Dear editor:

Thank you very much for your decision letter and advice on our manuscript (ID: 81462) entitled "Conditional survival probability of distant-metastatic hepatocellular carcinoma: a population-based study". We also thank the reviewers for their valuable and helpful comments and suggestions. Accordingly, we have revised the manuscript. Additionally, please find below our detailed responses to the comments raised in earlier reviews and the summary list of changes. Thank you very much!

We hope that the updated work is acceptable for the publication in your journal.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Jian Shi

**Replies to Reviewer 1**

**Comments:**

In this study, the authors investigated overall survival (OS), cancer specific survival (CSS) and conditional survival (CS) at 3 different moments from diagnosis, of patients affected by metastatic HCC. In particular, they investigated factors associated with shorter OS, CSS and CS. The majority of patients affected by metastatic HCC have a very short survival, with less than 20% of them surviving more than 12 months. In this context, the realiability of survival predictors of OS and CSS may be limited; CS may help to identify survival predictors at a particular time from diagnosis. The authors found that, as OS and CSS decreased over time, CS increased. They also found that factors impacting on survivals changed according to different CS time points. This study is overall quite well written and designed, however I have some comments. I suggest the authors to carefully review the manuscript: some grammar/ortograph mistakes can be found in the text, for example: introduction line 4, I suggest to replace "comprising" with "Accounting for". Paragraph "Comparison of OS and CSS", line 13 .And patients with bone metastases "who (add)" received radiotherapy even… . In particular, the discussion needs to be re-reviewed: some sentences have no verb and are difficult to understand. I suggest the authors to use in the tables, for p values values, real numbers (0.045) instead of notations like 4.57e-02. this may make the table more understandable. as acknoledged by the authors in the study limitations paragraph, patients survivals is affected by the use of combo therapy of new generation and, in this context, focusing on a study population of patients diagnosed in average 10 years ago may make the study results not reliable: please comment on this. finally, I suggest the authors to expand on the importance of their findings: how knowing CS and related predictors of survival may impact on clinical practice?

Response:

Thanks for your thoughtful and insightful comments on our work, to which we have the following responses:

# I suggest the authors to carefully review the manuscript: some grammar/ortograph mistakes can be found in the text, for example: introduction line 4, I suggest to replace "comprising" with "Accounting for". Paragraph "Comparison of OS and CSS", line 13 .And patients with bone metastases "who (add)" received radiotherapy even… . In particular, the discussion needs to be re-reviewed: some sentences have no verb and are difficult to understand.

Response: Sorry for the poor English writing and some grammar mistakes. We have checked the English writing and grammar in the manuscript and polished it. Please find the changes in the revised manuscript. The changes are listed in the summary list of changes.

# I suggest the authors to use in the tables, for p values values, real numbers (0.045) instead of notations like 4.57e-02. this may make the table more understandable.

Response: We have changed the style of the p value in the tables. We used scientific notation for those less than 0.01, but kept real numbers if the value was more than 0.01. Please find the changes in Table 2, Table S1, Table S4, and Table S5, .

# as acknowledged by the authors in the study limitations paragraph, patients survivals is affected by the use of combo therapy of new generation and, in this context, focusing on a study population of patients diagnosed in average 10 years ago may make the study results not reliable: please comment on this.

Response: In the discussion section, we have added comments on the use of combo therapy in the limitation part. We have listed the example of the combo use of sorafenib and nivolumab; while sorafenib, which is the first-line treatment, prolonged the survival of advanced-stage HCC, nivolumab could

be used for patients who had disease progression or unacceptable adverse effects with sorafenib. This combo therapy certainly improves overall survival and the conditional survival rate of distant metastatic hepatocellular carcinoma patients. As we did not have data on this, it is a limitation for our study and the use of our nomogram. Please find the changes in Line 12 to Line 17, the fifth paragraph of the discussion section.

# finally, I suggest the authors to expand on the importance of their findings: how knowing CS and related predictors of survival may impact on clinical practice?

Response: We have expanded on the importance of conditional survival in clinical practice. Evidence-based decisions could be made based on the dynamic risk profiles of patients. The nomograms constructed in our study may help assess patients' survival rates at different times and remind clinicians and family members that more continued surveillance and care should be given to patients with lower conditional survival rates. Furthermore, if patients have survived for a certain number of months, they have more opportunity to have a better prognosis, and the therapeutic goals and strategies can be more positive for them. Please find the changes in Line 12 to Line 17, the fourth paragraph of the discussion section.

**Replies to Reviewer 2**

**Comments:**

Dear authors. From my point of view your article needs minor revision. The number of references is small. References for conditional survival in other tumors are more than 20 years old. Large number of authors did not consider chemotherapy and radiation are able to boost OS rate in distant metastatic disease. So you have to be careful with such a conclusion. worse survival in not-chemo-radiotherapy patients may be due to poor condition of that patients (so they could not tolerate chemo-radiotherapy) or other factors.

Response:

Thanks for your valueble and helpful comments for our paper, our responses are as follow:

# References for conditional survival in other tumors are more than 20 years old.

Response: Thanks for this kind reminding. We have updated the reference for conditional survival with up-to-date articles. Please see the modified references 15–17.

# Large number of authors did not consider chemotherapy and radiation are able to boost OS rate in distant metastatic disease. So you have to be careful with such a conclusion. worse survival in not-chemo-radiotherapy patients may be due to poor condition of that patients (so they could not tolerate chemo-radiotherapy) or other factors.

Response: Thanks for this valuable advice. We completely agree with the reviewer on the influence of poor condition of patients on survival. We have added comments on this in the discussion section. Please see the highted sentence in the third paragraph of the discussion section. Please find the changes in Line 14 to Line 17, the third paragraph of the discussion section.

**Summary of changes in the revised manuscript**:

**Changes in Abstract:**

1) Line 5, the third paragraph: replaced "6-month CS" with "the 6-month CS", replaced "survival difference" with " the survival difference".

2) Line 7, the third paragraph: removed "even".

3) Line 11, the third paragraph:: added "and".

4) Line 3, the fourth paragraph: added "rates".

**Changes in Introduction:**

1) Line 4, the first paragraph: replaced "comprising" with "accounting for".

2) Line 9 - Line 10, the first paragraph: replaced "The prognosis was much poorer in HCC patients with extrahepatic metastasis than early stage patients" with "The prognosis in HCC patients with extrahepatic metastasis was much poorer than the prognosis of early-stage patients".

3) Line 11, the first paragraph: added "three" before "decades".

4) Line 15 - Line 16, the first paragraph: replaced "of expected median survival time" with "with a median expected survival time".

5) Line 10, the second paragraph: replaced "thus" with "therefore", replaced "the study" with "a study".

**Changes in Methods:**

1) Line 5 - Line 8, part of "Data collection": replaced "Patients were excluded if the diagnosis were made only at autopsy, and those with incomplete American Joint Committee on Cancer (AJCC) staging, alpha-fetoprotein (AFP) expression information, and unknown death reason were all excluded" with "Patients were excluded if the diagnosis were made only at autopsy. Those patients with incomplete American Joint Committee on Cancer (AJCC) staging, alpha-fetoprotein (AFP) expression information, and unknown death reason were all excluded".

2) Line 5 - Line 6, the second paragraph, part of "Statistical analysis": replaced "Based on variables selected by multivariate Cox regression model and competing risk model" with "Based on variables selected by the multivariate Cox regression model and the competing risk model".

3) Line 2, the third paragraph, part of "Statistical analysis": replaced "as" with "with".

**Changes in Results:**

1) Line 2 - Line 3, part of "Clinicopathological characteristics": replaced "65.11% patients were white race" with "65.11% of the patients were white".

2) Line 3, part of "Clinicopathological characteristics": replaced "in married status" with "married".

3) Line 5 - Line 6，part of "Clinicopathological characteristics": replaced"with T3 stage" with"in the T3 stage"。

4) Line 10, part of "Clinicopathological characteristics": replaced "only a few" with "relatively few".

5) Line 12, part of "Comparison of OS and CSS": replaced "this" with "which".

6) Line 13 - Line 14, part of "Comparison of OS and CSS": Replaced "And patients with bone metastasis who received radiotherapy even had a better survival and less cancer specific mortality rate" with "And patients with bone metastasis who received radiotherapy had better survival rates and less cancer specific mortality rates".

7) Line 1, part of "Nomograms for conditional survival": added "the" before "initial diagnosis".

**Changes in Discussion:**

1) Line 3, the first paragraph: added " had" before "focused on".

2) Line 3, the second paragraph: added "who" before "died".

3) Line 4, the second paragraph: replaced "changes" with "changed".

4) Line 6, the second paragraph: added "had" before "already".

5) Line 14, the second paragraph: replaced "As" with "Since".

6) Line 3, the third paragraph: replaced "have" with "had".

7) Line 12 - Line 14, the third paragraph: replaced "Chemotherapy and radiotherapy were considered to be protective factors for survival at initial diagnosis, and they may provide benefit in the first few months" with "This may be due to the difference in molecular pathology and resistance which appeared 10 months following the initial diagnosis".

8) Line 14 - Line 17, the third paragraph: added sentence "Also, patients who had a poorer condition could not tolerate chemotherapy and radiotherapy at the initial diagnosis and would have a shorter survival time, so poor conditions may explain worse survival for some non-chemotherapy or non-radiotherapy patients".

9) Line 19, the third paragraph: added "be" before "because".

10) Line 24 the third paragraph: replaced "tend to be" with "become".

11) Line 25, the third paragraph: replaced "female gender would have a higher CS rate than male gender" with "females have a higher CS rate than males".

12) Line 30, the third paragraph: replaced "this may" with "which may be".

13) Line 31, the third paragraph: replaced "This finding following" with "The findings which followed".

14) Line 4 - Line 5, the fourth paragraph : replaced "more accurately" with "with greater accuracy".

15) Line 5, the fourth paragraph : added " the" before "features".

16) Line 6, the fourth paragraph : removed "And" before "AFP expression".

17) Line 9 - Line 10, the fourth paragraph: replaced "while the value of AUC gradually slightly increased in models for conditional CSS" with "while the value of AUC showed a gradual and slight increase in models for conditional CSS".

18) Line 11, the fourth paragraph: replaced "reasons" with "causes".

19) Line 12 - Line 17, the fourth paragraph: added sentences "These nomograms may help assess patients' survival rates at different times. It can be used to remind clinicians and family members that more continued surveillance and care should be given to patients with lower conditional survival rates. Furthermore, if patients have survived for certain number of months, they have more opportunity to have a better prognosis, and the therapeutic goals and strategies can be more positive for them".

20) Line 5, the fifth paragraph: removed "And" before "Due to".

21) Line 6, the fifth paragraph: replaced "both limiting" with "which limits".

22) Line 7, the fifth paragraph: added "so" before "the metastasis events".

23) Line 8, the fifth paragraph: removed "And" before " we used".

24) Line 10, the fifth paragraph: replaced "in these years" with "in the years since".

25) Line 12 - Line 17, the fifth paragraph: added sentences "For example, as the first small oral molecular targeted medicine sorafenib successfully prolonged the overall survival of advancer HCC patients, and the novel programmed cell death 1 (PD-1) checkpoint inhibitor nivolumab could be used for patients who had disease progression or unacceptable adverse effects with sorafenib[39]. These are important factors which should be taken into consideration in the prediction model".

26) Line 17, the fifth paragraph: Replaced "due to the time period" with "due to the time".

27) Line 19, the fifth paragraph: Replaced "and" with "as".

28) Line 20 - Line 21: replaced"lacked" with "not present in our study".

**Changes in References:**

1) Modified references: 15-17

2) Added new references: 39-40

**Changes in Tables:**

Table 2, Table S1, Table S4, and Table S5: We used scientific notation for those less than 0.01, but kept real numbers if the value was more than 0.01. Please find the changes in the tables which we highlighted in red.