Postprint: A Study on Risk Factors for Calcification in Coronary Artery Lesions of Patients with Coronary Artery Disease Based on Intravascular Ultrasound

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Abstract

Background Percutaneous coronary intervention is an effective therapeutic modality in cardiology for the treatment of coronary artery disease. During coronary intervention procedures, various complex lesions are encountered, among which calcification of target vessels increases procedural difficulty, immediate surgical risks, and the occurrence of both short-term and long-term adverse cardiovascular events. Early identification and assessment of calcified lesions are of significant importance for improving procedural success rates, reducing procedure-related complications, decreasing cardiovascular events, and improving prognosis. Objective To explore the risk factors for calcification in target lesion vessels of patients with coronary artery disease, and to provide a basis for early prevention, early detection, and interventional treatment of coronary artery calcification. Methods: We retrospectively collected 353 patients who presented to the Department of Cardiology of Shaanxi Provincial People's Hospital with chest pain or chest tightness symptoms from January 2021 to December 2021 and were diagnosed with coronary artery disease by coronary angiography, of which 196 met the inclusion and exclusion criteria. All included patients underwent intravascular ultrasound examination. By analyzing the intravascular ultrasound imaging data of the diseased vessels, patients were divided into a non-calcified group (calcification index = 0, n = 73) and a calcified group (n = 123) based on whether calcification occurred in the lesion vessel. The calcified group was further divided into a low calcification index group (calcification index 0.0001–0.2166, n = 62) and a high calcification index group (calcification index > 0.2166, n = 61) based on the median calcification index (M = 0.2166). Multivariate Logistic regression analysis was used to analyze the risk factors for coronary calcification. Results

There were significant differences in general clinical data among the three groups in terms of age, sex composition, prevalence of hypertension, prevalence of diabetes, smoking history, and proportion of thyroid disease ($P < 0.05$). Laboratory indicators showed significant differences among the three groups in total protein, alkaline phosphatase, gamma-glutamyl transferase, albumin-to-globulin ratio, triglyceride-glucose index, triglycerides, serum phosphorus, and glycated hemoglobin ($P < 0.05$). Multivariate ordinal Logistic regression analysis results: age ($P = 0.001$, OR = 1.07, 95% CI: 0.029–0.107), alkaline phosphatase ($P = 0.003$, OR = 1.028, 95% CI: 0.009–0.046), triglycerides ($P = 0.015$, OR = 3.174, 95% CI: 0.299–2.081), and serum phosphorus ($P = 0.006$, OR = 13.681, 95% CI: 0.747–4.486) were independent risk factors for coronary artery calcification. Bivariate correlation (Spearman) analysis: age, alkaline phosphatase, triglyceride levels, and serum phosphorus showed significant positive correlations with the coronary calcification index ($P < 0.05$). Conclusion Age, alkaline phosphatase, triglycerides, and serum phosphorus are independent risk factors for coronary artery calcification.

Full Text

Analysis of Risk Factors for Coronary Artery Calcification in Lesions of Patients with Coronary Heart Disease Based on Intravascular Ultrasound

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Abstract

Background: Percutaneous coronary intervention (PCI) is an effective treatment for coronary heart disease. However, the procedure faces various complex lesions, among which calcification of target vessels increases procedural difficulty, immediate operative risk, and the incidence of short-term and long-term cardiovascular adverse events. Early identification and evaluation of calcified lesions are crucial for improving surgical success rates, reducing complications, decreasing cardiovascular events, and improving prognosis.

Objective: To explore the risk factors for calcification of target lesions in patients with coronary heart disease and provide evidence for early prevention, detection, and interventional therapy of coronary artery calcification.

Methods: We retrospectively collected data from 353 patients who presented with chest pain or discomfort at the Department of Cardiology, Shaanxi Provin-

cial People's Hospital between January and December 2021 and were diagnosed with coronary heart disease via coronary angiography. Of these, 196 patients met the inclusion criteria. All participants underwent intravascular ultrasound (IVUS) examination. Based on analysis of IVUS imaging data, patients were divided into a non-calcification group (calcification index = 0, n = 73) and a calcification group (n = 123). The calcification group was further divided into a low calcification index group (calcification index 0.0001–0.2166, n = 62) and a high calcification index group (calcification index > 0.2166, n = 61) based on the median calcification index (M = 0.2166). Multivariate logistic regression analysis was used to identify risk factors for coronary calcification.

Results: Significant differences were observed among the three groups in age, sex distribution, prevalence of hypertension, diabetes, smoking history, and thyroid disease ($P < 0.05$). Laboratory indicators also showed significant differences in total protein, alkaline phosphatase, γ-glutamyltransferase, albumin/globulin ratio, triglyceride-glucose index, triglycerides, serum phosphorus, and glycosylated hemoglobin ($P < 0.05$). Multivariate ordered logistic regression analysis revealed that age ($P = 0.001$, OR = 1.07, 95% CI: 0.029–0.107), alkaline phosphatase ($P = 0.003$, OR = 1.028, 95% CI: 0.009–0.046), triglycerides ($P = 0.015$, OR = 3.174, 95% CI: 0.299–2.081), and serum phosphorus ($P = 0.006$, OR = 13.681, 95% CI: 0.747–4.486) were independent risk factors for coronary artery calcification. Bivariate correlation (Spearman) analysis demonstrated significant positive correlations between age, alkaline phosphatase, triglyceride levels, serum phosphorus, and the coronary calcification index ($P < 0.05$).

Conclusion: Age, alkaline phosphatase, triglycerides, and serum phosphorus are independent risk factors for coronary artery calcification.

Keywords: Coronary atherosclerotic heart disease; Coronary artery calcification; Risk factors

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Coronary heart disease is a chronic, progressive cardiovascular disease caused by multiple risk factors, characterized by coronary atherosclerotic plaque formation, luminal stenosis, and myocardial ischemia. With continuous development of percutaneous coronary intervention (PCI) technology, PCI now faces increasingly complex lesions. Among these, coronary artery calcification (CAC) increases procedural difficulty, surgical risk, economic burden, and postoperative adverse cardiovascular events [1]. Early identification and assessment of risk factors and severity of calcified lesions are essential for selecting appropriate treatment strategies, improving PCI success rates, reducing complications, and improving short-term and long-term prognosis [1]. CAC represents the pathological deposition of calcium and phosphorus within coronary atherosclerotic plaques and serves as a specific marker of coronary atherosclerosis and a predictor of adverse cardiovascular events [2]. Previous studies have identified dyslipidemia, advanced age, sex differences, hypertension, diabetes, chronic kidney disease, smoking, sleep disorders, medications, abnormal uric acid levels,

and emotional factors as risk factors for CAC [3–6]. With rapid technological advancement, intravascular ultrasound (IVUS) has become the "gold standard" for detecting CAC in interventional therapy, with a sensitivity of 90–100% and specificity of 99–100% [7, 8]. IVUS imaging analysis enables accurate determination of calcification location, extent, and length, allowing for quantitative assessment of calcified plaques and providing imaging support for successful interventions. Current research findings on CAC and its risk factors remain inconsistent, and its pathogenesis requires further elucidation. This study collected data on risk factors, clinical characteristics, and laboratory parameters from coronary heart disease patients undergoing coronary angiography (CAG) and IVUS to investigate the relationship between multiple risk factors and CAC.

1.1 Study Subjects

This study retrospectively collected data from 353 patients who presented with chest pain or discomfort and were diagnosed with coronary heart disease via CAG at Shaanxi Provincial People's Hospital between January and December 2021. Of these, 196 patients met the inclusion criteria. All participants underwent IVUS examination. Based on analysis of IVUS imaging data, patients were divided into a non-calcification group (calcification index = 0, n = 73) and a calcification group (n = 123). The calcification group was further subdivided into a low calcification index group (calcification index 0.0001–0.2166, n = 62) and a high calcification index group (calcification index > 0.2166, n = 61) based on the median calcification index (M = 0.2166).

1.1.1 Inclusion Criteria

1. Age > 18 years
2. Patients admitted with chest pain or discomfort who were diagnosed with coronary heart disease by CAG
3. IVUS examination performed on lesions with $ $75% vessel stenosis
4. Complete clinical and imaging data available
5. Provided informed consent for CAG and IVUS examinations

1.1.2 Exclusion Criteria

1. Lesions with <75% stenosis, acute occlusion, or chronic total occlusion on CAG
2. Prior PCI history
3. Patients with hypertensive heart disease, cor pulmonale, dilated cardiomyopathy, or hypertrophic cardiomyopathy
4. Patients with severe arrhythmias causing clinical symptoms or hemodynamic instability
5. Patients with severe liver disease, chronic kidney disease, or serious complications of the hematopoietic system

1.2.2 Laboratory Examinations We collected routine biochemical indicators including complete blood count (red blood cells, white blood cells, platelets), liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase), total protein, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood urea nitrogen, creatinine, serum calcium, serum phosphorus, fasting glucose, glycosylated hemoglobin, and coagulation parameters. All blood samples were collected preoperatively and analyzed by our hospital's biochemistry laboratory.

1.2.3 Intravascular Ultrasound Examination Following coronary angiography, two experienced interventional cardiologists selected lesions with >75% coronary stenosis for IVUS examination. After intracoronary administration of 200 g nitroglycerin, an Opti Cross™ 40MHz Coronary Imaging catheter (Boston Scientific, 3.0F × 135 cm) was used with an automatic pullback device (Boston Scientific). The ultrasound catheter was advanced distal to the lesion, at least 10 mm beyond the target lesion, and automatically withdrawn at 0.5 mm/s. Images were stored on computer hard drives and analyzed using RadiAnt DICOM Viewer and Boston Scientific Image Viewer software to assess lesion length, presence of calcification, calcification type (superficial, deep, mixed, nodular, spotty), calcification length, and calcification angle. The calcification index was calculated as: (total calcium length / lesion length) × (maximum calcium arc / 360°). This method for evaluating total calcification burden has been shown to correlate highly with histopathological assessment of calcification [9] and is currently recognized as the optimal imaging approach for evaluating CAC lesions [10].

1.3 Statistical Methods Data were analyzed using SPSS 26.0 software. Normally distributed continuous variables are presented as mean ± standard deviation (SD) and compared using ANOVA with LSD test for pairwise comparisons. Non-normally distributed continuous variables are presented as median (P25, P75) and compared using nonparametric rank-sum tests. Categorical variables are described as frequencies and percentages. Factors showing statistical significance were included in multivariate logistic regression models. Spearman correlation analysis was used to examine correlations between CAC and various factors. Multivariate logistic regression analysis was used to assess relationships between risk factors and coronary artery calcification. $P < 0.05$ was considered statistically significant.

2. Results

2.1 Comparison of General Clinical Data Among Three Groups Significant differences were observed among the three groups in age, sex distribution, prevalence of hypertension, diabetes, smoking history, and thyroid disease ($P < 0.05$). Other parameters including body mass index, admission blood pressure, hyperlipidemia prevalence, and chronic lung disease showed no significant

differences ($P > 0.05$). The high calcification index group was older than both the low calcification index and non-calcification groups ($P < 0.05$). The low calcification index group was older than the non-calcification group, though this difference was not statistically significant. The high calcification index group had a higher prevalence of hypertension than the low calcification index and non-calcification groups. The low calcification index group had a higher prevalence of diabetes than the high calcification index and non-calcification groups .

2.2 Comparison of Laboratory Data Among Three Groups Significant differences were found among the three groups in total protein, alkaline phosphatase, γ-glutamyltransferase, albumin/globulin ratio, triglyceride-glucose index, triglycerides, serum phosphorus, and glycosylated hemoglobin ($P < 0.05$). Other parameters including white blood cell count, red blood cell count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, albumin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein A, apolipoprotein B, uric acid, urea nitrogen, creatinine, glucose, and fibrinogen showed no significant differences ($P > 0.05$) .

2.3 Comparison of IVUS Parameters Among Three Groups Differences were observed in the distribution of lesion vessels, which were primarily the left anterior descending artery, right coronary artery, and left circumflex artery. No significant differences were found among the three groups in lesion vessel distribution, luminal cross-sectional area, external elastic membrane cross-sectional area, or lesion length ($P > 0.05$). The minimum lumen area was smaller in the high calcification index group compared to the low calcification index and non-calcification groups. Plaque cross-sectional area was significantly larger in the low calcification index group compared to the non-calcification and high calcification index groups .

2.4 Risk Factor Analysis for CAC Using the degree of calcification on IVUS as the dependent variable and age, total protein, alkaline phosphatase, γ-glutamyltransferase, triglycerides, triglyceride-glucose index, glycosylated hemoglobin, serum phosphorus, diabetes prevalence, and hypertension prevalence as independent variables, multivariate ordered logistic regression analysis revealed that after adjusting for other factors, age, triglyceride levels, alkaline phosphatase, and serum phosphorus were independent risk factors for CAC .

3. Discussion

3.1 Coronary artery calcification represents both a regulated, bone formation-like active process and a pathological change involving calcium salt deposition in the coronary arterial wall. CAC may impede coronary re-endothelialization, ultimately leading to adverse outcomes [11]. Previous studies have shown that CAC

increases with age, with a prevalence of 50% in middle-aged populations and 80% in elderly populations [12]. Our study yielded consistent results, demonstrating that both the incidence and severity of CAC increase with age. Currently, CAC is recognized not only as a pathological manifestation of calcium and phosphorus deposition within coronary atherosclerotic plaques but also as a specific marker of coronary atherosclerosis and a predictor of adverse cardiovascular events [2]. Our study found significant differences among the three groups in age, sex distribution, hypertension prevalence, diabetes prevalence, smoking history, thyroid disease prevalence, total protein, alkaline phosphatase, γ-glutamyltransferase, albumin/globulin ratio, triglyceride-glucose index, triglycerides, serum phosphorus, and glycosylated hemoglobin ($P < 0.05$). Using the degree of calcification on IVUS as the dependent variable and age, total protein, alkaline phosphatase, γ-glutamyltransferase, triglycerides, triglyceride-glucose index, glycosylated hemoglobin, serum phosphorus, diabetes prevalence, and hypertension prevalence as independent variables, multivariate ordered logistic regression analysis demonstrated that after adjusting for other factors, age, triglyceride levels, alkaline phosphatase, and serum phosphorus were independent risk factors for CAC. Bivariate correlation (Spearman) analysis revealed significant positive correlations between age ($r = 0.335$), alkaline phosphatase ($r = 0.176$), triglyceride levels ($r = 0.156$), serum phosphorus ($r = 0.196$), and the coronary calcification index ($P < 0.05$).

3.2 Alkaline phosphatase is primarily found in the liver and bone, with smaller amounts in the intestine, placenta, and kidneys. It has been confirmed to play a role in metabolism and serves as a biomarker of vascular calcification [13, 14]. Furthermore, elevated alkaline phosphatase levels have been associated with increased incidence and mortality of cardiovascular events in various populations [15, 16], possibly mediated by alkaline phosphatase promoting the development and progression of coronary artery calcification. Inorganic pyrophosphate (PPi) is one of the most potent inhibitors of passive calcium-phosphorus deposition [17]. The biochemical role of PPi is to inhibit calcium and phosphorus aggregation [18], hydroxyapatite crystal growth, and crystal aggregation. In vivo, PPi is hydrolyzed to inorganic phosphorus by serum alkaline phosphatase. Therefore, increased alkaline phosphatase activity leads to an imbalance between inorganic phosphorus and pyrophosphate, promoting ectopic calcification. Consequently, pathologically elevated alkaline phosphatase activity is associated with vascular calcification, which contributes to accelerated atherosclerosis and cardiovascular events [19]. Ren et al. demonstrated that alkaline phosphatase may be a potential biomarker for predicting calcification and plaque vulnerability, with plasma alkaline phosphatase levels being an independent predictor of coronary spotty calcification incidence [20], consistent with our findings.

3.3 Our results showed a positive correlation between CAC severity and serum phosphorus concentration, with serum phosphorus levels being highest in the high calcification index group, followed by the low calcification index group, and

lowest in the non-calcification group ($P < 0.05$). Regression analysis identified serum phosphorus level as an independent risk factor for coronary calcification. Phosphorus plays crucial roles in various biological processes including energy metabolism, cell signaling, nucleic acid synthesis, and cell membrane stability. Park et al. found that in subjects with normal renal function, higher serum phosphorus concentrations, even within the normal range, may be associated with greater CAC [21]. Schlieper et al. reported that increased intracellular phosphorus concentration can stimulate transformation of human vascular smooth muscle cells toward an osteoblastic phenotype [22]. Kwak et al. found that serum phosphorus was significantly associated with CAC scores, with high serum phosphorus levels related to CAC prevalence, particularly CAC scores >100 [23]. Park et al. examined the relationship between serum phosphorus levels and CAC measured by electron beam computed tomography, identifying serum phosphorus >3.6 mg/dL (1.16 mmol/L) as a risk factor for CAC on multivariate analysis [24].

3.4 Our study demonstrated a positive correlation between CAC severity and triglyceride concentration, with serum triglyceride levels being highest in the low calcification index group, followed by the high calcification index group, and lowest in the non-calcification group ($P < 0.05$). Dyslipidemia is closely associated with atherosclerotic cardiovascular disease, with hypertriglyceridemia being the most common lipid metabolism abnormality. In 2008, Pollin et al. found that reducing triglyceride-rich lipoproteins could decrease coronary calcification in Lancaster Amish populations [25]. NATARAJAN et al. reported that lower plasma triglyceride levels were associated with reduced coronary calcification burden [26]. Previous studies have shown that elevated non-fasting triglyceride levels are associated with increased risk of myocardial infarction and mortality, representing an independent cardiovascular risk factor [27], while lower plasma triglyceride levels are associated with reduced risk of coronary heart disease and coronary calcification [25, 28, 29]. Recent studies have demonstrated that elevated triglyceride-glucose index is an independent risk factor for CAD and CAC [30, 31]. Fan et al. found that a novel index combining triglycerides, total cholesterol, and body weight was an independent risk factor for CAD, CAC, and CAD with coexisting CAC [32], consistent with our conclusions.

In summary, this study demonstrates that elderly patients with coronary heart disease have a high risk of coronary artery calcification. Independent risk factors for CAC include age, alkaline phosphatase, triglyceride levels, and serum phosphorus levels, all of which show significant positive correlations with the coronary calcification index. These findings have important clinical implications for diagnosis and treatment of CAC in coronary heart disease patients. However, this study is limited by its single-center, retrospective design and small sample size, which may introduce bias. Further research is needed to confirm these findings and better guide clinical practice.

Author Contributions: Ren Yuanyuan conceived the research, collected and

organized case data, and wrote the initial draft; Jiang Hongying collected and organized case data; Wang Yiyang revised the manuscript; Chen Liang, Zhao Hui, and Liang Chenyuan were responsible for patient management and data provision; Cheng Gong supervised quality control and revision and took overall responsibility for the article; all authors approved the final manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.