Peer Review File

<mark>Reviewer Comments</mark>

In this study, the authors analyzed the impact of inflammatory indexes on overall survival and progression-free survival in patients with locally advanced or metastatic pancreatic ductal adenocarcinoma.

1. As the authors mention in the Conclusions section, there have been multiple studies showing the predictive impact of SII on the prognosis of PDAC patients. Please describe the novelty of this study.

Reply 1: Thanks for your comment. In our study we investigated the prognostic role of the most investigated inflammatory indexes (NLR, PLR, LMR, ALI, SIRI, SII, PNI) in literature in a homogenous patient cohort (advanced non-resectable and metastatic pancreatic adenocarcinoma treated with chemotherapy) and we demonstrated for the first time for our knowledge that SII detained the strongest prognostic value compared to others. For example, the study of Zhang et al. took into account as inflammatory index only SII, in a cohort of advanced pancreatic cancer patients, and Jomrich G. et al analyzed the prognostic role of NRL, PLR and SII in a cohort of patients affected by PDAC who underwent surgical resection and not in the advanced setting.

In our study, among all inflammatory indexes, only SII maintained its statistical

significance at multivariate analysis, whereas other inflammation-based scores lost their independent prognostic role.

Changes in the test: We modified the Conclusions section according to the comment (see Page 14, lines 307-320)

2. In statistical analysis, the authors described that they included variables with statistical significance at univariate analysis in multivariate analysis. However, LDH, which showed statistical significance in univariate analysis, does not seem to be included in multivariate analysis. Why was "correction for multiple testing" done and was only "LDH" excluded? I understand if LDH was excluded from multivariate analysis because of the statistical association with SII as shown in the subsection of 3.3., however, why was albumin also not excluded because of the association with SII?

Reply 2: We understand the comment but as described in the Methods section of the article, we decided to use a correction for multiple testing to reduce risk of family wise error using the Holm-Sidak procedure because our analysis included scores deriving from different variables. LDH, PNI, albumin and SIRI were excluded from multivariate analysis applying the Holm-Sidak procedure.

3. Inflammatory indexes can be affected possibly by cholangitis before or after biliary stenting or any other inflammatory states. Data for statistical correlation between all

evaluated variables, including SII and other inflammatory indexes and biliary stenting, should be shown.

Reply 3:

Thanks for your comment. We agree and we think that this correlation could be very interesting. Unfortunately, our study is retrospective, and we the lack of baseline levels of other inflammatory markers such as C reactive protein, or procalcitonin, that are not routinely measured at our institution. We also lack of detailed informations about concurrent infections and inflammatory conditions, such as cholangitis.

Changes in the test: We modified the text and we highlighted these limitations of the paper (see page 15, lines 326-330)

4. Basic clinical variables, such as the location of primary PDAC in the pancreas, locally advanced vs. metastatic, and the site of metastasis, should also be considered in risk analyses for shorter OS.

Reply 4:

We accept the comment and we performed survival analysis according to location of primary tumor and site of metastasis. Correlation between survival and Stage (Locally advanced vs metastatic) was already reported.

Changes in the text: see Table 1 and Table 2

5. In Table 2, univariate analysis shows HRs to be >1 for variables, while multivariate analysis shows HR to be <1 for them. Please confirm statistical values.

Reply 5:

We reviewed the multivariate analysis method and we modified HRs as reported in Table 2.

Changes in the text: See page 9, lines 199-200 and Table 2

6. The authors should show statistical results of multivariate analysis with numbers, instead of just "NS".

Reply 6:

We understand the comment but we used Cox proportional-hazard regression with stepwise method which enter significant variables sequentially; after entering a variable in the model, check and possibly remove variables that became non-significant. Therefore the non significant variables were excluded from the model. We clarified this aspect in Methods section.

Changes in the text: see page 8 line 160

7. Figure 2 should be indicated in the sentence just before it is indicated in the current form of the text.

Reply 7:

We indicated Figure 2 in the sentence as suggested.

Changes in the text: see page 10, line 204

8. The authors should mention if there were any patients eventually undergoing resection of PDAC after systemic chemotherapy in this series. Please also comment on how they indicate conversion surgery in clinical practice.

Reply 8:

Thanks for your comment. Actually, conversion surgery is a very current and interesting topic. None of our patients underwent surgery after chemotherapy. The percentage of patients undergoing surgery refers to surgery prior to the start of chemotherapy for metastatic disease.

9. The authors should discuss how we can treat better for those patients with high SII.

Reply 9

Thanks for your comment. We have shown that SII has a strong negative prognostic value, characterized by worse OS and PFS. These patients may be candidate to earlier supportive care concurrently with chemotherapy. Moreover, as we wrote in the text, targeting inflammation pathways may become a novel

weapon to place side by side to standard chemotherapy and early trials have been already developed to test target therapies against inflammatory targets and immune tumor microenvironment". Therefore patients characterized by high SII may benefit from these anti-inflammatory strategies to start with chemotherapy in the near future. Clinical trials are needed to validate these drugs combinations and SII value may help clinicians to recognize eligible patients.

Changes in the test: See page 14, lines 311-320

10. The conclusions section should be divided into some more paragraphs for readability.

Reply 10: We agree with the comment and we divided the last section in a first paragraph (Discussion) and a second paragraph (Conclusions)

Changes in the text: see page 10, line 222 and page 14, line 305