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Medical History for Prognostic Risk Assessment and Diagnosis of Stable Patients with Suspected Coronary Artery Disease

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ABSTRACT

Aims: To develop a clinical cardiac risk algorithm for stable patients with suspected coronary artery disease based upon angina typicality and coronary artery disease risk factors.

Methods and Results: Between 2004 and 2011, 14,004 adults with suspected coronary artery disease referred for cardiac imaging were followed: 1) 9,093 patients for coronary computed tomography angiography (CCTA) (CCTA-1) followed for 2.0 years; 2) 2,132 patients for CCTA (CCTA-2) followed for 1·6 years, and 3) 2,779 patients for exercise myocardial perfusion scintigraphy (MPS) followed for 5.0 years. A best-fit model from CCTA-1 for prediction of death or myocardial infarction was developed, with integer values proportional to regression coefficients. Discrimination was assessed using C-statistic. The validated model was also tested for estimation of the likelihood of obstructive coronary artery disease, defined as ≥50% stenosis, as compared to method of Diamond and Forrester.

Primary outcomes included all-cause mortality and non-fatal myocardial infarction. Secondary outcomes included prevalence of angiographically obstructive coronary artery disease. In CCTA-1, best-fit model discriminated individuals at risk of death or myocardial infarction (C-statistic 0·76). The integer model ranged from 3-13, and corresponded to 3-year death risk or myocardial infarction of 0·25% to 53·8%. When applied to the CCTA-2 and MPS cohorts, the model demonstrated C-statistics of 0·71 and 0·77. Both best-fit (C=0·76, 95% CI 0·746-0·771) and integer model (C=0·71, 95% CI 0·693-0·719) performed better than Diamond and Forrester (C=0·64; 95% CI, 0·628-0·659) for estimating obstructive coronary artery disease.

Conclusions: For stable symptomatic patients with suspected coronary artery disease, we developed a history-based method for prediction of death and obstructive coronary artery disease.

Abbreviations

MPS= myocardial perfusion scintigraphy

CCTA= coronary computed tomography angiography

CONFIRM= Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry

BIC=Bayes' Information Criterion

INTRODUCTION

Medical history-based assessment of symptomatic stable patients with suspected coronary artery disease has relied upon estimating the likelihood of obstructive coronary artery disease rather than the risk of clinical events, such as death or myocardial infarction (1-5). Recent data have challenged these diagnostic algorithms, and suggest that they overestimate the prevalence of obstructive coronary artery disease in patients referred for non-invasive and invasive testing (6-8). The absence of a well-validated pre-test method for determining risk of coronary artery disease events, as well as an accurate method for estimating the likelihood of obstructive coronary artery disease, may evoke overutilization of testing for individuals at low risk for incident clinical events or obstructive coronary artery disease (9). We sought to determine whether information acquired through medical history taking alone could predict risk of myocardial infarction or death and obstructive coronary artery disease in symptomatic stable individuals with suspected coronary artery disease.

METHODS

Study Participants

This study comprised 3 distinct non-overlapping cohorts of symptomatic stable individuals with suspected but without prior history of coronary artery disease who were referred for non-invasive cardiac imaging between 2004-2011: 1) a development cohort of 9,093 patients from 8 centers and 6 countries referred for coronary computed tomography angiography (CCTA-1) followed for death or myocardial infarction; 2) a CCTA validation cohort of 2,132 patients from 4 centers and 4 countries referred for CCTA (CCTA-2) followed for death

or myocardial infarction; and 3) a validation cohort of 2,779 patients from 1 center referred for exercise stress myocardial perfusion scintigraphy (MPS) followed for death.

The CCTA-1 derivation cohort comprised patients referred for CCTA from Phase I of the CONFIRM registry (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry), which has been previously described (10). Among 12 participating sites, 4 were excluded due to lack of information related to symptoms or follow-up data for non-fatal myocardial infarction, leaving 17,226 patients from 8 sites in 6 countries that constituted the derivation dataset for the clinical model. Sites included 3 from the United States (N=5727), and 1 each from Canada (N=2171), Germany (N=1785), Italy (N=1895), South Korea (N=4912), and Switzerland (N=736). In sequential order, we excluded patients with prior coronary revascularization or myocardial infarction (n=1110); who were asymptomatic (n=4389); who did not have complete symptom and/or coronary artery disease risk factor collection (n=1959); who were referred for imaging from the emergency department or inpatient setting (n=604); or who were lost to follow-up (n=71). After exclusions, 9,093 patients comprised the final study dataset. The median follow-up time for CCTA-1 was 2.0 years (Interquartile Range [IQR] = 1.4 to 3.1 years).

The CCTA-2 validation cohort comprised patients from Phase II of CONFIRM, detailing identical elements to Phase I CONFIRM and prospectively designed specifically to serve as a validation dataset to Phase I CONFIRM findings[10]. Among the 5 participating sites, 1 was excluded due to lack of follow-up information for myocardial infarction, resulting in 3,996 patients from the United States (N=1016), Canada (N=636), South Korea (N=1404) and Austria (N=940). In sequential order, we excluded patients with prior coronary revascularization or myocardial infarction (n=250); who were asymptomatic (n=1072); who did

not have complete symptom and/or coronary artery disease risk factor collection (n=542); who were referred for imaging from the emergency department or inpatient setting (n=0); or who were lost to follow-up (n=0). 2132 patients comprised the dataset, and are herein referred to as CCTA-2. Median follow-up time for CCTA-2 was 1·6 years (IQR = 0·8-2·8 years).

The MPS validation cohort was referred for exercise myocardial perfusion scintigraphy (MPS) at Cedars-Sinai Medical Center and followed for all-cause mortality. Excluded patients included those undergoing prior coronary revascularization or myocardial infarction or who underwent pharmacologic stress testing (n=6405); who were asymptomatic (n=1095); did not have complete symptom and/or coronary artery disease risk factor collection (n=425); were referred for imaging from the emergency department or inpatient hospital setting (n=1903); or who were lost to follow-up (n=0). 2779 comprised the final study dataset and are herein referred to as the MPS validation cohort. Median follow-up time for MPS was 5·0 years (IQR 3·5-6·4 years).

Coronary Artery Disease Risk Factor and Symptom Type

Prior to testing, we performed medical histories to ascertain the presence of categorical coronary artery disease risk factors, which were defined in accordance to accepted guidelines. Hypertension was defined by a history of blood pressure ≥140/90 mmHg and/or treatment with anti-hypertensive medications (11). Diabetes mellitus was defined by a fasting glucose of ≥126 mg/dl and/or use of insulin or oral hypoglycemic agents (12). Dyslipidemia was defined in accordance with National Cholesterol Education Program Adult Treatment Panel III guidelines or by treatment with lipid lowering medication (13). Current smoking status was defined by

active smoking within 3 months of presentation. Family history of coronary artery disease was defined as myocardial infarction or cardiac death in a first-degree relative (14).

Symptoms were ascertained through interview by a physician or health professional, or written questionnaire. Chest pain was categorized according to criteria for angina pectoris (3, 15). Patients with typical angina experienced substernal jaw, and/or arm pressure-like pain that occurred with exertion and resolved within 15 minutes of rest and/or use of nitroglycerin. Patients with atypical angina experienced 2 of these characteristics. Patients with non-anginal chest pain experienced 1 or none of these characteristics. Dyspneic patients without chest pain were categorized as having typical angina, according to their prognostic risk (16). From these data, the pre-test likelihood of obstructive coronary artery disease was calculated by the method of Diamond and Forrester[3].

Event Ascertainment

All study individuals for CCTA-1 and CCTA-2 were followed for an endpoint of death or non-fatal myocardial infarction, and for an endpoint of death for MPS. Follow-up procedures were approved by all study centers' institutional review boards. Death status for non-United States centers was gathered by clinical visits, telephone contacts and questionnaires sent by mail; with verification of all reported events by hospital records or direct contact with a patient's attending physician. Death status for US centers was ascertained by query of the Social Security Death Index or by scripted in-person or phone interview by an experienced physician and/or nurse study investigator.

Statistical Methods

Categorical variables are displayed as frequencies and percents, while continuous variables are described as mean±SD, or medians with interquartile ranges. Variables were compared with chi-squared statistic for categorical variables and by Student's unpaired t-test or Wilcoxon non-parametric test where appropriate for continuous variables. A two-tailed p value <0.05 was considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute, www.sas.com, Cary, NC).

Development of a Medical History-Based Model for Adverse Clinical Events

Information from the CCTA-1 cohort was used to develop a clinical prediction model for death or MI (CCTA-1) or death (MPS) based on CAD risk factors and symptom type. The best overall clinical prediction algorithm was fit using Cox proportional hazards models. Eight variables were evaluated for risk prediction, and were restricted to those that could be easily obtained from standard cardiac medical history: age, gender, diabetes, hypertension, dyslipidemia, family history of coronary artery disease, current smoking status and symptom type. Symptom type was categorized dichotomously according to prognostic relevance for individuals referred for non-invasive imaging as typical angina or dyspnea versus atypical angina or non-anginal pain (16). The final best-fit Cox model was selected by applying backwards stepwise regression, examining the -2loglikelihood, and minimizing Bayes' Information Criterion (BIC) (17). Interactions between age and all risk factors were examined.

Once variables were selected for the final Cox model, an integer-based model was developed to predict 3-year probability of death or myocardial infarction. The integer-based model was created by transformation of Cox regression coefficients from the best-fit model. To maximize ease of use, risk score values were scaled and transposed such that age points

related to the decade of a patient's age (e.g., a 5 for patients aged 50-59) and each coronary artery disease risk factor present added an additional point to the total score.

Validation of Medical History-Based Model

External validation was conducted for the best-fit model using the CCTA-2 and MPS cohorts. For comparison, a best-fit Cox regression model was constructed based on the candidate variables as in the CCTA-1 model but using data from the validation cohorts. Similar to the CCTA-1 model, backwards stepwise regression was used to create the final best-fit model. For MPS, we adjusted the predicted risk based upon ratio of risk of death to risk of death or myocardial infarction from the CCTA-1 best-fit model. The accuracy of the CCTA-1 best-fit model was examined using discrimination and calibration. Discrimination was evaluated by C-statistic, while calibration was described by Nam and D'Agostino's modification of the Hosmer-Lemeshow goodness of fit procedures (18). We further examined discrimination and calibration of the integer-based model **(Figure 1)**. Observed versus predicted risk was computed based on categories defined by deciles of predicted risk, and compared by plotting predicted and actual event rates within each decile.

Discrimination of Medical History-Based Model for Obstructive Coronary Artery Disease

We evaluated the ability of the integer-based risk model to discriminate between individuals with and without obstructive coronary artery disease, defined by ≥50% luminal diameter stenosis in any coronary artery ≥1·5 mm in diameter. Obstructive CAD was determined from CCTAs from the CCTA-1 and CCTA-2 cohorts, but was unavailable within the

MPS validation cohort. CCTAs were performed and interpreted by Level III experts in an intent-to-diagnose fashion (19,20).

We applied the integer-based model from CCTA-1 to estimate the probability of obstructive coronary artery disease in CCTA-2. For obstructive coronary artery disease, the area under the receiver operator characteristics curve (21) of the integer-based model was directly compared to the method of Diamond and Forrester. We used the aggregate data from CCTA-1 and CCTA-2 to determine the rate of obstructive coronary artery disease by integer values from the developed model.

RESULTS

Clinical Characteristics of the Study Cohorts

Baseline characteristics of the CCTA-1 development and CCTA-2 and MPS validation cohorts are listed in **Table 1**. During follow-up, 65 deaths and 155 myocardial infarctions occurred in the CCTA-1 cohort, while 14 deaths and 90 myocardial infarctions occurred in the CCTA-2 validation cohort. In the MPS validation cohort, 51 deaths occurred during follow-up.

Clinical Prediction Model Derivation

In univariate Cox regression applied to CCTA-1, several coronary artery disease risk factors and symptom type predicted risk of death or myocardial infarction (**Appendix**). Despite its lack of significance in univariate models, gender was forced into multivariate models given its accepted clinical importance. As no significant interactions were identified, the final best-fit Cox model for prediction of death or myocardial infarction included age, gender, symptom type, diabetes, hypertension, family history of coronary artery disease and smoking status. The BIC

value for the best-fit Cox model was 3554·4, which represented a substantial improvement over the null model BIC of 3716.6. The β coefficients, standard errors, hazard ratios and p-values for each of the covariates in the best-fit Cox model are shown in **Table 2**. The C-statistic for this model was 0·76.

Discrimination and Calibration of Medical History-Based Prediction Model

Table 3 presents C-statistics for the best-fit and integer-based Cox model for the CCTA-1, CCTA-2 and MPS validation cohorts. For MPS, whereby only death was available during follow-up, probabilities were determined by multiplication of the risk of death or myocardial infarction by 0·405, which represented the ratio of the 3-year risk of death (1·17%) to the 3-year risk of death or myocardial infarction (2·89%) in CCTA-1. Discrimination of the best-fit model performed well in both CCTA-2 and MPS, achieving similar discrimination to the CCTA-1 best-fit model. **Figure 2** presents the decile plots for assessment of calibration of the CCTA-1 model. Integer models were based upon covariates categorized in binary fashion except for age, which was categorized by range as 18-39 years, 40-49 years, 50-59 years, 60-69 years, and ≥70 years **(Figure 1).**

Integer scores were calculated by the following formula: Total points = [Age 40-49 years = 4; 50-59 years = 5; 60-69 years = 6; ≥70 years = 7) + Gender (1=male, 0=female) + Diabetes (1=diabetic; 0=non-diabetic) + Hypertension (1=hypertensive; 0=normotensive) + Family history of CAD (1=yes, 2=no).

Discrimination of the Medical History-Based Model for Estimating the Likelihood of Obstructive Coronary Artery Disease

The AUC of the best-fit CCTA-1 model (0·76; 95% CI 0·746 to 0·771) was higher than the Diamond-Forrester (0·64; 95% CI 0·628 to 0·659) methods for discriminating individuals with versus without obstructive coronary artery disease (p<0·0001). Across the range of integer values, the likelihood of obstructive coronary artery disease ranged from 0 to 82·4% (**Table 4).**

DISCUSSION

We developed and validated a method for identifying stable individuals with suspected coronary artery disease who are at risk of death or myocardial infarction. Our aim was to create a parsimonious model that incorporates coronary artery disease factors that can be derived solely from a medical history. We demonstrated the effectiveness of this method for measures of risk stratification, discrimination, and calibration. Further, the model exhibited superior discriminatory performance when tested against the Diamond-Forrester method for determining pre-test likelihood of obstructive coronary artery disease.

One potential function of this model may be to serve as an effective "gatekeeper" to identify individuals who are at sufficiently low risk of incident death or myocardial infarction that the yield from further testing may be low. At present, more than 10 million coronary artery disease imaging tests are performed annually in the United States alone at high direct and indirect costs, with rates of test normalcy significantly higher today as compared to only a decade ago (9,21). As an example, in the largest CCTA study to date, more than 42% of individuals were identified as having no coronary artery disease (22). Similarly, the rates of

test normalcy for MPS have dramatically increased over time, with a prevalence of >90% in a study of 39,515 patients (21).

In this study, those with an integer value ≤7—which represented nearly half of the study population—only 1·0% experienced an adverse clinical event, and only 10% of these individuals possessed obstructive coronary artery disease. These findings may convey a greater sense of prognostic and diagnostic certainty towards avoidance of testing for individuals whose risk and prevalence of disease is sufficiently low to preclude the need for further evaluation. Conversely, this model may be used to identify individuals whose risk is high, and who may benefit from further testing. While representing only 3% of the combined cohort, 9% of individuals with an integer score >9 experienced an event and 54% possessed obstructive coronary artery disease. The need for testing is apparent in this group, and in accordance with societal guidance documents (23).

To date, no robust medical history-based prediction model has been available for identifying stable symptomatic patients at risk for death or myocardial infarction. In its absence, clinicians have relied upon estimates of the likelihood of an individual possessing obstructive coronary artery disease (3). These methods have served as the cornerstone for assessment of patients with suspected coronary artery disease for the last 40 years. Nevertheless, these methods were validated against invasive angiographic and pathologic correlates; and their application demonstrates a 3-fold overestimation of coronary artery disease in patients referred for non-invasive imaging that suggests the need for contemporary revision (6). In the present study, the developed medical history-based model was superior to the Diamond-Forrester method for discrimination of individuals with versus without obstructive

anatomic coronary artery disease. In this regard, this model may serve a dual role not only as a prognostic instrument but also as a diagnostic tool.

This study is not without limitations. We studied patients referred for CCTA and exercise MPS—given their common performance and similarities for indications considered appropriate for use—with our study findings robustly applicable to both modalities (24, 25). Yet, whether the model can be employed for patients being considered for exercise treadmill testing, other imaging tests, or in patients not considered for any testing remains unknown. Second, patient-reported histories may have resulted in ascertainment bias, and coronary artery disease risk factor profiles may have been more accurate with adjunctive confirmation by vital sign or laboratory values. One advantage of the present study is the applicability to practicing physicians who routinely solicit histories in the office setting. Third, the prediction model included all-cause rather than cardiac-specific death. In doing so, this study is disencumbered from information bias but may result in reduced prognostic specificity. Finally, we examined stable symptomatic individuals referred for outpatient imaging, and caution should be taken to apply the model to patients in the emergency department or inpatient setting.

CONCLUSIONS

We developed and validated a simple medical-history based method that predicts risk of death and myocardial infarction in symptomatic stable patients with suspected coronary artery disease. Further, this method exhibits superior performance to traditional methods for identifying individuals with obstructive coronary artery disease.

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