

Format for ANSWERING REVIEWERS

October 7, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13403-review.doc).

Title: Synchronous splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism: case-control study

Author: Xiaoyun Zhang, Chuan Li, Tianfu Wen, Lunan Yan, Bo Li, Jiyin Yang, Wentao Wang, Li Jiang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13403

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

- (1) Followed by the advice of science editor, we revised the title of our manuscript as "Synchronous splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism: case-control study".
- (2) In section of "DISCUSSION", we added the paragraphs "Interestingly, decreased tumor recurrence and prolonged the interval to recurrence; however.....the case-control groups were not significantly different." and "This study had several limitations.....for patients with HCC and hypersplenism." for answering the questions of the reviewer.

2 Revision has been made according to the suggestions of the reviewer

- (1) In the section of "DISCUSSION", we discussed the potential the mechanism of the decreased recurrence with splenectomy, as opposed to no effect on the overall survival for answering the question of the reviewer(Reviewer code: 01221925), as shown in the paragraphs "Interestingly, synchronous hepatectomy.....not significantly different."
- (2) In the section of "DISCUSSION", we summarized the limitations of the present study as shown in the paragraph "This study had several limitations.....for patients with HCC and hypersplenism."

3 References and typesetting were corrected

4 Answering reviewers

(1) Answering the first reviewer (Reviewer code: 01221925)

1) The paper could benefit from language editorial help

Thanks for your suggestion. We have sought for a copyediting service provided by professional English language editing company (American Journal Experts) and earned an editing certificate.

2) What do the authors consider as the mechanism of the decreased recurrence with splenectomy, as opposed to no effect on the overall survival?

Thanks for your question. Interestingly, synchronous hepatectomy and splenectomy decreased tumor recurrence and prolonged the interval to recurrence; however, this technique was not beneficial to the overall survival of patients with HCC and hypersplenism. The reduction of TGF- β levels after splenectomy was shown to lead to decreased recruitment of T regulatory (Treg) cells via the TGF- β -miRNA-34a-CCL22 pathway, which may reduce the ability of HCC cells to evade immune defenses and inhibit tumor metastasis. Intricate immunosuppressive mechanisms, such as abnormal T

cell receptor-CD3 complex, tumor-induced tolerance, suppression of NK cells, and impaired T cell function, may also be altered by splenectomy, thereby temporarily inducing tumor regression. However, sustained hepatitis viral infection results in inflammation and inflammatory microenvironments that promote fibrosis, cirrhosis and even permanent oncogenesis. As demonstrated in the present study, most patients were characterized as hepatitis b antigen-positive; thus, the outcomes of the case-control groups were not significantly different ($P=0.187$). This may be the potential mechanism of the decreased recurrence with splenectomy, as opposed to no effect on the overall survival.

3) Was there a difference in postoperative bleeding?

Thanks for your questions. As described in the "Surgical complications", 2 of 84 patients in the HS group were diagnosed with postoperatively intra-abdominal bleeding and underwent re-laparotomy. In contrast to the HA group, there was no patients suffering from postoperative bleeding. But it was not significantly different ($P=0.497$).

4) Is there potentially a selection bias, given the fact that it is not a randomized style and that the patients were chosen for the combined procedure? The control group should be comprised of patients fulfilling all the criteria for splenectomy.

Thanks for your questions. This is a retrospective study that is inherently prone to selection bias. To reduce the bias, we selected the contemporary case controls in a consecutive manner and excluded the patients who received splenectomy after the primary hepatectomy. In addition, the control group consisted of 84 patients selected from a pool of 268 patients who underwent HA for HCC and hypersplenism during the same period and met the selection criteria for hepatectomy and splenectomy.

(2) Answering the first reviewer (Reviewer code: 02938161)

The paper should be reviewed by someone with expertise in English before it can be published in the Journal of "WJG".

Thanks for your suggestion. We have sought for a copyediting service provided by professional English language editing company (American Journal Experts) and earned an editing certificate.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Tianfu Wen, professor,
Department of Liver Surgery and Liver Transplantation Centre,
West China Hospital of Sichuan University, Guoxuexiang 37,
Chengdu 610041, Sichuan Province, China.
Telephone: +86-28-85422871
Fax: +86-28-85422396
E-mail: cdwentianfu@sohu.com.