Peer Review File

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Reviewer A

The authors developed and validated a nomogram for patients with surgically resected LIMA. It is based on the very big cohorts. This reviewer has only one comment to the authors.

Comment 1: What is the definition of the 'differentiation grade'? Actually, as far as this reviewer knows, there is no official grading system for LIMA. If the definition can be described, it will be helpful to the readers.

Reply 1: Thank you very much for your detailed and constructive comments. Given that no well-established histological grading system with clearly defined criteria exists for LIMA, "differentiation grade" was determined according to the new histological grading paradigm for lung adenocarcinoma (8th edition TNM staging); this method is based on architectural predominant subtypes I) G1 for lepidic adenocarcinoma, II) G2 for acinar adenocarcinoma and papillary adenocarcinoma, and III) G3 for micropapillary adenocarcinoma and solid adenocarcinoma. We added the definition of the "differentiation grade" in the Methods section.

Changes in the text: We added the definition of the "differentiation grade" in the Methods section (see Pages 7–8, lines 150–155).

Reviewer B

As a reviewer, I enjoyed reading this article. It is well-written logically, and the authors developed a nomogram for predicting overall survival (OS) in LIMA patients after surgery and validated its utility by analyzing so many populations. That is greatly instructive for the readers. I can suggest just a few points to improve this paper.

Comment 1: LIMA can be divided into two types: pneumonic lesion and oligo-nodular lesion. Pneumonic lesion is usually spreading through airways, thus being difficult to be treated, whereas nodular lesions can be treated just as adenocarcinomas in general. The authors should clarify which type or both types were enrolled in this study.

Reply 1: We deeply appreciate your valuable suggestions. We enrolled patients with pneumonic

and oligo-nodular lesions in our study. The computed tomography (CT) findings were not available within the SEER database, so we did not show the data of pneumonic-type and solitary-type. In the external validation cohort, solitary-type was found in 348 (94.31%) patients, while pneumonic-type was found in 21 (5.69%) patients. We have added the CT findings to the Results section.

Changes in the text: Additional CT data was added to the Results section (see Pages 12, lines 259–260).

Comment 2: Prognostic nomogram which you established is interesting, but there is something wrong with the extent of surgery. Is pneumonectomy recommended rather than lobectomy? Is there significant difference between pneumonectomy and lobectomy by multivariate analysis? The authors should add some explanation to interpret your data more clearly, though I can understand that the larger extent of resection may lead to improved survival in LIMA, especially pneumonic lesion.

Reply 2: Thank you very much for these comments and suggestions for improving our article. The authors apologize for the ambiguity of our descriptions of the extent of surgery. Lobectomy remains the "gold standard" surgical intervention for patients with lung adenocarcinoma, including LIMA. In our study, patients who underwent pneumonectomy or lobectomy had a better prognosis than those who underwent sub-lobectomy. Although the risk score of pneumonectomy was less than lobectomy (0 vs. 23 points) in the prognostic nomogram, there was no significant difference between pneumonectomy and lobectomy (p=0.322). Following your advice, we added language to clarify these points to the Discussion section.

Changes in the text: We added additional language clarifying these points to the Discussion section (see Page 16, lines 342–346).

Comment 3: Can the authors prove the difference in prognostic estimation between the nomogram and conventional TNM staging?

Reply 3: Thank you very much for your kind comments. As we showed in Results 3.6: **Comparison of Predictive Accuracy for OS in the Current Nomogram versus the conventional AJCC staging systems**. The nomogram was *better* than the conventional TNM

staging system at predicting survival in LIMA patients using a decision curve analysis (Figure 5A, B, and C). The C-index for OS of our nomogram was significant higher than that of the conventional TNM staging system in the training cohort (0.735 vs. 0.694, respectively), in the test cohort (0.736 vs. 0.712, respectively), and the external validation cohort (0.773 vs. 0.741, respectively). Notably, the NRI values were 0.233 (95% CI: 0.128-0.384), 0.084 (95% CI: -0.015–0.288), and 0.245 (95% CI: -0.106–0.409) in the training, test, and external validation cohorts, respectively. The IDI values were 0.245 (95% CI: -0.106–0.409), 0.038 (95% CI: 0.014–0.087), and 0.032 (95% CI: 0.010–0.113) in the training, test, and external validation cohorts, respectively. These results demonstrated that our nomogram was superior to the conventional TNM staging in prognostic estimation.

Changes in the text: We modified text within the Methods (see Page 9, lines 185–187), Results (see Page 14, lines 288–297), and Discussion sections (see Page 19, line 391).

Minor concerns:

Comment 4: Line 82-84: Definitive diagnosis of LIMA via biopsy is challenging because the cytologic atypia of this tumor is usually inconspicuous or absent. I doubt this finding.

Reply 4: Thank you very much for your constructive comments. The non-mucinous lung adenocarcinoma features readily identifiable cytologic atypia, whereas the cytologic atypia of LIMA cells is usually inconspicuous. Additionally, LIMA often show lepidic-predominant growth, so it is more difficult to diagnose in the limited biopsy specimens and requires differentiation from metaplasia or bronchiolar adenoma. Moreover, the mixed mucinous adenocarcinoma may be difficult to diagnose from biopsy specimens, which depend on the biopsy site. Therefore, definitive diagnosis of LIMA via biopsy is challenging. We realized that our description of this sentence in the original manuscript was not clear, so we have revised this sentence.

Changes in the text: We modified text within the Introduction section (see Page 5, lines 101–108).

Comment 5: The authors should describe why female patients have a better survival than male patients.

Reply 5: Thank you very much for your constructive comments and valuable suggestions. On the one hand, females were more likely than males to be diagnosed with early stage disease in our study (65.2% vs. 56.0%, p=0.002); this finding is consistent with another study [Tolwin Y, et al. Ann. Epidemiol. 2020]. Early diagnosis of NSCLC reduces mortality in patients with lung cancers [Cykert S, et al. Cancer Med. 2019]. On the other hand, female patients were also younger, and more-likely to be never-smokers, and demonstrate EGFR-driver mutations and the p53 wild-type transcription factor—all of which are protective factors in lung cancer [Chapman AM, et al. lung cancer, 2016; Haupt S, et al. Nature communication, 2019]. Following your advice, we added more information about why female patients demonstrated better survival than male patients.

Changes in the text: We added language on sex-based differences to the Discussion section (see Page 16, lines 332–336); the references (25-32) were updated accordingly.