

## Peer Review File

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### Reviewer A

This is a hard work managing thousands of patients. The topic, the design and the results are interesting, despite limitations. Moreover, the epidemiological variables analyzed such as sex, married status, income, and others, are supported with previous studies showing poor OS.

A few comments:

1. -Line 112. The reason to exclude patients with less than 36 months of follow-up is not clear. This represents an important bias selection. All patients with early mortality are included here and it could be very interesting looking for an association between the variables analyzed and early CVD.

**Reply 1:** Thanks for the reviewer's comment. Early CVD in MM patients cannot be ignored. We agree with your opinion for including patients with less than 36 months of follow-up. The study aims to analyze the impact of epidemiological factors and therapy of MM on CVD. Therefore, we were concerned that patients with short follow-up time might receive short-term radiotherapy/chemotherapy and be more prone to be affected with non-tumor diseases. However, as mentioned in the limitation part, data about classic cardiovascular risk factors (cholesterol, diabetes, obesity, arterial hypertension) are lacking. Hence, we just include the MM survivors for more than 3 years and aim to discuss the long-term cancer survivors. To clarify the purpose, we redescribed the study subjects as "MM survivors" rather than "MM patients". Alexandra W. et al. also only include 5-year survivors of testicular cancer to study the cardiovascular risk in cancer patients<sup>(1)</sup>. As for early CVD in MM patients, we are collecting newly diagnosed multiple myeloma cases with comprehensive clinical information to discuss the question. (1). van den Belt-Dusebout AW, de Wit R, Gietema JA, et al. Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*. 2007;25(28):4370-4378. doi:10.1200/JCO.2006.10.5296

**Changes in the text:** we have modified "MM patients" to "MM survivors" in our text

(see Page 1, line 2; Page 2, line 28, 29, 37, 49, 51, 53; Page 3, line 59 (Highlight Box); Page 5, line 95; Page 6, line 108, 114, 116, 117; Page 7, line 126; Page 9, line 153, 154, 157, 162, 165; Page 10, line 178, 180, 186; Page 11, line 199; Page 12, line 219,223; Page 15, line 280, 283; Page 16, line 315, 318; Page 17, line 323, 326; Page 18, line 337; Page 19, line 340; Page 20, line 344; Page 21, line 348,365 in unmarked manuscript)

2. -Line 241-247. A reference to AL-amyloidosis is placed here. I suggest avoiding completely this reference that could be misleading. Inclusion criteria refers to MM as the first primary cancer. I assume that AL patients were excluded in the study.

**Reply 2:** Thanks for your kind reminder. These statements are misleading, and the citation is inappropriate. Therefore, we decided to remove these.

**Changes in the text:** We have removed the statement about AL-amyloidosis in the Discussion part (see Page 13, lines 242 in unmarked manuscript).

3. -The list of limitations could be higher. Data about classic cardiovascular risk factors (cholesterol, diabetes, obesity, arterial hypertension,...) are lacking.

**Reply 3:** We appreciate the reviewer's valuable comment. We have rewritten the limitations.

**Changes in the text:** We have rewritten the Limitation part (see Page 16, lines 310-314 in unmarked manuscript), as "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."

## **Reviewer B**

1. In the sentences below, you refer to "studies" but have only one citation. Please check and revise.

- "Recent studies have 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)."
- "Besides, current studies have 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)."

**Reply 1:** Thanks for your kind reminder. We have modified the description in the main text.

**Changes in the text:** We have changed the two sentences as

- "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)" (see Page 4, lines 76-77 in unmarked manuscript)

- "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)."

(see Page 15, lines 281-282 in unmarked manuscript)

2. Numbers in Figure 1 and Table S4 do not add up.

**Reply 2:** Thanks for the reviewer's comment.

In Figure 1, numbers do not add up due to some patients satisfying more than one exclusion criterion. Therefore, we add the number of these patients in **new Figure 1**.

In Table S4, we have corrected recording errors about the total number in the **new Supplementary Table 4**

3. "> 85 years" should be changed to "≥ 85 years" in Figure 2 and 4a.

**Reply 3:** Thanks for your kind reminder. We corrected this error in the modified **Figures 2 and 4a**.

4. Please add the age unit in Tables 1-2 and S1-S6.

**Reply 4:** Thanks for your kind reminder. We added the age unit in **Table 1-2 and S1-S6**

5. This description does not match with Figure 3.

384 **Figure 3.** Kaplan-Meier (KM) Survival Curves and Cumulative Incidence of  
385 Cardiovascular Death in Multiple Myeloma after **PSM** between Two Different  
386 Gender (A&B), Race (C&D), Marital Status (E&F), Income (G&H), Chemotherapy  
387 (I&J), and Radiotherapy (K&L).↵

**Reply 5:** Thanks for your kind reminder. We have revised the manuscript and fixed the problems.

**Changes in the text:** We have corrected this error in the Figure Legend (see Page 16, lines 397 in unmarked manuscript)

6. The legend of Figure 3E is incorrect.

Income > \$75000	8726	3233	1045	210	0
Income > \$75000	8727	3248	1025	197	0

**Reply 6:** Thanks for your kind reminder. We corrected this error in the modified **Figure 3**.

7. These numbers seem incorrect according to Table 1.

190 diagnosis (2000-2003 years: 9.48%, 2004-2007 years: 8.36%, 2008-2011 years:  
191 6.38%, 2012-2015 years: 3.43%). Besides, non-White (7.6%), unmarried (6.75%),  
192 lower-income (6.39%), non-chemotherapy (8.99%), and non-radiotherapy  
193 (6.80%) survivors were more prone to developing CVD.↵

**Reply 7:** Thanks for your kind reminder. These numbers mean the ratio of the percent of CVD to all deaths.

**Changes in the text:** To make it more clear, we have written this sentence as, "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 $\geq$  \$75000: 6.22%, Income $<$ \$75000: 6.39%), chemotherapy (chemotherapy: 4.96%, non-chemotherapy: 8.99%), and radiotherapy (radiotherapy: 4.16%, non-radiotherapy:6.80%).” (see Page 7, lines 198-204 in unmarked manuscript)

8. Indicate how the data are presented in Table 1, 2, and S1-S6.

**Reply 8:** Thanks for your kind reminder. We have added the description of numbers in **Tables 1, 2, and S1-S6.**

9. Confirm whether this race in Table 1 and 3 should be black or non-white.

Race
Black

**Reply 9:** Thanks for your kind reminder. We have corrected this error in the modified **Tables 1 and 3.**

10. This should be female according to Table 3.

204 HR=6.47, P < 0.001; 85+ years: HR = 9.94, P<0.001), male (HR = 1.35 P < 0.001),

**Reply 10:** Thanks for your kind reminder. We have modified the **table** to correct this error.

11. These descriptions do not match with Table 3.

205 non-White (HR = 1.20, P= 0.002), earlier period (2008-2011 year: HR = 1.30, P <  
207 0.001), unmarried status (HR = 1.20, P = 0.002), lower income (HR = 1.14, P = 0.03),  
208 no/unknown chemotherapy (HR = 1.39, P < 0.001), and no/unknown  
209 radiotherapy (HR = 1.35, P < 0.001) were all significantly associated with  
210 increased CVD risk in MM survivors.

**Reply 11:** Thanks for your kind reminder. In this version, we selected factors with higher risk. In order to keep the results consistent with Table 3, we have re-edited related description to make it more clearly for readers, as “Competing risk analysis showed that older age (55 - 59 years: 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 year: 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." (see Page 8, lines 212-221 in unmarked manuscript)

12. A header is missing in Table 3.

**Reply 12:** Thanks for your kind reminder. We have added the header in Table 3.

13. Add the age unit in Table S1-S6.

**Reply 13:** Thanks for your kind reminder. We have added the age unit in Tables S1-S6.

14. Numbers do not add up in Table S4.

**Reply 14:** In Table S4, we have corrected recording errors about the total number in the **new Supplementary Table 4**

15. "> 85 years" should be changed to "≥ 85 years" in Figure 2.

**Reply 15:** We have corrected picture errors in Figures 2 and 4.

16. Indicate the full name of the abbreviations that are marked yellow in the attached files.

**Reply 16:** Thanks for your kind reminder. We have indicated the full name of the abbreviations (**see Page 16, lines 390, 396, 403** in the unmarked manuscript; see the title of **Table S1-6** in Supplementary material)