Budapest, June 24, 2021

Dear Lian-Sheng Ma, Company Editor-in-Chief,
Dear Professor Dennis A Bloomfield, Professor Bao-Gan Peng, and Professor Sandro Vento, Editor-in-Chiefs,
Dear Science Editor,
Dear Managing Editor
Dear Reviewers,

On behalf of my fellow authors, first of all, I would like to thank you for your attention and opinion on our original article entitled “High plasma CD40 ligand level is associated with more advanced stages and worse prognosis in colorectal cancer”. We are grateful that you have found it to be interesting and suitable for publication in World Journal of Clinical Cases.

Our answers to the comments raised in the reviews are given below.

Reviewer 1

The strength of the study is that no previous study investigated the level of CD40L with the course of the disease. Observations In the conclusions it is mentioned; "Both the high CD40L level and the elevated platelet count were a poor prognostic sign of patient survival." In a strict sense, one can only speak of a poor prognosis for interleukin 6, the changing level of CD40L and the elevated platelet count had borderline significant values in the multivariate analysis. Do not forget that the multivariate model for survival is a more robust statistic than the univariate. Therefore, I recommend being more cautious when talking about poor prognostic factors.

Thank you for your positive comments and kind criticism on our manuscript, we agree with it, and in the light of that, we have refined the final conclusion and the abstract of our article. The sentences with the slight overinterpretations had been removed.
I recommend including table 2; the footer with the meaning of the acronym AJCC, although this is well known to readers.

Abbreviations within Tables has been resolved, as suggested by the Reviewer.

Reviewer 2

Herold et al. investigated serum sCD40L in 106 patients with colorectal cancer (CRC) and analyzed the relation of sCD40L and prognosis of CRC. They concluded that serum sCD40L correlated with platelet number, serum IL-6 value, and progression of CRC. According to the previously established paper for serum sCD40L, sCD40L is closely associated with platelet number, and most of serum sCD40L is derived from platelet. IL-6 is also known as a stimulatory factor for thrombocytosis. In this sense, the observation of the authors is quite predictable and not novel. Furthermore, as shown in figure 4 and 5, multivariate analysis did not show the independent impact of sCD40L on the prognosis or progression of CRC. It seems too speculative that there is an unknown factor that connected elevated sCD40L with pathogenesis and progression of CRC, and logically not appropriate. The findings in this paper is not novel, and logic and conclusion in the text seems inappropriate.

Thank you for bringing our attention to the fact that the message of our manuscript was not presented in sufficient detail. The majority of soluble CD40L originates from platelets, however a few publications are also known, where other sources of soluble CD40L elevation were also presented, e.g., the articles of Lin et al. (PMID15467191) or Danese et al. (PMID15194658). These observations have been all found in diseases which can be characterized by general inflammation, like diabetes or atherosclerosis. In the current study, the results of linear models revealed that the explanatory power of platelet count on CD40L was low. The highest explanatory power of 8% could have been achieved with the inclusion of more than one independent parameters to the model only. Parameters included platelet count, interleukin-6 and thrombopoietin. Results of our survival models, in which stratification was also applied, further strengthened the hypothesis, that an effect of an unknown factor (with high probability the general inflammation caused by the tumor) must be in place as well. If a parameter has a strong effect on another one (there is an interaction between the two parameters), in a Cox regression model after stratification with one of these parameters, the previously significant results should be eliminated or at least weekend. This effect occurs due to the different baseline hazards, which are assumed in those models. In the present problem, if stratification is used, it is assumed that patients with normal platelet count have lower baseline hazard than those with elevated platelet count. With this modification, the non-stratified p-value of platelet count changed from 0.0052 to 0.3310 in the stratified version of the model. The same effect would have been expected in the case of CD40L, however, the p-value changed
from 0.0159 to 0.0332, which indicated that “disabling” the effect of elevated platelet count on CD40L was not enough to decrease its effect on patient survival.
To clarify this finding and the related hypothesis, the second half of Discussion had been re-edited, and our hypothesis on ‘CD40L and other factor interactions’ had been completely refined. Abstract, Core tip, and Conclusion was also improved to better reflect the kind and legitimate criticism of the Reviewer.

Yours sincerely,

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