Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-22-886

Reviewer A

It has been a privilege to review this article. The design of the research method in the paper is reasonable, and the methods and evaluation indicators are described in detail. the language is fluent, the expression is clear, and the design of charts is reasonable, making the research results easier to understand. The application of haematological and nutritional prognostic biomarkers can give us valuable information within other clinical factors that will allow us to carry out an individualized and personalized management of each patient. As noted in the discussion, the main problem with NLR and PLR is their low specificity, given that these ratios can be affected by several circumstances such as inflammatory diseases, infections, or several drugs. When analyzing results, taking these variables into account is paramount. However, NLR and PLR could help us identify patients with better prognosis that may benefit of different approaches. The results and conclusions of the paper are supported by real data and data, and have good practical guiding significance.

Good manuscript, the identification of the analyzed biomarkers is a subject in which there are multiple publications on other gastrointestinal tumors but with little literature on tumors of the gastroesophageal junction, which gives it additional value.

Reply A

Thank you very much for your time and consideration reviewing our work. As you rightly highlight, these biomarkers are a coarse reflection of the host inflammatory state but are a readily available datapoint which hold clinical significance. Thank you also for highlighting the value of our findings especially with the large proportion of GOJ tumours. This is a tumour group which is certainly less represented in the emerging reports regarding the predictive and prognostic value of the neutrophil-lymphocyte ratio.

Reviewer B

The authors performed a retrospective review of patients with gastroesophageal cancers treated with either CROSS or FLOT regimens. They hypothesized that inflammatory marker NLR would be prognostic, and this is what their data demonstrates. However, in table 2 the multivariate analysis did not include standard prognostic factors such as stage, age, sex and margin status. It is also not entirely clear if all patients included in this study underwent surgery. This needs to be clarified in the methods and either non-surgical patients excluded, or this variable controlled for in multivariate analysis.

It is also not clear to me how many patients with NLR >2 at baseline improved to NLR <2 after therapy? Or vice versa? Was this number/percentage different for CROSS versus FLOT?

In other words did therapy change the negative impact of tumor induced inflammation as measured by NLR and was one therapy better than the other? did patients initially with a positive NLR2 while on therapy?

The authors chose NLR and PLR as their prognostic and predictive markers. These have been extensively studied in gastric cancer. There are literally hundreds of studies in pubmed evaluating them. I think the authors could significantly improve their paper by using other novel, more comprehensive, yet proven markers such as systemic immune-inflammatory index (SII) = platelet×neutrophil/lymphocyte counts, the prognostic nutritional index (PNI) = albumin (g/L)+5×total lymphocyte counts (10^9/L), and the modified glasgow prognostic score (albumin and CRP). These markers tend to be more stable over time. The authors failed to show that dynamic changes in NLPR and PLR were associated with DFS, OS or pCR rates and thus a more stable comprehensive marker might be better.

PNI has also been associated with increased toxicities in previous work.

Reply B

Thank you very much for your time and thoughtful review of our recent submission which has certainly helped improve our work.

Firstly, regarding the patient characteristics and methodology of our study. We included patients who were treated with at least one dose of the FLOT or CROSS regimens as discussed in lines 107 to 111. A description of the proportion of patients who did not subsequently undergo surgery is included in Table 1 alongside staging information, which was 28 of the total 168 patients. As such, we included all patients who received any treatment and had available data for the analysis, to have as accurate reflection of real-world experience as possible. For our patient dataset, we did not have reliable lymph node status and surgical margin status to include in the multivariate. This is an astute point you raise, and we have added this limitation to our discussion of the results in lines 259-260.

To your second point regarding the impact of systemic therapy on altering the NLR. This is certainly an interesting question and one which have a potential impact on practice and future research directions. Our approach was to examine baseline NLR/PLR, post-neoadjuvant systemic therapy NLR/PLR and sustained NLR/PLR (i.e. those who had an elevated NLR or PLR both at baseline and after systemic therapy). In this way we sought to identify those patients who may have a poorer outcome due to either an initial or persisting elevation in the NLR or PLR. Whilst there was a slightly higher proportion of patients with a post-neoadjuvant therapy elevated NLR (as reflected in table 2), our study is not large enough to draw meaningful conclusions from this. I have added an additional line to our discussion to better reflect this (line 227, 228) and appreciate your input. We sought to increase the power of the study by combining the CROSS and FLOT cohorts in our analysis and we observed similar trends in outcomes when the cohorts were analysed separately. This is included in our discussion at line 256.

To your third point regarding the available literature on this topic, we agree that there has been significant interest in this topic. Of note is our finding of the statistically significant improved response rate in those patients with an elevated NLR. This is an emerging area to which we feel we have contributed a significant result despite a limited study size. I have added further clarity in the discussion relevant to this on line 212-213.

Changes made in text:
Clarified row labels in table 2, (line 196), first column
Additional comment in discussion on line 227-228 on changes to NLR after systemic therapy.
Additional comment in discussion on line 212-213.