International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

Predicting the Degree of Coronary Artery Stenosis Through Retinal Vascular Characteristics and Minimal Clinical Information

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Purpose: To describe the correlative relationship between fundus vascular characteristics and the severity of coronary artery stenosis.

Patients and Methods: A total of 1447 patients scheduled for hospitalization at Beijing Anzhen Hospital Union Hospital for coronary angiography to assess coronary artery conditions between February 2022 and December 2022 were selected. Of these, 1418 cases were ultimately obtained, with 29 cases excluded due to failure to complete coronary angiography or fundus photography. Severity of coronary artery stenosis was assessed using Gensini score. Fundus images were obtained via non-dilated fundus photography, and retinal arteriovenous diameters, arteriovenous ratios, curvatures, and dimensions were subsequently measured automatically using a computer program.

Results: Pearson's correlation coefficients between the Gensini Score and fundus vascular characteristics were found to be as follows: The diameters of the superior temporal artery (−0.08), The diameters of the superior temporal vein (−0.03), the arteriovenous diameter ratio (−0.10), the retinal arterial dimension (−0.09), the retinal vein dimension (−0.06), the retinal arterial curvature (−0.06), the retinal vein curvature (−0.01). The area under the curve (AUC) for logistic regression modeling with the Gensini Score binarized (dichotomized into two categories based on a cutoff of 4 points) as the dependent variable and fundus vascular characteristics as the independent variable was 0.59 ± 0.05 (95% CI). The AUC for logistic regression modeling with the combination of fundus vascular characteristics and clinical information (sex, age, height, weight, smoking history, creatinine, total cholesterol, fasting blood glucose) yielded an AUC of 0.71 ± 0.07 (95% CI).

Conclusion: Coronary stenosis is inversely correlated with fundus vascular characteristics. The combination of fundus vascular characteristics with a limited amount of clinical data (sex, age, height, weight, smoking history, creatinine, total cholesterol, fasting blood glucose) may serve as a non-invasive tool for predicting the presence or absence of severe stenosis in coronary arteries.

Keywords: coronary artery stenosis, Gensini score, fundus images, fundus photography

Introduction

As indicated by data from the World Health Organization (WHO), cardiovascular diseases (CVDs) represent the leading cause of mortality globally.[1] The most common type of CVD is coronary heart disease(CAD). Approximately 50% of mortality from CVD is attributed to sudden cardiac death, which frequently represents the initial presentation of CVD in the United States and other developed countries.[2]

Therefore, the timely detection of CAD and early intervention are of paramount importance. The primary screening methods currently employed are coronary angiography or coronary CTA, both of which entail radiation hazards, are costly, and are time-consuming.[3]

The retinal vasculature is considered to be part of the systemic vascular system. Fundus images can be obtained rapidly and accurately through fundus photography. Several studies have corroborated that deep learning network

Received: 17 November 2024
Accepted: 29 January 2025
Published: 3 February 2025

modelling of fundus images can accurately predict risk factors for coronary heart disease-,[4–8] coronary heart disease risk,[9] and even the degree of coronary artery stenosis.[10,11] It has also been reported that the diameters and ratios of the fundus vasculature can only predict the risk of coronary heart disease in females, and do not have any predictive value for the risk of coronary heart disease in males. The fundus vessels belong to the microvascular system, whereas the coronary arteries belong to the macrovascular system. Risk factors are not identical between the two.[12,13] As the same time the deep learning network model is not interpretable, therefore the evidence is insufficient to determine whether changes in fundus vascular characteristics (retinal arteriolar and venous diameters, arteriolar-vein ratios, curvature, and dimensions) are correlated with coronary artery disease. The objective of this study is to investigate the potential of fundus vascular characteristics as predictors of coronary heart disease and coronary artery stenosis.

Materials and Methods

Study Population and Data Collection

A total of 1447 patients scheduled for hospitalization at Beijing Anzhen Hospital Union Hospital for coronary angiography to assess coronary artery conditions between February 2022 and December 2022 were selected. Of these, 1418 cases were ultimately obtained, with 29 cases excluded due to failure to complete coronary angiography or fundus photography. Patients who have undergone coronary artery bypass grafting surgery or coronary artery stenting, as well as those who are unable to complete retinal photography due to missing eyes or traumatic blindness, were excluded from the study. This study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Beijing Anzhen Hospital. All participants were required to sign an informed consent form prior to participation in this study.

Fundus Image Acquisition and Measurement

All participants underwent digital retinal photography using the digital camera (Topcon Medical Japan Co., Ltd. Tokyo, Japan) at an angle of 45 degrees, with the macula positioned at the center of the image and without mydriasis.[14] Subsequently, the image is automatically measured by an artificial intelligence platform developed by Airdoc (Beijing Airdoc Technology Co., Ltd., Beijing, China).[15] The arteriovenous coarse segmentation model in this AI retinal vascular measurement and analysis system constructs a semantic segmentation model of the arteriovenous veins of the fundus retinas based on iterative semi-supervised learning, and the detected localization model of the fundus disc is based on YOLO v3; The number of pixels intersecting the plumb line of the arteriovenous vessels with the vessels is calculated to obtain the diameters of the arteriovenous veins. The mean error of the measurement results of this model from the gold standard was 0.031, and the standard deviation of the error was 0.0103. The diameters of the superior temporal artery (DSTA) and superior temporal vein (DSTV), the arteriovenous diameter ratio (AVR), the retinal arterial dimension (RAD), the retinal vein dimension (RVD), the retinal arterial curvature (RAC) and the retinal vein curvature (RVC) of the bilateral fundus are obtained, respectively.[16]

Assessment of CAD

Coronary angiography was performed in accordance with the current standard operating procedure, utilizing the Seldinger method to puncture the radial or femoral artery.[17] The Gensini scores were calculated by a fixed group of two full-time physicians, and the Gensini scoring criteria were the same as those reported in the literature.[18]

Statistical Methods

The data pertaining to sex and smoking habits were categorical, whereas the remaining data were quantitative and expressed as mean ± standard deviation (SD). All the data exhibited a normal distribution. The chi-square test was employed to assess differences between groups for categorical data, while the *t*-test was utilized to evaluate differences between groups for quantitative data. Firstly, the Gensini score was employed as continuous dependent data, and the fundus vascular index was utilized as continuous independent data, for the purpose of performing a person correlation analysis. While the weak linear relationship between continuous Gensini scores and retinal features might initially suggest that linear regression would not be suitable, the Gensini score was converted into binary data, characterized by the presence of severe lesions. The dichotomization of the outcome and the inherent flexibility of logistic regression make it a suitable and appropriate choice for this analysis. All data analyses were conducted using the Anaconda software distribution (version 3–2.3.1, Austin, TX: Anaconda, 2016).

Results

A total of 1418 cases were included in the statistical analysis, with a minimum age of 24 years and a maximum age of 90 years, with a mean age of 61. 85± 10.30 years. Of these cases, 753 were males (53%) and 665 were females (47%). The Gensini score was dichotomized according to whether it was less than 4 points, with a score greater than or equal to 4 points indicating the presence of significant stenotic lesions in the coronary arteries. This included any stenotic lesion in the left main trunk, or four or more stenotic lesions in the remaining coronary arteries with less than 25% stenosis, or two stenotic lesions with 25% to 50% stenosis, or one stenotic lesion with 51% to 75% stenosis. The mean Gensini score was 22.87 ± 31.55 points, with 972 cases (68.55%) having a score of greater than or equal to 4 points and 446 cases (31.45%) having a score of less than 4 points. For further details, please refer to Table 1.

The participants were divided into two groups based on whether their Gensini score was less than 4. A series of statistical tests revealed that there were significant differences in the fundus vascular characteristics DSTA, AVR, RAC, and RVD between the two groups. Conversely, no statistically significant differences were identified in the DSTV, RAD, and RVC between the two groups. The clinical indicators (age, sex, body height, body weight, smoking history, total cholesterol, serum creatinine) exhibited statistically significant differences between the two groups, as illustrated in Table 1.

Table 1 Comparison of Clinical Data and Fundus Vascular Characteristics of Coronary Arteries in the Presence of Stenotic Lesions and in the Absence of Significant Stenotic Lesions

Characteristic	Gensini Score<4 (n = 446, 31.45%)	Gensini Score≥4 (n = 972, 68.55%)	X^2/t	*P*
Age, y	59.24 (10.32)	63.05 (10.07)	−6.56	<0.0001
Sex (M%)	0.35	0.61	80.61	<0.0001
Body height, m	162.86 (11.33)	165.22 (7.71)	−5.44	<0.0001
Body weight, kg	69.39 (11.42)	72.34 (11.69)	−4.45	<0.0001
BMI, kg/m^2	26.06 (3.37)	26.45 (3.44)	−2.00	0.0461
Smoking history, n (%)	148(33.18)	503(51.75)	41.69	<0.0001
Total cholesterol, mmol/L	4.55 (1.22)	4.02 (1.07)	8.35	<0.0001
Serum Creatinine, μmol/l	68.51 (18.86)	70.63 (19.22)	−6.43	0.0079
Fasting blood glucose, mmol/l	5.97(1.50)	6.42(1.9)	−4.43	<0.0001
DSTA, μm	60.80(14.01)	58.61(15.51)	2.53	0.0114
DSTV, μm	87.55(18.34)	86.31(20.55)	1.09	0.2778
AVR	0.70(0.16)	0.67(0.18)	2.43	0.0154
RAD	1.50(0.17)	1.44(0.21)	4.60	4.6360
RAC	0.98(0.33)	0.92(0.35)	2.95	0.0032
RVD	1.54(0.16)	1.50(0.20)	3.76	0.0001
RVC	1.31(0.35)	1.31(0.38)	0.08	0.9360

Abbreviations: DSTA, Diameters of Superior Temporal Artery; DSTV, Diameters of Superior Temporal Vein; AVR, Arteriovenous Diameter Ratio; RAD, Retinal Arterial Dimension; RVD, Retinal Vein Dimension; RAC, Retinal Arterial Curvature; RVC, Retinal Vein Curvature.

https://doi.org/10.2147/IJGM.S507016

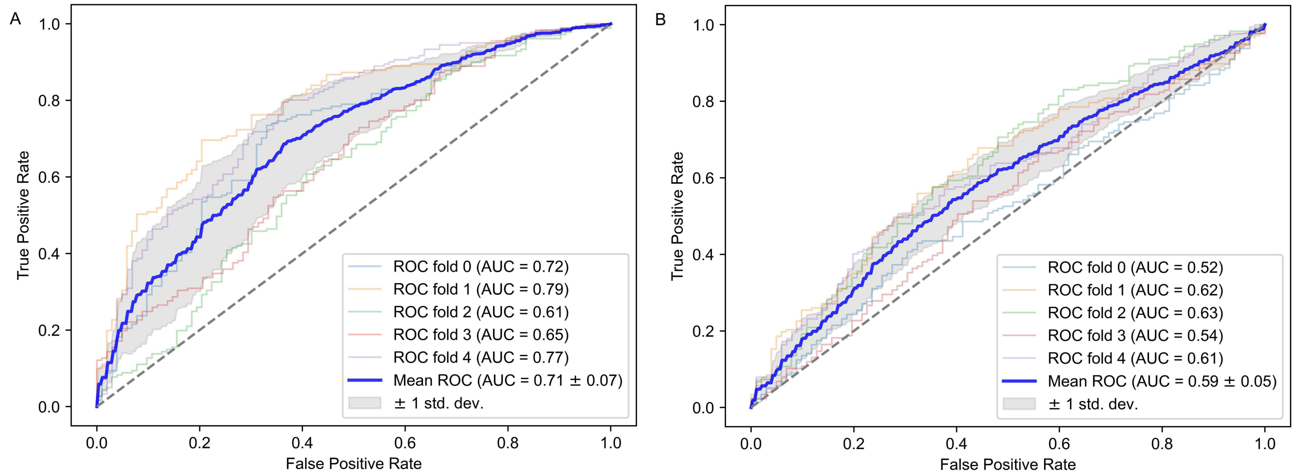

Figure 1 Receiver Operating Characteristic (ROC) curves and Area Under the Curve (AUC) for two logistic regression models. (**A**) Model A includes fundus vascular characteristics (DSTA, DSTV, AVR, RAD, RVD, RAC, RVC) and clinical information (sex, age, height, weight, smoking history, creatinine, total cholesterol, fasting blood glucose) as independent variables. AUC for Model A was 0.71 ± 0.07 (95% CI). (**B**) Model B utilizes only vascular characteristics (DSTA, DSTV, AVR, RAD, RVD, RAC, RVC). AUC for Model B was 0.59 ± 0.05 (95% CI).

Abbreviations: DSTA, Diameters of the Superior Temporal Artery; DSTV, Diameters of the Superior Temporal Vein; AVR, Arteriovenous Diameter Ratio; RAD, Retinal Arterial Diameter; RVD, Retinal Vein Diameter; RAC, Retinal Arterial Curvature; RVC, Retinal Vein Curvature.

Pearson's correlation coefficients were calculated between fundus vascular characteristics and primary Gensini scores (continuous data) for the following variables: DSTA (−0.08), DSTV (−0.03), AVR (−0.10), RAD (−0.09), RVD (−0.06), RAC (−0.06), RVC (−0.01). The linear correlations were found to be trivial.

The Gensini scores were dichotomized according to whether they were less than 4 points. Logistic regression analysis was performed with the Gensini dichotomized score data as the dependent variable and the fundus data and the combined fundus clinical data as the independent variables, respectively. The data set was divided into five using the stratified cross-validation method, and sampling was conducted with the same proportion of positive and negative samples in each sub-data set. Each sub-data set was then divided into a training set (80% of the samples) and a test set (20% of the samples). Ultimately, the 95% confidence interval of the AUC for each model was calculated.

The AUC of the logistic regression model using fundus vascular characteristics (DSTA, DSTV, AVR, RAD, RVD, RAC, RVC) as the independent variables was 0.59 ± 0.05 (95% CI). The AUC of the logistic regression model using fundus vascular characteristics and clinical information (sex, age, height, weight, smoking history, creatinine, total cholesterol, fasting blood glucose) as the independent variables was 0.71 ± 0.07 (95% CI).

The receiver operating characteristic (ROC) and AUC for the two logistic regression models are presented in Figure 1.

We used the Wilcoxon signed-rank test to compare whether there was a statistically significant difference between the two models, and the AUC of the fundus combined with clinical indicators model was significantly better than that of the fundus only model (W = 785.0, $P < 0.0001$).

Discussion

The main findings of our study are as follows: 1) DSTA, AVR, RAC, and RVD were significantly smaller in patients with significant coronary artery stenosis; 2) the linear correlation between fundus vascular characteristics and the degree of coronary artery disease (Gensini score) was weak; 3) by dichotomizing the Gensini score, the fundus vascular characteristics (DSTA, DSTV, AVR, RAD, RVD, RAC, RVC) combined with a small number of clinical indicators (sex, age, height, weight, smoking history, creatinine, total cholesterol, fasting blood glucose) in logistic regression modelling can play a positive classification of the presence of significant coronary artery lesions.

A number of studies have demonstrated that retinal arteriolar thinning and decreased arteriovenous ratio are significantly associated with a range of coronary risk factors, including age,[8] smoking history,[14] hypertension,[7] hyperlipidemia,[19] and diabetes mellitus.[8] Additionally, some studies have confirmed that retinal vascular diameter is also correlated with an increased risk of coronary artery disease.[10,11,20] Furthermore, the retinal arteriovenous ratio is significantly associated with the risk of coronary heart disease-related adverse cardiovascular events.[16,21,22] However, there are fewer studies that correlate the characteristics of the fundus vascular characteristics with the severity of coronary artery stenosis.

The present study corroborates previous findings that significant coronary artery stenosis is associated with a reduction in retinal arteriolar diameter, AVR, arteriolar curvature, and vein fractal dimension.[9–11,23] However, no statistically significant differences were identified between the two groups with respect to retinal vein diameter, arterial fractal dimension, and vein curvature. It has been demonstrated in numerous studies that retinal vein thickening is predominantly linked to chronological age.[24,25] The mean age difference between the two groups in this study was 2.12 years, which may account for the absence of statistically significant variations in retinal vein diameter between the two groups.

This study confirmed a weak linear correlation between fundus vascular characteristics and the severity of coronary stenosis by calculating the Pearson correlation coefficients between retinal arteriovenous diameter, curvature, and fractal dimension and coronary Gensini score. Previous studies with smaller sample have confirmed a significant linear correlation between retinal artery diameter, retinal vein diameter, AVR, and the Gensini score. Tabatabaee's study enrolled 221 patients with suspected coronary artery disease who were scheduled to undergo coronary angiography. The diameter, curvature, and presence of stenosis of the fundus vessels were converted into a 4-grade classification of the degree of sclerosis of the fundus into subtypes of data. It was found that the Pearson correlation coefficient of the degree of sclerosis of the fundus and the Gensini score was 0.47. The present study utilized raw continuous-type data on fundus vascular characteristics, a methodological choice that may account for the weak linear correlation observed.[11] A study by Ning Wan enrolled 120 patients aged 60–72 years who had undergone coronary angiography with a definitive diagnosis of coronary artery disease. The study found that the Pearson correlation coefficients of retinal arteriolar, venous, and arteriovenous ratios with Gensini scores were 0.612, 0.414, and 0. 773, respectively.[23] It is noteworthy that all participants in the study had a definitive diagnosis of coronary artery disease, suggesting the presence of greater than 50% lesions in all cases. This observation may provide a rationale for the high correlation coefficients observed between the degree of coronary stenosis and the fundus vascular characters. The distribution of Censini scores in our study is presumed to be closer to that of the general population; however, the sample size remains limited, and further validation with larger samples is necessary.

The coronary arteries are a constituent part of the aortic system. The principal independent risk factors are age, blood pressure, lipids, blood glucose, and smoking history.[5] Fundus vascularis are part of the microvascular system. Their diameters, curvatures, and fractal dimensions are primarily associated with age and blood pressure.[7,14,24] While there are similarities between the independent risk factors of the two, they are not identical. This is postulated to be the reason for the weak linear correlation between the two.

There is a paucity of literature examining the use of fundus vascular characteristics prediction of the Gensini score to identify the presence of severe lesions in the coronary arteries. We employed fundus vascular characteristics, including arteriovenous diameter, arteriovenous fractal dimension, and arteriovenous curvature, to predict the presence of severe coronary arteries, yielding an AUC of 0.59 ± 0.05. When these fundus vascular characteristics were combined with a limited amount of clinical data, the AUC increased to 0.71 ± 0.05. The present study corroborates the assertion that fundus vascular markers can serve as a valuable adjunct in the classification of severe stenosis in coronary arteries.

Changes in the fundus vasculature have been demonstrated to be indicative of a higher probability of severe coronary artery disease. However, the significance of these changes in relation to major cardiovascular events due to coronary artery disease remains to be elucidated through further long-term follow-up studies. Such studies are imperative in order to guide the selection of coronary artery disease prevention and therapeutic regimens in the population with abnormalities of the fundus vasculature.

The research is limited by a small sample size and the absence of external datasets for validation.

Conclusion

Coronary stenosis is inversely correlated with retinal artery diameter, AVR, arterial tortuosity, and venous fractal dimension. The combination of fundus vascular characteristics with a limited amount of clinical data may serve as a non-invasive tool for predicting the presence or absence of severe stenosis in coronary arteries.

Acknowledgments

We would like to express our gratitude to Beijing Airdoc Technology Co., Ltd. for their invaluable assistance in obtaining fundus data. We would also like to acknowledge our colleagues in the Department of Cardiology at Beijing Anzhen Hospital for their contributions to the collection, processing, and analysis of clinical data.

Disclosure

The authors report no conflicts of interest in this work.

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