Author's response to reviews

Title: Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: A prospective study

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Author's response to reviews: see over
Dear Dr. Norton:

We appreciate the comments made to our manuscript; undoubtedly they have increased the quality of our paper. Enclosed please find the revised manuscript and a detailed description point by point addressing the reviewers' comments.

All authors have read and approved the final version of this manuscript, and concur with the submission.

Waiting your reply, I remain.

Yours sincerely,

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Referee 1 William Rom (Comments to author):

This is a well-designed and executed study with excellent biostatistical support. The outcome measure was repeated after two cycles of chemotherapy. The only concern is level of scientific interest since malnutrition is common among cancer patients and malnourished patients always seem to do worse.

We appreciate your comments. It is well known that malnourishment is related with bad prognosis in oncology patients, despite this fact, there are few prospective trials that correlated malnutrition and particularly hypoalbuminemia with toxicity in chemotherapy. Reason why we think that it is important to publish our results in order to give an early nutritional assessment that will allow identification of patients at higher risk of developing chemotherapy toxicity and the implementation of an adequate nutritional support might be accompanied by beneficial effects when treating patients with NSCLC.

Referee 2. Donald C McMillan

It has long been recognized that hypoalbuminaemia is associated with nutritional decline and poor survival in patients with cancer. However recent evidence points to such relationships being secondary to the presence of a systemic inflammatory response. Indeed this has been shown clearly in patients with advanced NSCLC. Therefore, the present study is limited interest unless they have a measure of the systemic inflammatory response.

We appreciate your comments and references. The suggested references have been included throughout the manuscript.

We were able to expand our study by including NLR and PLR ratios as suggested, and information related to them has been included in the abstract, methods, results and discussion. This enriched the content of our study, unfortunately, we could not count with C reactive protein levels to integrate them in the study. We are currently developing other studies and have decided to include this
Some examples showing how this data has been added is shown as follows:

**Neutrophil Lymphocyte Ratio (NLR)** and the **Platelet Lymphocyte Ratio (PLR)** were used to determine the presence of systemic inflammatory response (SIR) and were related to the development of toxicity. (page 2, paragraph 2, line 2)

\[ NLR \geq 5 \] was associated with basal hypoalbuminemia (mean ranks, 55.7 vs. 39 \( p=0.006 \)), ECOG=2 (47.2 vs. 55.4 \( p=0.026 \)) and PLR \( \geq 150 \) were significantly related with a basal body mass index \( \leq 20 \) (56.6 vs. 43.5; \( p=0.02 \)) and hypoalbuminemia (58.9 vs. 41.3; \( p=0.02 \)). (page 2, paragraph 3, line 2)

\[ PLR \geq 150 \] was related with the development of toxicity grade III/IV (59.27 vs. 47.03 \( p=0.008 \)) and anemia (37.9 vs 53.8 \( p=0.004 \)). (page 2, paragraph 3, line 11)

The process of nutritional and functional decline in the patient with cancer is so common that it is often accepted as part of the disease itself and its treatment. Currently, there is evidence that the presence of a systemic inflammatory response (SIR) is associated with increased weight loss, an elevated resting energy expenditure, loss of lean tissue and functional decline [18]. (page 4, paragraph 4, line 2)

**Neutrophil Lymphocyte Ratio (NLR)** and the **Platelet Lymphocyte Ratio (PLR)** have also been demonstrated as indicators of systemic inflammatory response [18, 24-26]. Indeed, the magnitude of the increase PLR and NLR has been shown to be associated with poorer survival in patients with cancer, particularly in patients with advanced disease [27-30]. (page 5, paragraph 1, line 11)

It has been well known that the association between malnutrition and hypoalbuminemia and survival in cancer patients, but not as a chemotherapy toxicity factor, and therefore we consider our article of an adequate amount of impact and interest for the medical community.