Author's response to reviews

Title: Influence of laparoscopic-assisted gastrectomy and open gastrectomy on serum interleukin-6 levels in patients with gastric cancer among Asian populations

Authors:

Zhen Bo Shu (shuzhenbo0722@163.com)
Hai Ping Cao (caohaipin0722@163.com)
Yong Chao Li (liyongchao0722@163.com)
Li Bo Sun (sunlibo0722@163.com)

Version: 4 Date: 2 February 2015

Author's response to reviews: see over
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Authors:
Zhen-Bo Shu (shuzhenbo0722@163.com)
Hai-Ping Cao (caohaiping0722@163.com)
Yong-Chao Li (liyongchao0722@163.com)
Li-Bo Sun (sunlibo0722@163.com)

Version: 2 Date: 24 January 2015

Author's response to reviews: see over
Reviewer's report

Title: Influence of laparoscopic-assisted gastrectomy and open gastrectomy on serum interleukin-6 levels in patients with gastric cancer among Asian populations

Version: 3  Date: 13 January 2015

Reviewer: Toru Aoyama

Reviewer's report:

The authors reviewed and evaluated the influence of laparoscopic-assisted gastrectomy (LAG) and open gastrectomy (OG) on serum interleukin-6 (IL-6) levels in patients with gastric cancer (GC) among Asian populations. The paper is well written but there are some points to be clarified.

Major comments

1: It is unclear the inclusion and exclusion criteria. The authors need to show the details of the inclusion and exclusion criteria of the present study.

Response: Thank you. We added patients’ description, treatment of surgery, whether has a history of chemotherapy or radiation and detection time for IL-6 for a detailed inclusion and exclusion criteria of the present study. “(3) study subject: GC patients verified by endoscopy and biopsy and patients treated with LAG or OG;” (5) detection times for IL-6 levels: 24h before operation and 24h after operation; “Study with patients who had a history of previous treatment of GC, chemotherapy or radiation was also excluded.”

2: Why the authors only focused the IL-6 to evaluate the influence of LAG and open OG. Is IL-6 optimal marker to evaluate the surgical stress? More other cytokines and hormones, such as IL-1, TNF, IFN-c, catecholamine, and corticosteroids, also are related to surgical stress. How about were these cytokines or hormones?

Response: Thank you for the insightful comment. We used IL-6 as a surrogate marker for systemic inflammation post-surgery. As such, many inflammatory mediators and cell types are involved in this process, but unfortunately such data is not available for meta-analysis in relation to LAG and...
OG. Therefore, we analyzed the IL-6, which is one of the prominent markers of inflammation, and IL-6 data was available from all the selected studies. The inflammatory reaction might be activated by the surgical procedures, which is viewed as surgical stress, and there is an association between the extent of the surgical trauma and surgical stress. Absolutely, other cytokines and hormones, such as IL-1, TNF, IFN-c, catecholamine, and corticosteroids, also are related to surgical stress. We did not analyze then for the insufficient data and number of literature.

3: Was the IL-6 measured same points? If not, it is possible that the level of surgical stress was not accurately evaluated.

Response: Thank you for the important comment. Yes, IL-6 measurements are at the same time points before and after surgery and this was mentioned in the Methods. The serum IL-6 level was measured at 24h before operation and 24h after operative.

4: The authors should show the patients background. IL-6 might be affected the patients background.

Response: Thank you very much for your suggestion. We added information on patient background in Methods section. “GC patients verified by endoscopy and biopsy; Patients did not have a history of previous treatment of GC, chemotherapy or radiation.”

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Reviewer's report

Title: Influence of laparoscopic-assisted gastrectomy and open gastrectomy on serum interleukin-6 levels in patients with gastric cancer among Asian populations

Version: 3 Date: 20 January 2015

Reviewer: Konstantinos Tsimogiannis

Reviewer's report:
A well-presented paper, though the introduction feels quite long. Could be shortened

Response: Thank you for your helpful comment. In the Introduction section, we presented gastric cancer, IL-6, laparoscopic-assisted gastrectomy (LAG) and open gastrectomy (OG), and the study background and significance. We deleted irrelevant information to shorten this section.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report

Title: Influence of laparoscopic-assisted gastrectomy and open gastrectomy on serum interleukin-6 levels in patients with gastric cancer among Asian populations

Version: 3 Date: 15 January 2015

Reviewer: Makoto Meguro

Reviewer's report:

The paper is a meta-analysis with 54 studies selected by PubMed, EBSCO, Ovid, Wiley, Web of Science, WANFANG and VIP databases. Authors indicate “compared with OG, LAG reduces the expression of IL-6 effectively and further inhibits inflammatory reaction for GC patients among Asian population’’.

Although this study was well documented, there are significantly critical and crucial problems as described below

> Meta-analysis should be performed by including Cochrane Library and EMBASE databases.

Response: Thanks for your helpful advice. We added Cochrane Library and EMBASE databases in the Method section after searching relevant articles in the two databases.

> IL-6 values, tumor progression status, lymph node dissection status, and reconstruction methods such as B-I or Roux-Y are not shown in Table 1. Therefore, there are not easy to understand these reports.

Response: Thank you for the comment. The previous Table 1 presented baseline characteristics of the studies. A revised Table 1 is attached with details of IL-6 level changes. Due to insufficient information, we did not extract tumor progression status, lymph node dissection status, and reconstruction methods such as B-I or Roux-Y.

> In the results section (p8 the last paragraph), Figure 6C shows asymmetric shape, so there is existence of publication bias. Figure 6D shows symmetric shape, so there is no existence of
publication bias. A contradiction exists in this results section. And then, you should correspond to the existence of publication bias.

**Response:** Thank you very much for your suggestion. Fig. 6C shows comparison of postoperative serum IL-6 levels of GC patients between LAG group and OG group with a symmetric funnel plot, and Fig. 6D presents the comparison of postoperative increased serum IL-6 levels of GC patients between LAG group and OG group with an asymmetric funnel plot. The presence of bias may be resulted from the use of pre-operative data for the analysis of postoperative increase of IL-6.

> Authors described “Subgroup analysis based on country showed that, in Chinese and Japanese GC patients, both 40 postoperative and postoperative increased serum IL-6 levels in LAG group were significantly lower 41 than those in OG group (all P < 0.05); In Korean GC patients, postoperative and postoperative 42 increased serum IL-6 levels in LAG group and OG group had no obvious statistical differences (all 43 P > 0.05)’’.

Ref. 33 (Jung IK et al. reported) is shown only each 10 patients. This is not universal in Korea’s GC operation. Therefore, this paper’s conclusion is overstatement, so it is needed larger sample-sizes as you pointed out in conclusion.

**Response:** Thank you for your helpful suggestion. Overall, the sample size in this meta-analysis is relatively small. As you mentioned, (Jung IK et al.) reported only 10 patients. Other studies also had relatively small sample size. We had discussed this as our limitation in the Discussion section towards the end. Further investigations with large sample size are warranted to strengthen our results.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.