We thank the Editor and reviewers for all their constructive criticism which helped us to improve the manuscript. All the reviewers comments have been addressed and all changes was done in the manuscript using track changes. In addition to addressed points we also removed the forward stepwise conditional multivariate Cox regression analysis due to low number of patients and events which makes such analysis less reliable. The regular multivariate Cox analysis that was already used, taking into account the clinical co-variates, is a better and more robust model and therefore used.

Reviewer no 1 (02739495)

Classification: C: Good

Language evaluation: Grade A: Priority publishing

Conclusion: Minor revision

COMMENTS TO AUTHORS

The authors in this study investigated whether the circulating inflammatory factors were associated with worse long-term prognosis in colorectal cancer (CRC). The results showed that high plasma levels of inflammatory factors were associated with an increased risk of total and CRC specific mortality among CRC patients. The whole manuscript is well designed and used a fluency style.

1. Figure1 and Figure2 should add P-value.

Reply: *This has now been done.*

2. In table 5, there is not any significance between TNM stage I+II vs.TNM stage III+IV. How to explain this phenomenon? Add the explanation in Discussion.

Reply: *Since we got justified criticism (from reviewer 3) for grouping stage I+II and III+IV we have now reanalyzed our data with ungrouped stage on all the 40 factors (not only the ones significant in the univariate models). Table V was now removed and replaced with a table II describing the median levels of factors that were significant associated with stage. Still, only four factors remained significantly associated with stage, i.e, CCL20, CCL27, IL-8 and MIF. Of these, CCL20 was the only factor significant in analysis adjusted for clinical co-variates, which could then be explained by higher levels with higher TNM stages. Possible*

explanation for not finding more factors associated with stage is due to under power of the results due to low number of patients. This was now added to the discussion, p 11, paragraph 2 and p 12, paragraph 1.

3. Whether there is any difference among the plasma of CRC patients, patients with intestinal benign lesions, and healthy control?

Reply: *This comparison was not included in our study since we did not include controls. We focused our study on the CRC patients and prognosis based on plasma levels of different factors. Comparisons between controls and patients has been performed previously for several of the factors. This is discussed, p 10, paragraph 2 and 3 and p 12 paragraph 1.*

Reviewer no 2 (03317066)

Classification: D: Fair

Language evaluation: Grade B: Minor language polishing

Conclusion: Major revision

COMMENTS TO AUTHORS

1. Since there are low number of patients in stage I and CRC specific mortality is low in stage I, the authors should show whether the univariate Cox regression analysis is reasonable.

Reply*: The proportional hazard assumption was verified through visual inspection of log-log plots. We have added this information to the method section.*

2. The authors should show the grouping method about the inflammatory factors value. What is the difference between the grouping: "low-, median- or high levels" and "median levels".

Reply*: We agree that our wording may give rise to confusion. Due to the non-normal distribution of many variables we have divided them into tertiles. We have now changed the terms into "low, middle or high tertiles".*

We have also changed the wording in one sentence in the methods section and avoided the words "median levels" as the meaning referred rather to the distribution of the variable.

Reviewer no 3 (03552255**)**

Classification: B: Very good

Language evaluation: Grade A: Priority publishing

Conclusion: High priority for publication

COMMENTS TO AUTHORS

This manuscript represents a quite interesting topic concerning the serum level of circulating cytokines and their relation with cancer specific and/or total mortality in colorectal cancer patients. The overall structure of the manuscript is entirely complete and contains all the necessary attributes.

1. I would suggest in section Keywords the "colorectal cancer" to be added.

Reply: *This was now added.*

2. The authors clearly establish their own scientific hypothesis with the relevant endpoints in the Introduction section where they offer enough depth background on the issue. The authors give an adequate explanation of all steps of the technical implementation of the tests, which ensures reliability and repeatability of the results obtained. There have met the required ethical standards on the participation of patients in the study. The statistical processing of the data is accurate and adequate to draw conclusions from the relevant result. In Section Results authors identify certain types of cytokines that are associated with a worse specific cancers survival and another group which confer increased risk of total mortality rate. The authors carried out relevant adjustement regarding the influence of certain variables-covariates.

In my opinion, however, it is incorrect patients on stage in groups I + II and group III + IV to be grouped. Despite the insufficient number of patients, which determines the insufficient power of stage differentiation, stage IV (metastasis) particularly varies generally from other stages in terms of prognosis. Furthermore, it was shown in the recent past that certain patients in stage III have a better prognosis than those

in stage II due to worse ratio of T (T4b), and N (N3) categories. This requires making appropriate corrections in the manuscript.

***Reply**: All the survival analyses have been done on the ungrouped TNM-stages. The grouping of stages was done in the analysis in table 5 only. The aim of that analysis was to verify that the variables were not correlated to stage, which could give rise to a bias. Due to the small number we grouped them in order to minimize the risk of Type II error due to the small sample. However, we agree that this can be confusing and have now made this analysis by the use of a Jonkheere Terpstra test, which only showed an association between stage and four of the variables, now showed in a new table II since we now included the analysis of all 40 factors and not only the ones significant in the univariate models. Of these, CCL20 was the only factor significant in analysis adjusted for clinical co-variates, which could then be explained by higher levels with higher TNM stages. This was added to the discussion. See also reply to reviewer nr 1, comment 2.*

3. Analysis of the results in Discussion section is on a high scientific level and would be of interest to the audience. The authors indicate the shortcomings of their study as also highlighted the achievements of other studies on the subject to date. Major drawback is the lack of stratification of patients with respect to the type of surgery - elective or emergency - with inflammatory complicated CRC (peritumorous abscess; perforation; bowel obstruction/peritonitis) or another major underlying inflammation, such as CRC based on inflammatory precancerous as IBD. This would change the profile of the inflammatory markers during the surgery. However, analysis of the results gives a clear answer to the scientific hypothesis.

***Reply:** We agree that this would have improved the manuscript but all this information was not available for us and sub-grouping of the data would further underpower the result due to low number of patients. We included this drawback to the discussion, p 12, paragraph 1.*

4. The authors applied correct figures and data tables. There are cited 38 literature sources. On page 9 / last line into the passage "... associated with an increased risk of CRC as a result of ongoing CRC progression over time ...." should be added "specific mortality" regarding the increased risk of CRC.

***Reply**: We thank you for this important detail which was now changed.*

5. From my perspective the proposed manuscript coincides with the scope of the journal. It has practical scientific value, therefore I propose that it should be approved for publication after certain adjustments.

***Reply**: Thank you!*