Point by point responses to each of the issues raised in the peer-review report:

Reviewer #1:
Specific Comments to Authors:

1: "The innate immunity introduced by the authors is mostly associated with gastric pathogens such as HP infection and EBV infection, while the authors mention molecular and genotyping of gastric cancer into four types, is innate immunity associated with other types of gastric cancer? What are its possible mechanisms? Can you add to this section?"

R: Thank you for this comment. During the transition from premalignant lesions of the gastric epithelium to the final carcinoma, some microorganisms will play a determinant role promoting the neoplastic transformation or contributing with particular tumor phenotypes. It is very well documented that GC is strongly associated with infectious agents such as the bacterium *Helicobacter pylori (H. pylori)* and the Epstein-Barr virus (EBV).

On the other hand, recent observations have suggested that some intrinsic host factors, like the genetic background, may be secondary to external or environmental aspects during GC onset. Taking all this together, we could hypothesize that host`s innate immunity is not only associated but also contributes in shaping the tumor phenotype and its heterogeneity, together with different microorganisms, mutagenic agents and genomic aberrations.

Approximately 15–20% of human cancers are provoked by cancer-causing viruses; and at least 9% of GC are caused by EBV; however, the specific role of EBV in GC development is not clear yet.

Some aspects of the mechanisms have been illustrated (Figure 1).

We have added to the section, in the following parts of the manuscrit:

- Lines 65 - 74
- Lines 86 - 96
- Lines 583 - 598

2: "Immunotherapy seems to be less effective in the treatment of gastric cancer at present, what is the future of immunotherapy in the treatment of gastric cancer?"

R: We appreciated this comment, thank you. The overall immunogenicity of gastric carcinoma is relatively weak and the immune treatment efficiency is quite limited in GC. Therefore, treatment with an immune checkpoint inhibitor is applicable for only

a restrictive group of these patients, such as those with a gastric tumor subtype positive for the EB virus.

We have added the following text into the manuscrit:

- Lines 361 - 364
- Lines 369 - 374
- Lines 388 - 414
- Lines 444 - 452
- Lines 454 - 480
- Lines 491 - 502
- Lines 622 - 624

3: "Table 2 lists the countries with high incidence of gastric cancer, besides developing countries, there are also developed countries such as Japan and Korea, so does academic qualification affect the incidence of gastric cancer in these two countries? Please add the relevant analysis."

R: Thank you for this comment. We have updated the table 2 and added the following text into the manuscrit:

- Lines 56 - 59
- Lines 558 - 574

4: "Table I lists the expression of TOLL-like receptors in the gastric mucosa in the context of esophageal cancer, so is the innate immunity of the stomach affected by esophageal cancer?"

R: Thank you for this comment. We have updated the table 1 and added the following text into the manuscrit:

- Lines 148 - 159

Reviewer #2:
Specific Comments to Authors:

"This paper explored innate immune activation in the context of premalignant lesions of the gastric epithelium and established gastric tumors. The author thinks that Innate immunity is the beginning, and certainly, will be part of the final response against tumors. The article is well organized and logical, mainly focusing on the innate immunity mechanism of gastric mucosa induced by Helicobacter pylori and Epstein-Barr virus infection. It is of great significance for the prevention and treatment of gastric cancer. Although detailed, some aspects of the mechanism

are better illustrated graphically."

R: We appreciated this comment, thank you. An illustrated figure has been added to the article (Figure 1).

Reviewer #3:
Specific Comments to Authors: "This manuscript is perfectly written"

Reviewer #4:
Specific Comments to Authors:

"The Manuscript ID 80199 by Franz Villarroel-Espindola and Co-workers studied the review article Intersections between innate immune response and gastric cancer development. The title of the proposed work suits the Aims and scope of the Journal in a great extent and therefore can be taken into consideration for publication in the World Journal of Gastroenterology after incorporating the following corrections. Remarks:"

1. "Firstly, Please elaborate the introduction"

R: We appreciated this comment, thank you.We have added the following text into the introduction section of the manuscrit:

- Lines 56 - 59
- Lines 65 - 74
- Lines 86 - 96
- Lines 112 - 120

2. "This is a review article, add a figure to it."

R: Thank you for this comment. An illustrated figure has been added to the article (Figure 1).

3. "Add new references in the introduction part. (i) Curtale, G. (2018). MiRNAs at the crossroads between innate immunity and cancer: focus on macrophages. Cells, 7(2), 12. (ii) Sabry, M., & Lowdell, M. W. (2020). Killers at the crossroads: The use of innate immune cells in adoptive cellular therapy of cancer. Stem Cells Translational Medicine, 9(9), 974-984. (iii) Miao, L., Qi, J., Zhao, Q. I., Wu, Q. N., Wei, D. L., Wei, X. L., ... & Xu, R. H. (2020). Targeting the STING pathway in tumor-associated macrophages regulates innate immune sensing of gastric cancer cells. Theranostics, 10(2), 498. (iv) Kanaoujiya, R., Porwal, D., & Srivastava, S. (2022). Applications of nanomaterials for gastrointestinal tumors: A review. Frontiers in Medical

Technology, 4,997123. (v) Kanaoujiya, R., Saroj, S. K., Srivastava, S., & Chaudhary, M. K. (2022). Renewable Polysaccharide and Biomedical Application of Nanomaterials. Journal of Nanomaterials, Article ID 1050211,16. (vi) Deng, R., Zuo, C., Li, Y., Xue, B., Xun, Z., Guo, Y., ... & Zhu, H. (2020). The innate immune effector ISG12a promotes cancer immunity by suppressing the canonical Wnt/β-catenin signaling pathway. Cellular & molecular immunology, 17(11), 1163-1179."

R: We really appreciate this suggestion from the reviewer, we have added some of the recommended references in the article. Also, we have added a new section into the article:

- Lines 244 - 297

4. "Please elaborate the conclusion part."

R: Thank you for this comment. We have added the following text into the conclusion section of the manuscrit:

- Lines 583 - 598
- Lines 622 - 624