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RESPONSE TO LETTER

Comment on "Peripheral T Lymphocyte Predicts the Prognosis of Gastric Cancer Patients Undergoing Radical Gastrectomy: A Multicenter Retrospective Cohort Study" [Response to Letter]

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Dear editor

We appreciate the interest and comments submitted about our study entitled "Peripheral T Lymphocyte Predicts the Prognosis of Gastric Cancer Patients Undergoing Radical Gastrectomy: A Multicenter Retrospective Cohort Study".[1] In our study, a total of 390 gastric cancer (GC) patients who were examined with peripheral lymphocyte subsets and received curative resection in three tertiary hospitals were enrolled. Decreased T lymphocytes ($<0.84 \times 10^9$/L) were confirmed as an independent predictor for overall survival (OS) both in the training and validation groups. This indicated that peripheral T lymphocytes might serve as a reliable predictor for OS in GC patients undergoing radical gastrectomy.

We would hereby like to address the concerns raised in the letter to the editor:

As described in our manuscript, one of the main limitations of our study was its retrospective nature, thus, selective bias were inevitable. As shown in Table 4, 65 of the 259 (25.1%) patients with stage II or III diseases did not receive adjuvant chemotherapy (AC). Although AC had been recommended as standard treatment for stage II/III GC following radical gastrectomy, it is not uncommon to encounter patients who refuse to receive AC, or are unable to complete the planned AC for varied reasons, such as economic burden, poor patients' condition, and/or toxicity induced by AC. Even in a recent prospective large scale randomized controlled study, about 25% of patients did not start post-operative chemotherapy or chemo-radiotherapy as planned.[2] It was a pity that the exact reasons for not receiving, or discontinuing AC were not collected in detail in this study. Thus, we could not explore the relationship between reasons for not receiving AC and prognosis. Due to the retrospective nature, relatively long time duration of the study (from June 2018 to December 2022), and the fact it was a multicenter study, several chemotherapy regimen combinations were used, such as SOX and CapOx. SOX and CapOx were both recommended AC regimens for locally advanced GC following radical gastrectomy in Chinese GC treatment guidelines.[3] In an open-label, Phase 3 randomized controlled trial published in 2021, the 3-year disease-free survival rate (DFS) was 51.1% in the adjuvant-CapOx group, which was comparable to 56.5% in the adjuvant-SOX group ($P = 0.17$).[4] But, in the final analysis which was published in 2025, the 5-year OS rates were significantly higher in the adjuvant-SOX group compared with that in the adjuvant-CapOx group (61.0% vs 52.1%, $P = 0.033$).[5] SOX seemed to be superior to CapOx as AC regimens for locally advanced GC who had D2 gastrectomy. Thus, we agree that different AC regimens might act as a confounding factor, which we have described in our manuscript.

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The external group included 159 patients from another two tertiary hospitals in China. As described in Table 1, the basic clinicopathological characteristics between the training and validation groups differed significantly, such as comorbidities, pre-operative albumin and hemoglobin levels, operation procedure, type of resection, and intra-operative blood loss. Independent, external validation using a cohort with significantly different clinicopathological characteristics unequivocally improved the reliability and generalizability of our conclusions. As you mentioned, there were significant differences in treatment strategies for GC between the Eastern and Western counties. For example, peri-operative chemotherapy, even adjuvant chemo-radiotherapy and total adjuvant therapy, were usually performed in locally advanced GC in Western counties. Whereas operation and AC was generally recommended in Eastern counties. Because only about 15% of stage II/III patients received neo-adjuvant chemotherapy in our study, we could not investigate whether the conclusion was the same in those undergoing neo-adjuvant chemotherapy. We agree that it inevitably will influence the generalizability of our findings due to the lack of external validation with populations from Western countries. In addition, although 80% of stage II/III GC recurrence occurred within 3 years following surgery,[6] the median follow-up time of 26 months seemed too short to collect and analyze late tumor recurrence and deaths of patients. We really agree with your opinion and stressed it as a limitation of our study. According to your suggestion, maybe we can report the final results after a long enough follow-up time in several years time.

As far as we know, the normal reference value, quantile method, ROC curve with maximum Youden index, and even voluntary classifications were generally used to classify continuous variables into categorical variables. In addition, the X-tile plots is a well-validated computer program to determine optimal cut-off values using minimum *P* values from Log rank tests. It can control the inflated type I error problem and minimize the loss of information due to multiple testing in minimum *P* value approaches through cross-validation.[7,8] Thus the X-tile is also a commonly utilized tool for biomarker assessment and outcome-based cut-point optimization.[7–9] Nowadays, artificial intelligence based deep machine learning and interaction analyses could find nuanced biological relationships between variables and outcomes as possible. But it inevitably increases the complexity of the model and impacts its convenience when applying it in clinical practice. So please excuse that we did not explore the nuanced biological associations by machine learning or interaction analyses.

We agree that further prospective studies are needed to verify our conclusions. The purpose of our study was not to identify all influencing factors for the prognosis of stage II/III GC patients, but only to investigate the predictive value of T lymphocytes. Independent, external validation by relatively large sample size of patients from multi-centers with significant different basic characteristics could improve the reliability of our findings. We believe that our study showed some interesting findings to investigate the relationship between immunity and prognosis of stage II/III GC after curative resection.

Disclosure

The authors report no conflicts of interest for this communication.

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