A Non-invasive Diagnostic Tool to Rule Out Left Main Stem Stenosis: the MASTER Study

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INTRODUCTION

In patients with stable coronary artery disease (CAD), medical therapy alone does not increase the risk of ischemic cardiovascular events or deaths, as compared to an initial invasive strategy by percutaneous coronary intervention [1]. However, patients with left main coronary artery disease (LMCAD) have poorer prognosis, and current guidelines recommend revascularization [2]. Therefore, a non-invasive diagnostic method, less expensive than coronary angiography (CAG), which could reliably identify LMCAD, would allow a safe and more sustainable treatment of the vast majority of stable CAD patients.

OBJECTIVES

The MAin stem Stenosis prediction Through Exercise Response (MASTER) multicenter case-control study was designed to develop a diagnostic model for excluding LMCAD among subjects referred to coronary angiogram (CAG) for documented or suspected myocardial ischemia.

METHODS

Eligible subjects were suspected CAD patients with an interpretable exercise stress test (EST) performed before CAG. The training set included patients with a CAG performed between 2010 and 2021 in 5 Italian hospitals; the validation set included patients with a CAG performed between 2022 and 2024 in 3 of the centers used for model training and in two additional hospitals (one in Italy and one in the USA). Cases were patients with either ≥50% left main (LM) stenosis or ≥70% stenoses of both proximal left anterior descending and proximal circumflex arteries identified through CAG.

In all patients, we collected demographic, clinical, laboratory and EST variables. To deal with missing values, we performed a single imputation using predictive mean matching for numerical variables, logistic regression for binary variables and polytomous regression for categorical variables with more than two levels [3]. The diagnostic model was identified by applying logistic regression with Akaike Information Criterion (AIC)-based backward stepwise selection.

The performance of the selected model in terms of discrimination was quantified by the Area Under the Curve (AUC) with 95% confidence intervals (95% CI). The optimal threshold for the linear predictor corresponded to the point on the ROC curve closest to the top-left corner, assuming a ratio of the cost of misclassifying a case versus a control equal to 100 and a 5% prevalence of LMCAD among patients undergoing CAG for suspected CAD [4, 5]. Based on the optimal threshold, we estimated sensitivity, specificity, negative and positive predictive values (NPV and PPV).

We performed an internal validation estimating the optimism-adjusted AUC based on 500 samples [6].

We performed external validation in the complete validation set, and, as a sensitivity analysis, in the subset of patients from the centers not included in the training set.

RESULTS

The training set included 219 cases and 554 controls. The selected model showed an AUC of 0.80 (95% CI, 0.76-0.83), which after adjusting for optimism became 0.77 (see Figure 1).

The model had a sensitivity of 86.3% and a specificity of 56.2%, with a NPV of 98.7% and a PPV of 9.4%.

The validation set included 137 cases and 274 controls, of whom 53 and 91 in the two additional centers, respectively. The accuracy of the model on the complete validation set

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decreased, with an AUC of 0.70 (95% CI, 0.66-0.74). At the best threshold identified from the training set, sensitivity was 81.0% and specificity 45.3%. The NPV and PPV were 97.8% and 7.2%, respectively.

When we limited the external validation to the two centers not included in the training set, we obtained similar results (AUC 0.72, 95% CI 0.63-0.81, sensitivity 79.2%, specificity 47.2%, NPV 97.7% and PPV 7.3%).

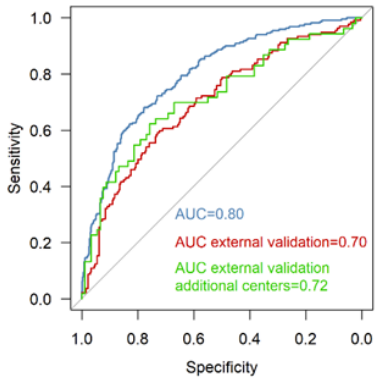

Figure 1. ROC curves in the training set (blue), complete validation set (red) and validation set including only the two additional centers not used for model training

CONCLUSIONS

This large and multicentric study showed that, based on demographic, clinical and EST variables, it is possible to rule out the presence of LMCAD in patients able to perform a maximal EST, with a negative predictive value of about 98%, with a small difference between internal and external validation. Such results might influence the clinical management of stable CAD patients, by sparing many CAGs to non LMCAD patients.

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