

Peer Review File

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Reviewer A

1. The paper has some language issues. For example, line 29 “were explored as”. Please have the paper polished by English-speaking professionals.

Reply 1: The paper has been polished by an English-speaking professor (supported by AME Editing Service).

2. Abstract. Please use PICOS criteria to define the inclusion of studies to be included.

Reply 2: the abstract has been re-written to define the inclusion of studies according to PICOS criteria.

Changes in the text: We modified the text in the abstract as follows: we included the studies which compared the outcomes of RFS and OS between different levels of NLR and PLR in HBV-related HCC patients underwent hepatectomy. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were considered as effective measures and were calculated by a pooled analysis ([page 2, line 29-31](#)).

3. Introduction.

3.1 Line 73-75, it would be helpful to briefly review existing knowledge of prognostic factors of HBV-related HCC.

Reply 3: as your advice, we have added common prognostic factors including tumor size, tumor differentiation, margin status, vascular invasion and Child-Pugh score in these patients.

Changes in the text: We added above factor in the sentence, which is described in the text of [page 4, line 70-72](#).

3.2 Line 81, please provide detailed examples for inconsistent findings in the patients with HBV-related HCC.

Reply 4: based on your advice, we described the inconsistent results of 4 studies as examples.

Changes in the text: we added examples to indicated inconsistent prognostic value of NLR and PLR ([page 4, line 84-88](#)).

4. Methodology.

4.1 The title indicated that the focus of this study is the biomarkers of relapse in patients with HBV-related HCC. In this part, the authors focused on both OS and RFS in both patients with HBV and non-HBV related HCC. So it seems that the current methodology cannot answer the research question or the work done by the authors is beyond the research question. A basic prerequisite to answer

the research question is that the analysis can only be limited to studies conducted with samples with HBV-related HCC.

Reply 5: it's a critical advice to this study. In fact, overall survival is a focused endpoint in present study. Accordingly, we have modified the title to state the endpoint of OS is also considered.

Changes in the text: we modified the title as *Neutrophil to lymphocyte and platelet to lymphocyte ratios as biomarkers to predict relapse and survival in posthepatectomy HBV-related hepatocellular carcinoma: a meta-analysis and preliminary immune perspective* (page 1,line 1-3).

4.2 Literature search may have language bias because only English-language databases were searched.

Reply 6: In fact, we had searched the Chinese-language databases in the preparing stage of this study, but the quality of the obtained studies was unsatisfactory. As our knowledge, most high-quality studies are from English-language databases. Moreover, we found that most published meta-analysis on high-quality journals like *Translation Cancer Research* also only reviewed and analyzed the studied from English-language databases. In addition, we examined the publication bias, and there was no obviously publication bias in present study.

4.3The search needs to be updated till at least 2020.

Reply 7: we have re-searched the databases in December 2020 and added several new published studies in the pooled analysis.

Changes in the text: 1. The flow diagram of study selection (figure 1) was updated. 2. we stated the new search date as December 2020 (page 5, line 101). 3. the characteristics of included studies have been modified (page 7-8, line 144-157 and table 1) 4. we modified the abstract according search and selected results (page 2, line 36).

4.4The authors should use PICOS criteria to define the eligibility of studies to be included.

Relay 8: as your advice, we have modified the inclusion and exclusion criteria of this study according to PICOS criteria.

Changes in the text: The modified inclusion and exclusion criteria has been described in page 5-6, line 105-114.

4.5Why not limiting studies to be those with HBV-related HCC only?

Replay 9: it is a good advice. We re-selected the studies in the re-searched results and excluded the studies containing patients with non HBV-related HCC. The followed analysis has also been re-calculated.

Changes in the text: 1. we stated only HBV-related HCC was been considered (page 2, line 26-27, line 30; page 5, line 90; page 6, line 111-112; page 11, line 231). 2. the results of pooled analysis has been modified (table 2; figure 2; page 8-9, line 159-179). 3. the abstract has been updated according to the pooled analysis results

(page 2, line 37-40). 4. the results of publication bias exam have also been modified (page 10, line 202-204; figure 4; table 2).

4.6 Line 118-119, it is very strange to perform univariate and multivariate analyses because this is not an original study.

Replay 10: this sentence is not correct and has been re-written (We prefer to select the HRs and their 95% CIs were calculated by multivariate analysis due to the better accuracy)

Changes in the text: we have re-written this sentence as a suitable one (We extracted the HRs, and their 95% CIs were calculated by multivariate analysis to achieve better accuracy) (page 6, line 121-122).

5. Statistics.

5.1 The authors need to use a separated paragraph to describe the statistical approaches used.

Replay 11: statistical approaches have been described in a separated paragraph.

Changes in the text: we have re-written the statistical analysis in the text (page 6-7, line 132-140)

5.2 Line 30, it is strange to describe “mean difference” because survival data are not continuous variables.

Replay 12: according to the advice from a statistician, the statistical analysis has been re-calculated and modified. In fact, the effective measures in this study are HRs and their 95% CIs instead of mean difference and associated 95% CIs.

Changes in the text: we have re-written the statistical analysis in the text (page 6-7, line 132-140)

5.3 Revman, in fact, has substantial limitations to handle survival data in meta-analysis. I suggest the authors to use Stata or R.

Replay 13: thanks for your advice, we re-performed a pooled analysis using Stata 14.0 in present study.

Changes in the text: we stated Stata 14.0 is the statistical software in this meta-analysis (page 7, line 139).

5.4 The authors did not specify the examination of sources of heterogeneity.

Reply 14: we performed a subgroup analysis to examine the sources of heterogeneity. To examine the stability of results, we held a sensitivity analysis with leave-one-out method.

Changes in the text: we added the results of subgroup analysis in the text (page 9, line 181-195; table 3 and 4). The results of sensitivity analysis was been added (page 10, line 198-201).

5.5 The stratification analysis based on % of HBV among the study sample (i.e., 50%) is at high risk of ecological fallacy, because this is study-level analysis. If no

studies focusing on HBV-related HCC patients only are available, I think the current study design is not able to answer the research question.

Replay 15: we agree with you. The stratification analysis has been removed. In present study, we only selected the study about HBV-related patients, which attempt to assess the prognostic value of NLR and PLR in HBV-related HCC.

Changes in the text: 1. We remove the results of the stratification ([page 10](#)) as well as associated figures([form figure 3](#)) and tables ([form table 3](#)).

Reviewer B

A good meta-analysis.

Rely 15: Thank you very much for giving us an opportunity to revise our manuscript.

Other changes: 1. We re-written the discussion according to the new results. 2.the limitations of present study has been re-defined ([page 14,line 219-285](#)).