

July 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11037-review.doc).

Title: Long term outcome of Diabetes and Hypertension after Gastrectomy in Gastric Cancer Patients: A Nationwide Cohort Study

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11037

First of all, we are pleased to have an opportunity to improve our article by reviewing from your journal. We corrected and revised our article thoroughly according to the reviewers' comments. The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. References and typesetting were corrected
3. Revision has been made according to the suggestions of the reviewer

Comment #1.

Abstract: Conclusion: The term “general population” can be misleading, as the population consists of patients with gastric patients. The same issue arises in the discussion part for a few more times.

SR1

Author’s reply #1.

Thank you for your important critic. The reason we used the word “general population” was that we **did not** select the population under any other criteria, such as severity of obesity. As you know, many articles described about the changes of diabetes or hypertensions after bariatric surgery especially in morbidly obese population; the key points of our article lied in the change of diabetes or hypertension after the treatment of gastric cancer using nationwide data. However, because there seems to be misleading in the word “general populations” as your comment, we changed all the word “general population” into “population” or “general population with gastric cancer”.

Comment #2.

Abstract: Conclusion: The authors concluded that “TG was found to improve glycemic control to a greater extent than either ER or STG in non-obese general population”. This is also mentioned in the conclusion of the main text. As the authors have no blood glucose levels or HbA1c levels for comparison, they cannot come to a direct conclusion such as “improvement of glycemic control”. They could better say “TG was found to decrease the need for antidiabetic medications which can be reflective of improved glycemic control, to a greater extent than either ER or STG in non-obese diabetic patients”.

Author's reply #2.

Thank you for your kind opinion. The sentences modified by the reviewer will clarify our intents, so we changed the text “TG was found to decrease **the need for anti-diabetic medications which can be reflective of improved glycemic control**, to a greater extent than either ER or STG in non-obese **diabetic patients**.” in CONCLUSION of abstract section.

Comment #3.

Methods: There seems to be a limitation in patient selection. If (1) all the gastric cancer patients for the selected time frame were included in the study and then (2) DM and HTN patients were selected among them and (3) patients were excluded according to the exclusion criteria; more patients would have been included in the study. Patients' insulin usage status and number of diabetic medications can be reflective of the disease stage of the diabetic patients. These factors could have been taken into account to determine whether the disease severity had an impact on the effect of TG on DM or not. If we think that diabetics on insulin are those at a more advanced stage of the disease, the ER patients could be considered to include more severe diabetic patients and perhaps (??) the positive effect of TG was only seen in the patients at an earlier stage of the disease. This could be assessed using appropriate statistical analysis.

Author's reply #3.

The reviewer's first concern about patient's selection was very important. As the reviewer mentioned, the dataset was constructed following the algorithm that gastric cancer patients were selected from patients with diabetes and hypertension, not diabetes or hypertensive patients from gastric cancer patients. However, the order of selection seems not to be critical,

because the prevalence of diabetes in gastric cancer patients were not different from general population. So we guess that the number of study population would not be so different even after the order of selection of study population has been changed as the reviewer's recommendation. We added some sentences in INTRODUCTION section; "The prevalence of DM in patients with gastric cancer was not different from that in general population; Ogle et al. reported comorbid DM was 8% of patients with gastric cancer using data from National Cancer Institute Surveillance, Epidemiology, and End Results program and Sarfati et al. reported DM with complication occurred in 10% of gastric cancer patients using administrative data from New Zealand Cancer Registry."

The second point was a very important issue when we discovered different proportion of insulin user among the groups and analyzed the meaning of the findings. We also speculated the usage of insulin would be related with more advanced diabetes at the first time. However, the number of insulin user was bigger in the gastrectomy group than in the endoscopic resection group. In other words, patients who treated with gastrectomy could reduce more easily or even stop anti-diabetic medication, even though they had more advanced diabetes (more insulin user). Since we don't have any evidence to confirm about the severity or duration of diabetes, we cannot reach definite conclusion at this point. In addition, we cannot analyze the change of insulin dosage in the insulin users, because the KNHI database had all list and duration of whole prescription in Korea, except for the dose of each medication. However, considering all cases of possibility, the observation that more patients of gastrectomy used insulin than those of endoscopic resection did not compromise the meaning of more frequent cessation of anti-diabetic medications after gastrectomy.

Comment #4.

Are the patients with both DM and HTN are counted only once? (I guess so.) If so, this should be mentioned in the text. If the authors could not reach the BMI data, how could they decide that the patients were not obese? This question should be answered, as this is the core of the study that would make this study deserve publication

Author's reply #4.

As the reviewer mentioned, patients with both DM and HTN were counted once. Although we have no BMI data, the 100,000 patients of DM or HTN were randomly sampled out of Korean people and the average of BMI in Korean population was known to be low. There were many reports who describe the BMI of gastric cancer patients. From this reason, we suggested the study population were not obese. And To clarify this issue, we Added a sentence, “Our study population was randomly sampled from all diabetic or hypertensive patients in Korea, which suggests the average BMI of study population would reflect that of the Korean population” in DISCUSSION section.

Comment #5.

Other: Other spelling/grammar and editorial revision suggestions are directly made on the text.

Author's reply #5.

According to the reviewer's kind comments, we corrected some mistakes exactly.

SR2

Comment #1.

Did the selection of surgery strategy dependent on the severity of DM or HTN (i.e. patients with more severe DM or HTN may be more likely to undergo STG or ER than TG)?

Author's reply #1.

Surgical strategy was not controlled under any special intention. Numerous surgeons in Korea decided their surgical strategy on their own medical knowledge and current recommendations.

Comment #2.

The author stated that BMI information is not available. How is non-obese assessed in this study? No description of this was made in the methods section.

Author's reply #2.

Although we have no BMI data, the 100,000 patients of DM or HTN were randomly sampled out of Korean people and the average of BMI in Korean population was known to be low. From this reason, we suggested the study population were not obese. And there were many reports who describe the BMI of gastric cancer patients. To clarify this issue, we rewrite the sentence “**This observation suggested that TG might be beneficial for glycemic control in even non-obese diabetic patients, who randomly sampled from general population**” in DISCUSSION section.

Comment #3.

The multivariate analyses only adjusted for sex, age, and coexistence of each disease. Are there any information on severity of DM or HTN in the dataset? Any efforts made to control for the baseline status of DM/HTN?

Author's reply #3.

Unfortunately, the information on severity of the two diseases was not available. However, to overcome this limitation of database, we meticulously selected study populations who prescribed the medication for 6 months or more preceded before starting active treatment of gastric cancer, and tightly defined the discontinuation as no historical prescription for 6 months or more. From this reason, the disease severity of DM or HTN could be postulated from the number of anti-diabetic or anti-hypertensive medication; for example, the use of three or more medication could reflect more advanced disease status.

Comment #4.

Abstract: The abbreviation "DM" and "HTN" should be defined at the first use.

Author's reply #4.

According to the reviewer's kind opinion, we changed the phrase correctly.

Comment #5.

Introduction: What is the prevalence or incidence of DM and HTN among gastric cancer patients?

Author's reply #5.

Sarfati et al. reported the prevalence of diabetes 2.3-13.3% from New Zealand Cancer Registry (AJCO2014). In other similar studies, the prevalence of diabetes ranged in 5-10%. According to the reviewer's comment, we added the sentences in INTRODUCTION; "The prevalence of DM in patients with gastric cancer was not different from that in general population; Ogle et al. reported comorbid DM was 8% of patients with gastric cancer using data from National Cancer Institute Surveillance, Epidemiology, and End Results program and Sarfati et al. reported DM with complication occurred in 10% of gastric cancer patients using administrative data from New Zealand Cancer Registry."

Comment #6.

Methods: What is the rationale to randomly sample 100,000 subjects for each disease? Why not include all patients with DM/HTN in 2004? Since only 360 diabetic and 351 hypertensive patients were finally included.

Author's reply #6.

The study project was designed for the assessment of crosstalk between cancer and metabolic diseases. So, the linkage of two big administrative databases, Korea national cancer registry program and Korean national health insurance database was required. With the consideration of protection of private information and handling size of database, 100,000 patients were selected out of Korean population. In addition, actual number of diabetic and hypertensive patients were bigger, however, we chose only subjects who prescribed the medication at least six months subsequently, which was why the number of study population were smaller than

expected.

Comment #7.

Methods: The definition of early stage is ambiguous: what stage at diagnosis were included? Stage 0 and Stage I? Was the information of stage at diagnosis available from the dataset?

Author's reply #7.

The information of stage was not available, but patients in advanced stage of gastric cancer should undergo adjuvant chemotherapy according to current NCCN guideline. To exclude the subjects with that condition, patients who treated with chemotherapeutic agents or died in observational periods were excluded.

Comment #8.

Results: Consider to put the number of excluded subjects in the section of study population instead of the methods section.

Author's reply #8.

The number of excluded patients was also described in the part of Subject characteristics in RESULTS section.

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

Sincerely yours,

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