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Cardiovascular-specific mortality among multiple myeloma patients: a population-based study

Xuejiao Yin, Fengjuan Fan, Bo Zhang, Yu Hu and Chunyan Sun

Abstract

Introduction: Multiple myeloma (MM) survival has greatly improved in recent decades. MM is usually diagnosed at a median age of 66–70 years. MM patients do not necessarily die from primary cancer, so cardiovascular health may be a key factor threatening long-term survival. This study was designed to explore the cardiovascular disease mortality (CVM) trends in MM patients and compare them with those in the general population.

Methods: In total, 88,328 MM patients from the Surveillance, Epidemiology, and End Results (SEER) database (1975–2016) were included. Standardized mortality ratios (SMRs) were used to assess CVM risk.

Results: The CVM risk was significantly higher in MM patients than in the general population (SMR, 1.84 (95% CI, 1.78–1.89)). MM patients had the highest CVM SMR, at 2.62 (95% CI, 2.49–2.75), in the first year after diagnosis, and it decreased over the follow-up period. Over the study period, the incidence of CVM continued to decrease in MM patients diagnosed at age 65–74 (APC, −1.2% (95% CI, −1.9% to −0.4%)) and ⩾75 years (APC, −1.9% (95% CI, −2.6% to −1.2%)) but not younger. CVM was the second-most common cause of death in patients ⩾75 years. In only MM case analyses, male sex, Black race, older age at diagnosis, and earlier year of diagnosis were poor prognostic factors for heart-specific mortality.

Conclusion: The CVM risk in MM patients was significantly higher than that in the general population. To improve survival, cardiovascular health should receive attention upon diagnosis.

Keywords: cardiovascular disease mortality, competing risk, multiple myeloma, prognosis, standardized mortality ratios, trends

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Introduction

With 30,770 new cases and 12,770 deaths in 2018,[1] multiple myeloma (MM) accounts for 1% of all cancers and is the second-most common hematologic malignancy.[2] MM is usually diagnosed at an older age, with a median age of 66–70 years. The survival rate of MM patients has significantly increased in recent decades due to many significant advances, including understanding the underlying pathophysiology, development of novel drugs with improved efficacy, better comorbidity management and nursing improvements, and science related to understanding individualized differences.[3] However, old age and long-term survival rates are high-risk factors for the incidence of heart disease and cardiovascular disease mortality (CVM).[4] MM is the third-most common type of malignant tumor that correlates with cardiovascular diseases (CVDs).[5] However, the most current research studying CVM is based only on the group of MM patients and is not compared with the general population, which could better reveal the impact of MM and treatment on CVM.

Given the lack of large, prospective studies evaluating the risk of cardiovascular death compared with the general population and the mortality trends of CVDs in patients with MM, we used the Surveillance, Epidemiology, and End Results (SEER) program to evaluate the risk and trends of cardiovascular death. The SEER database is the primary source of cancer incidence statistics in the United States, gathering and reporting demographics, morphology, primary tumor site, treatment information, and survival data of patients with tumors. It covers up to 28% of the population in the United States and includes 67% of the Pacific/Hawaiian Islander, 50% of the Asian, 44% of the Alaskan/American Indian Native, 38% of the Hispanic, and 26% of the Black populations. Although this analysis was based purely on the US population, the prevalence of MM cardiac mortality in different populations may have a certain degree of similarity.

In addition, in view of possible cardiotoxic effects related to treatment and different prevalence of healthcare access and lifestyle risk factors, the year of diagnosis representing various time intervals was divided into five groups (1975–1995, 1996–2000, 2001–2005, 2006–2011, and 2012–2016) based on the availability of autologous stem cell transplantation (ASCT) and novel agent therapy to explore the effects of changes in treatment methods, health awareness, and lifestyle on cardiovascular death.

Materials and methods

Data sources

Patients to estimate mortality: SEER 9. The cases used to estimate the mortality trend come from the Incidence-Based Mortality – SEER 9 Regs Research Data, November 2018 Sub (1975–2016) <Katrina/Rita Population Adjustment> . Unlike traditional cases whose mortality records were associated with incident cancer cases, incidence-based mortality (IBM) cases from 1985 to 2016 were involved to ensure that most deaths occurred after 1975 and that IBM rates were not underrated in the first several years. The reason to choose this period is that the average survival time of MM patients was 10 years by 2014.[6]

The cases used to calculate standardized mortality ratios (SMRs) come from the Incidence – SEER 9 Regs Custom Data (with additional treatment fields), November 2018 Sub (1975–2016) for SMRs.

Patients to estimate prognosis: SEER 18. The patients to estimate prognosis associated with CVM were enrolled from the Incidence – SEER 18 Regs Custom Data (with additional treatment fields), November 2018 Sub (1975–2016).

Study population selection

We collected patients diagnosed with MM per the International Classification of Diseases for Oncology, third edition, ICD-O-3 histology code 9732. The present study conformed with the guidelines of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[7] The exclusion criteria were as follows: (1) Myeloma was not the first malignancy; (2) Patients were diagnosed only by autopsy or death certificate; (3) The patient age at diagnosis was under 40. Less than 1% of newly diagnosed MM cases are under 40 years old. (4) The cause of death was unknown. (5) Patients who survived less than a month since the SEER database recorded their survival time as 0.

We collected information including year of diagnosis, age at diagnosis, sex, race, survival time, outcome, and cause of death. Because the SEER database does not include treatment-related information about each individual, the era of diagnosis was divided into five groups (1975–1995, 1996–2000, 2001–2005, 2006–2011, and 2012–2016) to explore the effects of changes in treatment methods on cardiovascular death. In 1996, autologous transplantation was used as a first-line treatment.[8] In 2001, bortezomib and lenalidomide were used as second-line treatments.[9] In 2006, bortezomib and lenalidomide were used as first-line treatments.[10] In 2012, carfilzomib and pomalidomide were used as second-line treatments.[11]

Cause of death data

In the SEER program, deaths were coded according to the Registry used International Classification of Diseases, Ninth Edition (ICD-9) and the ICD-10. Materials about cause of death categories in the general population originate in the Wide-ranging Online Data for Epidemiologic Research (WONDER) tool from the Centers for Disease Control and Prevention.

We grouped patients into four categories of cause of death: death from the primary disease, death from cardiovascular, death from other cancers, and death from other non-cancers. The primary endpoint was CVM. In addition, some cardiovascular-related deaths were grouped into a single composite variable in light of the ICD-10, including atherosclerosis, aortic aneurysm and dissection, disease of the heart, hypertension without heart disease, cerebrovascular diseases, or other diseases of the arteries, arterioles, and capillaries. The following 10 categories are classified as the most common causes of death from other non-cancer causes: other infectious and parasitic diseases, including HIV; septicemia; suicide, and self-inflicted injury; diabetes mellitus; chronic liver disease and cirrhosis; chronic obstructive pulmonary disease and allied conditions; pneumonia and influenza; nephritis, nephrotic syndrome, and nephrosis; stomach and duodenal ulcers; and accidents and adverse effects.

Statistical analysis

SEER*Stat software was used to calculate IBM rates. IBM rates were adjusted by age to the 2000 standard US population and expressed per 100,000 person-years. Joinpoint regression analysis software, version 4.5.0.1, was used to analyze the tendencies of CVD mortality in MM patients. Annual percentage change (APC) and 95% confidence intervals (95% CI) were used to estimate rate changes.

SMRs could assess the relative CVM risk for MM compared to the US general residents. The SMRs were calculated as observed-to-expected deaths *via* SEER*Stat software (version 8.1.5). We used the Poisson exact method for SMR to compute the 95% CI and corresponding p values, and the 95% CIs not including 1 with $p < 0.05$ were defined as significant differences for SMR. The absolute excess risk (AER) was computed as the excess deaths per 10,000 persons per year as follows: ([observed–expected deaths) $\times$ 10,000)/ person-years at risk. The general population data are included in the SEER registry, but they are not coded.

We made a rough cumulative mortality function for total cause-specific deaths while stratifying based on age to depict the possibility of meeting a specific endpoint under competitive risks. The Kaplan–Meier method with the log-rank test was used to evaluate cumulative incidence. Chi-square and correlation tests were applied to investigate the differences between respective, continuous, and discrete epidemiological, pathological, and clinical characteristics. The hazard ratios (HRs) and 95% CIs were used to estimate the associations between patient characteristics and heart-specific mortality in myeloma patients through univariable and multivariable Cox proportional hazards regression analysis.

Results

Trends in CVM over time

The overall incidence of CVM continued to decrease at a rate of −1.2% (95% CI, −1.6% to −0.8%, $p < 0.001$) per year over the study period (Figure 1). When age-specific trends were explored, we found a decline in CVM incidence in patients with a diagnosis age of 65–74 (APC, −1.2% (95% CI, −1.9% to −0.4%)) and older than 75 years (APC, −1.9% (95% CI, −2.6% to −1.2%)) but not in younger patients (Supplemental Figures S1–S4 and Table S1). All non-cardiovascular mortality incidence rates declined for all age groups (Supplemental Table S1).

Patient characteristics

In total, 88,328 patients diagnosed with MM were included from the SEER database from 1975 to 2016 (Table 1). Among those, most patients were male (53.25%) and white (74.46%). The distribution of age at diagnosis was as follows: 40–49 years, 7.14%; 50–64 years, 32.16%; 65–74 years, 30.26%; and ⩾75 years, 30.45%. At the end of the study period, 28.84% were still alive, 50.59% died of MM, and 8.22% died of CVD. Diseases of the heart and cerebrovascular were the two most common types of CVD death. Among other non-cancer-related deaths, except CVD, nephritis, nephrotic syndrome, and nephrosis were the most common causes of death (0.98%), followed by pneumonia and influenza (0.96%) and chronic obstructive pulmonary disease and allied conditions (0.82%)

Cumulative mortality

The cumulative incidence death rates for various causes of death in MM patients are shown in Figure 2. At 60 months of follow-up, the cumulative mortalities for CVD, other noncancer deaths,

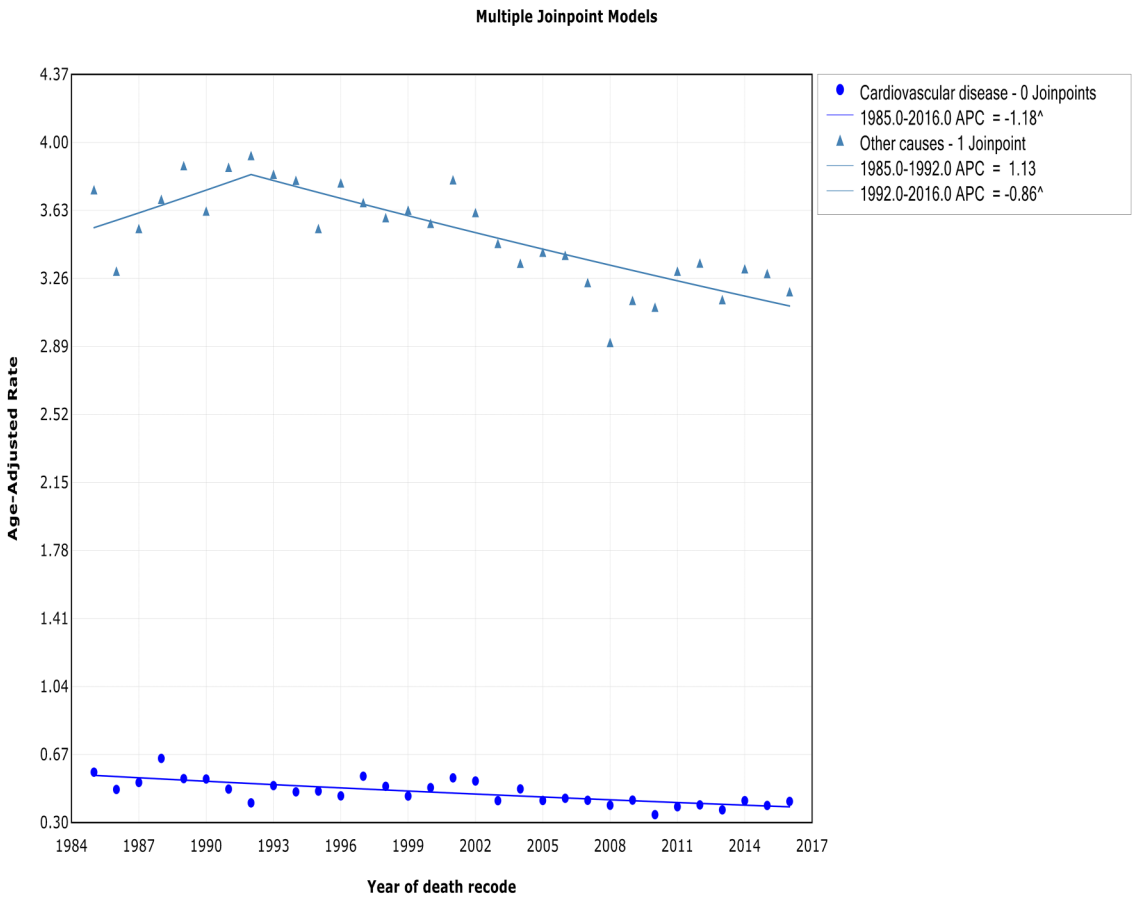

Figure 1. Trends in annual rates of death from cardiovascular disease and other causes in multiple myeloma patients by year.

MM and other cancers were 7.09% (SD: 8.49e−07), 8.55% (SD: 1.01e−06), 46.90% (SD: 3.30e−06), and 1.86% (SD: 2.33e−07), respectively (Figure 2). We noticed that the cumulative cardiovascular-specific mortality increased steadily with the length of follow-up and age at diagnosis (Supplemental Figure S5). In the oldest group (⩾75 years), the cumulative mortality from CVD exceeded that from other noncancer deaths.

CVM and all-cause mortality compared to the general population

Table 2 shows the comparison of the risk of CVM and all-cause mortality between MM patients and the general population.

When the risk of CVM among MM patients was compared to that of the general US population, the rate of CVM per 10,000 person-years was 123.95, and the SMR of CVM was 1.84 (1.78–1.89). We observed that Black patients had an increased risk of CVM (SMR for Black, 2.08; 95% CI, 1.94-2.22; SMR for White, 1.73; 95% CI, 1.67–1.79, Table 2). The SMR of CVM was higher among patients diagnosed at a younger age, and the SMR of CVM gradually dropped when patients were diagnosed at an older age. For example, the SMR of CVM for those with a diagnosis age of 40–49 was 2.78 (95% CI, 2.23–3.43) *vs* the SMR of CVM for those older than 75 years was 1.63 (95% CI, 1.57–1.70). MM patients had the highest SMR for CVM of 2.62 (95% CI, 2.49–2.75) in the first year after diagnosis, and this SMR decreased over the follow-up period. There was no significant change in the SMR of CVM when SMR was compared among different time periods of changing therapies. For the type of CVD death, the highest SMR was seen for hypertension without heart disease (SMR, 2.31

Table 1. Demographics and clinical characteristics of the patients.

Characteristic	Cases, no.	%
Overall	88,328	100.00
Age, year		
40–49	6305	7.14
50–64	28,404	32.16
65–74	26,727	30.26
75+	26,892	30.45
Sex		
Male	47,039	53.25
Female	41,289	46.75
Race		0
White	65,770	74.46
Black	16,886	19.12
Other	5175	5.86
Unknown	497	0.56
Era of diagnosis, year		
1975–1995	18,474	20.92
1996–2000	8719	9.87
2001–2005	16,120	18.25
2006–2011	22,712	25.71
2012–2016	22,303	25.25
Type of cardiovascular disease death	7257	8.22
Disease of the heart	5856	6.63
Hypertension without heart disease	304	0.34
Cerebrovascular diseases	877	0.99
Atherosclerosis	105	0.12
Aortic aneurysm and dissection	57	0.06
Other diseases of the arteries, arterioles, and capillaries	58	0.07
Died from multiple myeloma	44,684	50.59
Other non-cancer-related deaths	4437	5.02
Other infectious and parasitic diseases including HIV	379	0.43

(Continued)

Table 1. (Continued)

Characteristic	Cases, no.	%
Septicemia	389	0.44
Pneumonia and influenza	852	0.96
Suicide and self-inflicted injury	110	0.12
Diabetes mellitus	506	0.57
Chronic liver disease and cirrhosis	134	0.15
Stomach and duodenal ulcers	51	0.06
Chronic obstructive pulmonary disease and allied conditions	727	0.82
Nephritis, nephrotic syndrome, and nephrosis	870	0.98
Accidents and adverse effects	419	0.47
Other cause of death	6473	7.33

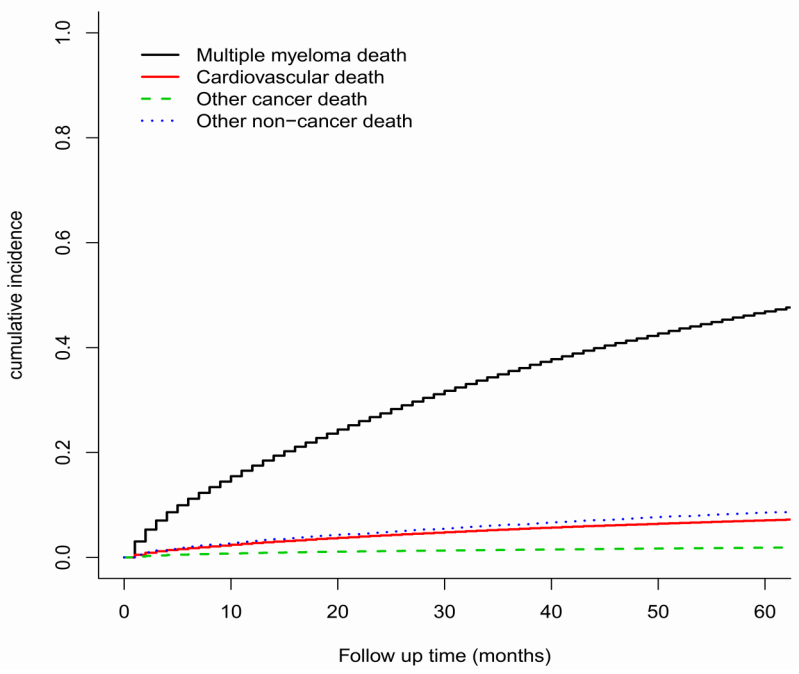

Figure 2. Cumulative incidence curves of death from cardiovascular disease, multiple myeloma, other cancer, and other noncancer diseases in multiple myeloma patients.

(95% CI, 1.92–2.77)), followed by atherosclerosis (SMR, 1.98 (95% CI, 1.57–2.46)) and disease of the heart (SMR, 1.94 (95% CI, 1.88–2.01)).

The SMRs for the leading causes of other noncancer-related deaths were significantly increased (Table 3), including other infectious and parasitic diseases (SMR, 5.42 (95% CI, 4.69–6.24)), nephritis, nephrotic syndrome, nephrosis (SMR, 4.44 (95% CI, 4.03–4.88)), septicemia (SMR, 2.71 (95% CI, 2.34–3.11)), and pneumonia and influenza (SMR, 3.32 (95% CI, 3.05–3.60)).

Table 2. Standardized mortality ratios of cardiovascular disease mortality among myeloma patients according to baseline characteristics.

Characteristic	Observed deaths	SMR (95% CI)	AER
Overall	4358	1.84 (1.78–1.89)	123.95
Age, year			
40–49	87	2.78 (2.23–3.43)	33.29
50–64	781	2.38 (2.22–2.56)	72.94
65–74	1277	1.93 (1.83–2.04)	128.3
75+	2213	1.63 (1.57–1.70)	258.93
Sex			
Male	2342	1.79 (1.72–1.86)	122.83
Female	2016	1.89 (1.81–1.98)	125.19
Race			
White	3238	1.73 (1.67–1.79)	113.81
Black	888	2.08 (1.94–2.22)	154.77
Other	232	2.94 (2.57–3.34)	154.61
Latency periods, months			
0–11	1513	2.62 (2.49–2.75)	248.16
12–59	1805	1.57 (1.50–1.65)	83.29
60–119	706	1.62 (1.50–1.74)	88.79
120+	334	1.57 (1.41–1.75)	93.37
Era of diagnosis, year			
1975–1995	2272	1.81 (1.74–1.88)	160.26
1996–2000	606	1.90 (1.75–2.06)	130.29
2001–2005	597	1.91 (1.76–2.07)	108.37
2006–2011	618	1.77 (1.63–1.92)	80.14
2012–2016	265	1.93 (1.70–2.17)	86
Type of cardiovascular disease death			
Disease of the heart	3531	1.94 (1.88–2.01)	107.16
Hypertension without heart disease	120	2.31 (1.92–2.77)	4.26
Cerebrovascular diseases	556	1.38 (1.26–1.49)	9.48
Atherosclerosis	81	1.98 (1.57–2.46)	2.51
Aortic aneurysm and dissection	41	1.11 (0.80–1.51)	0.26
Other diseases of the arteries, arterioles, and capillaries	29	1.19 (0.80–1.71)	0.29

AER, absolute excess risk; CI, confidence interval; SMR, standardized mortality ratio.

Table 3. Standardized mortality ratios of myeloma and specific noncancer mortality among myeloma patients.

Characteristic	Observed deaths	SMR (95% CI)	AER
Died from multiple myeloma	26,663	965.19 (953.64–976.85)	1663.79
Other non-cancer-related deaths			
Other infectious and parasitic diseases including HIV	196	5.42 (4.69–6.24)	9.99
Septicemia	196	2.71 (2.34–3.11)	7.72
Suicide and self-inflicted injury	72	2.57 (2.01–3.23)	2.75
Diabetes mellitus	235	1.47 (1.29–1.67)	4.68
Chronic liver disease and cirrhosis	93	1.96 (1.58–2.40)	2.84
Chronic obstructive pulmonary disease and allied conditions	413	1.38 (1.25–1.53)	7.17
Pneumonia and influenza	577	3.32 (3.05–3.60)	25.18
Nephritis, nephrotic syndrome, and nephrosis	437	4.44 (4.03–4.88)	21.15
Stomach and duodenal ulcers	37	3.11 (2.19–4.29)	1.57
Accidents and adverse effects	253	1.99 (1.75–2.25)	7.87

AER, absolute excess risk; CI, confidence interval; SMR, standardized mortality ratio.

Internal comparisons of CVM

We performed Cox regression analyses for only MM cases to estimate the independent prognostic effect of the patient characteristics on cardiovascular-specific mortality, and the results are shown in Table 4. Per the multivariate analysis, male sex (HR: 1.257, CI: 1.200–1.317) and Black race (HR: 1.436, CI: 1.357–1.520) were poor prognostic factors for heart-specific mortality. The HRs gradually increased with age, and cardiac-specific mortality increased significantly. For example, the HRs (95% CIs) were 2.462 (2.084–2.908), 5.442 (4.617–6.413), and 14.297 (12.150–16.823) for patients aged 50–64, 65–74, and ⩾75, respectively, compared to patients aged 40–49. In addition, patients who were diagnosed between 2012 and 2016 had a 53.4% decrease in heart-specific mortality (HR: 0.466, CI: 0.427–0.509) compared to those diagnosed between 1975 and 1995.

Discussion

To the best of our knowledge, this is the first large population-based study to conduct a contemporary analysis of CVM risk after MM diagnosis and conclude that CVM risk changes as a function of race, age, time after diagnosis, sex, and era of diagnosis. The SMR of CVM among MM patients is 1.84 times that of the general population and is highest in the first year after MM diagnosis. The SMR of CVM was higher in patients diagnosed at a younger age, and it gradually dropped when patients were diagnosed at an older age. In only MM case analyses, male sex, Black race, older age at diagnosis, and earlier year of diagnosis were poor prognostic factors for heart-specific mortality. Another new finding was that of all possible causes of death involved, CVM accounted for the second-most common cause of death in the oldest age group (⩾75 years). Notable findings also included that the incidence of cardiovascular mortality continued to decrease at a rate of −1.2% (95% CI, −1.6% to −0.8%, $p < 0.001$) per year among MM patients over the study period.

We noticed a drop in both CVD and non-CVD causes of death over the study period, although the drop in deaths from CVD was smaller than that from non-CVD causes, which is consistent with previous reports.[12] We hypothesize that the main reason for the decline in both CVD and other causes of death is the improvements in MM management and treatment options that improve

Table 4. Univariate and multivariate analysis for associations between patient characteristics and heart-specific mortality in myeloma patients (1975–2016).

Variable	Univariate analysis	*p*	Multivariate analysis	*p*
	HR (95% CI)		HR (95% CI)	
Age, year				
40–49	1	0.000	1	0.000
50–64	2.431 (2.058–2.872)	0.000	2.462 (2.084–2.908)	0.000
65–74	5.351 (4.541–6.306)	0.000	5.442 (4.617–6.413)	0.000
75+	13.629 (11.584–16.034)	0.000	14.297 (12.150–16.823)	0.000
Sex				
Female	1	0.000	1	
Male	1.071 (1.022–1.121)	0.004	1.257 (1.200–1.317)	0.000
Race				
White	1	0.000	1	0.000
Black	1.142 (1.079–1.208)	0.000	1.436 (1.357–1.520)	0.000
Other	0.972 (0.878–1.075)	0.577	1.062 (0.960–1.175)	0.243
Unknown	0.314 (0.186–0.531)	0.000	0.413 (0.244–0.697)	0.000
Era of diagnosis, year				
1975–1995	1	0.000	1	0.000
1996–2000	0.827 (0.767–0.892)	0.000	0.821 (0.762–0.885)	0.000
2001–2005	0.690 (0.646–0.736)	0.000	0.707 (0.663–0.754)	0.000
2006–2011	0.541 (0.508–0.577)	0.000	0.565 (0.530–0.602)	0.000
2012–2016	0.446 (0.409–0.487)	0.000	0.466 (0.427–0.509)	0.000

CI, confidence interval; HR, hazard ratio.

the survival rate.[13] In addition, MM itself and its treatment might increase the risk of death from cardiovascular events, especially in patients with other known cardiovascular risk factors. Keeping this knowledge in mind has helped decrease cardiovascular mortality in MM patients.[14] A decline in overall mortality in the SEER population, which indicates that a drop in age-standardized mortality existed in the United States,[15] could be another cause of the decline in both CVD and other causes of death.

We found that the SMR of CVM was highest when patients were diagnosed at a younger age and that the SMR gradually dropped when they were diagnosed at an older age, which is concordant with previous studies showing that cancer patients of young age have a higher all-cause mortality.[16] We hypothesize that the main reason for this phenomenon is that CVD is not prevalent in younger patients and is generally diagnosed in the elderly. Notably, SMRs are a measure of the standardized population. Another important cause is the different choice of medications for patients of different ages, which also results in no reduction in the CVM incidence in young patients. In addition, older patients tend to die earlier owing to their potential primary disease before they develop CVD in the long term. Older patients with severe comorbid conditions might

have also developed various adverse diseases, such as infection and acute renal failure,[17,18] so that they did not necessarily die from heart-specific diseases.

The relative risk of CVM is highest in those within the first year after MM diagnosis compared with the general population, which is in line with previous results that noncancer causes, including CVM, frequently occur within the first year after cancer diagnosis and probably result from treatment.[16,19,20] Potentially relevant systemic treatments include anthracyclines, corticosteroids, alkylating agents, immunomodulatory drugs, proteasome inhibitors, and autologous/allogeneic stem cell transplantation (SCT), which are known to be cardiotoxic.[14,20] The pathogenic/etiological mechanisms, as yet unknown, may be caused by the following: (1) impairing stress-protective signaling mechanisms in cardiomyocytes and resulting in damage to myocardial cells due to reactive oxygen species;[21] (2) causing significant structural anomalies in cardiomyocyte mitochondria, therefore leading to a decrease in adenosine triphosphate synthetics and cardiac contractility;[22,23] and (3) alterations in endothelial nitric oxide synthase activity resulting in a reduction in tissue nitric oxide levels and endothelial dysfunction.[24]

In addition, chemotherapy, particularly with the use of immunomodulatory agents, such as thalidomide and lenalidomide, will increase the risk of thrombotic complications.[25] Absolute venous thromboembolism incidence was highest close to the time of cancer diagnosis and decreased over time.[26] In addition, the sedimentation of the immunoglobulin light chain and amyloid in the heart are deemed a main risk factor for deteriorating heart function.[27,28] The amount of sediment was greatest at the initial diagnosis and could be decreased with the duration of treatment. Cardiac amyloidosis could lead to cardiac conduction defects and arrhythmias, especially atrial fibrillation.[27,28] The potential mechanisms include disordered autophagy, excess reactive oxygen species (ROS) production, and lysosomal and mitochondrial dysfunction.[28]

We characterized the rates of CVM from 1975 to 2016, and we found that the HR of CVM showed a 53.4% decrease in more recent years compared with previous years (i.e. 2012–2016 *vs* 1975–1995). The reasons might be that (1) factors related to MM, such as hyperviscosity, high-output failure, arteriovenous shunting, hypercalcemia, renal failure, and anemia, have been proven to be associated with a significantly increased risk of CVD.[14] Considerable advancements have been made in supportive measures in recent decades, which may have reduced heart disease risk in recent years. (2) Advanced progress in imaging studies, such as cardiac magnetic resonance imaging (MRI) and echocardiography, and individual cardiac biomarkers, such as cardiac troponins and N-terminal pro-B-type natriuretic peptide, may enable early detection of heart disease and early intervention in recent years.[29–31] (3) Recently, carvedilol, enalapril, angiotensin-converting enzyme inhibitors, and dexrazoxane have been proven to prevent heart dysfunction during chemotherapy.[32–34] These scientific advances may have greatly reduced heart-specific mortality in recent years.

However, the SMR of CVM in MM *versus* the general population is not decreased. The reasons might be that (1) HR is an internal comparison. It compares the probability of CVM of a group of MM patients with another reference group of MM patients. In contrast, SMR is a comparison of the relative risk of death with the general US population and forms a function of time after diagnosis. Therefore, if there is a change in the CVM rate in the subpopulations of patients between the two eras, this difference will appear in the HRs but probably not in the SMRs. Notably, SMRs should not be compared with each other or with HRs. (2) Patients who were diagnosed in recent years have a shorter follow-up time and show reduced mortality from any cause compared with those diagnosed in the 1975–1995 period. In addition, since the SMRs of CVM are higher in the first year after diagnosis in comparison to the follow-up of more than 2–10 years after diagnosis, the SMRs are skewed for the most recently diagnosed patients and are higher than those diagnosed in prior years.

We observed that Black patients had a higher SMR and HR for heart-specific mortality, which may confirm that socioeconomic factors are also closely related to cardiac mortality. People of Black race may have reduced access to new treatments and timely and high-quality supportive care due to higher cost.[35,36] Furthermore, people of Black race are more likely to be diagnosed at later stages of MM, when treatment choices are more limited and less effective.[36] Patients of Black

race also have higher rates of comorbid health conditions, which may affect the treatment effect and contribute to differences in CVM.[37,38]

In addition to cardiac mortality, infections are also an important noncancer cause of death in MM. Recently, Blimark *et al.*[39] reported that MM patients have a sevenfold higher risk of developing any infection than non-MM controls. Infections could be divided into two groups: (1) chronic comorbid conditions and (2) acute, iatrogenic, or treatment-induced infections. MM-related immunodeficiency, including B-cell dysfunction, hypogammaglobulinemia, T-cell, dendritic cell, and NK-cell abnormalities, and physical factors, such as indwelling vascular catheters and impaired mucosal integrity, both lead to a high frequency of infection.[40] In addition, proteasome inhibitors such as bortezomib and carfilzomib contribute to an increased risk of herpes viral reactivation.[41]

There are some limitations based on the information available in the SEER database in our findings. First, no individual-level information, such as hyperlipidemia, diabetes, alcohol use, dyslipidemia, smoking habit, obesity and history of CVDs, is available, which may be associated with an increased risk of CVM. Second, information regarding details of the chemotherapy (e.g. the type, dosage, and duration) is limited in SEER. Therefore, we could not further assess the risk of heart-specific death from chemotherapy drugs. We tried to solve this issue partially by separating the era of diagnosis into 1975–1995, 1996–2000, 2001–2005, 2006–2011, and 2012–2016, which represent different types of therapies. Finally, mortality from venous thromboembolism is an important component of cardiac mortality. However, there was no record of venous thromboembolism in SEER.

Our study demonstrates that the SMR of CVM in MM patients is 1.84 times higher than that of the general population and is highest in the first year after MM diagnosis. The SMR of CVM varies with the age at diagnosis, sex, race, time after diagnosis, and era of diagnosis. This research has the potential to improve the advancement of cardio-oncological risk stratification in MM patients and help clinicians make informed decisions about which patient groups have a higher risk and who would benefit more from precautions.

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Author contributions
Xuejiao Yin: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Fengjuan Fan: Formal analysis; Funding acquisition; Investigation; Methodology; Resources.

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This study fully complied with the publication guidelines provided by SEER. Because personal information of SEER participants could not be identified, approval from the ethics committee was not needed.

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Availability of data and materials
The data were obtained from the SEER database (https://seer.cancer.gov/seerstat/), which is freely accessible to the public.

Supplemental material
Supplemental material for this article is available online.

References

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; 68: 7–30.
2. Rajkumar SV. Treatment of multiple myeloma. *Nat Rev Clin Oncol* 2011; 8: 479–491.
3. Kazandjian D. Multiple myeloma epidemiology and survival: a unique malignancy. *Semin Oncol* 2016; 43: 676–681.
4. Austin PC, Lee DS and Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; 133: 601–609.
5. Al-Kindi SG and Oliveira GH. Prevalence of preexisting cardiovascular disease in patients with different types of cancer: the unmet need for onco-cardiology. *Mayo Clin Proc* 2016; 91: 81–83.
6. Kristinsson SY, Anderson WF and Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. *Leukemia* 2014; 28: 1346–1348.
7. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
8. Attal M, Harousseau JL, Stoppa AM, *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; 335: 91–97.
9. Richardson PG, Barlogie B, Berenson J, *et al*. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003; 348: 2609–2617.
10. Mateos MV, Hernandez JM, Hernandez MT, *et al*. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. *Blood* 2006; 108: 2165–2172.
11. Katsnelson A. Next-generation proteasome inhibitor approved in multiple myeloma. *Nat Biotechnol* 2012; 30: 1011–1012.
12. Castaneda-Avila MA, Ortiz-Ortiz KJ, Torres-Cintron CR, *et al*. Trends in cause of death among patients with multiple myeloma in Puerto Rico and the United States SEER population, 1987-2013. *Int J Cancer* 2020; 146: 35–43.
13. Rollig C, Knop S and Bornhauser M. Multiple myeloma. *Lancet* 2015; 385: 2197–2208.
14. Kistler KD, Kalman J, Sahni G, *et al*. Incidence and risk of cardiac events in patients with previously treated multiple myeloma versus matched patients without multiple myeloma: an observational, retrospective, cohort study. *Clin Lymphoma Myeloma Leuk* 2017; 17: 89–96.e83.
15. Xu J, Murphy SL, Kochanek KD, *et al*. Deaths: final data for 2013. *Natl Vital Stat Rep* 2016; 64: 1–119.
16. Zaorsky NG, Churilla TM, Egleston BL, *et al*. Causes of death among cancer patients. *Ann Oncol* 2017; 28: 400–407.
17. Hutchison CA, Batuman V, Behrens J, *et al*. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma. *Nat Rev Nephrol* 2011; 8: 43–51.
18. Gavriatopoulou M, Terpos E, Kastritis E, *et al*. Current treatments for renal failure due to multiple myeloma. *Expert Opin Pharmacother* 2016; 17: 2165–2177.
19. Fung C, Fossa SD, Milano MT, *et al*. Cardiovascular disease mortality after chemotherapy or surgery for testicular nonseminoma: a population-based study. *J Clin Oncol* 2015; 33: 3105–3115.
20. Bringhen S, Milan A, Ferri C, *et al*. Cardiovascular adverse events in modern myeloma therapy – incidence and risks. A review from the European myeloma network (EMN) and Italian society of arterial hypertension (SIIA). *Haematologica* 2018; 103: 1422–1432.
21. Ewer MS and Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol* 2005; 23: 2900–2902.
22. Gupta A, Pandey A and Sethi S. Bortezomib-induced congestive cardiac failure in a patient with multiple myeloma. *Cardiovasc Toxicol* 2012; 12: 184–187.
23. Hacihanefioglu A, Tarkun P and Gonullu E. Acute severe cardiac failure in a myeloma patient due to proteasome inhibitor bortezomib. *Int J Hematol* 2008; 88: 219–222.
24. Herrmann J, Wohlert C, Saguner AM, *et al*. Primary proteasome inhibition results in cardiac dysfunction. *Eur J Heart Fail* 2013; 15: 614–623.
25. Palumbo A, Rajkumar SV, Dimopoulos MA, *et al*. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008; 22: 414–423.
26. Strongman H, Gadd S, Matthews A, *et al*. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using

multiple linked UK electronic health records databases. *Lancet* 2019; 394: 1041–1054.

27. Grogan M and Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. *Heart Fail Rev* 2015; 20: 155–162.
28. Falk RH, Alexander KM, Liao R, *et al*. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J Am Coll Cardiol* 2016; 68: 1323–1341.
29. Foley PW, Hamilton MS and Leyva F. Myocardial scarring following chemotherapy for multiple myeloma detected using late gadolinium hyperenhancement cardiovascular magnetic resonance. *J Cardiovasc Med (Hagerstown)* 2010; 11: 386–388.
30. Dispenzieri A, Gertz MA, Kyle RA, *et al*. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004; 22: 3751–3757.
31. Mathur P, Thanendrarajan S, Paydak H, *et al*. Cardiovascular complications of multiple myeloma in the elderly. *Expert Rev Cardiovasc Ther* 2017; 15: 933–943.
32. Cardinale D, Colombo A, Sandri MT, *et al*. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006; 114: 2474–2481.
33. Bosch X, Rovira M, Sitges M, *et al*. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left ventricular dysfunction with enalapril and carvedilol in patients submitted to intensive chemotherapy for the treatment of malignant hemopathies). *J Am Coll Cardiol* 2013; 61: 2355–2362.
34. van Dalen EC, Caron HN, Dickinson HO, *et al*. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev* 2011; 2: CD003917.
35. Bach PB, Schrag D, Brawley OW, *et al*. Survival of blacks and whites after a cancer diagnosis. *JAMA* 2002; 287: 2106–2113.
36. DeSantis C, Naishadham D and Jemal A. Cancer statistics for African Americans, 2013. *CA Cancer J Clin* 2013; 63: 151–166.
37. Tammemagi CM, Nerenz D, Neslund-Dudas C, *et al*. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA* 2005; 294: 1765–1772.
38. Yancik R, Wesley MN, Ries LA, *et al*. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. *Cancer* 1998; 82: 2123–2134.
39. Blimark C, Holmberg E, Mellqvist UH, *et al*. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica* 2015; 100: 107–113.
40. Pratt G, Goodyear O and Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Haematol* 2007; 138: 563–579.
41. Chanan-Khan A, Sonneveld P, Schuster MW, *et al*. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol* 2008; 26: 4784–4790.