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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

Table 1
Characteristics of the CARDIIGAN patient group ($n = 4888$) by disease severity category[a].

Predictor	No coronary artery disease	Non-obstructive stenosis	One-vessel disease	Two-vessel disease	Three-vessel disease	Missing *n* (%)
	$n = 1381$ (28%)	$n = 1606$ (33%)	$n = 997$ (20%)	$n = 475$ (10%)	$n = 429$ (9%)	
Mean age in years (SD)	59.4 (11.2)	65.9 (9.7)	65.2 (10.3)	67.0 (9.9)	67.4 (10.7)	0
Male sex	45.0%	60.3%	73.1%	78.5%	78.6%	0
Chest pain	54.2%	57.7%	66.5%	70.3%	73.2%	0
Diabetes mellitus	9.0%	16.4%	16.8%	19.8%	25.2%	0
Hypertension	67.5%	79.3%	77.6%	83.6%	82.2%	0
Dyslipidaemia	59.7%	63.1%	64.3%	72.0%	68.5%	0
Ever smoked	41.0%	44.7%	49.4%	49.9%	51.7%	640 (13%)
Mean HDL cholesterol[b] (SD)	60.9 (18.9)	57.0 (17.0)	54.0 (15.1)	52.0 (14.9)	52.2 (15.9)	312 (6%)
Mean LDL cholesterol[b] (SD)	127 (34)	126 (36)	131 (40)	130 (38)	135 (40)	310 (6%)
Median fibrinogen[b] (IQR)	341 (277; 408)	362 (297; 443)	368 (301; 455)	370 (304; 462)	384 (318; 480)	119 (2%)
CRP > 1.00 mg/dl	10.3%	12.6%	17.9%	16.0%	18.8%	96 (2%)

CARDIIGAN = Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography cohort, CRP = C-reactive protein, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein, SD = standard deviation.
[a] Coronary artery disease cut-off at 70% stenosis, for the left main artery at 50%; the left main artery counts as three vessels.
[b] In mg/dl.

ratio test ($p < 0.0001$). To apply the model, we used model coefficients and predictions that were adjusted, thereby alleviating these calibration issues (Supplementary Table 3, Supplementary Appendix 2 and 3).

3.2. Application

In Fig. 1 the bar charts exemplify the application of the ordinal model for two theoretical patients. The first example patient (#1) is a rather young man with dyslipidaemia and who has ever smoked, but was otherwise not very unfavourable regarding the other predictors. The probability he does not have CAD is 44.6%, hence the risk of CAD is 55.4%. The risk of obstructive CAD is 21.0% (14.4% risk of one-vessel, 3.8% risk of two-vessel, and 2.8% risk of three-vessel disease). The baseline risk of CAD is 71.7%, therefore the relative risk for this patient (#1) versus baseline is 0.77 (55.4%/71.7%). The relative risk of a significant CAD is 0.54 (21.0%/38.9%). Suppose we would have a female patient with otherwise the same values, the predicted risk of CAD would be 26.5% and of obstructive CAD 9.0% (relative risks of 0.37 and 0.23, respectively). The other example patient (#2) concerns a somewhat older man with diabetes and dyslipidaemia, and rather low HDL cholesterol. His cumulative risk of having CAD was 87.1% and he had a 50.9% risk of one-, two- or three-vessel disease (relative risks of 1.21 and 1.31 respectively). The highest relative risk, of 1.40, was with one-vessel disease. Other examples are depicted in online Fig. 3, with a high-risk male (#3) (96.9% risk of CAD and relative risks of 2.44 and 3.07 of having two- and three-vessel disease respectively), compared to a female with otherwise identical predictor values (#4).

Table 2
Proportional odds estimates of predictors (with 95% confidence intervals) for a one disease category increase in the CARDIIGAN patient group ($n = 4888$).

Predictor	Odds ratio	95% confidence interval
Age (per 10 years)	1.78	1.69 to 1.89
Sex (male vs. female)	3.02	2.67 to 3.40
Chest pain	1.73	1.55 to 1.92
Diabetes mellitus	1.57	1.36 to 1.82
Hypertension	1.16	0.99 to 1.36
Dyslipidaemia	1.45	1.24 to 1.68
Ever smoked	1.21	1.08 to 1.36
HDL cholesterol (per 10 mg/dl)	0.84	0.81 to 0.87
LDL cholesterol (per 10 mg/dl)	1.05	1.03 to 1.06
ln(fibrinogen) (mg/dl)	1.76	1.43 to 2.17
C-reactive protein >1.00 mg/dl	1.13	0.95 to 1.35

CARDIIGAN = Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography cohort, HDL = high-density lipoprotein, LDL = low-density lipoprotein, ln = natural logarithm.

4. Discussion

This work presented a new diagnostic model to predict the presence and especially the extent of CAD based on risk factors and routine lab parameters. The proposed ordinal prediction model performed well in distinguishing between no CAD and each of the severe forms of CAD. Generally, discrimination was good between distant disease categories and in particular this was also true for non-obstructive versus multivessel disease, being especially of clinical importance. The model included eleven predictors, of which besides age and sex, HDL and LDL cholesterol and fibrinogen had the largest impact on the predicted risks, in other words on the pertaining probabilities of the various CAD extent categories.

4.1. Performance

The large number of patients led to a stable model. The internal validation showed only a marginal amount of optimism, with indiscernible effect on c statistics, therefore we showed optimism-corrected results. The overall calibration slope was near perfect (0.99) and the optimism of the calibration slopes was minimal (Supplementary Table 2). The aim of such a model is to introduce an extra tool for cardiologists to decide on the necessity of performing conventional coronary angiography and on further treatment steps, among the relevant patients. We consider that, at any particular centre, the distribution of the five disease categories is roughly known; this is the starting point of the diagnostic process. Next, the potential of the ordinal model is to estimate for

Table 3
Main performance measures (with 95% confidence intervals)[a] of the ordinal diagnostic model in the CARDIIGAN patient group ($n = 4888$).

Measure	Result	95% confidence interval
Ordinal c	0.71	0.69 to 0.73
Dichotomous[b] c:		
d_0 vs. d_{1-4}	0.77	0.75 to 0.78
d_{0-1} vs. d_{2-4}	0.72	0.70 to 0.73
d_{0-2} vs. d_{3-4}	0.73	0.71 to 0.74
d_{0-3} vs. d_4	0.72	0.69 to 0.74
General calibration slope	0.99	.
Dichotomous[b] calibration slope:		
d_0 vs. d_{1-4}	1.12	.
d_{0-1} vs. d_{2-4}	0.90	.
d_{0-2} vs. d_{3-4}	0.93	.
d_{0-3} vs. d_4	0.89	.

c = concordance statistic, CARDIIGAN = Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography cohort, d_x = disease category x.
[a] Corrected for optimism.
[b] Disease categories: (0) no coronary artery disease, (1) non-obstructive stenosis, (2) one-vessel disease, (3) two-vessel disease, (4) three-vessel disease.

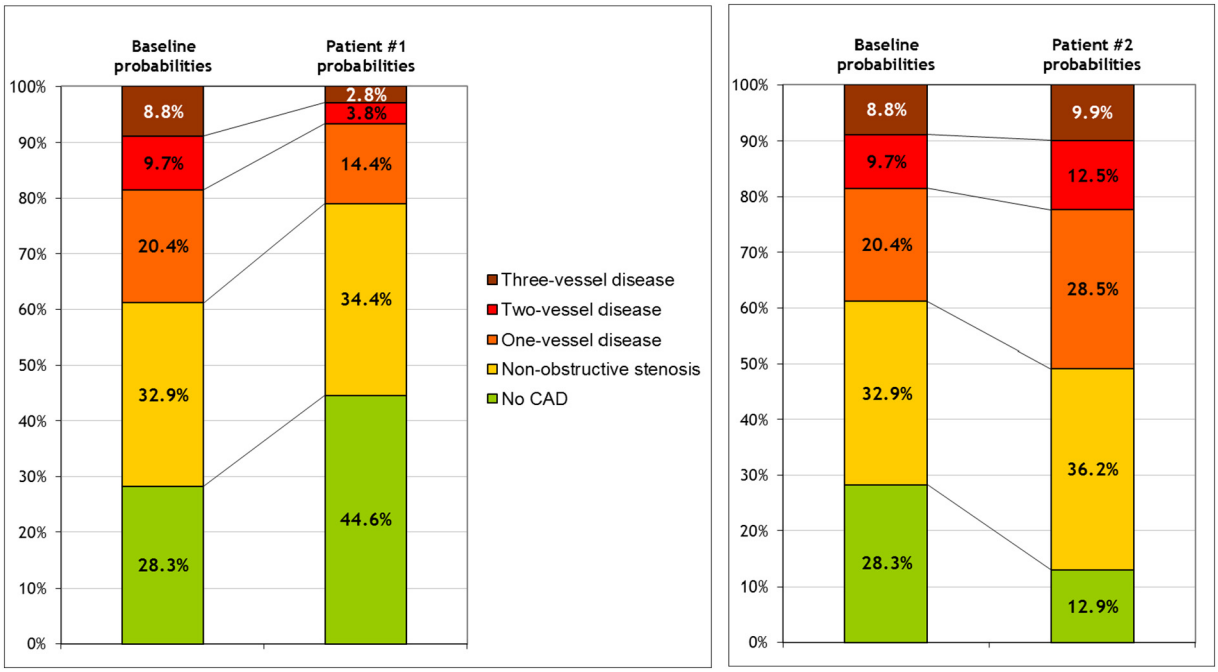

Fig. 1. Stacked bar charts of the baseline probability distribution of the ordinal disease categories compared to two patient examples[a] of diagnostic predictions and relative risks[b] in the CARDIIGAN patient group ($n = 4888$) [a] Patient #1: 48 years, male, no pain, no diabetes, no hypertension, dyslipidaemia, smoking, HDL 61, LDL 144, fibrinogen 372, CRP ≤ 1.00 Patient #2: 62 years, male, no pain, diabetes, no hypertension, dyslipidaemia, no smoking, HDL 30, LDL 130, fibrinogen 350, CRP ≤ 1.00 [b] relative risks of the five disease categories (from bottom to top): Patient #1: 1.58, 1.05, 0.71, 0.39, and 0.32 Patient #2: 0.46, 1.10, 1.40, 1.29, and 1.12 CARDIIGAN = Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography cohort, CRP = C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

each individual patient the chance that a certain disease category is present, based on the value of 11 predictors that are documented anyway. This is preferable to models that only distinguish between two groups of patients, for example presence or absence of high-risk CAD [25], and might become an additional helpful tool for better medical decision-making.

4.2. Application

Application of the model in its present form partly confirmed expected diagnoses and treatment strategies based on the given risk profile (Fig. 1). The first example patient (#1), although being male, had neither chest pain nor diabetes and therefore had only a small chance of an obstructive stenosis, and a conservative management strategy would be agreed upon. With the second example (#2), things however do not seem so obvious, the man being somewhat older and having diabetes, dyslipidaemia and low HDL cholesterol, but without symptoms. Looking at the probabilities, with only a 22% chance of multi-vessel disease, one might decide to do other testing first, like a stress test [26]. Another aspect, on which this model can shed light, is the extent of effect of the various predictors. Again for example, for the first patient (#1) we showed the difference in the distribution of the disease categories when only sex differed with a 44.6% probability of no CAD in the male and 73.5% in the female patient. Likewise, when considering a high-risk female patient (#4) in comparison to the male one (#3), the difference is striking (online Fig. 3). This female example patient (#4) has a probability distribution of the CAD categories very much like the second example patient (#2) in Fig. 1, while the male (#3) would probably profit from a revascularisation.

The diagnostic prediction model could not separate well between the two- and the three-vessel disease category. These two groups are relatively small compared to the others and, clinically speaking, the distinction between the two is not very important for the treatment decision-making since revascularisation would frequently be appropriate. One-vessel disease, where usually non-invasive treatment would be a good initial management option, was clearly distinguishable from no CAD. No CAD and non-obstructive stenosis, requiring a conservative non-invasive approach, is well differentiated from multi-vessel disease. On the other hand, various other discrimination comparisons showed somewhat moderate performance. For instance, the distinction between non-obstructive CAD and one-vessel disease was only limited. However, from a clinical perspective this is not too serious since conservative treatment is indicated for both and an intervention will only rarely be considered fitting as initial strategy [27]. Also, one has to recognise the fact that CAD reflects the gradual ageing and deterioration of the cardiovascular system and the disease categories are based on cut-off values of stenosis on visual inspection. So where one might think in terms of distinct levels, we are actually dealing with a continuum. All in all, for the various divides of all patients in just two groups, discrimination was good, like between several single categories (far apart), and indeed was better than in the binary model [13]. One of the major assets of the model is the good distinction between non-obstructive stenosis on the one hand and two- and three-vessel disease on the other.

4.3. Assumptions

Here the proportional odds model was applied and performed well, even though some miscalibration was encountered. This was likely due to some departure from the proportional odds assumption and we adjusted the model coefficients for this. Other types of ordinal models can be evaluated and compared. For example, partial proportional odds modelling has been proposed, in which proportional odds are assumed for some predictors, but not for others. Alternatively, models can be applied that do not assume proportional odds altogether [19]. For the present study the larger number of model coefficients was undesirable (44 for models without the assumption versus 11 for our proportional odds model), since the model then is less parsimonious and thus more complicated in application. Further methodological research may focus on how the trade-off between different algorithms for CAD risk prediction can be made.

4.4. Strengths and limitations

The strengths of the current study include the application, to our knowledge for the first time, of more than two ordinal disease categories confirmed by invasive coronary angiography in a diagnostic prediction model of CAD, with a different, more specific analytical modelling method and more complex interpretation of results. This leads to the use of more available information and is more efficient and elaborate [10,11], so more is gained from the data, but more importantly it is clinically relevant to split diagnosis up into multiple categories since the (treatment) consequences differ between them. It is also advantageous to have a large cohort of nearly 5000 patients, so estimates can be rather precise and robust. The data was collected prospectively and is of good quality, including several routine laboratory parameters.

As for the limitations, obviously as with all model development, external validation still has to be performed; then also a risk calculator can be presented to promote clinical use. Another limitation is the possibility of verification bias since some relevant patients might not have been referred for angiography, especially relevant among less affected patients. Also other predictors not included in this study might be valuable, for example information on carotid atherosclerosis [2], coronary calcium score [28] or results of non-invasive functional tests. Also, since this involves an observational study, there was missing data. However, by using multiple imputation we minimised its influence, thus results are more valid and more precise [29]. Finally, one could argue that the data was gathered quite some time ago. There is however no reason to believe that predictor effects might have changed and few predictive diagnostic studies are yet available.

4.5. Conclusion

In conclusion, using the proposed ordinal model among our patients makes it possible to discriminate between the various disease categories and especially also between non-obstructive CAD and multi-vessel disease. Thereby it has the potential to reduce the rate of diagnostic angiographies in CAD patients with no need of revascularisation. Also, the category of no CAD is distinguished, potentially enabling to reconsider the suspicion of a CAD diagnosis. The model is based on a limited number of variables used in daily clinical practice.

Disclosures

All authors have no relationships with industry relevant to the contents of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.05.092.

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