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Elevated fibrinogen plasma level is not an independent predictor of poor prognosis in a large cohort of Western patients undergoing surgery for colorectal cancer

Reviewers' comments:

Reviewer #1: *This paper tried to elucidate role of fibrinogen plasma level in the prediction of CRC prognosis. The manuscript is well written and the data and table is clear. However I think they should have an exclusion criteria. Those patients with unresected tumor and those underwent urgent operations seems not proper for this study (***Remark #1)**. *Another issue is that the minimum follow up period is 30 months, but they analysed the 5-year OS, I wonder how many cases were available for the study (***Remark #2).**

Thank you for the useful suggestions that allow us to improve the paper.

Remark #1. *I think those patients with unresected tumor and those patients who underwent urgent operations should be excluded from the analysis.*

We agree with the reviewer's idea that evaluation of fibrinogen levels in urgently operated and unresected patients should be considered confounding. Nonetheless, several considerations lead us to include them. First, inclusion and exclusion criteria were considered as reported in the section Methods (**page 4, lines 22-24**). Elective and urgent colorectal surgeries were included in absence of peritonitis or other infectious diseases. Second, in our series urgent and unresected cases represent a strict minority of patients (5% and 2%, respectively). Third, multivariable analysis controlled RR (95% CI) of high fibrinogen level controlling for other factors among which urgent vs. elective surgery and palliative vs. potentially curative resection. Fourth, our study is the only experience demonstrating that hyperfibrinogenemia should not be considered an independent predictor of poor prognosis but it is frequently observed in advanced cases submitted to palliative surgery. For all these reasons the authors think that the inclusion of unresected and urgent cases is justified.

Remark #2. *The minimum follow up period is 30 months, but the authors analysed the 5-year OS, I wonder how many cases were available for the study?*

Yes, the minimum follow-up period was 30 months. The median follow-up period for the surviving patients was 75,8 months, only 9% of patients had a follow-up period of 36 months or lower and less than 30% had a follow-up period of 60 months or lower. OS and cancer related survival has been computed by Kaplan-Meier estimate of survival probability. Multivariate analysis was performed by Cox regression model.

Reviewer #2: *This retrospective study investigates the role of fibrinogen as a prognostic biomarker in colorectal cancer. The study is well written and tries to shed new light on an extensively studied biomarkers, even though the results are not conclusive. Before publication, I suggest the following amendments: 1) Please specify a protocol (or ID) number for the Ethics Committee approval 2) Table 1 (and 3): have the authors corrected for multiple tests? If so, please specify. If not, please justify why. 3) Discussion. The authors should confront their findings with a larger meta-analysis, which has been recently published (PMID http://www.ncbi.nlm.nih.gov/pubmed/26604093) Why do they think their results are different?*

Thank you for the useful suggestions that allow us to improve the paper

Remark #1. *Please specify a protocol (or ID) number for the Ethics Committee approval*

The ID number is 42763 (CRINF-1034 CESC) **(page 4, line 26)**.

Remark #2. *Table 1 (and 3): have the authors corrected for multiple tests? If so, please specify. If not, please justify why.*

Table 1 reports clinico-pathological characteristics of the cohort under study according to Fibrinogen levels. Table 2 reports the prognostic value of preoperative fibrinogen levels controlled for age, gender, tumor location, type of surgery, presence of residual tumor, presence of systemic metastasis, pT category, pN category and histological type (multivariate analysis). Table 3 reports univariate analysis according to TNM stage for patients submitted to potentially curative resection (R0).

Remark #3. *Discussion. The authors should confront their findings with a larger meta-analysis, which has been recently published (PMID http://www.ncbi.nlm.nih.gov/pubmed/26604093). Why do they think their results are different?*

The data have been confronted with the above mentioned meta-analysis. The study has been discussed in the section “Discussion” (**page 8, lines 10**).