

## **Reviewed by 00724342**

**1. Reviewer:** *The manuscript is basically well written. What I particularly like is the description and the relationship of pathophysiological mechanisms and cancer. I do have a number questions and remarks concerning your manuscript. It contains pretty much already known fact that it reduces the value of a good review artical. In the part that explains the relationship of albumin and CRC, ther are lack of informations. Authors comments that the role of pretreatment serum albumin as a prognostic tool was demonstrated by many studies. They presented data that albumin was independent prognostic factor for localized CRC survival in patients. It should be clarified impact of level of albumin at specific stages of localized's disease, I or II.*

**Authors:** The data appears to be conflicting on the impact of the level of albumin in localized disease. In the fourth paragraph of Part III (Albumin in colorectal cancer), we clarified the findings of the cited study from Taiwan:

“...In a Taiwanese study of 3,849 colon cancer patients who underwent curative surgery, hypoalbuminemia predicted higher rates of postoperative mortality **for both localized (Stage I and II) and regionally advanced cancer. The impact was significant 30 days and 5 years after surgery, and remained significant on multivariate analysis**”.

In the last paragraph of Part III, we included results from other studies that had shown little impact of the albumin level in early disease. As included in the manuscript, this is to highlight that albumin levels alone may not be providing the full story:

“In other studies, it also was noted that albumin levels were normal among patients with early stages of cancer (stages I and II), which would limit its use in prognostication [8,14].”

**2. Reviewer:** *It should be explain in detail the impact of preoperative albumin levels in the wound healing process or the occurrence of anastomotic dehiscence.*

**Authors:**

In the fourth paragraph of the Part III (Albumin in colorectal cancer), we elaborated on the impact of the preoperative albumin levels as suggested:

“Further, preoperative hypoalbuminemia was associated with more common wound-healing and anastomotic complications, as well as postoperative pulmonary and urinary morbidity. Interestingly, the study found no statistically significant excess of

gastrointestinal or cardiovascular surgery-related morbidity in patients with lower albumin levels [35]”.

**3. Reviewer:** *It is not clear distinction between whether the preoperative albumin level is equally essential in the surgical treatment of colon and rectal cancer, respectively*

**Authors:** In the fifth paragraph of the Part III “Albumin in colorectal cancer”, we noted that there are no studies that allow us to quantify a difference in impact between the two cancers:

“Of note, we found no studies that assessed whether the impact of preoperative albumin levels is essentially equal in the surgical treatment of colon and rectal cancer”.

**4. Reviewer:** *In advanced disease is it remarkable that tumor size, but not the stage, is relevant to hypoalbuminemia?*

**Authors:** We clarified the reason behind this finding by Cengiz et al. [36] in the fourth paragraph of Part III:

“Among patients with advanced disease, albumin levels were more reflective of the tumor size rather than the specific tumor stage, with larger tumors having lower serum albumin levels. The authors suggest that the larger volume of tumor cells translates into a higher production of proinflammatory cytokines, which in turn suppress albumin’s hepatic production [36]”.

Also, we further elaborated on the findings of Boonpipattanapong et al. Please refer to the last paragraph of Part III.

“Hypoalbuminemia was not consistently a prognostic factor in colorectal cancer. Boonpipattanapong *et al.* showed that hypoalbuminemia, when taken alone, has no statistically significant effect on survival among patients who underwent curative surgery. If combined with the level of carcinogen embryonic antigen (CEA), a tumor marker that correlates with tumor size, the resulting score becomes significant in predicting the 5-year survival in all disease stages [25]. Their finding, however, had a low power (22%)”.

**5. Reviewer:** *No mention was made that what kind of surgical approach (open or laparoscopic) affects the postoperative level of albumin.*

**Authors:** The reviewer raises an interesting point. We found no data on the effect of the surgical approach on the postoperative levels of albumin. In addition, such effect was outside the scope of our manuscript: we attempted to review albumin's value in the long-term prognosis of colorectal cancer. Furthermore, all studies that we found looked at the prognostic value of the pretreatment level and gave no attention to the postoperative levels.

**6. Reviewer:** *Regardless of the clinical significance globulin, it is not clear why is in the manuscript unnecessarily given explanations?*

**Authors:** We shortened the background information about globulin. The introduction of Part IV "Globulin" is now more concise.

**7. Reviewer:** *You must clearly point out that which types of long-term survival ( overall, or 5 year survival, etc) is meant when it is said that patients with low albumin and high globulins were associated with worse long-term survival, and the AGR was an independent predictor of mortality in colorectal cancer.*

**Authors:** In the second paragraph of Part IV A. "Albumin-to-Globulin Ratio (AGR)", we clarified the long-term survival in questions.

"...A study conducted by Azab *et al.* demonstrated that, in colorectal cancer, a low ratio is an independent risk factor for 4-year mortality [43]."

"Overall, patients with low albumin and high globulins were associated with worse 4-year survival, and the AGR was an independent predictor of long-term mortality in colorectal cancer."

**8. Reviewer:** *What is the value of the AGR as a prognostic marker for predicting the chemotherapeutic response in patients with unresectable metastatic colorectal cancer who receive palliative chemotherapy?*

**Authors:** We added a third paragraph in Part IV. A "Albumin-to-Globulin Ratio" to answer this question:

"Another study of 66 patients with unresectable metastatic colorectal cancer receiving palliative chemotherapy showed that higher pretreatment AGR was associated with improved disease control rates. Patients with higher AGR also had more favorable progression free survival, a finding that was independent of clinicopathological features

on multivariate analysis. The objective response rate in the high-AGR group (44.1%) was higher than the low-AGR one (28.1%) but the difference did not reach statistical significance ( $p=0.208$ ). However, taken as a whole, the study suggests that palliative chemotherapy is less effective with low pretreatment AGR, a marker of underlying inflammatory conditions [44].

**9. Reviewer:** *It is known that GPS has significance as a predictor of survival in a variety of cancers of the gastrointestinal tract, but not at all stages of disease. Among patients with stage II, GPS was predictive of cancer-specific survival.*

**Authors:** Based on our literature review, we believe that GPS has been shown to be a significant predictor of survival at all stages of colorectal cancer, the focus of our review.

We have rectified the third paragraph in Part IV. B “Glasgow Prognostic Score” to clarify this issue.

“The mGPS has been remarkably consistent in predicting survival (Table 3). A recent pooled analysis of nine studies with a total of 2,227 colorectal cancer patients showed an association between higher scores and both poorer overall survival and cancer-specific survival across various disease stages [50].”

Further, in the same paragraph, we report:

“The review listed 18 colorectal studies that outlined widespread prognostic implications independent of a variety of clinical factors, such as tumor stage and emergency presentation”.

The specifics of GPS’s prognostic significance in other gastrointestinal tract cancers were outside the scope of our review. McMillan et al. 2012 [51] provided a comprehensive review of the topic.

**10. Reviewer:** *The paper should be complemented with a table of results from the literature.*

**Authors:** We added three tables to complement the text. Please find them at the end of the revised manuscript.

**11. Reviewer:** *Weaknesses or deficiencies in the manuscript is quite a bit of important informations about the significance of hypoalbuminemia in colorectal cancer prognosis. The content of the manuscript have value for publication just in case the corrections of the*

*manuscript.*

**Authors:** We attempted to address all points brought up by the reviewer. We thank the reviewer for his/her valuable feedback, and we hope the manuscript meets the criteria for publication.

**Reviewed by 00505466**

**Reviewer:** *The authors provide a comprehensive review on the relation between albumin (and other biomarkers) and prognosis in colorectal cancer. The role of albumin is discussed. The manuscript is well organized and well written.*

**Authors:** We thank the reviewer for his/her valuable feedback.