Answering Reviewers

1. Reply and revision in response to the comments provided by Ma Li, Science Editor, Editorial Office Director,Company Editor in-Chief

(1) The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Answer: Thank you for your meticulous attention to the language requirements of the manuscript. Prior to submission, we engaged MedE Editing Service, a professional translation company, to refine the manuscript in accordance with your journal's specifications. We have included the editorial certificate within the manuscript file (Figure. 1).

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EDITORIAL CERTIFICATE
(Ref. NEMEDEATT-MS2023052211-A)

We herein certify that the following document has been edited for English language by a native English speaking medical editor at MedE Medical Editing Group. The edited paper has reached grade A in language evaluation for SCI journals.

Manuscript title
Synchronous occurrence of gastric cancer and gastrointestinal stromal tumor: A report of 19 cases and literature review

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MedE provides services of translation and English language editing in medical sciences, and training and guidance of medical writing, editing and publishing. Our team consists of senior native-English-speaking medical editors with M.D./Ph.D, bilingual medical editors with over 20 years of experience, and translators with medical background and a good command of English.

Figure 1: the editorial certificate

(2) Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Answer: We greatly appreciate your valuable suggestions. We conducted an extensive search, meticulously organized, and thoroughly analyzed the existing research in the field of gastric cancer combined with gastrointestinal stromal tumor to enhance the manuscript's content. Due to the predominance of case reports in studies on gastric cancer complicated by

gastrointestinal stromal tumors, limited relevant data are available. We collected the latest research as follows, and kept a trace of revisions in the manuscript:

a: Liu Z, Liu S, Zheng G, Yang J, Hong L, Sun L, Fan D, Zhang H, Feng F. Clinicopathological features and prognosis of coexistence of gastric gastrointestinal stromal tumor and gastric cancer. Medicine (Baltimore). 2016 Nov;95(45):e5373. doi: 10.1097/MD.0000000000005373. PMID: 27828865; PMCID: PMC5106071.

b: Xu H, Zhou S, Hu Q, Cao D. Apatinib treatment for unresectable gastrointestinal stromal tumor with synchronous gastric cancer. Precis Clin Med. 2020 Mar;3(1):67-70. doi: 10.1093/pcmedi/pbaa005. Epub 2020 Feb 18. PMID: 35693429; PMCID: PMC8985806.

c: Liu XL, Wang JB, Huang CM, Zheng CH, Li P, Xie JW, Lin JX. [Clinicopathologic features and prognostic factors of gastric gastrointestinal stromal tumor with synchronous gastric cancer]. Zhonghua Wei Chang Wai Ke Za Zhi. 2012 Mar;15(3):247-50. Chinese. PMID: 22454170.

The Supplementary content is summarized as follows:

a: Liu et al. conducted a retrospective analysis on 24 patients diagnosed with gastric cancer combined with GISTs. The findings revealed that the occurrence of GIST combined with gastric cancer was more prevalent among elderly male patients, while GIST predominantly exhibited low-risk characteristics. Similarly, Liu et al. conducted an analysis on 26 patients diagnosed with gastric cancer and GISTs, revealing that the Fletcher classification typically indicates a very low or low risk of invasion in patients with GIST and gastric cancer.

b: Xu et al. demonstrated that apatinib exhibits promising therapeutic potential and tolerability in patients with gastric cancer complicated by GISTs who have shown resistance to IM in combination with chemotherapy.

c: Liu et al. conducted a comparative analysis between gastric cancer patients with GIST (n = 24) and gastric GIST patients (n = 217), revealing significantly lower 5-year disease-free survival rate and disease-specific survival rate in the former group compared to the non-synchronous group (54.9% vs 93.5%, $P < 0.001$; 37.9% vs 89.9%, $P < 0.001$). Similarly, Liu et al. conducted an analysis on a cohort of 26 patients with synchronous gastric cancer (group A) and 96 patients with gastric GIST (group B). The findings revealed that the Fletcher classification ($P < 0.05$) and synchronous gastric cancer ($P < 0.01$) were identified as independent prognostic factors.

(3) Authors are advised to apply a new tool, the Reference Citation Analysis (RCA).

Answer: We performed a reference citation analysis (RCA) of all references cited in the manuscript. Detailed details are provided in the "References" section. If there are any problems that need to be corrected, please feel free to contact us. Thank you very much!

(4) Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...;F: ...; G: ...".

Answer: Thank you for your valuable advice. We have standardized and unified the expression of the pictures in the manuscript. Please feel free to contact us if you need to modify anything. Thank you!

(5) Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original',

the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Answer: Firstly, we standardized and harmonized the images in the manuscript. Secondly, we submitted all images in PowerPoint format, allowing for easy editing and modification. Thirdly, all images included in the manuscript are original, with copyright information clearly marked in the lower right corner of each image. If any issues arise regarding these modifications, please do not hesitate to contact us; we will promptly make necessary adjustments. Thank you for your invaluable support!

2. Reply and amendment to Professor Omar J Shah:

(1) The genetic and molecular mechanisms of carcinogenesis and progression needs strong attention. The authors should consider adding a cascade table accordingly and also include recent studies of such kind in the discussion.

Answer: We sincerely appreciate your valuable feedback. In response, we have carefully addressed and incorporated the suggested modifications as follows:

The etiological mechanism underlying the co-occurrence of gastric cancer and GIST remains elusive. Although most existing studies are primarily comprised of case reports, they represent an exploratory stage in understanding the etiology. As emphasized by Professor Omar J Shah, it is imperative to focus on genetic and molecular biology mechanisms. Consequently, we have comprehensively summarized and discussed the etiological mechanism of gastric cancer complicated with GIST in the dedicated discussion section of this manuscript (paragraph 6). We posit that the majority of cancers arise from the interplay between genetic and environmental factors[1-3]. Similarly, it has been postulated by certain scholars that gastric cancer complicated with GIST may be attributed to unidentified carcinogens, such as nitrite and Helicobacter pylori, which induce concurrent proliferation of epithelial cells and stromal cells leading to tumorigenesis[4-8]. Leveraging next-generation sequencing technology, Liu et al.[9] identified significant molecular-level gene mutations distinguishing gastric cancer from GIST, primarily involving TP53 and KIT gene mutations.

Regarding the tables, we have included three tables in our manuscript, out of which two present original data from our unit and are recommended to be incorporated as primary tables within the text. The third table provides a comprehensive summary of global research findings on gastric cancer combined with GIST. Due to its extensive content, we propose utilizing it as supplementary information for readers' reference.

References

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2. Le Marchand L. The Predominance of the Environment over Genes in Cancer Causation: Implications for Genetic Epidemiology. Cancer Epidemiol Biomarkers Prev (2005) 14(5):1037-9. doi: 10.1158/1055-9965.Epi-04-0816.
3. Wade L. The Environment in Relation to Cancer. Arch Environ Health (1963) 7:172-8. doi: 10.1080/00039896.1963.10663509.

4 Maiorana A, Fante R, Maria Cesinaro A, Adriana Fano R. Synchronous occurrence of epithelial and stromal tumors in the stomach: a report of 6 cases. Arch Pathol Lab Med. 2000: 682 [PMID: 10782147 10.5858/2000-124-0682-sooeas: 10.5858/2000-124-0682-sooeas]
5 Bircan S, Candir O, Aydin S, Başpinar S, Bülbül M, Kapucuoğlu N, Karahan N, Ciriş M. Synchronous primary adenocarcinoma and gastrointestinal stromal tumor in the stomach: a report of two cases. Turk J Gastroenterol. 2004: 187 [PMID: 15492920
6 Lin YL, Tzeng JE, Wei CK, Lin CW. Small gastrointestinal stromal tumor concomitant with early gastric cancer: a case report. World J Gastroenterol. 2006: 815 [PMID: 16521203 10.3748/wjg.v12.i5.815: 10.3748/wjg.v12.i5.815]
7 Liu S, Liu H, Dong Y, Wang F, Wang H, Chen J. Gastric carcinoma with a gastrointestinal stromal tumor - A case report and literature review. Med Sci (Paris). 2018: 15 [PMID: 30403169 10.1051/medsci/201834f103: 10.1051/medsci/201834f103]
8 Wronski M, Ziarkiewicz-Wroblewska B, Gornicka B, Cebulski W, Slodkowski M, Wasiutynski A, Krasnodebski IW. Synchronous occurrence of gastrointestinal stromal tumors and other primary gastrointestinal neoplasms. World J Gastroenterol. 2006: 5360 [PMID: 16981268 10.3748/wjg.v12.i33.5360: 10.3748/wjg.v12.i33.5360]
9 Liu S, Liu H, Dong Y, Wang F, Wang H, Chen J. Gastric carcinoma with a gastrointestinal stromal tumor - A case report and literature review. Med Sci (Paris). 2018: 15 [PMID: 30403169 10.1051/medsci/201834f103: 10.1051/medsci/201834f103]

3. Reply and amendment to the reviewer 1:
(1) In the section "Chief complaints" clarify the symptoms of acid reflux: heartburn, eructation, etc.

Answer: Thank you sincerely for your invaluable guidance. After a thorough examination of our primary materials and data, we have incorporated the symptoms associated with acid reflux, such as heartburn and belching, into the "Chief complaints" section.
(2) Please clarify the name of tumor markers what you determined.

Answer: The tumor markers for each patient have been included in Table 1 and detailed in the "Laboratory examinations" section of the manuscript.
(3) Please specify the hemoglobin rate in patients with anemia.

Answer: Six patients(32%) with anemia (hemoglobin: No.1= 108g/L; No.7=102g/L; No.8=124g/L; No.10=129g/L; No.11=119g/L; No.17=88g/L).
(4) Please include information about percentage of patients with Helicobacter pylori infection.

Answer: Your valuable comments are highly appreciated, and we acknowledge the significance of obtaining data on H. pylori infection. However, regrettably, our study was a retrospective analysis covering the period from December 2010 to December 2020. We meticulously reviewed the medical records but found no available data pertaining to H. pylori infection. In future investigations, we will diligently focus on detecting Helicobacter pylori infection in gastric cancer patients with gastrointestinal stromal tumors (GIST).

4. Reply and amendment to the reviewer 2:
(1)The authors stated that it is possible that the incidence of GC simultaneou sly occurring with GIST is higher because most GISTs are small and it is easy to miss diagnosis. But is this argument only due to the small size of the tumor? I would think that 1~2cm SMT would be noticed to some extent by endoscopy.

Answer: Thank you for your inquiry. I will provide an explanation to address your questions comprehensively, focusing on three key aspects:

1)Firstly, our analysis encompasses a comprehensive review of medical records from our unit as well as reported cases worldwide. Notably, extensive research indicates that the majority of gastrointestinal stromal tumors (GISG) exhibit diminutive sizes (68%≤2 cm). Consequently, their detection through preoperative examinations generally poses significant challenges.

2) Furthermore, empirical research has indeed demonstrated a low preoperative diagnostic rate of gastrointestinal stromal tumors (GIST) when they coexist with gastric cancer [1-2]. In a study conducted by Liu et al.[2], patients with synchronous gastric gastrointestinal stromal tumor (GIST) complicated with gastric cancer were compared to GIST patients without gastric cancer. The results demonstrated that the mean tumor diameter of gastric GIST in the former group was significantly smaller ($P < 0.01$), and the rate of preoperative diagnosis was considerably lower (23.1% vs. 97.9%, $P < 0.01$).

3) Gastrointestinal Stromal Tumors (GISTs) are a type of neoplasm originating from the mesenchymal tissue within the gastrointestinal tract. Gastroscopy is considered the gold standard for detecting GISTs; however, patients with gastric cancer complicated by GIST often undergo conventional gastroscopy instead of ultrasonic gastroscopy due to uncertainty regarding the presence of GIST. Endoscopic ultrasound (EUS) surpasses conventional gastroscopy in diagnosing mesenchymal tissue-related GISTs.

4) We highly value your suggestion and acknowledge that, apart from the aforementioned reasons, there are indeed other factors contributing to the low preoperative diagnosis rate of GIST. Given that patients with gastric cancer combined with GIST primarily seek medical attention due to symptoms related to gastric cancer, it is possible for some clinicians to prioritize the diagnosis of gastric cancer while overlooking the diagnosis of GIST.

5) As noted by the reviewer, some GISTs are extraluminal and difficult to detect during gastroscopy.

References

1. Liu YJ, Yang Z, Hao LS, Xia L, Jia QB, Wu XT. Synchronous incidental gastrointestinal stromal and epithelial malignant tumors. World J Gastroenterol. 2009: 2027 [PMID: 19399938 10.3748/wjg.15.2027: 10.3748/wjg.15.2027]
2. Liu XL, Wang JB, Huang CM, Zheng CH, Li P, Xie JW, Lin JX. [Clinicopathologic features and prognostic factors of gastric gastrointestinal stromal tumor with synchronous gastric cancer]. Zhonghua Wei Chang Wai Ke Za Zhi. 2012 Mar;15(3):247-50. Chinese. PMID: 22454170.

(2) The authors stated that the occurrence of GIST might have an inhibitory effect on the progression of GC. I am not sure of the rationale for this. Is this some kind of statistical difference? I think you should explain the evidence so that we can understand it. Overall, the data are preliminary and do not fully support the conclusions that have been drawn.

Answer: The suggestions proposed by the reviewers are of great significance, and we have thoroughly considered them. Consequently, we have made substantial adjustments and revisions to both the content and conclusion of the manuscript.

Currently, the research on gastric cancer combined with GIST is predominantly limited to case reports worldwide, which is uncommon in clinical practice and lacks comprehensive investigation into molecular biological mechanisms. Based on our unit's data results and in conjunction with relevant global research findings, we deduce that: Gastric cancer typically manifests in the lower third of the stomach (42%), at stage I (42%), exhibiting poor differentiation (42%) and intestinal adenocarcinoma histology (51%). Considering that stage 1 gastric cancers account for the majority (42%) of cases, we initially hypothesized a potential inhibitory effect of GIST on gastric cancer progression. However, after careful consideration of the reviewers' suggestions, we acknowledge that making conjectures based on limited data is not scientifically sound. Therefore, we have provided additional supporting evidence to strengthen our hypotheses: However, this conjecture is solely based on the findings of pertinent global research due to limited case numbers and a dearth of molecular biological mechanism investigations, thereby insufficiently substantiating this conclusion.

(3) What was the background of H. pylori infection in this study? What is the relationship with the history of eradication, including references?

Answer: We express our gratitude to the commenters for their highly nuanced inquiries. We meticulously examined the pertinent references cited in our manuscript, which unequivocally substantiate numerous studies elucidating the etiological mechanism underlying the co-occurrence of gastric cancer and GIST. Some researchers believe that it is an accidental phenomenon, and others believe that several unknown carcinogens induce simultaneous proliferation and tumorigenesis of epithelial and stromal cells, such as gene mutation, nitrite, and Helicobacter pylori. The relevant references are in the manuscript [6, 7, 9-11, 18, 30, 34, 37, 38, 47-50].

Unfortunately, almost all the references only reported cases of gastric cancer with GIST. In the etiological analysis, the authors employ the terms 'postulate' and 'potentially,' indicating that H. pylori could potentially function as an environmental factor by stimulating both epithelial and stromal cells, thereby potentially contributing to the concurrent occurrence and progression of gastric cancer and GIST. The reviewer's inquiry will be addressed as a focal point in our future research endeavors, with the aim of obtaining conclusive results.

(4)The authors stated that there may be mutual inhibition between GC and GIST in the pathogenesis and progression. If you state it this way, I still think w e need more pathological studies, etc. Shouldn't there be a comparison with pa thological studies of cases treated for GIST alone at the same time? Also, the re are mixed GIST cases other than intragastric cases, but do you interpret th is way including all of them? In general, I think the evidence is lacking.

Answer: We greatly appreciate your valuable feedback. In the subsequent sections, we will provide a comprehensive explanation from the following perspectives.

1) The occurrence of gastric cancer complicated with gastrointestinal stromal tumor is infrequent in clinical practice. Our retrospective analysis was limited to a small sample size of 19 patients, and there is a dearth of supportive data and pathological investigations, which represents a constraint in our study. In future endeavors, we aim to enhance our research methodology and delve deeper into this subject matter to yield more conclusive outcomes.

2) Our study focuses on the clinicopathological features, diagnosis, treatment, and prognosis of gastric cancer with gastrointestinal stromal tumors (GIST). Given the compelling

evidence that clinical symptoms, diagnosis, treatment, and prognosis in cases of simultaneous occurrence of gastric cancer and GIST are primarily influenced by gastric cancer itself, our research aims to investigate the impact of GIST on the development and progression of gastric cancer as well as elucidate their unique correlation. The comparative analysis between GIST patients and gastric cancer patients with GIST holds significant value in the field. However, existing studies have consistently demonstrated that the prognosis of gastric cancer patients with GIST is generally inferior to that of standalone GIST patients, a finding rarely disputed due to the predominant influence of gastric cancer on treatment decisions and overall prognosis. Furthermore, the incidence of gastric cancer combined with GIST in our unit is relatively low. Due to significant differences in the number of cases and controls when comparing and analyzing GIST patients, drawing a conclusive result remains controversial. Therefore, we have chosen to present this study as a case report rather than an article. Nevertheless, we acknowledge the value of conducting case-control studies and prospective studies by continuously accumulating data in future stages.

Round 2

Specific Comments To Authors: Some minor details need to be further clarified before this work could be accepted for publication. The authors answer many questions, but the quality of the data is not good. Based on the content, the LIMITATION should be more carefully described.

Dear editor and reviewers. Thanks very much for your kind work and consideration on our paper. On behalf of my co-authors, we would like to express our great appreciation to editor and reviewers. We would like to express our sincere gratitude to you and the reviewers for your valuable comments. We have taken great care in addressing the " LIMITATION" and have incorporated visible traces of modifications in the manuscript." The modified file is attached as a zip package to the mailbox attachment. The details of our modifications to " LIMITATION " are as follows: Our study had some limitations. Firstly, the research data quality could be better, with a limited number of cases (19 cases) and insufficient pathological research data. Additionally, more comprehensive test results and genetic and molecular data must be needed to support statistically significant conclusions based on limited information. Methodologically, this study is a retrospective single-centre investigation lacking prospective and case-control studies (including patients with superficial gastric cancer and Simple GIST patients) and molecular biological mechanism exploration. Regarding the study's content, an in-depth investigation of H. pylori was not conducted. Consequently, this study remains at a preliminary stage of exploration. This study concludes that further investigations are required to validate and supplement the conjecture. The future research will require enhancements in data quality, research methods, and a deeper exploration of the content. If any issues arise regarding these modifications, please do not hesitate to contact us; we will promptly make necessary adjustments. Thank you for your invaluable support! Thank you and best regards. Yours sincerely, Yumin Li Jie Liu