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Prediction of risk of cardiovascular events in patients with mild to moderate coronary artery lesions using naïve Bayesian networks

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Abstract

Background This prospective study integrated multiple clinical indexes and inflammatory markers associated with coronary atherosclerotic vulnerable plaque to establish a risk prediction model that can evaluate a patient with certain risk factors for the likelihood of the occurrence of a coronary heart disease event within one year. **Methods** This study enrolled in 2686 patients with mild to moderate coronary artery lesions. Eighty-five indexes were recorded, included baseline clinical data, laboratory studies, and procedural characteristics. During the 1-year follow-up, 233 events occurred, five patients died, four patients suffered a nonfatal myocardial infarction, four patients underwent revascularization, and 220 patients were readmitted for angina pectoris. The Risk Estimation Model and the Simplified Model were conducted using Bayesian networks and compared with the Single Factor Models. **Results** The area under the curve was 0.88 for the Bayesian Model and 0.85 for the Simplified Model, while the Single Factor Model had a maximum area under the curve of 0.65. **Conclusion** The new models can be used to assess the short-term risk of individual coronary heart disease events and may assist in guiding preventive care.

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Keywords: Bayesian networks; Cardiovascular events; Prediction

1 Introduction

Coronary heart disease (CHD) remains a life-threatening complication with a high mortality and morbidity rate.[1] According to current estimates, 15.4 million Americans ≥ 20 years of age have CHD. Approximately every 34 s, an American will experience a coronary event, and every minute someone will die from one.[2] Similarly, over one million people in China experience sudden cardiac death every year[3]. A large proportion of this population has no prior symptoms.[4] There is considerable demand for the early recognition and intervention of high-risk populations.

Most patients with acute coronary syndrome present as mild to moderate stenosis and are associated with vulnerable plaque.[5,6] Detecting vulnerable plaque may be helpful to identify high-risk patients. But this is not the only factor for the development of acute coronary events. Vulnerable blood (prone to thrombosis) and vulnerable myocardium (prone to fatal arrhythmia) play an important role in the outcome.[7] Therefore, a quantitative method for cumulative risk assessment of high-risk patients needs to be developed, which may include multiple clinical indexes and inflammatory markers associated with vulnerable plaque.

Despite extensive studies and the development of several risk prediction models, traditional CHD risk prediction models developed on the basis of data from long-term population-based follow-up studies fall short in predicting near-future events, particularly in individual clinical practice.[8–12] A quantitative method showing the likelihood of a patient with only mild to moderate stenosis by coronary angiography having a cardiac event in the coming year would be very beneficial to guide clinical practice. Use of state-of-the-art bioinformatics tools may provide substantial improvements in risk calculations.[13]

The Bayesian approach is a probability-based derivation method, which is suitable for combining evidence from

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multiple heterogeneous biological features, and is especially robust for incomplete and uncertain data.[14] We established a risk prediction model using Bayesian methods that can evaluate a patient with certain risk factors (especially inflammatory markers) on the likelihood of developing a coronary event in the short-term. This may enable patients with mild to moderate coronary artery lesions to be treated with the most appropriate individualized treatment as early as possible.

2 Methods

2.1 Patient population

Patients aged 18–80 years hospitalized in Anzhen Hospital and 10 other hospitals in Beijing from February 2007 to August 2009 and who showed segmental stenosis resulting in > 20% and < 70% lumen diameter reduction at least in one or more major coronary artery branches on coronary angiography (CAG) were enrolled in the study. The possible and potential confounders were excluded, such as infection which led to the activation of inflammation factors or patients whose life expectancy was too low. Specific exclusion criteria were as follows: left main coronary disease (all patients with stenosis in the left main coronary artery were excluded from our study); acute myocardial infarction; cardiac shock; left ventricular ejection fraction < 30%; history of revascularization; valvular heart disease; cardiomyopathy; cerebral vascular or peripheral vascular disease; systemic inflammatory diseases such as infection; autoimmune system diseases or connective tissue disease; baseline creatinine > 2.5 mg/dL (if male) or > 2.0 mg/dL (if female) and baseline alanine aminotransferase or aspartate aminotransferase 3 times greater than normal; heart transplant recipients; patients with advanced cancer and multiple organ failure; and patients who could not comply with research programs.

2.2 Baseline characteristics and biomarkers

After evaluating the lesion with CAG, the demographic, clinical and procedural characteristics of patients were recorded. The baseline clinical data included age, sex, history of hypertension, history of diabetes mellitus, history of dyslipidemia, history of myocardial infarction, history of Percutaneous Coronary Intervention, history of typical chest pain, if a typical chest pain attacked within 48 hours, premature CHD family history, smoking status, the number of cigarettes smoked per day, hypertension grade, systolic blood pressure, diastolic blood pressure, body mass index (BMI), estimated Glomerular Filtration Rate, diabetes duration, hypertension duration, dyslipidemia duration and discharge diagnosis. The procedural characteristics included degree of coronary artery stenosis, percentage area stenosis, morphology of coronary lesions, distribution of coronary artery lesion, Thrombolysis in myocardial infarction (TIMI) flow grades, lesion length, area of lesions, shape of lesions, reference vessel diameter, plaque area, minimal lumen area, minimum diameter and Corrected TIMI Frame Count. Routine blood biochemical examination as white blood count, platelet count, red blood cell counts (RBC), proportion of neutrophil, hemoglobin, creatine kinase isoenzyme (CKMB), troponin T (TNT), troponin I (TNI), hs-CRP, triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), uric acid, serum creatinine levels, blood urea nitrogen, fasting blood-glucose, 2-hour post-meal blood glucose, albumin, fibrinogen, alanine aminotransferase and aspartate aminotransferase were recorded too. Meanwhile, we assessed 20 inflammatory factors from 833 participants who were selected by random number table method, included Cathepsin S, Cystatin C, CD40 ligand (CD40L), CXC chemokine ligand 16 (CXCL16), Growth differentiation factor-15 (GDF-15), Granulocyte-macrophage colony-stimulating factor (GM- CSF), interleukin 6 (IL-6), interleukin 10 (IL-10), interferon-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage colony stimulation factor (M-CSF), macrophage migration inhibitory factor (MIF), macrophage inflammatory protein (MIP)-1β (MIP-1β), matrix metalloproteinase 9 (MMP-9), osteoprotegerin (OPG), placental growth factor (PIGF), resistin, Tie-2, tissue inhibitor of matrix metalloproteinase (TIMP)-1 (TIMP-1) and C-reactive protein (CRP).

2.3 Laboratory assay

Fasting venous blood samples were collected from the antecubital vein on the morning after the coronary angiography procedure using ethylene diamine tetraacetic acid (EDTA) as an anticoagulant. Blood samples were centrifuged at 1500 rpm for 10 minutes. The plasma samples were immediately separated into multiple aliquots and stored at –80°C until use. Plasma TC, LDL-C, HDL-C, TG, serum creatinine and the other routine blood biochemical examination were tested in a biochemical analyser (Hitachi-7600, Tokyo). Plasma high- sensitivity CRP was determined by enzyme-linked immunosorbent assay (ELISA). The concentrations of the plasma Cathepsin S, CD40L, CXCL16, GDF-15, GM-CSF, IL-6, IL-10, IP-10, MCP-1, M-CSF, MIF, MIP-1b, MMP-9, OPG, PIGF, Resistin, Tie-2, TIMP-1 and CRP were determined using commercially available protein arrays (RayBiotech, Norcross, GA, USA).

2.4 Endpoints and follow-up

All the patients were followed up by telephone at 1, 3, 6 and 12 months after CAG. The primary endpoint (major adverse cardiac events, MACEs) was a composite of all-cause death, non-fatal acute myocardial infarction, revascularization (except for myocardial infarction) and readmission due to refractory angina pectoris (without revascularization). Refractory angina pectoris is defined as the persistence of anginal symptoms despite maximal conventional.

2.5 Statistical analyses

Baseline categorical variables are reported as percentages, and continuous variables are reported as mean ± SD or median (interquartile range), depending on the distribution of the variables. The correlation of variables and events was assessed using Spearman's correlation analysis. Statistical analyses were performed using SPSS 17.0 for Windows software (SPSS, Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

2.6 Bayesian network approaches

The Bayesian rules have been described extensively in several studies previously.[15] Following a derivation of the Bayesian rules, the posterior odds (Opost) can be calculated as the product of the prior odds (Oprior) and the likelihood ratio LR (f):

$$O_{post} = O_{prior} \times LR\,(f), \tag{1}$$

$$O_{prior} = P\,(pos) \div P\,(neg), \tag{2}$$

$$O_{post} = P\,(pos|f) \div P\,(neg|f), \tag{3}$$

P (pos) and P (neg) represent the probabilities of the occurrence of the major adverse cardiac events (MACEs) and the probability of the nonoccurrence of the MACEs, respectively, without any clinical indicator. P ($pos|f$) and P ($neg|f$) represent the probabilities of the occurrence of the MACEs and the probability of the nonoccurrence of the MACEs, respectively, after considering the clinical indicator f. P ($f|pos$) and P ($f|neg$) represent the probabilities of meeting the standards of the clinical indicator f of patients who experienced MACEs and those who do not experience, respectively. From Equations (1), (2), and (3), the LR can be computed as:

$$LR\,(f) = P\,(f|pos) \div P\,(f|neg) = \frac{TPF_f}{FPF_f} = \frac{TP_f / P}{FP_f / N}, \tag{4}$$

where P and n are the number of patients who experienced and did not experience MACEs, respectively; and TP_f and FP_f are the number of patients with the biological evidence f who experienced and did not experience MACEs, respectively. According to Equation (4), we can evaluate the LR (f) of clinical indicator f using the standard data set. LR (f) may reflect the early warning capability of clinical indicator f. Patients with a higher LR (f) value of clinical indicator f may be more likely to suffer MACEs, as shown in Equations (5) and (6). If LR (f) > 1, it shows that the clinical indicator f can identify the positive lesions.

If $y = P\,(pos|f)$, $x = LR$, $a = P\,(pos) \in (0,1)$, it can infer that:

$$y = ax / (1 - a + ax), \tag{5}$$

$$dy/dx = a(1 - a)/(1 - a + ax)^2 > 0, \tag{6}$$

The advantages of Bayesian rules in this system permit us to integrate multiple heterogeneous data sources into a probabilistic model. Therefore, we can get the composite LR (LR comp) by simply multiplying the LRs from individual sources, which is namely the naïve Bayesian network shown in Equation (7).

$$LR(f_1 \ldots f_n) = \prod_{i=1}^{i=n} (P(f_i|pos) \div P(f_i|neg)) = \prod_{i=1}^{i=n} LR(f_i) \tag{7}$$

2.7 Receiver operating characteristic (ROC) curve and cross-validation

A ROC curve can show the efficacy of one test by presenting both sensitivity and specificity for different cutoff points. Sensitivity and specificity can measure the ability of a test to identify true positives and false positives in a data set.

The ROC curves are plotted and smoothed by SPSS software with the sensitivity on the y axis and 1-specificity on the X axis. To test the efficacy of the overall performance of various assessment models, the 5-fold cross-validation protocol is used. The gold standard positive and negative data sets are randomly divided into five approximately equal subsets. Four sets are used as training data sets to compute the likelihood ratios of the individual evidence. The remaining set is used as the test data set to count the number of predicted true positives (TP) and false positives (FP). This process is done in turn five times, and finally the number of TPs and FPs against different likelihood ratios across five test data sets are summed to calculate the TP/FP ratio and the sensitivity (TP/T) and specificity [1 − (FP/F)] for the ROC curve.

2.8 Ethical considerations

Written consent was obtained from all participants, with explicit consent given for linking to healthcare-use databases, and for the storage and future use of blood assays. Institutional review board approval was initially obtained from Beijing Anzhen Hospital, Capital Medical University

and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China. Approval for the specific analyses presented came from the Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China.

3 Results

3.1 Patients' characteristics

A total of 2686 patients were recruited between February 2007 and August 2009. All patients were followed up until August 2010. Eighty-five factors of different types were recorded. The main clinical, laboratory and operative features of the patients are shown in Table 1. Twenty inflammatory factors of the patients are shown in Table 2. The cohort consisted of middle-aged to older adults (median age, 60.5 years) and 65.7% were men. During a follow-up of one year, 233 events occurred, five patients died, four patients suffered a nonfatal myocardial infarction, four patients underwent revascularization and 220 patients were readmitted for angina pectoris.

3.2 Correlation of various factors and cardiovascular events

Using Spearman's correlation analysis, we found that there was a significant correlation between cardiovascular events and 13 factors (OPG, PIGF, Cathepsin S, GM-CSF, IP-10, CXCL-16, MIP-1b, LDL-C, HDL-C, BMI, morphology of coronary lesions, creatinine, and high blood pressure grade) (Table 3). In theory, LR (f) > 1 indicates that factor f has the ability to identify the risk of events, and patients with a higher LR (f) value of clinical indicator f may be more likely to suffer MACEs [Equations (5) and (6)]. From Table 3, it is evident that all these factors have the ability to identify the risk of MACEs, but single factor reliability was not strong; the highest LR (f) was GM-CSF, which was only 2.28.

The combined likelihood ratio was used to identify the risk of cardiovascular events.

Because Oprior is a constant, Opost is proportional to LR. Therefore, LR can theoretically measure the reliability of cardiovascular events [Equation (1)]. To test this speculation,

Table 1. Baseline characteristics of patients.

Characteristic	Overall cohort (n = 2686)
Age, yrs	60.5 (52.7,68.1)
Male sex	65.7%
Hypertension	65.1%
DM	23.0%
Systolic blood pressure, mmHg	130 (120, 140)
Diastolic blood pressure, mmHg	80 (70, 84)
White blood count × 10^9/L	6.30 (5.38, 7.50)
Platelet count × 10^9/L	203.00 (171.00, 237.00)
Percentage area stenosis	60.75 ± 14.27
Percentage diameter stenosis	38.87 (30.78, 46.23)
Eccentric lesion, morphology of coronary lesions	27%
Body mass index, kg/m^2	25.68 (23.87,27.34)
CKMB, mmol/L	8.00 (7.00,12.00)
Creatinine, umol/L	81.00 (69.00,97.00)
hs-CRP, mg/L	1.70 (0.70,4.60)
Total cholesterol, mmol/L	4.40 (3.74,5.08)
LDL-C, mmol/L	2.72 (2.16,3.29)
HDL-C, mmol/L	1.01 (0.87,1.18)

Data presented are percentages, mean ± SD or median (IQR). CKMB: creatine kinase isoenzyme; DM: diabetes mellitus; HDL-C: high density lipoprotein cholesterol; hs-CRP: high sensitive C reaction protein; IQR: interquartile range; LDL-C: low density lipoprotein cholesterol.

Table 2. Twenty inflammatory factors.

Variable	Overall cohort (n = 833)
Cathepsin S, pg/mL	9555.12 (7087.12, 13079.42)
Cystatin C, pg/mL	0.96 (0.77, 1.15)
CD40L, CD40 ligand	94.42 (39.44, 198.66)
CXCL16, CXC chemokine ligand 16	7118.30 (5511.13, 8846.24)
GDF-15, growth differentiation factor-15	1012.01 (677.04, 1510.48)
GM-CSF, granulocyte-macrophage colony-stimulating factor	4.49 (1.26, 9.08)
IL-6	139.62 (56.30, 267.54)
IL-10	55.87 (30.29, 92.96)
IP-10	406.80 (228.91, 739.86)
MCP-1	128.22 (72.51, 227.91)
M-CSF	22.25 (10.46, 40.26)
MIF	2125.72 (906.76, 4601.03)
MIP-1b	99.28 (51.32, 185.16)
MMP-9	13787.69 (6682.46, 28337.75)
OPG	3151.86 (1871.36, 6342.98)
PIGF	55.62 (31.32,94.63)
Resistin	1.91 (1.07, 3.40)
Tie-2	1165.31 (703.13, 1813.12)
TIMP-1	3.66 (2.40, 5.27)
CRP	3.80 (1.27, 10.77)

Data are presented as median (IQR). CD40L: CD40 ligand; CRP: C-reactive protein; IL-6: interleukin 6; IL-10: interleukin 10; IP-10: interferon-inducible protein-10; IQR: interquartile range; MCP-1: monocyte chemoattractant protein-1; M-CSF: Macrophage colony stimulation factor; MIF: macrophage migration inhibitory facto; MIP-1b: macrophage inflammatory protein-1b; MMP-9: matrix metalloproteinase 9; OPG: Osteoprotegerin; PIGF: placental growth factor; TIMP-1: tissue inhibitor of matrix metalloproteinase -1.

Table 3. Thirteen factors related to cardiovascular events.

Clinical index	Correlation coefficient	*P* value	Likelihood ratio (max)
OPG	0.13	< 0.01	2.08
PIGF	0.13	< 0.01	1.97
BMI	–0.06	< 0.01	1.47
Creatinine	–0.06	< 0.01	1.53
Cathepsin S	0.1	0.01	1.67
LDL-C	0.05	0.01	1.43
Morphology of lesion	0.06	0.02	1.13
HPB grade	0.04	0.03	1.23
GM-CSF	0.08	0.03	2.28
IP-10	0.08	0.03	1.51
CXCL16	0.07	0.03	1.78
MIP-1β	0.07	0.05	1.8
HDL-C	0.04	0.05	1.43

BMI: body mass index; CXCL16: chemokine ligand 16; GM-CSF: granulocyte-macrophage colony-stimulating factor; HDL-C: high density lipoprotein cholesterol; HPB grade: high blood pressure grade; IP-10: interferon-inducible protein-10; LDL-C: low density lipoprotein cholesterol; LR: ikelihood ratio; MIP-1β: macrophage inflammatory protein-1β; OPG: osteoprotegerin; PIGF: placental growth factor.

during the 5-fold cross-validation, we changed the LR cutoff and plotted the accuracy (Figure 1). We found that the accuracy increased monotonically with the cutoff of likelihood ratio, confirming that the combined likelihood ratio can be used as an appropriate confidence score to the individual likelihood ratios. For instance, if the combined likelihood ratio reached 100, the accuracy can reach 70% (Figure 1).

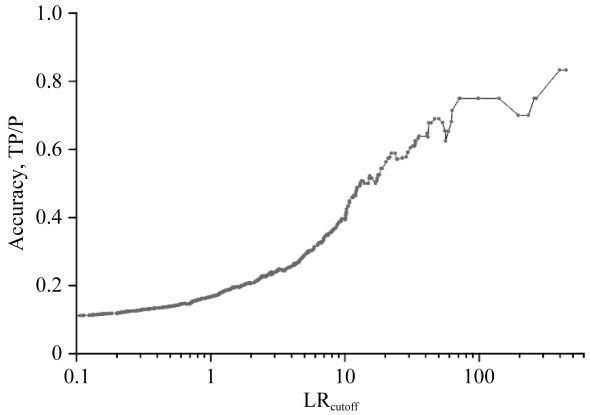

Figure 1. TP/P ratio as a function of likelihood ratio cutoff for the Bayesian Risk Estimation Model. This figure plots the TP / P ratio as a function of likelihood ratio cutoff. The number of true positives and false positives are from the 5-fold cross-validation. **LR: ikelihood ratio.**

3.3 Risk prediction model

To better predict the cardiovascular events, we established a Bayesian Risk Estimation Model using combined LRs and the Single Factor Models, where the confidence of predicting the cardiovascular events is assigned by LR of the confidence bins of individual factors. Unlike other models established using conventional statistical methods, a model established using the Bayesian approach can use real objective data as much as possible. Therefore, although only 833 cases with inflammatory markers were involved in the analysis, this did not affect the robustness of the model. The resulting ROC curves are illustrated in Figure 2. The area under the ROC curve (AUC) is an indicator of the efficacy of the assessment system. Our Bayesian Risk Estimation Model has an area of approximately 0.88, suggesting that it has a high ability to identify the cardiovascular events against the single factors, which have the greatest AUC of 0.65, as shown in Figure 2.

Considering that limited indexes can be collected in the process of clinical diagnosis, we established a Simplified Model by integrating 26 factors with the highest AUC: CD40L, CKMB, CXCL16, Cathepsin S, Cystatin C, GM-CSF, HDL-C, IL-6, IP-10, LDL-C, MIP-1b, OPG, PIGF, TC, TG, hs-CRP, BMI, diastolic blood pressure, systolic blood pressure, white blood cell count, PLT count, morphology of coronary lesions, creatinine, high blood pressure grade, percentage diameter stenosis, and percentage area stenosis (Figure 2). This model has an area of approximately 0.85 (Figure 2), suggesting that it also has a higher ability to identify the cardiovascular events than single factors.

4 Discussion

Classical risk factors for CHD have been identified from the Framingham study and include age, gender, tobacco use status, blood pressure levels, and blood cholesterol levels.[8] A number of similar formulations of absolute CHD risk have also been proposed in a variety of settings where cohort studies were conducted to evaluate the usefulness of absolute CHD risk scores in predicting CHD events.[9–12] However, all of these studies examined CHD risk in the long-term, and cannot predict cardiovascular events in the short-term.[16] There is a large body of research suggesting that some inflammatory factors may indicate the short-term risk of cardiovascular events.[7,17]

We examined 20 inflammatory factors associated with CHD in patients with mild to moderate lesions to identify the high-risk group early. We found 13 factors associated

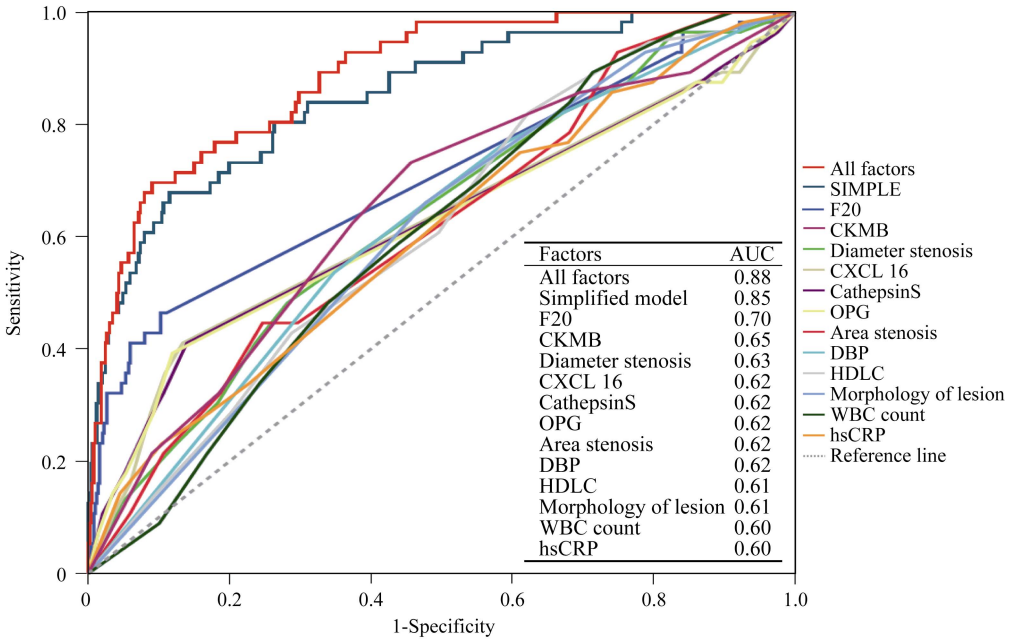

Figure 2. ROC curves for various assessment models using 5-fold cross-validation against golden standard data sets. Each point on the ROC curves of various assessment models corresponds to sensitivity and specificity against a particular likelihood ratio cutoff. The names of the different assessment models corresponding to the curves are shown in the legend. Different colors are used to distinguish the curves for different models. The area under the curve is shown. Sensitivity and specificity were computed during 5-fold cross-validation. SPSS software was used to smooth the curves. AUC: area under the ROC curve; CKMB: creatine kinase isoenzyme; CXCL16: CXC chemokine ligand 16; DBP: Diastolic blood pressure; F20: 20 factors; HDL-C: high density lipoprotein cholesterol; hs-CRP: high sensitive C reaction protein; OPG: osteoprotegerin; ROC: receiver operating characteristic; WBC: white blood cell.

with MACEs, most of which are inflammatory factors, including OPG, PIGF, Cathepsin S, GM-CSF, IP-10, CXCL-16, and MIP-1β. Some of these factors have been detailed elsewhere,[18–20] and our findings are consistent with many other studies.[21]

We found that the morphology of the coronary lesion and hypertension grade were associated with MACEs, which is consistent with current knowledge. This being that an eccentric lesion and the higher the grade of hypertension may mean that the patient is more likely to suffer MACEs. We also found that BMI, LDL-C, HDL-C, and creatinine did not seem to be associated with short-term MACEs. For example, simply because a person has a high BMI does not mean that they will be more likely to experience an acute cardiovascular event in the coming year. Another study of a large cohort of patients hospitalized with an incident of myocardial infarction found that in-hospital mortality was inversely related to the number of traditional coronary heart disease risk factors.[22] Similar results have been observed in smaller cohorts.[23] Even so, because of the complexities of CHD pathogenesis, there is no single factor available to estimate absolute risk of future cardiovascular events.

In this study, we measured the reliability of individual factors using LR and then naïve Bayesian networks to combine the individual factors for a confidence assessment. The Bayesian Model and the Simplified Model had higher sensitivity and better specificity to predict true relationships between multiple factors and cardiovascular events by cross-validation compared with single factors, which will be beneficial to clinical practice. According to an individual person's differences, we can quantitatively calculate the odds of that person having a cardiovascular event within the coming year. For example, using Figure 1, if the combined likelihood ratio of a person is 19, the probability of a CHD event happening within one year is 55%. And if the combined likelihood ratio reached 100, the probability of a CHD event happening within one year is 70%.

Patients at the highest level of CHD risk will benefit substantially if they are identified early and treated appropriately. This Bayesian Model can provide information about the short-term risk of a cardiovascular event for patients with intermediate coronary artery lesions in a quantifiable manner, and allow for the avoidance of insufficient attention, and remind them about changing their unhealthy lifestyle behaviors and to implement coronary secondary prevention as early as possible. Additionally, the Simplified Model was established with the Bayesian approach, which has been shown in other domains to be data efficient and to address some of the limitations of conventional statistical methods, and its indexes are readily available. This will make clinical

practice more efficient and effective.

This study had some limitations. First, since there is no ideal method to predict short-term cardiovascular events, this model is lacking a gold standard by which the advantages and disadvantages can be compared. Second, many inflammatory factors are involved, making it difficult for the model to be used for routine clinical purposes. However, it is beneficial and useful for certain patients. Last, further clinical trials are necessary to determine whether the model is beneficial and applicable to more patients.

In conclusions, our model can be used to assess the short-term risk of individual CHD events and will therefore allow more accurate targeting of preventive therapy.

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