

Development and evaluation of a radiomics model of resting ¹³N-ammonia positron emission tomography myocardial perfusion imaging to predict coronary artery stenosis in patients with suspected coronary heart disease

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Background: Coronary angiography (CAG) is usually performed in patients with coronary heart disease (CHD) to evaluate the coronary artery stenosis. However, patients with iodine allergy and renal dysfunction are not suitable for CAG. We try to develop a radiomics machine learning model based on rest ¹³N-ammonia (¹³N-NH₃) positron emission tomography (PET) myocardial perfusion imaging (MPI) to predict coronary stenosis.

Methods: Eighty-four patients were included with the inclusion criteria: adult patients; suspected CHD; resting MPI and CAG were performed; and complete data. Coronary artery stenosis >75% were considered to be significant stenosis. Patients were randomly divided into a training group and a testing group with a ratio of 1:1. Myocardial blood flow (MBF), perfusion defect extent (EXT), total perfusion deficit (TPD), and summed rest score (SRS) were obtained. Myocardial static images of the left ventricular (LV) coronary segments were segmented, and radiomics features were extracted. In the training set, the conventional parameter (MPI model) and radiomics (Rad model) models were constructed using the machine learning method and were combined to construct a nomogram. The models' performance was evaluated by area under the curve (AUC), accuracy, sensitivity, specificity, decision analysis curve (DCA), and calibration curves. Testing and subgroup analysis were performed.

Results: MPI model was composed of MBF and EXT, and Rad model was composed of 12 radiomics features. In the training set, the AUC/accuracy/sensitivity/specificity of the MPI model, Rad model, and the nomogram were 0.795/0.778/0.937/0.511, 0.912/0.825/0.760/0.936 and 0.911/0.865/0.924/0.766 respectively. In the testing set, the AUC/accuracy/sensitivity/specificity of the MPI model, Rad model, and the nomogram were 0.798/0.722/0.659/0.841, 0.887/0.810/0.744/0.932 and 0.900/0.849/0.854/0.841 respectively. The AUC of Rad model and nomogram were significantly higher than that of MPI model. The DCA curve also showed that the clinical net benefit of the Rad model and nomogram was similar but greater than that of MPI model. The calibration curve showed good agreement between the observed and predicted values of the Rad model. In the subgroup analysis of Rad model, there was no significant difference in AUC between subgroups.

Conclusions: The Rad model is more accurate than the MPI model in predicting coronary stenosis. This noninvasive technique could help improve risk stratification and had good generalization ability.

Keywords: Coronary heart disease (CHD); radiomics; myocardial perfusion imaging (MPI); ¹³N-ammonia; coronary artery stenosis

Submitted Sep 06, 2022. Accepted for publication Oct 21, 2022. doi: 10.21037/atm-22-4692 View this article at: https://dx.doi.org/10.21037/atm-22-4692

Introduction

Coronary heart disease (CHD) is characterized by myocardial ischemia, hypoxia, and necrosis due to coronary artery stenosis or occlusion, and is often accompanied by symptoms of chest distress and chest pain, posing a serious hazard to human health (1-3). Severe coronary stenosis often requires revascularization (4,5). Comprehensive preoperative examination is of great importance for correct decision-making and improving the curative effect and prognosis.

Coronary stenosis is often evaluated using coronary angiography (CAG) or coronary computed tomography (CT) angiography, of which CAG is the gold standard (6-8). Both methods use iodine contrast agents, which can cause allergic reactions or kidney damage (9,10). In addition, CAG is expensive, complex, and invasive and may lead to various complications (11).

Myocardial positron emission tomography (PET) imaging can be used to qualitatively or quantitatively evaluate pathological changes in the myocardium in CHD patients (12). For example, resting ¹³N-ammonia (¹³N-NH₃) PET myocardial perfusion imaging (MPI) is commonly used, and it can be combined with stress MPI and used in the diagnosis of myocardial ischemia and infarction. It can also be combined with ¹⁸F-FDG PET myocardial metabolic imaging (MMI) and used for the assessment of myocardial vitality (13).

A study has reported that stress MPI can be used to predict coronary artery stenosis (14). A study in our center also confirmed that resting MPI-MMI parametric results can be used to predict coronary stenosis (15). However, stress MPI has certain risks, and the preparation process of MMI is complicated. Additionally, it may be affected by diabetes, blood glucose level, and other factors. Moreover, the image quality is not ideal in some cases (16). Therefore, it is necessary to develop a safe, noninvasive, and accurate method for predicting coronary stenosis.

Severe coronary stenosis results in reduced myocardial blood flow (MBF) and microstructural damage (13,17-19). This change affects grayscale patterns and pixel interrelationships in the image, which may not be detected by the naked eye. Currently, it can be quantitatively evaluated using radiomics (20,21). In recent years, several studies have evaluated the application value of myocardial radiomics in CHD, but there are few studies on the prediction of coronary artery stenosis using myocardial radiomics (22-24).

Radiomics features usually have a large amount of data, and it is difficult to obtain ideal results by traditional methods. However, machine learning algorithms can improve the prediction performance and outperform the traditional one-dimensional statistical methods by specifically finding associations between data. Therefore, we extracted the radiomics features of 3 coronary segments of the left ventricular (LV) myocardium on resting MPI and constructed a model using the machine learning method to predict coronary stenosis. The radiomics model was comprehensively evaluated through comparison with the conventional parameter model and through subgroup analysis. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/ view/10.21037/atm-22-4692/rc).

Methods

Owing to the particularity of cardiac research, in this work, we followed the recommendations of the European Association of Cardiovascular Imaging and the European Association of Nuclear Medicine to standardize the application of artificial intelligence in multimodal cardiovascular imaging (25).

Patients

This retrospective diagnostic study included patients who underwent resting ¹³N-NH₃ PET MPI and CAG at Guangdong Provincial People's Hospital from November 2016 to December 2021 due to suspected CHD.

The inclusion criteria were as follows: (I) adult patients; (II) suspected CHD due to chest tightness, chest pain, and abnormal electrocardiogram (ECG); (III) resting MPI and CAG performed successively with an interval of no more than 30 days; and (IV) complete clinical and imaging data.

The exclusion criteria were as follows: (I) previous



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Figure 1 Flow chart of the study population. "n=112/n=101/n=9/n=3/n=2/n=42" is the numbers of patients and "n=126" is the number of coronary segments. CHD, coronary heart disease; MPI, myocardial perfusion imaging; CAG, coronary angiography.

history of CHD; (II) history of coronary revascularization; (III) history of arrhythmia or pacemaker implantation; and (IV) inability to evaluate the original image due to dislocation artifacts caused by poor breath-holding, body movement, and other reasons.

The patient selection process is illustrated in *Figure 1*. The demographic and clinical information of the selected patients were recorded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of the Guangdong Provincial People's Hospital (No. KY-Q-2022-345-01), and individual patient consent for this retrospective analysis was waived.

PET/CT acquisition and data analysis

The resting MPI scans were performed in 3D list-mode on a Siemens Biograph 16 PET/CT scanner. In the resting state, the patient was intravenously injected with 15–25 mCi $(555–925 \text{ Mbq})^{13}$ N-NH₃ on the scanner, and continuous perfusion acquisition for 15 min was immediately initiated. ECGs were collected during the cardiac-gated triggering scan. The patients were instructed to breathe normally and to avoid deep breathing, speaking, and body movements to prevent image dislocation.

Data were reconstructed by an ordered subset expectation maximization algorithm with 2 iterations per 24 subsets, a matrix size of 168×168, a voxel size of 4.1×4.1×2.0 mm, and a gaussian filter at 5.0 mm full-width at half-maximum. MPI data were reconstructed into static and dynamic images, and the dynamic images were reconstructed into 21 frames (12×10, 6×30, 2×60, and 1×180 seconds). A doctor (Doctor 1) with 10 years of experience who was blinded to original MPI measurements determined the LV contour and generated a polar map using the commercially available QPS/QGS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA). Manual corrections of LV position, angle orientation, and valve plane position were performed when necessary. The LV image was divided into 3 coronary segments [left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA)] on a polar map according to the American Heart Association criteria. The conventional parameters of each segment were obtained: MBF, perfusion defect extent (EXT), total perfusion deficit (TPD), and summed rest score (SRS) (Figure 2). MBF was obtained from dynamic imaging data and represented absolute blood flow quantification through a unit mass of myocardium per unit Page 4 of 17



Figure 2 Parameter analysis of MPI PET. A 59-year-old man presented with chest tightness for more than 1 month. Recent CAG suggested that the LCX had 30% stenosis and RCA occlusion. (A) The time/activity curves display radiotracer activity within 3 segments. (B) The polar map that is segmented into 3 shows rest MBF in mL/g/min. The MBFs of the LAD/LCX/RCA segment were 0.75/0.81/0.53 mL/g/min, respectively. (C,D) Hypoperfused myocardium is displayed in polar map coordinates (C) and 3D parametric surfaces (D) with 3 segments. TPD represents the EXT (black part) and the severity of the hypoperfused myocardium. The TPDs of the LAD/LCX/RCA segment were 0%/10%/63%, respectively. The EXT of the LAD/LCX/RCA segment were 2%/16%/78%, respectively. (E) The polar map was scored based on a 17-segment model and a categorical scale of 0–4 (0= normal; 4= absent perfusion). The SRSs for LAD/LCX/RCA were 0/1/11, respectively. MPI, myocardial perfusion imaging; PET, myocardial perfusion imaging; CAG, coronary angiography; LCX, left circumflex coronary artery; RCA, right coronary artery; MBF, myocardial blood flow; LAD, left anterior descending coronary artery; TPD, total perfusion deficit; EXT, defect extent; SRS, summed rest score.

time (mL/min/g). The EXT, TPD, and SRS were obtained from static images. EXT represents the percentage of the perfusion defect extent, TPD comprehensively reflects the percentage of the extent and severity of perfusion defects, and SRS is a semi-quantitative parameter used to evaluate the severity of perfusion defects. This was the sum of the tracer uptake scores in each segment (0: normal, 1: slight reduction, 2: moderate reduction, 3: severe reduction, 4: no distribution).

CAG

All the patients underwent CAG within 30 days of the myocardial PET scan. A doctor (Doctor 2) reviewed the



Figure 3 Workflow of myocardial segmentation of MMI PET. (A) Load image. (B) Reposition the 3 positions of the heart (LV apex, LV base, and RV). (C) Search the ventricular boundaries and generate the VOI and MASK. (D) Three coronary segments were outlined on the LV polar map. (E) Generated VOI and MASK of the LAD/LCX/RCA segment. MMI, myocardial metabolic imaging; PET, myocardial perfusion imaging; LV, left ventricular; RV, right ventricular; VOI, volume of interest; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

CAG report and determined the degree of stenosis of the left main coronary artery (LM) and the 3 coronary arteries. LM lumen stenosis >50%, LAD, LCX, and RCA lumen stenosis >75% were considered to be significant stenosis and were used as the standard for obstructive CHD.

Segmentation and radiomics feature extraction

The myocardium of the LV coronary segments was segmented using a semi-automatic segmentation algorithm based on the Carimas version 2.10 software (Turku PET Center, Finland) by Doctor 1 who was blinded to patient characteristics and CAG results. First, the DICOM image of the static image was loaded. Second, 3 locations of the heart (the apex of the LV, base of the LV, and RV) were repositioned. Third, the software automatically searched ventricular boundaries to obtain the initial 3D-volume of interest (VOI) and generate a MASK, which could be manually adjusted to improve quality. Finally, LAD, LCX, and RCA segment masks were delineated based on the LV MASK for feature extraction (*Figure 3*).

Radiomics features were extracted using the PyRadiomics package on Feature Explorer Pro (FAE version 0.4.4), an open-source machine learning platform based on Python. Three feature categories were extracted: (I) first-order (statistics) features; (II) shape-based features; and (III) texture features [including gray-level co-occurrence matrix (GLCM), gray-level run-length matrix (GLRLM), graylevel size zone matrix (GLSZM), gray-level dependence matrix (GLDM), and neighborhood grav-level difference matrix (NGTDM)]. In addition, 9 filters [including wavelet transform, square, square root, Laplacian of Gaussian, logarithm, exponential, gradient, local binary pattern (2D), and local binary pattern (3D)] were applied to the original images to obtain derived images. Except for the shapebased images, all the other features were calculated for the original and derived images.

Reproducibility of radiomics features

Thirty patients were randomly selected, and image segmentation of 90 coronary segments was performed again by 2 nuclear medicine doctors (Doctor 1 with 10 years of experience and Doctor 3 with 20 years of experience). Intraclass correlation coefficients (ICCs) for each radiomics feature were calculated after segmentation to assess interobserver repeatability.

Modeling

All patients were randomly divided into the training and testing groups at a 1:1 ratio, and their coronary segments were used as the training and testing sets, respectively. The training set was used for feature and parameter selection

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and model development, while the testing set was used for model evaluation and subgroup analysis. In the training set, FAE software was used to implement the machine learning algorithm according to the process of "balance data" - "normalization" - "preprocess" - "feature selection" - "classifier", and the conventional parameter (MPI model) and radiomics (Rad model) models for predicting significant coronary stenosis (>75%) were established. The synthetic minority oversampling technique was used to balance positive and negative samples. Z-scores were used for normalization. If the Pearson correlation coefficient value of the feature pair was larger than 0.9, one of them was randomly removed. The maximum number of features was 20, the feature selection method was recursive feature extraction (RFE), and the classifier was a support vector machine (SVM). A 5-fold cross-validation was applied to the training set for model evaluation. The model with the largest area under the curve (AUC) in the cross-validation set was selected as the best model and tested in the testing set. After the best MPI and Rad models were selected, the MPI and Rad scores of each segment were calculated. The 2 models were combined to establish a nomogram, and the risk score for each segment was calculated. The discriminant ability of the models was evaluated using the AUC, accuracy, sensitivity, and specificity. The net clinical benefit of the models was assessed using decision curve analysis (DCA). The agreement between the observed and predicted values of the model was demonstrated by the calibration curves.

Subgroup analysis

To evaluate whether the selected models had good and stable performance under different conditions, we conducted multiple subgroup analyses in the testing set including the following: (I) different myocardial segments (LAD, LCX, RCA); (II) number of stenotic vessels (0–1, 2–3 coronary stenoses); (III) presence of LM stenosis; (IV) different cardiac risk factors (hypertension, diabetes); (V) the total injection dose of ¹³N-NH₃ (15–20, 20–25 mCi); and (VI) the unit injection dose of ¹³N-NH₃ (0.20–0.30, 0.30–0.50 mCi/kg). The performance of the models was evaluated using the AUC.

Statistical analysis

Classification variables are presented as frequency (percentage), and normally distributed continuous variables

are presented as mean \pm standard deviation. Continuous variables with a non-normal distribution are presented as median (interquartile range). The independent-sample *t*-test, χ^2 test, or Mann-Whitney U test were used to evaluate the differences between sets. The differences between AUCs were assessed using the DeLong test. The matching degree of the calibration curves was evaluated by the unreliability test. Statistical significance was set at P<0.05, and bilateral tests were used. SPSS (version 20.0; IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. R (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) with RStudio (version 1.4.1717) was used to draw parts of the figures.

Results

Patients and coronary segments

This study included 84 patients (42 in the training group and 42 in the testing group). The average age was 57.3±10.1 years old, and 91.7% of the patients were male. CAG confirmed that 75 (89.3%) patients had CHD and 9 (10.7%) did not. Among them, 15 (17.9%), 34 (40.5%), and 26 (31.0%) patients had 1-, 2-, and 3-vessel stenosis, respectively, and 22 (26.2%) had LM stenosis. The baseline characteristics and CAG results of patients are shown in Table 1. The results showed no significant difference between the training and testing groups (P>0.05). There were 252 coronary segments in 84 patients (both the training and testing sets included 126 coronary segments). CAG showed 161 coronary artery stenoses (63.9%) and 61 (72.6%), 38 (45.2%), and 62 (73.8%) stenoses of the LAD, LCX, and RCA, respectively. Quantitative analysis of resting MPI showed that the medians (interquartile ranges) of MBF, EXT, TPD and SRS of all segments were 0.61 mL/g/min (0.47-0.76 mL/g/min), 22% (8-49%), 20% (7-45%), and 6 [2-10], respectively. The CAG and resting MPI results of the segments are shown in Table 2. No significant differences were observed between the 2 sets (P>0.05).

Modeling

We extracted 1,781 radiomics features from the original and derived images of the resting MPI. After excluding features with a variance close to 0, 1,206 features were obtained. After removing features with an ICC <0.9, 996 features remained. After "balance data", "normalization",

Table 1 Patient characteristics (n=84)	
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Variables	Training group, n=42	Testing group, n=42	P value
Demographic			
Gender			
Male	37 (88.1)	40 (95.2)	0.430
Female	5 (11.9)	2 (4.8)	
Age (years)	56.2±9.8	58.4±10.5	0.335
Body mass index (kg/m ²)	23.3±2.6	24.0±3.2	0.268
Cardiac risk factors			
Smoking			
Yes	19 (45.2)	20 (47.6)	0.827
No	23 (54.8)	22 (52.4)	
Alcoholism			
Yes	3 (7.1)	4 (9.5)	1.000
No	39 (92.9)	38 (90.5)	
Diabetes mellitus			
Yes	17 (40.5)	15 (35.7)	0.653
No	25 (59.5)	27 (64.3)	
Hypertension			
Yes	17 (40.5)	16 (38.1)	0.823
No	25 (59.5)	26 (61.9)	
Dyslipidemia			
Yes	6 (14.3)	4 (9.5)	0.736
No	36 (85.7)	38 (90.5)	
Family history of CHD			
Yes	2 (4.8)	2 (4.8)	1.000
No	40 (95.2)	40 (95.2)	
Number of stenotic vessels			
0–1 vessel	13 (31.0)	11 (26.2)	0.629
2–3 vessels	29 (69.0)	31 (73.8)	
Left main trunk stenosis			
Yes	10 (23.8)	12 (28.6)	0.620
No	32 (76.2)	30 (71.4)	
Dose of ¹³ N-NH ₃			
Total dose (mCi)	19.7±2.8	20.8±3.4	0.101
15–20	21 (50.0)	18 (42.9)	0.512
20–25	21 (50.0)	24 (57.1)	
Unit dose (mCi/kg)	0.32±0.073	0.32±0.081	0.801
0.20-0.30	18 (42.9)	19 (45.2)	0.826
0.30–0.50	24 (57.1)	23 (54.8)	

Classification variables are presented as n (%), and normally distributed continuous variables are presented as mean ± SD. CHD, coronary heart disease.

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Yes

No

Yes

No

Yes

No

P value

0.336 0.989 0.977 0.877

0.694

0.807

0.661

MPI parameters and CAG results	Training set	Testing set	
Number of segments, n	126	126	
MBF (mL/g/min)	0.57 [0.46–0.76]	0.65 [0.48–0.79]	
EXT (%)	21 [9–50]	25 [8–48]	
TPD (%)	20 [8–46]	21 [6–44]	
SRS	6 [2–10]	6 [2–10]	

42/42/42

79 (62.7)

47 (37.3)

31 (73.8)

11 (26.2)

18 (42.9)

24 (57.1)

Table 2 MPI parameters of segments and CAG results of coronary arteries

Yes30 (71.4)32 (76.2)0.620No12 (28.6)10 (23.8)Continuous variables with a non-normal distribution are presented as median [interquartile range], and classification variables are
presented as n (%). MPI, myocardial perfusion imaging; CAG, coronary angiography; MBF, myocardial blood flow; EXT, defect extent;
TPD, total perfusion deficit; SRS, summed rest score; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery;

RCA, right coronary artery.

Number of LAD/LCX/RCA, n

Vascular stenosis of LAD

Vascular stenosis of LCX

Vascular stenosis of RCA

Vascular stenosis of 3 vessels

and "preprocess" (Pearson correlation analysis), 211 features remained (Figure 4). Through the SVM-RFE machine learning process of 5-fold cross-validation, 20 radiomics models were generated, and the model with the largest AUC (0.788) in the cross-validation set was selected as the Rad model (Figure 5A). The Rad model was composed of 12 radiomics features. The selected features and their corresponding coefficients are shown in Figure 5B. The radiomics score of each segment, calculated using the Rad model, is shown in Figure S1. After approximately the same modeling process, the obtained MPI model was composed of 2 parameters: MBF and EXT. The model selection process and parameter coefficients are shown in Figure 5C, 5D. The Rad model was combined with the MPI model to establish a combined model in the form of a nomogram (Figure 6).

Machine learning model performance

42/42/42

82 (65.1)

44 (34.9)

30 (71.4)

12 (28.6)

20 (47.6)

22 (52.4)

The AUC, accuracy, sensitivity, and specificity of the MPI model were, respectively, 0.795, 0.778, 0.937, and 0.511 in the training set and 0.798, 0.722, 0.659, and 0.841 in the testing set. The AUC, accuracy, sensitivity, and specificity of the Rad model were, respectively, 0.912, 0.825, 0.760, and 0.936 in the training set and 0.887, 0.810, 0.744, and 0.932 in the testing set. The AUC, accuracy, sensitivity, and specificity of the nomogram were, respectively, 0.911, 0.865, 0.924, and 0.766, in the training set and 0.900, 0.849, 0.854, and 0.841 in the testing set. The results are shown in *Table 3* and *Figure 7A*, 7B. The DeLong test showed that the AUCs of the Rad model and nomogram were significantly higher than that of the MPI model, but there was no significant difference between the AUC of the Rad model and

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Figure 4 Heat map chart between radiomics features. Red indicates a positive correlation and blue indicates a negative correlation. The darker the color, the higher the correlation between the 2 features. (A) Cross-correlation of 996 features. (B) The cross-correlation of the remaining 211 features after Pearson correlation analysis.

nomogram (*Figure 7C*, 7D). The DCA showed that the net clinical benefit of the Rad model and nomogram was similar but greater than that of the MPI model (*Figure 7E*, 7F). The calibration curve showed good agreement between the observed and predicted values of the Rad model, and the P values of the unreliability test in the 2 sets were greater than 0.05 (Figure S2). Based on these results, we conducted a subgroup analysis of the Rad model.

Subgroup analysis

Subgroup analysis in the testing set showed that the ability of the Rad model to distinguish coronary stenosis (ROC AUC) was not significantly different (DeLong test) among subgroups divided by myocardial segments, number of stenotic vessels, LM stenosis, CHD risk factors, and total and unit injection dose of ¹³N-NH₃. The AUCs between the LAD and RCA subgroups showed the largest difference (0.939 *vs.* 0.806), but there was no statistical difference between them (P=0.096) (*Table 4, Figure 8*).

Discussion

In patients with CHD, resting MPI is rarely used alone. It is usually combined with stress MPI or MMI for the evaluation of ischemia, infarction, hibernation, and myocardial scarring, thus providing a basis for subsequent treatment decisions (13). If the resting MPI data can be used to accurately predict coronary stenosis and reduce the risk of injury caused by CAG, this will be of great significance.

Radiomics has been widely used in medical research as a novel, inexpensive, and noninvasive quantitative imaging technique (26,27). However, PET radiomics studies are mainly focused on ¹⁸F-FDG imaging of tumors, while there are few radiomics studies on cardiac PET imaging, let alone ¹³N-NH₃ (25). Although there are many studies on cardiac MRI radiomics, most of them evaluated myocardial ischemia, infarction, or fibrosis, while there are none on the prediction of coronary stenosis (28). To our knowledge, this is the first study to predict coronary stenosis using ¹³N-NH₃ PET radiomics.

¹³N-NH₃ is a fat-soluble substance that can pass freely through the cell membrane. ¹³N-NH₃ enters and remains in cardiomyocytes via the cell membrane through passive diffusion (29). Myocardial uptake of ¹³N-NH₃ was positively correlated with MBF. When coronary artery stenosis is severe, MBF is reduced and the myocardial microstructure is destroyed (13,17-19). Both factors change the distribution of ¹³N-NH₃ in myocardial tissue and then change the radiomics features of MPI. Therefore,

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Figure 5 Model selection and weights of features. (A) Rad model for feature selection; 12 radiomics features corresponding to the optimal validation AUC were selected. (B) Coefficients of 12 features in the Rad model. (C) MPI model for feature selection; 2 features that correspond to the optimal validation AUC were selected. (D) Coefficients of 22 features in the MPI model. Rad, radiomics; AUC, area under the curve; EXT, defect extent; MBF, myocardial blood flow; MPI, myocardial perfusion imaging.

we attempted to establish a statistical association between radiomics features and coronary stenosis using machine learning methods. The Rad model is composed of firstorder and texture features without shape-based features. The first-order features mainly reflect changes in MBF, and the texture features mainly reflect changes in the myocardial microstructure. We believe that the Rad model reveals an association between the 2 categories of features and coronary stenosis.

Image segmentation has always been the focus and difficulty of radiomics (30). In the study of cardiac magnetic resonance radiomics, the combination of automatic contour drawing and limited manual correction is advocated, which has high efficiency and repeatability (20). Our segmentation task consisted of LV segmentation and coronary segment segmentation, which were completed using Carimas software. In LV segmentation, the MASK file of LV VOI could be obtained through the semi-automatic segmentation algorithm of the software and manual adjustment (31,32). In coronary segment segmentation, the VOI-MASK was further divided into MASK files of 3 coronary segments (LAD-MASK, LCX-MASK, and RCA-MASK) according to the American Heart Association standards. The advantages of this segmentation method are as follows: (I) the operation is convenient and fast, as it takes only 2–3 min to complete the segmentation of 3 coronary segments in a patient; (II) the obtained radiomics information is complete and rich because MASK files cover 3D and continuous layers of coronary segments, which is different from those studies that only analyze the maximum section or even polar map



Figure 6 Nomogram integrating the Rad and MPI models. The nomogram was developed from the data of the training set, which integrated the Rad and MPI scores. In the nomogram, we drew an upward vertical line according to the values of the Rad and MPI scores to determine the corresponding points. The sum of these 2 points was the total number of points. We drew a downward vertical line to determine the risk of coronary stenosis. Rad, radiomics; MPI, myocardial perfusion imaging.

Table 3 The performance of the models

Models	AUC (95% CI)	Cut off	Accuracy	Sensitivity	Specificity
Training group					
MPI model	0.795 (0.713–0.876)	-0.777	0.778	0.937	0.511
Rad model	0.912 (0.862–0.962)	0.808	0.825	0.760	0.936
Nomogram	0.911 (0.860–0.962)	0.455	0.865	0.924	0.766
Testing group					
MPI model	0.798 (0.721–0.875)	0.158	0.722	0.659	0.841
Rad model	0.887 (0.830–0.943)	0.705	0.810	0.744	0.932
Nomogram	0.900 (0.847–0.953)	0.641	0.849	0.854	0.841

AUC, area under the curve; CI, confidence interval; MPI, myocardial perfusion imaging; Rad, radiomics.

(33,34); (III) the repeatability is good, and >80% (996/1,206) radiomics features show high inter-observer repeatability (ICC \geq 0.9).

With the advent of the era of precision medicine, various types of "big data" have been applied in clinical research (35,36). For complex available data, algorithms can be specifically used to find correlations between data, improve the predictive power of the model, and provide clinically relevant and useful results (37). Therefore, machine learning is increasingly used in the cardiovascular field (38). The FAE software is a Python-based radiomics

and machine learning modelling tool developed by Song *et al.* It integrates the processes of feature extraction, data cleaning, binary classification modelling, result analysis, and visualization (39). The FAE software provides 4 classifiers and 10 feature selection methods, with a total of 40 combinations. To simplify the research process, only SVM-RFE was selected. SVM-RFE is a backward recursive elimination feature-selection algorithm that applies an SVM to high-dimensional data. It was first proposed by Guyon *et al.* for gene selection and achieved very good results (40). After continuous improvements, its performance and

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Figure 7 Performance of the models in the training set and testing set. (A,B) ROC for predicting coronary stenosis. In the training (A) and testing (B) sets, the AUCs of the Rad model and nomogram were higher than that of the MPI model, but the AUC between the 2 was close. (C,D) Comparison of the AUC using the DeLong test. In the training (C) and testing (D) sets, the AUCs of the Rad model and nomogram were significantly different from that of the MPI model, but there was no significant difference between the AUC of the Rad model and nomogram. (E,F) Decision curve analysis. The y-axis measures the net benefit, which is calculated by adding true positives and subtracting false positives. The closer the curve is to the upper right, the higher the net benefit. In the training (E) and testing (F) sets, the Rad model and nomogram have a closer net benefit, which is higher than that of the MPI model. AUC, area under the curve; RAD, Rad model; NOM, nomogram; MPI, myocardial perfusion imaging; ROC, receiver operating characteristic curve; Rad, radiomics.

Subgroups	Number of patients	Number of segments	AUC (95% CI)	Accuracy	Sensitivity	Specificity	P value
Myocardial segment							
LAD	42	42	0.939 (0.871–1.000)	0.905	0.867	1.000	0.258ª
LCX	42	42	0.857 (0.733–0.980)	0.857	0.850	0.864	0.096 ^b
RCA	42	42	0.806 (0.669–0.944)	0.786	0.781	0.800	0.594°
Number of stenotic vessel	s						
0–1	11	33	0.895 (0.745–1.000)	0.879	0.875	0.880	0.931
2–3	31	93	0.888 (0.817–0.958)	0.785	0.743	0.947	
Left main trunk stenosis							
No	30	90	0.885 (0.817–0.953)	0.833	0.836	0.829	0.999
Yes	12	36	0.885 (0.772–0.997)	0.861	0.815	1.000	
Cardiac risk factors							
Hypertension	16	48	0.886 (0.795–0.978)	0.833	0.774	0.941	0.932
Diabetes	15	45	0.892 (0.799–0.985)	0.844	0.781	1.000	
Total dose of ¹³ N-NH ₃							
15–20 mCi	18	54	0.895 (0.812–0.978)	0.852	0.844	0.864	0.823
20–25 mCi	24	72	0.882 (0.803–0.960)	0.819	0.760	0.955	
Unit dose of ¹³ N-NH ₃							
0.20–0.30 mCi/kg	19	57	0.909 (0.834–0.984)	0.842	0.800	0.909	0.570
0.30–0.50 mCi/kg	23	69	0.877 (0.797–0.957)	0.783	0.702	0.955	

Table 4 The performance of the Rad model in the subgroup analysis

The P value represents the result of the DeLong test of AUCs between subgroups. ^a, P value between the LAD and LCX subgroup; ^b, P value between the LAD and RCA subgroup; ^c, P value between the LCX and RCA subgroup. Rad, radiomics; AUC, area under the curve; CI, confidence interval; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

efficiency continued to increase. Currently, it is also applied to proteomics, radiomics, and other fields to improve the prediction accuracy of models (41-44). In our study, SVM-RFE was used to screen out 12 radiomics features to construct the Rad model, as well as 2 MPI parameters to construct the MPI model. These 2 models were then combined to construct a nomogram.

The 3 models calculated the risk score of each segment and predicted high-risk coronary arteries. In a study conducted at our center, MPI and MMI conventional parameters were combined to predict coronary stenosis using the machine learning method (15). The AUC of the best model was 0.856, which was better than that of the MPI model (AUC: 0.795) but inferior to the Rad model (AUC: 0.912) and nomogram (AUC: 0.911). In general, the nomogram showed better performance than the Rad model; however, there was no significant difference in the AUCs between them. This was because in the nomogram, the relative weights of the Rad model were far greater than those of the MPI model, and the nomogram was weighted heavily towards the Rad model, which produced better performance. Specifically, the radiomics features of the Rad model could have covered or even replaced the conventional parameters of the MPI model. Whether it indicates that radiomics features can predict conventional MPI parameters needs to be tested in future studies. The DCA for evaluating the net clinical benefit yielded similar results. Therefore, we chose the Rad model for subgroup analysis.

To ensure a sufficient sample size in each subgroup in the subgroup analysis, we divided the training and testing sets in a 1:1 ratio. As no relevant study has been conducted before, it was unclear which factors would affect the performance of the Rad model. Based on our



Figure 8 ROC for predicting coronary stenosis in the subgroup analysis. (A) Myocardial segment. (B) Number of stenotic vessels. (C) Left main trunk stenosis. (D) Cardiac risk factors. (E) Total dose of ¹³N-NH₃. (F) Unit dose of ¹³N-NH₃. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; ROC, receiver operating characteristic curve.

experience, we selected specific factors for the subgroup analysis. First were the different myocardial segments (LAD, LCX, and RCA). Second was the injection dose of ¹³N-NH₃, including total and unit doses. ¹³N-NH₃ has a short half-life of approximately 10 min, making fixedunit dose injection difficult to achieve (29). Therefore, in clinical practice, the total dose is often controlled between 10-30 mCi (13). The total dose in our study was within this range; however, the unit dose varied widely from 0.20 to 0.50 mCi/kg. We divided them into 2 subgroups (0.20-0.30 and 0.30-0.50 mCi/kg) for analysis and comparison. Third were the factors affecting hemodynamic status, including LM stenosis and the number of stenotic coronary arteries (45-47). For the former, we divided LM into stenosis and non-stenosis subgroups with >50% as the threshold, and the latter was divided into 2 subgroups: 0-1 vessel stenoses and 2-3 vessels stenoses. Fourth were the factors that may lead to microcirculatory lesions, including hypertension and diabetes (48-50), which were analyzed in separate subgroups. The final result showed that the AUC difference between the LAD and RCA subgroups was the largest (0.939 vs. 0.806), but there was no statistical difference between them (P=0.096). There was no statistical difference between the other subgroups (*Figure 8, Table 4*). This shows that the Rad model is not affected by subgroup factors and has good generalization ability.

This study has some limitations. First, this was a singlecenter, small-sample, retrospective study without external validation, and sampling error may affect the statistical results. Second, only patients with suspected CHD were included, excluding confirmed cases with a history of CHD. We speculated that the treatment process (drugs or surgery) of CHD might change myocardial radiomics characteristics and affect the prediction efficiency of the

model. Therefore, only suspected untreated patients were included in the study. However, this might lead to selection bias and render the prediction model unsuitable for the general population. Third, stress MPI was excluded in this study. The Rad model was not compared with stress MPI, Rad model + stress MPI, or even stress MPI radiomics models. Therefore, in future research, efforts should be made in several aspects: obtaining a prospective, external independent validation cohort; extending the model to general patients with CHD; and incorporating stress MPI into the evaluation system.

Conclusions

In patients with suspected CHD, the radiomics machine learning model based on resting MPI can accurately predict coronary stenosis, which is better than the resting MPI conventional parameter model. In clinical practice, this noninvasive tool can help improve risk stratification. In the subgroup analysis, the Rad model was not affected by grouping factors and had good generalization ability.

Acknowledgments

We thank Professor Chunlei Han from Turku PET Centre for his guidance on the use of Carimas software. *Funding*: None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm. amegroups.com/article/view/10.21037/atm-22-4692/rc

Data Sharing Statement: Available at https://atm.amegroups. com/article/view/10.21037/atm-22-4692/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm. amegroups.com/article/view/10.21037/atm-22-4692/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics

committee of the Guangdong Provincial People's Hospital (No. KY-Q-2022-345-01), and individual patient consent for this retrospective analysis was waived.

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Cite this article as: Zhang X, Sun T, Liu E, Xu W, Wang S, Wang Q. Development and evaluation of a radiomics model of resting ¹³N-ammonia positron emission tomography myocardial perfusion imaging to predict coronary artery stenosis in patients with suspected coronary heart disease. Ann Transl Med 2022;10(21):1167. doi: 10.21037/atm-22-4692

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Figure S1 Rad score of each segment calculated by the Rad model. In the training (A) and testing (B) sets, the Rad score of each segment is calculated by the Rad model. In this waterfall plot, the red bar represents the Rad score of the segment with significant coronary stenosis, and the green bar represents the Rad score of the segment without significant coronary stenosis.



Figure S2 Calibration curves for the Rad model. The calibration curves indicate the goodness-of-fit of the Rad model. The p values of the unreliability test were >0.05 in the training (P=0.260) (A) and testing (P=0.463) (B) sets. The 45° gray line represents the ideal prediction, and the solid black line represents the predictive performance of the nomogram. The closer the solid line approaches the ideal prediction line, the better the predictive efficacy of the model.