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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Interaction between age and gender on survival outcomes in extramedullary multiple myeloma over the past two decades

Ayrton I Bangolo, Pierre Fwelo, Chinmay Trivedi, Sowmya Sagireddy, Hamed Aljanaahi, Auda Auda, Maryama Mohamed, Sonia Onyeka, Miriam Fisher, Jyoti Thapa, Erwin J Tabucanon, Lyuben Georgiev, Annetta Wishart, Shilpee Kumari, Conrad Erikson, Mary Bangura, Orent Paddy, Rashmi Madhukar, Eugenio L Gomez, Joshua Rathod, Mansi Naria, Basel Hajal, Mohammad Awadhalla, David Siegel, Harsh Parmar, Noa Biran, David H Vesole, Pooja Phull, Simcha Weissman

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Abstract

BACKGROUND

Extramedullary multiple myeloma (MM) (EMM) is a rare and aggressive sub-entity of MM that can be present at diagnosis or develop anytime during the disease course. There is a paucity of data on the clinical characteristics and overall epidemiology of EMM. Furthermore, there is a scarcity of data on how the interaction of age and gender influences the survival of EMM.

AIM

To evaluate the clinical characteristics of patients with EMM over the past 2 decades and to identify epidemiologic characteristics that may impact overall prognosis.

METHODS

A total of 858 patients diagnosed with EMM, between 2000 and 2017, were ultimately enrolled in our study by retrieving the Surveillance, Epidemiology, and

End Results database. We analyzed demographics, clinical characteristics, and overall mortality (OM) as well as cancer-specific mortality (CSM) of EMM. Variables with a *P* value < 0.1 in the univariate Cox regression were incorporated into the multivariate Cox model to determine the independent prognostic factors, with a hazard ratio (HR) of greater than 1 representing adverse prognostic factors.

RESULTS

From a sample of 858 EMM, the male gender (63.25%), age range 60-79 years (51.05%), and non-Hispanic whites (66.78%) were the most represented. Central Nervous System and the vertebral column was the most affected site (33.10%). Crude analysis revealed higher OM in the age group 80+ [HR = 6.951, 95% confidence interval (95%CI): 3.299-14.647, *P* = 0], Non-Hispanic Black population (HR = 1.339, 95%CI: 1.02-1.759, *P* = 0.036), Bones not otherwise specified (NOS) (HR = 1.74, 95%CI: 1.043-2.902, *P* = 0.034), and widowed individuals (HR = 2.107, 95%CI: 1.511-2.938, *P* = 0). Skin involvement (HR = 0.241, 95%CI: 0.06-0.974, *P* = 0.046) and a yearly income of $75000+ (HR = 0.259, 95%CI: 0.125-0.538, *P* = 0) had the lowest OM in the crude analysis. Crude analysis revealed higher CSM in the age group 80+, Non-Hispanic Black, Bones NOS, and widowed. Multivariate cox proportional hazard regression analyses only revealed higher OM in the age group 80+ (HR = 9.792, 95%CI: 4.403-21.774, *P* = 0) and widowed individuals (HR = 1.609, 95%CI: 1.101-2.35, *P* = 0.014). Multivariate cox proportional hazard regression analyses of CSM also revealed higher mortality of the same groups. Eyes, mouth, and ENT involvement had the lowest CSM in the multivariate analysis. There was no interaction between age and gender in the adjusted analysis for OM and CSM.

CONCLUSION

EMM is a rare entity. To our knowledge, there is a scarcity of data on the clinical characteristics and prognosis factors of patients with extramedullary multiple myeloma. In this retrospective cohort, using a United States-based population, we found that age, marital status, and tumor site were independent prognostic factors. Furthermore, we found that age and gender did not interact to influence the mortality of patients with EMM.

Key Words: Multiple myeloma; Age; Gender; Mortality; Plasmacytoma

Core Tip: Very little is known about extramedullary multiple myeloma (EMM), owing to its rarity and scarcity of data on the subject. So far it was found that advanced age was the single most important prognostic value for poor outcome in EMM. However, how age interacts with gender to affect mortality in EMM remains unknown. We found that age did not interact with gender to affect mortality in EMM.

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INTRODUCTION

Multiple myeloma (MM) is a rare cancer with the hallmark of monoclonal plasma cell proliferation in the bone marrow[1]. MM accounts for approximately 1%-2% of all cancers. A subclone can thrive and grow independent of the bone marrow microenvironment resulting in extramedullary MM (EMM) which is an aggressive subentity of MM[2]. Affecting up to 30% of patients with MM, EMM can be present either at diagnosis or anytime during the disease process[1,2].

EMM is frequently associated with high-risk cytogenetics. As evidenced by a pilot study, which revealed an association of chromosome 1 abnormalities in bone marrow myeloma cells with extramedullary progression. Optical mapping showed the potential for refining the complex genomic architecture in MM and its phenotypes[3]. Only few studies in the literature have addressed the clinical characteristics of patients with EMM[4-8]. Age at the diagnosis of MM and the site of extramedullary

disease have been shown to be independent prognostic factors[4,9]. Furthermore, there is some data associating the male gender with MM[5]. However, to the best of our knowledge, there is a lack of studies addressing the interaction between age and gender in EMM, which makes our study the first of its kind.

To fill in the gaps in the literature, we conducted a retrospective cohort study amongst patients with EMM using the Surveillance, Epidemiology, and End Results (SEER) database, to evaluate the interaction of age and gender in regard to mortality of EMM as well as independent prognostic factors of patients with EMM over the past 2 decades.

MATERIALS AND METHODS

Study design

A population-based retrospective cohort study of patients with EMM was conducted using the SEER research. In addition, 18 registries in the November 2020 submission database were also utilized (http://www.seer.cancer.gov). The SEER Program is one of the largest and most authoritative sources of the cancer-related dataset in the United States, which is sponsored by the United States National Cancer Institute. The SEER 18 database collects cancer incidence, patients' clinicopathological features, and survival data from 18 population-based cancer registries and covers nearly 28% of the United States population[9]. This dataset is de-identified and publicly available, thus, the study is exempt from an Institutional Review Board's review. A detailed description of the database and data collection can be found elsewhere[10].

Patient selection

Inclusion criteria: All patients with EMM diagnosed from 2000 to 2017 were identified following criteria from previous studies[11]. We used site and morphology ICD-O-3 histology/behavior, malignant variables codes 9731/3 (*i.e.*, solitary plasmacytoma of bone) and 9734/3 (*i.e.*, extraosseous plasmacytoma) to identify patients with EMM. We also restricted our cohort to patients with 2 tumors and diagnostic confirmation through positive histology, immunotherapy, or genetic studies. Thus, increasing the accuracy of our findings and eliminating possible false-positive diagnoses.

Exclusion criteria: We excluded patients with unknown age at diagnosis, tumor stage, tumor site, or race. Lastly, we excluded patients diagnosed through autopsy.

Study variables

Main exposures: Gender (male and female), age (0-39, 40-59, 60-79, and 80+), and their interaction were the main exposures of interest.

Sociodemographic and tumor characteristics: Gender, year of diagnosis, extramedullary site of the tumor, location, annual salary, Civil status, year of diagnosis, surgical resection, as well as chemotherapy, were assessed for the purpose of the study.

Statistical analysis

We performed a crude and adjusted Cox proportional hazard regression to investigate the impact of the interaction between age and gender on EMM mortality. Variables with a value < 0.1 in the univariate Cox regression model were incorporated into the multivariate Cox proportional analysis to determine the independent prognostic factors associated with overall mortality (OM) and cancer-specific mortality (CSM), with a hazard ratio (HR) > 1 representing adverse prognostic factors. All tests were two-sided, with a confidence interval set as 95% and P value < 0.05 deemed statistically significant. All statistical tests were performed by using Software STATA16.1.

RESULTS

We enrolled 858 patients with EMM in our study. The baseline characteristics of our study are summarized in Table 1. The male gender (63.25%), age range 60-79 at diagnosis (51.05%), Non-Hispanic Whites (66.78 %), and married patients (66.32%) were the most represented groups. The Central Nervous System and vertebral column were the most affected location (33.10%). Most patients were living in metropolitan areas with a population of at least 1 million people (56.06%). Most patients did not receive chemotherapy (81.47%).

A crude analysis of factors associated with all-cause mortality and EMM-related mortality among United States patients between 2000 and 2017 is demonstrated in Table 2. Crude analysis revealed higher OM in the age group 80+ [HR = 6.951, 95% confidence interval (95%CI): 3.299-14.647, P = 0], Non-Hispanic Black population (HR = 1.339, 95%CI: 1.02-1.759, P = 0.036), other bones (HR = 1.74,

Table 1 Demographic and Clinicopathologic characteristics of United States patients with extramedullary multiple myeloma between 2000 and 2017

Characteristics	*n*	%
Total	858	100
Gender		
Female	311	36.25
Male	547	63.25
Age at diagnosis, yr		
0-39	41	4.78
40-59	309	36.01
60-79	438	51.05
80+	70	8.16
Race		
Non-Hispanic white	573	66.78
Non-Hispanic black	133	15.50
Hispanic	110	12.82
Other	42	4.90
Extramedullary site		
CNS and vertebral column	284	33.10
Bones, subcutaneous tissues, connective tissues, and soft tissues of the trunk	108	12.59
Bones, soft tissues, subcutaneous tissues, and connective tissues of the pelvis and sacrum	97	11.31
Bones, soft tissues, subcutaneous tissues, connective tissues, and lymph nodes of the upper extremities	64	7.46
Bones, soft tissues, subcutaneous tissues, and connective tissues of the lower extremities	45	5.24
Bones, soft tissues, subcutaneous tissues, connective tissues, and lymph nodes of the face and skull	60	6.99
Other bones, NOS	37	4.31
Eyes, mouth, and ENT	101	11.77
Lung, breast, and mediastinum	26	3.03
Gastrointestinal tract	18	2.10
Skin	12	1.40
Kidney, suprarenal glands, and retroperitoneum	6	0.70
Living area		
Counties in metropolitan areas of 1 million persons	481	56.06
Counties in metropolitan areas of 250000 to 1 million persons	173	20.16
Counties in metropolitan areas of 250000 persons	76	8.86
Nonmetropolitan counties adjacent to a metropolitan area	77	8.97
Nonmetropolitan counties not adjacent to a metropolitan area	51	5.94
Income per year		
< $35000	12	1.40
$35000-44999	74	8.62
$45000-54999	154	17.95
$55000-64999	232	27.04
$65000-74999	183	21.33
$75000+	203	23.66

Marital Status		
Married	569	66.32
Single	106	12.35
Divorced/separated	79	9.21
Widowed	62	7.23
Unknown	42	4.90

CNS: Central Nervous System; NOS: Not otherwise specified.

95%CI: 1.043-2.902, P = 0.034), and widowed individuals (HR = 2.107, 95%CI: 1.511-2.938, P = 0). Skin involvement (HR = 0.241, 95%CI: 0.06-0.974, P = 0.046) and a yearly income of $75000+ (HR = 0.259, 95%CI: 0.125-0.538, P = 0) had the lowest OM in the crude analysis. Crude analysis revealed higher CSM in age group 80+ (HR = 10.111, 95%CI: 3.083-33.159, P = 0), Non-Hispanic Black (HR = 1.446, 95%CI: 1.017-2.055, P = 0.04), other bones (HR = 1.887, 95%CI: 1.044-3.411, P = 0.035) and widowed individuals (HR = 2.463, 95%CI: 1.612-3.765, P = 0).

Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and EMM-related mortality among United States patients between 2000 and 2017 are demonstrated in Table 3. Multivariate cox proportional hazard regression analyses only revealed higher OM in the age group 80+ (HR = 9.792, 95%CI: 4.403-21.774, P = 0) and widowed individuals (HR = 1.609, 95%CI: 1.101-2.35, P = 0.014). Multivariate cox proportional hazard regression analyses of CSM showed similar findings revealing higher mortality in the age group 80+ (HR = 13.672, 95%CI: 3.915-47.746, P = 0) and widowed individuals (HR = 2.085, 95%CI: 1.275-3.409, P = 0.003). Involvement of eyes, mouth and ENT sites (HR = 0.425, 95%CI: 0.235-0.768, P = 0.005) had the lowest CSM in the multivariate analysis. Importantly, the study also revealed that the interaction between age and gender was not a statistically significant predictor of mortality in patients with EMM as shown in Table 4.

DISCUSSION

In this large SEER data-based retrospective cohort study, we demonstrated that EMM was associated with a higher OM and CSM in patients greater than 80 years of age and those patients who had been widowed. However, interestingly, the interaction between age and gender was not found to be statistically significant in predicting mortality in EMM patients.

EMM is a highly aggressive entity of MM, with clinical behavior distinct from marrow-restricted myeloma[12]. EMM is historically known to bear a worse prognosis compared to marrow-restricted myeloma[13]. Several studies have been carried out to investigate clinical characteristics and prognostic factors of EMM[4-8,12]. However, there is a paucity of data investigating the interaction of age and gender in regard to the mortality of EMM.

The interaction between gender and race and its influence on survival disparities in head and neck cancers has been well-documented[13]. Furthermore, gender was found to be the most important predictor with young and middle-aged females having the most favorable prognosis in non-smokers with oral squamous cell carcinoma[14]. However, no study has evaluated the impact of these interactions in the EMM population subgroup.

Our study did not reveal any interaction between age, gender, and race in regard to adjusted mortality in patients with EMM. Age was found to be the single most important prognostic factor for OM and CSM. Age was also found to be an important prognostic factor for the survival of EMM in a study by Li *et al*[5]. Gender and race were not of prognostic value in our cohort reaffirming the similar results found in the Li series[5].

Several retrospective studies have found marital status to be an independent prognostic factor in the survival of oncologic patients[15-19]. Patients that were married had better survival compared to their nonmarried counterparts[20-24]. This was also true in our study, where widowed patients had the highest OM and CSM, followed by single and divorced patients. This is perhaps due to the lack of psychological and emotional support as well as the increased incidence of depression and other mood disorders amongst these individuals, which could directly, or indirectly influence the treatment and regular oncology follow-up.

We hope that the results of this study will shed some light on the clinical presentation of this rare and aggressive manifestation of MM. In better understanding EMM, we hope to inspire larger prospective studies on the management of this subset of patients, which is particularly important in the era of novel agents including immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, and, more recently, the advent of chimeric antigen receptor T-cell therapy and bispecific agents. This can be especially important with the new emergence of microRNAs that help prevent drug resistance when

Table 2 Crude analysis of factors associated with all-cause mortality and extramedullary multiple myeloma; related mortality among United States patients between 2000 and 2017

Characteristics	Overall mortality	EMD MM mortality
	Crude proportional-hazard ratio (95% confidence interval)	
Gender		
Female	1 (reference)	1 (reference)
Male	1.02 (0.826-1.259)	0.804 (0.611-1.056)
Age at diagnosis, yr		
0-39	1 (reference)	1 (reference)
40-59	1.683 (0.82-3.452)	2.409 (0.754-7.696)
60-79	3.271 (1.615-6.627)[c]	4.918 (1.565-15.461)[c]
80+	6.951 (3.299-14.647)[c]	10.111 (3.083-33.159)[c]
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.339 (1.02-1.759)[b]	1.446 (1.017-2.055)[b]
Hispanic	0.991 (0.719-1.365)	0.791 (0.495-1.263)
Other	1.016 (0.63-1.639)	1.209 (0.67-2.179)
Extramedullary site		
CNS and vertebral column	1 (reference)	1 (reference)
Bones, subcutaneous tissues, connective tissues, and soft tissues of the trunk	1.53 (1.113-2.102)[c]	1.187 (0.774-1.82)
Bones, soft tissues, subcutaneous tissues, and connective tissues of the pelvis and sacrum	1.027 (0.716-1.475)	1.15 (0.746-1.772)
Bones, soft tissues, subcutaneous tissues, connective tissues, and lymph nodes of the upper extremities	1.036 (0.682-1.573)	0.718 (0.391-1.32)
Bones, soft tissues, subcutaneous tissues, and connective tissues of the lower extremities	1.668 (1.058-2.63)[b]	1.466 (0.814-2.642)
Bones, soft tissues, subcutaneous tissues, connective tissues, and lymph nodes of the face and skull	1.135 (0.756-1.702)	0.919 (0.529-1.598)
Other bones, NOS	1.74 (1.043-2.902)[b]	1.887 (1.044-3.411)[b]
Eyes, mouth, and ENT	0.929 (0.668-1.293)	0.451 (0.259-0.783)[c]
Lung, breast, and mediastinum	1.588 (0.895-2.816)	1.278 (0.589-2.773)
Gastrointestinal tract	0.787 (0.367-1.688)	0.55 (0.174-1.745)
Skin	0.241 (0.06-0.974)[b]	0.195 (0.027-1.403)
Kidney, suprarenal glands, and retroperitoneum	1.861 (0.591-5.86)	0.907 (0.126-6.531)
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250000 to 1 million persons	1.021 (0.789-1.322)	0.803 (0.556-1.158)
Counties in metropolitan areas of 250000 persons	0.794 (0.538-1.17)	0.8 (0.482-1.327)
Nonmetropolitan counties adjacent to a metropolitan area	1.099 (0.775-1.559)	0.937 (0.578-1.518)
Nonmetropolitan counties not adjacent to a metropolitan area	1.191 (0.798-1.779)	1.105 (0.647-1.888)
Income per year		
< $35000	1 (reference)	1 (reference)
$35000-44999	0.457 (0.213-0.984)[b]	0.412 (0.167-1.014)[a]
$45000-54999	0.356 (0.17-0.745)[c]	0.33 (0.139-0.782)[b]
$55000-64999	0.358 (0.174-0.737)[c]	0.236 (0.101-0.554)[c]

$65000-74999	0.328 (0.158-0.681)[c]	0.292 (0.124-0.685)[c]
$75000+	0.259 (0.125-0.538)[c]	0.24 (0.102-0.563)[c]
Marital status		
Married	1 (reference)	1 (reference)
Single	1.305 (0.967-1.763)[a]	1.515 (1.027-2.236)[b]
Divorced/separated	1.531 (1.094-2.142)[b]	1.681 (1.084-2.605)[b]
Widowed	2.107 (1.511-2.938)[c]	2.463 (1.612-3.765)[c]

[a]$P < 0.1$.
[b]$P < 0.05$.
[c]$P < 0.01$.
EMD: Extramedullary disease; MM: Multiple myeloma; CNS: Central Nervous System; NOS: Not otherwise specified.

Table 3 Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and extramedullary disease multiple myeloma related mortality among United States patients between 2000 and 2017

Characteristics	Overall mortality	EMD MM mortality
	Adjusted proportional hazard ratio (95% confidence interval)	
Gender		
Female	1 (reference)	1 (reference)
Male	1.256 (0.989-1.594)[a]	1.022 (0.748-1.397)
Age at diagnosis, yr		
0-39	1 (reference)	1 (reference)
40-59	2.206 (1.047-4.647)[b]	3.154 (0.957-10.395)[a]
60-79	4.129 (1.974-8.635)[c]	5.667 (1.738-18.48)[c]
80+	9.792 (4.403-21.774)[c]	13.672 (3.915-47.746)[c]
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.315 (0.96-1.802)[a]	1.34 (0.884-2.03)
Hispanic	1.034 (0.734-1.457)	0.833 (0.506-1.371)
Other	1.25 (0.743-2.104)	1.741 (0.916-3.308)[a]
Extramedullary site		
CNS and vertebral column	1 (reference)	1 (reference)
Bones, subcutaneous tissues, connective tissues, and soft tissues of the trunk	1.401 (0.996-1.972)[a]	1.046 (0.664-1.649)
Bones, soft tissues, subcutaneous tissues, and connective tissues of the pelvis and sacrum	0.98 (0.671-1.432)	1.091 (0.689-1.729)
Bones, soft tissues, subcutaneous tissues, connective tissues, and lymph nodes of the upper extremities	1.024 (0.661-1.586)	0.672 (0.353-1.279)
Bones, soft tissues, subcutaneous tissues, and connective tissues of the lower extremities	1.488 (0.909-2.436)	1.382 (0.733-2.605)
Bones, soft tissues, subcutaneous tissues, connective tissues, and lymph nodes of the face and skull	0.99 (0.641-1.53)	0.76 (0.414-1.394)
Other bones, NOS	1.195 (0.694-2.058)	1.199 (0.629-2.284)
Eyes, mouth, and ENT	0.902 (0.631-1.29)	0.425 (0.235-0.768)[c]
Lung, breast, and mediastinum	1.187 (0.628-2.246)	0.959 (0.392-2.346)
Gastrointestinal tract	0.677 (0.303-1.512)	0.383 (0.114-1.283)
Skin	0.327 (0.08-1.34)	0.325 (0.044-2.394)

Kidney, suprarenal glands, and retroperitoneum	3.055 (0.881-10.601)[a]	0.865 (0.108-6.901)
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250000 to 1 million persons	0.957 (0.715-1.282)	0.778 (0.512-1.181)
Counties in metropolitan areas of 250000 persons	0.819 (0.523-1.282)	0.85 (0.47-1.539)
Nonmetropolitan counties adjacent to a metropolitan area	0.997 (0.653-1.522)	0.836 (0.461-1.516)
Nonmetropolitan counties not adjacent to a metropolitan area	0.877 (0.533-1.442)	0.757 (0.379-1.512)
Income per year		
< $35000	1 (reference)	1 (reference)
$35000-44999	0.48 (0.21-1.095)[a]	0.381 (0.14-1.036)[a]
$45000-54999	0.452 (0.196-1.04)[a]	0.375 (0.135-1.044)[a]
$55000-64,999	0.446 (0.192-1.036)[a]	0.275 (0.096-0.788)[b]
$65000-74999	0.413 (0.173-0.983)[b]	0.381 (0.129-1.121)[a]
$75000+	0.324 (0.134-0.783)[b]	0.29 (0.095-0.878)[b]
Marital status		
Married	1 (reference)	1 (reference)
Single	1.5 (1.079-2.086)[b]	1.668 (1.089-2.556)[b]
Divorced/separated	1.49 (1.037-2.139)[b]	1.463 (0.908-2.355)
Widowed	1.609 (1.101-2.35)[b]	2.085 (1.275-3.409)[c]

[a]$P < 0.1$.
[b]$P < 0.05$.
[c]$P < 0.01$.
EMD: Extramedullary disease; MM: Multiple myeloma; CNS: Central Nervous System; NOS: Not otherwise specified.

Table 4 Joint test analysis of the predictors of extramedullary multiple myeloma and overall mortality among United States extramedullary multiple myeloma patients, 2000-2017

Variables	MM mortality			Overall mortality	
	DF	χ^2	*P* value	χ^2	*P* value
Race/ethnicity	3	5.7436	0.1248	3.2403	0.3560
Age at diagnosis	3	21.2193	< 0.0001	49.2869	< 0.0001
Gender	1	0.5044	0.4776	0.5168	0.4722
Extramedullary Site	11	16.6070	0.1200	15.6578	0.1543
Living area	4	2.1023	0.7169	0.8175	0.9361
Income	5	7.3539	0.1956	7.4157	0.1915
Marital status	3	10.8183	0.0128	11.7967	0.0081
chemotherapy	1	2.3104	0.1285	1.4536	0.2280
Year of diagnosis	17	25.3142	0.0879	16.1848	0.5108
Interaction between age and gender	3	2.1285	0.5462	1.0296	0.7941

DF: Degree of freedom; MM: Multiple myeloma.

combined with anti-MM drug regimens and improve the patient's management[25].

Our study has several strengths. Firstly, the database used is the largest cancer database in the United States. The sample size of the study is non-negligible. Also, owing to the stringent inclusion criteria and the fact that we used patients with only confirmed EMM for our diagnosis, we eliminated false positive results which increase the accuracy of our study findings. However, a few limitations should be

considered in our study. Information could not be obtained on radiotherapy and Hematopoietic Stem Cell Transplant. The information on chemotherapy was unfulfilled. Furthermore, the SEER database publicly available lacks information on comorbidities, which could lead to missing data on potential confounders owing to the retrospective nature of the study.

CONCLUSION

EMM is a rare entity of MM that can be present at diagnosis or develop during the disease course. In this large retrospective SEER database-based study, we found that age and gender do not interact to influence the mortality of patients with EMM. Age was the single most important prognostic factor. We hope that the results of this study will shed light on this important non-significant interaction between age and gender in regard to mortality amongst EMM patients and perhaps inspire larger prospective studies on this subject.

ARTICLE HIGHLIGHTS

Research background

Age has been established as the single most important prognostic factor of extramedullary multiple myeloma (EMM). However, the interaction between age and gender in the mortality of EMM has yet to be studied.

Research motivation

The main motivation of this study was to identify independent predictors of outcomes, as well as how age and gender interact to affect mortality in EMM.

Research objectives

This study has the objective to establish the overall epidemiology of EMM, as well as the interaction between age and gender on mortality.

Research methods

This is a retrospective study involving 858 patients diagnosed with EMM, between 2000 and 2017 using the Surveillance, Epidemiology, and End Results database.

Research results

Patients older than 80 years and widowed had higher overall mortality (OM) and cancer-specific mortality (CSM). Eyes, mouth, and ENT involvement were protective factors regarding CSM. There was no interaction between age and gender in the adjusted analysis for OM and CSM.

Research conclusions

Although age is the single most important prognostic value of mortality in EMM, it does not interact with gender to affect mortality in patients with EMM.

Research perspectives

Future prospective studies are needed to better understand the impact of newer agents in the management of this aggressive subset of MM.

FOOTNOTES

Author contributions: Bangolo AI searched the literature, wrote, and revised the manuscript; Fwelo P extracted and analysed the data, revised, and edited the manuscript; Trivedi C, Sagireddy S, Aljanaahi H, Auda A, Mohamed M, Onyeka S, Fisher M, Thapa J, Tabucanon EJ, Georgiev L, Wishart A, Kumari S, Erikson C, Bangura M, Paddy O, Madhukar R, Gomez EL, Rathod J, Naria M, Hajal B, Awadhalla M, Siegel D, Parmar H, Biran N, and Vesole DH revised and edited the manuscript; Phull P and Weissman S revised and approved the final version and are the article's guarantors; All authors certify that they contributed sufficiently to the intellectual content and data analysis; Each author has reviewed the final version of the manuscript and approved it for publication.

Institutional review board statement: The study protocol was reviewed by the Ethics Committee at Palisades Medical Center and the need for IRB approval was waived as the SEER database is a public-use dataset.

Informed consent statement: The Surveillance, Epidemiology, and End Results (SEER) database was a public-use

dataset, of which the informed consent was waived.

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Data sharing statement: The data used and/or analyzed in this study are available in the Surveillance, Epidemiology, and End Results (SEER) Database of the National Cancer Institute (http://seer.cancer.gov).

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