Peer Review File

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Reviewer A

The manuscript is very good, very well written and with good figures and tables.

We have appreciated the reviewer comments. We have modified the manuscript accordingly and the modified content in the revised manuscript have been highlighted in red. In the following comment, our point by point responses have been marked in blue.

Comment 1:

A limit of the manuscript is the lack of sub-analysis for luminal type.

Reply 1: Thanks for your comment. We had analyzed luminal type of breast cancer patients as a clinical feature in our study and the luminal type was missed in the original manuscript. We have added the related content and modified our text as advised.

Changes in the text (see Page 8, lines 3-6):

"Clinical features included the clinical stage of the tumor, luminal type, Miller-Payne grade, tumor marker, chemotherapy regimen and cycle, complete blood count, liver function, creatinine, D-dimer, and left ventricular ejection fraction".

Comment 2:

When you mention FDG PET/CT in the setting of predicting response to NAC you could cite and briefly discuss this recent paper in the field. ^{18}F-FDG PET-Derived Volume-Based Parameters to Predict Disease-Free Survival in Patients with Grade III Breast Cancer of Different Molecular Subtypes Candidates to Neoadjuvant Chemotherapy. Cancers 2023, 15, 2715. https://doi.org/10.3390/cancers15102715

Reply 2: Thank you for your thought-provoking comment and provided reference. We agree with your comment. We have cited the relevant reference (Cancers (Basel) 2023;15:2715) which was recommended by you and the related content was added and modified in the revised manuscript.

Changes in the text (see Page 4, lines 27-29):

"Notably, volumetric parameters of ^{18}F-FDG PET/CT before NAC, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), correlate significantly with disease-free survival (DFS) of breast cancer patients (20)".

We also have cited relevant references in the revised manuscript.

20. Quartuccio N, Alongi P, Urso L, et al. (18)F-FDG PET-Derived Volume-Based Parameters to Predict Disease-Free Survival in Patients with Grade III Breast Cancer of Different Molecular Subtypes Candidates to Neoadjuvant Chemotherapy. Cancers (Basel) 2023;15:2715.

Reviewer B

We have appreciated the reviewer comments. We have modified the manuscript accordingly. The modified content has been highlighted in the revised version. In the following content, our point by point responses have been marked in blue.

Page 3 Introduction

Comment 1:

Lines 10-18: Lack of understanding as to why liquid biopsies are ineffective. What does panic of patient mean? There is no financial burden on patient if a patient signs up for IRB, it is more so voluntary. So molecular biomarkers, liquid biopsies are more so effective and less of financial burden on patients. Studies such as these have shown effectiveness of neoadjuvant chemo using molecular biomarkers and liquid biopsies:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9490628/

https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.551

https://www.mdpi.com/2306-5354/10/4/485

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9456236/

Reply 1: Thanks for your kind comments. We have agreed with your comments sincerely. We have rewritten the paragraph in the revised manuscript and removed the relevant content from the text. We have applied the references you had provided to support those views. The modified content has been added in the revised manuscript.

Changes in the text (see Page 4, lines 9-19):

"Predicting the efficacy of NAC early and choosing the appropriate timing for radical mastectomy are especially important. The histopathological features and genomic expression of tumors are used for monitoring the disease progress and response to treatment, detecting the relapse of the tumor, and evaluating the prognosis of patients with breast cancer (**错误!未找到引用源。,错误!未找到引用源。**). Some reports have shown that histopathologic features of tumor tissue, including PD-L1 expression, Ki-67 status, etc., were related to the NAC efficacy of breast cancer patients (**错误!未找到引用源。,错误!未找到引用源。**). Moreover, the predictive effects of molecular marker and liquid biopsy in the neoadjuvant treatment of breast cancer have received widespread attention (**错误!未找到引用源。,错误!未找到引用源。**). And previous studies have shown the effectiveness of neoadjuvant chemotherapy using molecular biomarkers and liquid biopsies (**错误!未找到引用源。-错误!未找到引用源。**)".

We also have cited relevant references in the revised manuscript.

6. Wang H, Mao XY. Evaluation of the Efficacy of Neoadjuvant Chemotherapy for Breast Cancer. Drug Des Dev Ther 2020;14:2423-33.
12. Janssen LM, Suelmann BBM, Elias SG, et al. Improving prediction of response to neoadjuvant treatment in patients with breast cancer by combining liquid biopsies with multiparametric MRI: protocol of the LIMA study - a multicentre prospective observational cohort study. BMJ Open 2022;12: e061334.
13. Ma G, Wang JY, Liu XA, et al. Prediction of neoadjuvant chemotherapeutic efficacy by CTC and cfDNA in patients with locally advanced breast cancer. J Clin Oncol 2019;37:551.
14. Pore AA, Dhanasekara CS, Navaid HB, et al. Comprehensive Profiling of Cancer-Associated Cells in the Blood of Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy to Predict Pathological Complete Response. Bioengineering-Basel 2023;10:485.
15. Freitas AJA, Causin RL, Varuzza MB, et al. Liquid Biopsy as a Tool for the Diagnosis, Treatment, and Monitoring of Breast Cancer. Int J Mol Sci 2022;23:9952.

Comment 2:

Please rewrite the paragraph more effectively as to what are the real challenges and limitations of these studies.

Reply 2: Thanks for your positive comments. We agree with your comments. We have rewritten the paragraph in the revised manuscript. And the real challenge and limitations of these studies has been added in the revised manuscript.

Changes in the text (see Page 5, lines 9-11):

"However, few studies have reported on the relationship between NAC response and multiparametric features of breast cancer patients including clinical, pathological, and MRI features by a prediction model".

Comment 3:

Lines 27- Page 4 lines 6: What is the significance of this paragraph? What are the limitations of the studies you mentioned? How is the current study better?

Reply 3: Thanks for your positive comments. We think that MRI imaging is also a way to predict the efficacy of NAC in breast cancer. Although imaging and pathology play a very important role in the evaluation of NAC efficacy, there is a lack of a model that combines clinical features, pathology and imaging to predict NAC efficacy. The aim of our study is to propose a multi-parameter prognostic factor that utilizes a statistical approach to screen for correlation with NAC efficacy. Your suggestions are very valuable, therefore, we have reorganized the paragraphs and made additional revisions.

Changes in the text (see Page 4, line 20- Page 5, line 2):

"In addition to molecular biomarkers and liquid biopsies, significant progress has been made in predicting the efficacy of neoadjuvant chemotherapy for breast cancer through radiomics methods. Several researchers collected multidimensional features of tumor tissues through imaging parameters, such as ultrasound, ^{18}FDG-PET/CT and MRI scanning to early predict the response to treatment and prognosis for patients with breast cancer (**错误!未找到引用源。-错误!未找到引用源。**). Changes in the maximum size of breast cancer combined with ultrasonography can be informative in predicting NAC efficacy and evaluating residual lesions (**错误!未找到引用源。**). Notably, volumetric parameters of ^{18}F-FDG PET/CT before NAC, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), correlate

significantly with disease-free survival (DFS) of breast cancer patients (19). Recent studies have also indicated that MRI features of tumors are related to the response to NAC in breast cancer patients by pretreatment multiparametric MRI examination which have shown advantages in predicting the sensitivity of NAC in breast cancer (**错误!未找到引用源。-错误!未找到引用源。**)" .

We have cited the relevant reference in the revised manuscript:

19. Liu Q, Tang L, Chen M. Ultrasound Strain Elastography and Contrast-Enhanced Ultrasound in Predicting the Efficacy of Neoadjuvant Chemotherapy for Breast Cancer A Nomogram Integrating Ki-67 and Ultrasound Features. J. Ultrasound Med 2022;41:2191-201.
20. Quartuccio N, Alongi P, Urso L, et al. (18)F-FDG PET-Derived Volume-Based Parameters to Predict Disease-Free Survival in Patients with Grade III Breast Cancer of Different Molecular Subtypes Candidates to Neoadjuvant Chemotherapy. Cancers (Basel) 2023;15:2715.

Changes in the text (see Page 4, lines 13-15):

"Some reports have shown that histopathologic features of tumor tissue, including PD-L1 expression, Ki-67 status, etc., were related to the NAC efficacy of breast cancer patients (**错误!未找到引用源。,错误!未找到引用源。**)" .

Changes in the text (see Page 5, line 9-11):

"However, few studies have reported on the relationship between NAC response and multiparametric features of breast cancer patients including clinical, pathological, and MRI features by a prediction model".

Comment 4:

Overall, Introduction needs to be re-written and needs significant improvement, as the significance and the uniqueness of the study is not coming through.

Reply 4: Thanks for your positive comment. Although imaging and pathology play a very important role in the evaluation of NAC efficacy, there is a lack of a model that combines clinical features, pathology and imaging to predict NAC efficacy. The aim of our study is to propose a multi-parameter prognostic factor that utilizes a statistical approach to screen for correlation with NAC efficacy. We have rewritten and reorganized the "introduction" section.

And the significance and the uniqueness of the study has been added in the revised manuscript.

Changes in the text (see Page 4, line 20- Page 5, line 2):

“In addition to molecular biomarkers and liquid biopsies, significant progress has been made in predicting the efficacy of neoadjuvant chemotherapy for breast cancer through radiomics methods. Several researchers collected multidimensional features of tumor tissues through imaging parameters, such as ultrasound, ^{18}FDG-PET/CT and MRI scanning to early predict the response to treatment and prognosis for patients with breast cancer (**错误!未找到引用源。-错误!未找到引用源。**). Changes in the maximum size of breast cancer combined with ultrasonography can be informative in predicting NAC efficacy and evaluating residual lesions (**错误!未找到引用源。**). Notably, volumetric parameters of ^{18}F-FDG PET/CT before NAC, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), correlate significantly with disease-free survival (DFS) of breast cancer patients (19). Recent studies have also indicated that MRI features of tumors are related to the response to NAC in breast cancer patients by pretreatment multiparametric MRI examination which have shown advantages in predicting the sensitivity of NAC in breast cancer (**错误!未找到引用源。-错误!未找到引用源。**)” .

We have cited the relevant reference in the revised manuscript:

19. Liu Q, Tang L, Chen M. Ultrasound Strain Elastography and Contrast-Enhanced Ultrasound in Predicting the Efficacy of Neoadjuvant Chemotherapy for Breast Cancer A Nomogram Integrating Ki-67 and Ultrasound Features. J. Ultrasound Med 2022;41:2191-201.
20. Quartuccio N, Alongi P, Urso L, et al. (18)F-FDG PET-Derived Volume-Based Parameters to Predict Disease-Free Survival in Patients with Grade III Breast Cancer of Different Molecular Subtypes Candidates to Neoadjuvant Chemotherapy. Cancers (Basel) 2023;15:2715.

Changes in the text (see Page 4, lines 13-15):

“Some reports have shown that histopathologic features of tumor tissue, including PD-L1 expression, Ki-67 status, etc., were related to the NAC efficacy of breast cancer patients (**错误!未找到引用源。,错误!未找到引用源。**)” .

Changes in the text (see Page 5, line 9-11):

"However, few studies have reported on the relationship between NAC response and multiparametric features of breast cancer patients including clinical, pathological, and MRI features by a prediction model".

Changes in the text (see Page 5, line 19-22):

"The established multiparametric model based on clinical-pathology-MRI features can early predict the effect of neoadjuvant chemotherapy for patients with locally advanced breast cancer and for timely patient treatment regimens for clinicians".

Methods

Comment 5:

Page 4 line 19: Please mention the IRB

Reply 5: Thanks for your suggestion. We have already mentioned IRB in the revised manuscript. We have modified our text as advised.

Changes in the text (see Page 5, line 26- Page 6, line 1):

"The retrospective study was approved by the Medical Research Ethics Committee (an institutional review board) of the First Affiliated Hospital of University of Science and Technology of China (Number: 2020-P-045) and all participants agreed to participate in the study and signed the informed consent".

Changes in the "Footnote" section (see Page 15, lines 14-16):

"This retrospective study was approved by the Medical Research Ethics Committee (an institutional review board) of the First Affiliated Hospital of University of Science and Technology of China (Number: 2020-P-045)".

Comment 6:

Page 4 lines 22-page 5 line 4: Please put the inclusion and exclusion criteria in a table format so it is easy to read.

Reply 6: Your suggestion is valuable. We have added the inclusion and exclusion criteria by a new table and the added table has been attached and uploaded with the revised manuscript. At the same time, the order of other tables in the text has been changed. We have modified our text as advised. The following table was noted as Table 1 in the revised manuscript.

Changes in the table 1:

Table 1 The inclusion and exclusion criteria of patients

	Inclusion criteria	Exclusion criteria
1	the enrolled patients with stage II-III were confirmed to have locally advanced breast cancer without distant metastasis by pathological biopsy and imaging examination	Pathology test was not available.
2	Multiparameter MRI examinations at baseline were performed for every patient before NAC.	Preoperative or postoperative pathological assessment was not performed.
3	The patients did not receive radiotherapy or endocrine therapy before NAC.	The patients received radiotherapy or endocrine therapy before NAC.
4	Pathological examinations of tumor tissues for every patient were performed by radical surgery of breast cancer.	The quality of multiparameter MRI images was not good, and the obtained data could not be calculated and analyzed.

Changes in the text (see Page 6, line 4-5):

"The inclusion and exclusion criteria of patients in the study are shown in Table 1".

Comment 7:

Page 5 line 5: Please give more information on MR imaging. Please explain what is intravoxel incoherent motion, diffusion-weighted imaging, and dynamic contrast-enhanced MRI. Please explain how the values were evaluated.

Reply 7: Thanks for your positive suggestion. More detailed information on the MRI images has been already described in our previous paper (MC Med Imag 2021;21:155). The information on the intravoxel incoherent motion, diffusion-weighted imaging, and dynamic contrast-enhanced MRI have been described and the evaluation methods for the above values have been explained in our previous article. We added our paper as a new reference in the revised version. We have modified our text as advised.

Changes in the text (see Page 6, lines 22-26):

"All patients accepted MRI imaged using a 3.0 T MRI (GE Signa HD × T, USA) with an 8-channel dedicated breast coil. More detailed information on the MRI images and evaluation methods of different sequence and parameter have been already described in our previous study (29)".

We have cited our previous article in the revised manuscript:

29. Lu N, Dong J, Fang X, et al. Predicting pathologic response to neoadjuvant chemotherapy in patients with locally advanced breast cancer using multiparametric MRI. BMC Med Imag 2021;21:155.

Comment 8:

Page 5 line 13: What about Her2+ receptor? Please write in detail with reagents used for IHC. Saying that IHC was performed using experimental operation manual is not sufficient. Please provide detailed methodology with incubation times, washing steps etc.

Reply 8: Thanks for your kind suggestion. The samples of immunohistochemistry were performed on a fully automated staining system (Ventana, USA) using the VENTANA anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody (Ventana, USA). We have added information about the Her2 receptor in the revised manuscript. We also have cited the relevant reference (J Clin Oncol 2018;36:2105-22).

Changes in the text (see Page 7, line 4-14):

"Immunohistochemical expression of Her2 protein was performed on the BenchMark ULTRA automated stainer (Ventana, USA) using the VENTANA anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody (Ventana, USA). We combined Anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody and the ultraView Universal DAB text kit on the BenchMark ULTRA automated stainer, and anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody was incubated for 12 minutes at 36 ℃. Hematoxylin 2 was used as counterstain for 4 minutes. The expression level of Her2 protein was scored as 0, 1+, 2+, or 3+. A score of 0 or 1+ was considered negative, while a score of 3+ was considered positive. Samples with a score of 2+ were subsequently confirmed by fluorescence in situ hybridization (FISH), as commended in the guideline (32)".

We have cited a relevant reference in the revised manuscript:

32. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105-22.

Comment 9:

Page 5 line 23: Full forms for EC, EC-TH, TEC. Abbreviations cannot be used without the mention of their respective full forms. Define pCR and non-pCR better.

Reply 9: Thanks for your kind suggestion. We have added the full name of EC, EC-TH and TEC in the revised manuscript. We also added the definitions of pCR and non-pCR, along with their respective meanings, in the revised manuscript. We have modified our text as advised.

Changes in the "method" section (see Page 7, lines 17-20):

"Enrolled patients had received two-eight cycles of NAC, and chemotherapy regimens were recommended by guidelines including EC (epirubicin plus cyclophosphamide), EC-TH (epirubicin plus cyclophosphamide), and TEC (docetaxel, epirubicin, plus cyclophosphamide), etc".

Changes in the "method" section (see Page 7, lines 22-27):

"Pathological reaction grade 5 was considered as pCR, whereas grades 1-4 were considered as non-pCR. pCR means the absence of invasive cancer cells in the surgical specimen after neoadjuvant treatment for cancer, but ductal invasive carcinoma may be present. On the other hand, non-pCR refers to the presence of invasive cancer cells in the surgical specimen after neoadjuvant treatment".

Changes in the "Abbreviations" section (see Page 14, lines 21-23):

"EC (epirubicin plus cyclophosphamide); EC-TH (epirubicin plus cyclophosphamide); TEC (docetaxel, epirubicin, plus cyclophosphamide)".

Comment 10:

Page 6 line 23: BI-RADS fullform.

Reply 10: Thanks for your kind suggestion. The full name of BI-RADS is Breast Imaging Reporting and Data System, and we have added related content in the revised manuscript. We have modified our text as advised.

Changes in the text (see Page 8, lines 25-27):

"Other features included Breast Imaging Reporting and Data System (BI-RADS) grades of the tumor, pleural effusion, contralateral breast diseases, and disease of other organs".

Changes in the “Abbreviations” section (see Page 14, line 23):

“BI-RADS: Breast Imaging Reporting and Data System”.

Comment 11:

Page 8 lines 7-16: What do the results signify? Her2+ patients are always non-pCR? Please translate the significance of your results.

Reply 11: Thanks for your comments. The Her-2 and Ki-67 proteins are two important parameters in the molecular type and pathological characteristics of patients with breast cancer. Some studies showed that there was correlation between the expression of Her-2 and Ki-67 protein and the prognosis of breast cancer patients. Therefore, we have analyzed the expression differences of tumor samples with pCR or non-pCR in different cohorts, and the results indicated that there was no correlation of Her-2 and Ki-67 expression between the pCR and non-pCR groups.

Comment 12:

Overall results and discussions need to emphasize on key results based on the findings and need to be worded better.

Reply 12: Thanks for your kind suggestion, and we agree with you. We have modified the results and discussions sections accordingly.

Changes in the “results” section (see Page 11, lines 18-21):

“The features included lymph node metastasis, the first standard ADC at baseline, change in standard ADC at first follow-up, change in tumor volume at first follow-up, and clinical stage at baseline in the established model”.

Changes in the “results” section (see Page 11, lines 24-27):

“By multiple logistic and linear regression analysis, a multiparametric and predictive model was established based on the five features, and a nomogram was developed based on the model (Figure 2A). As shown in Figure 2B, the long and point gray line (ideal) represents perfect prediction”.

Changes in the “discussions” section (see Page 13, lines 4-12):

“The standard is based on the postoperative pathological results and thus it cannot predict the

chemotherapy effect before breast cancer surgery. In clinical practice, breast cancer patients need new efficacy prediction methods for predicting NAC efficacy and choosing the optimal treatment plan early. Dammu et al. established a new neural network based on MRI omics for predicting lymph node metastasis and the survival time of breast cancer patients (**错误!未找到引用源。**). Some scholars have established predictive models by multiparametric MRI sequences that which can predict pCR early and lifetime after NAC for patients with breast cancer (**错误!未找到引用源。,错误!未找到引用源。**)".

Changes in the "discussions" section (see Page 13, line 27- Page 14, line 2):

"The specificity and 95% confidence interval in the primary cohort were also shown (0.642; 95% CI: 33.33%, 100.00%). Due to the small sample size of our study, the PPV and specificity were not high".

Reviewer C

Although the complexity of the statistical processing is beyond my knowledge, I congratulate you for finding a nomogram which helps to predict the response of tumors to NAC. Of course, a larger number of patients are needed to confirm these results.

Just a few questions.

We have appreciated the reviewer comments. We have modified the manuscript accordingly. The modified contents are highlighted in the revised version in red. In the following content, our point by point responses are marked in blue.

Comment 1:

Could you tell us the brand and Teslas of your MRI machine? Why to you state that patients have locally advanced tumors when there are a number of them with stages I and II? Furthermore, why there are patients with non-invasive cancers receiving NAC? I think that these points needs clarification.

Reply 1:

a) Thanks for your positive comments. In our previous research, our work had done by the same MRI machine and the detailed information was described in our previous article

(BMC Med Imaging, 2021, 21(1): 155). All patients were imaged using a 3.0 T MRI (GE Signa HD × T, America) with an 8-channel dedicated breast coil (BMC Med. Imag 2021;21:155).

b) We had a clerical mistake in the table 1. In our study, the rolled patients with breast cancer were stage II-III. We have corrected the error in the original Table 1 (Table 2 in the revised manuscript). The related content has been added with the clinical stage II-III in the revised "Inclusion criteria" section.

Table 2 Characteristics of patients in clinical prediction model

Characteristic	Primary cohort			Validation cohort		
	non-pCR	pCR	p	non-pCR	pCR	p
Age						
Mean ± SD, years	48.56 ± 11.85	47.33 ± 18.56	0.894	49.88 ± 10.45	45.91 ± 9.45	0.260
Histological type *			0.211			0.397
Invasive	17 (89.5%)	5 (71.4%)		43 (84.3%)	11(78.6%)	
Mixed invasive	2 (10.5%)	2 (28.6%)		8 (15.7%)	3 (21.4%)	
Clinical stage *						
II	5 (26.3%)	6 (85.7%)	0.007	18 (35.3%)	10(71.4%)	0.014
III	14 (73.7%)	1 (14.3%)		33 (64.7%)	4 (28.6%)	
Her-2 status, No (%)			0.548			0.541
Positive	10 (55.6%)	3 (42.9%)		19 (37.3%)	7 (50.0%)	
Negative	8 (44.4%)	4 (57.1%)		32 (62.7%)	7 (50.0%)	
Ki-67 status, No (%)			0.369			0.527
≤ 20%	7 (38.9%)	4 (57.1%)		16 (31.4%)	6 (42.9%)	
> 20%	11 (61.1%)	3 (42.9%)		35 (68.6%)	8 (57.1%)	

*Data are measured at baseline.

c) The original Table 1 have showed the histological type and the "Others" category included mixed histological types of breast cancer, such as infiltrating ductal carcinoma, infiltrating lobular carcinoma, mucinous adenocarcinoma, ductal carcinoma with local infiltration and so on. So the "Others" category represents mixed invasive histological types of breast cancer. The "Others" in the original table 1 is replaced with "mixed invasive types" in the revised table 2.

Changes in the text (see Page 6, lines 22-26):

"All patients accepted MRI imaged using a 3.0 T MRI (GE Signa HD × T, USA) with an 8-channel dedicated breast coil. More detailed information on the MRI images and evaluation methods of different sequence and parameter have been already described in our previous study (错误!未找到引用源。)".

Changes in the text (see Page 6, lines 5-7):

"the enrolled patients with stage II-III were confirmed to have locally advanced breast cancer without distant metastasis by pathological biopsy and imaging examination;"

We have cited a relevant reference in the revised manuscript:

29. Lu N, Dong J, Fang X, et al. Predicting pathologic response to neoadjuvant chemotherapy in patients with locally advanced breast cancer using multiparametric MRI. BMC Med. Imag 2021;21:155.

Comment 2:

And a request, useful for most of the clinicians reading your paper, could you add some easy explanation (if this could be easy) on the functioning of the LASSO regression model?

Reply 2: Thanks for your positive comment. We have added some easy explanation on the functioning of the LASSO regression model in the revised manuscript.

Changes in the text (see Page 9, line 19- Page 10, line 3):

"The LASSO regression model can study the relationship between the dependent variable (target) and the independent variable (predictor), and therefore has a wide range of uses in clinical applications. Such as follows: (1) Disease prediction: The LASSO regression can be used to predict the occurrence and progression of diseases. By choosing appropriate independent variables, prediction models can be built to help doctors identify high-risk patients and take appropriate interventions. (2) Biomarker research: The LASSO regression can be used to screen biomarkers associated with diseases. By analyzing large-scale biological data, key biomarkers related to diseases can be identified, which can help in the early diagnosis and treatment of diseases. (3) Drug discovery and developments: The LASSO regression can be used to build effect prediction models for screening for new drugs. By building the LASSO regression model, it can predict the efficacy of some new drugs. Drug development can help clinicians formulate individualized treatment scheme".

Comment 3:

A few type-writing errors need correction (e.g. fig. 3).

Reply 3: Thanks for your positive comment. Taking your advice, we have rechecked the type-writing errors in Figure 3, but did not find the errors.