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Dear Editor:

Here are the responses to the reviewer's comments.

Reviewer 1

The study is well designed but some issues should be addressed
Thank you for pointing out these issues, these have been clarified below.

- there is no need to repeat the aim of study in method section
  - This sentence was deleted from the methods section.

- you described the association between LMR and surgery as marginal significant relationship as p value was 0.05 but the same p vlaue was present for race
  - After review of the data, both race and surgery were marginally significant at p=0.05. This has been corrected in the manuscript.

- univariate survival analysis should be applied in all clinicopathological parameters of pancreatic cancer including the absolute values of lymphocyte count and monocyte count. The authors just applied survival analysis on the ratio only
  - The absolute counts (ALC, AMC) have not been found individually to be significant markers in our study or in other studies, just the ratio. That is why we only did analysis on the LMR.

-some grammer and typographical errors should be corrected especially the spaces between words.
  - Thank you. We have reviewed and corrected these errors.

Reviewer 2

The subject is not in the area of World Journal of Gastrointestinal Pharmacology and Therapeutics. It is about the prognostic role of lymphocyte to monocyte Ratio in Pancreatic Adenocarcinoma. It is better might be send to other journals.

Reviewer 3

This is an interesting paper about the hot topic of inflammation and cancer. With a survival analysis, the Authors show that an increased lymphocyte to monocyte

ratio was a significant indicator of improved overall survival in patients with pancreatic adenocarcinoma. The Authors have also recognized the most important limitations of their study. I think that this article can merit the publication, but the Authors for me should discuss, before publication, some important points.

Thank you for your detailed and insightful suggestions. Please see the changes we have made under each point.

1. Have the Authors some data about the type of lymphocytes) CD3, CD4, CD8? The Authors, also if they have not the data, should discuss the potential role of the different types of lymphocytes in cancer-inflammation.

We do not have any data on specific types of lymphocytes. The following has been added to our discussion:

The different types of lymphocytes have different roles in identifying and eliminating tumor cells. This phenomenon referred to as 'immunoediting' include the NK cells, the NKT cells, macrophages, CD4 T cells and CD8 T cells. Several studies have shown that high numbers of CD8 T cells portend a better prognosis.

Immune surveillance of tumors. *Journal of Clinical Investigation*. **117**:1137–1146 (2007). doi:10.1172/JCI31405.

Also, please see below, as our discussion of your 3rd point, which also adds to the discussion of role of different types of lymphocytes in malignancy.

2. The Authors should discuss also the feasibility of such determination on FFPE tissue. In other words, if this work will be validated by future research (trials – prospective, not only retrospective!) the determination of lymphocyte-types may be assess with immunohistochemistry.

The tumor microenvironment is what has established the theory that lymphocytes may be anti-inflammatory, and their role in impeding progression of tumor may be vital in the immune surveillence of the cancer. It was established by flow cytometry that the regulatory T cells that played a role in this surveillence of pancreatic adenocarcinoma specifically contained the FOXP3+ protein [1]. This was further evaluated in a study by Jiang et al., which looked at the lymphocyte density and the correlation with lymph node metastasis. They found, through immunohistochemical staining that that the FOXP3+ lymphocyte density did not correlate with age, gender, or T stage. However, the number of

FOXP3+ lymphocytes were higher in patient who had a higher histological grade of tumor, lymph node metastasis, and advanced stage tumors (stage III and IV vs. stage I and II). [2] While the studies were not prospective in nature, they do validate the fact that there is a difference in density and nature of inflammatory cells which is related to the aggressiveness of the cancer.

[1] Shibuya KC, Goel VK, Xiong W, Sham JG, Pollack SM, et al.Pancreatic Ductal Adenocarcinoma Contains an Effector and Regulatory Immune Cell Infiltrate. 2014. PLoS1.

[2] Yongjian Jiang ,Zunguo Du Feng Yang, Yang Di, Ji Li, Zhongwen Zhou, Venu G. Pillarisetty, Deliang Fu. FOXP3+ Lymphocyte Density in Pancreatic Cancer Correlates with Lymph Node Metastasis..
2014, http://dx.doi.org/10.1371/journal.pone.0106741

3. The Authors should also discuss the importance of Th-1 and Th-2 immuno-response in inflammation and cancer. I think that just a small paragraph, summarizing the state of art in the literature about this topic, is important in a manuscript like this. This is a good example: Ling et al. The infiltration, and prognostic importance, of Th1 lymphocytes vary in molecular subgroups of colorectal cancer. J Pathol Clin Res. 2015;2:21-31.

Cytokines released by these lymphocytes have roles in both promoting and suppressing a cancer. Haabeth et. al. conducted a study measuring the cytokine response in mice against cancers (myeloma and B-cell lymphoma). They found that inflammation which was driven by tumor specific Th1, allowed release of IFN-gamma which stimulated macrophages that were cytotoxic to the cancer cells [3]. The CD4+ Th1 cells also help cytotoxic T cells in tumor rejection. On the other hand, the CD4+ Th2 cells are implicated in production of cytokines which lead to B-cell activation. The role of Th1 lymphoctes in colorectal cancer is delineated by Ling et al. as they found that high numbers of lymphocytes in tumor tissue was associated with improved prognosis of patient's with colorectal cancer [4].

[3] Haabeth O, Lorvik K, Hammarstrom C, et al. Inflammation driven by tumour-specific Th1 cells protect against B-cell cancer.

[4] Ling A, Lundberg I, Eklof V, et. al. The infiltration, and prognostic importance, of Th1 lymphocytes vary in molecular subgourps of colorectal cancer. J Pathol Clin Res. 2015;2:21-31.

4. A last point to discuss more in depth is the potential role of target – immune – therapy in cancer on the basis of the result of this paper (like a perspective for the future).
The following has been added to our discussion:

There is definitely a role of immune-targeted therapies in the future. Immunotherapies such as chemicals that resemble cytokines can be used to up-regulate the cancer fighting immune cells, as is the basis for many of the newer chemotherapeutic agents. Clarifying the specific type of immune cells and chemical cytokines that attract tumor suppressing cells requires further research and understanding of the tumor biology, specifically for the different types of malignancies. Pancreatic adenocarcinoma, despite being one of the more aggressive cancers, still is in the nascent stages of research and investigators are continuing to learn the tumor biology and immunologic effects.