Evaluation of the diagnostic value of joint PET myocardial perfusion and metabolic imaging for vascular stenosis in patients with obstructive coronary artery disease

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Running title: Joint evaluation of cardiac PET imaging

Abstract

Background. To investigate the diagnostic value of joint PET myocardial perfusion and metabolic imaging for vascular stenosis in patients with suspected obstructive coronary artery disease (CAD).

Methods. Eighty-eight patients (53 and 35 applied for training and validation, respectively) with suspected obstructive CAD were referred to ^{13}N-NH_3 PET/CT myocardial perfusion imaging (MPI) and ^{18}F-FDG PET/CT myocardial metabolic imaging (MMI) with available coronary angiography for analysis. One semi-quantitative indicator summed rest score (SRS) and five quantitative indicators, namely, perfusion defect extent (EXT), total perfusion deficit (TPD), myocardial blood flow (MBF), scar degree (SCR), and metabolism-perfusion mismatch (MIS), were extracted from the PET rest MPI and MMI scans. Different combinations of indicators and seven machine learning methods were used to construct diagnostic models. Diagnostic performance was evaluated using the sum of four metrics (noted as sumScore), namely, area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity.

Results. In univariate analysis, MIS outperformed other individual indicators in terms of sumScore (2.816–3.042 vs. 2.138–2.908). In multivariate analysis, support vector machine (SVM) consisting of three indicators (MBF, SCR, and MIS) achieved the best performance (AUC 0.856, accuracy 0.810, sensitivity 0.838, specificity 0.757, and sumScore 3.261). This model consistently achieved significantly higher AUC compared with the SRS method for four specific subgroups (0.897, 0.833, 0.875, and 0.949 vs. 0.775, 0.606, 0.713, and 0.744; p=0.041, 0.005, 0.034 0.003, respectively).

Conclusions. The joint evaluation of PET rest MPI and MMI could improve the diagnostic performance for obstructive CAD. The multivariate model (MBF, SCR, and MIS) combined with SVM outperformed other methods.

Keywords: myocardial perfusion imaging, myocardial metabolic imaging, machine learning, coronary artery disease

Abbreviations

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
LAD	Left anterior descending coronary artery
LCx	Left circumflex coronary artery
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
^{18}F-FDG	Fluorodeoxyglucose
MPI	Myocardial perfusion imaging
PET	Positron emission tomography
SRS	Summed rest score

Introduction

Coronary artery disease (CAD) refers to coronary artery atherosclerotic lesions that cause stenosis or vascular lumen obstruction, resulting in heart disease caused by myocardial ischemia, hypoxia, or necrosis.[1] CAD was the second leading cause of chronic diseases in China until 2017.[2] Thus, effective and accurate diagnosis is particularly important for the management of patients with suspected or known CAD. Obstructive CAD diagnosis is mainly based on coronary stenosis detection. Coronary angiography (CAG) can effectively determine the presence and degree of coronary stenosis and is the gold standard for CAD diagnosis.[3] However, CAG is a costly, invasive procedure with risk for complications that may be life-threatening and cause irreversible damage.[4, 5] Furthermore, CAG is contraindicated in patients allergic to contrast media and with liver and kidney dysfunction because of contrast medium use.[6]

Positron emission tomography myocardial perfusion imaging (PET MPI) has higher accuracy, sensitivity, and specificity for CAD detection than single-photon emission computed tomography (SPECT) MPI.[7-10] Coronary artery calcium (CAC) is a global marker of atherosclerosis,[11] and regional CAC scores improve the accuracy in CAD detection.[12] Ischemic total perfusion deficit (ITPD), which is a measure of hypoperfusion change between stress and rest in the entire ventricle,[13] has been combined with regional and global CAC to enhance the overall diagnostic value of PET/CT for obstructive CAD detection.[14] The combination of CAC score, ITPD, and quantitative coronary vascular function further improves the diagnostic accuracy of ^{82}Rb PET/CT in predicting obstructive CAD.[15] However, these studies require rest and stress PET MPI.

For CAD diagnosis, pharmacological and exercise stress PET MPI are more sensitive and have higher clinical value than resting PET MPI and have been used in the clinic. However, stress PET is not widely applied in the clinics in China because patients that undergo cardiac PET imaging, mostly those with moderate to severe CAD and especially the elderly, are prone to cardiovascular dysfunctions, such as fatal arrhythmias and serious cardiac malignant events, during stress tests. Hence, doctors and patients are under tremendous psychological stress and risk. The clinical routine management involves performing myocardial metabolic imaging (MMI) PET, followed by a rest PET MPI. MMI reveals scar

degree (SCR) and is the gold standard for evaluating the presence and extent of viable myocardium.[16, 17] MPI can provide summed rest score (SRS), perfusion defect extent (EXT), total perfusion deficit (TPD), and myocardial blood flow (MBF).[18] A joint evaluation of MMI and MPI PET can provide "metabolism-perfusion mismatch" (MIS), which reflects myocardial tissue showing local defects in MPI with no abnormality in the corresponding region of MMI.[19]

Therefore, we evaluated the joint value of PET rest MPI and MMI quantification in predicting obstructive CAD. The semi-quantitative SRS and the five quantitative indicators (EXT, TPD, MBF, SCR, and MIS) were combined with seven machine learning (ML) algorithms to derive the optimal combination model and classification method.

Materials and Methods

Study population

This retrospective study was approved by the Institutional Review Board, and informed consent was waived. This study initially included 159 patients with suspected or known CAD that underwent ^{13}N-ammonia (^{13}N-NH_3) PET/CT MPI and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT MMI in rest between October 2017 and June 2019 in Guangdong Provincial People's Hospital, Guangzhou, Guangdong, China. However, 22 patients were excluded due to the following reasons: (1) having severe valvular heart disease, acute myocarditis, uncontrolled arrhythmias, or (2) poor image quality and incomplete clinical information. Among the 137 remaining patients, 88 referred by a clinical physician to CAG within 1 month of PET/CT imaging were finally considered for subsequent analysis.

PET/CT imaging

All patients separately underwent rest ^{13}N-NH_3 PET/CT MPI and ^{18}F-FDG PET/CT MMI scanning on a whole-body Siemens Biography 16 PET/CT scanner in the next 2 days. As a routine preparation for MMI and MPI, the patients were requested to fast for 6 h and discontinue taking caffeine-containing drugs for 12 h before examination. The patients were given 50 g of oral glucose and 3 IU insulin load when their fasting blood glucose was ≤8.4 mmol/L for MMI scanning. Rest ^{13}N-NH_3 PET/CT MPI and ^{18}F-FDG PET/CT MMI scanning protocols were conducted as follows. Following a CT scout acquisition (120 kVp, 10 mA) for patient positioning, a CT transmission scan was obtained (140 kVp, 80 mA) for subsequent attenuation correction. The patients were instructed to breathe normally during PET acquisition. Afterward, 555–925 MBq (15–25 mCi) of ^{13}N-NH_3 and ^{18}F-FDG were injected intravenously for MPI and MMI, respectively. A 20 min dynamic acquisition PET study was obtained. Rest MMI and MPI dynamic images were reconstructed into 21 time frames (12×10, 6×30, 2×60, and 1×180 s, 10 min) after a delay of 180 s by using attenuation-weighted ordered-subset expectation–maximization (two iterations, 24 subsets) and a Gaussian filter (FWHM=5 mm). CT-based attenuation, scatter, decay, and random corrections were applied to the reconstructed images.

PET quantitative image analysis

Transaxial PET images were automatically reoriented into short-axis and vertical and horizontal long-axis slices. Polar maps of myocardial perfusion and metabolism were generated according to the 17-segment American Heart Association model.[18] The commercially available QPS/QGS software, version 3.0 (Cedars-Sinai Medical Center, Los Angeles, CA, USA) was used to calculate the regional

quantitative indicators for each vascular territory: left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx), and right coronary artery (RCA). Quantitative indicators were divided into three categories based on data sources. (i) Perfusion: EXT, TPD, and MBF were calculated from perfusion data; EXT and TPD are percentages indicating the extent and degree of perfusion defect, respectively. MBF is a continuous value of each vascular territory, representing the volume of blood flow through a unit mass of myocardium in a unit time (mL/min/g), it was computed from the dynamic rest myocardial perfusion imaging series. (ii) Metabolic: after myocardial infarction, the infarcts were replaced by scars, which appeared as defects on both the perfusion and metabolic images, and SCR was calculated from metabolic data, which is a percentage that indicates the degree of scarring. (iii) Perfusion-metabolic: MIS is a percentage that indicates the degree of perfusion metabolism mismatch, which refers to myocardial tissues show reduced or defective in MPI, while with normal or relatively increased ^{18}F-FDG uptake during MMI, and was calculated from combined perfusion and metabolic data.

PET semi-quantitative image analysis

Semi-quantitative myocardial perfusion defects during rest were scored using the same 17-segment polar map; we used a five-point scale ranging from 0 to 4, corresponding to normal perfusion, slight reduction, moderate reduction, severe reduction, and no radiotracer uptake in each segment, respectively.[20, 21] The summed rest scores in segments 1, 2, 7, 8, 13, 14, and 17; 5, 6, 11, 12, and 16; and 3, 4, 9, 10, and 15 were the regional SRS of LAD, LCx, and RCA, respectively. The possible value of SRS in LAD is 0-28, while it is 0-20 for LCx and RCA.

Coronary angiography (CAG)

All patients underwent CAG by using the standard clinical technique within 1 month of PET/CT imaging. Experienced cardiologists visually interpreted the presence and degree of luminal stenosis of each coronary artery, and stenosis of a diameter of ≥75% in at least one of the three major coronary arteries was considered as obstructive CAD.[15]

Statistical analysis

Statistical analysis was performed with the Statistical Program for Social Sciences (SPSS) software version 22.0 (SPSS, Chicago, IL, USA)[22] and the MedCalc software version 15.2.2 (MedCalc Software, Mariakerke, Belgium).[23] The reported statistical significance levels were all two sided, and p-value<0.05 was considered indicative of statistically significant difference. Nonparametric rank-sum test or Chi-squared test (where appropriate) was used to compare differences in SRS, EXT, TPD, MBF, SCR, and MIS between the group with and without CAD. Correlation between each pair of quantitative indicators was assessed using Spearman's correlation coefficient (r). For a pair with $|r| > 0.8$, the less significant indicator was eliminated. All possible combinations of the remained indicators were input into the classification models. We investigated seven types of ML algorithms, namely, logistic regression (LR),[24] linear discriminant analysis (LDA),[25] decision trees (DT),[26] support vector machines (SVM),[27] naive Bayes (NB),[28] K-nearest neighbors (KNN),[29] and random forest (RF).[30] Diagnostic performance was assessed using the sum of area under the receiver operating characteristic (ROC) curve (AUC), accuracy, sensitivity, and specificity, noted as sumScore. Statistically significant

differences between AUCs were using DeLong's method.[31] Computer-generated random numbers were used to build a training set (159 vessels of 53 patients) and a validation set (105 vessels of 35 patients). The training set was used for indicator selection and model development, and the validation set was used for performance evaluation.

Subgroups analysis

Four subgroup analyses were conducted on the validation set to verify whether the final selected model has good classification ability in specific populations. The four populations consisted of patients with the following: (i) old myocardial infarction (OMI) or/and revascularization history, (ii) with 0–1 or 2–3 vessel disease categorized based on the number of vessel with CAD, (iii) hypertension, and (iv) diabetes. Subgroup performance was compared with the SRS model by using ROC analysis.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. As confirmed by CAG, 80 patients (91%) had obstructive CAD, and 8 patients (9%) had no obstructive CAD. Among the patients with obstructive CAD, 25 (31%) had single-vessel disease, 30 (38%) had two-vessel disease, and 25 (31%) had three-vessel disease. Patients with obstructive CAD were mostly male and had higher diastolic and systolic blood pressure than those without obstructive CAD.

Selection of predictors

From the analysis of 159 vessels in 53 patients on the training set, obstructive CAD in 92 (58%) vessels and non-obstructive CAD in 67 vessels (42%) were observed. The results for semi-quantitative SRS and five quantitative indicators (EXT, TPD, MBF, SCR, and MIS) derived from myocardial perfusion and metabolic imaging according to the presence of obstructive CAD in per-vessel analysis are shown in Table 2. Vessels with obstructive CAD showed significantly higher SRS, EXT, TPD, SCR, and MIS but lower MBF compared with the vessels without CAD (all $p<0.001$).

All five quantitative indicators showed Spearman's correlation coefficients $|r|<0.8$ (range 0.33–0.74, Supplementary Table S1), except for EXT and TPD with $|r|=0.94$. EXT was retained, whereas TPD was removed as EXT is more significant than TPD on the training set ($p=2.84\times10^{-13}$ vs. 2.93×10^{-10}). Thus, the remaining four indicators EXT, MBF, SCR, and MIS (noted as 1, 2, 3, and 4, respectively) and all of their 11 different combinations (model_12, model_13, model_14… and model_1234) were used for subsequent model construction by adopting the seven ML methods.

Model performance

The sumScore (the sum of AUC, accuracy, sensitivity, and specificity) of all models under seven different ML methods is shown in Fig. 1**a**. All 15 quantitative models showed higher sumScore than the semi-quantitative model (SRS) for each ML method (2.652–3.261 vs. 2.412–2.703), except for model_3 (SCR) with a sumScore of 2.138–2.507 and model_123 in DT with a sumScore of 2.692. Details on the AUC, accuracy, sensitivity, and specificity of all models under the seven ML methods can be found in Supplementary Table S2. Among the four individual indicators, perfusion and metabolic indicator MIS (model_4) achieved better performance than the remaining three and showed

a sumScore of 2.816–3.042 vs. 2.138–2.908. The metabolic indicator SCR showed the lowest sumScore of 2.138–2.507.

In the multivariate analysis, we separately selected the optimal model for each method on basis of the sumScore value as shown in Fig. 1**b**. The optimal models for the DT, NB, KNN, and RF methods were model_134, model_12, model_24, and model_124, with sumScores of 3.042, 3.195, 3.154, and 3.147, respectively. The remaining LR, LDA, and SVM methods achieved the best performance in model_234, with sumScores of 3.229, 3.242, and 3.261, respectively. The lowest and highest sumScores of each model and corresponding ML methods as shown in Fig. 1**c** and Supplementary Table S3. None of the highest sumScores of these 15 models was achieved by LR, while there are 6/15 models were achieved by SVM, we also noted that DT, RF, LDA, KNN, and NB also showed best performance for several models, while LR, KNN, DT, and RF showed lowest sumScore in 1, 3, 4, and 8 models, respectively, and none of the lowest sumScores were achieved by LDA, NB and SVM.

The diagnostic performances of the seven optimal models in the validation set are shown in Fig. 2 and Supplementary Table S4. Among these seven optimal models, SVM achieved the highest AUC (0.856), accuracy (0.810), and sensitivity (0.838) and moderate specificity (0.757) and thus was selected as the final optimal method, which includes the perfusion indicator MBF, the metabolic indicator SCR, and the joint indicator MIS, noted as model_234. The diagnostic performance of the semi-quantitative SRS model and 15 quantitative models on the validation set by using SVM is shown in Fig. 3. The AUC, accuracy, sensitivity, and specificity of the semi-quantitative SRS model were 0.714, 0.657, 0.956, and 0.189, respectively.

Comparison with semi-quantitative SRS

In the SVM method, the models including only perfusion indicators were model_1, model_2, and especially model_12, which had the best classification performance (sumScore: 3.192 vs. 2.798–2.815). The model including only metabolic indicator was model_3 with a sumScore of 2.37. The 11 remaining models were combined perfusion and metabolic models, of which model_234 exhibited the best performance. Thus, model_12, model_3, and model_234 were selected as the representative models of perfusion, metabolic, and perfusion+metabolic models, respectively. The ROCs of these three quantitative models and semi-quantitative SRS model are shown in the Fig. 4. The AUC of model_234 was higher than that of model_12 (0.856 vs. 0.808) without significant difference (p=0.084). Model_234 and model_12 both had significant higher AUC than SRS, while model_234 had stronger significant difference (p=0.0008 vs. 0.0127). Model_3 had lower AUC than SRS (0.651 vs. 0.714). The quantitative MMI (model_3) had unfavorable identification ability for coronary stenosis and may be inappropriate for the diagnosis of obstructive CAD. In general, quantitative MPI and joint MPI-MMI show good ability to identify coronary stenosis and diagnostic CAD.

ROC analysis in a subgroups of patients

As shown in Fig. 5**a**, model_234 achieved significantly higher AUC than the SRS model (0.897 vs. 0.775, p=0.041) in detecting stenosis in 15 patients with OMI or/and revascularization history in the validation set.

At the cut-off ≥75% coronary stenosis, we divided the 35 validation patients into two groups of having 0–1 or 2–3 vessel disease. For the 11 patients with 0–1 vessel disease (Fig. 5**b**), model_234 and

model_SRS showed AUCs of 0.935 and 0.924, respectively, without significant difference. For the 24 patients with 2–3 vessel disease (Fig. 5**c**), model_234 showed significantly higher AUC than model_SRS (0.893 vs. 0.606, p=0.005). This result indicates that model_234 consistently obtained good performance irrespective of the number of vessels with CAD. SRS showed limited ability in patients with multi-vessel disease.

Model_234 showed significantly higher AUC compared with model_SRS for the 18 patients with hypertension (0.875 vs. 0.713, p=0.034, Fig. 5**d**) and 12 patients with diabetes (0.949 vs. 0.744, p=0.003, Fig. 5**e**).

Discussion

Nuclear cardiology experts traditionally rely on visual evaluation and semi-quantitative analysis to interpret PET/CT MPI and MMI.[32, 33] However, the diagnostic accuracy of these methods is limited and influenced by expert subjectivity. MPI quantitative analysis has been widely studied, and quantified PET MPI has substantially improved the accuracy of CAD diagnosis.[14, 34] In China, the clinical routine for patients starts with MMI PET, followed by rest MPI PET. Therefore, we evaluated the joint value of PET rest MPI and MMI quantification in predicting obstructive CAD. Semi-quantitative SRS and five quantitative indicators (EXT, TPD, MBF, SCR, and MIS) were combined with seven ML algorithms to derive the optimal combination model and classification method.

Experimental results, which include MBF, SCR, and MIS, showed that model_234 based on the SVM method revealed the best diagnostic performance on the validation set, achieved the highest AUC and sumScore, and showed superiority over specific groups. As shown in Fig. 5, model_234 achieved significantly higher AUC compared with model_SRS in patients with OMI or/and revascularization history, multi-vessel disease, hypertension, and diabetes. This result indicates that model_234 has good diagnostic accuracy for patients with CAD and related chronic diseases.

In this study, luminal stenosis with a diameter of ≥75% was defined as the disease according to the results of CAG. To assess whether 75% is a suitable classification cut-off, luminal stenosis with diameters ≥50%[15, 35] and ≥90%[36] were defined on the same training and validation set, respectively. Thus, the ratio of normal to narrow in 264 vessels of 88 patients was 53:211 and 130:134, respectively. The ROCs of the best performing SVM models and semi-quantitative SRS were compared for the identification of coronary artery stenosis, and the results are shown in Fig. 6. At ≥75% cut-off (Fig. 6**b**), the AUC values of the models obtained by ≥50% (Fig. 6**a**) and ≥90% (Fig. 6**c**) were reduced (0.622 and 0.755 vs. 0.856). No significant difference was observed with the SRS model. Therefore, 75% is an appropriate classification cut-off to aid clinicians to accurately and effectively screen moderate and severe stenotic vessels requiring intervention, such as percutaneous coronary intervention or coronary artery bypass grafting.

Although CAG has been the gold standard for CAD diagnosis,[37-40] it has evident drawbacks, including its invasiveness and contrast agents, which can lead to complications and allergic reactions. Non-invasive imaging modalities, such as echocardiography and SPECT, are relatively insensitive for CAD detection.[41, 42] Cardiac imaging with PET/CT is an accurate non-invasive and practical approach, and stress PET MPI is the most effective method to assess coronary microvascular disease.[43] Stress PET has been used in clinical practice for patients with mild CAD.[44-47] However, this method cannot be used for patients with moderate to severe CAD because it may cause acute cardiac events (ACE),

such as shock. The cohort of this study mostly included patients with moderate to severe CAD and was only subjected to rest PET MMI and MPI scanning. This study investigated the diagnostic value of PET rest MPI and MMI for vascular stenosis in patients with obstructive CAD, and it indeed showed improved accuracy for the diagnosis of obstructive CAD. We believe that PET rest MPI and MMI can be used as the "gatekeeper" of CAG to reduce unnecessary CAG and save medical expenses for those patients who underwent both PET rest MPI and MMI, as this approach is currently not the standard clinical practice.

In the SVM method, we tried three kinds of kernel functions, namely linear-, radial basis- (RBF), and polynomial functions. The results of the three functions in 15 quantitative models are shown in Supplementary Fig. S1. In most models (10/15), the linear function achieved the highest sumScores. Therefore, we finally chose linear as the kernel function of SVM in this work, and set the kernel scale to auto. When comparing the results of linear SVM and LR in 15 models, we can see that in most models (14/15), the sumScore of linear SVM is slightly higher or equal to LR. Detailed sumScore of each model was listed in Supplementary Table S5. Both linear SVM and LR are linear classifiers, but on small-scale data sets, linear SVM is slightly better than LR, probably because linear SVM only considers a small part of the data that are most relevant to classification (i.e. support vectors), which improves the generalization and robustness; while LR considers the entire data set, each data point will affect the outcome of the decision.

This study showed some limitations. First, conventional stress PET MPI is the standard approach for patients to diagnose ischemia and CAD. Given the limitation of data, the experiment did not include stress study. Thus, the superiority of perfusion and metabolic combined approach over stress study was not assessed. We will continue to improve the experiments and strive to explore the value of joint FDG and perfusion. Second, the sample size was limited. Many patients undergo ^{13}N-NH3 PET rest MPI, ^{18}F-FDG PET MMI, and CAG alone, but only a few underwent the three examinations in the short period of this study. Furthermore, patients with specific diseases (severe valvular heart disease, severe myocarditis, and arrhythmia) and incomplete clinical information were excluded. Thus, the study population is difficult to expand in a short period. Current data clearly showed significant differences between PET cardiac imaging quantification and semi-quantification. Although the findings were sufficient to confirm the diagnostic value of joint PET rest MPI and MMI quantification for obstructive CAD diagnosis, a substantial cohort or multiple centers is required to validate the present model in future studies.

To conclude, this study investigated the diagnostic value of joint PET rest MPI and MMI quantitative indicator combined with ML for obstructive CAD diagnosis. The multivariate model (MBF, SCR, and MIS) combined with SVM outperformed other methods and thus may aid clinicians in accurately predicting the presence of obstructive CAD without performing invasive CAG. But in this work, we only investigated the superiority of the FDG/resting perfusion approach over semi-quantitative SRS. We have not investigated, and thus not shown, the superiority of joint FDG and resting perfusion approach over stress MPI.

New Knowledge Gained

The diagnostic performance of model_234 (MBF, SCR, and MIS) with SVM for coronary stenosis detection was better than that of other machine learning methods. The AUC of quantitative model_234

combining MPI and MMI information was significantly higher than that of the semi-quantitative model_SRS whether in the validation set or four specific subgroups.

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Compliance with Ethical Standards
This retrospective study was approved by the institutional review board and informed consent was waived.

Conflict of interest
The authors declare that they have no conflict of interest.

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Table and figure legends

Table 1. Clinical characteristics of patients with and without obstructive CAD. Values are expressed as means ± standard deviations or frequency (percentage) of patients.

Table 2. Comparison of the six indicators in vessels with and without obstructive CAD on the training set. Values are expressed as means ± standard deviations. Significant differences were found in all indicators.

Figure 1. (a) The sumScore of all models under seven different machine learning methods, **(b)** the

optimal model of each method, and **(c)** the lowest and highest sumScores of each model and corresponding machine learning methods.

Figure 2. Diagnostic performance of seven optimal ML models in the validation set. The model_234 based on SVM achieved the highest AUC, accuracy, sensitivity and moderate specificity among these models.

Figure 3. The diagnostic performance of the semi-quantitative SRS model and 15 quantitative models on the validation set by using SVM method.

Figure 4. Receiver operating characteristics (ROC) analysis of the model_12, the model _3 and the model_234 compared with the SRS model by using the SVM method. Model_SRS only including the semi-quantitative indicator SRS; Model_12 including the perfusion indicator EXT and MBF; Model_3 only including the metabolic indicator SCR; and Model_234 combines perfusion and metabolic indicators, including MBF, SCR and MIS.

Figure 5. Receiver operating characteristics (ROC) analysis of patient subgroups with **(a)** old myocardial infarction (OMI) or/and revascularization, **(b)** 0-1-vessel disease, **(c)** 2-3-vessel disease, **(d)** hypertension and **(e)** diabetes in the validation study.

Figure 6. Receiver operating characteristics (ROC) analysis for identifying coronary stenosis **(a)** ⩾ 50%, **(b)** ⩾75% and **(c)**⩾90% for the model_234 and SRS.

Table 1 Clinical characteristics of patients with and without obstructive CAD. Values are expressed as means ± standard deviations or frequency (percentage) of patients.

	All patients (*n*=88)	Without CAD (*n*=8)	With CAD (*n*=80)	*p* value
Age(years)	57±10	55±9	58±10	0.57
Male gender	83(94%)	6(75%)	77(96%)	<0.05
Weight(kg)	66.1±10.1	62.6±11.0	66.6±10.0	0.31
Respiratory rate (times / minute)	78±14	74±12	79±14	0.39
Diastolic blood pressure(mmHg)	75±10	65±6	76±10	<0.005
systolic blood pressure(mmHg)	121±17	107±14	122±16	<0.05
Hypertension	38(43%)	2(25%)	36(45%)	0.28
Diabetes	34(39%)	2(25%)	32(40%)	0.41
Smoking history	32(36%)	3(38%)	29(36%)	0.94
History of myocardial infarction	32(36%)	4(50%)	28(35%)	0.40
History of revascularization	18(20%)	3(38%)	15(19%)	0.21

Table 2 Comparison of the six indicators in vessels with and without obstructive CAD on the training set. Values are expressed as means ± standard deviations. Significant differences were found in all indicators.

	All vessels (n=159)	Without CAD (n=67)	With CAD (n=92)	p value
SRS	7.06±5.54	3.66±3.70	9.54±5.35	<0.001
EXT (%)	31.74±25.38	15.81±18.03	43.34±23.66	<0.001
TPD (%)	8.34±8.67	3.54±4.64	11.83±9.26	<0.001
MBF (ml/min/g)	0.65±0.28	0.81±0.28	0.53±0.22	<0.001
SCR (%)	14.60±18.77	8.24±13.54	19.23±20.67	<0.001
MIS (%)	15.01±16.61	6.55±10.70	21.16±17.47	<0.001