Round 1

Editor in Chief
Monday, 18 April 2022

Dear Editor

We appreciate the constructive comments made by the reviewers and editor, our responses are as follows:
Reviewer #1:

1. *The introduction was short, and the relationship between the immune system and cancer could have been explained a little longer.*

We have added the contents, as suggested, it now reads: "

Helicobacter pylori, a spiral Gram-negative rod that infects and colonizes the human stomach in 50% of the human population, is a definite human oncogenic agent [11]. In addition, it has been suggested that *H. pylori* contributes to > 60% of all stomach cancers, although the precise underlying mechanisms are complex [12]. It has been well illustrated by the Nobel laureate Barry Marshal that chronic gastric ulceration is caused by *H. pylori* infection, which can be eliminated by a cocktail of antibiotics [13]. It has been reported that the constitutive levels of interleukin 32 (IL-32) in both the gastric mucosa and gastric cancer tissue is upregulated in *H. pylori*-infection [14]. Thus, it is reasonable to speculate that host immunity plays a critical role during the development of gastric cancer.

The cell-mediated immune response is extremely important in defence against tumour development, since compromised host immunity is known to contribute to the establishment, proliferation and metastasis of malignant tumours [15]. Although high host inflammatory status has been reported in the tumour microenvironment, an incompetent inflammatory/immune response will lead to tumour progression [16].

IL-31, an immunoregulatory cytokine secreted mainly by activated Th2 cells, plays a major role in the process of chronic inflammation [17]. However, the involvement of this IL-31 in the pathogenesis of cancer is unclear. Recent studies have shown that malignant T-cells produce IL-31, with an associated increase in serum levels of IL-31 [18]. Additionally, in the advanced stages of cutaneous T cell lymphoma, improved pruritus in patients correlates with lower levels of IL-31 [19].

IL-32, a proinflammatory cytokine, is highly produced in several autoimmune diseases, e.g. rheumatoid arthritis, inflammatory bowel disease and atopic dermatitis [20, 21]. However, by contrast with autoimmune and inflammatory diseases, the role of IL-32 appears to differ amongst different forms of cancer, e.g. IL-32 exhibits anti-tumour effects in human colon cancer and leukaemia [22, 23], however, it promotes tumorigenesis in human pancreatic cancers [24]. The role of IL-32 in GC is controversial, i.e. one study found that IL-32 expression is elevated in GC compared with normal stomach tissue [14], while another study reported that there is no significant difference between GC and normal stomach tissue [25]. The precise role of IL-32 in tumorigenesis of GC and other malignancies remains to be fully explored. An additional controversial finding, however, has also reported substantially reduced IL-32 expression in the GC tissue of patients with the diffuse type of GC [26]. These divergent observations concerning IL-32 expression in GC may be due to different races and/or different tumour micro-environments.

IL-33, a member of the IL-1 family, regulates innate and adaptive immunity as a potent inducer of pro-inflammatory cytokines. The involvement of IL-33 in non-small cell lung cancer is controversial, i.e. high IL-33 has been found to be of diagnostic and prognostic value [27], but another group has reported no significant associations [28]. The possible role IL-33 in GC remains to be explored. IL-33 promotes GC invasion and migration *via* stimulating production of MMP-3 and IL-6 *in vitro*, using the ST2-ERK1/2 pathway [29], which has been confirmed in a gastric cancer animal model by ablation of the cognate IL-33 receptor ST2 [30]. IL-33 mRNA expression is significantly higher in GC tissue compared to that of non-cancer tissue [31], suggesting that IL-33 promotes the development of GC. However, another controversial report failed to demonstrate an association between IL-33 and overall 5 year survival rate [32]. ”

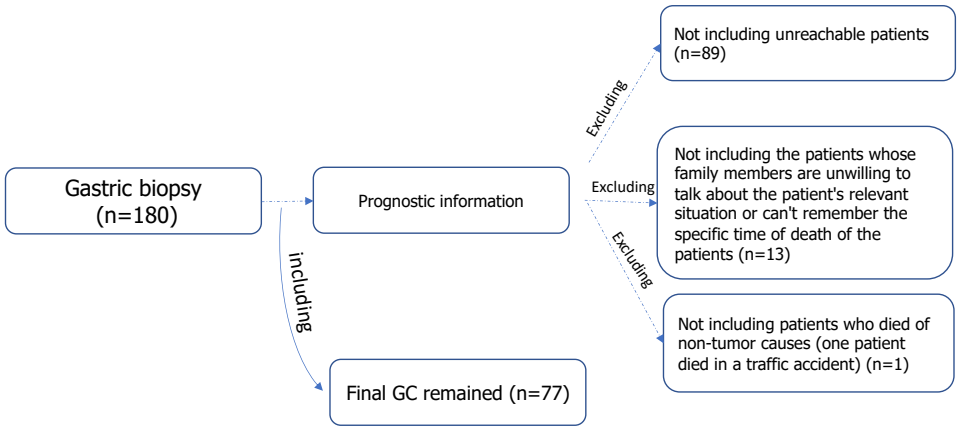
2. *Patients do not have treatment information, and these factors should be added as they are effective factors in prognosis.*
   To clarify this point, we have added the following sentence: “The management of patients after gastric resection uniformly followed Chinese guidelines for diagnosis and treatment of gastric cancer 2018, the National Health Commission of The People's Republic of China [36].
3. *Figures should be sequential in the text. The 'letters' on the figures are difficult to read, they should be corrected.*
   The Letters on the figures have been modified and arranged sequentially as well.

Reviewer #2:

1. *(P4L2-6) The "Patients and samples" section seems strange, which contains patients' characteristics. Those information should be described in the Results section.*
   This section has been moved to Results section accordingly.

2. *Figure 5 may cause confusing for readers. The position of arrows should be located not from "Prognostic information" but between "Cancer" and "Prognostic information". Furthermore, the information regarding "Non-cancer" biopsy should not be described at the same figure. I recommend it is described only in the text.*
   We have moved and modified the figure 5 accordingly, as below.

Figure 5



We have modified our manuscript accordingly and hope the quality of the manuscript meets the standard for publication in *World Journal of Gastrointestinal Oncology*.

Shisan Bao

Round 2

Thank you for revising the manuscript according to my suggestion. The revised manuscript is much improved. However, a following minor issue remains unresolved: 1. Information regarding "non-cancer" biopsy (159 samples) should be described in the main text.

Answer:

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Dear Dr Ma,

We appreciate the constructive comments made by the reviewers and our responses are as follows:

1. *Information regarding "non-cancer" biopsy (159 samples) should be described in the main text.*
   The information has been added in the manuscript accordingly, it now reads: "Non-cancer tissues were also collected (n=159), but did not include cases without a mucosal layer present under microscopic examination (n=21)" (Materials and Methods, page 7, para 1, line 7).
2. *Audio core tip: Maximum file size: 10 MB To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.*
   Audio core tip has been added
3. *The manuscript will require further language polishing, to fix all grammatical, syntactical, formatting and other related errors, in order to meet the publication requirement (Grade A). Now, you are requested to send the revised manuscript to a professional English language editing company or a native English-speaking expert to polish the language further. When you submit the subsequent polished manuscript to us, you must provide a language certificate along with it. Once this step is completed, your manuscript will be quickly accepted and published online.*
   We have modified our manuscript thoroughly with certification (see attached)
4. *Please don't include any *, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as $aP < 0.05$, $bP < 0.01$ ($P > 0.05$ usually does not need to be denoted). If there are other series of P values, $cP < 0.05$ and $dP < 0.01$ are used, and a third series of P values is expressed as $eP < 0.05$ and $fP < 0.01$.*
   We have modified these points accordingly.
5. *You need to provide the grant application form(s) or certificate of funding agency for every grant, or we will delete the part of "Supported by...This study was supported by grants from National Natural Science Foundation of China (NO. 81502030). SJTU research grant 2019, Sydney University. Liu was a recipient of a Travel Fellowship, Minster of Education, Jiangsu Province, China.".*
   We have attached a certificate for the *National Natural Science Foundation of China* (NO. 81502030) and removed the others.
6. *Please verify whether the supporting documents are consistent with the type and number of funds listed in the manuscript. If not, delete those without supporting documents.*
   We have modified these points accordingly.
7. *Figures must be presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3, etc.)*

We have modified these points accordingly.

8. *Please complete all the revisions based on the version of "1272-76064_Auto_Edited-v1", and upload above mentioned files in a ".zip" file.*
   We have uploaded the zipped file accordingly.

We hope our modification is sufficient for publication in World Journal of Gastrointestinal Oncology