had an uptrend of mortality between 1999 to 2020 with an APC of 0.51% (95%CI=0.3 to 0.7).

State. In the 1999-2020-time range, Hawaii has the lowest average AAMR, with 24.7 per 1,000,000. South Carolina has the highest average AAMR, with 41.2 per 1,000,000. States in the southeast region, such as Kentucky, Tennessee, Louisiana, Mississippi, Alabama, and Georgia, have a high AAMR compared to the other areas of the US (Figure 4).

Discussion

The national CDC Wonder database provided information regarding mortality rates due to MM and demographic information, such as sex, race, and age. Previous studies have investigated MM mortality over time in the US; however, we report, for the first time to our knowledge, an analysis using the CDC's database to analyze mortality trends of various demographic groups within the U.S due to the ICD code C90: C90.0 (Multiple myeloma – Malignant Neoplasm), C90.1 (Plasma cell leukemia – Malignant neoplasm), C90.2 (Plasmacytoma, extramedullary – Malignant neoplasm). This study gathered the total deaths due to MM of various demographic groups for each year from 1999 to 2020. This data was used to create a joinpoint plot and identify significant trends for these groups over the past 22 years.

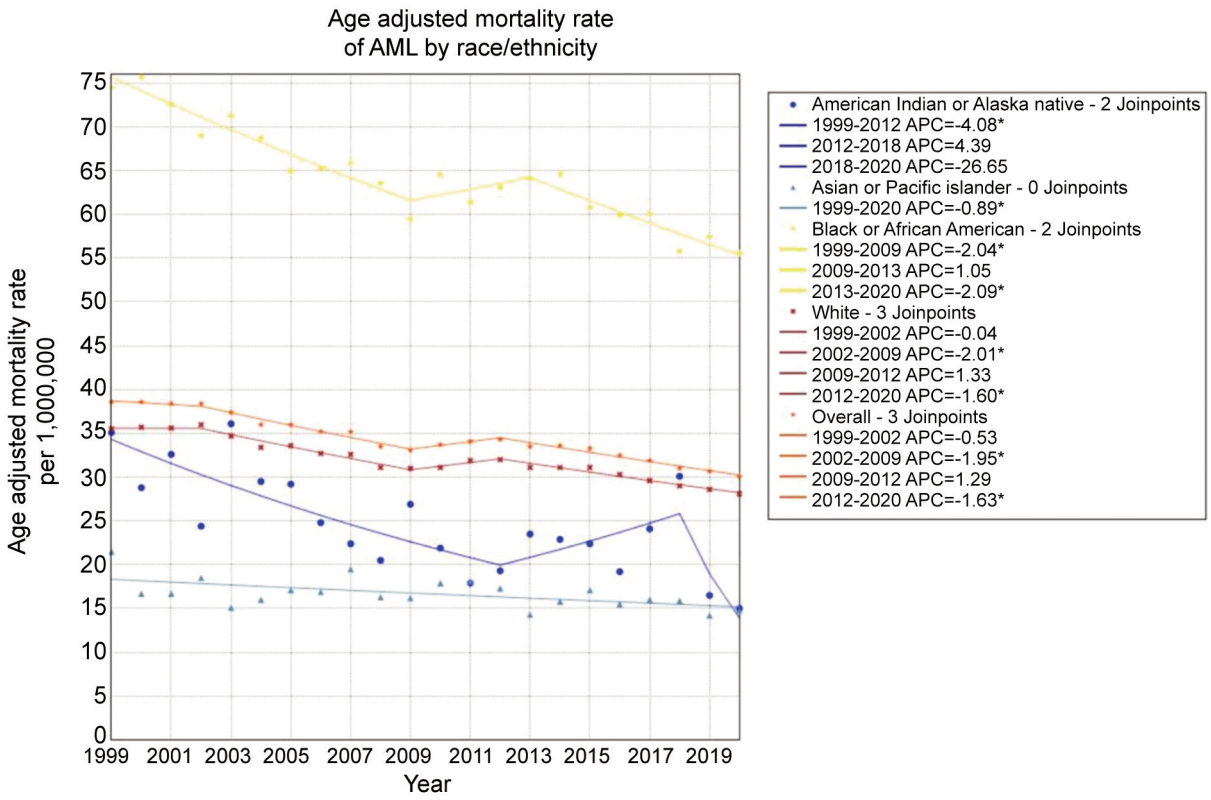

Figure 2. *Age adjusted mortality rate (AAMR) due to multiple myeloma (MM) between 1999 and 2020 by race. AAMR per 1,000,000 between 1999 and 2020 separated according to race: American Indian or Alaskan Native, Asian or Pacific Islander, Black or African American, and White. *Significant APC.*

Over the last 22 years, the AAMR of MM has decreased from 1999 to 2020 overall; however, rates and trends during this period varied between demographic groups: men have a higher rate of mortality compared to women, and the Black/African American population has a much higher AAMR than the rest of the population.

Data from the CDC's database identified that men had a higher AAMR due to MM compared to women in the US. A previous study investigating MM mortality in China found similar results across all age groups (16). While the sex differences of MM are not known, it was previously found that women are at a higher risk of having t(14;16) and del(17p) deleterious lesions, which may correspond to poorer prognosis (17). Additionally, mortality may differ due to response to treatment, as hormones may influence the pharmacology of therapeutics (18).

When investing AAMR in relation to race, AAPI had the lowest AAMR, and the Black/African American population had the highest AAMR (Figure 2). Each race group from 1999 to 2020 had an overall decrease in AAMR, with the Black/African American population having the most significant reduction (Figure 3). A notable finding was that the Black/African American AAMR in 2020 was over three times that of the AAPI and AIAN populations and almost twice as high as the White population. Racial disparities have been documented in MM, where access to treatment is different for various populations (19-22). In addition to race, socioeconomic factors contribute to differing outcomes, specifically access to cancer care centers, payment approval, and related expenses (23, 24). Also, it has been previously found that living in a low socioeconomic status (SES) is associated with a poorer prognosis (6). These SES factors and their connection to race may contribute to the discrepancy of AAMR between US populations. Our findings suggest that further efforts and resources should be employed to investigate solutions in outcome disparities. Both biological factors and social determinants of health studies should be conducted to determine how sex differences, race, and SES contribute to cancer prognosis and outcomes.

When assessing the risk of age and mortality due to MM, our findings of increased AAMR with increased age are concordant with the current literature (25). Between 1999 and 2020, the AAMR decreased overall for all age groups except for the 85+ age group.

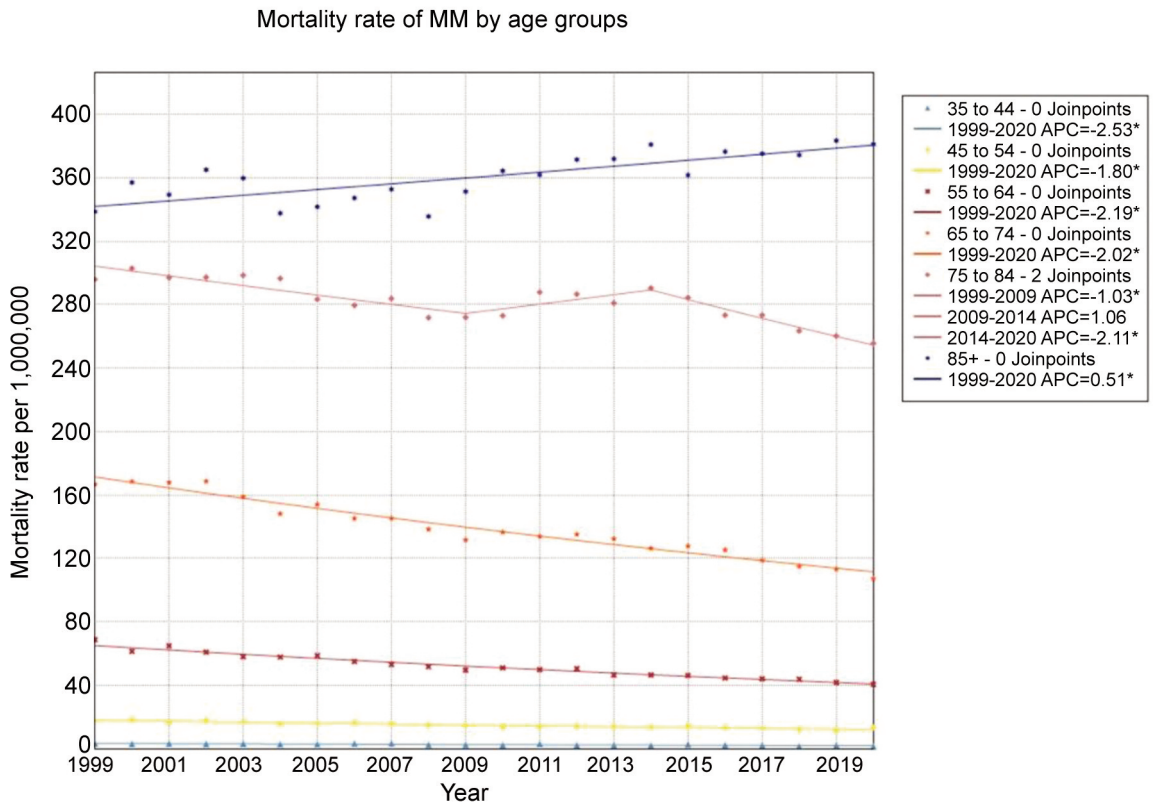

Figure 3. *Mortality rate due to multiple myeloma (MM) between 1999 and 2020 by Age Group. The graph depicts mortality rate per 1,000,000 due to MM for 10-year age groups. *Significant APC.*

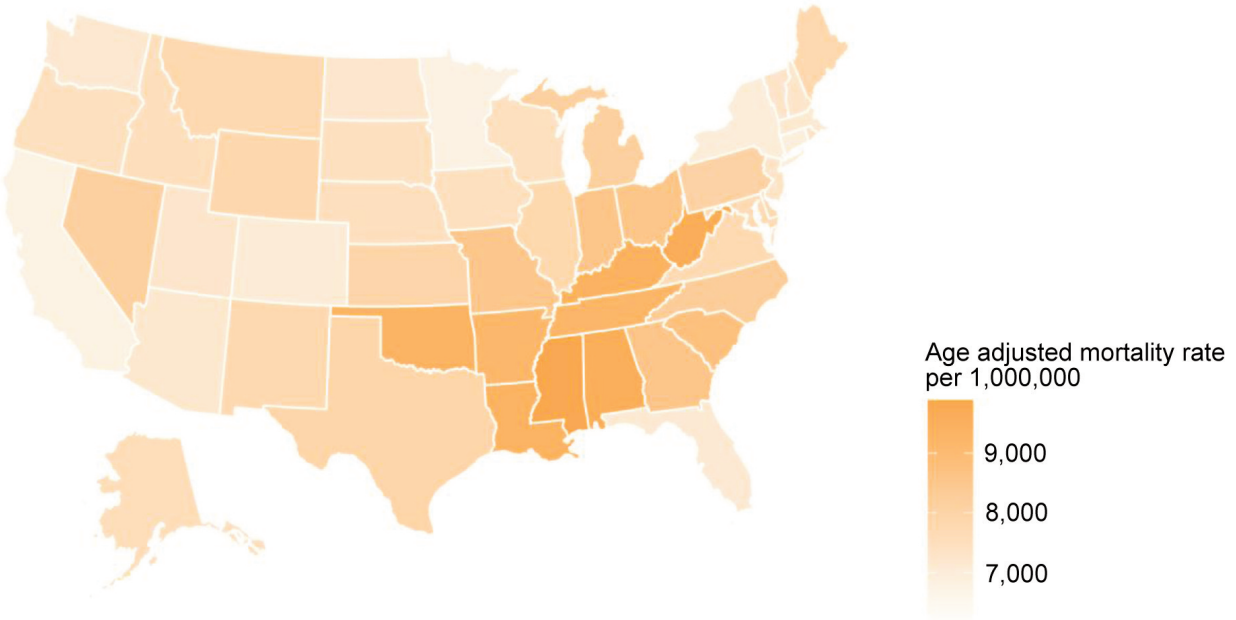

Figure 4. *Choropleth map of multiple myeloma (MM) age adjusted mortality rate (AAMR) in US from 1999 to 2020. Figure illustrates average AAMR per 1,000,000 due to MM in various states. Increasing AAMR of a state is depicted by a darker shade of orange.*

Investigating MM mortality among age groups, we found that the largest leap in AAMR is between the 65 to 74 and 75 to 84 age groups (Figure 3). This finding suggests that after the age of 74 there is a severely increased mortality risk due to MM.

When analyzing temporal trends, there was a significant increase in overall MM mortality rates in the 2009 to 2012 time period. The latest drug to be approved by the FDA before this period was pegylated liposomal doxorubicin (PLD) on 5/17/2007. In a randomized Phase III trial, PLD plus bortezomib combined immunotherapy compared to bortezomib monotherapy had a median time to progression of 9.3 months compared to 6.5 months [$p<0.01$; hazard ratio (HR)=1.82 (95%CI=1.41 to 2.35)], and 15-month survival rate of 73% compared to 65% ($p>0.05$) (26). The next FDA-approved drug for MM was Carfilzomib on 7/20/2012 (27). The significant uptrend observed could partially be attributed to the lack of novel therapies approved for MM; suggesting that the development of novel therapeutics contribute to lowering the AAMR. These findings support continued efforts of novel therapeutics to improve MM's prognosis.

Study limitations. The CDC Wonder database relies on information from US death certificates, which list up to 20 multiple causes of death. There is uncertainty on how MM was included in the multiple causes of death. For instance, patients with a clinical diagnosis of MM who later expired were included; however, patients with underlying undiagnosed MM who passed from infection due to immunodeficiency were not included unless MM was diagnosed during an autopsy. Moreover, patients of lower socioeconomic status or without access to proper medical resources may be disproportionately underrepresented due to a lack of MM diagnosis before expiration.

The overall AAMR for MM declined for the US population between the recent 1999 to 2020 time period. While a general decrease was observed, AAMR differences between various demographic groups within the US were found. Overall, the AAMR for men was greater than that of females. Compared to the overall population, the Black/African American population had the highest AAMR, while AAPI had the lowest. In addition, states in the mid-southeast region had a higher AAMR than other regions in the US. This investigation identified the impact demographics had on the prognosis of MM. These disparities can suggest where additional support and resources should be placed and that biological factors and SES should be investigated to improve MM outcomes.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Sishir Doddi developed the research idea, completed data collection, completed statistical analysis, wrote the manuscript, and prepared figures. M. Hammad Rashid supervised the project. All Authors reviewed the manuscript.

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