

Format for answering reviewers

June 3rd, 2017

Dear editor:

Title: Novel systemic immune-inflammation index for predicting the prognosis of colorectal cancer

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The manuscript has been improved according to the suggestions of the reviewers:

Que1: The introduction is too long. It should be shorter and more focused.

Answer: The introduction of this study was divided into three parts: Part I: the overview of the incidence as well as treatment effect of colorectal cancer nowadays and the defect of TNM stage. Part II: introduction of systemic inflammation and the local immune response to tell the theoretical value of SII. Part III: The aim of this study. The three parts were all important to the introduction in this study. I have made it shorter and more focused.

Que2: The Material and Method Section the new index SII should be specified in detail, so that everybody who is interested in the paper can read it and understand immediately, before continuing to read the paper.

Answer: I have corrected it as "SII was calculated by the formula $SII = (P \times N) / L$; where P, N, and L refer to the peripheral platelet, neutrophil, and lymphocyte counts, respectively.". And the corrected sentence was more clear.

Que3: A colour drawing expalining the different phases which correlate inflmmation and cancer progression can be useful-. I reccommend to look at the picture of a paper recently published in New Englinsd Journal of Medicine about clear cellll renal carcinoma from the Sloan Kettering in New York (NEJM 2017;23: 326). The Authors can have nade a drawing in which inflmmaotry cells produce growth factors which stimulate cancer growth. At the same time (this is my old hypothesis) new replicating

cancer cells, stimulated in such an anolous situation, could express surface antigens not recognized by the host, recrurting more inflasmmatory cells, with consequent production of growth factor, determining a cascade effect.

Answer: I remodify all the figure.

Que4: They used univariate and multivariate analysis, which currently are the most common used method in medical statistics. I think that the analysed problem is very complex and these two analyses are inevitable superficial.

Answer: Univariate and multivariate analysis were the most popular research methods to investigate the prognostic value of the variables.

Que5: The importance of this SII index should be confirmed in a propsective study.

The conclusion of this study, based on a retrospective study presents so many statistical biases that the results can not be accepted until they are confirmed by a prospective study. This should be clearly addressed in the discussion.

Answer: The sentence "A larger prospective study is warranted for the validation of the preliminary results obtained in the present study." as added in the last paragraph of discussion.

Que6: In the discussion, I would like to advice to introduce a new concept (I expressed in a letter to Annals of Surgery: Sterpetti et al 2012): there is a good and a bad inflammatory reaction. In other words if the inflammation is based on the production of simply growth factors, the inflammatory reaction has a negative effect. But if the inflammatory reaction consists on neutralizing antibodies produced by activated lymph nodes, this reaction can have a positive effect.

Answer: I add the great implement in the discussion of my study. However, I can't find the paper referred by the reviewer "Annals of Surgery: Sterpetti et al 2012".

Que7: In methods - data collection: SII calculation is unclear. $SII = (P \times N) \text{ all divided by } L$. Or only N is divided by L?

Answer: I have corrected it as "SII was calculated by the formula $SII = (P \times N) / L$; where P, N, and L refer to the peripheral platelet, neutrophil, and lymphocyte counts, respectively.". And the corrected sentence was more clear.