Dear editor,

Thank you for your e-mail together with the reviewer's kind comments concerning our manuscript entitled "Risk of cardiovascular death in patients with hepatocellular carcinoma based on the Fine-Gray model".

We have revised the manuscript according to the reviewer's comments. When the text was changed, it is highlighted by yellow-coloring in the revised version for easier tracking. Enclosed below are the revised points including point-by-point response to the comments made by the reviewers.

Response to Reviewer #1:

Thank you for your decision and constructive comments on our manuscript. We have answered each of your points below.

1. The SEER data if have should report BMI, diabetes, hyperlipidemia, hypertension, alcohol history, hepatitis B, hepatitis C etc as these are confounders and not reported.

Response:

Thanks for the suggestion. First of all, at the beginning of the study design, we had plan to incorporate the above factors. However, we were unable to obtain more factors beyond those included in the current study, due to limitations of the SEER database. Based on this, we chose the Fine-Gray model in order to better utilize the data we were able to obtain, with the goal of excluding the effects of the competing events and obtaining a more accurate factors of the influences associated with the primary endpoint. To better solve this problem, we have made appropriate additions to the limitations section of the article.

2. The HCC patients have a typical and unique form of chemotherapy delivery i.e. TACE = transarterial chemoembolisation which in theory has less systemic effects including low cardiotoxicity. So authors should try and idenfity the type of chemotherapy modality/delivery route to enhance the results reporting.

Response:

Thank you very much for the suggestion. First, it has to be acknowledged that we could not obtain specific chemotherapy modalities and the chemotherapeutic agents used from the SEER database. Meanwhile, this limitation was made clear in the manuscript. However, in order to solve this problem, we have reviewed a large amount of literature and made additional supplementary analysis.We believe that there are two reasons that lead to chemotherapy being a protective factor. The first reason is that there are differences in baseline conditions between patients who receive chemotherapy and those who do not, such as younger age at diagnosis, higher grading, and no cardiovascular diseases. In addition, consider that patients with higher grades may receive a higher cardiotoxicity burden. In the supplemental analysis (**Supplementary table 1**), we discussed the proportion of patients who received both chemotherapy and radiotherapy. We found that the higher the grade, the higher the proportion of patients receiving both radiotherapy and chemotherapy. Therefore, it is necessary for us to take into account that patients at higher grades, who receive potentially cardiotoxic treatment, are also more likely to die earlier due to their underly HCC disease before they might develop a heart-specific disease in the long term.

3. 5 year survival of HCC patients is in the range of 50% patients i.e. half will be dead within 5 years which is too short for cardiovascular disease manifestations, unless high grade toxicity is being discussed from immunotherapy.

Response:

Thank you for the suggestion. First of all, it is very regrettable that we were unable to obtain more detailed drug information on the study participants from the SEER database, so it is difficult to make further discussion of the toxicity of immunotherapy. However, we believe that the bias brought to this study by immunotherapy is acceptable. Through a search of the literature, we learned that immunotherapy does not appear to be widespread in the

population we chose to study. When immunotherapy was not widely available, we continued to see cardiotoxicity during treatment in HCC patients. This is all the more reason why we need to do what we can to minimize cardiovascular death in HCC patients in advance. In addition, we agree that your suggestions have served as a reminder of the research we will be conducting next, and again, we are grateful to you.

4. It makes sense to study cardiovascular in other cancers like breast and colon as they are more common forms with good proportion of population receiving chemotherapy with a higher likelihood of 10yr and beyond survival and thus studying cardiovascular disease is good and relevant - for HCC the argument doesnt remain so strong after all.

Response:

Thank you for pointing out this issue. In response to your question, we have conducted some data collection as well as a literature search. First, the mortality rates reported by the National Vital Statistics System do show that HCC patients have significantly higher CVD mortality rates than the general population. (The general US population (2010-2015) vs HCC patients (2010-2015), about 0.3% vs. about 3%). Second, studies have clearly indicated that the point of cancer diagnosis forward into survivorship cancer patients (all sites) are at elevated risk of dying from CVDs compared to the general US population (Sturgeon KM, Deng L, Bluethmann SM, et al. Eur Heart J. 2019 Dec 21.). In addition, in a study of HCC, it was suggested that a considerable improvement in survival has been observed (5-year survival up from 40% to 70%) when patients are diagnosed at an early stage and receive potentially curative therapy in the form of liver transplantation, surgical resection, or tumor ablation.(Kim DY, Han KH. Liver Cancer. 2012 Jun.). And the conclusion was supported by a number of related studies. Therefore, we have reason to believe that HCC patients have a chance to achieve longer survival.

5. Surprisingly your discussion segment is silent on pertinent and relevant theme of paraneoplastic syndrome of HCC which can actually increase or modify the risk of cardiovascular illness!

Response:

Thank you for the suggestion. We have added a discussion of the impact of paraneoplastic syndrome of HCC on CVD death risk in the manuscript, based on your suggestion.