Response to the reviewer 2

Dear Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Development and validation of nomogram for predicting pathological complete response to neoadjuvant chemotherapy and immunotherapy for locally advanced gastric cancer: A multicenter real-world study in China" (Manuscript ID: 1603196). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red and blue in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Comment of the reviewer 2: The authors of this manuscript try to retrospectively evaluate a nomogram that can predict the pCR response to chemoimmunotherapeutic treatment of patients with gastric cancer. The work is methodologically well conducted; the results are convincing but do not adequately clarify the weight of immunotherapy treatment in determining complete response and given the short follow-up it is not even possible to provide indications on the prognostic role and on the potential implications on the surgical choices of patients who could potentially obtain a complete response. Highlighting these aspects in the discussion would add significant value and depth to the manuscript. Regarding the readability of the tables, refining their graphics to enhance clarity is a practical and necessary improvement.

Response to the reviewer: We sincerely appreciate your thoughtful comments and constructive criticism, which have helped us to further refine and strengthen our manuscript.

Weight of Immunotherapy in Complete Response: We acknowledge your insightful point regarding the need to better elucidate the specific contribution of immunotherapy to the observed complete responses. While our study demonstrates the predictive value of the nomogram for pCR following NICT, it is inherently limited in its ability to isolate the independent effect of immunotherapy from the combined chemo-immunotherapy regimen.

However, our study is specifically designed to predict pCR after NICT based on preoperative laboratory tests and imaging examination indicators. We aim to develop a predictive tool that can be used before surgery to identify patients who are more likely to achieve pCR after neoadjuvant chemotherapy and immunotherapy. Regarding your concern about "insufficient clarification of the weight of immunotherapy in determining complete response," we have previously conducted thorough research, as demonstrated in our meta-analysis, PD-1 inhibitor combined with neoadjuvant chemotherapy (NCT) significantly improves the likelihood of achieving radical surgery and prognosis in LAGC patients. Specifically, the NICT group exhibited significantly higher rates of pCR ($P < 0.001$) and R0 resection ($P = 0.001$), alongside a notably lower 2-year recurrence rate ($P = 0.001$) compared to the NCT group[1]. Moreover, we have now emphasized in the revised discussion that Multiple clinical trials, including CheckMate-649, ORIENT-16, RATIONALE-305, and KEYNOTE-585, have confirmed that PD-1/PD-L1 inhibitors combined with chemotherapy can significantly improve the pCR rate and prolong survival in patients with advanced gastric cancer[2-5]. the addition of immunotherapy to neoadjuvant chemotherapy represents a significant paradigm shift in the treatment of locally advanced gastric cancer. We agree that future prospective randomized trials comparing chemo-immunotherapy to chemotherapy alone are urgently needed to

definitively establish the incremental benefit of immunotherapy in this context. The modifications we made in the discussion are shown in the following figure.

In recent years, immunotherapy has progressively revolutionized the therapeutic landscape of gastric cancer, demonstrating a paradigm shift from third-line to first-line settings (8,9,41). Immunotherapy has now become a standard treatment for advanced gastric cancer, and its application in the perioperative setting is being actively explored in multiple countries (42-43). The potential benefits of immunotherapy in the perioperative management of gastric cancer are likely mediated by several mechanisms: (1) Neoadjuvant immunotherapy reactivates tissue-resident memory CD8+ T cells, promoting their expansion and diversification (44-45). (2) Following resection of the primary tumor, circulating tumor-specific CD8+ T cells persist, potentially enhancing T cell infiltration in residual micrometastatic sites and broadening the spectrum of tumor-specific T cell responses. (3) Preclinical studies have demonstrated that eradication of tumor cells can establish tumor-specific CD8+ T cell memory, conferring long-term survival advantages (45). Consequently, the integration of immunotherapy during perioperative treatment may yield clinical benefits for patients (46). As demonstrated in our meta-analysis, PD-1 inhibitor combined with neoadjuvant chemotherapy (NCT) significantly improves the likelihood of achieving radical surgery and prognosis in LAGC patients. Specifically, the NICT group exhibited significantly higher rates of pCR ($P < 0.001$) and R0 resection ($P = 0.001$), alongside a notably lower 2-year recurrence rate ($P = 0.001$) compared to the NCT group(47). At the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI), the pivotal phase III KEYNOTE-585 trial(9)—a randomized, double-blind study of neoadjuvant immunotherapy for gastric cancer—reported a statistically significant pCR improvement with pembrolizumab plus FLOT versus placebo plus FLOT (14% vs. 6.8%, $P < 0.05$). Subsequently, at the 2025 ASCO Annual Meeting, the MATTERHORN study(48)—the first phase III trial to demonstrate positive perioperative immunotherapy outcomes in gastric cancer—showed a significantly higher pCR rate with durvalumab plus FLOT compared to placebo plus FLOT (19% vs. 7%, $P < 0.001$). These landmark studies collectively demonstrate the efficacy of neoadjuvant immunotherapy combined with chemotherapy for LAGC, establishing a robust foundation for the future development of perioperative treatment paradigms in gastric cancer and offering renewed hope for long-term survival benefits in LAGC patients.↵

Short Follow-up and Prognostic Role: We fully concur with you that the relatively short follow-up period in our study limits our ability to draw definitive conclusions about the prognostic significance of pCR and its implications for surgical decision-making. While pCR is a well-established early indicator of treatment efficacy, the durability of this response and its correlation with long-term survival endpoints like overall survival (OS) and disease-free survival (DFS) require longer-term follow-up. We have now explicitly acknowledged this limitation in the discussion and emphasized the need for extended follow-up to confirm the prognostic value of pCR in this patient population. Furthermore,

we have highlighted that while the nomogram was developed to predict pCR, its potential utility in guiding surgical strategy, such as the extent of lymphadenectomy or the feasibility of organ-preserving approaches in patients with a high likelihood of pCR, remains to be prospectively validated. The modifications we made in the discussion are shown in the following figure.

Some limitations need to be declared in this study. Firstly, this was a retrospective study with inherent limitations in data collection, particularly regarding preoperative molecular biomarkers.~~retrospective analysis in this study led to limited enrolled clinicopathological indexes.~~ Further studies should focus on the potential predictive value of the preoperative pathological indicators such as PD-L1 expression (CPS score), tumor mutation burden (TMB), MSI status, and multi-omics indicators, etc. Secondly, we mainly present the prediction of pathological response rather than the long-term prognosis because of the limited follow-up time. Thirdly, we didn't unit the NICT regimens and cycles due to the small sample size. Fourthly, an independent external validation set need to be conducted to further explore the predictive ability of this nomogram. Despite these limitations, this nomogram represents a valuable step towards personalized prediction of treatment response in gastric cancer. Large-scale prospective studies should be conducted to provide high-level evidence in predicting the special population with better tumor response and survival benefits in the future.↵

Table Readability: We thank the reviewer for highlighting the importance of table readability. In response to this valuable feedback, we have meticulously reviewed all tables in the manuscript and implemented several revisions to enhance clarity and visual appeal. We believe that these revisions have significantly improved the readability and accessibility of our tables, making the presentation of our results clearer and more impactful. We are grateful to you for your careful review and constructive suggestions, which have helped us to produce a more robust and polished manuscript.

Reference:

[1] Yu Z, Liang C, Xu Q, Yuan Z, Chen M, Li R, et al. The safety and efficacy of neoadjuvant PD-1 inhibitor plus chemotherapy for patients with locally advanced gastric cancer: a systematic review and meta-analysis. Int J Surg (2025) 111(1):1415-1426. doi:

10.1097/JS9.0000000000002056

[2] Shitara K, Janjigian YY, Ajani J, et al. Nivolumab plus chemotherapy or ipilimumab in gastroesophageal cancer: exploratory biomarker analyses of a randomized phase 3 trial. *Nat Med*, 2025. doi: 10.1038/s41591-025-03575-0

[3] Xu J, Jiang H, Pan Y, et al. Sintilimab plus chemotherapy for unresectable gastric or gastroesophageal junction cancer: the ORIENT-16 randomized clinical trial. *JAMA*, 2023, 330(21): 2064-2074. doi: 10.1001/jama.2023.19918

[4] Qiu MZ, Oh DY, Kato K, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ*, 2024, 385: e078876. doi: 10.1136/bmj-2023-078876

[5] Shitara K, Rha SY, Wyrwicz LS, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol*, 2024, 25(2): 212-224. doi: 10.1016/S1470-2045(23) 00541-7

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for reviewers' and editor's warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

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