# Impact of race and ethnicity on early mortality in multiple myeloma: a SEER analysis

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# Abstract

Over the past two decades, there have been significant advances in the treatment of multiple myeloma which has led to an improvement in overall survival.<sup>1,2</sup> However, a notable proportion of patients continue to experience early mortality (EM), defined as 2 years from the time of diagnosis. This raises the possibility that improvements in myeloma survival have not extended equally to all groups. Using the latest data drawn from the Surveillance Epidemiology and End Results database of patients in the United States spanning 2000-2019, we study impact of important sociodemographic factors on EM. Through regression modeling, we demonstrate that patients diagnosed from 2000-2005, of older age, male sex, and of certain racial minority status (non-Hispanic Black and Hispanic) have higher odds of EM. Of these factors, minority status contributed to worse 2-year overall survival as well. We evaluate whether income, as a surrogate to access to care, could potentially explain this finding, but find that race has a distinct relationship with EM that is not modified by income. This is further reinforced by subgroup analysis. After characterizing groups vulnerable to EM, we examine reasons for these disparities and potential avenues to address them.

# Introduction

Early mortality (EM), defined as patients dying within a certain period of disease diagnosis, is a concern across hematologic malignancies. For leukemias, such as acute myeloid leukemia (AML), patients typically present acutely in oncologic emergencies and a significant proportion of death occurs within the first few months; 2-month EM has been noted as high as 11%.<sup>3,4</sup> In lymphomas, such as the diffuse large B-cell lymphoma (DLBCL) population, reports have ranged from 15.7% within 90 days of diagnosis at one institution to 23% within 100 days at another.<sup>5,6</sup>

For multiple myeloma (MM), advances in therapies over the past 20 years have contributed substantially to improved overall survival (OS), but improvement has not been uniform. The heterogeneity of outcomes in MM is well known with survival for patients ranging from a few months to more than 10 years.<sup>7-11</sup> In the context of this heterogeneity, a significant portion of patients with MM experiencing EM have been identified, but this population is still poorly defined. For instance, definitions of EM vary significantly

across studies, ranging from 2 months to 2 years.<sup>12</sup> The issue of EM in MM patients is problematic with some studies showing mortality as high as 20% within 6 months.<sup>2,12,13</sup> Both clinical and sociodemographic factors have been identified as contributors. The clinical factors have been encapsulated in the latest Revised International Staging System for MM, which risk stratifies patients by high-risk genetic features and serum markers.<sup>11</sup> However, sociodemographic factors remain less defined. Previous population-level studies have noted factors including race and sex.<sup>2,12,13</sup> Studies have attributed worse OS to certain minority groups, mostly non-Hispanic Blacks (NHB). The reasoning behind racial disparities is controversial and has been attributed to confounding, possibly by other sociodemographic factors including differences in access to care.<sup>14-19</sup> A better understanding of the sociodemographic factors contributing to EM in MM will improve risk stratification at a population level, a concept explored in oncologic follow-up care.<sup>20</sup> This has broad implications for improving care and allocation of resources to the highest risk groups. We aim to study sociodemographic characteristics that contribute

to 2-year mortality, with a focus on race-ethnicity and evaluate potential interactions with income.

## **Methods**

Data was obtained from the Surveillance Epidemiology and End Results (SEER) registry, a public database sponsored by the National Cancer Institute that collects cancer statistics from across the United States. We accessed SEER Research Plus Data 17 Registries (2000-2019) via the SEER\*Stat 8.4.0 platform. Cases were selected by filtering for the following criteria: histologic type (international Classification of Disease [ICD]-03=9,732-9,733), microscopically confirmed diagnosis, and age at diagnosis between 18-99 years old. We excluded cases with incomplete data, such as unknown age or follow-up survival months. Patients of Native American and unknown race-ethnicity were also excluded given the small sample sizes. All data analysis for this study was performed in RStudio 4.1.2.

Logistic regression was performed to assess relationship with EM, defined as survival less than or equal to 2 years. We used 2 years as the cut-off to account for the increasing median survival with new therapeutics over the years. Of the information available in the dataset, we selected age, sex, race-ethnicity, year of diagnosis, and income as variables of interest and EM was the primary outcome of this study. Patients were stratified by age into quartiles, by year of diagnosis into three cohorts (2000-2005, 2006-2011, and 2012-2017), and by income into two levels (<\$70,000,  $\geq$ \$70,000). In order to better evaluate the relationship between race-ethnicity and income, interaction was assessed, along with analysis of EM in racial and income subgroups. For the final regression models, the first quartile age group (18-58 years), male sex, non-Hispanic White (NHW) race, yearly income <\$70,000, and year of diagnosis cohort between 2000-2005 were utilized as reference groups.

Cox proportional hazards regression was utilized to assess the relationship between the predictors identified in the EM models and OS. Analysis was conducted on both the total cohort and a left-truncated cohort. Left truncation was undertaken with the criteria of survival >2 years to assess relationship of variables with survival after the EM time point. Hazard ratios (HR) and associated 95% confidence intervals (CI) were calculated with HR=<1 indicating reduced mortality.

### Results

We identified 77,374 MM patients in SEER registry diagnosed from 2000-2019 (Figure 1; Table 1). There were more males than females (55.8% vs. 44.2%). Most patients were NHW (64.2%), but there was a sizable non-White (Hispanic, NHB, Asian) population (35.8%). The age-adjusted incidence was greatest in the NHB group at 14 per 100,000. The distribution of age was skewed to the third and fourth quartiles. Of all MM patients diagnosed in this period, 36% of patients died in the first 2 years.

Female patients with MM had lower odds of experiencing EM (odd ratio [OR]=0.89; range, 0.86-0.92;  $P \le 0.01$ ) than males (Table 2). Minorities, including NHB and Hispanics, had higher odds of experiencing EM (OR=1.10; range, 1.04-1.15;  $P \le 0.01$  vs. OR=1.21; range, 1.14-1.28;  $P \le 0.01$ ). Older age was also associated with increased EM while higher income was clearly associated with decreased odds of EM. Overall, the odds of EM decreased relative to the reference 2000-2005 period. The integration of the race-ethnicity



**Figure 1. CONSORT diagram.** The generation of the final study sample is detailed. MM: multiple myeloma; SEER: Surveillance Epidemiology and End Results database. Table 1. Characteristics and distribution of patients diagnosed with multiple myeloma from 2000-2017, N=77,374.

	Age-adjusted incidence rate per 100,000 (range)	Count (%)
Sex Male Female	8.4 (8.3-8.5) 5.4 (5.4-5.5)	43,181 (55.8) 34,193 (44.2)
Race NHW NHB Hispanic Asian	6.1 (6.1-6.2) 14 (13.8-14.3) 6.4 (6.3-6.6) 4.3 (4.1-4.4)	49,653 (64.2) 14,293 (18.5) 8,960 (11.6) 4,494 (5.8)
Age quartiles, range in years Q1, 18-58 Q2, 59-67 Q3, 68-76 Q4, 77-99	NA NA NA NA	17,854 (23.1) 18,788 (24.3) 20,613 (26.6) 20,119 (26.0)
Diagnosis interval 2000-2005 2006-2011 2012-2017	6.2 (6.1-6.3) 6.6 (6.5-6.7) 7.2 (7.1-7.3)	20,858 (27.0) 24,966 (32.3) 31,550 (40.7)
Median income in US \$ <70,000 >70,000	*	45,821 (59.2) 31,553 (40.8)

\*Not available (NA) from Surveillance Epidemiology and End Results database (SEER) data import. NHW: non-Hispanic White; NHB: non-Hispanic Black.

Table 2. Logistic regression of total cohort. Odds of early mortality, defined as ≤2 years, were examined through multivariate and univariate logistic regression.

	OR multivariate	95% CI	P	OR univariate	95% CI	P
Sex Male Female	Ref 0.89	0.86-0.92	<0.01	Ref 0.94	0.91-0.97	<0.01
Race NHW NHB Hispanic Asian	Ref 1.10 1.21 1.16	1.04-1.15 1.14-1.28 1.04-1.29	<0.01 <0.01 <0.01	Ref 0.94 1.01 0.94	0.90-0.97 0.97-1.06 0.88-1.00	<0.01 0.63 0.07
Age quartiles, range in years Q1, 18-58 Q2, 59-67 Q3, 68-76 Q4, 77-99	Ref 1.31 2.01 4.23	1.25-1.37 1.92-2.10 4.05-4.43	<0.01 <0.01 <0.01	Ref 1.26 1.94 4.01	1.20-1.32 1.85-2.02 3.84-4.20	<0.01 <0.01 <0.01
Diagnosis interval 2000-2005 2006-2011 2012-2017	Ref 0.68 0.59	0.66-0.71 0.56-0.61	<0.01 <0.01	Ref 0.70 0.60	0.67-0.72 0.58-0.63	<0.01 <0.01
Median income in US \$ <70,000 ≥70,000	Ref 0.81	0.78-0.85	<0.01	Ref 0.87	0.85-0.90	<0.01
Interaction ethnicity and income in US \$ NHB* ≥70,000 Hispanic* ≥70,000 Asian* ≥70,000	1.07 1.09 0.91	0.98-1.16 0.98-1.20 0.80-1.05	0.2 0.11 0.2	-	-	-

OR: odds ratio; CI: confidence interval; Ref: reference; NHW: non-Hispanic White; NHB: non-Hispanic Black; NA: not available; \*P<0.01.

Analysis of EM in the income-based and racial subgroups but notably odds of EM among Hispanic and Asian females

and income interaction term did not yield any significance. were mostly consistent with the whole cohort analysis,

were similar to males respectively. Hispanics and NHB in higher income category continued to have higher odds of EM as compared to NHW (Table 3).

Total cohort OS analysis with the variables derived from EM analysis (sex, race, age, and income) paralleled findings of logistic regression. Females had better median OS than males (46 months vs. 43 months) and had significantly decreased risk for mortality (HR=0.89-0.93; P<0.01) (Table 4). Among different race-ethnicities, median OS appeared similar across minorities at 48 months, higher than NHW at 43 months. However, the risk for mortality was greatest amongst Hispanic and NHB minorities. By age quartiles, there was a consistent decrease in OS with increasing age, accompanied by higher risk of mortality as well. And like the logistic regression analysis, the data demonstrated improved OS with higher income. Notably median survival was highest in the ≥\$70,000 bracket at 48 months. On examination of the left-truncated cohort, significant relationships highlighted in the total cohort were maintained among all variables aside from race, where NHB and Hispanic status was no longer associated with worse survival.

## Discussion

Using data from the latest SEER publication we have identified risk factors independently associated with increased EM in patients with MM: increased age, male sex, early years of diagnosis (2000-2005), lower income (<\$70,000), and NHB/Hispanic race-ethnicity status.

Our observation of age being associated with higher odds of EM is consistent with literature that reports worse survival outcomes across multiple cancer types.<sup>21</sup> Older adults are disproportionately affected by a range of social, economic, and health factors. In our study, we account for a number of these social and economic factors, but still see a difference among age groups. We believe this difference is likely reflective of underlying health characteristics, such as higher rates of comorbidity, immune exhaustion, and frailty among older adults. These characteristics are known to contribute negatively to treatment outcomes and may be of particular importance in MM.<sup>22,23</sup>

For disparities between sexes, it has been shown that the incidence of MM is higher in males than females, but females still undergo higher frequency of autologous stem

	Subgroups OR (95% CI)							
Income \$ <\$70,000		Income \$ ≥\$70,000	NHW	NHB	Hispanic	Asian		
Sex Male Female	Ref 0.89 (0.86-0.93)*	Ref 0.88 (0.84-0.92)*	Ref 0.92 (0.88-0.95)*	Ref 0.76 (0.71-0.81)*	Ref 0.94 (0.86-1.02) <i>P</i> =0.2	Ref 0.91 (0.80-1.04) <i>P</i> =0.2		
Race NHW NHB Hispanic Asian	Ref 1.09 (1.04-1.15)* 1.20 (1.13-1.27)* 1.15 (1.04-1.28)*	Ref 1.18 (1.10-1.27)* 1.32 (1.22-1.44)* 1.06 (0.98-1.16) <i>P</i> =0.2	NA NA NA NA	NA NA NA NA	NA NA NA NA	NA NA NA NA		
Age quartiles, range in years Q1, 18-58 Q2, 59-67 Q3, 68-76 Q4, 77-99	Ref 1.31 (1.24-1.39)* 1.99 (1.88-2.11)* 4.10 (3.87-4.35)*	Ref 1.29 (1.20-1.39)* 2.03 (1.89-2.19)* 4.42 (4.13-4.76)*	Ref 1.38 (1.29-1.47)* 2.18 (2.05-2.31)* 4.69 (4.42-4.97)*	Ref 1.16 (1.06-1.28)* 1.79 (1.62-1.97)* 3.46 (3.12-3.84)*	Ref 1.31 (1.16-1.48)* 1.85 (1.64-2.08)* 3.61 (3.18-4.10)*	Ref 1.38 (1.14-1.68)* 2.00 (1.66-2.41)* 4.14 (3.44-4.99)*		
DX interval 2000-2005 2006-2011 2012-2017	Ref 0.71 (0.67-0.74)* 0.60 (0.57-0.63)*	Ref 0.65 (0.61-0.69)* 0.57 (0.54-0.61)*	Ref 0.68 (0.65-0.72)* 0.59 (0.56-0.62)*	Ref 0.66 (0.60-0.72)* 0.54 (0.50-0.59)*	Ref 0.69 (0.62-0.78)* 0.64 (0.57-0.71)*	Ref 0.72 (0.61-0.86)* 0.60 (0.51-0.70)*		
Median income in US \$ <70,000 ≥70,000	NA NA	NA NA	Ref 0.81 (0.78-0.85)*	Ref 0.86 (0.79-0.93)*	Ref 0.89 (0.81-0.97) <i>P</i> =0.013	Ref 0.75 (0.66-0.85)*		

**Table 3.** Odds of early mortality, defined as ≤2 years, were examined by race-ethnicity and income subgroups of interest.

OR: odds ratio; CI: confidence interval; Ref: reference; NHW: non-Hispanic White; NHB: non-Hispanic Black; NA: not available; DX: diagnosis; \*P<0.01.

	Median OS in months	HR	95% CI	Р	Left truncated median OS in months	TC HR	TC 95% CI	TC P
Sex Male Female	43 46	Ref 0.91	Ref 0.89-0.93	<0.01	81 85	Ref 0.91	Ref 0.88-0.93	<0.01
Race NHW NHB Hispanic Asian	43 48 48 48	Ref 1.03 1.05 0.98	Ref 1.01-1.05 1.02-1.08 0.95-1.02	0.011 <0.01 0.4	81 88 87 85	Ref 1.01 1.03 1.01	Ref 0.98-1.04 0.99-1.07 0.95-1.06	0.6 0.2 0.8
Age quartiles, range in years Q1, 18-58 Q2, 59-67 Q3, 68-76 Q4, 77-99	87 64 41 20	Ref 1.36 2.02 3.47	Ref 1.32-1.40 1.96-2.07 3.38-3.56	<0.01 <0.01 <0.01	128 96 73 54	Ref 1.42 2.13 3.50	Ref 1.37-1.47 2.06-2.21 3.37-3.63	<0.01 <0.01 <0.01
Median income in US \$ <70,000 >70,000	42 48	Ref 0.90	Ref 0.88-0.92	<0.01	81 86	Ref 0.93	Ref 0.90-0.95	<0.01

 Table 4. Cox proportional hazards regression analysis.

Analysis of full cohort was conducted with variables utilized in EM analysis. OS: overall survival: HR: hazard ratio; CI confidence interval; TC: truncated; Ref: reference; NHW: non-Hispanic White; NHB: non-Hispanic Black.

cell transplantation.<sup>24</sup> As we noted for age, this is likely multifactorial with biologic and behavioral components. Biologically, there are differences in innate and adaptive immune systems between men and women. Men have higher frequencies of regulatory T cells, which have been associated with adverse clinical features in MM.<sup>24</sup> In terms of behavior, women tend to have healthier attitudes and better social support networks, especially in adherence and choice of therapy. Though our model does not account for biologic and behavioral differences among men and women, we do note an interesting finding that differences between sexes disappear in analysis of EM for Hispanic and Asian subgroups, a phenomenon which could benefit from further study.

Our study examines EM in a cohort spanning two decades, during which there have been several major pharmaceutical developments in myeloma care. Our results are consistent with these developments improving EM. The proteasome inhibitor bortezomib was granted accelerated approval by the Food and Drug Adminstration in 2003 followed by full approval in 2005, and then the immunemodulatory drugs (IMiD), thalidomide (Thalomid) and lenalidomide (Revlimid) were approved in 2006, followed by pomalidomide (Pomalyst) in 2010, with the first monoclonal antibodies (daratumumab and elotuzumab) approved in 2015.<sup>25,26</sup> In our analysis, EM odds subsequently fell in 2006-2011 and 2012-2017, which aligns with the introduction of the next generation proteasome inhibitors, including ixazomib and carfilzomib, both approved during this time, as well as with bortezomib, the IMiD, and monoclonal antibodies.

Access to the latest therapy and care was an important

consideration that led us to include income status in the model. Those of lower socioeconomic status have been shown to be less likely to attend cancer screening programs or access the latest clinical trials resulting in poorer outcomes.<sup>21</sup> For our cohort, we see higher odds of EM in the group of patients with median income <\$70,000, which is consistent with the literature.

We sought to better understand the nature of disparities in outcomes between minorities and NHW. It has been suggested that worse survival outcomes in minorities may be a result of confounding with social factors, such as access to appropriate care.<sup>14-19</sup> Our results show that NHB and Hispanics have higher odds of EM than Whites. We note that this is an independent association after accounting for income, a variable often tied to access to care. We assessed the cross-section between income and race through an interaction term but noted no significant relationship. Furthermore, the subgroup EM analysis was consistent between the two income groups. Our results would support the notion that the disparities between minorities and NHW are beyond that of access to care tied to socioeconomic status. There may be further merit in evaluating biologic differences. The incidence of MM is higher in NHB, which is supported by our study. Minorities may have higher rates of comorbidities contributing; it has been noted that NHB have higher rates of renal disease, diabetes, and liver disease in the VHA Central Cancer Registry.<sup>27</sup> Differences in cytogenetics and molecular mutations have also been documented in NHB, such as higher frequencies of BCL7A, BRWD3, and AUTS2 mutations, and lower frequencies of TP53 and IRF4 mutations.<sup>28</sup> An important area of study in this setting is also Duffy null status and its impact on outcome.<sup>29,30</sup>

Additionally, through left-truncation survival analysis, examining only the cohort of patients who have survived past the 2-year mark we were able to see that NHB and Hispanic status were no longer associated with worse survival than NHW after the 2-year point. This would suggest that minority status exclusively contributes to worse OS in the 2-year period from diagnosis. We see that EM status is of particular concern for minorities and that more needs to be done for this group; tailored approaches as a future direction remain key as exemplified by the results from the DETERMINATION trial, where a large representation of NHB patients (approximately 20%) did not show significant advantage to early transplant compared to delayed transplant utilizing triplet induction.<sup>31,32</sup>

As for possible interventions to improve outcomes for minorities, increased representation in clinical trials is an important consideration. Inclusion is important to ensure generalizability of trials for new pharmaceuticals.<sup>33</sup> Minorities are underrepresented in clinical trials for MM therapeutics.<sup>34</sup> Some reasons for this underrepresentation include language and cultural barriers and distrust of the medical system. Applying minority recruitment goals to studies can directly help address this issue. Additionally, outreach initiatives, such as making screening information available in local shops and making educational materials more accessible in video-form rather than written-form may be useful for patients.<sup>35</sup> These populational strategies can complement other more patient-specific approaches being developed; considering cytogenetic differences among races noted above, there have been attempts to evaluate specific genetic factors as laboratory parameters including next generation sequencing and high sensitivity flow cytometry to identify high risk patients.<sup>36</sup> These patients at risk of EM may need to be treated more aggressively such as recommended by the Myeloma Optimum trial as well as the GMMG-Concept trial.<sup>37,38</sup>

Ultimately, the topic of EM in myeloma is important to investigate. In our study, we have identified sociodemographic groups of patients that are prone to EM. We have also identified a particularly vulnerable subset of minorities (Hispanics and NHB) in which EM within the first 2 years of diagnosis is the primary contributor to worse survival outcomes. This relationship was not confounded by income, a common proxy for access to care. We have explored the etiology of these disparities and potential solutions, but further investigation is required. Given the observational nature of our study and the SEER database, we cannot establish cause-effects relationships between the factors investigated and EM/OS. There is also the possibility of unaccounted confounding, which we attempted to minimize through screening of variables during the generation of the logistic regression models. We do not have information on disease-specific variables, such cytogenetics, fluorescent in situ hybridization, next generation sequencing for these patients as well as data on their treatment such as use of novel agents, transplantation, and maintenance therapy. It would be valuable to further investigate changes in EM with a different data set with more complete information on risk factors at diagnosis as well as treatment. This could help us refine our understanding of the populations prone to EM in MM and guide treatment choices as well as future public health and investigational endeavors to improve outcome.

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#### Contributions

The authors confirm contribution to the paper as follows: study conception and design by NS and JXW. Data collection by JXW. Analysis and interpretation of results by JXW, AS, RAS, IM, NK, US, MJ, KG, AV, MG, DC and NS. Draft manuscript preparation by NS, JXW and DC. All authors reviewed the results and approved the final version of the manuscript.

#### **Data-sharing statement**

All data can be obtained through SEER: https://seer.cancer. gov/data-software/

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