Author's response to reviews

Title: Significantly higher serum concentration of alpha-1 antitrypsin in colorectal cancer patients than in healthy controls

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Dear Editor,

We would like to first thank the Editorial Board and the Referees for their interest in the evaluation of our manuscript, as well as for their valuable suggestions and useful ideas to improve the quality of our paper.

Please find below the issues raised by both reviewers, and our point by point responses.

Reviewer 1:

1). Abstract: In the results section change Pi*S nor Pi*Z.
Answer: Right. The requested change has been made.

2). MATERIALS AND METHODS: Have you considered performing IHC for AAT to document expression (or even overexpression in tumor)?
Answer: Actually, the initial aim our study was to analyze the prevalence of AAT deficiency in patients with colorectal cancer from our geographic region. Honestly, we had not thought about it, but it seems a good idea to develop in future studies.

3). DISCUSSION: Could AAT levels be correlated with stage?
Answer: Highly significant differences were found when comparing the mean serum concentration of AAT from the CRC group (in total and by TNM subgroups) vs. Controls. However, the comparison of the mean value of the whole CRC group vs. each of the CRC stages (I, II, III and IV) separately not evidenced significant differences among them (p:0.502). These data are now summarized into a new table (Table 5).

4). DISCUSSION: Outcomes?
The recruitment of patients was done for 4 years (2008 to 2012), and there were large fluctuations in the number of cases collected each year. Consequently, the follow-up time of patients was highly dependent on the date they were recruited,
and this has been very variable. Thus, patients recruited at baseline were followed for about 3-4 years, but those recruited in the following years and in the end were followed less time (e.g., the last ones for only a few weeks or months). Of several cases detected before the start of the study, some of them deceased but other controlled long have not been included in the analysis. In the future, we would need to double the number of cases and follow up them for several years to analyze their clinical course.

5). TABLES: Perhaps reformat tables as they are wider and thus have less less. This may make it easier to read.

Answer: We have tried to improve the format and content of tables. We also removed the old table 5, "Serum Concentrations of Alpha-1 antitrypsin for the different Pi * Genotypes AAT ...", being very theoretical and known to those skilled in AAT data. Instead it has been added a new small table (Table 5) to illustrate a "Comparison of Serum Concentrations of AAT in the group of patients with colorectal cancer (total and classified by TNM stages) vs. Controls".

Reviewer 2:

1) We understand that this reviewer believes that the discussion and conclusions are not properly balanced with the reported data, nor the title corresponds with the findings. Therefore, she recommends changing the title and reworking the discussion section. She also considers of interest to compare AAT levels with the severity of the disease instead of AAT phenotypes.

Answer: We believe that this reviewer's comments are absolutely appropriate, and we gladly accept them, because the change of the initial wording by the current one provides to this paper a significant improvement.

Therefore, we changed the original title: “Alpha-1-Antitrypsin Serum Levels and Phenotypes Distribution. Case-Control Study in Colorectal-Cancer Patients”, by the following one by the following, which advances the study findings: “Significantly higher serum concentration of alpha-1 antitrypsin in colorectal cancer patients than in healthy controls”.

2) Discussion. The first paragraph is repeated like in the introduction.

We agree; this paragraph has been deleted.

3) Discussion. For the start of discussion would be better sentence from page 11, “The only statistically significant finding in this study was the markedly higher AAT serum concentrations in CRC subjects compared to HUP controls, regardless of their Pi phenotype were normal (MM) or deficient (MS, MZ and SZ)”.

We agree, and we did so in the new version of the paper.

4) Authors shell focus on the findings and significance. I recommend totally rework Discussion section.

We agree, and we did so in the new version. We have made major changes in the new wording of the discussion, which is much more focused now on the meaning of the findings, eliminates many theoretical concepts of alpha-1
antitrypsin we assume they are well known by those skilled in this field. These changes have involved the removal of the old Table 5, creating a new one that summarizes some of the important findings. For this reason, we had to increase a significant number of citations about serum AAT in CRC and in other types of tumors, as well as several references on expression of AAT in tumor tissues, etc.

We look forward that, once these changes made, this manuscript is considered of your interest and suitable to be published in publication in the journal you lead.

Yours sincerely.

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