

REPLY TO REVIEWERS

REVIEWER #1

Thank you very much for your kind suggestions, which substantially improve the quality and readability of our manuscript.

1) We have shortened the title and changed the proposed citation.

2) Abstract:

- We have shortened the methods section.
- “Cost-effective strategy”: as we have stated in the results/conclusions sections, our risk scores successfully predicted patient survival, and the features that we included in these scores are easily available in clinical practice. To calculate our scores it is sufficient to perform a conventional histological study, and they do not need complementary tests. For this reason, the use of our prognostic scores for predicting prognosis in gastric cancer can be considered a cost-effective strategy.

3) Introduction:

- We have changed the sentence.

4) Methods

- We have deleted the numbers in parentheses in the Immunohistochemical study and the Inclusion criteria sections. We have included these data in the Results section.

5) Results

- We have calculated and specified the mean follow-up of our study.
- We have simplified and grouped Supplementary Tables 2 and 3. We have tried to group Table 1 and Supplementary Table 1, but the resulting table was too long and confusing.
- Supplementary tables are cited in the results section, and we have included them as a separate word file.
- Supplementary figures 1 and 2 have been added and included in the separate word file “Supplementary material”.

6) Discussion

- We have summarized the conclusions of our review article. On the other hand, this article is an original study, and not a continuation of the previous article, which is a review of the literature on the new roles of Laurén classification in gastric cancer.

7) Neoadjuvant therapy

Neoadjuvant therapy has gained acceptance for gastric cancer, but evidence is not as solid as it is for other solid tumors (esophagus or rectum), and in our practice it is not widely used for these patients. A meta-analysis published in the World J Gastroenterol concluded that the evidence was not enough to recommend neoadjuvant therapy in gastric carcinoma as few clinical trials have been made (World Journal of Gastroenterology, 2018;24:274-289). Since then, several clinical trials have been published, but most of them have been carried out in the Eastern countries, where gastric cancer is fairly different from western countries. A recent clinical trial by Iwasaki et al (Gastric Cancer, 2021; 24: 492-502) has failed to show the survival benefit of neoadjuvant therapy over surgery with D2 lymph node dissection. Thus, we feel that this issue is still far from settled and many hospitals still prefer surgery over neoadjuvant therapy in gastric cancer. Despite this, even in the context of neoadjuvant therapy, our article shows significant differences between patients with intestinal and diffuse-type tumors and highlights the usefulness of developing specific prognostic scores for these patients.

REVIEWER #2

Thank you very much for your review.

We have extensively studied the role of lymph node dissection, lymph node ratio, and other methods for assessing lymph node metastases in gastric cancer in previous studies. We support your suggestion: lymph node ratio, which takes into account the number of lymph nodes dissected, has been found to be a better prognosticator than the traditional N stage or location-based staging systems for patients with gastric cancer.

In this study, we have included the type of lymphadenectomy in the Supplementary Table 1. However, as reported by other authors, the type of lymphadenectomy was not specified in an important number of patients (55%). These authors stated that the number of examined lymph nodes can be used as a surrogate marker of the quality /extent of lymph node dissection. Thus, as you have suggested, we have included the average number of lymph nodes examined and the average number of metastatic lymph nodes in this table (Supplementary Table 1).

We have also evaluated the differences in the number of lymph nodes dissected and the number of metastatic lymph nodes between Laurén subtypes; we found no significant differences in the number of lymph nodes dissected between these subtypes ($p=0.483$). We found significant differences in the number of metastatic lymph nodes between intestinal and diffuse-type gastric cancer, and we have included this information in Table 1.

In addition, due to the importance of the number of lymph nodes dissected, we included lymph node ratio (the ratio of metastatic lymph nodes vs examined lymph nodes) in our risk factor analysis. In fact, as you have stated, lymph node ratio was an important risk factor for both intestinal and diffuse-type GC, and it was included in our prognostic scores, because it resulted to be superior to N stage in predicting patient prognosis.

In summary, the number of lymph nodes dissected is included in the lymph node ratio, which we included in our risk factor analysis and prognostic scores.

REVIEWER #3

Thank you very much for your kind suggestions.

1) We have shortened the conclusions section. We have also shortened the Abstract and simplified and combined Supplementary Tables 2 and 3, in order to reduce the number of Tables and improve readability.

2) Validation of our scores

- In this study, we have proposed prognostic scores for patients with intestinal and diffuse-type gastric cancer. Our specific aims were to 1) evaluate the clinicopathological differences between Laurén subtypes; to 2) identify specific risk factors for these subtypes; and 3) to propose prognostic scores and to perform an internal validation and assessment of these scores. As we have stated in the conclusion section, additional external validation studies should be performed. Based on the current knowledge of gastric cancer, we believe that validation studies should be performed in other populations, due to the differences reported between geographical areas in gastric cancer (western / eastern). Besides that, we are trying to

collaborate with other hospitals in order to recruit a large enough population of patients to externally validate our results.

REPLY TO THE EDITORIAL MEMBERS

Language polishing: an English-speaking expert has performed language polishing.

Changes have been made.

Tables: we have modified the tables.

Figures: figures are original. We have included the copyright statement on the right bottom of the pictures.