[2020-03-22]

**Title:** Prognosis factors of advanced gastric cancer according to sex and age

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Please find attached a revised version of our manuscript **"Prognosis factors of advanced gastric cancer according to sex and age."** which we would like to re-submit for consideration for publication as an original article in the *World Journal of Clinical Cases*
Your comments and those of the reviewer were highly insightful and enabled us to greatly improve the quality of our manuscript. We have provided our point-by-point responses to each comment of the Peer-reviewers . Revisions in the text are indicated in yellow highlight for additions and strikethrough for deletions.
We hope that the revisions in the manuscript and our accompanying responses are sufficient to make our manuscript suitable for publication in the *World Journal of Clinical Cases.*

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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**First Peer-Reviewer:**
   Nice work with low degree of novelty.

**Response :**
Thank you for your time in reviewing our study and we consider your comment to improve our project more.
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**Second Peer-Reviewer :**

   In the manuscript "Prognosis of advanced gastric cancer according to sex and age", the authors analyzed data from 2005 patients, found the prognostic factors varied according to sex and age，and older age independently predicted poor overall survival and relapse-free survival. The manuscript was well organized and provided some useful information.

**Response :**
Thank you for your taking the time to review our manuscript. We are also grateful for you insightful comments. We agree to your point and have made the necessary changes in the revised manuscript.

1- There were some mistakes in the manuscript. For example, "The mean tumour size was 6.3 ± 3.5 cm (range: 1–48 mm)", is it correct? The largest tumor size was 4.8cm? The same question in the table 1.

**Response:**

Yes, this is typing mistake. It is ( range: 1-48 cm ). And the smallest tumor is 1 cm while the larges tumor is 48 cm .
Same correction was made in table 1.

2- In discussion section, "These findings may be related to younger patients typically presenting with more advanced disease", is it younger or older?

**Response:**

Yes. These finding may be related to younger patients. Because most of younger patients with gastric adenocarcinoma have significantly higher incidences of diffuse-type tumor histologic findings and both locally advanced and metastatic disease at presentation.

Reference: **Smith BR**, Stabile BE. Extreme aggressiveness and lethality of gastric adenocarcinoma in the very young. *Arch Surg* 2009; **144**: 506–510 [DOI: 10.1001/archsurg.2009.77]

3- "The better outcomes among older patients may also be related to two factors", the same question, younger or older?

**Response :**

The better outcomes among advanced gastric cancer patients found to be better in elderly patients comparing to younger patients due to the elderly patients can not tolerate extensive lymphadenectomy (like D2 and D3) or standardised chemotherapy, so minimum lymphadenectomy usually enough in this group. And on the other hand, younger patient usually more tolerate the advanced chemotherapy management which is offered in advanced gastric cancer patients instead to go to surgery and lymphadenectomy.

**4-** The authors should further analyze that dividing patients by 60 has difference or not compare to 30 or 45, which could provide more information on age related OS or PFS.

**Response:**

we used an age cut-off at 60 years based on on recent studies and the new age subdivision suggested by the WHO considering ≤60 years as young patients and >60 years as elderly patient and we analyse our data according to this division. In our data analysis we found the most of patients age in young group is from 45-60 years. So we prefer to compare the whole group as 60 years and below to get better outcome for this study.

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**Third Peer Reviewer :**

This study investigated the prognosis factors of gastric cancer with a sample size of 2005 patients. A lot of previous studies have been investigated the factors, which associated with the prognosis of gastric cancer. The finding of this study was also similar to and validated those from previous studies.

**Response:**
Thank you for your taking the time to review our paper. We agree with your comments and revised our manuscript on the basis of your comments.

1. The title of the manuscript was suggested as "The Prognosis factors of gastric cancer according to sex and age".

**Response:**
Thank you for your suggestion about the title. We totally considering your point here and we adjusted the title to be " The Prognosis factors of gastric cancer according to sex and age".

2. there were some duplicate expression in the manuscript, for example, "with approximately 53.3% and 46.7% of the patients being ≤ 60 and > 60 years old" can be expressed as "with approximately 53.3% of the patients being ≤ 60 years old,".

**Response:**
we agree with your comment here and we made the changes in the main manuscript.

3. In materials and Methods, "Overall survival (OS) was defined as the time from tumour resection until death by any cause or the last follow-up", if the patients died of other reasons out of cancer, the data from these patients should be regarded as censored values.

**Response:**
Thank you for your point here, we actually put this issue in our concern during collecting data and we do our analysis according to the period and issues related to target disease.

4. There were many multple regression models (logistic and COX), which were used in the study. What's the confouding factors being adjusted?

**Response:**
In our study, we consider histological subtypes, depth of invasion level, lymphovascular and the size of tumor as factors which may affecting the result according to the patient age and gender.

5. The P value of "0.000" should be presented as " < 0.001".

**Response:**
The P value was corrected to "<0.001" in the main manuscript

6. In table 3 and 4, when analyzing the association of depth of invasion with survival, which group was set as reference?

**Response:**
we compare the result of those groups (Muscularis propria,MP, Sub-serosal,SS, Serosal invasion and Serosal exposing, SI and SE) to the Submucosal group which we found in our data. As the following tables

**Table 3: Multivariate analysis of factors influencing survival using a cox proportional hazards model (within each gender)**

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | **P value** | **HR** | **95.0% CI for HR** | | **P value** | **HR** | **95.0% CI for HR** | |
| MM or SM (EGC) | | 1.000 | | | | 1.000 | | |
| MP | **0.025** | 0.521 | 0.295 - | 0.920 | 0.736 | 1.220 | 0.385 - | 3.866 |
| SE | **0.039** | 0.551 | 0.314 - | 0.970 | 0.986 | 0.990 | 0.311 - | 3.147 |
| SI | 0.264 | 0.669 | 0.330 - | 1.354 | 0.653 | 0.693 | 0.140 - | 3.434 |
| SS | **0.044** | 0.565 | 0.324 - | 0.986 | 0.824 | 1.139 | 0.362 - | 3.587 |

HR= Hazards ratio, CI= confidence interval.

**Table 4: Multivariate analysis of factors influencing survival using a cox proportional hazards model (within each age group)**

| | Age ≤ 60 | | | | Age > 60 | | | |
|---|---|---|---|---|---|---|---|---|
| | **P value** | **HR** | **95.0% CI for HR** | | **P value** | **HR** | **95.0% CI for HR** | |
| MM or SM (EGC) | | 1.000 | | | | 1.000 | | |
| MP | 0.185 | 0.570 | 0.249 - | 1.308 | 0.371 | 0.746 | 0.392 - | 1.418 |
| SE | 0.214 | 0.594 | 0.262 - | 1.350 | 0.465 | 0.786 | 0.412 - | 1.500 |
| SI | 0.518 | 0.724 | 0.272 - | 1.929 | 0.549 | 0.765 | 0.318 - | 1.839 |
| SS | 0.280 | 0.638 | 0.283 - | 1.441 | 0.472 | 0.792 | 0.420 - | 1.495 |

HR= Hazards ratio, CI= confidence interv