Peer Review File

Article Information: https://dx.doi.org/10.21037/tlcr-21-267

Reviewer A

The authors have done a massive effort to collect and analyse clinical data from over 1,000 NSCLC patients. They have checked if the immune-inflammation index computed from blood cell counts data could be a predictor of RFS and OS. The clinical and statistical part of the project is sound and performed in a proper way. Actually, whenever a question arose during the reading of the manuscript, the answer was some lines later in the manuscript. Thus, I recommend the paper for publication as it is.

Some very minor questions:

Comment 1: *Why patients were treated only with surgery even if the cancer was stage III?*

Reply 1: Thanks for your valuable comment. Previously, we didn't describe the criteria of patient enrollment clearly. In our institution, we recommended adjuvant therapy for selected patients according to lung cancer guidelines. For most patients with stage IIIA NSCLC, upfront surgery and adjuvant therapy were recommended, and they had favorable survival outcomes(1). Therefore, we have added the details of adjuvant therapy of enrolled patients and revised the survival analyses. To eliminate the effect of chemotherapy on SII, the patients receiving neoadjuvant chemotherapy were also excluded, and only patients with upfront surgery were included.

Changes in the text: Line 115-118.

Comment 2: *What is the difference between recurrence-free interval and progression-free interval in the presented manuscript? In my opinion, PFS sounds better as it is known more in the clinic than RFS.*

Reply 2: Thanks for your comments. In our opinion, PFS is defined as time from the confirmation of disease to disease progression or death from any cause. Since the events of PFS are disease progression or death, PFS is widely used in studies focusing on patients with advanced lung cancer(2,3). However, the event of RFS is recurrence of lung cancer, and death from other causes is censored. RFS is a sensitive variable for early-stage lung cancer, especially for patients with recurrence but no death. Therefore, we believe that RFS is a more suitable survival variable for patients receiving curative-intent surgery.

Changes in the text: N/A.

Reviewer B

Overall, this is an interesting manuscript suggesting that higher values of SII was associated with worse survival among patients with NSCLC. My comments are mostly minor.

Comment 1: *Two sources of bias in studies of this type are missing values and competing risks. Please carefully address these concerns and provide appropriate sensitivity analyses.*

Reply 1: Thanks for your constructive advice. For missing values, we used multiple imputation to fill the missing values in SII and GGO appearance. Survival analyses were re-conducted after multiple imputation (Supplementary Table 1 and Supplementary Table 3). For competing risks, we also conducted competing risk analyses using R package "*cmprsk*" on the main results. The results were similar with previous conclusions (Supplementary Figure 2 and Supplementary Figure 3).

Changes in the text: Line 208-210, line 231-234, line 269-271, and line 279-282.

Comment 2: *How many participants received radiotherapy?*

Reply 2: Thanks for your comments. In this study, 156 patients received postoperative radiotherapy as adjuvant therapy, which has been added in Table 1. Adjuvant radiotherapy was also added in the Cox multivariable models to adjust for its survival

effect.

Changes in the text: Line 179, line 217, line 227, line 242, and line 251.

Comment 3: *Please specify what chemo drugs were given as some are more myelosuppressive than others. A stratified analysis in this respect would be informative.*

Reply 3: Thanks for your comments. Previously, we didn't describe the criteria of patient enrollment clearly. To avoid the effect of chemotherapy, patients receiving neoadjuvant chemotherapy were excluded, and only patients with upfront surgery were included in this study. We have emphasized it in the method part.

Changes in the text: Line 115-118.

Comment 4: *SII has been found to be predictive of survival in locally advanced Staged 3A/B NSCLC (Int J Environ Res Public Health 2020 doi: 10.3390/ijerph17217995). Since your study included Stage 3A patients, please suggest why your results are different.*

Reply 4: Thanks for your comments. Biswas et al. investigated the survival effect of SII in patients with stage III non-squamous NSCLC receiving chemotherapy and radiotherapy. There are two reasons resulting in different results. Firstly, the target population was distinct. Biswas's study focused on patients receiving chemotherapy

and radiotherapy, while our study investigated patients receiving curative-intent surgery. Recently, radiotherapy was reported to exert its anti-tumor effect by recruiting tumor-specific immunity(4). Therefore, SII might have prognostic value in patients receiving radiotherapy. Secondly, the timing of measuring SII was also different. In this study, SII was measured before surgery, and patients did not receive any treatments. This study focused on the "baseline" SII. As for Biswas's study, SII was measured during weeks 3-4 of six weeks of radiotherapy, and SII in Biswas's study could be considered as "changed" SII after radiotherapy. Therefore, the above two factors, distinct enrolled patients and timing of measuring SII might account for the different conclusions from two studies.

Changes in the text: N/A