

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 77060

Title: Liver transplantation with simultaneous splenectomy increases risk of cancer development and mortality in hepatocellular carcinoma patients

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02860506

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Professor, Surgeon

Reviewer's Country/Territory: China

Author's Country/Territory: Taiwan

Manuscript submission date: 2022-04-13

Reviewer chosen by: AI Technique

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Review time: 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Please supplement the tables and figures. I cannot find the figures or tables in the manuscript or the review system.

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Title: Liver transplantation with simultaneous splenectomy increases risk of cancer development and mortality in hepatocellular carcinoma patients

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05426772

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Taiwan

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this paper, the authors present the results of a retrospective case-control study in which the oncologic outcomes were compared between patients with HCC with and without splenectomy. The authors may wish to consider the following comments:

Abstract: Passive voice in the background of the abstract makes it unclear whether it is a result of your study or what is known so far. Conclusions in the abstract refer only to patients with hepatitis C, while sub-analysis by HCV status is only one part of the results.

Page 2: Splenectomy cannot have a higher risk of cancer, patients with splenectomy can. Or change in "having a splenectomy was not associated with a higher risk of cancer."

Background: There are more suitable recent studies such as meta-analyses on the safety of the splenectomy, to be cited instead of the reference 8: - Yang J, Li Y, Li Z, Jiang W. Spleen plays a two-way role in cancer incidence and cancer progression (still a preprint).

- He, Chao; Liu, Xiaojuan; Peng, Wei; Li, Chuan; Wen, Tian-fu. Evaluation of the efficacy and safety of simultaneous splenectomy in liver transplantation patients, *Medicine*: March 2018 - Volume 97 - Issue 10 - p e0087 doi: 10.1097/MD.00000000000010087. The second meta-analysis is cited by the authors at the end of the discussion regardless it is an important piece of evidence on this topic. Therefore, the statement "The effects of splenectomy in cancer development after LT has not been discussed in previous literature." should be deleted from the introduction, abstract and discussion, results of this meta-analysis should be reported and a better rationale for this study should be provided. **Methods:** "Between May 2009 and August 2019, 179 patients with HCC underwent LT and received follow-up management." Were all of them included? It is not clear what is the main oncologic outcome in the study,

from the text I have the impression that it was overall cancer, from methods that it was only HCC recurrence while the tables report also non-HCC cancers. Statistical analysis:

Risk ratios from time-dependent Poisson regression for cohort data with 95%CI would be much more appropriate than p values. Due to the small sample size, even 10% difference in the cancer recurrence between groups was statistically insignificant due to the small power of the study (Table 1). Variables selection in the multivariate regression cannot be based solely on univariate analysis results but also on the clinical significance. P-value is affected by sample size indeed in a small sample, variables may have substantive importance, although they are not significant. Was the multicollinearity and model diagnostics, such as goodness of fit, assessed? Results: How “NLR \geq 3 months after LT” was the main predictor of death since there are patients who died the same day of the surgery (with a survival of 0 days)? The confidence interval in the association between splenectomy and mortality is too wide, being a consequence of a small sample size. This must be addressed in the limitations as this substantially limits making the inference about splenectomy being a risk factor for mortality. 95%CI for AFP was 1.096-76.667, in this case, the p-value has no value. “Because of surgical indications for simultaneous splenectomy, more HCV patients underwent simultaneous splenectomy. There may be biases in patient selection.” This is more appropriate and important for the limitations. Is there a result of the splenectomy indications, how many of them were due to surgical indications? Tables: It might be useful to list the 5 non-liver cancers below the table 1 or in the results. * is redundant, it is clear that for example 0.02 is smaller than 0.05. General comments The manuscript needs some reworking/rephrasing to simplify the text and make it more comprehensible. A native English speaker needs to fine-tune the text.

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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

The authors retrospectively analyzed the effect of splenectomy on tumor prognosis after liver transplantation for hepatocellular carcinoma which conducted a retrospective cohort study, and suggested that splenectomy should be avoided in patients with hepatitis C complicated with hepatocellular carcinoma. This article has certain clinical value, but some studies on this aspect have been reported (PMID: 34619907), and there have been several studies on the indication of spleen resection for liver transplantation (PMID: 32827564, PMID: 31555908, PMID: 29517676, PMID:33642835). There are also some shortcomings in the study design of this paper, such as mismatching of baseline data and small sample of HCV subgroups. Generally speaking, the innovation of this paper is not recommended, and it can be transferred to other journals of the company.

A meta analysis has indicated that Splenectomy benefits LT patients in increasing platelet count. However, splenectomy is a morbid procedure as splenectomy increases operation time, intraoperative blood loss, intraoperative RBC transfusion, and postoperative complications. Splenectomy does not improve OS but increase perioperative mortality. Therefore, Splenectomy should be performed only in selective patients (PMID: 29517676). In this paper, the research results for the clinical application value, and is not recommended for patients with port of most scholars directly line resection, splenic artery blood platelets, splenic artery ligation can solve the problems such as (DOI: <http://dx.doi.org/10.3748/wjg.v20.i41.15367>). There were many problems in the experimental design of this study. First of all, of the 120 patients included by the author, only 35 cases were included in the splenectomy group. The sample size was too small, about 1:3 compared with the control group, and the

experimental results were not convincing. Secondly, as a clinical study, what is the calculation standard of sample size? How do you calculate a sample of 120? Whether the indications for splenectomy were used as the basis for calculating sample size and were explained evenly, all of these led to the unreliability of the research results of this paper, and there were also the following main problems. 1. in splenectomy or not, HBV patients accounted for 66.7%, affecting the results of subgroup data analysis 2. If baseline data do not match, it is recommended to use the principle of bias matching to correct and re-analyze 3. Most studies have confirmed that NLR is an independent risk factor for the prognosis of patients after liver transplantation for liver cancer. How to determine the cutoff value of NLR in this paper? 4. Survival analysis should be performed for different subgroups of HCC co-infection 5. What are the surgical indications for splenectomy in liver transplantation patients with hepatocellular carcinoma? The author's description is too broad 6. Language needs to be partially corrected