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Global disparities in drug-related adverse events of patients with multiple myeloma: a pharmacovigilance study

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Multiple myeloma (MM) is a complex hematological malignancy of clonal plasma cells driven by alterations to the chromosomal material leading to uncontrolled proliferation in the bone marrow. Ethnic and racial disparities persist in the prevalence, diagnosis, management, and outcomes of MM. These disparities are multifaceted and intersect with various factors, including demographics, geography, socioeconomic status, genetics, and access to healthcare. This study utilized the openFDA human drug adverse events (AEs) to analyze global data pertaining to MM patients and patterns of treatment-related AEs. We identified ten most frequently used drugs and drug regimens in six distinct regions, including North America (NA), Europe (EU), Asia (AS), Africa (AF), Oceania (OC), and Latin America & the Caribbean (LA). AE patterns were evaluated using the reporting odds ratio combined with a 95% confidence interval. AE reports were more prevalent in men than in women across all regions. Cardiotoxicities were more likely observed in AS and EU, while secondary neoplasms were more frequently reported in the EU. Nephropathies were prominent in OC, AF (in males), and AS (in females), while vascular toxicity, including embolism and thrombosis, was more common in NA (in males). A notable improvement in survival, particularly in AS, EU, and NA, with a significant decline in death rates was observed. Hospitalization rates displayed less variation in AS and EU but exhibited more pronounced fluctuations in AF, LA, and OC. In conclusion, this comprehensive analysis offers valuable insights into the demographic, geographic, and AE patterns of MM patients across the globe.

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INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy in adults worldwide, and it is characterized by the abnormal proliferation of malignant clonal plasma cells. Over the years, significant racial and ethnic disparities in prevalence and outcomes have been noted [1–3]. In the United States (US), the incidence of MM in black individuals is 2 to 3-fold higher compared to non-Hispanic whites (NHWs). In addition, black individuals tend to have a higher burden of disease, more aggressive phenotype, are often diagnosed at a younger age, and have more than double the mortality rates. Baris et al. have reported an increased prevalence of MM in individuals with low Socioeconmic status. [4]. A Meta-analysis of 16 studies also reported that poor socioeconomic status was an adverse prognostic factor for MM globally [5]. In a large study of two separate cohorts of patients with MM, socioeconomic factors including higher income, education, and occupation were independently associated with improved survival rates among these patients [6].

Over the past few years, the introduction of novel therapies has shifted the treatment paradigm of MM, offering prolonged disease-free intervals and overall survival (OS). However, different patterns of drug utilization have been noted based on several parameters including but not limited to geographical location, race, or novel agent. Notably, prior reports showed lower utilization rates of novel therapies such as proteasome inhibitors, and immunomodulatory drugs, as well as autologous stem cell transplantation in black patients when compared to NHWs [7–11]. Understanding the factors that may lead to imbalances in drug utilization patterns beyond race, particularly drug toxicity provides valuable insights into safety and overall patient outcomes. A previous study by Mateos et al. reported that in the US male patients had worse OS compared to females, despite women facing more challenges in access to treatment [12]. Similar healthcare inequalities were observed among Black, Asian, and Hispanic patients. Additional studies have focused on racial disparities in MM outcomes, particularly Black patients [3, 13, 14], with recent evidence suggesting no significant differences between races when equitable healthcare opportunities are available [14, 15]. Studies using machine learning and cancer-omics data have also attempted to shed light on inequalities and discrepancies in patient outcomes across ethnic groups [16, 17]. However, there are no studies specifically focusing on the

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distribution of drug-related adverse events (AEs) and their on impact patient outcomes across different geographic regions and ethnic groups. Our study aimed to analyze global pharmacovigilance data of MM patients and assess how AE patterns of the most common myeloma drug regimens may differ across regions, ethnic, and gender groups.

METHODS

Data source

Global MM patient data were retrieved from the openFDA Human Drug Adverse Events endpoint [18]. The openFDA MM dataset contains various patient-related information, including demographics (e.g., age, body weight, and sex), case received dates, reporting country, reported AEs, and active substances of medications. Here, we introduce a structured approach to connect large, complex public health data to a working hypothesis. The methodological steps include data extraction with error correction, integration of various data sources, multi-stage statistical analysis, and data science methods for utilizing pharmacovigilance data from spontaneous reporting systems. Additionally, we employ multi-stage statistical methods to evaluate the significance of our findings, ensuring a detailed analysis of the dataset. A summary of our detailed methodology, based on our previous published work, is included in the supplementary attachment.

Ethics approval and consent to participate

The data used in this research, obtained from the FDA Adverse Event Reporting System (FAERS) and OpenFDA, were collected and made publicly available by the FDA in compliance with applicable federal regulations.

Data processing and aggregation

To standardize the AE data and facilitate analysis, the Medical Dictionary for Regulatory Activities (MedDRA) was utilized. MedDRA is a validated international medical terminology that enables the grouping of AEs into High-Level Group Terms (HLGTs: related to grouping AEs based on anatomy, pathology, physiology, etiology or function) and System Organ Classes (SyOC: related to grouping AEs based on etiology, manifestation site, purpose, or social circumstance) [19]. This aggregation process is instrumental in organizing and consistently categorizing the AEs.

Drugs within the dataset were characterized according to the Anatomical Therapeutic Chemical classification system. This classification system categorizes drugs based on their therapeutic indication, pharmacological properties, and chemical structure. It offers a standardized approach to identifying and analyzing drugs across different regions and datasets.

Inclusion/exclusion criteria

We first identified all AE reports associated with treatments for MM. Next, we captured detailed patient demographics based on geographical locations. Cases that included complete information on gender and reported location were retained. We excluded cases with incomplete data or those not directly related to MM therapies to minimize bias.

Data collection period

Data were collected from the beginning of 2004 to the 4th quarter of 2022, capturing a 20-year timeframe of MM patient cases and associated adverse events.

Identification of top ten used drugs and drug regimens

A selection process was employed to determine the most frequently used drugs in six distinct regions: North America (NA), Europe (EU), Asia (AS), Africa (AF), Oceania (OC), and Latin America & the Caribbean (LA). In cases where a drug was involved in different reports, only a single drug with one active substance was retained. However, if a drug regimen was associated with a report, all the active substances of that regimen were retained for further analysis. In addition, a drug (regimen) had to be associated with a minimum of 20 different reports to consider for the analysis.

Table 1. Overall features of AE reports of MM patients in openFDA from 2004 to 2022.

Region	Number (%)	#M/F (Age: M/F)
NA	330,187 (82.9%)	1.1 (68.9/69.4)
EU	43,586 (10.9%)	1.3 (67.4/68.0)
AS	17,611 (4.4%)	1.2 (68.6/69.8)
OC	4265 (1.1%)	1.4 (67.8/67.9)
LA	2490 (0.6%)	1.0 (64.8/65.6)
AF	394 (0.1%)	1.4 (60.2/59.4)
Reporting year	**Total case number**	**%**
2004–2011	24,381	6.16%
2012–2014	40,447	10.23%
2015	38,514	9.74%
2016	30,871	7.80%
2017	35,025	8.86%
2018	34,334	8.68%
2019	39,252	9.92%
2020	43,907	11.10%
2021	63,084	15.95%
2022	45,722	11.56
Adverse events	**Number**	**%**
Cardiac	20,564	5.20%
Neoplasm	41,660	10.53%
Renal	17,056	4.31%
Vascular	24,194	6.12%

Assessment of geographical and gender disparities

Instead of relying solely on raw incidence rates, we used the reporting odds ratio (ROR) combined with a 95% confidence interval to assess the association between adverse events and potential disparities in geographical regions and sexes. The ROR provides a measure of the elevated incidence of an adverse event in a particular population compared to the background population. By applying the ROR analysis, we aimed to identify any potential variations or disparities in the occurrence of adverse events among different geographical regions and sexes, shedding light on potential differences in drug safety profiles. ROR excludes the AE cases caused by other drugs, or other AEs due to the targeted drug. Hence, the controls in b, c, and d (Supplementary Table S1) were independent of the targeted drug-AE pair. The confidence interval of ROR can be derived through the Delta method for the significance level $\alpha = 0.05$. We have shown the average age difference across six regions (Table 1). Other treatment information, such as duration, dosage, weight, and comorbidities, was not always available. To aggregate the majority of cases and reduce the model complexity, stratification was applied to fix the level for regions and genders.

Drug regimens

There were 22 different drug regimens among the top 10 regimens used in six regions (Table 2). We retrieved the reports with no more than four different active substances in a regimen.

RESULTS

Patient characteristics

Our analysis encompassed a substantial dataset of 395,538 MM cases, sourced from NA, EU, AS, AF, OC, and LA, spanning 129 countries between 2004 and December 2022. These cases encompassed 27 phenotypic systems/organs categories utilizing MedDRA. Approximately 80% of these reported cases were concentrated in NA. We found that NA exhibited a ratio of 1.1 for male vs female, EU 1.3, AS 1.2, OC 1.4, LA 1.0, and AF 1.4. We

Table 2. Examples of the top 10 common regimens used in different regions.

Drug regimen included active substances	Abbreviation
Bortezomib, Lenalidomide, Carfilzomib Thalidomide**	KVRT
Ixazomib, Lenalidomide, Glucocorticoide*	NRd
Bortezomib, Glucocorticoids*, Lenalidomide	VRd
Lenalidomide, Glucocorticoid*	Rd
Bortezomib, Glucocorticoids*	Vd
Daratumumab, Glucocorticoids*, Lenalidomide	DRd
Bortezomib, Glucocorticoids*, Thalidomide	VTd
Bortezomib, Cyclophosphamide, Glucocorticoids*	VCd
Bortezomib, Daratumumab, Glucocorticoids*	DVd
Bortezomib, Daratumumab	VD
Glucocorticoids*, Pomalidomide	Pd
Bortezomib, Lenalidomide	VR
Ixazomib, Lenalidomide	NR
Thalidomide	T
Bortezomib	V
Ixazomib	N
Carfilzomib	K
Bisphosphonates	Bp
Daratumumab	D
Lenalidomide	R
Pomalidomide	P

Drug Regimen Abbreviation: Bortezomib (V for Velcade), Carfilzomib (K for Kyprolis), Lenalidomide (R for Revlimid), Thalidomide (T for Thalomid), Glucocorticoids (d for dexamethasone*), Ixazomib (N for Ninlaro), Daratumumab (D for Darzalex), Cyclophosphamide (C for Cytoxan), Pomalidomide (P for Pomalyst), Bisphosphonates (Bp).

* Over 90% of the data for Glucocorticoids was curated from dexamethasone.

** The administration of these active substances might be on different timelines. AEs were reported to one regimen per report ID.

observed variations in the mean age of MM patients, with North American men and Asian women exhibiting higher mean ages compared to their counterparts in other regions. MM patients in AF had the youngest mean age. Notably, general disorders (Administration site reactions, body temperature conditions, complications associated with devices, fatal outcomes, general system disorders NEC, therapeutic and non-therapeutic effects (excl toxicity), and tissue disorders NEC) and administration site conditions emerged as the most frequently reported SyOC, primarily driven by NA data, accounting for 87.3% of the reports. This was followed by HLGTs related to gastrointestinal disorders. Conversely, SyOCs related to cardiac toxicity, vascular toxicity, secondary neoplasms (benign, malignant, and unspecified), and renal and urinary toxicities constituted less than 10% of the reported cases (as illustrated in Table 1). Our study has demonstrated regional distinctions in the prevalence of adverse events, with cardiac (2.9%), neoplastic (5.7%), renal (2.4%), and vascular (3.4%) AEs being prominent. When focusing on gender, reported AEs were higher in men compared to women across all six regions. Furthermore, a closer examination of MM report rates over time revealed a gradual accumulation from 2004 to 2012, followed by a more rapid increase from 2012 to 2014. Subsequently, the number of MM cases consistently rose, with a notable surge in 2021, witnessing an unprecedented annual report count exceeding 60,000 cases.

Plasma cell-directed agents

Irrespective of geographical regions, our analysis revealed a consistent pattern of plasma cell-directed drugs used. Lenalidomide (R) emerged as the most frequently utilized agent, at 260,859 reported cases (66.0%), followed by dexamethasone (d) at 126,948 cases (32.1%), pomalidomide (P) at 70,230 cases (17.8%), and bortezomib (V) at 54,333 cases (13.7%). These drugs were the most commonly used agents. Additional drugs included thalidomide (T) at 19,260 cases, daratumumab (D) at 17,838 cases, carfilzomib (K) at 16,485 cases, and cyclophosphamide (C) at 13,674 cases. Many treatment regimens included multiple drugs administered together. To account for this, we grouped drugs into drug regimens to offer a more comprehensive and realistic view of treatment patterns across six regions.

The top ten drug regimens for each region are shown in Fig. 1; the remaining regimens were grouped into "others". In NA, the use of a single agent, R, dominated treatment regimens, accounting for a substantial 61.5% of cases. Notably, the top ten regimens collectively represented nearly 90% of MM drug usage in NA. In contrast, in the EU, drug combinations exhibited greater diversity, with the top ten most frequently used regimens contributing to 53.1% of cases. Use of R single agent was most common in the EU accounting for 9.5% of cases, followed by Rd at 8.3%. Across various regions, R consistently stood out as the most frequent component of MM treatment. However, it is worth noting that OC exhibited a unique pattern where V was notably prevalent, representing 38.1% of cases in the region. Nonetheless, R remained the predominant choice in the remaining five regions.

ROR

We conducted comparisons of the 95% confidence intervals of the RORs across different geographical locations and genders for four key SyOCs related to AEs: cardiac (Card), neoplasm (Neopl), renal and urinary tract disorders (Renal), and vascular disorders (Vasc) (Fig. 2). These RORs were employed to measure the association between geographical locations and AEs for both males and females. One noteworthy finding was the increased likelihood of cardiotoxicities observed in AS and EU. This suggests that patients in these regions may be more susceptible to cardiac-related AEs when compared to other regions. Furthermore, myocardial disorders exhibited a stronger association with OC in males (ROR 3.6, CI 2.4), indicating a higher prevalence of these disorders among male MM patients in this region.

The analysis also revealed that neoplasms were more frequent in OC, in both males and females. Additionally, secondary leukemias were noted more frequently in the EU compared to other regions and gender combinations. Conversely, nephrotoxicity exhibited less distinct associations across all subgroups, indicating a relatively consistent reporting pattern across regions and genders. However, nephropathies, a subset of renal disorders, were reported more frequently in OC among both females (ROR 5.7, CI 3.1) and males (ROR 4.3, CI 2.4). Additionally, among males, AF showed a substantial association with nephropathies (ROR 9.2, CI 2.3). Vascular toxicities, including embolism and thrombosis, as well as vascular hemorrhagic disorders, were more likely to be reported in NA among males. These findings provide valuable insights into the association between geographical locations, genders, and reported adverse events related to MM treatments, shedding light on potential disparities in the safety profiles of MM treatments across different regions and patient demographics when investigating the occurrence of reported AEs and associated drugs.

Death and hospitalization trends

While regions like NA have witnessed substantial improvements in survival, other regions exhibit more varied patterns. The trends in death rates and hospitalization rates (HRs) among MM patients over time were visually depicted in Fig. 3. The descending bubbles

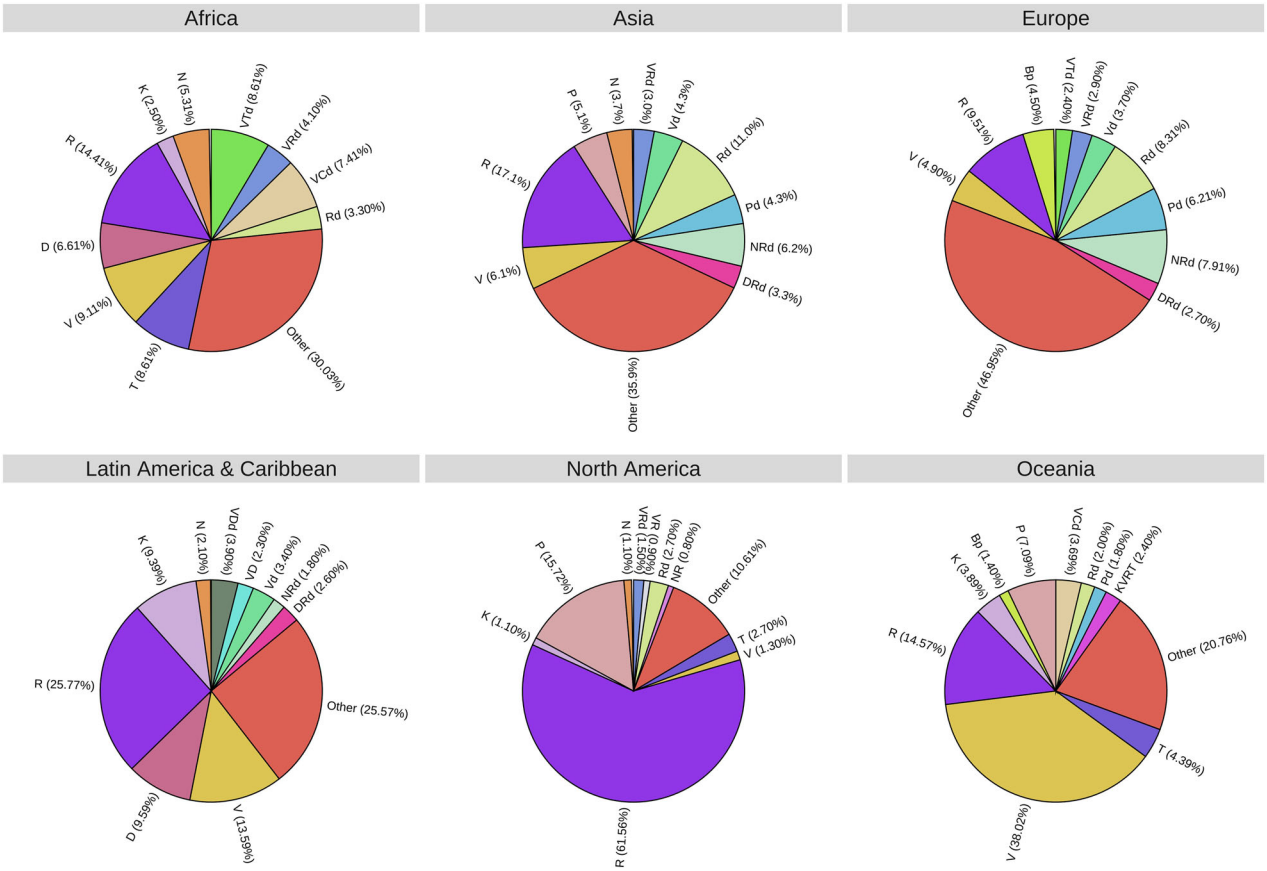

Fig. 1 Usage of top MM drug regimens across six continents. Each pie chart represents the distribution of drug regimens used in a different continent, with each section of the chart corresponding to a specific regimen and its percentage of usage. The color scheme is consistent across all continents, allowing for easy comparison of the relative usage of each drug regimen.

in the figure symbolize a notable improvement in survival rates, particularly in AS, EU, and NA. Figures 3 and 4 exclude data from 2003 to 2004 while AE reports were only collected from NA across six regions, which limited the geographic information of data.

In NA, the death rates witnessed a remarkable decline annually, dropping from 50.4% of reported cases in 2004 to a substantially lower 5.5% in 2021. This substantial decrease suggests significant advancements in the management and treatment of MM patients, contributing to higher survival rates. In contrast, the EU exhibited the least fluctuation in death rates over the years and maintained an average value of ~27.0%. The trends in AS displayed a pattern with two peaks in death rates happening in 2008 and 2016. After 2016, the decline continued when it reached the lowest recorded value of 27.1% in 2022. However, it's important to note that large variations in death rates were observed in AF, LA, and OC. These variations can be attributed to the limited number of reported cases from these regions, making it challenging to draw definitive conclusions about trends in MM patient outcomes. HRs are represented by the size of the bubbles in Fig. 3. In AS and EU, there were fewer variations in HRs over time, indicating relatively stable patterns of hospitalization among MM patients. In contrast, to 17.0% in 2022, MM cases collected in AF, LA, and OC exhibited more pronounced variations NA experienced a decline in HRs, reaching 14.4% in 2021 and 17.0% in 2022.

When analyzing the reported death percentages involving different MM drug regimens across continents, we observe notable variations, though we aim to avoid direct causality due to medications since death might be caused by disease progression. In NA, where multiple regimens are prevalent, the death percentages range from 6.4% for patients on VRd to 45.0% for patients on T. This indicates substantial diversity in patient outcomes, and the exact cause of death for individual subjects is not known in this large cohort. In the EU, the death percentages vary from 6.2% for patients on bisphosphonates (Bp) to 53.4% for those on R. AS presents its own set of figures, with death percentages ranging from 25.0% for patients on VRd to 76.7% for patients on P. OC records high death percentages for patients on P (76.5%) and R (60.0%). While these numbers provide insights into mortality rates across these regions, it is essential to consider individual factors contributing to these outcomes. Additionally, it is worth noting that the data from AF is not as reliable, limiting the depth of our analysis.

Analyzing the percent hospitalization data based on different MM drug regimens across continents reveals a range of HR. In NA, patients on various regimens exhibit hospitalization percentages ranging from 29.80% for VRd to 41.65% for patients on V regardless of other covariates (i.e., age, comorbidities, reasons for hospitalization). EU shows diverse figures, with hospitalization percentages spanning from 16.56% for patients on Bp to 52.19% for those on Pd. In AS, the hospitalization percentages range from 18.11% for patients on P to 36.45% for patients on NRd. OC records notably high hospitalization percentages, such as 62% for patients on Pd and 61.6% for those on T. While the data from AF is limited, it still provides insights into the trends in HRs for MM patients across different continents (Fig. 4).

DISCUSSION

In this comprehensive analysis of MM disparities across different continents, we sourced global MM patient report data from the openFDA Human Drug Adverse Events endpoint, a dataset

AE	AF (F)	AF (M)	AS (F)	AS (M)	EU (F)	EU (M)	LA (F)	LA (M)	NA (F)	NA (M)	OC (F)	OC (M)
Cardiac	0.45	0.48	1.12	1.27	1.32	1.74	0.99	1.43	0.59	1.11	0.82	1.07
Cardiac arrhythmias	0.68	0.60	0.96	1.18	1.50	1.99	1.06	1.65	0.53	1.03	1.00	1.01
Cardiac disorders, signs and symptoms nec	0.33	0.06	0.56	0.39	0.48	0.44	0.74	0.68	0.82	1.41	0.39	0.57
Cardiac valve disorders		0.40	0.39	0.17	0.89	0.69	0.07	0.22	0.61	1.17	1.25	1.06
Coronary artery disorders	0.10		0.48	1.02	0.87	2.01	0.58	1.22	0.44	1.37	0.46	1.23
Heart failures		0.21	1.69	1.88	1.51	1.90	0.73	0.43	0.57	0.86	0.22	0.45
Myocardial disorders			2.20	1.53	2.33	2.19	0.85	0.49	0.45	0.58	0.99	2.36
Pericardial disorders	0.68	0.46	1.03	1.14	0.81	1.22	0.27	0.25	0.62	0.80	0.27	0.77
Neoplasm	1.37	2.32	2.77	2.94	1.69	2.23	1.09	1.00	0.49	0.72	8.03	8.10
Breast neoplasms benign (incl nipple)									2.83	0.04		
Breast neoplasms malignant and unspecified (incl nipple)			1.70		6.59	0.01	0.87		2.10	0.00	0.84	
Cutaneous neoplasms benign				0.24	0.26	0.63	0.17		0.89	0.84	0.58	0.11
Gastrointestinal neoplasms benign			0.33	0.88	0.99	2.42			0.60	0.15	0.59	
Gastrointestinal neoplasms malignant and unspecified			1.78	2.78	3.04	4.84	0.10	0.28	0.22	0.46	1.33	2.41
Leukaemias	0.17	0.12	1.37	1.88	2.69	5.28	1.26	0.27	0.21	0.56	1.75	3.19
Lymphomas Hodgkin's disease						5.00			0.18	0.02		
Lymphomas nec			0.21	1.03	0.09	0.72	0.39	0.36	0.56	0.67		0.94
Lymphomas non-Hodgkin's b-cell			0.18	0.31	1.57	3.03			0.25	0.56		0.82
Lymphomas non-Hodgkin's t-cell				0.18	1.42	3.49			0.01	0.53		
Lymphomas non-hodgkin's unspecified histology			0.23		3.42	0.90			0.09	0.39		
Nervous system neoplasms benign				0.12	1.56	0.17		0.85	0.55	0.35		0.62
Nervous system neoplasms malignant and unspecified nec			0.15	0.46	1.34	1.97	1.01	0.48	0.52	0.66	0.14	0.10
Plasma cell neoplasms	1.89	3.27	3.03	3.17	1.26	1.38	1.09	1.06	0.53	0.74	9.96	9.20
Renal and urinary tract neoplasms malignant and unspecified			0.48	1.51	1.02	4.18	0.07		0.18	0.98	1.06	0.53
Reproductive neoplasms female benign			1.92		0.07				3.47			
Reproductive neoplasms female malignant and unspecified	1.83		2.52	0.03	9.51		0.21		1.03		0.20	
Reproductive neoplasms male benign						10.83				0.09		
Reproductive neoplasms male malignant and unspecified		0.49		0.88		7.98		0.08		1.46		2.39
Skin neoplasms malignant and unspecified			0.03	0.17	1.46	3.29	0.02	0.11	0.33	1.12	2.97	4.86
Renal	0.54	1.97	1.14	1.32	1.19	1.36	0.92	0.91	0.67	1.09	0.69	1.13
Bladder and bladder neck disorders (excl calculi)			1.45	2.06	0.30	0.62	0.08	0.77	0.59	0.98	0.08	1.00
Genitourinary tract disorders nec			0.34	0.30	0.23	0.59		0.30	0.29	1.55		
Nephropathies	2.29		2.67	0.96	1.93	1.67	1.08	0.72	0.42	0.55	3.12	2.41
Renal disorders (excl nephropathies)	0.31	2.02	1.12	1.28	1.31	1.37	1.01	0.82	0.66	1.06	0.72	1.04
Ureteric disorders			0.27	0.85	0.11	0.09			0.15	0.58		4.31
Urethral disorders (excl calculi)					0.38	1.36			0.51	0.51		
Urinary tract signs and symptoms	0.13	1.29	0.46	1.08	0.52	1.12	0.15	0.38	0.74	1.17	0.21	0.73
Urolithiases			0.04	0.13	0.07	0.25			0.59	2.01		0.16
Vascular	0.30	0.25	0.47	0.45	0.74	0.81	0.79	0.67	0.92	1.23	0.48	0.48
Aneurysms and artery dissections			0.58	0.39	0.14	1.23	0.71	0.18	0.34	1.32		0.13
Arteriosclerosis, stenosis, vascular insufficiency and necrosis			0.27	0.51	0.73	1.37	0.79	1.09	0.71	0.96	0.14	0.79
Decreased and nonspecific blood pressure disorders and shock	0.27	0.36	0.64	0.73	1.16	1.19	1.05	0.78	0.69	1.11	0.64	1.12
Embolism and thrombosis	0.10	0.13	0.25	0.20	0.37	0.43	0.11	0.15	0.95	1.53	0.20	0.07
Lymphatic vessel disorders					0.41	0.33			1.61	0.39		
Vascular disorders nec			0.20	0.49	0.56	0.41	0.88	0.71	1.34	0.79	1.08	0.10
Vascular haemorrhagic disorders	0.27	0.18	0.76	0.47	0.57	0.96	0.73	0.54	0.74	1.11	0.71	0.14
Vascular hypertensive disorders	0.17	0.11	0.60	0.54	1.21	1.10	1.86	1.43	0.98	0.72	0.61	0.75
Vascular infections and inflammations			0.76	0.47	1.70	2.53	0.53	0.49	0.54	0.44		0.69
Venous varices			0.05		0.75		0.33		2.17	0.27		

Fig. 2 Lower confidence interval of ORR by regions, genders, and classification for four key SyOCs related to AEs: cardiac, neoplasm, renal and urinary tract disorders (Renal), and vascular disorders. Green to red color codes are used for low certainty to high certainty.

encompassing diverse patient-related information. Similar to a study that observed declines in early mortality in all MM patients including those younger than 65 years and older than 65 years [20], our findings revealed distinct characteristics in mortality but ultimately demonstrated a decreasing trend across continents. Differences in various reported outcomes could be due to various factors related to disparities including utilization and availability of different drug regimens in different regions. In terms of age and gender distribution, the male-to-female ratios were consistent across regions, with slight regional variations.

In the MM Research Foundation (MMRF) CoMMpass study via NCI's Genomic Data Commons Data Portal, the largest MM dataset in the public domain, d, R, and V are the top three drug components in combination therapy [21]. However, in our dataset, R emerged as the most frequently reported drug, followed by glucocorticoids, V, and P among all regions. Notably, T, D, K, and cyclophosphamide-based regimens were also used frequently. To account for multiple drugs within a single report, we grouped drugs into regimens across six different regions. Single use of R was highly prevalent in NA, whereas in the EU, drug regimens were more diverse, NRd, Pd, Rd, and R consist of AEs in the United Kingdom and France as the top two countries of report AEs in the EU. Nevertheless, R or R-related regimens remained dominant in the EU, while in other regions, single use of R was consistently the most widely used drug.

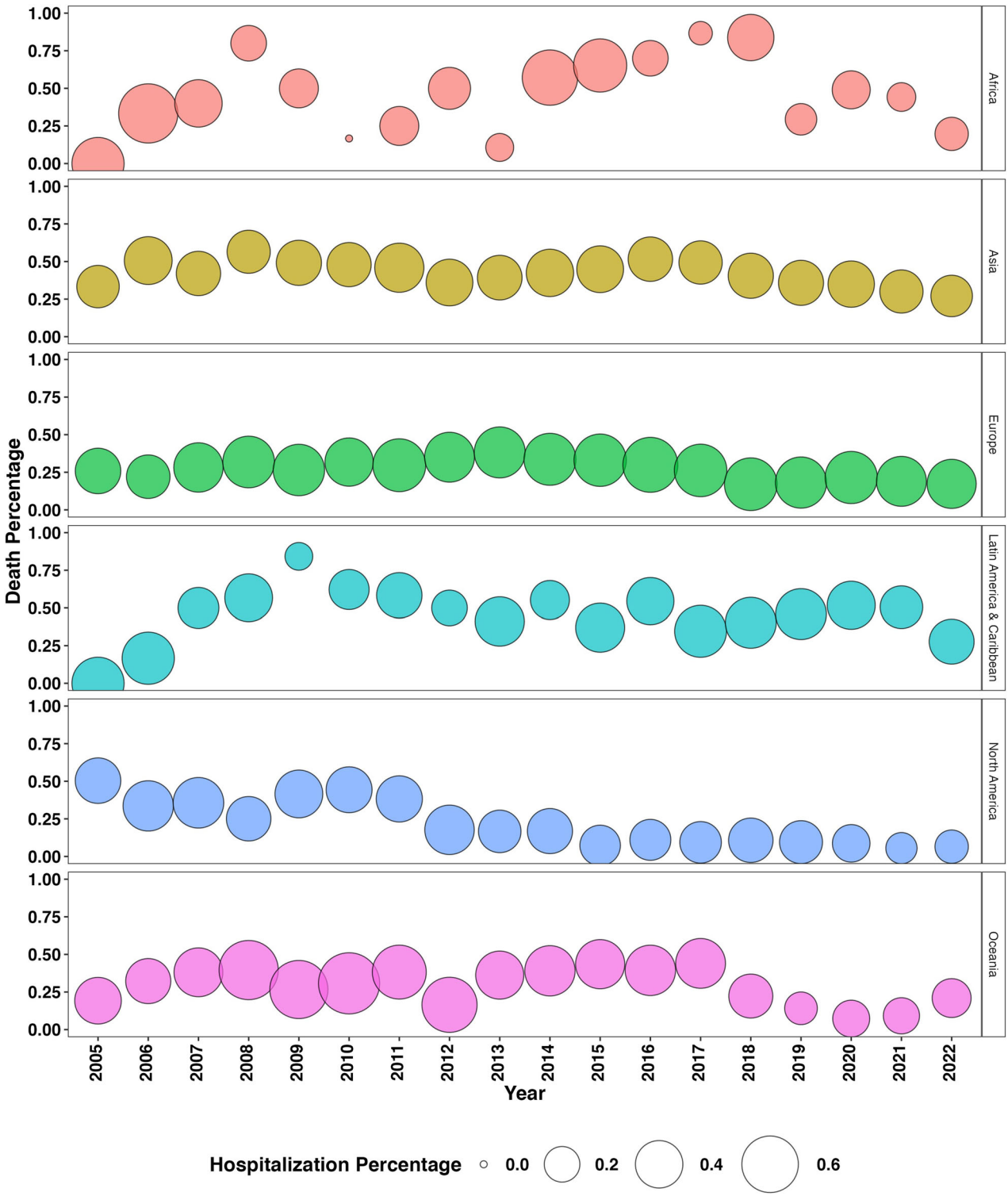

Fig. 3 The trends of death rate and hospitalization rate from 2005 to 2022 for six different continents.

According to the FDA, death, and hospitalization are two serious outcomes in patient reports, however, the occurrence of one or more deaths and hospitalization in a report does not necessarily mean that drug was the cause of these two serious outcomes [22]. Our findings revealed intriguing trends in death rates and hospitalization rates of MM patients over time, as depicted in Fig. 3. The descending bubbles in Fig. 3 symbolize a marked improvement in survival rates, particularly in AS, EU, and NA. The introduction of novel therapies significantly improved survival rates for MM patients in the US, evident in data from both the Mayo Clinic and the Surveillance, Epidemiology, and End Results (SEER) program over a 14-year period [23]. A study also showed that survival rates for MM patients in Germany have improved remarkedly since 2000 due to the novel therapeutic [24]. Based on our findings, death rates (mean value of 27%) exhibited fluctuations with no drug regimen usage exceeding 10% of total

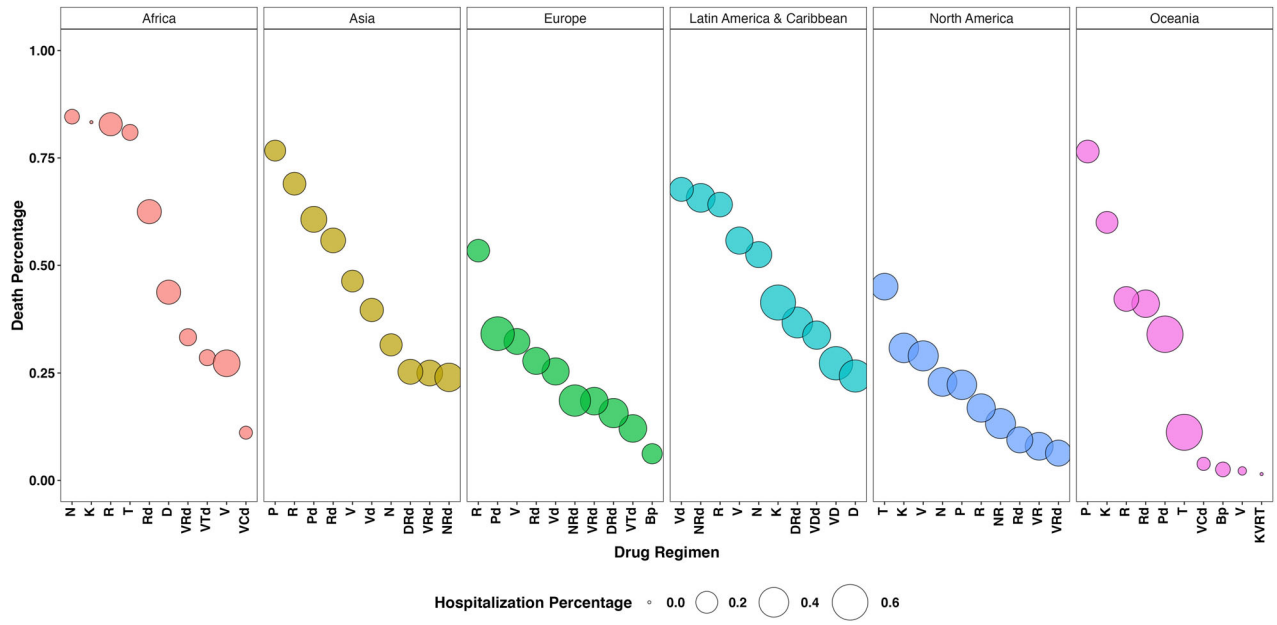

Fig. 4 Percent MM drug use with respect to mortality and hospitalization from 2005 to 2022 for six different continents.

reports in the EU. It is important to highlight the variability in drug availability or use across the EU. AS experienced an initial decrease in death rates until 2012, followed by an ascending trend until 2016. However, it witnessed a substantial drop to the lowest value of 27.1% in 2022. Significant variations in death and HR were also observed in AF, LA, and OC, primarily attributed to the limited number of cases reported from these regions. In AS and EU, hospitalization rates displayed comparatively less variation over time, whereas NA saw a decline in HR. These intriguing trends in death and hospitalization rates underscore the multifaceted nature of MM disparities across different continents and emphasize the importance of further research in this domain, leveraging advanced technologies like artificial intelligence (AI) and machine learning, as demonstrated in different studies [16, 17, 25, 26].

A previous analysis focusing on MM outcomes across different races and ethnicities in the US aligns with the disparities observed in our mortality and hospitalization data across continents [8]. This study revealed significant variations in MM diagnosis and outcomes, highlighting that Hispanics were diagnosed at the youngest median age, while Whites were at the oldest median age. Age at diagnosis emerged as an independent predictor of OS and MM-specific survival, suggesting that demographic and possibly genetic factors may influence MM outcomes and would have implications on access and utilization of healthcare. Similarly, in our analysis, we observed variations in mortality and HR across different continents, which are likely due to differences in healthcare delivery, drug access, supportive care strategies, and patient demographics. The observation that Asians exhibited the most favorable median survival in the prior study aligns with the trends seen in our data, where some regions, like AS and EU, showed lower mortality and HR compared to others, while Hispanics faced the least favorable outcomes.

Our study has also shown a higher prevalence of AE reports in males versus females. These differences could be due to multiple factors, such as subjective differences in reporting including gender-related differences in symptom perception, reporting and interpretation of AEs, body composition variations, differences in sex hormones, and changes in pharmacokinetics, pharmacodynamics, and pharmacogenomics. To ensure that clinically relevant differences are not overlooked, the relationship between dose, efficacy, and toxicity should be evaluated separately in men and women, using data from large clinical studies and pooled analyses. Zavala et al. highlighted health disparities in various racial and ethnic minority populations in the US and underscored the ongoing persistence of inequities despite concerted efforts to understand their root causes [27]. This notion reverberates with our findings, which show disparities in MM mortality and HR across continents, which are likely significantly due to variability in care, but also likely indicate inequities in healthcare access and outcomes, which persist on a global scale. In a study led by Baughn et al., the role of cytogenetic abnormalities in driving racial disparities in MM was explored [28]. Their findings suggested that a significant proportion of the racial disparity in MM outcomes could be attributed to variations in the occurrence of specific cytogenetic abnormalities, such as t(11;14), t(14;16), and t(14;20) types of MM. While our data did not directly assess genetic factors, the geographic disparities in MM outcomes observed in our analysis might reflect a combination of genetic, demographic, and healthcare-related factors that warrant further investigation [29].

Atkins et al. conducted a retrospective cohort study involving over 340,000 patients diagnosed with lung cancer between 2000 and 2006 [30]. They gathered data from various geographical areas in the US, including metropolitan, urban, suburban, and rural areas, utilizing the SEER Program database and found that the increase of lung cancer mortality correlated with dosage and rurality across rural-urban regions. Xu et al. employed the SEER database to identify patients with hepatocellular carcinoma (HCC) in the US between 1998 and 2012 [31]. Their research highlighted significant racial differences in presentation, treatment, and survival among HCC patients. Further research is essential to gain a better understanding of the socio-demographic and biological factors contributing to racial disparities in care.

Recently, chimeric antigen receptor T Cells (CAR-T) have emerged as a promising treatment for managing relapsed-refractory MM (RRMM) [32]. This therapy involves a complex process and treatment is usually given in large academic institutions after a robust selection process. All CAR-T centers use tools for selection criteria, selection timelines, and priority scores. Kourelis et al. explored the issue's scope and examined how major medical centers were tackling the challenges associated with the allocation of manufacturing slots for CAR-T therapy [33]. This approach would not only streamline access to

CAR-T therapy but also safeguard the needs of both current and future patients and physicians for utilization of such resource-intensive therapeutic options. Recently, Peres et al. collected data from several institutions across the US that provided CAR T-cell therapy for MM patients and found non-Hispanic Black (NHB) patients are likely to develop any grade Cytokine release syndrome compared Hispanic and NHW patients [34]. Possible reason attributed to high CRS is due to an elevated proinflammatory state among NHB patients before CAR-T cell therapy. Three T cell redirecting bispecific antibodies (Teclistamab, Elranatamab, Talquetamab) are now approved for the management of RRMM [32], however, these drugs are mostly available in academic centers in developed countries. Outside of the USA, there is variability in access and scarcity of newer drugs and cellular therapies in many regions.

In conclusion, the pronounced disparities in health outcomes among different populations present significant moral and public health concerns. While our research sheds light on the multifaceted nature of these disparities and advocates the pivotal role of social and economic factors, it is evident that new technologies like AI and machine learning will be instrumental in shaping our future understanding of these complex issues. Studies such as Gao & Cui et al. or Meng et al. have demonstrated the potential of AI and machine learning to uncover critical insights into population-level disparities [16, 17]. Striking data highlights the fundamental influence of social factors on health outcomes, exemplified by studies that examined the impact of socioeconomic and race on MM survival in the US [35]. The understanding of MM disparities will undoubtedly require an interdisciplinary approach that considers the interplay of genetics, socioeconomic factors, and advanced technologies, ultimately guiding us toward more equitable and effective healthcare solutions.

Limitations

One limitation inherent in our present study is its retrospective nature, as it relies on the analysis of curated ADE databases from reporting systems [36–39]. The natural confounding of age and medical comorbidities on MM-related outcomes is frequently encountered in attempts to discern the impact of medications on clinical outcomes. This challenge is exacerbated by the fact that older adults are more likely to be affected by MM and age-related comorbidity. The OpenFDA datasets have many limitations for pharmacovigilance research. These include underreporting of AEs which can result in incomplete information on the true occurrence of AEs, particularly in regions with fewer reported cases or where there is a higher incidence of severe AEs. Severe or unusual AEs are more likely to be reported than common, mild ones, which are more prevalent in openFDA, contributing to a skewed safety profile. Confounding factors are also difficult to disclose within the openFDA. Further limitations include a lack of comprehensive clinical data, which can impede the assessment of trends, the accurate estimation of true AE occurrences, and the availability of clinical context. Additionally, there may be selection biases arising from the non-random selection of patients exposed to the drug or the inaccurate selection of contributors from distorted spontaneous reports. These biases may be driven by covariates other than the drug under investigation, such as a patient's disease stage, delay in diagnosis, or disease duration. To address these bias-related challenges, we implemented comprehensive data validation procedures and statistical methods to enhance the accuracy and completeness of the reported AEs. We also standardized the reporting framework to minimize inconsistencies and biases within the dataset. Complementing these efforts, a longitudinal review of available data enables us to track temporal trends over time, allowing for a more nuanced understanding of AEs.

Moreover, several other confounding variables prevalent in cancer studies involving spontaneous reporting systems can introduce potentially detrimental bias or variation. Due to the limited information available, a comprehensive meta-analysis of the observational evidence concerning the source, magnitude, and impact of these factors remains inconclusive [36–42].

Future directions

Our findings have shown that global disparities in myeloma care result in poorer outcomes in low- and middle-income countries due to limited access to novel drugs, and specialized healthcare professionals, highlighting the need for better resources and access to new therapies.

We recommend advocating for policies that promote equitable access to resources and care for underserved populations. Most importantly, global and governmental measures to address fundamental issues such as poverty, increased government spending on health care (including cancer care), and provision of universal basic health care are critical to cancer care globally. Global and governmental efforts are crucial for improving health care funding for cancer care, as well as providing universal health care to ensure access to high-quality cancer care treatment worldwide. For clinical practice, health practitioners could enhance awareness and improve patient outcomes by understanding different AE patterns across the globe. For future research, we suggest conducting longitudinal studies to assess the long-term impacts of myeloma drug therapies, understanding race, social and biological factors of drug disparity from the pooled analysis, and conducting more clinical trials in low-income countries.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

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AUTHOR CONTRIBUTIONS

Conceptualization and Study design: MJD, XX, SR; methodology: MJD, XX, SR; statistical methods and analysis: MJD, XX. Initial draft was written by MJD and XX. MJD, XX, DD, SA, FA, JV, MHH, SM, JR, SR reviewed the draft, edits and approved the final version of manuscript. All authors have read and agreed to the final version of the manuscript. MJD and XX have contributed equally as co-first authors.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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