

Peer review file

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Comment 1: First, you described that you set cut off value of PNI in study to 45, referenced #16. Please consider evaluating cut off value of PNI for PFS and OS in your cohort using ROC analysis.

Reply 1: According to the reviewer's comment, we have used ROC curve to evaluate PNI for PFS and OS with cut off value of 45. The results showed that the AUC of ROC was 0.689 for OS (sensitivity: 90%, specificity: 51.6%) and 0.730 for PFS (sensitivity: 97.3%, specificity: 50%).

Changes in the text: We have added we have modified our text as advised in Statistical analyses (see Page 8, line 164-165) and Results (see Page 9, Line 187-189).

Comment 2: Please provide more of a background of this index as most clinicians are not familiar with this index.

Reply 2: Thank you for your valuable advice. We carefully reviewed the literature of PNI and supplemented the background information in our paper.

Changes in the text: We further added the research background of PNI in the section of introduction (see Page 5-6, line 93-111).

Comment 3: More detail is needed regarding the timing of the blood draw providing the measures for the indices. All of components of measure should have been drawn before treatment and within a specific time period before treatment to accurately reflect the patient. It is a potential confounder if there is a wide variation in timing of the draw before treatment between patients and, more importantly, if the measures were obtained from blood drawn after treatment as the treatment will impact the results. Please clarify.

Reply 3: Thank you for your valuable comments. We selected patients who had not received anti-tumor treatment in the two weeks before blood collection, and patients must meet the requirements of hematological indicators (no blood transfusion within 14 days, hemoglobin (HB) $\geq 90\text{g/L}$, absolute value of neutrophils (ANC) $\geq 1.5 \times 10^9/\text{L}$, platelets (PLT) $\geq 80 \times 10^9/\text{L}$). Furthermore, blood must be collected and tested within 7 days prior to anlotinib treatment.

Changes in the text: We have modified our text as advised in the section of patient enroll criteria and therapeutic procedure (see Page 6-7, line 129-134).

Comment 4: Regarding the covariates and analytic method of multivariate analyses, more detail descriptions are needed. Which variables were included as covariates to make final model? Which analytic methods did you use? Did you use “Enter or backward stepwise selection” methods? Please clarify.

Reply 4: Thank you very much. We included all the factors that might affect into the COX regression model, regardless of whether the results of the univariate analysis were statistically different or not. The factors include age, sex, BMI, ECOG PS, smoking history, CNS metastasis, liver metastasis, LDH and PNI. To arrive at the final multivariate model, all candidate variables were included whether which were significant on univariate analysis or not with enter selection.

Changes in the text: We have added the description in the section of statistical analyses. (see Page 8, line 167-173).

Comment 5: Variables “age, sex, and BMI” should be included to the multivariate process. If these variables are not included in the model, it cannot be insisted that pretreatment PNI is an independent risk factor for outcomes in this study.

Reply 5: Thank you for your instructive suggestions. According to your suggestion, we have included "age, sex, and BMI" in the multivariate process and modified the results.

Changes in the text: We have added the description in the section of statistical analyses (see Page 8, line 167-173). The groups of BMI were added in Table 1(see Page 21, line 421). We also added some data in the results (see Page 10, line 208-209, Page 11, line 219-221; Page 24, line 439, Table 3; Page 286, line 455, Table 4).

Comment 6: Please check the multicollinearity between PNI and LDH. If these two variables have strong linear association (variation inflation factor >4), then only one of the variables between LDH or PNI should be include in the model.

Reply 6: We have checked the multicollinearity between PNI and LDH. The value of variation inflation factor was 1.000, showed there was no linear association between two variables. Thus, two variables were both included in COX model.

Comment 7: In the results, please add median OS and PFS in the overall patients.

Reply 7: Thank you very much. Median OS and PFS were described in the section of efficacy of anlotinib in overall patients(see Page 9-10, line 192-196). Figure 1 shows the PFS and OS survival curves for overall patients(see Page 128, line 471).

Changes in the text: We modified the title “Efficacy of anlotinib” to “Efficacy of anlotinib in overall patients” (see Page 9, line 191).

Comment 8: Lines 144 and 150, please correct the HR of PNI. Set the reference value of HR to a high PNI arm.

Reply 8: Thank you for your careful reading of our manuscript. We have modified it according to your suggestion.

Changes in the text: we have modified our text as advised (see Page 10, line 210, 215)

Comment 9: If you know the cause of death, cancer specific survival could be analyzed in addition to recurrence free survival. Deaths from non-cancer causes would need to be censored at last alive.

Reply 9: Thank you very much. We have carefully analyzed the causes of death of the patients and all the patients died due to small-cell lung cancer progression and tumor-related complications.

Changes in the text: We have added corresponding descriptions in the paper (see Page 9, line 193-194).

Comment 10: In Table 1, median age of low PNI arm is younger than the high group. Isn't this a typo? With my experience, this seems to be the opposite.

Reply 10: Thank you for your valuable advice. We have carefully checked the original data and re-analyzed the data, and the results were the same as in the manuscript. However, there was no statistical difference in the age of diagnosis between the PNI high and PNI low groups ($P=0.453$). The difference of median age in the two groups may be caused by the small sample size, but the range of high group was wider, and the minimum value of high group was 33, which was far below the minimum value of low group(44).And we made a box plot of diagnosed age to see the overall age distribution of the two groups more clearly.