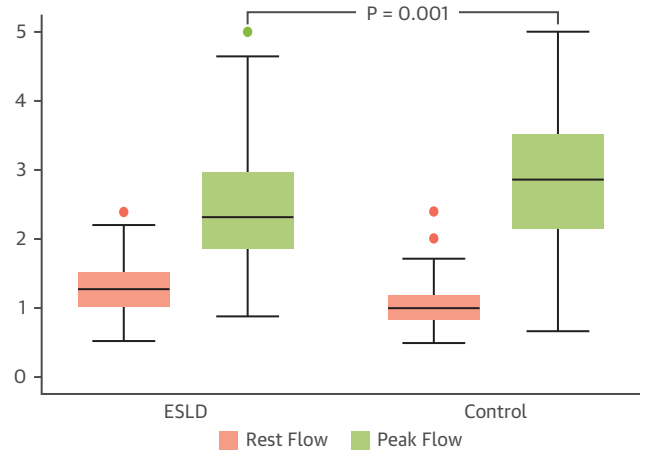
**FIGURE 1** Rest and Stress Myocardial Blood Flow of Patients and Control Subjects




Boxplot of the rest myocardial blood flow and peak myocardial blood flow. **Middle bar** indicates median, while the **box boundaries** indicate the 25th and 75th percentile. The **whisker lengths** are the 91st and 9th percentile. ESLD = end-stage liver disease.

of diabetes and other cardiovascular risk factors in our cohort. Our study has few limitations, which include relatively small sample size, single-center experience, and retrospective design.

In conclusion, our analysis demonstrated that patients with ESLD undergoing vasodilator stress $^{82}$Rb PET MPI achieve adequate coronary vasodilation with both dipyridamole and regadenoson. Therefore, vasodilator stress test can be used for the assessment of CAD in this population.

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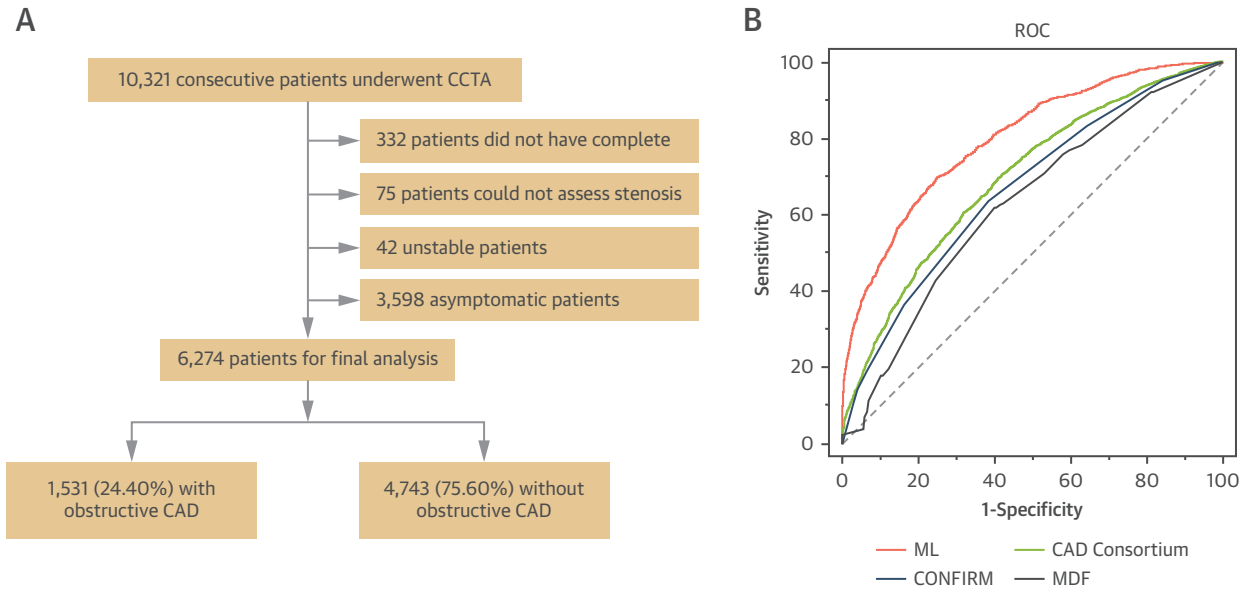
## Machine Learning for Pretest Probability of Obstructive Coronary Stenosis in Symptomatic Patients

The management of stable coronary artery disease guideline recommends clinical risk assessment for estimating pretest probability of disease using Bayesian reasoning as a key initial step in the evaluation of patients with suspected coronary artery disease (CAD) (1). However, the diagnostic performance of traditional models is limited in estimation of obstructive CAD in contemporary cohorts (2). The aim of this cohort study CREATION (Coronary Atherosclerosis Disease Early Identification and Risk Stratification by Noninvasive Imaging; NCT03518437) was to build a machine learning (ML) model for calculating pretest probability of obstructive CAD and hypothesize that it will provide better accuracy and discrimination compared with existing traditional models.

A total of 6,274 symptomatic patients (3,309 men and 2,965 women; mean age 57.83 years) were enrolled for final analysis (**Figure 1A**). The patients were suspected of having CAD and had undergone coronary computed tomography angiography (CCTA) between January 2016 and November 2017. All of these patients were initially referred for CCTA studies by their cardiologists. Obstructive CAD was defined as at least 1 coronary segment with a lesion of ≥50% luminal stenosis in CCTA. ML was built with a boosted ensemble algorithm (extreme gradient boosting, XGBoost) and 10-fold cross-validation was used.

A total of 1,531 (24.40%) patients were found to have obstructive CAD. Presence of obstructive CAD was more strongly associated with male sex, age, and existence of typical angina symptoms, as well with

**FIGURE 1 Flow Chart of the Study and Discrimination for Obstructive CAD of the Models**




**(A)** Flow chart of the studied patients. **(B)** Receiver-operator characteristic curves (ROC) of the 4 models. The machine learning (ML) model had significantly higher discrimination for obstructive coronary artery disease (CAD) ($p < 0.001$). Using guideline-recommended thresholds (15%, 85%), the diagnostic performance of the ML model was as: 15%: sensitivity 91.9%, specificity 38.8%, positive predictive value 32.6%, and negative predictive value 93.7%; 85%: sensitivity 3.7%, specificity 100.0%, positive predictive value 100.0%, and negative predictive value 76.3%. MDF = modified Diamond-Forrester.

traditional cardiovascular risk factors except for dyslipidemia and presence of family history. The ML model had significantly higher discrimination for obstructive CAD: the area under the receiver operating characteristic curve was 0.801 (95% confidence interval [CI]: 0.790 to 0.810) compared with 0.673 (95% CI: 0.662 to 0.685) ($p < 0.001$) for modified Diamond-Forrester (MDF), 0.697 (95% CI: 0.685 to 0.708) ($p < 0.001$) for the CAD consortium score and 0.669 (95% CI: 0.657 to 0.681) ($p < 0.001$) for the CONFIRM (COronary CT angiography evaluatioN For clinical outcomes: An InteRnational Multicenter registry) score (Figure 1B). The discordance between predicted ML and observed prevalence of obstructive CAD (+0.53%) was significantly lower than the other 3 methods (+27.79% for MDF, -58.61% for CAD consortium score, -29.63% for CONFIRM score, $p < 0.001$). To evaluate how ML, instead of traditional models, might influence the use of downstream noninvasive and invasive testing, we stratified each score result as low (<15%), intermediate (15% to 85%), or high (>85%) pretest probability of obstructive CAD based on the management of stable coronary artery disease guideline (1). Using the ML method instead of MDF, the diagnostic strategy for 22.2% of patients would be correctly changed ($p < 0.001$). Using the ML method instead of the CAD consortium score and CONFIRM score would imply a correctly change in diagnostic strategy in 10.7% and 8.8% of the patients ($p < 0.001$).

The observed efficacy suggested that ML had an important clinical role in evaluating pretest probability of obstructive CAD in individual symptomatic patients with suspected CAD. The strength of our study was that we build an ML model for calculating pretest probability of obstructive CAD and demonstrated that it had superior calibration and risk discrimination compared with existing risk models. In our modeling, beyond the traditional variables, we also considered the duration of traditional risk factors and quantified biochemical results to build ML model. Last, we used 23 factors, which allows for an agnostic exploration of all available data for nonlinear patterns that may predict a particular individual's probability. This important concept represents a divergence from a hypothesis-driven approach conventional in traditional assessments (3). The ML method would correctly change the clinical pathway of 22.2% patients compared with the recent guideline-recommended MDF model. In the net

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reclassification improvement analysis, we found ML could avoid exposing 19.7% of low-risk patients to unnecessary downstream testing. In low-risk patients, ML also overestimated the probability of obstructive CAD according to the calibration plot. That was why the discriminative power was not excellent. Future research can be improved in this regard.

In symptomatic patients evaluated for suspected CAD, the ML method allows for a more accurate estimation of pretest probabilities of obstructive CAD than the guideline-recommended method. These findings support potential and further validation of ML-derived estimates to guide risk estimates and subsequent management decisions that may positively change the lower risk of downstream, unnecessary investigation as well increase diagnostic yield of both noninvasive and invasive testing.

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## Extracellular Volume in Dilated Cardiomyopathy

### A New Prognostic Marker on Top of Late Gadolinium Enhancement?

The value of cardiovascular magnetic resonance (CMR) in assessing cardiac morphology, function, and tissue characterization is well established in nonischemic dilated cardiomyopathy (DCM) (1). Nevertheless, as compared with the extensive literature on late gadolinium enhancement (LGE) (2), there are still very few studies addressing the prognostic role of native T1, gadolinium partition coefficient (λGd), and extracellular volume fraction (ECV) in DCM. Therefore, we read with utmost interest the 3.0-T CMR study by Vita et al. (3), on 240 patients with DCM (62% men, age 49 ± 13 years, left ventricular ejection fraction [LVEF] 43 ± 15%; 92% New York Heart Association [NYHA] functional class I to II), in which the authors confirmed and expanded the results we previously published in a smaller population of 89 patients with DCM at 1.5 T (71% men, age 59 ± 14 years) (4), with similar baseline clinical characteristics (LVEF 41% ± 13%, 97% NYHA functional class I to II) and comparable ECV values (25 ± 4% vs. 28 ± 3% in controls; 31 ± 5% vs. 32 ± 7% in patients with DCM). In our cohort, we demonstrated an independent prognostic role of higher ECV values for the occurrence of a composite endpoint, including cardiovascular death, hospitalization for heart failure, and appropriate defibrillator intervention.

We feel that the study by Vita et al. (3) paves the way toward extensive clinical research on T1 and ECV in DCM, on top of LGE, which has already an established diagnostic role for detection of fibrosis, as well as an established prognostic role for the prediction of both heart failure and arrhythmic endpoints (1,2). Interestingly, the authors found that ECV was the only independent prognostic predictor after correction for age, sex, NYHA functional class, and LVEF; moreover, ECV remained an independent prognostic variable over native T1, LGE presence and extent, even in the two-thirds of patients without LGE. In particular, major adverse cardiovascular events (MACEs) were defined as a composite of death from any cause and heart failure hospitalization, with no consideration of arrhythmic endpoints; this might explain why annualized MACE rates escalated more (from 2.6% to 5.9% to 18.3% from the lowest to the highest ECV tertile, respectively) in patients with LVEF <30%, being patients with LVEF ≥30% more likely affected by arrhythmic