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An ordinal prediction model of the diagnosis of non-obstructive coronary artery and multi-vessel disease in the CARDIIGAN cohort☆

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ABSTRACT

Background: The extent of coronary artery disease (CAD) is relevant for the evaluation and the choice of treatment of patients and consists of the severity of stenoses and their distribution within the coronary tree. Diagnosis is not easy and severe CAD should not be missed. For low-risk patients one wants to avoid the invasive angiography. We aim to propose a diagnostic prediction model of CAD respecting the degree of disease severity.
Methods: We included 4888 patients from the Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) cohort. An ordinal regression model was applied to estimate the probabilities of five incrementally disease categories: no CAD, non-obstructive stenosis, and one-, two- and three-vessel disease. We included 11 predictors in the model: age, sex, chest pain, diabetes, hypertension, dyslipidaemia, smoking, HDL and LDL cholesterol, fibrinogen, and C-reactive protein. Bootstrapping was used to validate model performance (discrimination and calibration).
Results: Age, sex, and three laboratory measures had a large predictive effect. The model poorly separated most adjacent disease categories, but performed well for categories far apart, with little optimism. The overall discrimination added up to a c statistic of 0.71 (95% CI 0.69 to 0.73). The model enables the estimation of individual patient probabilities of disease severity categories.
Conclusions: The proposed ordinal diagnostic risk model, employing routinely obtainable variables, allows distinguishing the extent of CAD and can especially discriminate between non-obstructive stenosis and multi-vessel disease in our CARDIIGAN patients. This can help to decide on treatment strategy and thereby reduce the number of unnecessary angiographies.

1. Introduction

The reference standard to diagnose coronary artery disease (CAD) is conventional coronary angiography, but this procedure can be harmful and involves considerable costs. Therefore, attempts have been made to find diagnostic predictors, since pre-selection of patients based on easily obtained information could be advantageous. Some recently suggested predictors are high-sensitivity C-reactive protein (hs-CRP), IL-6 levels, sex, diabetes mellitus, hypertension, dyslipidaemia, triglycerides, HDL cholesterol, glucose, insulin, smoking, and impaired renal function [1–5].

Genders et al. [6] recently presented a multivariable model with performance evaluation. The main aim of this model was to predict the presence or absence of obstructive stenosis among a group of patients with suspected CAD. Patients with low probability of a stenosis can be treated conservatively with lifestyle recommendations and optimal medical therapy, with no need for an interventional procedure unless symptoms increase or acute coronary syndrome occurs. On the other

Abbreviations: c, concordance statistic; CAD, coronary artery disease; CARDIIGAN, Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography cohort; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio.

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hand, when the probability of severe CAD is high an invasive strategy might be appropriate. Consequently, knowledge and additional information on the extent of the disease and anatomic settings is of importance, often resulting in different therapeutic strategies [7]. Interventional and surgical revascularisation is more frequent in multi-vessel disease and optimal medical therapy a therapeutic option in one-vessel disease [8].

In other areas the use of ordinal modelling has already been applied prosperously, for instance with aneurysmal subarachnoid haemorrhage [9] and with traumatic brain injury [10–12]. It has been stressed in such prognostic research that the initial situation makes a difference for the possibilities of the future outcome. When a patient has a poor prognosis just survival would be particularly relevant, but on the other hand for a patient with good prospects complete recovery is the only improvement that can be achieved. In a diagnostic setting, dealing more specifically with the extent of disease is relevant when different treatment options are available. It has already been suggested to perform more elaborate research by differentiating CAD by its severity, because it can be helpful in the decision-making process concerning the application of an invasive angiography and the treatment strategy [13]. It is important to reduce, as much as possible, the number of angiographies for the patients who do not need an intensive treatment, that is to say one wants to increase the rate of revascularisation per angiography. This can be achieved if one can better estimate the prevalence of multi-vessel disease. On the other hand, being able to estimate the probability of the complete absence of CAD is also advantageous to enhance the diagnostic process. Thus, we aimed to propose a prediction model that respects the ordering in severity of disease (with five categories) in patients with suspected CAD, who were referred for diagnostic coronary angiography, using easily accessible, inexpensive, non-invasive parameters.

2. Material and methods

2.1. Material

The Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) cohort has been described previously [13]. In short, during 2004 to 2008 the inclusion was performed of 8296 consecutive patients with chest pain or symptoms suggestive of CAD undergoing elective coronary angiography at a single-centre secondary and tertiary cardiology clinic. After applying the in- and exclusion criteria, 4888 patients without known previous CAD or other heart diseases and without a history of coronary revascularisation were available for the current study. Data were recorded as in routine clinical practice in a prospective quality enhancement initiative. Patients gave their written informed consent for the coronary angiography and approval has been attained from the ethics committee of the Medical University Innsbruck.

Data included patient characteristics, medical history, symptoms, laboratory results, and therapy decision. Applied definitions and procedures have been summed up before [13]. The cut-off of stenosis in the current study was 70% for left anterior descending, circumflex, and right coronary artery. The left main artery had a cut-off at ≥50% stenosis and was weighted as three vessels. The outcome variable consisted of the following five categories: no CAD, non-obstructive stenosis, one-vessel disease, two-vessel disease, and three-vessel disease [14].

2.2. Methods

Baseline results are presented as proportions for categorical variables and means and standard deviations (or medians and interquartile ranges) for continuous ones. Since 1.7% of the clinical data was missing, concerning about a quarter of the participants and 27 variables (15 variables were complete, of which four temporal and regional auxiliary variables), multiple imputation (20 times) was applied to avoid potential biases from this source (Supplementary Appendix 1) [15–17]. We based the ordinal prediction model on earlier work with a binary model [13] and a priori used the same predictors, under the assumption that they would be relevant here. Model development and validation was performed for each of the 20 imputed datasets, and results were combined according to Rubin's rules [18]. We used the cumulative logit model (also called the proportional odds model) in which the ordinal outcome with 5 disease categories is characterised in terms of 4 cumulative binary contrasts: 1) no CAD vs. other, 2) no CAD and non-obstructive stenosis vs. other, 3) no CAD, non-obstructive stenosis and one-vessel disease vs. other, and 4) no CAD, non-obstructive stenosis, one-vessel disease and two-vessel disease vs. three-vessel disease. The regression model assumes that the odds ratio for a predictive factor is the same for each binary contrast [19]. Hence the model estimates one coefficient per predictor, but a different intercept for each contrast. The resulting model was visualised by a nomogram to depict the relative contribution of the predictors for the risk estimates. Nomograms translate values for each predictor into a number of points (depicted through lines). More points imply more impact on the predicted risks (thus longer lines). For predictors with strong effects the attributed points change considerably depending on the predictor value, whereas for those with weak effects they do not.

Performance was evaluated in terms of discrimination and calibration. We did internal validation by bootstrapping for optimism correction based on 200 samples, drawn with replacement [20]. We reported results for discrimination and calibration performance. For discrimination, the main measure is the ordinal concordance (c) statistic [21] (the c statistic gives the probability that the model can correctly order two patients that belong to different outcome categories). Additionally, we calculated c statistics for the discrimination between each pair of outcome categories (e.g. non-obstructive stenosis vs. two-vessel disease) [22]. Calibration assesses the correspondence between the observed and the predicted outcomes. We calculated the general calibration slope to check for model overfitting (excluding the intercept), the amount of which is indicated by the extent to which the slope is below 1. In addition, dichotomous calibration slopes for each binary contrast were determined. These dichotomous slopes can be affected by overfitting, but also by violations of the proportional odds assumption: if there is no overfitting and the proportional odds assumption is fully satisfied, these slopes should equal 1). The optimism-corrected dichotomous calibration slopes were used to readjust the ordinal prediction model. This readjustment is in line with the rationale behind the stereotype model [23,24]. Technical details are given in the Supplementary material.

To illustrate how the model provides individual risk estimates, we compared model predictions with the baseline risk (i.e. the prevalence) of each disease category in the total study group. We used relative risks as an indication of the extent to which risk estimates for an individual patient differed from the baseline risks.

The data preparation was performed with SPSS version 19.0, the multiple imputations with Stata/MP version 11.2, and the main analyses with R version 3.4.1 (including the VGAM, HMISC, MITOOLS, and RMS libraries).

3. Results

Of the total of 4888 CAD-suspected patients, 3028 (62%) were male and age ranged from 18 to 89 years. Among these patients, 1381 (28%) did not have CAD while 1901 (39%) had at least one significantly affected artery (one-, two-, or three-vessel disease). For most predictors the value (or proportion affected) increased with each next category of disease severity, except for HDL cholesterol with an opposite tendency. For age, sex, hypertension, dyslipidaemia, and HDL cholesterol the patients with two- and three-vessel disease looked very similar. The data on smoking and the laboratory findings were not complete (Table 1).

The odds ratios of the predictors in the ordinal model (Table 2) and the nomogram (online Fig. 1) indicated that age (OR per 10 years 1.78, 95% CI 1.69 to 1.89), HDL cholesterol (OR per 10 mg/dl 0.84, 95% CI 0.81 to 0.87), and male sex (OR 3.02, 95% CI 2.67 to 3.40) had the largest predictive effects. In contrast, hypertension (OR 1.16, 95% CI 0.99 to 1.36), smoking (OR 1.21, 95% CI 1.08 to 1.36), and C-reactive protein (OR 1.13, 95% CI 0.95 to 1.35) had the smallest. Regression model coefficients and standard errors are given in Supplementary Table 1.

3.1. Model performance

The ordinal c statistic of the diagnostic model was 0.71 (95% CI 0.69 to 0.73) (Table 3). The dichotomous c statistics for the discrimination between pairs of categories varied between 0.54 (95% CI 0.50 to 0.58) for the distinction between two- and three-vessel disease and 0.86 (95% CI 0.84 to 0.88) for no CAD versus three-vessel disease (Supplementary Table 2). Generally, discrimination improved as the difference in severity between disease categories increased (online Fig. 2). The model could discriminate well between no CAD and each of the other disease categories (c statistics > 0.70) and between non-obstructive stenosis and multivessel disease (c statistics > 0.67). For no CAD versus all other categories combined, the c statistic was 0.77 (95% CI 0.75 to 0.78). The general calibration slope was 0.99 (Table 3), indicating a marginal 1% overfitting. The dichotomous calibration slopes were still good, yet deviated more from 1: the probability of no CAD versus the rest had a slope of 1.12, suggesting that these predicted risks were not extreme enough. The estimates of the other disease categories were overfitted (too extreme), for example the risk of three-vessel disease versus the rest had a calibration slope of 0.89. Given that the overall calibration slope was almost 1, the dichotomous slopes reflect minor violations of the proportional odds assumption. This was further supported by the result of a likelihood

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