Original Article

Competing risk analysis of cardiovascular mortality in multiple myeloma survivors

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Background: The survival of multiple myeloma (MM) patients has significantly improved, and several factors increase the risk of cardiovascular death (CVD) mortality in MM. This study aims to determine the prognostic significance of factors associated with long-term CVD risk in MM survivors.

Methods: The data of MM survivors whose survival time was longer than 36 months were retrieved from the Surveillance, Epidemiology, and End Result (SEER) database between 2000 and 2015. Cox proportional hazards regressions and competing risk survival analyses were utilized to assess the CVD-associated risk factors. Propensity score matching (PSM) was further conducted to ensure the comparability of cardiovascular risk factors. The nomogram was based on these epidemiological factors to estimate individualized CVD probabilities for MM survivors, and its performance was assessed by Harrell's concordance index (C-index) and calibration curve.

Results: A total of 32,528 survivors with MM were enrolled, and 2,061 (6.34%) suffered from CVD. In Cox proportional hazards regressions and competing risk survival analyses, age, period of diagnosis, sex, race, married status, income, chemotherapy, and radiotherapy were the independent risk factors for CVD. After PSM, there was a significant difference in cumulative incidence curves, using a competing-risks method, between the following matched groups: male *vs.* female group, white *vs.* non-white group, married *vs.* unmarried group, income <$75,000 *vs.* income ≥$75,000 group, chemotherapy *vs.* non-chemotherapy group, and radiotherapy *vs.* non-radiotherapy group. The nomogram predicted CVD probabilities with a training C-index of 0.700 and a validation C-index of 0.726. Calibration curves validated that the nomograms could accurately predict the CVD probabilities both in the training and validation group.

Conclusions: Among MM survivors, the mortality risk of cardiovascular diseases differs with age, sex, period at diagnosis, race/ethnicity, marital status, chemotherapy, and radiotherapy. Our nomograms, based on epidemiological variables, may be used to predict 5-, 10-, and 15-year cardiovascular disease outcomes of MM survivors.

Keywords: Cardiovascular mortality; multiple myeloma (MM); cardio-oncology; nomograms; Surveillance, Epidemiology, and End Result (SEER)

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Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by neoplastic proliferation with the overproduction of monoclonal immunoglobulins, which often causes multiple bone destruction (severe bone pain, diffuse osteopenia, osteolytic bone lesions, and pathologic fractures, and so on), anemias, hypercalcemia, renal insufficiency (1). MM, constituting up to 10% of all hematologic malignancies, are treated by proteasome inhibitors, glucocorticoids, immunomodulatory drugs, conventional chemotherapy, radiotherapy, and stem cell transplantation (1). With the advanced understanding and the application of new treatment methods and antineoplastic drugs, tumor-specific mortality in patients with myeloma has greatly decreased (2). However, it is estimated that close to 10% of patients with MM die from heart disease rather than their primary tumors (3). In patients with MM, severe cardiovascular damage and failure occur due to not only hematopoietic abnormalities, renal insufficiency, and neuropathy, but also the deposition of a large number of monoclonal immunoglobulins and light-chain proteins in various organs. Besides, the older average age of patients, prolonged therapy, and its severe adverse effects all likely contribute to increased cardiovascular risk (4-6). A variety of chemotherapeutic drugs has been demonstrated to be associated with cardiotoxicity (7). All in all, both the tumor itself and its treatment could bring about poor cardiovascular prognosis (8). A recent study has found that the cardiovascular death (CVD) risk of MM patients is significantly higher than the general population, especially in the early period at diagnosis, and gradually decreased, probably owing to acute cardiotoxic from tumor treatment in the first year (3). Additionally, a study of arrhythmia in MM also suggested that approximately half of patients have experienced arrhythmias, in which sinus bradycardia and atrial fibrillation might influence MM prognosis (9). Similar research suggested that the prognosis of MM partly depends on their cardiovascular status and higher heart rate level means higher all-cause mortality (10). We conducted a sizeable population-level analysis based on the Surveillance, Epidemiology, and End Results (SEER) database to better understand the long term consequence of CVD in MM survivors and to describe the trends and predictors further.

However, the shared risk factors of cardiac disease and MM and the presence of other comorbidities may confound the analysis of CVD risk. Considering the presence of competing events, this study combined the traditional Cox proportional hazards model and competing risk model because the latter took competing events into account with the capacity to differentiate between cardiovascular events and others (11). After the secondary evaluation of risk factors using propensity score matching (PSM), a prognostic nomogram was constructed to predict individual long-term cardiovascular-specific mortality of MM survivors for the first time. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1213/rc).

Highlight box

Key findings

- The large population-based study focused on identifying risk factors for cardiovascular death (CVD) risk among multiple myeloma (MM) survivors and established a comprehensive prognostic nomogram.

What is known and what is new?

- MM survivors are associated with increased cardiovascular risk.
- Competing-risk model and propensity score matching were used to establish a nomogram model of CVD risk among MM survivors.

What is the implication, and what should change now?

- The novel nomogram could predict 5-, 10-, and 15-year cardiovascular outcomes, which can identify high-risk patients to develop better clinical strategies and improve the prognosis of MM survivors.

Methods

Data source

Data for the study were extracted from 18 cancer registries of the SEER database [Incidence-SEER Research Plus data, 17 Registries, Nov 2021 Sub (2000–2019); https://seer.cancer.gov], containing information about approximately 28% of the U.S. population. All participant data were extracted from public SEER dataset, ethics approval and consent to participate could be provided at the SEER sites. We had permission to access the SEER database with an authorization number. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population and design

All survivors were diagnosed with MM according to the International Classification of Diseases for Oncology (third edition, ICD-O-3 histology code 9732) by positive

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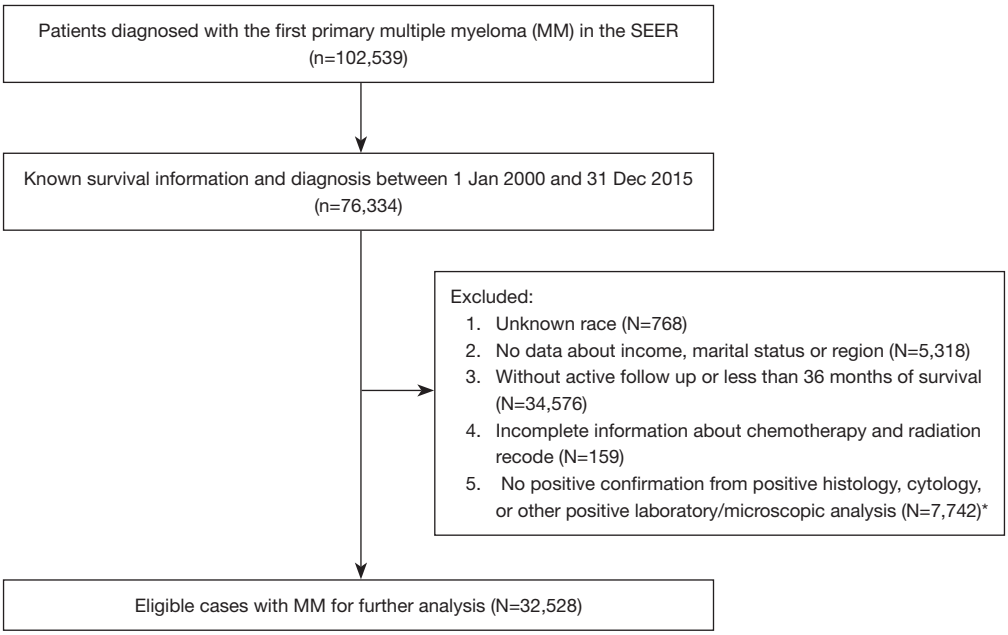

Figure 1 Flowchart of selection of multiple myeloma survivors. *, patients satisfying more than one exclusion criterion (N=4,757). SEER, the Surveillance, Epidemiology, and End Result.

histology, cytology, or other positive laboratories/microscopic analysis (12). We included cases that met the following criteria: (I) MM was the first primary cancer, and the diagnosis was between 2000 and 2015; (II) the duration for the follow-up period was longer than 36 months for all survivors; (III) the age of the selected survivors was older than 40 years old; (IV) complete demographic information (including race, income, and marital status) and treatment data (chemotherapy and radiation therapy) were available for all survivors (*Figure 1*).

According to their outcomes, the survivors were divided into three categories: alive, CVD, and non-CVD. CVD included diseases of the heart, hypertension without heart disease, atherosclerosis, cerebrovascular diseases, aortic aneurysm/dissection, and other diseases of the arteries, arterioles, and capillaries. The non-CVD included cancer-related and other non-cancer death.

All sample was randomized into training and validation groups at a ratio of 7:3, respectively, before the multivariable analysis. To make our results more credible, a PSM method was used to balance the potential biases and enhance comparability by adjusting confounding factors and reducing the potential selection bias in a nonrandomized cohort. In the subgroup analysis of risk factors, survivors were 1:1 case-control matched for a propensity score based on the nearest-neighbor matching method. Kaplan-Meier analyses are unreliable in competing events because they always overestimate the probabilities of the event of interest. Therefore, the cumulative mortality functions were calculated to estimate the probability of experiencing a cardiovascular-specific death when competing risks were present between the two groups. Following the above analyses, the nomogram was developed based on the multivariable and PSM analysis results to predict the 5-, 10-, and 15-year overall survival. Besides, the concordance index (C-Index) and calibration curves were applied to quantify discrimination and consistency of the nomogram, respectively, in the training and validation cohort.

Statistical analysis

Continuous variables were presented as mean/median and standard deviation (SD)/interquartile range (IQR) as applicable, while categorical variables were described as frequencies and percentages. Student's *t*-test was used for continuous variables normally distributed, the Mann-Whitney test for continuous variables not normally distributed, and the Chi-squared test for categorical data. Kaplan-Meier curves were analyzed by the log-rank tests. The proportional hazards assumption was assessed by

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Table 1 Clinical characteristics of multiple myeloma survivors with different causes of death

Characteristic	Cardiovascular death (n=2,061)	All (n=32,528)
Age at diagnosis (years), mean ± standard deviation	71.55±10.17	64.96±11.00
Gender, n (%)		
Male	1,195 (57.98)	17,908 (55.05)
Female	866 (42.02)	14,620 (44.95)
Year, n (%)		
2000–2003	522 (25.33)	5,505 (16.92)
2004–2007	586 (28.43)	7,007 (21.54)
2008–2011	576 (27.95)	9,030 (27.76)
2012–2015	377 (18.29)	10,986 (33.77)
Marital status, n (%)		
Unmarried	845 (41.00)	11,051 (33.97)
Married	1,216 (59.00)	21,477 (66.03)
Race, n (%)		
Non-White	547 (26.54)	8,108 (24.93)
White	1,514 (73.46)	24,420 (75.07)
Income, n (%)		
<$75,000	1,402 (68.03)	21,931 (67.42)
≥$75,000	659 (31.97)	10,597 (32.58)
Chemotherapy, n (%)		
No	997 (48.37)	11,084 (34.08)
Yes	1,064 (51.63)	21,444 (65.92)
Radiotherapy, n (%)		
No	1,822 (88.40)	26,779 (82.33)
Yes	239 (11.60)	5,749 (17.67)

the scaled Schoenfeld residuals. Calibration curves were constructed through a bootstrap approach to compare the predicted CVD probabilities with the observed CVD probabilities in the study, while C-index was obtained by 10-fold cross-validation. All statistical analyses were conducted by SPSS (version 24.0) and R software (version 4.0.2). The P value of less than 0.05 indicated statistical significance.

Results

Patient characteristics

The clinical characteristics of all MM survivors are summarized in *Table 1*. A total of 32,528 survivors were enrolled, showing a relatively higher proportion (6.34%) of subjects who died from CVD during a mean follow-up time of 85.47±40.85 months per patient. The mean age of all MM survivors was 64.96±11.00 years, while the mean age was 71.55±10.17 years for those suffering from CVD. And the ratio of percent of CVD to all deaths differed according to gender (male: 6.67%, female: 5.92%), period at diagnosis (2000–2003 years: 9.48%, 2004–2007 years: 8.36%, 2008–2011 years: 6.38%, 2012–2015 years: 3.43%), marital status (married: 5.66%, unmarried: 7.65%), race (White: 6.20%, non-White: 6.75%), income (income ≥$75,000: 6.22%, income <$75,000: 6.39%), chemotherapy (chemotherapy:

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Table 2 Baseline characteristics of survivors diagnosed with multiple myeloma in the training set and the verification set

Characteristic	Training cohort (n=22,769)	Validation cohort (n=9,759)	P value
Age at diagnosis (years), mean ± standard deviation	64.90±11.00	65.08±10.99	0.174
Gender, n (%)			
Male	12,595 (55.32)	5,313 (54.44)	0.146
Female	10,174 (44.68)	4,446 (45.56)	–
Year, n (%)			
2000–2003	3,860 (16.95)	1,645 (16.86)	0.674
2004–2007	4,870 (21.39)	2,137 (21.9)	–
2008–2011	6,311 (27.72)	2,719 (27.86)	–
2012–2015	7,728 (33.94)	3,258 (33.38)	–
Marital status, n (%)			
Unmarried	7,708 (33.85)	3,343 (34.26)	0.482
Married	15,061 (66.15)	6,416 (65.74)	–
Race, n (%)			
Non-White	5,662 (24.87)	2,446 (25.06)	0.707
White	17,107 (75.13)	7,313 (74.94)	–
Income, n (%)			
<$75,000	15,312 (67.25)	6,619 (67.82)	0.310
≥$75,000	7,457 (32.75)	3,140 (32.18)	–
Chemotherapy, n (%)			
No	7,716 (33.89)	3,368 (34.51)	0.277
Yes	15,053 (66.11)	6,391 (65.49)	–
Radiotherapy, n (%)			
No	18,742 (82.31)	8,037 (82.35)	0.929
Yes	4,027 (17.69)	1,722 (17.65)	–

4.96%, non-chemotherapy: 8.99%), and radiotherapy (radiotherapy: 4.16%, non-radiotherapy: 6.80%).

Multivariate analysis on the cardiovascular mortality

MM survivors in the training and validation cohorts showed similar clinical characteristics (*Table 2*). As shown in *Table 3* and *Figure 2*, multivariate Cox proportional hazards regression and Fine-Gray hazard model analyses all revealed eight independent prognostic factors, including age, gender, period at diagnosis, marital status, race, income, chemotherapy, and radiotherapy, in the training cohort. Competing risk analysis showed that older age [55–59 years: hazard ratio (HR) =1.45, P=0.001; 60–64 years: HR =2.10, P<0.001; 65–69 years: HR =2.60, P<0.001; 70–74 years: HR =4.05, P<0.001; 75–79 years: HR =4.92, P<0.001; 80–84 years: HR =6.47, P<0.001; 85+ years: HR =9.94, P<0.001], male (HR =1.35, P<0.001), earlier period (2008–2011 years: HR =1.30, P<0.001; 2004–2007 years: HR =1.53, P<0.001; 2000–2003 years: HR =1.70, P<0.001) were all significantly associated with increased CVD risk in MM survivors. Conversely, married (HR =0.83, P=0.002), White (HR =0.83, P=0.002), higher-income (HR =0.88, P=0.030), chemotherapy (HR =0.72, P<0.001), and radiotherapy (HR =0.74, P<0.001) survivors had a significantly lower risk of CVD.

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Table 3 Multivariate analysis on the cardiovascular mortality in multiple myeloma survivors

Characteristic	Cox analysis		Competing risks analysis	
	Cancer-specific mortality, HR (95% CI)	P value	Cancer-specific mortality, HR (95% CI)	P value
Age at diagnosis				
<55 years	Reference	–	Reference	–
55–59 years	1.56 (1.17–2.08)	0.002	1.45 (1.09–1.93)	0.001
60–64 years	2.47 (1.9–3.19)	<0.001	2.10 (1.62–2.71)	<0.001
65–69 years	3.46 (2.7–4.43)	<0.001	2.60 (2.03–3.32)	<0.001
70–74 years	6.14 (4.84–7.8)	<0.001	4.05 (3.19–5.11)	<0.001
75–79 years	8.67 (6.81–11.03)	<0.001	4.92 (3.88–6.24)	<0.001
80–84 years	13.84 (10.75–17.8)	<0.001	6.47 (5.05–8.28)	<0.001
85+ years	25.94 (19.76–34.06)	<0.001	9.94 (7.61–13.00)	<0.001
Gender				
Female	Reference	–	Reference	–
Male	1.47 (1.31–1.64)	<0.001	1.35 (1.21–1.51)	<0.001
Year				
2012–2015	Reference	–	Reference	–
2008–2011	1.09 (0.93–1.28)	0.268	1.30 (1.11–1.52)	<0.001
2004–2007	1.24 (1.05–1.46)	0.010	1.53 (1.31–1.79)	<0.001
2000–2003	1.41 (1.19–1.68)	<0.001	1.70 (1.45–2.00)	<0.001
Marital status				
Unmarried	Reference	–	Reference	–
Married	0.78 (0.7–0.88)	<0.001	0.83 (0.74–0.94)	0.002
Race				
Non-White	Reference	–	Reference	–
White	0.82 (0.72–0.93)	0.002	0.83 (0.73–0.93)	0.002
Income				
<$75,000	Reference	–	Reference	–
≥$75,000	0.85 (0.76–0.95)	0.004	0.88 (0.79–0.99)	0.030
Chemotherapy				
No	Reference	–	Reference	–
Yes	0.89 (0.8–0.99)	0.041	0.72 (0.65–0.81)	<0.001
Radiotherapy				
No	Reference	–	Reference	–
Yes	0.81 (0.68–0.95)	0.011	0.74 (0.63–0.87)	<0.001

HR, hazard ratio; CI, confidence interval.

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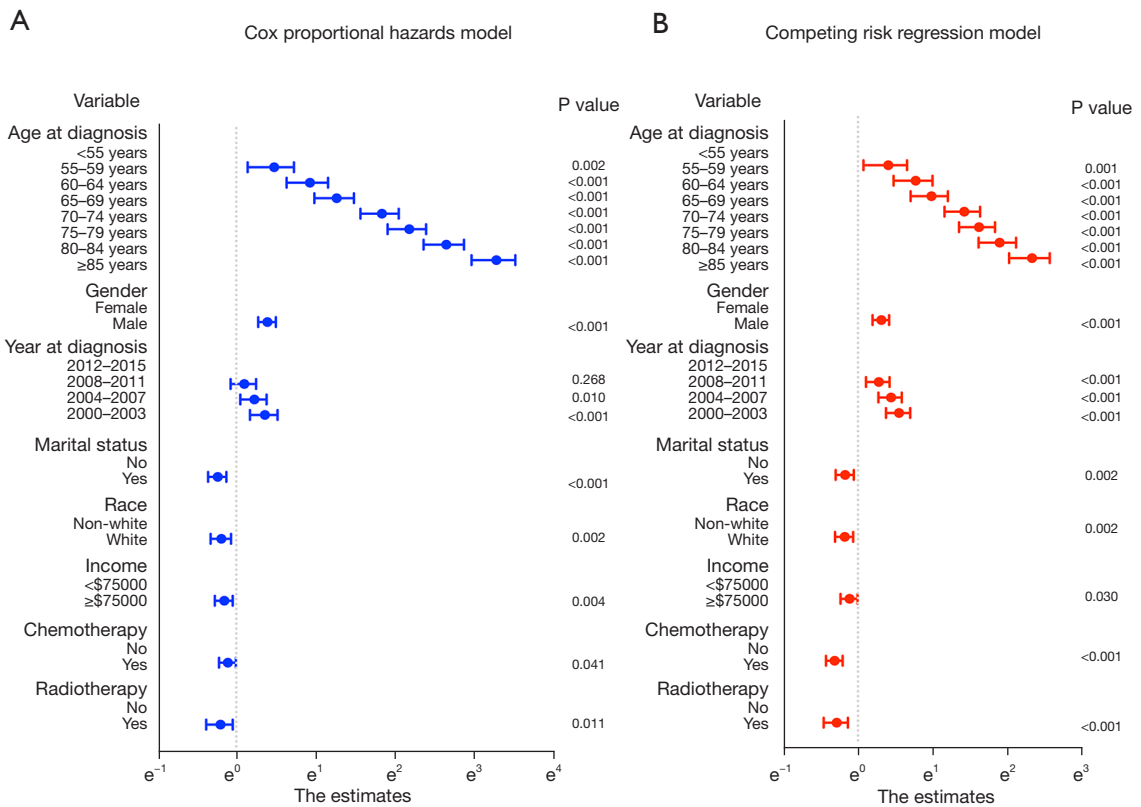

Figure 2 Forest plot of risk factors associated with cardiovasular death in multivariate Cox regression analysis (A) and competing risk models (B).

The cumulative incidence of cardiovascular-specific death for MM survivors with different risk factors after PSM

We further evaluated the impact of risk factors identified in multivariate analysis on CVD. After PSM, the distributions of most demographic and clinical factors were well balanced between groups (Tables S1-S6). In the Kaplan-Meier analysis, the male (HR =1.22, P<0.001), non-White (HR =1.23, P=0.002), unmarried (HR =1.29, P<0.001) survivors and those without chemotherapy (HR =1.42, P<0.001), and radiotherapy treatment (HR =1.39, P<0.001) were at a higher risk for CVD. Based on competing risk analysis, the cumulative incidence rate (CIR) of cardiovascular mortality showed significant differences between the following conditions: male *vs.* female (CIR: 10.49% *vs.* 9.52%, P<0.001), White *vs.* non-White race (CIR: 9.39% *vs.* 11.45%, P<0.001), marital *vs.* non-marital status (CIR: 9.26% *vs.* 10.95%, P<0.001), chemotherapy *vs.* no/unknown chemotherapy (CIR: 8.62% *vs.* 12.69%, P<0.001), and radiotherapy *vs.* no/unknown radiotherapy (CIR: 6.93% *vs.* 8.79%, P<0.001). There was no significant difference in the cumulative risk between individuals with more than $7,500 and less than $7,500 income (CIR: 9.29% *vs.* 10.43%, P=0.395; *Figure 3*).

Nomogram construction and validation

A nomogram based on the prognostic factors identified in the above analysis from the training cohort was established for the prediction of MM survivors' probability of CVD at 5, 10, and 15 years (*Figure 4A*). The nomogram demonstrated that age at diagnosis and period of diagnosis contributed the most to prognosis, followed by sex, race, married status, chemotherapy, and radiotherapy. Every risk factor was assigned a score on the points scale according to each subtype or level. The total CVD score was obtained by adding individual component scores of each variable. The prediction corresponding to this total score at the bottom of the nomogram helped estimate cardiovascular risk for each MM patient at various time points. The C-index of the nomogram for the training cohort was 0.700, and for the validation cohort was 0.726. As shown in *Figure 4B-4G*, the calibration plots for the 5-, 10-, and 15-year CVD

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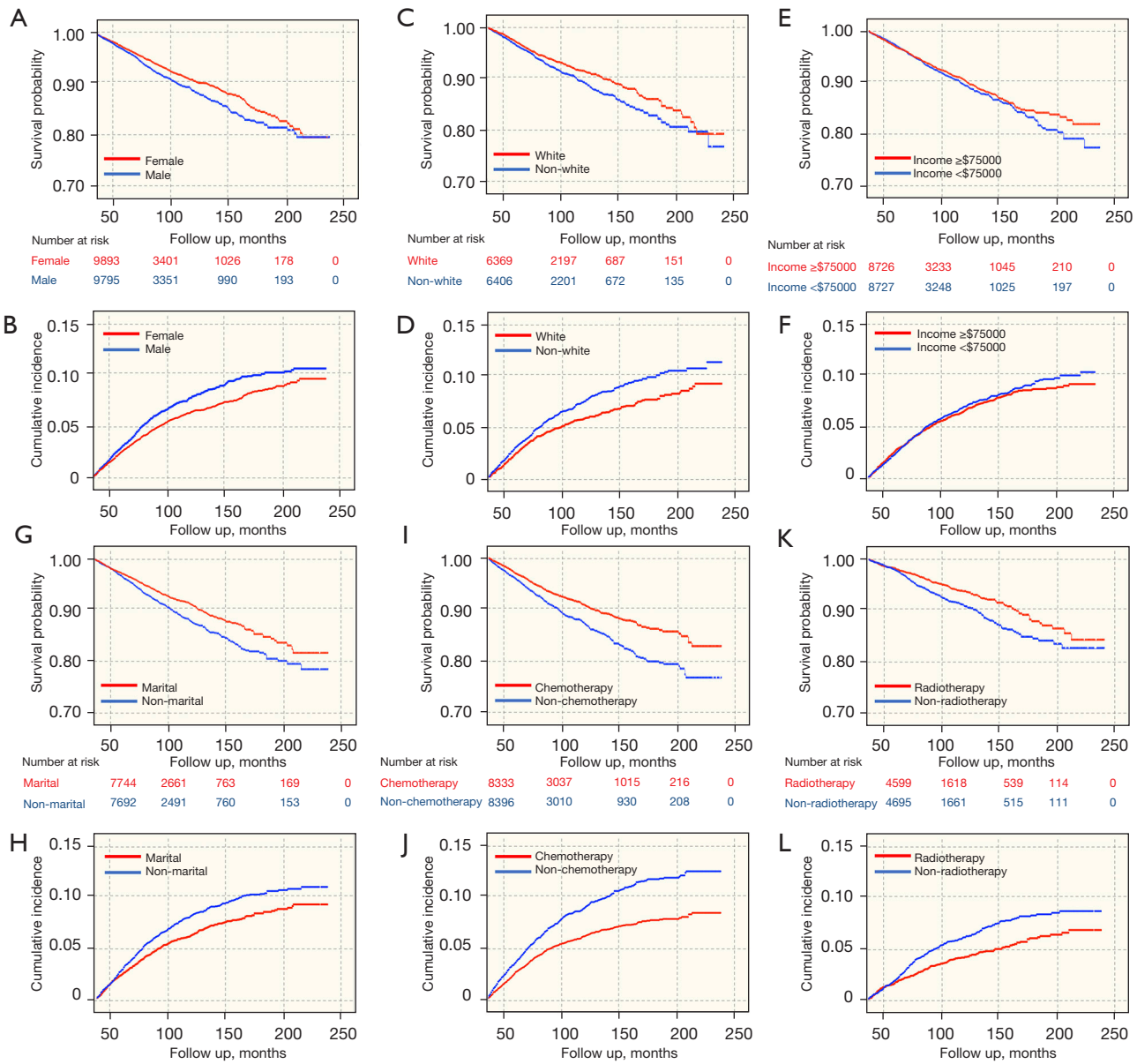

Figure 3 Kaplan-Meier survival curves and cumulative incidence of cardiovascular death in multiple myeloma after propensity score matching between two different gender (A,B), race (C,D), income (E,F), marital status (G,H), chemotherapy (I,J), and radiotherapy (K,L).

probability illustrated good consistency between the actual observations and predictions based on the nomogram in both the training cohort and the validation cohort.

Discussion

It is well documented that MM patients are at increased risk for cardiovascular diseases. In this SEER population-based study, heart-specific mortality, as an essential competing risk in MM prognosis, was observed to be varied based on demographic characteristics and treatment status (*Figure 5*). Previously, a study utilized Cox hazards regression analysis to estimate the associations between patient characteristics and heart-specific mortality in myeloma patients (3). Unlike, the large population-based study focused on identifying risk factors for CVD risk among MM survivors and established a comprehensive prognostic nomogram using competing risk and PSM approaches.

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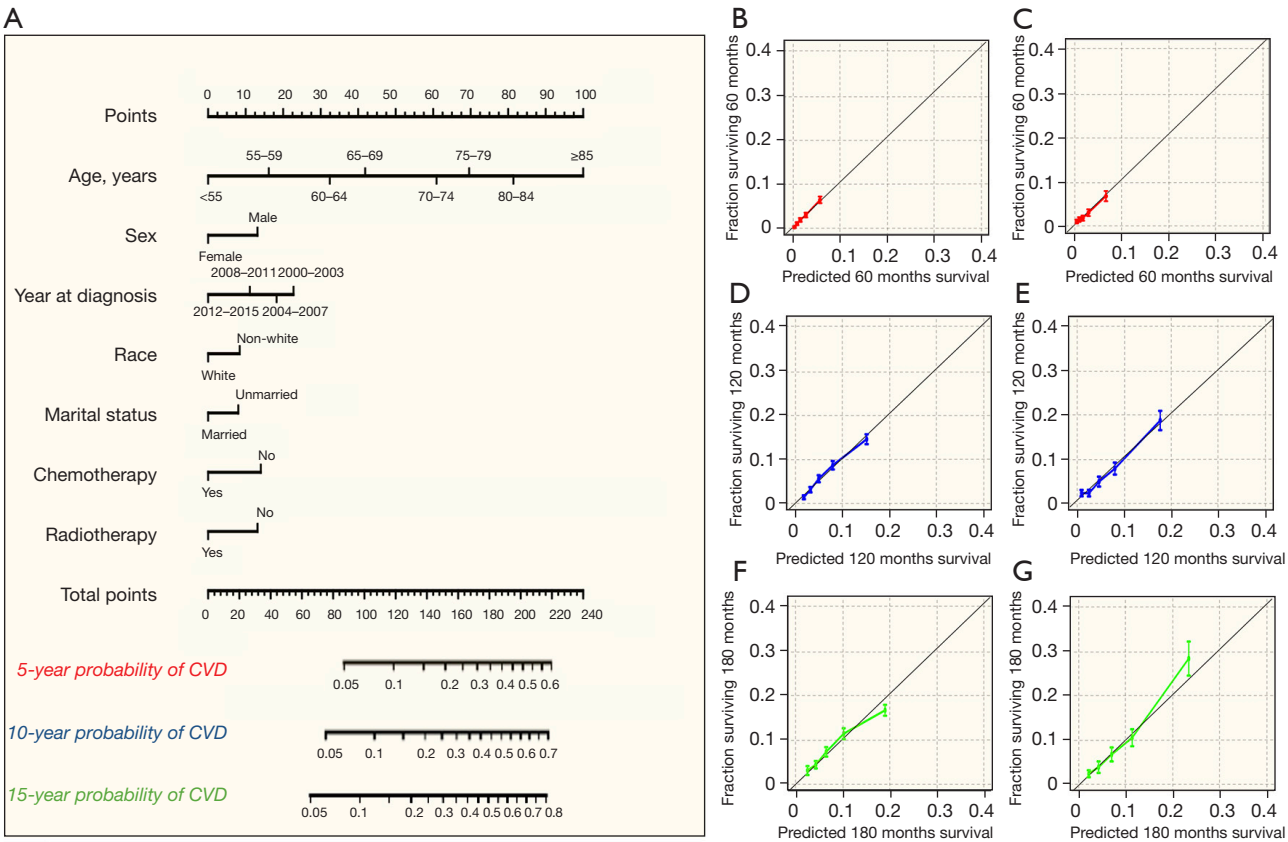

Figure 4 Nomogram for predicting the probability of cardiovascular death in multiple myeloma (A), 5- (B,C), 10- (D,E), and 15-year (F,G) nomogram calibration curves in training and validation set. CVD, cardiovascular death.

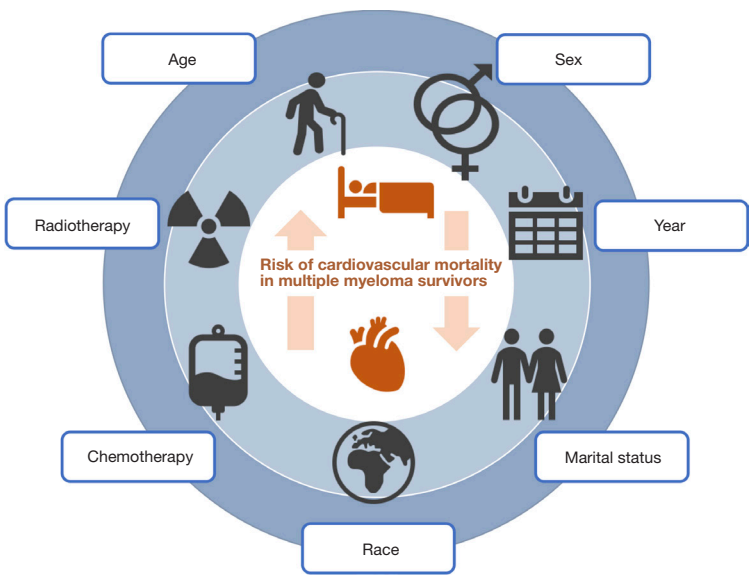

Figure 5 The abstract plot of main content of the study. This study informs that several factors, including age at diagnosis, period of diagnosis, sex, race, married status, chemotherapy, and radiotherapy, act together and influence cardiovascular outcomes in multiple myeloma survivors.

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The present study demonstrated the high cardiovascular mortality in MM survivors during follow-up (2,061/32,528, 6.34%). It was found that MM patients suffered from higher risk of cardiac events, including dysrhythmias, heart failure, cardiomyopathy, and heart conduction disorders, compared with non-MM patients of the same age and gender (8). However, nontumor-related factors, cancer-related comorbidities, treatment-related toxicity, and a combination of them are all likely to increase the cardiac risk for MM survivors. Thus, it may not be easy to find the specific etiology (1). First of all, the majority of MM patients were old, which are more susceptible to cardiovascular injury and ultimately result in severe complications during the survival time in oncological management. Besides, the onset of cardiovascular and MM presumably shares some risk factors, like obesity, sleep disturbance, environmental pollution, and so on (13). Hypertension and malignant hypertension are more prevalent among MM patients than non-MM ones (14). The risk of MM is proven to be associated with overweight body condition weight throughout life, and a healthy weight is beneficial for risk reduction of MM risk in all age groups. In the research, the authors speculated that subclinical immunologic dysregulation of excess weight and excess adiposity might lead to myeloma genesis (13,15). Sleep quality is also linked to myeloma risk through obesity-dependent or -independent mechanisms. Specifically, Gu *et al.* found an almost two-fold increased risk of MM in individuals sleeping less than 5 h/night compared with those sleeping 7–8 h/night (16). Lastly, it is well-known that anticancer drugs could result in severe side effects throughout a MM patient's clinical course and treatment, which will be discussed later.

After evaluating the mortalities at different periods, we characterized that the rate has declined yearly since 2000. A possible and sensible interpretation of these results may be attributed to the advances in the prevention and cure of cardiovascular diseases in normal and MM patients. Admittedly, as for non-cancer patients, continued advances have been made in cardiovascular therapeutic technologies, which have lowered the mortality rate considerably in recent years. In other words, progress in imaging studies and cardiac biomarkers can support early detection and intervention of heart disease in recent years, especially in high-risk cardiovascular patients (17). Meanwhile, increasing attention is also given to the initial assessment and monitoring of cardiac function before and during treatment in MM patients. For example, hypercalcemia, arteriovenous shunting, anemia, renal failure, hyperviscosity syndrome, and high-output cardiac failure were proven to be associated with a significantly increased risk of CVD and were always evaluated repeatedly by the hematologist/oncologist and cardiologists (8,18,19). The presently developed drugs, dexrazoxane, have also been approved to prevent myocardium damage during chemotherapy (20).

As an essential biological, social, and psychological event, marriage has also been found to be associated with cardiovascular outcomes in multiple cancers (21,22). In our study, unmarried patients had a higher considerable risk of CVD, which was consistent with the result obtained after PSM. From a psychological standpoint, emotional support from spousal promotes married people to be free from anxiety symptoms in oncological patients (23). Rather, unmarried one may be less tolerant of negative psychological stress from cancer and more vulnerable to the development of depression status, which has been demonstrated as a risk factor in CVD risk by many studies (24,25). With regard to the underlying mechanisms, oxidative stress, cortisol, and telomeres length have all been shown to be involved in a higher risk of CVD events (26,27).

In this longitudinal comparison of ethnic groups, the white race was found to have better survival rates than non-White races. In fact, in the general population, a recent study found that the risk of acute coronary heart disease events was higher among black men, which was associated with known risk factors (28). However, in the study, the ethnic differences in MM still remained between cohorts with matched baseline characteristics. Several explanations might account for this. First of all, the prevalence of obesity is also elevated among African Americans than other population groups, which have been examined as a risk for MM (15). It is conceivable that the higher overweight/obesity rate would threaten cardiovascular outcomes. Besides, a current study has also found several race disparities in MM survivors, like diagnosed time, treatment choices, comorbid health problems, and supportive care level, suggesting that optimizing well-established heart disease risk factors among different races might reduce these disparities (29). We found survivors with higher incomes had less risk of CVD than those with lower incomes. Similarly, another study found that income changes had implications for subsequent incidents of CVD (30). Socioeconomic differences in dietary/lifestyle habits, health inputs, insurance coverage, and psychological status could account for this phenomenon.

With the development of pharmacotherapy for MM, many novel effective drugs have significantly improved

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MM prognosis. Meanwhile, the new agent classes, together with traditional chemotherapeutics, were all more or less associated with cardiovascular adverse events (1). For instance, a SEER-Medicare study of 7,330 MM patients found 815 carfilzomib users had a statistically higher HR for all cardiovascular adverse events than nonusers (31). In our study, chemotherapy decreased the risk of CVD, contrary to common sense. One of the possible explanations might be that there were higher proportions of cases considered with a poor MM prognosis in chemotherapy recipients. These patients were more susceptible to death from non-cardiovascular diseases, implying that those were less likely to suffer from CVD. However, the study had miniatured biased risks as much as possible by applying competing risk analysis. Whether chemotherapy recipients have acquired medical intervention in reducing cardiovascular risk deserves ongoing study. Besides, MM patients with cardiovascular complications or markedly impaired heart function might have been excluded after chemotherapy cardiovascular risk evaluation. Research based on a French nationwide database recently demonstrated that MM patients did not show a significantly higher risk of CVD but were associated with major and intracranial bleedings, which could be due to the primary/secondary preventions and intensive follow-up before initiating anti-MM treatment (32). All in all, the disease and anti-MM treatment are bound to increase the risk of CVD, but this effect can be counteracted by careful risk assessment, monitoring, and prophylactic treatment from multidisciplinary teams.

In the study, major limitations mainly include those inherent to the SEER database, including lack of lifestyle habits information, common complications record, and detailed treatment data regarding chemotherapy/radiotherapy. Besides, there are missing clinical indicators, including cholesterol, diabetes, obesity, and arterial hypertension, which may be associated with an increased risk of CVD. As a retrospective observational study, selection bias for MM survivors cannot be avoided. Therefore, we used PSM to adjust underlying confounding factors contributing to CVD. Finally, a nomogram was constructed by combining the seven predictors, which facilitate individualized prediction of CVD of MM survivors. However, our study lacks external verification in the real world, which should be addressed in the future.

Conclusions

Based on a competing-risks analysis model, the independent prognostic factors of CVD among MM survivors were determined in this study. A novel nomogram for predicting 5-, 10-, and 15-year cardiovascular outcomes was also established and validated, which can identify high-risk ones to develop better clinical decisions and improve the prognosis of MM survivors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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