Peer review file
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Reviewer A

Major concerns:
Comment 1: The authors emphasized the importance of this article is fitted the clinical practice with first-line EGFR-TKI in treating EGFR-mutated NSCLC. However, this study excluded those with comorbidities that may affect CRP but that turned this study out of reality.

→In order to evaluate CRP purely, we thought that inflammatory diseases should be excluded and analyzed. However, as you pointed out, it was found that inflammatory diseases should not necessarily be excluded in order to consider whether they can be used as indicators in the real world.
Based on the suggestion, the analysis target is changed in the revised manuscript (Figure A). The changes in the statistical analysis results are shown below.

We added the following description to the revised manuscript:
"Based on multivariate analysis, high CRP level (EGFR-mutated, HR: 2.479, 95% CI: 1.331–4.619, p = 0.004; EGFR-wild, HR: 3.625, 95% CI: 2.149–6.116, p <0.001) was a significant and independent negative prognostic factor for overall survival in patients with or without EGFR mutations." on page 3 in the Abstract (Results) section.
"High CRP levels predicted a lack of response to treatment in patients with advanced lung adenocarcinoma with or without EGFR mutations. Thus, the CRP level is a good and easy to use prognostic factor and objective indicator for clinical practice" on page 4 in the Abstract (Conclusions) section.
"Of the 286 total cases of advanced lung adenocarcinoma, 213 (EGFR+ [n=168], EGFR wild [n=118]) were included to analyze PFS and OS." on page 8 in the Results section.
"Patients with high CRP levels had significantly shorter PFS than those with normal CRP levels (Figure 2A: EGFR (+), median 7.3 versus 12.6 months, HR 1.813, 95% CI: 1.041-3.159, p = 0.011; Figure 2B: EGFR (-), median 2.0 versus 5.4 months, HR 2.568, 95% CI: 1.330-4.958, p < 0.0001). Similar to PFS, OS was shorter in the adenocarcinoma subtype in patients with high CRP levels (Figure 2C: EGFR (+), median 10.1 versus 37.4 months, HR 2.686, 95% CI 1.383-5.214, p < 0.0001; Figure 2D: EGFR (-), median 8.6 versus 19.2 months, HR 3.052, 95% CI 1.507-6.183, p < 0.0001)." on page 9 in the Results section.
"Brain metastases (HR: 2.438; 95% CI: 1.314–4.522; p = 0.005), ECOG PS 2-3 (HR: 2.744; 95% CI: 1.453–5.180; p = 0.002), and high CRP levels (HR: 2.479; 95% CI: 1.331–4.619; p = 0.004) were significant and independent negative prognostic factors for OS according to the multivariate analysis." on page 10 in the Results section.
"The results of the present study indicated that CRP level was a useful indicator in adenocarcinoma. Since a different treatment method is selected for squamous cell lung carcinoma than for adenocarcinoma, showing data only for adenocarcinoma is a strength of this study." on page 11 in the Conclusions section.

Comment 2: What's the importance or impact of those excluded for first-line PSF and OS analysis? Since the CRP level was different in total EGFR-mutant and EGFR-wild patients with adenocarcinoma, but the difference became insignificant once those were excluded?

→Based on the proposal, adding and analyzing the first excluded cases reduced the difference in mean CRP values.

(All) Mean CRP 13.39mg/L (EFGR+) vs 21.19mg/L (EGFR-)
(After excluded) Mean CRP 1.5 mg/L (EFGR+) vs 2.5mg/L (EGFR-)

We added the following description to the revised manuscript:
"Mean serum CRP level in treated NSCLC patients were not significantly different in patients with or without EGFR mutations." on page 3 in the Abstract (Results) section.

Comment 3: From the Table 2, we learned the difference of two groups regarding the baseline CRP. And those with lower CRP tended to be younger, female gender, fewer brain metastasis, better performance status, and that may explain why the lower CRP group got better outcome. Besides, although there no significant difference in choice of first-line EGFR-TKIs. But if we tested those TKIs with Gefitinib and non-Gefitinib and the result would be significantly different with a $p < 0.0001$.

→The treatment content should have been examined in more detail. We analyzed not only EGFR positive but also wild type treatment.

We added the following description to the revised manuscript:
"first-line EGFR-TKI (gefitinib vs. others)," on page 9 in the Results section.
"The use of osimertinib for the EGFR T790M mutation (HR: 0.318; 95% CI: 0.140–0.720; $p = 0.006$) was a significant positive prognostic factor for OS in the multivariate analysis." on page 10 in the Results section.

"Characteristics of patients in the EGFR wild-type adenocarcinoma group are shown in Table 4 for each serum CRP level. The EGFR wild-type adenocarcinoma group were investigated for history of platinum and immune checkpoint inhibitor (ICI) use. Only high CRP levels contributed to prognosis with significant differences in both univariate and multivariate analysis (Table 5)." on page 10 in the Results section.

Minor concerns:
Comment 4: Could we just focus on EGFR-mutant adenocarcinoma? Then we don't have to discuss mGPS. Or the authors want to discuss all adenocarcinoma and change the title and structure?

→The structure itself has been changed. SCC and SCLC are excluded from the analysis target. We are changing to focus on the examination of adenocarcinoma as a whole.

→The following corrections have been made based on major concern 1, 2 and minor concern 3.
An alternative title to refine could be: "High serum C-reactive protein levels predict survival in patients with treated advanced lung adenocarcinoma."
We added the following description to the revised manuscript:
"We investigated the clinical utility of C-reactive protein (CRP) levels measured at the time of diagnosis in EGFR-mutant and wild-type NSCLC patients who had undergone first-line therapy." on page 3 in the abstract (background) section.
"The presence or absence of EGFR gene mutations is an important prognostic factor in advanced NSCLC." on page 5 in the background section.

Comment 5: What's the different between CRP and NLR or LMR?
Comment 7: The interaction between EGFR mutations and CRP?

→We changed the title and structure. As a result, we decided to discuss not only EGFR-positive lung cancer but also adenocarcinoma as a whole. The description that emphasizes only NLR or LMR and EGFR positive has been deleted.

Comment 8: The writing could be better.

→The manuscript has been edited again. The edit was performed by professional editors at Japan Medical Communication, English grammar and usage, and that appropriate revisions have been suggested.

Finally, the Conclusions were modified due to the change of the analysis group. Could you confirm the Conclusions section on page 12.

Reviewer B

Major issues
Comment 1: The authors opted to analyze SCLC and SCC along with the EGFR mutated NSCLC cases. This does not add any relevant information and does not reflect what has been proposed in the title and in the background. I believe this analysis should be excluded.

→Based on the suggestion, SCLC and SCC were excluded from the analysis. In addition, based on the indications from another reviewer, cases with inflammatory diseases were included in the analysis. The title had also changed due to changes in the analysis cases. An alternative title to refine could be:" High serum C-reactive

protein levels predict survival in patients with treated advanced lung adenocarcinoma."

Comment 2: It would be more informative if the authors evaluated the prognostic impact of CRP in non-squamous NSCLC with EGFR mutations that did not receive TKI, besides the group of adenocarcinomas without EGFR mutation.

→As you pointed out, we think it will be the most important control group. However, the number of cases is small and it has not been examined. There were only 6 non-squamous NSCLC with EGFR mutations that did not receive TKI, of which only 1 had high CRP. Except for cases with interstitial pneumonia, it is rare that EGFR-TKI is not used in the 1st Line, and it is considered difficult to collect cases in the future.

Comment 3: Similarly, the study population in fact should be represented by patients selected after all the exclusion criteria has applied (EGFR++88; EGFR-=99). This should be corrected in the manuscript and in the tables.

→Each table has been changed due to the change of the analysis group. Also, as you pointed out, we have listed patient information after the exclusion criteria have been applied (Table 1-5).

Comment 4: Since the authors are exploring CRP as a prognostic factor, I would be better to determine the best cut-off in the studied population, instead of using a pre-stablished cut-off. It might happen that the best CRP level to differentiate good and poor prognosis patients among EGFR mutated and non-mutated patients is not the same.

→Based on the suggestion, we calculated and analyzed the CRP cutoff using the ROC curve. We added the following description to the revised manuscript:

"CRP cutoff values were obtained from the receiver operating characteristic curve." on page 3 in the Abstract (Methods) section.

"The optimal CRP cutoff values were 8.1 mg/L for EGFR-mutated NSCLC and 16.7 mg/L for EGFR-wild NSCLC." on page 3 in the Abstract (Results) section.

"Receiver operating characteristic (ROC) curves or Youden's index was used to determine the best cutoff values for CRP levels as a prognostic factor." on page 8 in the Methods section.

"The best cutoff points of CRP levels as determined by ROC curve or Youden's Index were 8.1mg/L (EGFR+) and 16.7mg/L (EGFR wild), respectively." on page 8 in the Results section.

Comment 5: It would be interesting if the authors incorporated comorbidity (Charlson score or number of comorbidities) in the multivariate analysis.

→Based on the suggestion, we included the "Charleson score index (CCI)" on page 6 in the Methods section.

We added the following description to the revised manuscript:
"Patients with wild-type EGFR tended to have poor ECOG PS and high CCI, but there was no difference in mean serum CRP levels relative to the patients with mutant EGFR." on page 8 in the Results section.

Minor comments
Comment 6: The manuscript must be revised to improve clarity, preferably by a native English speaker.

→The manuscript has been edited again. The edit was performed by professional editors at Japan Medical Communication, English grammar and usage, and that appropriate revisions have been suggested.

Finally, the Conclusions were modified due to the change of the analysis group. Could you confirm the Conclusions section on page 12.