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A clinical model to identify patients with high-risk plaque by coronary computed tomography angiography☆

Nobuo Tomizawa [a,*], Kodai Yamamoto [a], Yayoi Hayakawa [a], Shinichi Inoh [a], Takeshi Nojo [a], Sunao Nakamura [b]

[a] Department of Radiology, New Tokyo Hospital, 1271 Wanagaya, Matsudo, Chiba 270-2232, Japan
[b] Department of Cardiology, New Tokyo Hospital, 1271 Wanagaya, Matsudo, Chiba 270-2232, Japan

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ABSTRACT

Objectives: Current clinical models predict the pre-test probability of obstructive coronary artery disease, but these models do not predict the presence of high-risk plaques. Thus the objective of this study was to propose a model to predict high-risk plaque assessed by coronary computed tomography (CT) angiography.
Methods: This study was a retrospective cross-sectional study. A clinical model was derived from 2392 patients and verified by 733 patients who underwent coronary CT suspected of coronary artery disease. High-risk plaque was defined as a plaque with positive remodeling (remodeling index > 1.1), low attenuation (<30 Hounsfield units) and napkin-ring sign. The risk score was calculated from the following 6 variables with a maximum of 24 points: age, sex, hemoglobin A1c, systolic blood pressure, high-density lipoprotein and smoking status.
Results: The proportion of patients with high-risk plaque was 11% and 17% in the derivation and validation cohort, respectively. The area under the receiver operation characteristic curve was 0.71 (95% confidence interval (CI): 0.68 to 0.74) in the derivation cohort and 0.75 (95% CI: 0.70 to 0.79) in the validation cohort. The frequency of high-risk plaques was 4% in the low-risk group (≤8 points) while it was 53% in the high-risk group (≥17 points) of the derivation cohort.
Conclusions: We propose a scoring system to detect high-risk plaque assessed by coronary CT. Patients in the high-risk group have a high prevalence of high-risk plaque and might benefit from lipid lowering therapy.

1. Introduction

Acute coronary syndrome occurs as a result from rupture in the protective fibrous cap of a plaque [1]. Pathological studies have shown that thin-cap fibroatheroma (TCFA) is related to plaque rupture [2]. Advances in computed tomography (CT) allowed the depiction of coronary plaques. Plaques with positive remodeling, low attenuation and napkin-ring sign are known to be related to TCFA and thus mentioned as high-risk plaques [3–5]. High-risk plaques detected by CT could be used for the prediction of future acute coronary syndrome [3,5,6] and transient no-reflow syndrome during coronary intervention [7–9].

Scoring systems such as Duke [10], Diamond and Forrester [11] and Morise [12] methods have been proposed to estimate the pre-test probability of anatomically significant stenosis. Recently, Yang et al. proposed a clinical model to predict high-risk coronary anatomy which was defined as left main diameter stenosis ≥50%, 3-vessel disease with diameter stenosis ≥70% or 2-vessel disease involving the proximal left anterior descending artery [13]. However, there are no scoring system to predict the presence of high-risk plaques assessed by CT. A previous study showed that a significant proportion of patients with low to intermediate Framingham risk score had coronary atherosclerosis [14]. Therefore, the purpose of the present study was to develop and verify a clinical model to identify the presence of high-risk plaques assessed by coronary CT.

2. Materials and methods

This retrospective study was approved by the local ethics committee, and the requirement for informed consent to participate in this study was waived.

2.1. Patients

The records of 3769 consecutive patients without renal dysfunction (effective glomerular filtration rate < 40 ml/min) and history of coronary intervention who underwent coronary CT angiography from January 2014 to December 2015 were retrospectively examined. These patients were suspected of coronary artery disease with chest symptoms and/or multiple risk factors and/or abnormal electrocardiogram or treadmill tests. Laboratory data was missing in 636 patients and image quality was poor for diagnosis in 8 patients. Therefore, the final study group included 3125 patients. The first 2392 patients and the last 733 patients were used as a derivation and validation cohort, respectively.

The following conventional cardiovascular risk factors were assessed: 1) diabetes mellitus (hemoglobin A1c (HbA1c) ≥ 6.5% and/or fasting plasma glucose ≥ 126 mg/dl and/or random plasma glucose ≥ 200 mg/dl and/or use of antidiabetic drugs [15]);

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* Corresponding author at: Department of Radiology, New Tokyo Hospital, 1271 Wanagaya, Matsudo City, Chiba, 270-2232, Japan.
E-mail address: tomizawa-tky@umin.ac.jp (N. Tomizawa).

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2) hypertension (blood pressure > 140/90 mmHg and/or use of antihypertensive drugs); 3) dyslipidemia (low-density lipoprotein (LDL) ≥ 140 mg/dl or high-density lipoprotein (HDL) < 40 mg/dl or triglyceride (TG) ≥ 150 mg/dl or need for antilipidemic drugs [16]); 4) smoking (currently or previously); and 5) family history of coronary artery disease.

2.2. CT data acquisition

All patients underwent CT angiography with 64-row CT (Brilliance 64; Philips, Tokyo, Japan). Coronary CT angiography was performed by retrospectively electrocardiogram-gated helical scan because prospective scan was not available in this scanner. The scanning parameters were as follows: detector configuration, 64 × 0.625 mm; tube potential, 120 kVp; tube current-time product, 800–1050 mAs, depending on the body weight; gantry rotation time, 420 ms; and helical pitch, 0.2.

The patients received 21.0 mgI/kg/s of iopamidol 370 mgI/ml (Iopamiron 370; Bayer, Osaka, Japan). Contrast medium was injected for acquisition duration plus 7 s, followed by a 30 ml saline flush. Bolus tracking method was performed to determine the scan timing. The scan started 6 s after the descending aorta reached 100 Hounsfield unit.

Patients with heart rate > 65 beats per minute at the out patient department were told to take an oral β-blocker (20 mg of metoprolol) 1 h prior to CT angiography. If the heart rate was over 65 beats per minute on site, a maximum dose of 12.5 mg of landiolol (Corebeta; Ono Pharmaceutical, Tokyo, Japan) was given intravenously. All patients received 0.3 mg sublingual nitroglycerin (Nitropen; Nippon Kayaku, Tokyo, Japan) before imaging.

For each patient, a senior technologist determined the phase with minimum artifacts at the CT console. Multiple phases were reconstructed when artifacts resisted in the image. The reconstructed slice thickness was 0.67 mm, and the increment was 0.33 mm. Images were reconstructed using a cardiac sharp kernel. For processing, images were transferred to a workstation (Syanpse Vincent; Fuji Medical, Tokyo, Japan).

2.3. Analysis of coronary artery plaque

Atherosclerotic plaque was defined as any clearly discernable structure larger than 1 mm^2 which could be assigned to the coronary artery wall in at least two independent image planes. Remodeling index was obtained by dividing the vessel diameter at the plaque site by the diameter at the reference site. Positive remodeling was reported when the remodeling index was > 1.1. Minimum CT number of the plaque was measured using several circular regions of interest (area of 1 mm^2) at each plaque area. When the minimum CT number was < 30 Hounsfield unit, the plaque was referred to as a low attenuation plaque [3]. Napkin-ring sign was defined as a plaque core with low attenuation surrounded by a rim-like area of higher attenuation not exceeding 130 Hounsfield unit [5]. We assessed all plaques in the coronary arteries and analysis was performed by a per-patient basis. A patient was determined to have a high-risk plaque when all three criteria were fulfilled (Fig. 1).

2.4. Stenosis analysis

Coronary artery diameter stenosis was assessed in the validation cohort. When a patient had either left main stenosis ≥ 50%, 3-vessel disease (≥70%) or 2-vessel disease (≥70%) involving the left anterior descending, the patient was determined to have a high-risk anatomic stenosis [13].

2.5. Statistical analysis

Continuous variables were shown as mean ± standard deviation and categorical variables as number (%) unless otherwise described. The Student's *t*-test was used to compare continuous variables. The Chi square (χ [2]) test and Fisher's exact test were used to compare categorical variables and skewed variables.

All clinical variables which were potentially associated with high-risk plaque were evaluated. Medications were not included to create a model based on clinical history. The variables of age, sex, body weight, diabetes mellitus, hypertension, dyslipidemia, smoking status and family history of coronary artery disease were included for the univariable analysis. We used continuous variables for diabetes mellitus (HbA1c), hypertension (systolic blood pressure) and dyslipidemia (TG, LDL and HDL) to reflect the severity of each disease. Significant variables in the univariable analysis ($p < 0.10$) were included in the multivariable analysis. From a multivariable model, a scoring system was developed by assigning points for each variable using the method demonstrated by the Framingham Risk Score [17]. The receiver operating characteristic (ROC) curve for the score was generated. The area under the curve (AUC) was calculated to evaluate the discrimination ability of the score over the Morise method [12]. The classification performance was tested using an external validation cohort.

The difference in AUC was assessed by the DeLong method [18] using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing) [19]. The remaining statistical analyses were performed using JMP software (version 12.0.0; SAS, Cary, NC). A *p*-value < 0.05 was deemed to indicate significance.

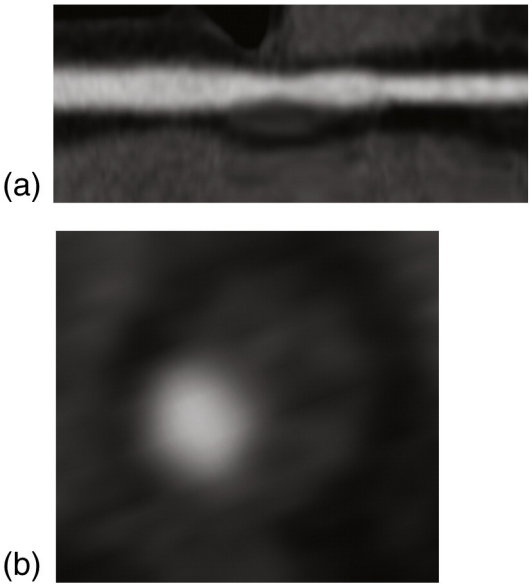

Fig. 1. Stretched (a) and cross-sectional view (b) of a typical high-risk plaque. A plaque was defined as high-risk when low attenuation (<30 Hounsfield unit), positive remodeling (remodeling index > 1.1) and napkin-ring sign were present.

3. Results

A total of 257 patients (11%) in the derivation cohort and 122 patients (17%) in the validation cohort showed high-risk plaque. Patients with high-risk plaque were more often male, older and heavier than patients without high-risk plaque (Table 1). The frequencies of diabetes mellitus, hypertension, dyslipidemia and smoking were higher in patients with high-risk plaque, but the frequency of family history did not show significant difference. Although HbA1c, TG was higher and HDL was lower in patients with high-risk plaque, the LDL value was similar between patients with or without high-risk plaque.

3.1. Derivation cohort

Using univariable analysis, age, sex, body weight, HbA1c, systolic blood pressure, TG, HDL and smoking status were associated with the presence of high-risk plaque (Table 2) and these parameters were initial candidates for the multivariable model. Body weight and TG were no longer significant in the multivariable analysis (Table 3). Therefore, points for age, sex, HbA1c, systolic blood pressure, HDL and smoking status were assigned based on the regression coefficient (Table 4). We divided the patients into three groups by the score: low-risk group (≤8 points), intermediate-risk group (9–16 points) and high-risk group (≥17 points). The frequency of patients with high-risk plaque in the high-risk group was 31% while it was 3% in the low-risk group (Fig. 2).

The proposed model to predict the presence of high-risk plaque showed an AUC of 0.71 which was significantly higher ($p < 0.01$) than the AUC of 0.53 using the Morise score (Fig. 3).

3.2. Validation cohort

Using a non-overlapping validation cohort, the proposed model showed an AUC of 0.75 (Fig. 4). The frequency of patients with high-risk plaque was 4% in the low-risk group, while it was 53% in the high-risk group (Fig. 2). The number of patients with high-risk stenosis were 67 (9%) in total; 1 patient (0.7%) in the low-risk group, 52 patients (10%) in the intermediate-risk group and 14 patients (27%) in the high-risk group.