Supplemental Data

Methods

Image Acquisition

All MPI scans were performed on high-efficiency, solid-state SPECT scanners at each site. Four sites used a Spectrum Dynamics scanner (D-SPECT, Spectrum-Dynamics, Haifa, Israel) while the other five sites used Discovery NM 530c or NM/CT570c scanners (GE Healthcare, Haifa Israel). Perfusion imaging was performed using either ^{99m}Tc-tetrofosmin or ^{99m}Tc-sestamibi radiotracers. Weight-adjusted activities for stress imaging (recommended by vendor) were used. Prior to stress imaging, patients underwent either symptom-limited Bruce protocol exercise testing or pharmacologic stress testing with injection of radiotracer at peak stress. Patients that needed pharmacologic stress for inadequate heart rate response were classified as pharmacologic stress rather than exercise. SPECT-MPI data were acquired using two stress-imaging positions (supine/prone or upright/supine) or a single stress imaging view with or without attenuation correction (AC) (supine, GE 570c). AC images were not used to generate the MLS. Stress images were acquired 15-60 minutes after stress testing over 4-6 minutes. Stress-only MPI protocols were implemented at two European centers. At these institutions, all patients underwent stress-first imaging and additional rest imaging was performed when stress-MPI data was abnormal or suboptimal. The remaining centers performed rest imaging as part of a standard rest-stress or stress-rest protocol.

Automated Image Processing

Raw stress images were available for automated diagnosis. Reconstructed images were generated from the list-mode data by vendor-recommended reconstruction optimized for each

scanner. The reconstructed stress image datasets were de-identified and transferred to a single imaging core laboratory (Cedars-Sinai Medical Center). Images were automatically re-oriented into short-axis slices with Quantitative Perfusion SPECT (QPS)/Quantitative Gated SPECT (QGS) software (Cedars-Sinai Medical Center, Los Angeles, California)(1).

Automatically generated myocardial contours were evaluated by an experienced technician blinded to any clinical data. If necessary, contours were manually adjusted to correspond to the left ventricular (LV) myocardium. Counts in the LV were obtained by planar projections defined during the first step of data reconstruction(1,2). Images with verified contours were used to generate an automated total perfusion deficit (TPD), a quantitative perfusion variable that reflects a combination of deficit extent and severity and produces stress, rest, and ischemic (stress – rest) values(2). Automated TPD was generated using stress-only myocardial perfusion data using a previously validated 2-position method for upright-supine and (3) supine-prone images(4). This method has been shown to improve the area under the receiver operating characteristic curve (AUC) for detection of obstructive CAD compared to TPD generated from a single stress imaging view (3,4). In the minority of cases where only one stress imaging position was available, the TPD was generated from the single stress imaging position. Different normal databases were used for each combination of camera system and imaging position (2). Attenuation corrected images were not used to generate TPD. An integer stress TPD value of ≥1% was considered abnormal.

Visual Perfusion Analysis

Visual perfusion analysis was performed at each participating center at the time of clinical interpretation, with full details in the supplement. SPECT perfusion images were scored using either segmental scoring or a four-point assessment of perfusion abnormality scoring according

to site-specific protocols. The overall interpretations were performed by expert readers based on all available data, including stress and rest perfusion data, raw projection data, gated functional data, stress test results, and the patient's medical record. To achieve consistency of reader diagnosis among all centers, the clinical perfusion findings in the REFINE SPECT have been homogenized to the four-point score (0: normal, 1: probably normal, 2: equivocal, 3: abnormal). Segmental scoring was performed at 5 participating sites during clinical review and a visual summed stress score (SSS) was available in these patients. An SSS threshold of ≥1 was applied based on recommendations for stress-only MPI studies without the application of AC (5). The diagnostic properties of the MLS were compared to reader diagnosis (using the four-point visual score) and SSS. From this point hereon "reader diagnosis" will refer to the 4-point REFINE SPECT diagnostic scale and "SSS" will refer to the visual SSS applied by the clinical reader at each site.

Model Building

The LogitBoost method involves two steps: 1) automatic variable selection using only variables that contribute to a positive (>0) information gain ratio (IGR), 2) model building that applies an ensemble LogitBoost algorithm. With the LogitBoost model, 50 decision stumps are generated, each of which uses a variable to split the population. This split yields two leaves that each are associated with a weight. A positive weight increases the overall logit of an event, and a negative weight decreases the logit of an event. In this model, each variable may be selected multiple times.

Clinical Validation of Stress-Only MPI

The purpose of the machine learning score (MLS) is to correctly identify patients who are appropriate candidates for stress-only imaging. However, because the MLS was developed to

predict obstructive coronary artery disease (CAD), an additional analysis was performed to determine its diagnostic performance in stress-first myocardial perfusion imaging (MPI) using a clinical validation cohort. Two board-certified cardiologists with training in advanced cardiac imaging reviewed cases with stress-first imaging to determine whether rest imaging could be cancelled. The readers were blinded to the patients' rest images, cardiac catheterization results, and the visual scores provided by each clinical site. Rest images could be cancelled in patients when the stress images displayed: homogenous perfusion throughout the myocardium, a normal left ventricular cavity size with normal regional wall motion, and a left ventricular ejection fraction greater than or equal to 50% (5) . Results of this validation cohort were then compared to the MLS (threshold of 0.29) and TPD (threshold of 1%).

External Validation of the MLS

To assess the external validity of the proposed MLS, we performed an external validation in which 9 of the 10 sites were used to generate a new MLS which was then applied to the excluded population.

Results

Diagnostic Properties of the MLS in Different Sub-Populations

The MLS was generated from the entire population; however, different normal databases were available for different scanning protocols, cameras, and stressors. In patients with low-dose, stress-first imaging, the diagnostic properties of the MLS for prediction of obstructive CAD were not significantly different compared to stress images acquired after rest imaging using higher isotope dosages (AUC 0.832 [0.80-0.86] vs 0.837 [0.82-0.86], p=0.9). In patients with ultra-low

dose stress-first MPI (<160 MBq, n=122), there was no difference between the area under the receiver operating characteristic curve (AUC) for prediction of obstructive CAD by MLS compared to images acquired using higher isotope dosages (AUC 0.839 [0.77- 0.91] vs 0.837 [0.82-0.86], p=0.9). The 4-point visual diagnosis collected as part of REFINE SPECT was compared to the summed stress score (SSS), which has been well validated to reflect underlying CAD on SPECT-MPI. There were no differences in the AUC between the two methods, which confirms that this visual scoring technique accurately reflects visual diagnosis. The AUC and diagnostic sensitivity for prediction of obstructive CAD using different stress protocols, scanners and stress dosages by MLS, TPD, and reader diagnosis are shown in Supplemental Table 3.

MLS for Prediction of Future Revascularization

Coronary artery revascularization was performed in 931 (45%) patients by either percutaneous coronary intervention (669 [72%]) or coronary artery bypass grafting (262 [28%]). The average time interval from ICA to revascularization was 12 days (±28). Although developed for prediction of obstructive CAD, the MLS had superior AUC compared to reader diagnosis (score 0-3) or automated TPD (0.80 vs 0.73 vs 0.67, p<0.01). Additionally, the MLS was significantly more sensitive than both reader diagnosis and TPD for prediction of future revascularization (Sensitivity 95.3% vs 87.0% vs 87.4%, p<0.01).

Clinical Validation of Stress-Only MPI Protocols

The diagnostic performance of the MLS (threshold 0.29) to identify appropriate patients for stress-only MPI was assessed using a clinical validation cohort of patients with stress-first imaging. Of the 676 cases reviewed, obstructive CAD was present in 441 (65%) and high-risk CAD was present in 156 (23%). In this population, additional rest imaging could be cancelled by readers in 114 (16.8%) cases, TPD in 118 (17.4%) and MLS in 82 (12.1%) (p=0.012). The

sensitivity for obstructive CAD in the stress-first cohort was 91.6% for readers, 91.6% by TPD, and 95.4% by MLS (p=0.005). The sensitivity for high-risk CAD was higher by MLS compared to readers and TPD but did not reach statistical significance (Readers 91% vs TPD 91% vs MLS 95%, p=0.16).

External Validation Results

A new MLS was generated using the data from 9 sites (n=1723) and then applied this score on the single excluded site (n=356). The new MLS was then compared to readers and TPD for prediction of obstructive CAD. This MLS was superior to both readers and TPD for prediction of obstructive CAD (Supplemental Figure 6).

Missing Variables and Information Gain Ratio

As noted in Supplemental Table 2, there was a relatively high frequency of missing values for certain clinical variables. The MLS must be able to maintain its high sensitivity for prediction of obstructive CAD in general clinical practice and thus an analysis was performed to evaluate whether the MLS would be significantly influenced by missing clinical variables. We developed an additional MLS that excluded the variables with a missing frequency >40%. This MLS was also trained using the data from 9 sites (n=1723) and then tested in the single excluded site (n=356). The resulting MLS did not have significantly different AUC characteristics than the MLS that was developed with the full set of variables (AUC 0.82 vs 0.82, p=NS), as shown in Supplemental Figure 7.

References

1. Germano G, Kavanagh PB, Slomka PJ, Van Kriekinge SD, Pollard G, Berman DS. Quantitation in gated perfusion SPECT imaging: the Cedars-Sinai approach. J Nucl Cardiol 2007;14:433-54.
2. Slomka PJ, Nishina H, Berman DS et al. Automated quantification of myocardial perfusion SPECT using simplified normal limits. J Nucl Cardiol 2005;12:66-77.
3. Nakazato R, Tamarappoo BK, Kang X et al. Quantitative upright-supine high-speed SPECT myocardial perfusion imaging for detection of coronary artery disease: correlation with invasive coronary angiography. J Nucl Med 2010;51:1724-31.
4. Nishina H, Slomka PJ, Abidov A et al. Combined supine and prone quantitative myocardial perfusion SPECT: method development and clinical validation in patients with no known coronary artery disease. J Nucl Med 2006;47:51-8.
5. Gowd BM, Heller GV, Parker MW. Stress-only SPECT myocardial perfusion imaging: a review. J Nucl Cardiol 2014;21:1200-12.

Supplemental Table 1. Clinical and Imaging Variables Available for the MLS.

General Clinical Variables	General Imaging Variables
Patient location (in-patient, out-patient, ED)	Myocardial counts (kCounts)
Age	LV segmentation QC metrics
Gender	Patient position (supine, upright, prone)
Height (cm), weight (kg), BMI (kg/m²)	LV dimensions (mm)
Clinical indication for test*	Myocardial mass (g)
Family history of coronary artery disease	LV Shape Index, eccentricity
Hypertension	Injected dose (MBq)
Diabetes mellitus	**Perfusion Variables**
Dyslipidemia	Total perfusion deficit (%)
Currently smoking	Perfusion defect severity
Under Drug Influence (currently)*	Perfusion defect extent (%)
Anginal presenting symptoms*	Segmental scores
Peripheral artery disease	Normalized raw perfusion uptake
Left ventricular hypertrophy	**Functional Variables**
Conduction disease	Ejection fraction (%)
Stress Variables	Stress EDV (mL)
Pharmacologic stress agent*	Stress ESV (mL)
Stress test type*	Ventricle length: diastolic, systolic (mm)
Imaging protocol*	Wall motion (mm)
Exercise protocol (Bruce, Modified Bruce)	Wall motion defect extent (%)
Resting heart rate (bpm)	Wall motion score
Peak heart rate at stress (bpm)	Wall thickening (mm)
Resting blood pressure: systolic, diastolic (mmHg)	Wall thickening defect extent (%)
Peak blood pressure at stress: systolic, diastolic (mmHg)	Wall thickening score
% Maximal Predicted Heart Rate	Phase SD
Exercise duration (min)	Phase bandwidth
Reason for termination*	Phase dyssynchrony
ECG response to stress*	Phase entropy
Clinical response to stress*	Diastolic parameters: PER (EDV/s), PFR (EDV/s), MFR (EDV/s), TTPF (ms)
ECG ST deviation (mm), direction, and slope	Average RR interval in ECG (ms)

*__Clinical Indication for Test (1-23):__ 1:Preoperative evaluation, 2: Suspected Angina, 3: Low EF unexplained, 4: Significant Arrythmias, 5: Abnormal rest ECG, 6: Wall Motion

Abnormalities by Echo, 7:Viability, 8: High Coronary calcium score, 9: Abnormal exercise stress test, 10: Abnormal coronary CTA, 11: Multiple CAD risk factors, 12: Significant family history, 13: none, 14: Shortness of Breath, 15: Peripheral Vascular Disease, 16: Troponin elevation, 17: CHF, 18: Cardiomyopathy, 19: Syncope, 20: Palpitations, 21: Dizziness, 22: Valve disease, 23: other. **Under Drug Influence (0-5):** 0: none, 1: b-blockers, 2: Ca-blockers, 3: Digitalis, 4: Nitrates-sublingual and long-acting, 5: Antiarrhythmics. **Anginal Presenting Symptoms (1-4):** 1: Asymptomatic, 2: Atypical, 3: Non-anginal, 4: Typical. **Pharmacologic Stress Agent (1-5):** 1: Persantine, 2: Adenosine, 3: Regadenosen, 4: Dobutamine, 5: Dipyridamole. **Stress Test Type (1-5):** 1: Exercise, 2: Pharmacologic, 3: Adenosine + walk, 4: Dipryridamole + walk, 5: Regadenosen + walk. **Imaging Protocol (1-3):** 1: Rest and stress imaging done on same day, 2: Rest and stress imaging done on separate days, 3: Stress-only (rest study not needed). **Reason for Termination (1-11):** 1: Fatigue, 2: Chest Pain, 3: Pharmacological Protocol Completed, 4: 85% MPHR Reached, 5: Arrhythmia, 6: Ischemic ECG Changes, 7: Hypertension, 8: Hypotension, 9: Unstable Gait, 10: SOB/dyspnea, 11: Chest tightness. **ECG Response to Stress (1-5):** 1: Negative, 2: Positive, 3: Equivocal, 4: Nondiagnostic, 5: Borderline. **Clinical Response to Stress (1-5):** 1: Ischemic, 2: Non-ischemic, 3: Nondiagnostic, 4: Abnormal, 5: Equivocal. BPM=beats per minute; BMI= body mass index; CAD= coronary artery disease; ECG= electrocardiogram; EDV= end diastolic volume; ESV= end systolic volume; LV= left ventricle; MBq= megaBecquerel; QC= automatic quality control; SD= standard deviation

Supplemental Table 2. Frequency of Missing Clinical and Imaging Variables

Variable Name	Missing Rate (%)
Under drug influence (0-5)	44.4
Clinical indication for test (0-23)	40.9
Stress EF * (%)	35.3
Stress wall thickening * (%)	35.3
Left ventricular hypertrophy (0,1)	25.2
Reason for termination (1-11)	20.4
Clinical response to stress (1-5)	17.2
Perfusion defect severity * (sd)	14.4
Perfusion defect extent * (%)	14.4
Stress ungated volume * (mL)	14.4
ST Deviation (mm)	10.3
ECG Response to stress (1-5)	10.2
Symptoms (1-4)	6
Abnormal Resting ECG (0,1)	2.7
Peak SBP at stress (mmHg)	2.3
Resting SBP (mmHg)	2
Location (outpatient, inpatient, ER)	1.8
Peak heart rate at stress (BPM)	1.7
Resting heart rate (BPM)	1.4
Stress EF (%)	0.8
Stress wall thickening (%)	0.8
Stress phase bandwidth (degree)	0.8
Exercise duration (minutes)	0.6
Perfusion defect extent (%)	0.5
Perfusion defect severity (sd)	0.5
Stress ungated volume (mL)	0.5
Pharmacologic stress agent (1-4, na)	0.2
Stress test type (1-5)	0.1
BMI (kg/m2)	0
Gender (male, female)	0
Age (years)	0
Conduction abnormalities (0-5)	0
Dyslipidemia (0,1)	0
Peripheral vascular disease (0,1)	0
Family history (0,1)	0
Diabetes mellitus (0,1)	0
Hypertension (0,1)	0
Current smoker (0,1)	0
Stress imaging position (u, s, p, su, sp)	0
Combined perfusion defect severity (sd)	0
Combined perfusion defect extent (%)	0

*denotes the alternative view (supine for D-SPECT or prone for Discovery). For the imaging

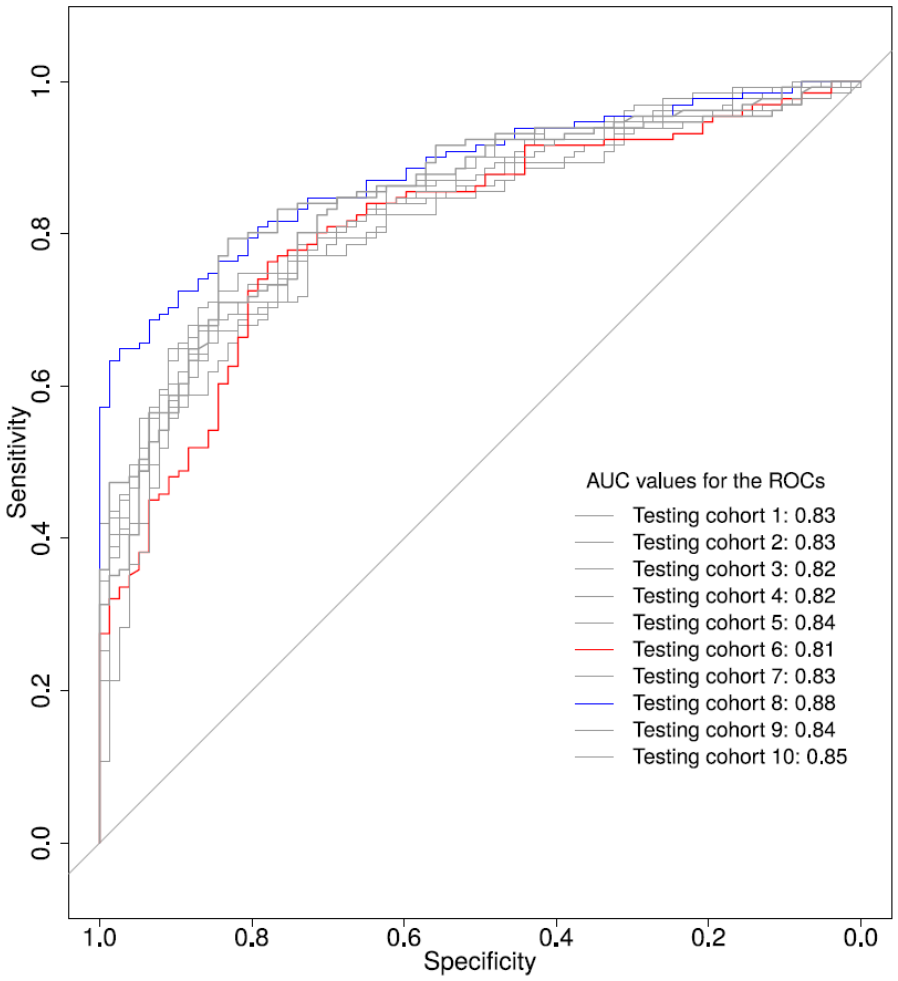
variables, the major source of data missing was that the images of an alternative view were not obtained for stress imaging. ECG = electrocardiogram; ED = emergency department; EF = ejection fraction; kg = kilograms; LV = left ventricle; m2 = meters squared; ml = milliliters; mmHg = millimeters of mercury; p = prone; s = supine; SBP = systolic blood pressure; sd = standard deviation; sp = supine & prone; su = supine & upright; u = upright.

Supplemental Table 3. Receiver Operator Characteristics and Sensitivity Analysis for Prediction of Obstructive CAD Using Different Cameras and Stress Protocols.

	ROC AUC [95% CI]				Sensitivity			
	Reader Diagnosis	TPD	MLS	p-value*	Reader Diagnosis	TPD	MLS	p-value†
Camera								
DSPECT	0.73 [0.70-0.76]	0.77 [0.75-0.80]	0.83 [0.81-0.86]	<0.01	85%	82%	94%	<0.01
GE530/GE570c	0.68 [0.64-0.72]	0.81 [0.78-0.84]	0.86 [0.83-0.88]	<0.01	89%	89%	95%	<0.01
Imaging Protocol								
Stress-first	0.69 [0.66-0.73]	0.80 [0.76-0.83]	0.84 [0.81-0.86]	<0.01	93%	89%	95%	<0.01
Rest-stress	0.70 [0.67-0.73]	0.78 [0.76-0.81]	0.84 [0.82-0.86]	<0.01	83%	85%	94%	<0.01
Stress-test Type								
Exercise	0.70 [0.66-0.74]	0.82 [0.80-0.85]	0.87 [0.84-0.89]	<0.01	86%	86%	95%	<0.01
Pharmacologic	0.69 [0.66-0.72]	0.76 [0.73-0.79]	0.82 [0.80-0.84]	<0.01	88%	88%	95%	<0.01

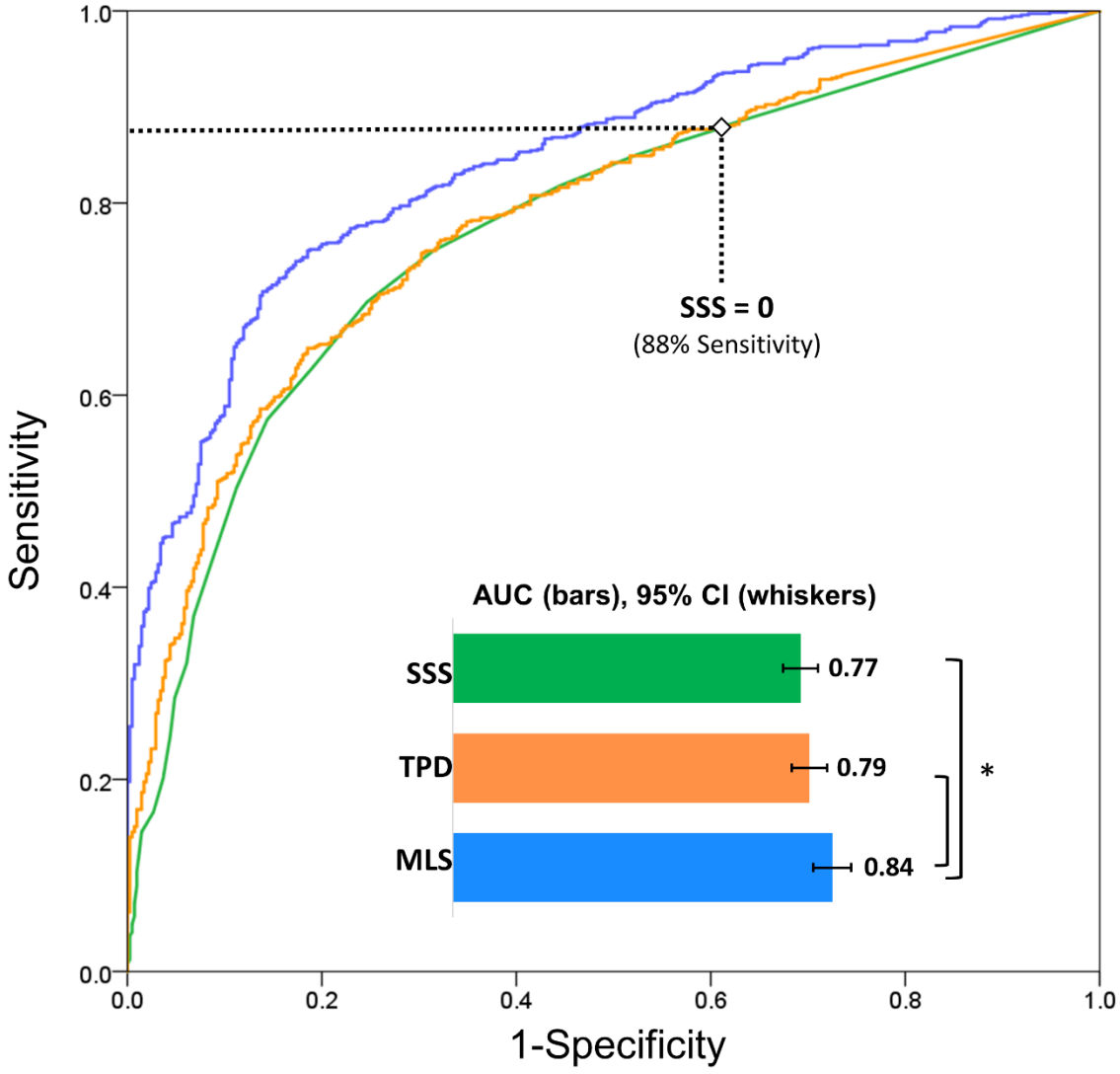
ROC AUC and sensitivity analysis for prediction of obstructive CAD. Sensitivity Thresholds: Reader diagnosis > 0, TPD ≥1%, MLS ≥0.29. *p-values calculated using DeLong test, † p-values calculated using Cochran's Q-test

Supplemental Figure 1. Machine learning score diagnostic accuracy from each of the 10 testing cohorts and models.



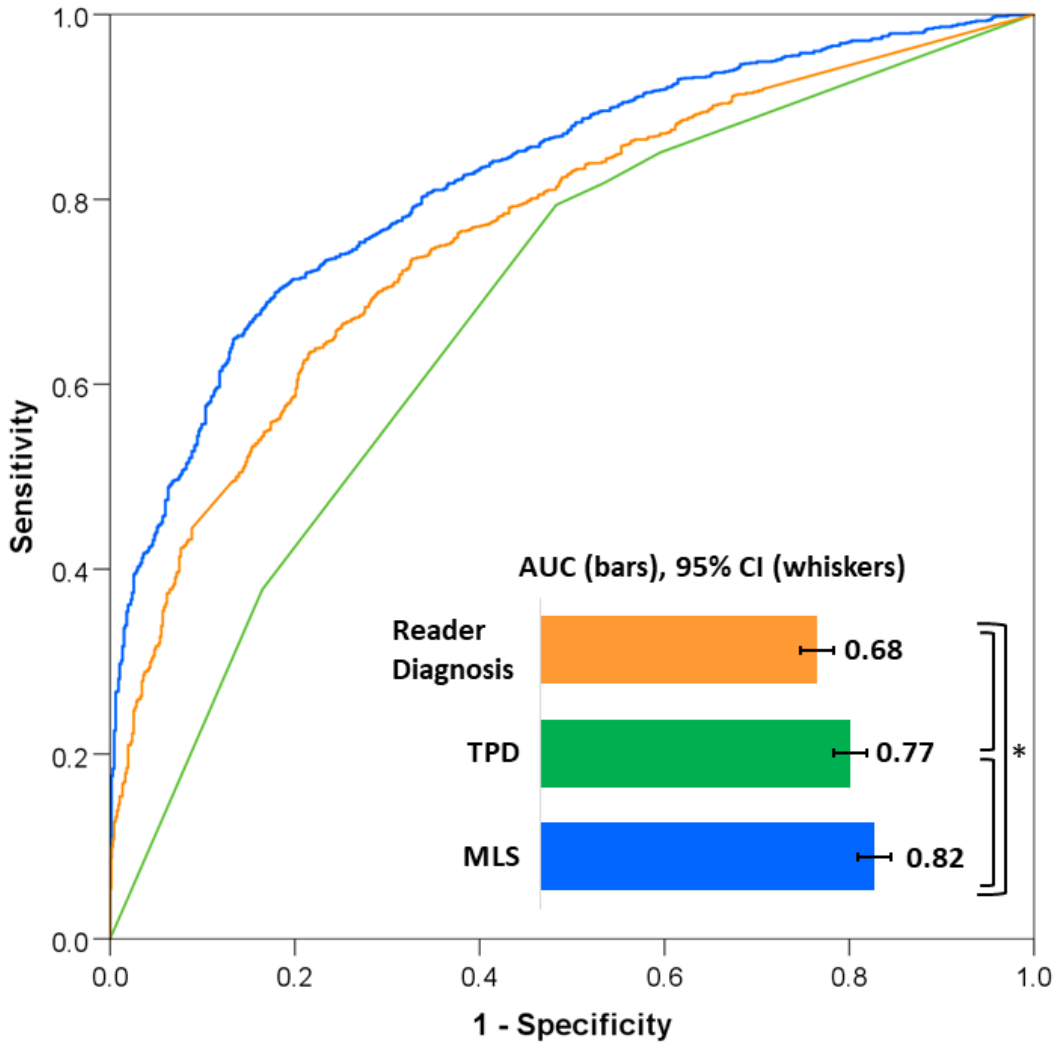
AUC=area under the receiver operating characteristic curve, ROC=receiver operating characteristic.

Supplemental Figure 2. Receiver operator characteristics for prediction of obstructive CAD in patients with available segmental scores (prevalence 729/1139 [64%]).



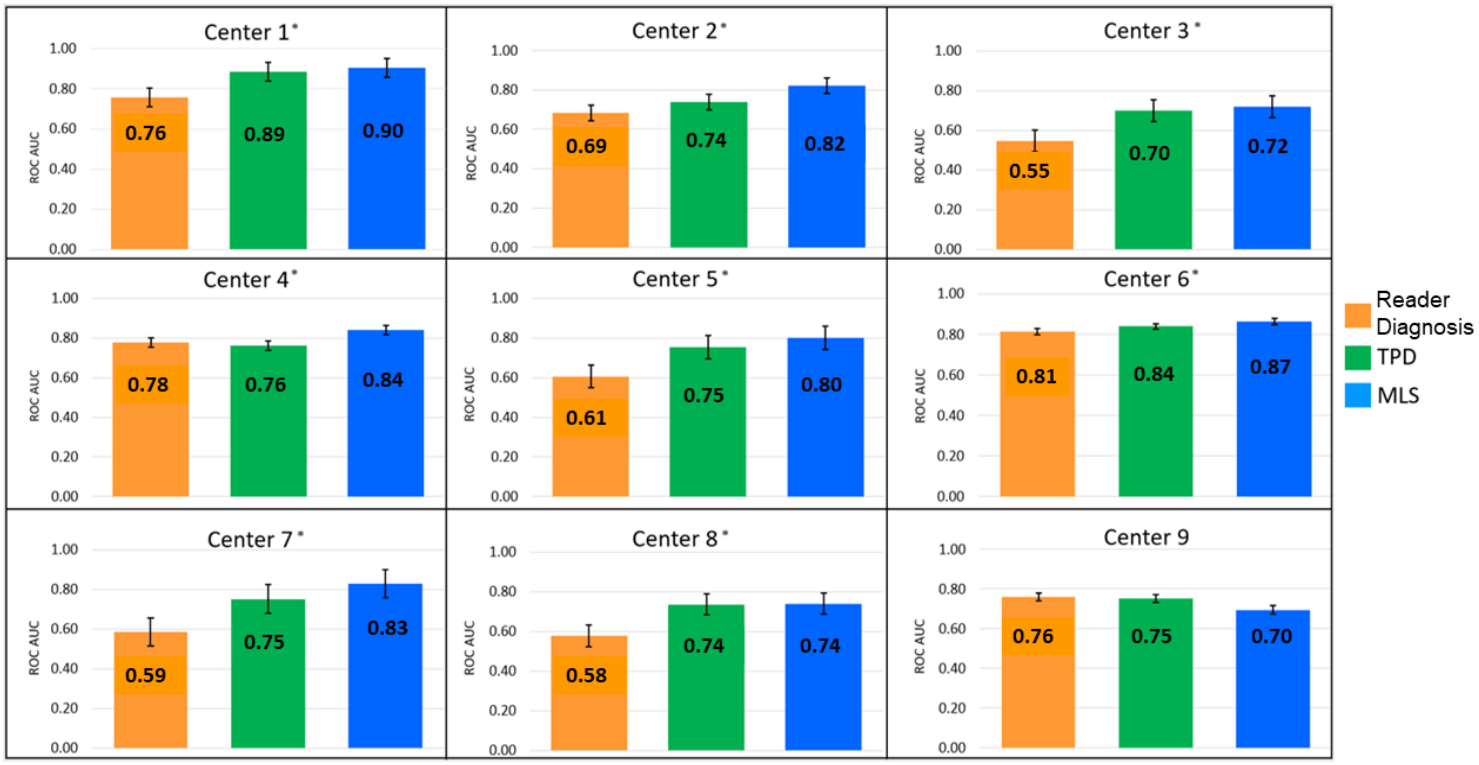
The MLS had a significantly higher AUC than both SSS and TPD for prediction of obstructive CAD (0.84 vs 0.77 vs 0.79, p<0.01). There was no difference in the AUC between SSS and TPD (0.77 vs 0.79, p=0.25). *p<0.01 for AUC comparison by Delong Test. AUC: area under the receiver operating characteristic curve, CAD: coronary artery disease, CI: confidence interval, MLS: machine learning score, SSS: summed stress score, TPD: total perfusion deficit

Supplemental Figure 3. Receiver Operator Characteristics for Prediction of Obstructive CAD (≥50%, n=1412).



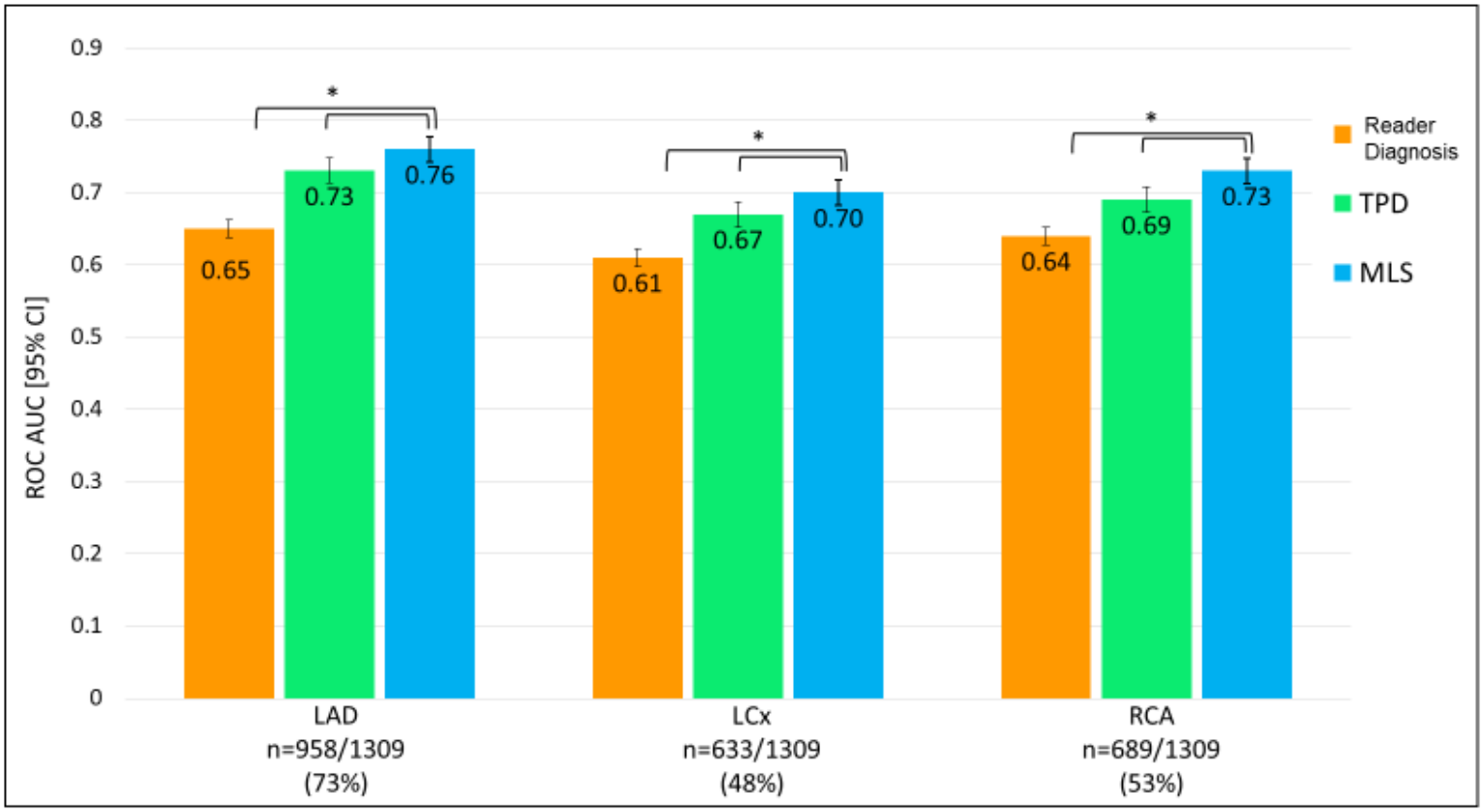
*p<0.01 for AUC comparison by Delong Test. AUC=area under the receiver operating characteristic curve, CI=confidence interval, MLS=machine learning score, TPD=total perfusion deficit.

Supplemental Figure 4. Receiver Operator Characteristics Per Recruiting Center.



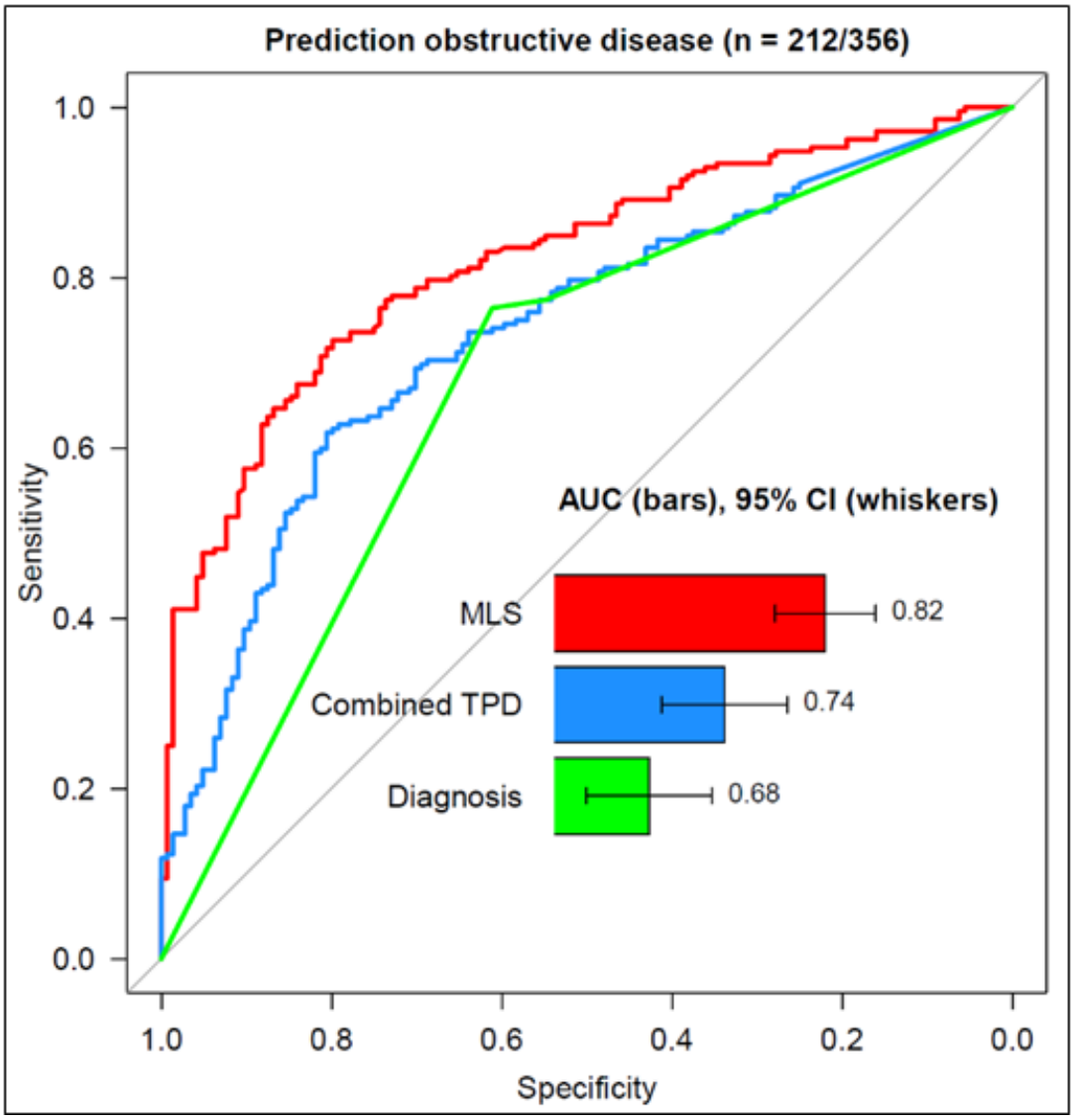
*p<0.01 for AUC comparison between MLS (≤0.29), TPD (≤1) and reader diagnosis (normal) by DeLong test. Prevalence of Obstructive CAD Per Site: 1: 222/315 (70.4%), 2: 212/356 (59.5%); 3: 48/116 (41.3%); 4: 123/199 (61.8%); 5: 180/280 (64.3%); 6: 200/336 (59.2%); 7: 259/377 (68.7%); 8: 38/64 (59%); 9: 27/36 (75%). AUC= area under the receiver operating characteristic curve, CAD=coronary artery disease, MLS=machine learning score, TPD=total perfusion deficit.

Supplemental Figure 5. Comparison of diagnostic accuracy by vascular territory.



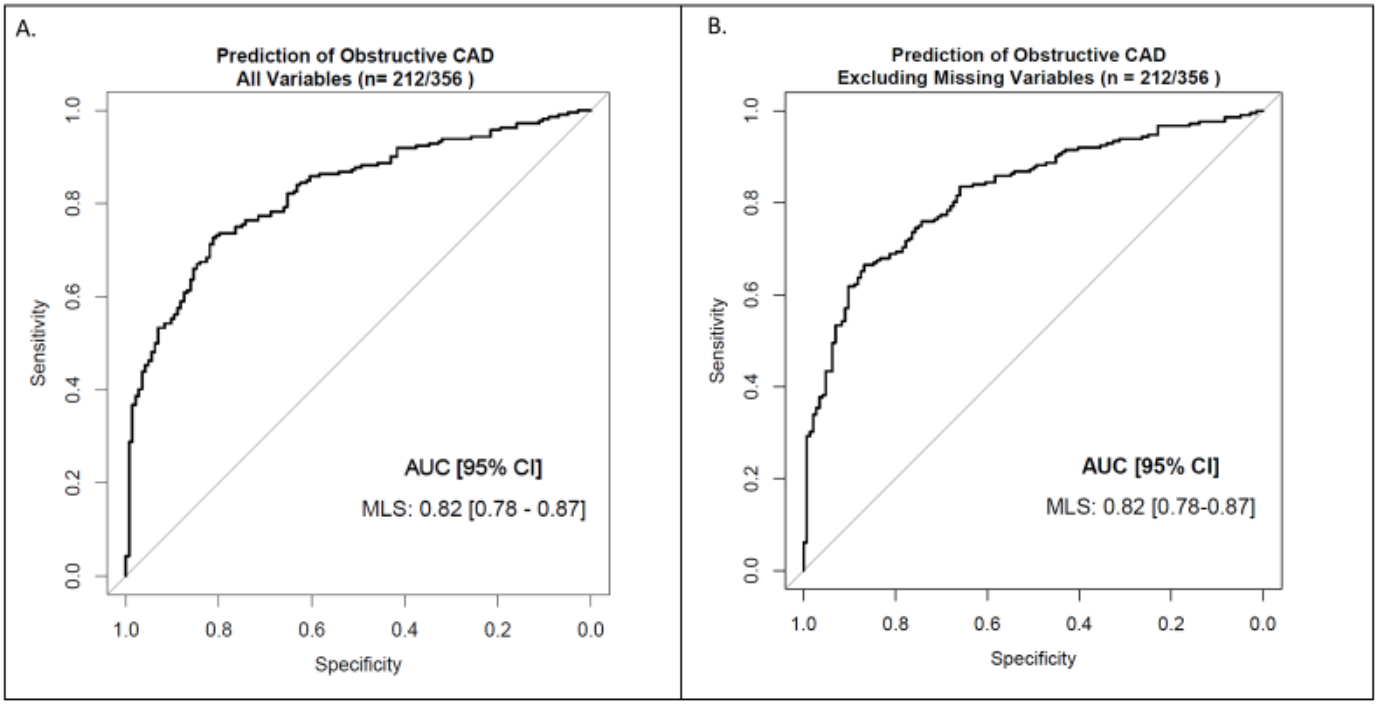
*p<0.01 for AUC comparison by Delong test. AUC= area under the receiver operating characteristic curve, LAD= left anterior descending, LCx=Left circumflex, MLS=machine learning score, RCA=right coronary artery, TPD=total perfusion deficit.

Supplemental Figure 6. Receiver Operator Characteristics for Prediction of Obstructive CAD in external validation.



A new MLS was generated using the data from 9 sites (n=1723) and then tested in the excluded site (n=356)

Supplemental Figure 7. Prediction of Obstructive CAD After Excluding Missing Variables



Both the MLS with all variables (a) and excluding variables with >40% missing values (b) were trained with data from 9 sites (n=1723) and then tested in the single excluded site (n=356). AUC=area under the receiver operating characteristic curve, CI=confidence interval, MLS=machine learning score.