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Peer review file

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Reviewer A

Comment 1: The authors tried to verify the prognostic effect of lymph node ratio in N1 and N2 patients. However, the authors only categorize the cohort on the bases of lymph node status and positive ratio. In the prognostic model, stratification of stage IIA-IIIB NSCLC patients through pN-NR method should be combined with TNM stage system as the manuscript said. The model proposed by the authors ignored the prognostic impact from the T stage.

Reply 1: Thank you for your advice. In this article we tried to verify the prognostic effect of combined node station and node ratio. This is supposed to improve the current TNM classification system, which is only based on the location of metastasis lymph node. The index pN-NR in this study contains the pN, which is based on the TNM system. So, we believe that the TNM stage system is reflected in this study. We didn't ignore the prognostic impact of T stage. Actually, we found that the T stage is an independent prognostic factor in the logistic regression model.

Changes in the text: no change is made.

Comment 2: In the exclusion criteria, the authors stated that patients with number of examined LNs less than 6 were excluded. Please provide evidence or reference to elucidate the cut-off point. A study concerning the dissected lymph node number suggested that 16 lymph nodes would be an ideal number.

Reply 2: Thank you for your advice. We determined this cut point based on reference 17, which is the lower limit recommended by the European Society of Thoracic Surgery. We agree that some studies also suggested 10 LNs, even 16 LNs for accurate assessment of nodal status. To keep a balance between the quality of surgery and study sample size, we set resection of 6 LNs as the threshold for inclusion. we made some further discussion about this in the revised manuscript.

Changes in the text: line 235-237, line 319-323.

Comment 3: According to the NCCN guideline, the patients in authors' cohort were highly suggested to receive adjuvant chemotherapy. Otherwise, the survival outcomes

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would be worse. In this study, the authors failed to provide evidence of adjuvant chemotherapy or neo-adjuvant chemotherapy in N2 patients.

Reply 3: We agree that we are unable to provide the adjuvant or neoadjuvant chemotherapy information from the SEER database, which is a limitation of this study. Neoadjuvant chemotherapy may have more effect on the study result than adjuvant chemotherapy due to the possibility of lymph node downstage. However, according to EMERGING-CTONG 1103 trial, the lymph node downstage occurred in only 2.9% patients in the neoadjuvant chemotherapy group. What's more, this is a real world study involving large sample size. So, we believe that the pre-operative chemotherapy could have very limited effect to our result. We made some further discussion about this question in the revised manuscript.

Changes in the text: line 475-478.

Comment 4: SEER database has renewed its data and updated it to 2016. The patients in this cohort were included from 2004-2012. Please provide the reason for such inclusion criteria.

Reply 4: On one hand the most recently released data in the SEER database was till 2012 when this study was started. On the other hand, we hope to have longer follow up time. The year 2004 was chosen because the 6th edition of the TNM classification was not uniformly available in the database until then. So, in our study cases between 2004 and 2012 were selected.

Changes in the text: no change is made.

Comment 5: Although the idea of lymph node positive ratio in lung cancer is interesting, the authors did not choose the proper method to veriy its prognostic effect. Besides, the inclusion and exclusion criteria are not convincing. Therefore, the results and conclusion of this study are far from persuasive.

Reply 5: Thank you for your valuable advice. It's true that research with the SEER database has some unavoidable problems, and we point this out in the discussion part. This study is based on real-world data sets with robust statistics, and we employed standard survival analysis methods. The inclusion and exclusion criteria are based on published paper. So, we believe that the conclusion could be meaningful in clinical practice.

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Reviewer B

Comment 1: First, please justify the absence of an IRB approval.

Reply 1: We justified the absence of IRB approval in the revised manuscript.

Changes in the text: line 101-103.

Comment 2: Secondly, the paper should be written according to the STROBE (Strengthening the reporting of observational studies in epidemiology) [www.strobe-statement.org]. A STROBE checklist should also be added [https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.doc].

Reply 2: this studied is exactly written according to the STROBE, and we added some relevant information in the revised manuscript.

Changes in the text: line 160-162. And a STROBE checklist is provided in the supplemental material.

Comment 3: The statistical analysis should be written according to the recently published guidelines (Hickey GL, Dunning J, Seifert B, Sodeck G, Carr MJ, Beyersdorf F on behalf of the EJCTS and ICVTS Editorial Committees Editor's Choice: Statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery. Eur J Cardiothorac Surg 2015;48:180-93).

Reply 3: the statistical analysis is written according to this guideline.
Changes in the text: line 162-164.

Comment 4: The limitations section should be improved with a better discussion.

Reply 4: Thank you for your advice. We have modified our limitations section as advised.

Changes in the test: line 452-463.

Comment 5: Besides, the discussion should be improved with a better search of the

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literature.

Reply 5: Thank you for your advice. We have done more literature search in the discussion part and added some literature to the reference list as advised.
Changes in the test: line 326-331, line 416-418, line 424-428, line441-443, line445-447.

Comment 6: About minor points, there are grammars and typos errors in the text. Please thoroughly check the article.

Reply 6: We have asked a native English-speaking expert in this field to help us review the language and grammar.
Change in the text: grammars and typos errors were checked and corrected in the revised manuscript.

Reviewer C
This is an interesting study with important implications. I think this will be of interest to the thoracic surgery community and will generate debate around the proper methods of lymph node staging, including both operative technique and how we group patients into stages.

I have some minor revisions to suggest:

Comment 1: There are grammatical and spelling errors throughout. Having the manuscript reviewed by a native English speaker would be beneficial. For example, do not start sentences with "And", avoid statements like "we noticed" and ensure proper and consistent use of abbreviations (LN is inconsistently used throughout) and plurals (is it LN or LNs? choose one). Along these lines there are several passages that need to be clarified as they are hard to understand as written. This includes lines 134-138 (last section of the results), lines 170-174 (discussion regarding selection of cutpoints for NR-it is not clear why the method used here is better than that used in previous studies) and lines 207-209 (I think I understand what you are trying to say about skip metastases but it needs to be written more clearly).

Reply 1: Thank you for your advice. We have asked a native English-speaking expert in this field to help us review the language and grammar and rewritten some unclear part.

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Changes in the text: We have corrected all the grammatical and spelling errors in the revised manuscript.

Comment 2: Abstract: specify "resected" NSCLC in lines 9 and 11

Reply 2: in the manuscript we use “resected NSCLC” to mean NSCLC patients who received radical surgical treatment (lobectomy/bilobectomy/pneumonectomy and LN dissection). We have clarified the expression in the manuscript.

Changes in the text: line 64-65.

Comment 3: Background: References are needed in line 34 and line 47

Reply 3: we provided the reference for this part.

Changes in the text: reference 2 and 3.

Comment 4: Methods: Line 56 states only patients undergoing LN dissection were included-did you exclude patients undergoing LN sampling? Is that data available from SEER? If so, why, and if not, how might the difference between sampling and dissection have affected the results?-a crucial question for this study

Reply 4: This is a very good question. Systemic LN dissection or LN sampling is about whether patient received sufficient lymph node dissection. Actually, we are unable to distinguish systemic LN dissection and LN sampling in the SEER database. But we used the lower limit of resected LN number to ensure relatively sufficient LN dissection, and all patients in this study were node positive. Thus, we believe that patients in this study received sufficient lymph node dissection. We made some discussion about this question in the revised manuscript.
Changes in the text: line 328-331.

Comment 5: Line 69-Delete the sentence starting with "And the NR..."

Reply 5: Thank you for your advice. We deleted this sentence in the revised manuscript.

Changes in the text: this sentence was deleted in page 129.

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Comment 6: Why were patients with pN0 excluded? It would be very interesting to know if pN1-NR<0.3 is statistically different from pN0-at least discuss this

Reply 6: In this study, we focused on the prognostic effect of pN-NR. For pN0 patients, we are unable to calculate the NR. That's why we excluded these patients. What's more, pN0 patients are believed to have better survival than node positive patients.

Changes in the text: line 326-328.

Comment 7: The study should include the total number of nodes resected as a separate variable. It may be that NR is just a marker for the total number of nodes resected (the more nodes resected, the lower the NR), and that the number of nodes resected could either be a marker of aggressive, effective surgery or a therapeutic benefit on its own. For NR to be an important prognostic measure we need to know that it is predictive independent of the number of nodes resected.

Reply 7: Thank you for your advice. The prognostic effect of of resected LN number has been proved (reference 6), but this number could be significantly affected by the surgery quality. We don't agree that the more LN resected, the lower the NR. Actually, the more LN resected, the higher chance of finding more positive LN, which is not equal to lower NR. The NR is a marker taking into account both the number of resected LN and the number of positive LN. The prognostic effect of resected LN number could be reflected by the NR, and the effect of surgery quality could be partially controlled. So, we believe it's unnecessary to prove that NR is independent of resected LN number.

Changes in the text: No change was made.

Comment 8: Discussion: A more thorough discussion is needed of the surprising finding that pN2-NR<0.3 has better survival than pN1-NR>0.3. This discussion should include an exploration of the possible influence of stage migration (mentioned here but not in any depth) as well as the impact of the total number of nodes resected, as mentioned above. This needs to be connected to the debate on LN sampling vs dissection. (Expand on the comment in line 204 regarding insufficient lymphadenectomy)

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Reply 8: Thank you for your advice. We made some further discussion about this finding in the revised manuscript.

Changes in the text: line 424-428, line 437-439, line 441-447, line 481-484.

Comment 9: Along similar lines, the authors state that NR "reflects the relative tumour burden of metastatic LN" but omit that NR also reflects the number of nodes resected overall, this needs to be corrected.

Reply 9: Thank you for your advice. We have changed this expression in the revised manuscript.

Changes in the text: line 230, line 382.

Comment 10: The statement that "aggressive adjuvant therapy is necessary for pN1-NR>0.3" is unsupported by the data in this study. Just because they have worse prognosis does not mean they will benefit more from adjuvant treatment. This statement should be removed or phrased in a more hypothetical manner.

Reply 10: thank you for your advice. We modified the expression as you recommended.

Changes in the text: line 455-457.

Comment 11: Table 2-histological type-squamous cell carcinoma displays across several rows of the table, this should be adjusted.

Reply 11: thank you for your advice. The table will be carefully adjusted in the final printed version.

Changes in the text: The table 2 is adjusted.

Comment 12: The figures are difficult to read at the scale provided and in black and white. Are all 20 graphs necessary?

Reply 12: Thank you for your advice. we will provide high resolution figures in the final version. And we will discuss with the editor to see if we can put some figures in the supplemental material.

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Reviewer D

Comment 1: Did you include patients with pre-operative chemotherapy. This group of patients should be removed because downstaging is possible.

Reply 1: we are unable to obtain the neoadjuvant chemotherapy information from the SEER database. This is one of the limitations of our study. However, the node downstage rate after neoadjuvant is quite low. According to EMERGING-CTONG 1103 trial, the lymph node downstage occurred in only 2.9% patients in the neoadjuvant chemotherapy group. So, we believe that the pre-operative chemotherapy could have very limited effect to our result. We made some further discussion about this question in the limitation part.

Changes in the text: line 454-457.

Comment 2: One important limitation is about the number of lymph node which is very dependant on the quality of the procedure and fragmentation of the specimen.

Reply 2: we totally agree with your idea. This is an unavoidable limitation for all LN number related researches. So, the results of this study should not be over-interpreted. We made some further discussion about this question in the revised manuscript.

Change in the text: line 460-463.

Comment 3: We have also patients with both N1 and N2 involvement. How were these patients categorized?

Reply 3: For patients with both N1 and N2 involvement, they were grouped as N2 disease. This is in accordance with the current TNM classification system.

Changes in the text: No change was made.