In this study, the authors reported that higher preoperative PLR-FIB, which were calculated by platelet-to-lymphocyte ration (PLR) x fibrinogen (FIB), could be a poor predictive factor of overall survival (OS) in resected non-small cell lung cancer (NSCLC) patients. I have some serious concerns and comments listed below.

Comment 1: First, what does PLR-FIB reflect in patients with cancer? And why is it necessary to combine PLR and FIB? This is my serious major concern. They should address much more clearly.

Answer 1: PLR is associated with systemic inflammatory response (SIR), which plays a critical role in tumor progression and metastasis. In several studies, PLR as a prognostic indicator for many malignant tumors has been reported. FIB can reflect blood coagulability. The imbalance of coagulation system is associated with malignant tumor progression. PLR and FIB are both potential biomarkers in predicting survival in patient with cancer. PLR-FIB is an indicator reflecting SIR and coagulation concurrently, and few studies have investigated the prognostic utility of a combination of SIR and the coagulation system in NSCLC. Thus, the combination of PLR and FIB would be a novel prognostic indicator in NSCLC. According to the results of this study, PLR-FIB low and high had significant difference in overall survival, prompting us that the valuable of combination of inflammatory response and coagulation can be explored in further study.

Comment 2: They draw the ROC curve for PLR-FIB in supplemental Table 1. The sensitivity, specificity and AUC were 76.8%, 36.6% and 0.502, respectively. I felt these are quite low, and unreliable. What was the p-value? Anyway, I think their PLR-FIB could not be a good predictive factor. How the authors explain?

Answer 2: Although the AUC was low, according to the cut-off value calculated by Youden index, the low PLR-FIB was an independent factor for a better prognosis in multivariate analysis (HR, 0.587; 95% CI: 0.350–0.985; P=0.044). It may be because the simple size of this study was not large enough so that AUC was not such appreciable. However, the prognostic tendency was adoptable for further study.

Comment 3: Line 142 and Table 1; The complications after surgery were 96.5%, which were too many not to be tolerate for me. How about this?

Answer 3: Please excuse this clerical error. Due to assignment in analytical process, the data was reversed. The incidence of complication was 3.5% instead of 96.5%. And other clerical errors have been revised in the text and Table 1.

Changes in the text: Line 162-165 and Table 1.

Comment 4: Pathology of this study; There were just eleven cases of ASC, which was quite small number, even though it was associated with 5-y OS. Maybe this should be included in

others. On the other hand, SCC accounted for 55.1%, which was quite large number. This seems different from the current situation where there are many adenocarcinomas. Why and what was in the background? The difference of this histological background could influence the prognosis in this study. They should address.

Answer 4: Although the cases of ASC were minor, the outcome of this pathology type were quiet poor. The median survival was 29.8 months in ASC group and 57.7 months in "Other" group. Classifying ASC into "Other" group may conceal the poor outcome of ASC. Therefore, we divide ASC as an independent group. In the matter of SCC proportion, after checking raw data, it is still a clerical error. Due to assignment in analytical process, the data was reversed. It was ADC that accounted for 55.1% while SCC accounted for 33.4%, which was accord with the epidemiology of NSCLC.

Changes in the text: Line 166-168 and Line 187, Table 1 and Figure 1.

Reviewer B

Thank you for the opportunity to review this manuscript by Luo et al entitled "Combination of the platelet-to-lymphocyte ratio and fibrinogen as a novel biomarker for predicting patient in non-small cell lung cancer treated with surgery." This work the author retrospectively review 314 patients who underwent operative resection for non-small cell lung cancer. They correlate overall survival to platelet-to-lymphocyte ratio and fibrinogen level. I have several questions/comments outlines below.

Comment 1: The title is missing a word after "predicting." I assume this is either "survival" or "overall survival" but should be corrected in either case.
Answer 1: Revised it.
Changes in the text: Title.

Comment 2: The authors state that TNM staging and genetic testing "limit their clinical application." TNM staging is essentially no cost after standard preoperative staging and operative resection. Genetic testing for targetable mutations may be slightly more expensive but is standard of care. It is also of enormous benefit to the patient is actionable mutations are discovered.
Answer 2: This sentence was inappropriate, so we revised it.
Changes in the text: Line 78-79.

Comment 3: How did the authors get the consent for patients in a retrospective study design? Did they call and ask at some point after discharge? How many patients declined participation? Typically informed consent is waived in this type of study.
Answer 3: Signing the informed consent for collecting clinical data was routine process at this center. Thus, every patient signed the informed consent when them were hospitalized.

Comment 4: If this is a retrospective study design how did the authors get lab data including Fibrinogen and LDH 1 week prior to surgery? Is this the standard for all patients at the study

institution?

Answer 4: To ensure safety of surgery, fibrinogen and LDH were routine tests before surgery within 1 week at this center. It is standard for all patients in this study.

Comment 5: Can the authors describe what they mean by "underlying disease." What specific comorbidities did they capture? In addition, the complication rate of 96.5% is extremely high. This needs more explanation. Lastly, what types of resections were performed in the sublobar and other groups.

Answer 5: The underlying disease include hypertension, diabetes mellitus, COPD, coronary heart disease, HBV and other chronic diseases. Due to assignment in analytical process, the data was reversed. The incidence of complication was 3.5% instead of 96.5%. And other clerical errors have been revised in the text and Table 1. Wedge resection was performed in sublobectomy. Different types of palliative resection according to patients' condition were performed in the other group.

Changes in the text: Line 162-165 and Table 1.

Comment 6: How many patients received adjuvant therapy and did this correlate with survival?

Answer 6: None of patients in this received adjuvant therapy.

Comment 7: Survival should be stratified by TNM stage.

Answer 7: Already stratified. See figure 1.

The paper titled "Combination of the platelet-to-lymphocyte ratio and fibrinogen as a novel biomarker for predicting patient in non-small cell lung cancer treated with surgery" is interesting. PLR-FIB was found to be an independent prognostic factor, with little effect linked to TNM stage. Preoperative PLR-FIB is suggested to be a potential biomarker for predicting the outcome of patients with NSCLC treated with surgery. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1: This study only investigated the relationship between PLR-FIB and OS, and the results were too simplistic. Suggest adding results analysis for progression-free survival.

Answer 1: It is one of limitation in this study. Because lack of some clinical data, PFS have not been analyzed in this study.

Comment 2: The abstract is not adequate and needs further revisions. The research background does not indicate the clinical needs of this research focus. The study results need to show the clinical characteristics of the two groups of patients.

Answer 2: Revied it.

Changes in the text: Line 37-45 and Line 57-60.

Comment 3: This study is a retrospective analysis, which is likely to cause some deviations in

the results. It needs to be further confirmed by multi-center clinical trials.

Answer 3: Agree.

Comment 4: In addition to PLR-FIB, what other parameters play an important role in the prediction of NSCLC treated with surgery? It is recommended to add relevant content.

Answer 4: Due to retrospective study, some data was lack. According to the data existing, all parameters probably predicting survival were analyzed in the univariate and multivariate analysis.

Comment 5: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "The role of platelet-lymphocyte ratio in hepatocellular carcinoma: a valuable prognostic marker, Transl Cancer Res, PMID: 36644176". It is recommended to quote this article.

Answer 5: Quoted it.

Changes in the text: references

Comment 6: What are the main structural and functional properties of fibrinogen? What are its clinical manifestations, laboratory diagnosis and treatment methods? It is recommended to add relevant content.

Answer 6: Added some information of FIB in the text.

Changes in the text: Line 92-94.

Reviewer D

Comment 1: First, the title needs to indicate the prognosis outcome to be predicted, as well as the clinical research design such as a retrospective cohort study. The title also needs to focuses on prognostic roles of the biomarker, not the prediction since the authors did not examine predictive accuracy.

Answer 1: revised it

Changes in the text: Title.

Comment 2: Second, the abstract needs further revisions. The background did not explain the clinical significance of this research focus. The methods need to describe the inclusion of subjects, the assessment of baseline clinical factors, laboratory methods for testing PLR and FIB, follow up procedures, and measurement of prognosis outcomes. The results need to briefly summarize the clinical characteristics of the study sample and clinical covariates adjusted in the multiple Cox regression analysis. The conclusion should not mention prediction because of my above comments.

Answer 2: The background, results and conclusions were revised according to advice. However, due to the limitation words of abstract, the method could not include such much information.

Changes in the text: Line 37-45 and Line 57-63.

Comment 3: Third, in the introduction, the authors need to explain why the combination of the

two biomarkers is better than either one alone, otherwise I cannot see the necessity of this research focus.

Answer 3: revised it

Changes in the text: Line 100-105.

Comment 4: Fourth, the methodology of the main text needs to describe the clinical research design, sample size estimation, follow up procedures, and measurement of prognosis outcomes. "a retrospective, single-center study design" is inadequate to describe the research design. In statistics, please ensure P<0.05 is two-sided. Please also describe the details of multiple Cox regression analysis, in particular how to determine the independent prognostic role of the combination of the two biomarkers. A further question is to provide data to support that the combination is better than either one alone.

Answer 4: Except patients reaching exclusion criteria, all patients with NSCLC accepted for surgery in the period from December 2017 to December 2021 at Fujian Medical University Cancer Hospital were enrolled. Thus, sample size estimation was not applicative in this study. Clinical research design, follow up procedures, and measurement of prognosis outcomes already described. See line 121-138. Some detail has been added in statistics. Added the data of PLR ($P>0.05$) and FIB ($P>0.05$) in univariate analysis to support that the combination is better than either one alone.

Changes in the text: Line 150-152 and Table 2.

Comment 5: Finally, please cite several related papers: 1. Li DZ, Guo J, Song QK, Hu XJ, Bao XL, Lu J. Prognostic prediction of the platelet-to-lymphocyte ratio in hepatocellular carcinoma: a systematic review and meta-analysis. Transl Cancer Res 2022;11(11):4037-4050. doi: 10.21037/tcr-22-1197. 2. Jin X, Wang K, Shao X, Huang J. Prognostic implications of the peripheral platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in predicting pathologic complete response after neoadjuvant chemotherapy in breast cancer patients. Gland Surg 2022;11(6):1057-1066. doi: 10.21037/gs-22-244. 3. Wu J, Zhang Y, Liu G, Ge L. New use of preoperative fibrinogen in ovarian cancer management. Transl Cancer Res 2023;12(11):3105-3112. doi: 10.21037/tcr-23-908. 4. Cortinovis D, Malapelle U, Pagni F, Russo A, Banna GL, Sala E, Rolfo C. Diagnostic and prognostic biomarkers in oligometastatic non-small cell lung cancer: a literature review. Transl Lung Cancer Res 2021;10(7):3385-3400. doi: 10.21037/tlcr-20-1067. 5. Duchemann B, Remon J, Naigeon M, Cassard L, Jouniaux JM, Boselli L, Grivel J, Auclin E, Desnoyer A, Besse B, Chaput N. Current and future biomarkers for outcomes with immunotherapy in non-small cell lung cancer. Transl Lung Cancer Res 2021;10(6):2937-2954. doi: 10.21037/tlcr-20-839.

Answer 5: Quoted.

Changes in the text: References.