

Peer Review File

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Reviewer A

I should congratulate authors for this manuscript. But I need some clarifications.

Comment 1: There is no mention of ECG and Echocardiographic parameters in the study. Was it considered in your study?

Reply 1: ECG and Echocardiographic results were included in this study. The results were divided into binary variable, normal ECG and Echocardiographic were considered negative. Ventricular arrhythmias, Q wave, ST-T changes, EF decrease, wall motion abnormality and left ventricular chamber dilation were consider positive(see Table 1).
Changes in the text: No changes.

Comment 2: How was the correlation of CCTA model with CMR findings?

Reply 2: In this study, the patients diagnosed with acute myocarditis was confirmed by CMR in the study. CMR was used as a key reference of clinical diagnosis of myocarditis (see Page 2, line 47-49), and we did not analyze the correlation of CCTA model with CMR findings. We think the correlation analysis would be helpful when acute myocarditis was confirmed by endomyocardial biopsy.

Changes in the text: No changes.

Comment 3: Was endomyocardial biopsy done in any of these patients?

Reply 3: No, all patients clinically diagnosed with acute myocarditis was confirmed by CMR,

Changes in the text: No changes.

Comment 4: Was CCTA the primary investigation for diagnosing myocarditis in these patients?

Reply 4: No, in these two centers, we usually do CCTA to exclude coronary heart disease, because most acute myocarditis patients were young or low risk patients, so CCTA was prior to angiography.

Changes in the text: No changes.

Comment 5: Are you planning any prospective studies with your model?I think these will make your study complete.

Reply 5: We agree. We did plan to prospective collect some data to validate the model. To our disappointment, we collect less than 10 myocarditis patients in half a year. This is also a major reason for the small sample size of our two centers, and we believe multi-center, large sample study may be promising in future.

Changes in the text: No changes.

Reviewer B

The paper details a study focused on developing a predictive model for acute

myocarditis by utilizing radiomics features from CCTA. The study involved 215 patients, with radiomics features extracted from CCTA images and analyzed using Pearson correlation and LASSO regression. Key radiomics and clinical features were integrated into multiple models, with the best-performing model combining both feature sets to achieve high predictive accuracy for acute myocarditis. The findings underscore the potential of integrating CCTA-based radiomics with clinical data to enhance diagnostic precision in acute myocarditis.

Comment 1: The abstract provides a concise summary. However, it could benefit from including specific metrics of the model's performance (e.g., accuracy, AUC) to provide a clearer picture.

Reply 1: We have modified replaced the pictures with clearer ones as advised (see Figures),and replaced the pictures with clearer ones.

Changes in the text: see Figures.

Comment 2: The introduction could benefit from a more detailed discussion on the novelty of the study, particularly how it advances the existing body of work in radiomics and CCTA.

Reply 2: We have modified our Abstract text as advised (see Page 2, line 33-36)

Changes in the text: Page 2, line 33-36

Comment 3: More details on the data preprocessing steps, such as how missing data were handled and how the images were standardized for radiomics feature extraction, would enhance the reproducibility of the study. Additionally, the rationale behind choosing specific hyperparameters for LASSO regression could be further elaborated.

Reply 3: We have modified our text as advised (see Page 5,Line 115-128).

Changes in the text: Page 5, Line 115-128

Comment 4: The limitations section could be expanded to include a discussion on potential biases in the dataset

Reply 4: We have modified our text as advised (see Page 12, line 331-336)

Changes in the text: Page 12, line 331-336

Comment 5: To further elevate the study's impact, the authors could consider more detailed exploration of the model's clinical applicability, such as how it might be implemented in practice or how it compares with other imaging modalities.

Reply 5: We agree with the reviewer's comment. Exploration of the model's clinical applicability is always a key part of clinical research, in this study, we did plan to do prospective data validation in center 1, but collected less than 10 myocarditis patients in half a year. We consider that the inclusion criteria (all patient had CMR and CCTA data) of this study may limit data collection. We also believe multi-center and prospective data validation is important in future work. In this study, CCTA radiomics is promising, but still be limited in direct clinical diagnosis when it compares with CMR. We would add this in limitation part(see Page 12, line 333-335).

Changes in the text: Page 12, line 333-335.

Comment 6: Figures are of poor quality and blurred

Reply 6: We have replaced the pictures with clearer ones as advised (see Figures).

Changes in the text: Figures

Comment 7: Please correct grammatical errors. Multiple instances found in the paper.
Example: Table 1 says "baseline characteridtics".

Reply 7: We have modified our Abstract text as advised (see Table 1)

Changes in the text: Table 1

Reviewer C

The authors have suggested a model for diagnosing acute myocarditis using CT angiogram. The study has 215 patients which were enrolled during the study period which was further strengthened by 5-fold cross validation. The proposed model showed an excellent predictive accuracy with AUC approximating near perfection. The authors have to be congratulated on strong work but I have following comments.

Comment 1: How does the underlying cause of myocarditis affect the performance of the model?

Reply 1:10 radiomics features and seven significant clinical features revealed by LASSO analysis, which were included in the final model. The clinical features included chest pain, BNP level, prodromal respiratory infection, cTnI elevation, which were also considered to be correlated with myocarditis in clinical work, and supported the result. The radiomics features revealed the heterogeneity of radiomics features between myocarditis patients and normal cohorts, which could not assessed visually. The result also indicated the radiomics features are data which are more than we see.

Changes in the text: No changes

Comment 2: There are multiple grammatical errors which should be removed such as not capitalizing initial letters in columns of tables?

Reply 2: We have modified our Tables as advised (see Table 1 and 4).

Changes in the text: see Table 1 and 4.

Comment 3: P values are not reported with AUCs

Reply 3: Comparisons between Model 1, Model 2 and Model 3 using Delong test, P values were . 0.5153 (Model1 vs Model2) 0.8401 (Model1 vs Model3) and 0.0823

(Model2 vs Model3) respectively, did not reach statistically significant. AUCs for three Models indicated Model 3 was the best. For the small sample size of this study, we think large size sample study could improving the performance of Models.

Changes in the text: Table 3

Comment 4: No layout for large scale external validations are provided

Reply 4: We agree and add this to the limitation part. This could be promising in future work(see Page 12, line 22-23).

Changes in the text: Page 12, line 335-336

Comment 5: The figures are of poor quality.

Reply 5: We have modified our figures as advised(see Figures)

Changes in the text: Figures

Comment 6: Can the authors explain with respect to pathophysiology, why the proposed model was able to perform so good?

Reply 6: The clinical diagnosis was confirmed by CMR in this study. Although the diagnostic performance of CCTA was much lower than CMR, but we noticed that 25 patients (29.07%) exhibited a mild decrease in the left ventricular myocardium density during the retrospective comparison of the CMR and CCTA(see Page 6-7,Line 170-173).These patients were not demonstrated abnormal myocardial density on CCTA before. Therefore, we think the radiomics features of CCTA and CMR may correlated well,and radiomics could explore more data and help the performance of the model to be better.

Changes in the text: No changes.

Comment 7: Relevant notification number, by the ethics review committee should be provided

Reply 7: We have added ethics review committee approval number in the text(see Page 3, line 68).

Changes in the text: Page 3, line 68

Comment 8: I don't see if any echocardiographic measures are included in the manuscript. Can, theoretically, some of those measures have affected the performance of the model?

Reply 8: We planned to included echocardiographic measures, but we found many myocarditis patients underwent bedside echocardiography, which lacked many measures and were not saved on pacs system. Therefore, we used binary variable, abnormal echocardiographic result(wall motion abnormality, pericardial effusion, EF decrease, etc.) and normal echocardiographic result.

Changes in the text: No changes.

Comment 9: Grammatical errors such as this was the first study should be changed to this is the first study

Reply 9: we have modified our text as advised (see Page 10, line 282)

Changes in the text: Page 10, line 282; Table 1.

Comment 10: Could the results be impacted if a different device was used for CCTA (the CT scanner)

Reply 10: We consider this may be true, and we included three different CT scanner.

But most myocarditis patients and control patients were collected by Philips scanner, a few were collected by Siemens and GE scanners. We also add these to the limitation part (see Page 12, Line 332-334).

Changes in the text: Page 12, Line 332-334.

Reviewer D

The manuscript is interesting but I have some comments:

Comment 1: did you use center 1 data to train and test models and center 2 to validate? It is not clear.

Reply 1: Yes, we did this work before, and add this to the limitation part. The AUC training and test sets was 0.998 and 0.908 for center 1 data, The AUC using the external test dataset (center 2) was 0.782(see Page 11-12,Line 312-323). The mixed data from two centres reached better performance.

Changes in the text: Page 11-12, Line 312-323.

Comment 2: Why did you not used an ensemble machine learning model? I think it could increase diagnostic performance, even though your models have very high diagnostic performance.

Reply 2: For the excellent performance of Model 3, we did not do an ensemble machine learning model. This may be limited by the small sample size, we believed ensemble machine learning model could be helpful in large sample size study in future work.

Changes in the text: No changes.

Comment 3: CCTA is a promising method, thanks to radiomics, to detect myocarditis, but can you report mean exposition dose?

Reply 3:For the exposition dose, the dose of Philips scanner was between 900-1700 DLP (mGy*cm), the dose of Siemens scanner was between 300-700 DLP (mGy*cm) , the dose of GE scanner was between 200-600 DLP (mGy*cm),the protocol of prospective scan indicated low dose.We add this as advised(see Page 4,Line 97-99).

Changes in the text: Page 4, Line 97-99

Reviewer E

I congratulate authors in conducting this technically challenging research which is very timely given the increase in interest and advances in utilizing cardiac CT radiomics and AI for clinical purposes.

I find the information presented difficult to follow. There are a lot of technical terms uses in the paper which need better description to make is more apprehensible for most clinical cardiologists and radiologists as the main audience. There are also significant amount of important stylistic correction that needs to be taken into consideration. I have summarized a small portion of them below:

Comment 1: Abbreviation need to be spelled out on first use (ECV, MACE, LLC, LIE, GLDM, GLRLM, etc).

Reply 1: We have modified our text as advised (see Page 1-7,9 Line 18-19,41,48-49,65,105,120,137,151-152,186,190,197-198,238,240).

Changes in the text: Page 1-7,9 Line 18-19,41,48-49,65,105,120,137,151-152,186,190,197-198,238,240.

Comment 2: More clear definition of MACE

Reply 2: MACE included all-cause mortality, ventricular fibrillation or tachycardia, Implantable Cardiac Defibrillators (ICD) discharge, and hospitalization due to progression of heart failure. We have made a definition of MACE(see Page 3,Line 64-66).

Changes in the text: No changes.

Comment 3: Prospective ECG-triggered rather than ECG-gated

Reply 3: We have modified our text as advised (see Page 3, line 79).

Changes in the text: Page 3, line 79

Comment 4: Why CMR as the reference rather than biopsy or FDG-PET since the sensitivity of CMR for acute myocarditis is only 60-80% based on most studies.

Reply 4: In our centers, CMR was recommended by most cardiologist, and we acquired large amount of CMR data. Although biopsy was considered the golden standard, high risk of biopsy limited its application in our centers. For FDG-PET, it was also limited by high cost.

Changes in the text: No changes.

Comment 5: Contrast dose of 1.5-2 mL/kg appears higher than standard. Please explain.

Reply 5: We are so sorry for the mistake, the contrast dose was 0.8-1.0 mL/kg. The dose was 1.0 mL/kg when we used Philips scanners,0.8 mL/kg when we used Siemens and GE scanners. We have modified our text as advised (see Page 3, line 83).

Changes in the text: Page 3, line 83

Comment 6: I am not sure if we can use presence of a small pericardial effusion as a diagnostic characteristic for myocarditis as this is commonly seen in patients without myocarditis as well.

Reply 6: According to Lake Louise Criteria I and II, myocardial edema, hyperemia, necrosis, fibrosis indicated by T1 or T2 based imaging were considered main criteria, and pericardial effusion was listed as supportive criteria. We agree that pericardial effusion is commonly seen in patients without myocarditis as well, but for myocarditis patients, pericardial effusion was often seen when epicardial myocardium or pericardium were involved.

Changes in the text: No changes.

Comment 7: I do believe “auto-Log-sigma-3-0...” and “auto_wavelet...” desrve some description as readers might not be familiar with the terms.

Reply 7: We have modified our text as advised (see Page 7, line 185-191).

Changes in the text: Page 7, Line 185-191.

Comment 8: Limitations of the study should be separated from the discussion

Reply 8: We have modified our text as advised (see Page 11, line 311).

Changes in the text: Page 11, line 311

Comment 9: Figure 2 hard to read and needs better resolution

Reply 9: We have modified our figures as advised (see Figure 2)

Changes in the text: Figure 2

Comment 10: Table 1: What does baseline disease mean?

Reply 10: In this study, baseline disease included co-existence diseases except myocarditis, hypertension, diabetes mellitus and coronary heart disease(see Table 1 caption).

Changes in the text: No changes

Comment 11: Although Model 3 seems to have the best accuracy, but the other two models also seem to have very good sensitivity, specificity, and AUC

Reply 11: The performance of three models were excellent, we believed the potential reason may be radiomics features and clinical variables selected were well correlated with myocarditis. The second potential reason may be the sample size is small, and the results may be related to potential bias, we had added this to limitation part(see Page 12,Line 330-333).

Changes in the text: No changes.