OPEN

The clinical implications of choroidal thickness combined with tear VEGFA in coronary artery disease

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Objective **The purpose of this study was to evaluate the effect of choroidal thickness and tear vascular endothelial growth factor A (VEGFA) as biomarkers of coronary artery disease (CAD).**

Methods **This study was a retrospective observational case–control trial. A total of 637 patients who underwent coronary angiography to assess their coronary artery status were included. The patients were divided into two groups: 200 people in the No CAD group and 437 people in the CAD group. We evaluated the choroidal thickness of the right foveal membrane in all patients through optical coherence tomography angiography examination. We also collected tear samples from patients to measure VEGFA. The ROC curve and its area under the curve (AUC) were used for analysis.**

Results **The central foveal choroid in the No CAD group was significantly thicker than that in the CAD group (289.09 μm ± 38.41; 229.03 μm ± 33.44, $P < 0.01$). The tear VEGFA in the CAD group was higher than that in the No CAD group (706.15 ng/mL ± 147.42; 419.66 ng/mL ± 105.85, $P < 0.01$). Spearman analysis showed that the correlation between choroidal thickness and Gensini score was −0.7387 ($P < 0.01$). The correlation between tear VEGFA level and Gensini score was 0.8636 ($P < 0.01$). Taking choroidal thickness and tear VEGFA as independent variables, we obtained AUC = 0.9647 (95% CI 0.9506–0.9789, $P < 0.01$) through binary logic regression and ROC curve analysis.**

Conclusion **The combination of choroidal thickness and tear VEGFA in patients can serve as a clinical marker of CAD and its severity. *Coron Artery Dis* 34: 510–516**

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Keywords: choroidal thickness, coronary artery disease, optical coherence tomography angiography, ROC curve, vascular endothelial growth factor A

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Introduction

Coronary artery disease (CAD) is one of the diseases with the highest incidence rates and mortality rates in the world [1–3]. It is not only a health problem but also a financial challenge for the whole health system. It will show exponential growth in the future [3]. The fundamental cause of CAD is coronary atherosclerosis [4]. Multiple studies have shown a correlation between the status of the coronary artery and the statuses of many peripheral blood vessels in the human body, such as the carotid artery, cerebral artery, and ophthalmic vascular system [5–8]. Coronary angiography (CAG) is the gold standard for evaluating the severity of CAD, but this examination is invasive. Practical noninvasive examination methods are particularly important for screening CAD.

Some studies have attempted to determine the risk of CAD by evaluating the ocular vascular system. Fundus blood vessels and coronary microvessels are basically the same size, so they can to some extent reflect the condition of CAD [9,10]. Studies have shown that changes in retinal blood vessel diameter are associated with an increased risk of cardiovascular disease [11]. Although other studies have found conflicting results, many scholars still propose that retinal microvascular system examination, as a noninvasive imaging examination, can serve as an easy screening method for coronary arteries.

In recent years, optical coherence tomography angiography (OCTA) has been widely used in clinical practice as a new noninvasive detection method [12–14]. The use of advanced imaging techniques to evaluate choroidal thickness makes the fundus vascular system a window into CAD. However, choroidal thickness decreases with age and is affected by various systemic diseases (hypertension, diabetes, carotid stenosis, heart failure, hyperlipidemia) and eye diseases (ocular ischemic syndrome, central serous chorioretinopathy) [15]. The choroid, similar to other terminal organs, is sensitive to arteriosclerosis and is an extremely vascularized terminal organ. In previous studies, it was found that the choroid membrane of patients with CAD was thinner than that of the control group [11]. However, the predictive value of choroidal thickness in the severity of CAD is still unclear.

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Research has shown that vascular endothelial growth factor A (VEGFA) plays an important role in cardiovascular diseases, but there is still no consensus on the changes in VEGF in different clinical manifestations. One study found a significant increase in blood VEGFA expression in acute CAD [16]. Other studies have found that compared to control vessels, VEGF expression is significantly reduced in stable coronary lesions [17]. Therefore, further exploration of the relationship between VEGF and the degree of CAD has clinical value.

In this study, we aimed to compare the differences in choroidal thickness between patients with CAD and those with No CAD to explore the relationship between choroidal thickness and the degree of CAD. At the same time, we detected the level of VEGFA in patients' tears to explore the correlation between VEGFA and CAD. Finally, we analyzed the predictive value of choroidal thickness combined with tear VEGFA for CAD.

Methods

This is a cross-sectional observational case–control trial study. Patients were assessed in the Cardiology Department of Shanghai Sixth People's Hospital from January 2020 to December 2021. This study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Hospital Ethics Committee. All individuals agreed to participate in this study. A total of 437 patients with CAD and 200 patients with No CAD were included. All participants underwent CAG and ophthalmic examinations, including visual acuity and intraocular pressure tests.

Inclusion criteria

Inpatients suspected of having coronary artery stenosis were included if they met the following: (1) age 30 to 60 years; (2) heart-related symptoms indicating possible CAD underwent CAG examination after admission; (3) normal blood pressure and blood sugar or with hypertension and diabetes were effectively controlled after treatment; (4) ophthalmic examination excluded omental lesions; (5) no history of ophthalmic surgery; (6) no severe cataracts or age-related macular degeneration; (7) refractive error less than ± 3.0 D, normal intraocular pressure 10-21 mmHg and BCVA > 6/7.5.

Exclusion criteria

(1) Late-stage renal failure (glomerular filtration rate below 30 ml per minute); (2) retinal diseases (including diabetes or hypertensive retinopathy, diabetes macular edema, vein obstruction, retinal dystrophy, epiretinal membrane, vitreomacular traction, age-related macular degeneration or central serous cortical retinopathy); (3) amblyopia in either eye; (4) eye diseases such as severe cataracts that affect OCTA images; (5) moderate to high myopia/hyperopia (≥ ±3 diopters or axial length ≥ 26 mm).

Coronary angiography

All patients were treated with CAG via the radial artery or femoral artery. We used visual evaluation methods on multiple orthogonal angiography views. We defined CAD as stenosis of the epicardial coronary artery lumen diameter ≥50% (vessel diameter ≥2 mm). During the study period, all participants underwent CAG by the same experienced interventional cardiologist. Two experienced cardiologists independently evaluated the severity of CAD and recorded it. We calculated the Gensini score from the medical records. The Gensini score has been widely used for evaluating the severity of CAD [18]. According to the Gensini score, coronary arteries with stenosis ranging from 1 to 25%, 26 to 50%, 51 to 75%, 76 to 90%, 91 to 99%, and 100% (completely occluded) scored 1, 2, 4, 8, 16, and 32 points, respectively. The score was multiplied by the multiplier of the segment where the lesion was: The left main coronary artery scored 5, while the proximal left anterior descending branch (LAD) and left circumflex branch (LCX) scored 2.5. The middle section of LAD scored 1.5 points, and the middle/distal section of LCX scored 1.0 point. Obtuse marginal branch (OM), right coronary artery (RCA), and posterior descending artery are generally multiplied by 1.0 point. The Gensini calculation method is based on the guidelines published by Gensini GG in 1983 [17]. Based on the results of CAG, we divided the patients into two study object groups: the No CAD group and the CAD group.

Ophthalmic examination

All subjects underwent a detailed questionnaire survey, including medical history. Complete ophthalmic examinations, including refractive evaluation, slit lamp examination, intraocular pressure measurement, and fundoscopic examination, were performed within 1 month after CAG. The choroidal thickness of the right eye was measured using OCTA. Choroidal thickness was measured between 9 a.m. and 10 a.m. after pupil dilation to avoid changes in circadian rhythm. The same ophthalmologist conducted eye examinations at the same time period of the day. Measure choroidal thickness below the central fovea at the lowest point of the retina. All images were taken by two experienced ophthalmologists, and the choroidal thickness measurement value was the average of the two experts' measurements. During the measurement of images, ophthalmologists were blinded to the degree of CAD. We also studied the levels of VEGFA in tear samples. To do this, we placed the paper strip at the bottom of the eye and let it sit for 5 min. Effective samples were immediately frozen at –80 °C after collection and kept at this temperature until the level of tear VEGFA was detected.

Statistical analysis

Statistical analysis was conducted using IBM SPSS 22, with statistical significance defined as a *P* value

Table 1 Baseline clinical characteristics of patients

Demographics	Control (n = 200)	CAD (n = 437)	*P*-value
Male	123 (61.5%)	301 (68.9%)	=0.07
Age (year)	51.41 ± 5.45	53.43 ± 5.26	=0.36
Smoking	46 (23.0%)	167 (38.2%)	<0.01
Hypertension	79 (39.5%)	211 (48.3%)	<0.04
Diabetes mellitus	47 (23.5%)	172 (39.4%)	<0.01
Hemoglobin (g/L)	137.29 ± 12.94	140.66 ± 18.43	=0.02
Creatinine (mmol/L)	64.87 ± 20.20	72.77 ± 21.93	<0.33
Total cholesterol (mmol/L)	4.52 ± 0.87	5.11 ± 1.12	<0.03
Triglyceride (mmol/L)	1.56 ± 1.10	1.87 ± 1.00	<0.29
HDL-C (mmol/L)	1.21 ± 0.34	1.04 ± 0.28	<0.01
LDL-C (mmol/L)	2.63 ± 0.64	3.27 ± 0.96	<0.01
Glycated hemoglobin	6.14 ± 0.98	6.95 ± 1.78	<0.01
CRP (mg/L)	13.94 ± 13.57	22.83 ± 15.35	<0.01
BNP (pg/mL)	51.73 ± 69.99	129.37 ± 132.11	<0.01
Ejection fraction (%)	62.31 ± 4.90	55.17 ± 7.71	<0.01
LVEDD (mm)	46.60 ± 7.72	51.36 ± 8.88	<0.01
LAD (mm)	28.88 ± 5.03	33.46 ± 18.95	<0.01
E/A	1.63 ± 0.40	1.27 ± 0.53	<0.01
E' (cm/s)	10.98 ± 1.93	8.77 ± 2.58	<0.01
E/E'	6.14 ± 2.40	10.40 ± 4.49	<0.01

BNP, brain natriuretic peptide; CRP, C-reactive protein; EF, ejection fraction; HDL-C, high density lipoprotein; LAD, left atrium diameter; LDL-C, low density lipoprotein; LVEDD, left ventricular end-diastolic diameter.

Table 2 Clinical and laboratory ophthalmological variables

Results	Control (n = 200)	CAD (n = 437)	*P*-value
Choroidal thickness (μm)	289.09 ± 38.41	229.03 ± 33.44	<0.01
VEGFA (ng/mL)	419.66 ± 105.85	706.15 ± 147.42	<0.01

VEGFA, vascular endothelial growth factor A.

<0.05. When evaluating data, the frequency distribution of categorical variables and descriptive statistics of numerical variables (mean ± SD) are given. First, the Kolmogorov–Smirnov normality test was applied to determine numerical variables. The test results showed that all parameters conformed to a normal distribution. Based on the measured mean, whether there was a difference between the two independent groups was checked using Student's t-tests for the following variables: age, hemoglobin, creatinine, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glycosylated hemoglobin (HbA1c), c-reactive protein, brain natriuretic peptide, ejection fraction (EF), left ventricular end-diastolic diameter, left atrium diameter, E/A, E', E/E', choroidal thickness, VEGFA, and Gensini score. The chi-square test was used to check whether there were differences between two independent categorical variables (sex, smoking, hypertension, diabetes). The Spearman correlation coefficient was used to determine the degree of correlation between two numerical variables (correlation between choroidal thickness and Gensini score, correlation between VEGFA and Gensini score). For the predictive role of bivariate choroidal thickness and tear VEGFA in CAD, the probability value was calculated by binary metalogic regression, and the diagnostic value of choroidal thickness combined with tear VEGFA in CAD was evaluated by the ROC curve.

Results

Patient characteristics

This study analyzed 637 hospitalized patients who underwent CAG for coronary artery assessment. There were 200 cases in the No CAD group and 437 cases in the CAD group. A total of 637 patients underwent a separate analysis of their right eye. Table 1 summarizes the clinical characteristics of all patients. There was no statistically significant difference between the two groups in terms of average age, creatinine, or triglycerides. The incidence rates of smoking, hypertension, diabetes and hyperlipidemia were higher in the CAD group, while this group had lower EF.

Outcomes

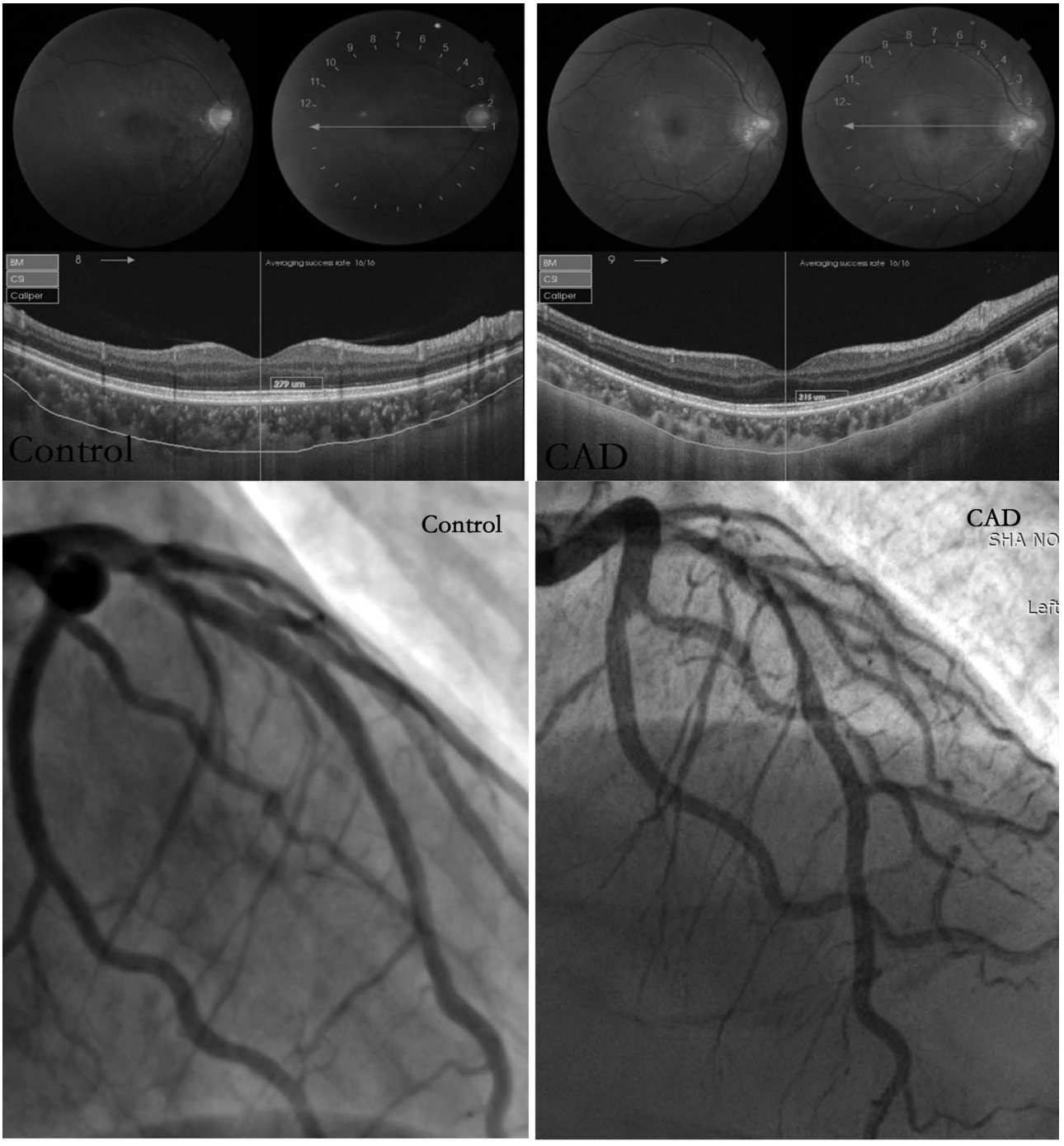
Table 2 shows the comparative study results of the two groups of patients in terms of the evaluated ophthalmic variables. Compared with the No CAD group, the thickness of the central foveal choroid in the CAD group was significantly reduced (229.03 μm ± 33.44 vs. 289.09 μm ± 38.41, $P < 0.01$) (Table 2 and Fig. 1). Compared with the No CAD group, the tear VEGFA in the CAD group was significantly increased (706.15 ng/mL ± 147.42 vs. 419.66 ng/mL ± 105.85, $P < 0.01$). Spearman correlation analysis suggested a correlation of –0.7387 between choroidal thickness and Gensini score and a correlation of 0.8636 between VEGFA level and Gensini score (Fig. 2). Taking choroidal thickness and tear VEGF A as independent variables, the probability of CAD was calculated by binary logistic regression. The ROC curve showed that the area under the curve (AUC) = 0.9647, 95% CI 0.9506–0.9789 ($P < 0.01$). According to ROC curve analysis, $P \geq 0.7074$ predicted the presence of CAD, with a sensitivity of 90.85% and a specificity of 91.5% (Fig. 3). The choroidal thickness cutoff value was < 257.5 (with a sensitivity of 90.85% and a specificity of 91.5%). The VEGFA cutoff value was > 526.5 (with a sensitivity of 91.08% and a specificity of 84.5%). The logistic regression study found choroidal thickness and tear VEGFA levels predict the presence of CAD independent of traditional CAD risk factors (Tables 3–5).

Discussion

In this study, we examined the differences in choroidal thickness and changes in VEGFA levels in tears between patients with No CAD and those with CAD. At the same time, we analyzed the predictive value of choroidal thickness combined with tear VEGFA for CAD and its severity through ROC curve analysis. Our results indicate that fundus vascular system examination and tear examination are simple, effective, and noninvasive methods for the clinical screening of CAD.

There is a negative correlation between the thickness of the membrane and the severity of CAD. CAD is a public health issue that amounts to the main cause of death

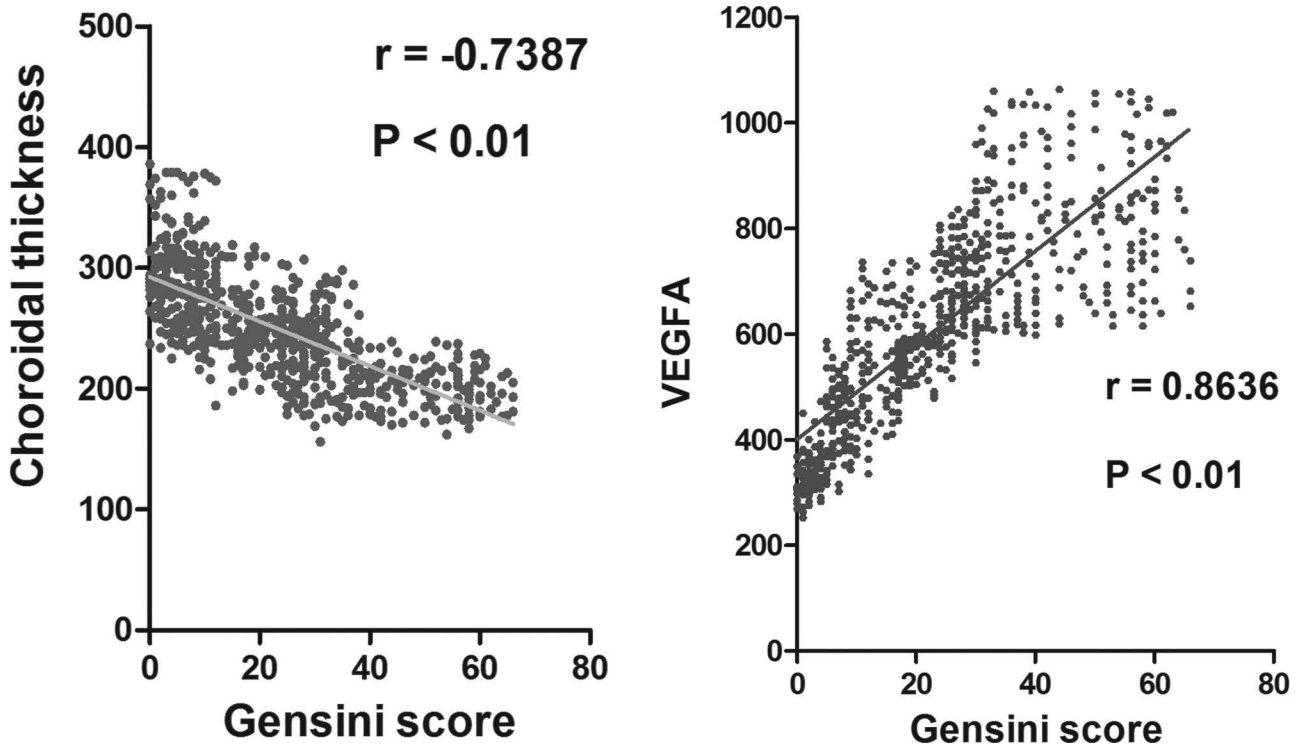
Fig. 1



The choroidal thickness in the two groups. The choroidal thickness of the central foveal choroid in the normal coronary group was significantly higher than that in the CAD group (289.09 μm ± 38.41; 229.03 μm ± 33.44, $P < 0.01$).

worldwide [1–3]. Due to the high risk of death, early identification of this disease is crucial. Cardiac catheterization is the gold standard for diagnosing CAD, but its cost and risks make it difficult to use for the early screening of high-risk patients. In recent years, it has been proposed that the choroid membrane, as the terminal vascular organ, can be used for risk assessment of CAD [19,20]. The retinal blood vessels are almost the same size as the coronary microvessels, so it is believed that choroidal blood vessels can serve as identifiers for cardiac microvascular lesions [20–22]. However, there are many inconsistencies in the results of previous studies, especially in the lack of unified standards for observed indicators.

Fig. 2



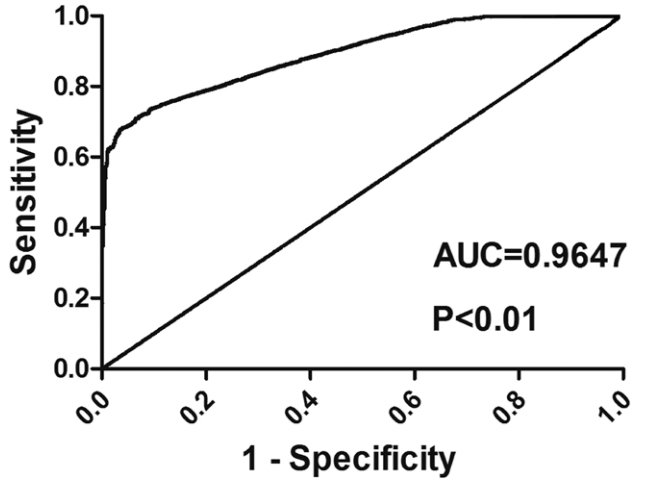
The relationships between choroidal thickness, tear VEDFA and Gensini score. Spearman correlation analysis suggests a correlation of −0.7387 between choroidal thickness and Gensini and a correlation of 0.8636 between VEGFA levels and Gensini score.

In recent years, OCTA has been widely used in the detection of the choroidal vascular system [23]. Choroidal thickness is the most direct and reliable parameter among various parameters. The choroid membrane is composed of a dense network of blood vessels located between the retina and the sclera. Its function is to provide nutrients for the outer layer of the retina and the pigment epithelium, the central fovea avascular area, and the optic nerve. Mounting evidence suggests that changes in the choroidal microvascular system may indicate other systemic diseases that affect blood vessels [24–27]. Therefore, the relationship between the choroid and CAD represents a field of clinical concern and a potential source of biomarkers for such diseases. OCTA is an effective and noninvasive measurement method for screening CAD by detecting the choroid. Research has shown that decreased capillary density and decreased choroidal blood flow may be correlated with general thinning of the choroid in CAD [28]. Other studies have found a correlation between CAD and a decrease in choroidal blood flow [29]. Our study shows that compared to patients with No CAD, patients with CAD had significantly lower choroidal thickness. A recent study found that the choroid became thinner in multiple regions [30], which is similar to our results. In this study, the proportions of hypertension, diabetes and dyslipidemia in the CAD group were the same as those in the control group [30]. Choroidal thickness is significantly influenced by age and is thinner in elderly individuals. There was no significant difference in average age between our study group and the control group.

The Gensini score was proposed by Gensini GG in 1983 and has been widely used to evaluate coronary artery stenosis. In this study, we found a significant negative correlation between choroidal thickness and Gensini score. For early CAD patients, the degree of thinning of the choroid membrane can guide the timing of CAG, helping clarify the degree of CAD and preventing myocardial infarction. The changes in atherosclerosis in eye ground vessels are related to lipid precipitation. Narrow fundus arterioles can serve as an early indicator of microvascular injury. The coronary arteries of CAD patients exhibit similar pathological features as the choroid, so changes in choroidal microvessels may indicate changes in the systemic vascular system, especially CAD.

There is a positive correlation between tear VEGFA levels and the severity of CAD. VEGFA was discovered by Senger *et al.* [31] in 1983. VEGFA is the main

Fig. 3



The choroidal thickness and tear VEGFA levels predict the presence of CAD. Taking choroidal thickness and tear VEGF A as independent variables, the probability value was calculated by binary logistic regression. The ROC characteristic curve showed that AUC = 0.9647, 95% CI 0.9506–0.9789, $P < 0.01$. According to ROC curve analysis, $P \geq 0.7074$ can predict the presence of coronary heart disease, with a sensitivity of 90.85% and a specificity of 91.5%.

Table 3 Logistic regression analysis for choroidal thickness and tear VEGFA

Variables	β	OR	95% CI	*P*-value
Choroidal thickness (μm)	−0.044	0.957	−0.071 to −0.033	<0.01
VEGFA (ng/mL)	0.026	1.026	0.022 to 0.038	<0.01
Smoking	4.242	69.578	3.3762 to 6.784	<0.01
Hypertension	−0.508	0.601	−1.7562 to 0.480	0.254
Diabetes mellitus	−0.221	0.802	−1.3842 to 1.054	0.649
LDL-C (mmol/L)	0.768	2.155	0.2532 to 1.583	0.012
LVEDD (mm)	−0.053	0.948	−0.1612 to 0.034	0.153
LAD (mm)	0.095	1.100	−0.0192 to 0.279	0.188
E (cm/s)	0.173	1.188	−0.2502 to 0.673	0.361
E/A	0.021	1.022	−1.3132 to 1586	0.971
E/E'	0.400	1.491	0.1332 to 0.845	<0.01

LAD, left atrium diameter; LDL-C, low density lipoprotein; LVEDD, left ventricular end-diastolic diameter; VEGFA, vascular endothelial growth factor A.

Table 4 Logistic regression analysis for choroidal thickness and tear VEGFA in smokers

Variables	β	OR	95% CI	*P*-value
Choroidal thickness (μm)	−0.037	0.964	−0.057 to −0.025	0.01
VEGFA (ng/mL)	0.026	1.020	0.015 to 0.031	0.01

VEGFA, vascular endothelial growth factor A.

Table 5 Logistic regression analysis for choroidal thickness and tear VEGFA in non-smokers

Variables	β	OR	95% CI	*P*-value
Choroidal thickness (μm)	−0.048	0.953	−0.081 to −0.033	<0.01
VEGFA (ng/mL)	0.033	1.033	0.026 to 0.049	<0.01

VEGFA, vascular endothelial growth factor A.

proangiogenic factor and is closely related to changes in blood flow in tissues [32]. VEGFA can cause changes in vascular caliber and blood flow velocity, and its spatial distribution is crucial for balancing capillary branching and vascular size growth [33,34]. During the exploration of predictive factors for CAD in this study, it was found that collecting choroidal tissue is very inconvenient. Collecting tears has the advantages of being safe, non-invasive, easy to operate, easy to repeat, and acceptable. Therefore, collecting patient tears has become a simple, feasible, and reliable method. At present, tear detection is mainly used for the analysis of ophthalmic diseases. Using changes in tear composition to draw any conclusions about CAD is somewhat controversial, but such connections are being explored and new methods innovated. This study selected patients' tears and tested their VEGFA content. This study found that compared to the group with No CAD, the expression of VEGFA in tears in CAD patients increased significantly. This study found a positive correlation between tear VEGFA and the severity of CAD. To our knowledge, this is the first study to link the VEGFA value in tears with CAD; an increase in its level may constitute a protective factor, while higher levels are associated with CAD. To further elucidate the role of VEGFA in CAD, it is necessary to investigate the mechanism by which VEGFA regulates the choroid membrane in CAD.

Our results indicate that there is a significant negative correlation between choroidal thickness and coronary Gensini score and a significant positive correlation between tear VEGFA concentration and coronary Gensini score in the studied patients. ROC curves and AUC calculations suggest that choroidal thickness combined with tear VEGFA has a good predictive effect on CAD and its severity. The prevention of cardiovascular diseases requires identifying high-risk groups to propose appropriate intervention measures. In recent decades, various prediction models have been developed for high-risk populations, but in most cases, their applicability is unclear due to the heterogeneity of the selected predictive variables. In the era of information overload, new predictive factors should be discovered and applied to suitable populations based on existing models. Therefore, we propose two ophthalmic variables, choroidal thickness and tear VEGFA values, as predictive factors for CAD. At present, CAD patients rarely receive appropriate ophthalmic follow-up. Single-discipline management of diseases may not be the best approach, and more scientific decision-making is urgently needed.

Limitations

The limitations of this study include using a patient population from one hospital, a relatively small sample size, and a lack of long-term follow-up, which may bias the study results. Considering these shortcomings,

it is necessary to conduct prospective studies on more patients in the future to validate these results and evaluate their effectiveness in a wider population. In addition, we did not collect data on the patient's plasma VEGFA, coronary plaque properties between CAD patients and the control group.

Conclusion

Our study suggests that choroidal thickness combined with tear VEGFA concentration are good biomarkers for predicting CAD and its severity. As a noninvasive, effective, simple, and feasible measurement method for early screening of CAD, these markers have clinical significance. The clinical impact of these findings warrants further investigation.

Acknowledgements

TQZ and XJ analyzed the data and were major contributors in writing the manuscript. TQZ and YC collected the data. SXM and CXS were in charge of the study design. All authors reviewed the manuscript. This research was funded by the Shanghai Hospital Development Center Foundation of Shanghai (NO. SHDC2020CR1042B, Shanghai, China), and Shanghai Municipal Hospital Cardiovascular Specialist Alliance, SHDC22021302.

Conflicts of interest

There are no conflicts of interest.

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