Peer Review File

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Reviewer A

The authors investigated the value of procalcitonin (PCT) as a prognostic factor in patients with SCLC using analysis of discovery and validation cohorts. The authors concluded pretreatment PCT level have a significant negative correlation with prognosis in SCLC patients. From the perspective of providing this information, the present study is interesting. However, the present study has a few limitations, such as a small sample size and analysis of discovery and validation cohorts in single-institution. Therefore, multiple issues should be addressed in this article.

1. The authors reported PCT may not be useful in differentiating bacterial infections during fever in SCLC patients. How did you determine the cause of fever in SCLC patients? ex; bronchoscopy samples, and/or several cultures etc….. The method of differential diagnosis for fever should be mentioned in the 'materials and methods'.

Replay 1: Thank you for your valuable advice. The validation cohort received CT scans to confirm there was no active infections prior the initial treatment. We have revised the first paragraph on page 7, lines 12-14 to include this information in the materials and methods section.

2. In introduction, there is a lack of background knowledge related the purpose of the study.

Reply 2: We agree with the reviewer's comment. We have cited three new studies which investigated serum PCT level in lung cancer patients. We have revised the first paragraph on page 6, lines 6-9 to include these studies.

3. "As the validation cohort, 30 of 48 patients who met the eligibility criteria and developed SCLC within the study period were enrolled in the study and analyzed" (lines 30-31 of 4page). What are the eligibility criteria? I couldn't read the eligibility

criteria.

Reply 3: As mentioned in the materials and methods section, we enrolled consecutive patients who were pathologically diagnosed with SCLC at our institution between February 2013 and June 2017 and had target lesions according to the Response Evaluation Criteria for Solid Tumors (version 1.0) as validation cohort. To make this clear, we have revised the first paragraph on page 7, lines 6-11.

4. Were there any patients with SCLC who received CCRT? And, "~~~ prior radiation therapy" What's the reason?

Reply 4: We apologize for our mistake. This study included total 23 patients with LD-SCLC. These patients received chemoradiotherapy as first-line treatment. We have revised the first paragraph on page 9, line 4 and 10 to reflect these corrections.

5. "There was no correlation between PCT and the WBC count or increase in CRP level." (line 2 of page 5). However, figure 1D was showed p=0.02

Reply 5: We are thankful for the reviewer's valuable advice. There was a weak correlation between PCT and CRP. We have revised the abstract on page 3, lines 14-16 and the first paragraph on page 9, lines 16-17.

6. As mentioned in the discussion, ECOG PS and stage are significant prognostic factors in SCLC patients. In table 3, ECOG PS is not significant prognostic factor in univariate and multivariate analysis. These causes should be mentioned in the discussion. Also, any limitation of this study should be mentioned in the discussion.

Reply 6: We agree with the reviewer's comment. Previous studies have demonstrated the impact of ECOG-PS on the prognosis of SCLC patients. Our study also showed relatively higher HR for OS in patients with PS 2 or more, which was not significantly different. The number of patients included in this study was relatively small, and this may affect the results. We have added the limitation of this study to discuss these findings. We have revised the second paragraph on page 13, lines 8-23 and the first paragraph on page 14, lines 1-4.

7. The article showed the survival curve for OS according to PCT levels (figure 3A, B).

What is the meaning of showing figure 3 C and D?

Reply 7: We demonstrated the differences of OS between PCT-high and PCT-normal groups in Figure 3A and B. In Figure 3C and D, the relationship between PCT concentration and survival time was shown. Figure 3C and D demonstrated that patients with higher PCT value had shorter survival time. To make this clear, we have revised the third paragraph on page 10, line 22.

8.Please provide references to the following contents.

"~however, few reports so far have evaluated the increase in serum levels in patients with SCLC." (lines 19-20 of page 3)

"The current standard of care for ED-SCLC is shifting to combination therapy with cytotoxic anticancer agents and immune checkpoint inhibitors" (lines 26-28 of page 6)

Reply 8: Thank you for your valuable comment. According to the reviewer's comment, we have added references (10, 11, 12, 26 and 27).

Reviewer B

The authors reported the first prospective study showing that pretreatment PCT levels have a significant negative correlation with prognosis in SCLC patients.

Despite some minor issues, the manuscript is highly interesting and should be further evaluated for publication.

Abstract

p.2 l.8: please add "lung" in "...PCT remains unclear in lung cancer patients."

Reply: Thank you for your advice. We have revised the first paragraph on page 3, line 5.

Method

The Discovery cohort was recruited between February 2005 and January 2007 and the validation cohort between February 2013 and June 2017. Despite a long recruitment time, the proportion of the discovery and validation cohort is still limited. An increase of patients included in the validation cohort is highly recommended and

would increase statistical power and strengthen the manuscript.

Reply: We agree with this reviewer's comment. The limitation of this study was relatively small sample size. We are now investigating the relationship between PCT values, prognosis and immune status in SCLC patients treated with chemo-immunotherapy. The findings of this study will be confirmed in the future. We have mentioned that the number of patients in this study was relatively small as the limitation in the discussion section (the second paragraph on page 13, lines 8-10).

Results:

Is it possible to get PCT at different time points? Dynamic changes and their value for prognosis could contribute to the manuscript.

Reply: Thank you for your variable advice. The evaluation of PCT values at different time points during and after chemotherapy may provide useful information about the relationship between decrease of PCT values and treatment outcomes in SCLC patients. Unfortunately, we collected blood samples only before the start of initial treatment. In the future, we will evaluate PCT levels at different time points. These were mentioned in the second paragraph on page 13, lines 15-18.

Discussion

Please include important studies concerning PCT such as Avrillon et al. (https://pubmed.ncbi.nlm.nih.gov/25809625/) and Patout et al. (https://pubmed.ncbi.nlm.nih.gov/25218831/) and Itoga et al. (https://pubmed.ncbi.nlm.nih.gov/33451319/). Please discuss conflicting data and why your study contributes new knowledge in the field.

Reply: Thank you for the valuable comment. According to this advice, we have revised the first paragraph on page 6, lines 6-9, the second paragraph on page 11, lines 22-23 and the first paragraph on page 12, lines 1-8 to include these studies as references and discussed conflicting data.

The discussion part is rather short and several issues need to be included: recent literature (see above) and limitations of the study, etc.

Reply: Thank you for your advice. We have added the limitation of this study in the discussion section. We have also included recent studies to discuss conflicting findings. We have revised the second paragraph on page 11, lines 22-23, the first paragraph on page 12, lines 1-8, the second paragraph on page 13, lines 8-23 and the first paragraph on page 14, lines 1-4.

Acknowledgment:

Please add a statement that the study was partly presented at the 12th Annual Meeting of the Japanese Society of Medical Oncology: https://doi.org/10.1093/annonc/mdu435.119

Reply: Thank you for your advice. We have added this information in the acknowledgements.

Reviewer C

There are several reports that PCT can be increased in lung cancer, but I think this is an interesting paper that showed that PCT can affect the prognosis especially in SCLC patients.

1. According to previous report (Infect Disord Drug Targets. 2015;15(1):57-63.), PCT was increased in lung cancer c neuroendocrine component or having 2 or more metastatic sites. Can you add the detailed results about metastasis of study subjects?

Reply: Thank you for your valuable advice. In the current study, patients with 2 or more metastatic organs tended to have high PCT level. We have included this information in Table 2 and added the previous study as a reference. We have also revised the second paragraph on page 11, lines 22-23 and the first paragraph on page 12, lines 1-8.

2. DIscussion line 40

-Although PCT is higher in SCLC patients, the median value is 0.39, which is not higher than the reference value of 0.2-0.5 suggesting bacterial infection. It seems that the expression that it is not useful for distinguishg bacterial infection should be reconsidered. (Ann Lab Med. 2014 Jul; 34(4): 263–273.)

Reply: Thank you for your comment. According to the reviewer's comment, we have revised the fourth paragraph on page 3, lines 20-21, the second paragraph on page 11, lines 10-11 and the first paragraph on page 14, lines 5-6.

3. Please explain the limitation of your study including small sample size.

Reply: As mentioned above, we have added the limitation of this study in the discussion section. We have revised the second paragraph on page 13, lines 8-23 and the first paragraph on page 14, lines 1-4.