Peer Review File

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Reviewer A

This study evaluating radiographic predictors for lung adenocarcinomas that are T1 and T2 lesions is very important in the current era of sublobar resections that is evolving as we speak. Therefore, having this type of predictive information is very valuable.

Comment 1: Why were the sizes for the training and testing cohorts determined to be a 2:8 ratio? More importantly, can the investigators provide some explanation as to why and how their total cohort of 244 and their division into their training and testing cohorts were "powered" enough to truly create a robust and accurate nomogram? Could increasing the size of the entire cohort and thus the subsets made for a better nomogram? The lack of statistically significant associations between ALK rearrangements and EGFR mutations and with other more macroscopic features hint at this need for greater power.

Reply 1: We sincerely thank the reviewer for these questions.

(1) We feel sorry for the mistake in Figure 1. The size for the training and testing cohorts was determined to be an 8:2 ratio, and we have changed the figure in the revised manuscript. In addition, we mentioned this in the Methods section (see Page5, line127-128).
(2) We conducted preliminary experiments and estimated the sample size to ensure statistical significance so as to establish a robust and accurate nomogram. A larger sample size would be better for making a nomogram. The issue of the small sample size has been raised in the Limitation section (see Page15, line413-415), and studies of large multicenter populations will be conducted in the future for further validation.
(3) The lack of statistically significant associations between STAS and ALK rearrangements and EGFR mutations may be related to sample size, as well as to the low number of people undergoing ALK (47%,115/244) and EGFR testing (34.4%,84/244), and we have added this in the Discussion section (see Page13, line349-351).

Comment 2: All patients were reported to undergo unenhanced CT imaging a week before their operation? Can the investigators explain why they relied upon non-contrasted imaging versus contrasted imaging for something so critical as STAS that may be enhanced with contrast?

Reply 2: We thank the reviewer for the question. As this was a retrospective study, patients were routinely given unenhanced scans preoperatively in our hospital. Thus, the degree of tumor enhancement cannot be observed. We have added this point to the Limitations section (see Page15, line420-422).

Comment 3: One basic question I have is that STAS has been thought to be present with the more aggressive histology subtypes. Therefore, if a biopsy shows micropapillary or solid histology, would it be not reasonable to assume that STAS is present and therefore a lobectomy

should be performed regardless of size especially in light of their own margin findings?

Reply 3: We sincerely thank the reviewer for the comments.

(1) Although STAS is typically associated with the more aggressive histological subtypes, it is not limited to aggressive histological subtypes. In this study, we included patients with T1, T2 stage lung adenocarcinoma and the main histological subtypes of STAS-positive adenocarcinomas were acinar (43.4%,36/83) and papillary (31.3%,26/83).
(2) Moreover, preoperative detection of STAS could help select an appropriate surgery type, but it is not a determining factor. The decision to perform a lobectomy takes into account multiple factors, such as the patient's health condition, tumor size, location, surgical margin and so on, not just STAS and histological subtypes.

We have added this point to the Discussion section (see Page12, line324-331).

Comment 4: Can the investigators share exactly how grading or categorizing the likelihood of STAS in accordance with the GGO ratio was conducted? Was the ratio evaluated as a continuum retroactively in their analysis or was there some thought given to establishing cut-offs and analysing them using this approach?

Reply 4: We thank the reviewer for the question.

(1) The GGO ratio was evaluated as a continuum retroactively in the analysis. And we have added the performance of the ratio in predicting STAS in the Results section (see Page10, line280-282). It had a sensitivity of 86.7% and a specificity of 70% in the testing set.
(2) According to the suggestion of the reviewer, we have established a cut-off value of GGO ratio in the Statistical analysis (see Page8, line211-213) and Results section (see Page10, line283-285). The optimal cut-off value was 0.43 with a sensitivity of 80.9% and a specificity of 62.6%.

Comment 5: The end of their results leaves the reader desiring for a little more. It would be more impactful for them to reveal in the text of their results an example of how the nomogram was effective rather than leaving it to evaluating an AUC curve in a more quantitative manner. As they mention in their discussion, the features they have used in their nomogram have previously been shown to be associated with STAS. Their final paragraph in their results really lacks some punch in describing how combining these features makes a more realizable difference. Also, focusing on spiculations in their results and discussion is not as helpful as they believe because as stand-alone features, many tumors have it with or without STAS and so again, the impact of it alone (and even being discussed as an individual feature) is not very meaningful.

Reply 5: We thank the reviewer for the suggestions.

(1) We have added the performance of individual signs in predicting STAS which were all lower than the nomogram combining all features in the Results section (see Page10, line280-283).
(2) We have made deletions and euphemistic wording to the relevant content of the manuscript to avoid misleading in the Discussion section (see Page13, line361-374). We developed a

nomogram to predict STAS before surgery, which including GGO ratio, shape and spiculation. The results indicated that these signs may be related to STAS, caused by infiltrative tumour growth.

Comment 6: In their nomogram, it is not clear how to “plug in” shape. Which shape in their nomogram gets a “1”. Indicating this what triggers a 1 in this category and what exactly triggers a “1” in spiculations seems necessary for their actual nomogram.

Reply 6: We sincerely thank you for kind reminder. Tumours with irregular shape (not round or oval), signs of spiculations and GGO radio of 0 gets a “1” in the nomogram. We have added this to the Results section (see Page10, line277-278) and the legend of Figure4.

Comment 7: Please add some commentary as to how machine learning or artificial intelligence will either replace or improve upon their findings? It will not be surprising to observe that this type of investigation will most certainly emerge over the next year or so. Overall, reading about this study was both informative and enjoyable. It can be a valuable and useful contribution to the scientific literature on STAS.

Reply 7: We sincerely thank the reviewer for the comments. We have added some commentary as to machine learning or artificial intelligence in predicting STAS in the Discussion section (see Page14-15, line403-412).

Reviewer B

Comment 1: The authors aimed to establish a nomogram to predict a spread through air spaces (STAS) in lung adenocarcinoma. Toyokawa et al. has already published the similar findings in 2018 (Toyokawa G, et al. J Thorac Cardiovasc Surg 2018;156:1670-6), though they did not make a nomogram. From the point of originality, this paper lacks the novelty in the study of STAS. As this is a retrospective study, the prognosis or recurrence pattern of the patients with STAS could be investigated.

Reply 1: We sincerely thank the reviewer for the insightful suggestions. We have conducted telephone follow-up on patients, and collected their prognosis data. The Kaplan-Meier method and the multivariable Cox proportional hazards regression model were used for survival analysis. We have added the content, tables and figures about the prognosis of STAS to enhance the innovation of the manuscript in the Methods (see Page5, line130-134), Statistical analysis (see Page8, line218-221), Results (see Page11, line294-313) and the Discussion section (see Page14, line393-402).

Comment 2: In the method, the reason of 1:2 matching by only 3 factors is not clear. If the authors are going to increase the ratio of STAS, they should exclude the case with adenocarcinoma in situ and minimally invasive adenocarcinoma. Moreover, the authors divided the training sets at a ratio of 2:8. There is no explanation of this point. The number of testing cohort is much smaller than training cohort. I wonder if the discrepancy is acceptable or not.

Regarding with the adjustment of patient's number, I am afraid that it could lead the distortion of the results.

Reply 2: We sincerely thank the reviewer for the questions.

(1) According to Kim [1], we adopted a matching method to choose STAS-negative patients who were similar to the STAS-positive patients regarding age, sex and smoking status. We selected 1:2 ratio matching because it yielded the most balanced data set. We have added this in the Methods section (see Page5, line120-126).
(2) We feel sorry for the mistake in Figure 1. The size for the testing and training cohorts was determined to be a 2:8 ratio, and we have changed the figure in the revised manuscript. We also mentioned this in the Methods section (see Page5, line127-128). In addition, we conducted preliminary experiments and estimated the sample size to ensure statistical significance so as to establish a robust and accurate nomogram.

[1] Kim SK, Kim TJ, Chung MJ, et al. Lung Adenocarcinoma: CT Features Associated with Spread through Air Spaces. Radiology. 2018 Dec;289(3):831-840.

Comment 3: CT image interpretation is essential in this paper. The authors had better demonstrate the typical figure of GGO or other radiological findings.

Reply 3: We sincerely thank you for kind reminder. We have added CT images which demonstrate the typical radiological findings in Figure 3.

Comment 4: Lymphadenoma should be changed to lymphadenopathy.

Reply 4: We sincerely thank you for kind reminder and have changed "lymphadenoma" to "lymphadenopathy" in the text (see Page6, line 167 and Page7, line 189) and Table1,2,3.

Comment 5: Pathological findings of Figure 2 does not show the clear feature of STAS. Clearer photograph of STAS is needed.

Reply 5: We sincerely thank you for kind reminder. We have changed Figure 2 with a clearer photograph of STAS.