Peer Review File

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Reviewer A

Comment 1: First of all, there is a lack of statistical details on how the validation was done for the number n. There is no explanation of how the training set and validation set were divided.

Reply 1: Thank you very much for your comments on our manuscript. We randomly grouped the enrolled people by the "complete_ra" function of the "randomizr" package in R software version 4.3.2 in a ratio of 7:3. We have made corresponding changes in lines 123-126 of the manuscript.

Changes in the text: Ultimately, 254 patients with stage IA lung ADC with an MIP component were eligible for this study and were randomly assigned to the training (n=169) and validation (n=85) cohorts in a 7:3 ratio using the "complete_ra" function of the "randomizr" package in R software version 4.3.2.

Comment 2: How do you define recurrence and what is the clinical information of patients who have recurred (how many patients have recurred, where did they recur, what was the treatment, etc.

Reply 2: Thank you very much for pointing out our shortcomings. The types of progression in this study included local recurrence (the recurrence within the lung on the side where the primary tumor was located or local lymph node recurrence) and distant metastasis (nonregional lymph node metastasis, systemic metastasis, or malignant pleural effusion)。Since the purpose of this study is to predict patients with high risk of postoperative recurrence, it is recommended that these patients receive postoperative adjuvant therapy. Therefore, none of the patients enrolled in this study had received any postoperative adjuvant therapy. Clinical information about the progressive patient has been described in lines 203-207 of the manuscript.

Changes in the text: As of the end of follow-up, a total of 117 patients (46.1%) had progressed, of which 45 patients (38.5%) had local recurrence (the recurrence within the lung on the side where the primary tumor was located or local lymph node recurrence) and 72 patients (61.5%) had distant metastasis (nonregional lymph node metastasis, systemic metastasis, or malignant pleural effusion); A total of 103 patients (40.6%) died.

Comment 3: If you did PET, US, Endo, MRI, bone scan as required at post-op follow up, how did you do it and to what extent did you do additional work up due to suspicion?

Reply 3: Thank you very much for your comments on our manuscript. As we described in lines 139-150 of the manuscript, all enrolled patients routinely received CT examination, and when other clinical symptoms appeared or CT showed the possible presence of metastatic lesions, patients were examined with PET, US, Endo, MRI, bone scan, etc. To further assess the patient's condition.

Changes in the text: The study endpoints in this study were OS and disease-free survival

(DFS), with OS defined as the span between radical lung cancer resection and death due to cancer or the last follow-up. DFS was defined as the time interval between radical resection of lung cancer and the first recorded recurrence, death due to a cancer-related cause, or the last follow-up visit. All enrolled patients received regular outpatient reviews and telephone follow-up after admission, with regular physical examination and chest-enhancing computed tomography (CT) during follow-up, as well as positron emission tomography–CT, ultrasound, endoscopy, magnetic resonance imaging, or whole-body skeletal imaging when necessary. For patients whose last case record in the case system was recorded more than 1 month before the cut-off time of this study, telephone follow-up was used to complete the collection of patients' clinical data and establish a database for statistical analysis, and they were asked for details of their disease progression and survival. Follow-up ended on July 31, 2023, and the median duration of follow-up for all patients was 73 months (range 17–133 months).

Comment 4: It would be nice to have a simple table for 3-2 and 3-3. It's confusing to see so many CIs, p values, and HRs. It's hard to read. In the footnote to Figure 2, it would be better to indicate whether each A, B, C, and D is a trainnig set or a validation set, rather than just writing Time dependent ROC for A B C D.

Reply 4: Thank you very much for your suggestions on our manuscript. We have split Table 3 into two simple tables for you and modified Figure 2 as you suggested.

Changes in the text:

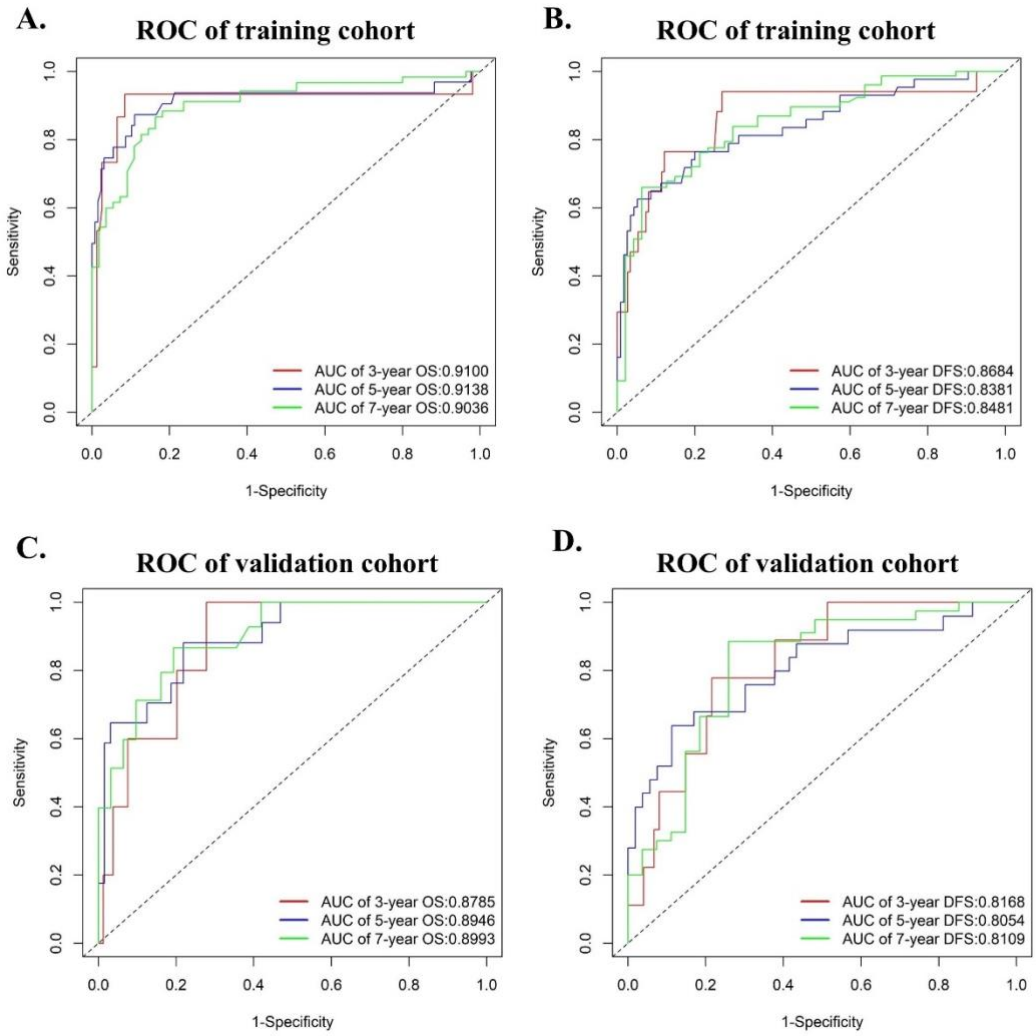
3-1 Univariate analysis

Univariate analysis			
Characteristics	***Progression (n = 71)***	***No (n = 98)***	***P-value***
Sex (%)			
Female	38 (53.5)	51 (52.0)	0.887
Male	33 (46.5)	47 (48.0)	
Age (%)			
< 60	26 (36.6)	48 (49.0)	0.099
≥60	45 (63.4)	50 (51.0)	
Smoking (%)			
YES	23(32.4)	23(23.5)	0.369
NO	48(67.6)	75(76.5)	
Drinking (%)			
YES	18(25.4)	16(16.3)	0.352
NO	53(74.6)	82(83.7)	
Family history (%)			
YES	10(14.1)	27(27.6)	0.075
NO	61(85.9)	71(72.4)	
Proportion of MIP (%)			
＜1%	17 (23.9)	61(62.2)	<0.001
1~5% (ref="＜1%")	29 (40.8)	20(20.4)	
≥5% (ref="＜1%")	25 (35.2)	17(17.3)	
≥5% (ref="1~5%")			0.868
FEV1 (%)			
≤70%	10 (14.1)	13(13.3)	0.689
＞70%	61 (85.9)	85(86.7)	
T stage (%)			
T1a-1b	54 (76.1)	84(85.7)	0.007

T1c	17 (23.9)	14(14.3)	
Location (%)			
Lower lobe	27(38.0)	33(33.7)	0.824
Middle lobe	8(11.3)	8(8.2)	
Upper lobe	36 (50.7)	57(58.2)	
CEA (%)			
≤ 5 μg/L	39 (54.9)	89(90.8)	<0.001
> 5 μg/L	32 (45.1)	9(9.2)	
STAS (%)			
YES	14 (19.7)	7(7.1)	<0.001
NO	57 (80.3)	91(92.9)	
Surgical excision method (%)			
Lung lobectomy	63 (88.7)	86(87.8)	0.929
Non-lobectomy	8 (11.3)	12(12.2)	
Length of surgery[a]	113.30±33.52	117.21±33.95	0.311
Amount of intraoperative bleeding[a]	84.37±36.63	103.06±76.89	0.060
Rad score[a]	-1.58±2.56	-2.07±2.10	0.047

3-2 Multivariate analysis

Multivariate analysis			
Characteristics	***Regression coefficient***	***HR (95% CI)***	***P-value***
Proportion of MIP (%)			
＜1%	Ref	Ref	
1~5% (ref="＜1%")	1.335	3.800(2.012,7.178)	<0.001
≥5% (ref="＜1%")	1.170	3.221(1.634,6.349)	<0.001
≥5% (ref="1~5%")	-0.165	0.848(0.474,1.517)	0.577
T stage (%)			
T1a-1b	Ref	Ref	
T1c	0.736	2.089(1.157,3.772)	0.015
CEA (%)			
≤ 5 μg/L	Ref	Ref	
> 5 μg/L	1.408	1.245(1.144,2.416)	<0.001
STAS (%)			
YES	1.055	2.872(1.517,5.436)	0.001
NO	Ref	Ref	
Rad score[a]	0.132	1.141(1.016,1.282)	0.026



Comment 5: Analytical review is needed for the main factor, MIP. Looking at Table 3, you divided the MIP proportion into three groups: <1%, 1-5%, and >= 5%, but it is questionable whether you should do so, because you divided the cases with the same MIP proportion into two groups (<1% and 1-5% as Ref), and it seems that you wanted to see if there was a difference between 1-5% and >=5%, because 1-5% and >=5% were meaningful compared to <1%, but in this case, you should not analyze it this way, but should do multinomial cox regression, competing risk analysis. Also, it is questionable wheter Cox PH consumption is satisfied.

Reply 5: Thank you very much for your comments on our manuscript. The reason why this study is grouped in this way is that previous relevant literature has been grouped according to similar conditions [1]. In the univariate analysis, we have compared these three groups in pairs, and in the multivariate analysis, we have also grouped each micropapillary component with statistical difference.

[1] Lee G, Lee HY, Jeong JY, et al. Clinical impact of minimal micropapillary pattern in invasive lung adenocarcinoma: prognostic significance and survival outcomes. *Am J Surg Pathol*. 2015;39(5):660-666. doi:10.1097/PAS.0000000000000399

Changes in the text: N/A

Comment 6: Radiomics needs further explanation. If there are multiple tumor cuts visible on the CT, which image was used? Was the largest tumor area used or did the oncologist arbitrarily pick an image that they thought was representative? If the ROI was confirmed by another clinician, was it the radiologist?

Reply 6: Thank you very much for your questions about our manuscript. 1. In this study, only NSCLC patients with single-source lesions were included, while NSCLC patients with multi-source lesions were not included. Therefore, when sketching ROI, the main primary lesions were sketched. 2.The delineation of ROI in this study was done by the first author (oncologist) and confirmed by the co-first author (radiologist). We have made a change in line 167 of the manuscript.

Changes in the text: All tumor target areas were manually depicted layer by layer by an oncologist using the medical image processing and navigation software 3D Slicer (version 5.2.1). The regions of interest were subsequently confirmed by an radiologist with advanced experience in chest CT analysis.

Comment 7: Supplementary figure 1 should be Figure 1 because it is an overview of what was done with the flowchart in the study. It is not a supplementary figure and the each steps of statistical analysis is not usually written in the flowchart.

Reply 7: Thank you very much for your comments on our manuscript. We have changed the supplementary figure 1 to Figure 1 and changed the order of all the images and supplementary images.

Changes in the text: N/A

Comment 8: The data for medaistinal lymph node evaluation is needed. Was the systematic dissection or samplnig? What is the nubmer of resected nodes?

Reply8: Thank you very much for your comments on our manuscript. All patients enrolled in this study underwent systematic dissection. Meanwhile, we have added the dissected lymph node count of patients in Table 1.

Changes in the text:

Table 1. Clinicopathologic characteristics of patients in the training and validation cohorts

Characteristics	***Training(n=169)***	***Validation(n=85)***	***P***
Sex (%)			
Female	89 (52.7)	53 (62.4)	0.182
Male	80 (47.3)	32 (37.6)	
Age (%)			
<60	75 (44.4)	49 (57.6)	0.126
≥60	94 (55.6)	36 (42.4)	
Smoking (%)			
YES	46 (27.2)	22 (25.9)	0.939

NO	123(72.8)	63(74.1)	
Drinking (%)			
YES	34 (20.1)	21 (24.7)	0.499
NO	135 (79.9)	64 (75.3)	
Family history (%)			
YES	37 (21.9)	20 (23.5)	0.892
NO	132 (78.1)	65 (76.5)	
Proportion of MIP (%)			
＜1%	78 (46.2)	47 (55.3)	0.386
1~5%	49 (29.0)	20 (23.5)	
⩾5%	42 (24.9)	18 (21.2)	
ECOG (%)			
0	10 (5.9)	7 (8.2)	0.666
1	159 (94.1)	78 (91.8)	
FEV1% (%)			
⩽70%	23 (13.6)	7 (8.2)	0.295
＞70%	146 (86.4)	78 (91.8)	
Tstage (%)			
T1a-1b	138 (81.7)	69 (81.2)	1.000
T1c	31 (18.3)	16 (18.8)	
Surgical excision method (%)			
Lobectomy	149 (88.2)	76 (89.4)	0.932
Non-lobectomy	20(11.8)	9(10.6)	
Location (%)			
Lower lobe	60 (35.5)	31 (36.5)	0.811
Middle lobe	16 (9.5)	10 (11.8)	
Upper lobe	93 (55.0)	44 (51.8)	
CEA (%)			
≤ 5 μg/L	128 (75.7)	69 (81.2)	0.412
> 5 μg/L	41 (24.3)	16 (18.8)	
STAS (%)			
YES	21 (12.4)	9 (10.6)	0.824
NO	148 (87.6)	76 (89.4)	
Length of surgery[a]	115.57±33.73	118.21±36.82	0.568
Amount of intraoperative bleeding[a]	95.21±63.71	93.76±40.68	0.849
Dissected lymph node count[a]	12.93±5.23	11.93±6.36	0.902
Rad score[a]	-1.99±2.22	-1.79±1.87	0.469

Abbreviations: MIP, micropapillary; ECOG, Eastern Cooperative Oncology Group; FEV1%, forced expiratory volume in one second; CEA, carcinoembryonic antigen; STAS, spread through air space; Rad score, radiomics score; [a], data presented as mean ± standard deviation.

Comment 9: It is already known that there is a correlation between T stage and micropapillary pattern. Therefore, if we wanted to know the prognostic impact of the MIP pattern as described in the title, we should have controlled for the division of strata within the T stage rather than T1a to T1c.

Reply 9: Thank you very much for your comments on our manuscript. The reason why we stratified patients according to T1a-T1c was based on the existing literature to stratify patients according to T stage[1]. Secondly, postoperative adjuvant therapy is not recommended for stage I patients (especially stage IA patients). Since this study is intended to screen out patients with micropapillary components at high risk of postoperative recurrence for postoperative adjuvant therapy, patients with T1a-T1c are included in this study.

[1] Huang W, Zhang H, Zhang Z, et al. A prognostic nomogram based on a new classification of combined micropapillary and solid components for stage IA invasive lung adenocarcinoma. *J Surg Oncol*. 2022;125(4):796-808. doi:10.1002/jso.26760

Changes in the text: N/A

Reviewer B

The authors have presented prediction models based on clinicopathological factors in stage 1A lung adenocarcinoma with micropapillary components. While this study interests the journal's readers, I have the following questions that should be addressed before publication.

Comment 1: The authors developed two nomograms: one for OS and the other for DFS. Does this help predict each endpoint better?

Reply 1: Thank you very much for your suggestions for our manuscript. We established two nomograms because the incidence of progression and death was not the same (lines 203-3207), and the final survival analysis was different.

Changes in the text: As of the end of follow-up, a total of 117 patients (46.1%) had progressed, of which 45 patients (38.5%) had local recurrence (the recurrence within the lung on the side where the primary tumor was located or local lymph node recurrence) and 72 patients (61.5%) had distant metastasis (nonregional lymph node metastasis, systemic metastasis, or malignant pleural effusion); A total of 103 patients (40.6%) died.

Comment 2: In section 3.4 (lines 221-222), the authors said, “cut-off values were calculated in the training cohort…”; however, the indicated numbers were “n=217/n=37 for OS” and “n=173/n=81 for DFS”. Did the authors analyze all cases (n=254) or training cohort (n=169)?

Reply 2: Thank you very much for pointing out our error, the calculation of cutoff value is done in the total population, and the final survival analysis is also done in the total population. We have already made changes in lines 252-260 of the manuscript.

Changes in the text: Based on the individual total scores calculated from the nomograms predicting OS and DFS, cut-off values were calculated in the total population using the X-tile procedure, which classified the total population into two risk groups: low risk (n=217, total point ⩽111.9; n=173, total point ⩽97.2) and high risk (n=37, total point >111.9; n=81, total

point >97.2). Subsequent Kaplan–Meier survival analyses of the two risk groups in the total population based on the above cut-off values showed good differentiation, with significant differences in OS at 3, 5, and 7 years (3-year OS: 97.7% vs. 56.9%; 5-year OS: 90.6% vs. 15.1%; and 7-year OS: 75.3% vs. 3.4%; $P < 0.001$) and the same significant differences in DFS at 3, 5, and 7 years (3-year DFS: 96.0% vs. 70.3%; 5-year DFS: 86.5% vs. 34.0%; and 7-year DFS: 75.8% vs. 0.0%; $P < 0.001$) (Figure 4).

Comment 3: In section 4.2 (lines 344-345), the authors said, "We recommend postoperative adjuvant therapy to improve the patient's prognosis"; however, the manuscript did not include data to support this recommendation, even though it sounds reasonable. Please provide the data to support your suggestion. If not, please tone down the expression.

Reply 3: Thank you very much for your questions about our manuscript, which are critical. In the survival analysis, we divided the total population into low-risk and high-risk patients based on the nomogram. The survival curve showed that the DFS and OS of high-risk patients were significantly worse than those of low-risk patients. Therefore, this study suggests that high-risk patients may receive postoperative adjuvant therapy to improve prognosis.

Changes in the text: In the survival analysis between different risk subgroups, we found that the higher the risk, i.e., the higher the score, the higher the probability of postoperative progression of the patient and the worse the patient's prognosis. Thus, for the patients who were judged to be at high risk by the prediction model used in this study, we recommend postoperative adjuvant therapy to improve the patient's prognosis. For low-risk patients, although we do not recommend postoperative adjuvant therapy, we should conduct regular reviews and pay close attention to the changes in each risk factor.

Comment 4: Minor; "X-tile" or "X-Tile"? Please use the same expression.

Reply 4: Thank you very much for your suggestions on our manuscript, which will make our article more rigorous. We have already unified it as "X-tile" in lines 187, 253, 291 and 377 of the manuscript.

Changes in the text: "X-tile".

Reviewer C

Authors developed a nomogram_based model predicting the prognosis of lung Stage IA-ADC with a micropapillary component.

Comment 1: One point of concern is the exclusion of solid subtype ADC. Because it is believed that there are nodules containing MIP components among solid subtype ADC, there is also literature indicating that even small amounts of MIP components can affect prognosis (ref. 29), and the interior of nodules is often histologically heterogenous, with differences in the component ratios being the only difference between solid and MIP components and are by no means in an exclusive relationship, I believe that solid subtype ADC with MIP components cannot be ignored. If the relationship between MIP components and prognosis is to be discussed

in this study, I believe that the analysis should include all nodules with MIP components and that solid subtype ADC should not be excluded. I request a reevaluation that includes solid subtype ADC.

Reply 1: Thank you very much for this suggestion on our manuscript, it can be seen that you are indeed very knowledgeable in this field.

1. As you said, micropapillary subtype and solid subtype of lung adenocarcinoma are two pathological subtypes with a high risk of recurrence, and the two subtypes are indeed analyzed together in most studies. However, in addition to focusing on the impact of micropapillary subtypes on prognosis, this study also preliminarily identified the causes that are prone to recurrence and metastasis by analyzing clinicopathological factors, thus excluding solid subtypes, laying a solid foundation for further research on micropapillary subtypes in the future.

2. Compared with other tissue subtypes, micropapillary subtypes are more prone to pleural invasion and lymph node metastasis, showing stronger invasiveness [1,2]. From a pathological point of view, the micropapillary structure can be connected to the alveolar wall or floating in the alveolar cavity in a ring structure, which makes the micropapillary subtype more prone to spread through air spaces [3,4], which will lead to a higher recurrence rate and poor prognosis of patients, which has been supported by literature [5] and also confirmed in our results. Unfortunately, for the further reasons of how micropapillary subtypes cause spread through air spaces and what other reasons cause micropapillary subtypes to affect the prognosis of patients, we still have not got a clear answer, which is also the direction of our research group in the future.

3. According to previous studies and pathological results of this research institution, most lung adenocarcinomas are mixed subtypes, and the pathological subtypes contained in tumor tissues are not nearly the same. This study only included patients with no solid subtypes in the pathological results, and it is intended to conduct further research on micropapillary subtypes. Through the predictive model of this study, we can screen out which part of patients are suitable for receiving postoperative adjuvant chemotherapy. However, the mutation rate of EGFR gene in lung adenocarcinoma containing micropapillary is very high, which is significantly higher than that of other subtypes, up to 85% in our study [6], and this group of people is most likely to benefit from EGFR-TKI. In the era of precision medicine, postoperative treatment plans for patients with early lung adenocarcinoma are also different. This also shows the importance of studying micropapillary subtypes. However, our current study has not analyzed why patients with micropapillary subtypes have a high EGFR mutation rate, and whether targeted therapy should be selected after surgery, which is also the direction of our future research.

[1] Amin MB, Tamboli P, Merchant SH, et al. Micropapillary component in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. *Am J Surg Pathol*. 2002;26(3):358-364. doi:10.1097/00000478-200203000-00010

[2] TSUBOKAWA N, MIMAE T, SASADA S, et al. Negative prognostic influence of micropapillary pattern in stage IA lung adenocarcinoma [J]. European Journal of Cardio-Thoracic Surgery, 2016, 49(1): 293-9.

[3] KAMIYA K, HAYASHI Y, DOUGUCHI J, et al. Histopathological features and prognostic significance of the micropapillary pattern in lung adenocarcinoma [J]. Modern Pathology, 2008, 21(8): 992-1001.

[4] WATANABE K, SAKAMAKI K, ITO H, et al. Impact of the micropapillary component on the

timing of recurrence in patients with resected lung adenocarcinoma [J]. European Journal of Cardio-Thoracic Surgery, 2020, 58(5): 1010-8.
[5] Kadota K, Nitadori JI, Sima CS, et al. Tumor Spread through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency and Location of Recurrences after Limited Resection for Small Stage I Lung Adenocarcinomas. J Thorac Oncol. 2015;10(5):806-814. doi:10.1097/JTO.0000000000000486
[6] Li C, Shen Y, Hu F, et al. Micropapillary pattern is associated with the development of brain metastases and the reduction of survival time in EGFR-mutation lung adenocarcinoma patients with surgery. Lung Cancer. 2020;141:72-77. doi:10.1016/j.lungcan.2020.01.007
Changes in the text: N/A

Comment 2: If possible, please add a test evaluation of the model using external data or a sample of resected cases from the same facility since 2019.
Reply 2: Thank you very much for your suggestions on our manuscript. We can see that you are a very rigorous professor. Due to the limited sample size, we could not verify this condition with external data, which is indeed a shortcoming of our study. Your suggestions will encourage us to apply large sample, multi-center data in future studies to make the results more reliable.
Changes in the text: N/A

Comment 3: The overall text is too long, and there are some overlapping contents in the Discussion sections. Please avoid redundancy and concisely summarize the new findings and points you wish to make.
Reply 3: Thank you very much for your suggestions on our manuscript, which will greatly increase the readability of our manuscript. We have condensed this manuscript accordingly.
Changes in the text: N/A