Peer Review File

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Reviewer A

1. English language of the paper needs extensive editing, for example, in the title, “elevate” should be “improve”. Line 5-9, page 3, a problematic sentence.

Reply:

Thanks for your good recommendations. We agree with you that some ambiguous and problematic words and sentences exist in this manuscript. Therefore, the main text of this paper has been comprehensively edited and carefully corrected for wording, spelling, and grammar usage by a native English-speaking expert who majors in the field of hepatobiliary surgery in EditSprings (http://www.editsprings.com/). We believe that the language editing will improve the readability of our article.

2. Abstract. In the methods part, please use PICOS criteria to define the inclusion of eligible studies. The risk of bias of included studies is also necessary. Results part should also provide the results of assessment of risk of bias.

Reply:

Thank you for your nice suggestions. In the methods part of the abstract, we have used PICOS criteria to accurately define the inclusion of eligible studies. The detailed PICOS items are presented as follows. P (Participants): HCC with hypersplenism **(see Page 3, line 8)**; I (Intervention): the combination of hepatectomy or transhepatic arterial infusion (TAI) with splenectomy **(see Page 3, line 6–7)**; C (Control): hepatectomy or TAI alone (see Page 3, line 7–8); O (Outcomes): relevant outcomes, including patients’ demographics, clinicopathologic characteristics, perioperative indices and long-term outcomes (overall survival and disease-free survival) **(see Page 3, line 10–13)**; S (Study

design): Prospective clinical trials or retrospective cohort studies from inception to May 10, 2020 were considered eligible for this analysis **(see Page 3, line 9–10)**. The risks of bias of the included studies are also presented as "Publication bias for overall survival (OS) and disease-free survival (DFS) was qualitatively assessed by funnel plots and quantitatively evaluated by Begg's and Egger's tests." in the methods part and "Funnel plots suggested an HRs symmetric distribution for OS and DFS. Begg's and Egger's tests confirmed that there was no significant HR publication bias for OS and DFS." in the results part, respectively **(see Page 3, line 12–14 and Page 3, line 27–29)**.

3. Introduction. In the last paragraph, the authors need to specify debates regarding the long-term prognosis of splenectomy in HCC patients. Also, please comment on why these debates exist. This is important, as the rationale for a meta-analysis.

Reply:

Thank you for your good suggestions. High-evidence research, such as randomized clinical trials, regarding investigating the effect of splenectomy on hepatocellular carcinoma (HCC) patients with hypersplenism is presently limited. As a consequence, meta-analysis can be regarded as an indispensable supplement to this field and add to the current knowledge and literature.

We totally agree with you that it is important to clearly specify the related debates in the Introduction section, because it is the rationale for a meta-analysis. Thus, we have added "Kong et al. (1) suggested that synchronous splenectomy is associated with a significant improvement of overall survival (OS). Contrarily, Xie et al. (2) revealed that it does not lead to a significantly higher OS after concomitant splenectomy when compared with hepatectomy alone. Therefore, it is controversial whether splenectomy can improve the long-term prognosis of HCC patients with hypersplenism." in the third paragraph of the Introduction **(see Page 5, line 28–29 and Page 6, line 1–3)**. We suppose that the retrospective nature of the published studies and the small number of patients included in each study may lead to the heterogenous results and controversial conclusions.

4. Methodology. The literature search has language bias because only English database were searched. Please use PICOS criteria to define the inclusion of eligible studies, in particular the design of studies. I do not think abstract should be excluded if its study meets the criteria for inclusion. NOS could be used for assessing risk of bias of both case-control and cohort studies, but the authors did not specify the design of studies to be included. If studies of both types were included, it is problematic to combine findings from studies of both designs. Line 20, page 7, please provide the reference for the cut-off score of 6 for high quality studies.

Reply:

Thank you for raising so many valuable questions. At the initial stage of the literature retrieval, we also searched the Chinese academic databases (CNKI, Sino Med, VIP, Wan Fang). Regrettably, the methodological qualities of the Chinese articles are relatively low, as most of the articles written in Chinese do not have survival data or survival curves, or do not make univariate or multivariate analyses, which makes it impossible to evaluate the impact of splenectomy on the long-term outcomes of HCC patients with hypersplenism. On the other hand, some articles in Chinese are overlapped with papers written in English in terms of authors, affiliations, and study subjects. Due to the above two reasons, we decide not to include articles written in Chinese, and only restrict to English written full-text articles **(see Page 6, line 13–14)**. We agree with you that language bias may occur, but the quality of included studies is another concern to guarantee the stable results of our meta-analysis.

In this article, abstracts are excluded in the eligibility criteria **(see Page 6, line 26–27)** due to the following reasons. First, many abstracts lack sufficient descriptions of survival outcomes and prognosis assessment. Moreover, some high-quality meta-analyses exclude abstracts as well (3,4).

Newcastle-Ottawa Scale (NOS) scoring is widely used to assess the methodological quality of observational studies, including case-control and cohort studies. Case-control studies and cohort studies are distinct in nature. Odds ratios (ORs)

are commonly used in combing findings from case-control studies, while relative risks (RRs) or hazard ratios (HRs) are frequently used in pooling findings from cohort studies. In the revised version of our manuscript, we have more clearly specified the study design of the included studies as "prospective randomized controlled trials (RCTs) or retrospective cohort studies" **(see Page 6, line 20–21)**.

In Line 20, Page 7, we decide not to use the cut-off score of 6 to distinguish study qualities, because the cut-off score is various among different studies (5–7). As this meta-analysis is designed to include RCTs or cohort studies, we write in the revised text "The Cochrane Collaboration's tool was used to assess the methodological quality of RCT. The quality evaluation for retrospective cohort studies was based on the modified Newcastle-Ottawa Scale (NOS)" **(see Page 7, line 19–21)**.

5. Statistics. Please specify whether the HR values obtained from includes studies are from adjustment regression models. If yes, how to consider the influence of different covariates adjusted across included studies. Line 28, page 7, please specify which variables are secondary indicators. Please also explain why OR was used to pool results from survival data, I think this is not acceptable unless there are case-control studies included, but case-control studies cannot be used to assess prognosis. Line 5-6, page 8, subgroups analyses should not be limited to the two variables only.

Reply:

Thank you for putting forward these good questions. We have specified the type of HR values obtained from original studies **(see Page 7, line 23–29)**. If the original study performed univariate and multivariate Cox hazards regression analyses, HRs and the corresponding 95% CIs for overall survival (OS) and disease-free survival (DFS) were directly obtained from the results. If the original study did not report HRs in the unadjusted or adjusted models, Kaplan-Meier survival curves were used to estimate HR values, the significance of which is equal to univariate unadjusted HRs.

In this systematic review and meta-analysis, the primary outcomes of interest are OS and DFS. The other variables displayed in Table 2 were described as secondary

indicators in the initial version of our manuscript. These variables included perioperative data (clinicopathological characteristics, operative variables, and postoperative short-term indices) and postoperative long-term variables. In order not to confuse the reviewers and readers, we have modified the text as "The pooled odds ratios (ORs) with 95% CIs and the weighted mean differences (WMDs) with 95% CIs were appropriately reported for other perioperative and postoperative long-term variables" **(see Page 7, line 29–30 and Page 8, line 1)**.

We totally agree with you that case-control studies cannot be used to assess prognosis, because the main outcomes of interest have occurred at the initiation of case-control studies. The pooled hazard ratios (HRs) for OS and DFS, the main outcomes of interest in this study, were calculated for prognosis evaluation. HR is used here because it takes the time factor into account. For the comparison of long-term mortality and tumor progress or recurrence rates between the splenectomy and non-splenectomy groups, relative risk (RR) is frequently used because it only compares the differences of rates between the two groups and does not take the time sequence into consideration. RR here is suggestive of "the mortality rate or tumor progress/recurrence rate in the splenectomy group, divided by the mortality rate or tumor progress/recurrence rate in the non-splenectomy group", which applies the conception of absolute and relative numbers. In the condition of cohort studies, the values of odds ratio (OR) approximately equals to those of RR. Additionally, a series of meta-analysis also used pooled ORs to combine OS or DFS rates, which implies that it is acceptable and correct (1,6-8). These are the reasons that why we use ORs to pool results from long-term mortality and tumor progress or recurrence rates.

In subgroup analysis, besides the two variables (the published year, the type of hazard ratio) analyzed, we have added two other variables (hepatitis viral infection, Child-Pugh classification) to provide more relevant information to reviewers and readers **(see Page 8, line 7–8; Page 11, line 3–4 and Page 11, line 11–21)**.

References

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hepatectomy for selected patients with hepatocellular carcinoma and clinically significant portal hypertension: A systematic review and meta-analysis. J Surg Oncol 2019;119:964-73.
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7. Zhang XP, Wang K, Li N, et al. Survival benefit of hepatic resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. BMC Cancer 2017;17:902.
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Reviewer B

Well-conducted meta-analysis.

I have one major concern.

1. Please present the subgroup analysis adjusted by the tumor characteristics (size,

number, tumor differentiation, and vascular invasion). This will add more information to this manuscript.

Reply:

Thank you for your good recommendations! In this systematic review and meta-analysis, subgroup analyses were performed to explore and explain the potential heterogeneity across the included studies. As shown in **Supplementary Table 1**, the tumor characteristics (tumor diameter, tumor number, tumor differentiation and microvascular invasion) of the patients were presented. We totally agree with you reviewer that subgroup analyses stratified by these tumor characteristics are very meaningful and can provide more additional information, because these tumor-related features have repeatedly reported to be associated with the long-term prognosis of HCC patients. Unfortunately, although we tried to investigate the potential heterogeneity in terms of these tumor characteristics, we failed to make it due to the following reasons. Firstly, the data types and cutoff values were heterogeneous across studies. Take the tumor diameter for example, some were continuous variables (mean and standard deviation, or median and interquartile range), the others were categorical variables (2cm, 3cm or 5cm as the cutoff point), which made the subgroup analysis difficult. Secondly, some tumor-related characteristics showed good consistency and tendency between the splenectomy and non-splenectomy groups. That is, the majority of patients of the two groups had a solitary tumor, well to moderate tumor differentiation, and presence of microvascular invasion, in almost all of the included studies. Subgroup analyses in this condition are somewhat difficult because it is hard to identify an optimal cutoff point to group the patients into distinct subsets. Therefore, we performed the subgroup analyses based on two commonly used variables (the published year, the type of hazard ratio) in the initial version of our manuscript **(see Page 8, line 6–7 and Page 11, line 1–3)**. We found that the studies published in 2010 or later, or with multivariate analyses, significantly favored the splenectomy group **(see Page 11, line 5–10)**. Considering that the viral hepatitis background (HBV infection > 50% or HCV infection > 50%) and the liver function of patients (Child-Pugh class A > 50% or class

B > 50%) are also important factors affecting survival, we additionally performed subgroup analyses in the revised version of our manuscript adding these two grouping factors **(see Page 8, line 7–8; Page 11, line 3–4 and Page 11, line 11–21)**, with the aim to provide more relevant information to reviewers and readers.