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ARTICLE

Predictive Value of Ocular Fundus Hemorrhage for Severe Coronary Artery Disease Assessed via SYNTAX Score

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Abstract

Aims/Background The relationship between retinal fundus hemorrhage and the severity of coronary artery lesions remains unclear. This study aimed to explore the incidence of fundus hemorrhage in patients at high risk of coronary heart disease (CHD) and to examine its correlation with the SYNTAX score, a tool used to assess the complexity of coronary artery disease.

Methods This retrospective study consecutively enrolled patients undergoing coronary angiography (CAG) at Beijing Anzhen Hospital Hospital from June 2019 to January 2020. Bilateral non-mydriatic fundus photography was performed to detect fundus hemorrhages. The SYNTAX score was calculated to quantify the severity of coronary artery lesions, and patients were divided into two groups: a high SYNTAX score (hSS) group ($\geq$23 points) and a low SYNTAX score (lSS) group ($\leq$22 points). Baseline demographic and clinical data were collected, along with relevant laboratory tests.

Results A total of 878 patients were included in the study, with 177 in the hSS group and 701 in the lSS group. Fundus hemorrhage was observed in 91 patients (incidence: 10.36%, 95% confidence interval (CI): 8.35%–12.38%). The incidence of fundus hemorrhage was significantly higher in the hSS group compared to the lSS group (21.47% [38/177] vs. 7.56% [53/701], $p < 0.001$). Multivariate logistic regression analysis identified fundus hemorrhage, body mass index (BMI), and low-density lipoprotein cholesterol (LDL-C) as independent predictors of high SYNTAX scores.

Conclusion Fundus hemorrhage is significantly associated with a higher SYNTAX score and may serve as a potential predictor of severe coronary artery lesions in clinical practice.

Key words: coronary artery disease; SYNTAX score; coronary angiography; fundus hemorrhage; retinal diseases

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Introduction

Fundus hemorrhage is a common ocular condition, especially in the elderly. A recent cohort study reported an incidence of 12.7% in individuals over the age of 50 (Zhou et al, 2019). According to the Preferred Practice Pattern from the American Academy of Ophthalmology, aspirin does not significantly increase the incidence of fundus hemorrhage in patients with diabetic retinopathy (Flaxel et al, 2020). However, previous research has shown that anticoagulant or antiplatelet

therapy may aggravate fundus hemorrhage in individuals with pre-existing retinal conditions (Kuhli-Hattenbach et al, 2010). Due to concerns about worsening retinal hemorrhage, coronary angiography (CAG) is rarely performed in patients with this condition. As a result, there is limited data on the occurrence of fundus hemorrhage in high-risk coronary heart disease (CHD) patients and on the severity of coronary lesions in these individuals.

Furthermore, a study by Kralev et al (2010) examined the ocular manifestations of a small group of patients with acute coronary syndrome (ACS) and stable CHD, noting a relatively high prevalence of retinal microaneurysms and patchy hemorrhages in the ACS population. The "Slow Coronary Flow" (SCF) phenomenon, characterized by reduced blood flow in the angiographically normal coronary arteries, is thought to result from microvascular and endothelial dysfunction. Patients with SCF are known to have higher coronary Leaman scores after undergoing CAG (Cheng et al, 2018). While the Leaman score is not widely used, the American College of Cardiology/American Heart Association Joint Committee (ACC/AHA) guidelines for coronary artery revascularization recommend the SYNTAX score to quantitatively assess coronary lesions severity and evaluate long-term outcomes in CHD patients (Lawton et al, 2022). The SYNTAX score, introduced by Sianos et al (2005), is a validated tool used to quantify the complexity of coronary artery lesions. It provides an accurate multivessel coronary disease assessment and guides clinical decisions of coronary artery bypass grafting or percutaneous coronary intervention (Lin et al, 2022). A high SYNTAX score ($\geq$23) has been shown to predict an increased risk of major cardiovascular events over five years, as demonstrated in the BARI-2D trial (Ikeno et al, 2017).

To address the knowledge gap regarding the relationship between coronary artery disease and fundus hemorrhage, this study aimed to investigate the incidence of fundus hemorrhage in patients at high risk for CHD and to explore the correlation between retinal hemorrhage and SYNTAX scores in these individuals.

Methods

Sample Collection

This study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association, 2013). Our research was a retrospective study that enrolled 878 patients admitted to Beijing Anzhen Hospital for CAG between June 2019 and January 2020, based on the order of their admission (Fig. 1). The mean age of the participants was 60.16 $\pm$ 10.07 years. The study was approved by the Institutional Ethics Committee of Beijing Anzhen Hospital (Approval No. AZ20190514), and informed consent was obtained from all participants.

Inclusion criterion:

(1) Patients with clinical indications for coronary angiography.

(2) Patients who underwent fundus photography within 48 hours before CAG.

Exclusion criteria:

(1) Patients with post-operative fundus diseases or severe cataracts.

(2) Patients with contraindications to antithrombotic therapy.

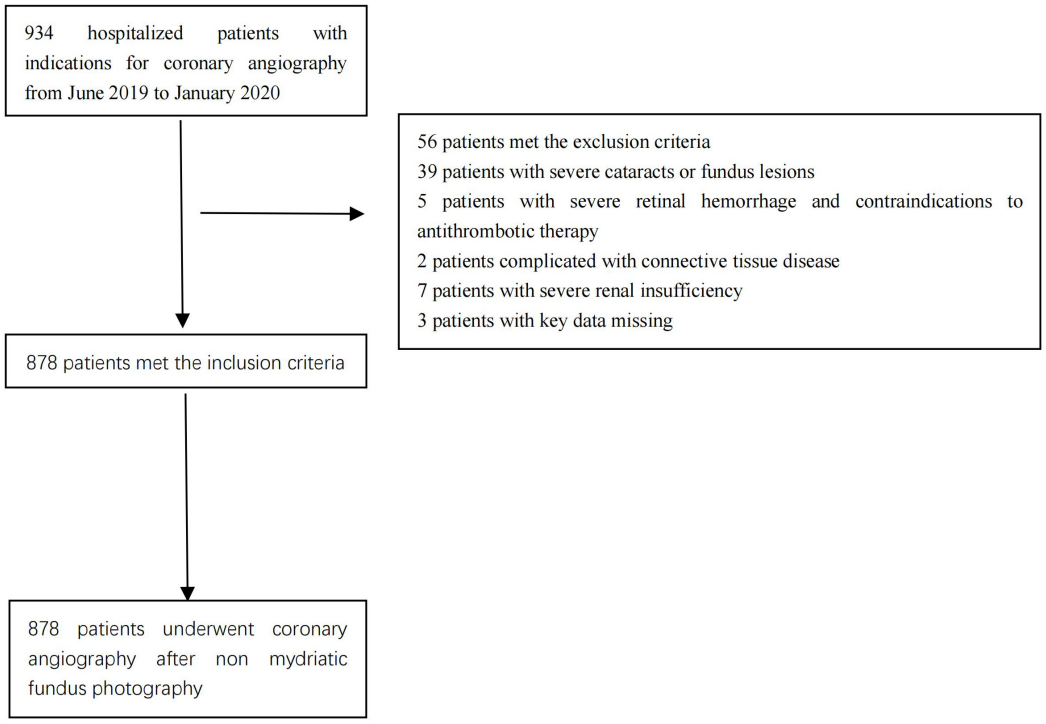

Fig. 1. Flow chart of patient inclusion and grouping criteria.

(3) Patients with immunological diseases and/or connective tissue disorders.
(4) Patients with severe liver and/or kidney diseases.
(5) Patients with malignancies.

Study Methods

Two experienced interventional cardiologists independently assessed the coronary artery lesions using the SYNTAX score software (https://syntaxscore.org), blinded to the clinical and laboratory data of the patients. The Spearman correlation coefficient between the SYNTAX scores calculated by the two doctors was 0.956 ($p < 0.001$), indicating strong agreement. The interobserver consistency was 0.96 (95% confidence interval (CI): 0.93–0.98), and the Kappa coefficient between the two cardiologists was 0.86, signifying higher inter-rater reliability.

The patients were divided into two groups based on their SYNTAX scores: a high SYNTAX score (hSS) group ($\geq$23 points) and a low SYNTAX score (lSS) group ($\leq$22 points) (Ikeno et al, 2017). Baseline clinical data were collected for all participants, including gender, age, body mass index (BMI), smoking status, and history of hypertension and diabetes. Laboratory tests performed included complete blood counts (hemoglobin, red blood cell count, platelet count), liver function tests, estimated glomerular filtration rate (eGFR), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and blood glucose levels.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 23.0, SPSS Inc., Chicago, IL, USA). Continuous variables were

presented as means ± standard deviation ($\bar{x} \pm$ SD) or medians (P25–P75). The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Depending on the distribution, the Student's *t*-test or Wilcoxon rank-sum test was applied to compare continuous variables, while the chi-square (χ^2) test was used for categorical variables of the hSS and lSS group.

A logistic regression model was employed to identify variables associated with the SYNTAX. Using the SYNTAX score as a binary dependent variable, independent variables such as gender, age, smoking history, hyperlipidemia, history of stroke, aspirin use, eGFR, total cholesterol, HDL-C, LDL-C, fundus hemorrhage, diabetes history, and BMI were included in the model. Multivariate logistic regression was performed to investigate the relationship between these variables and the SYNTAX score. Factors were trained in the model if they reached statistical significance at an alpha level of 0.05. A p-value < 0.05 was considered statistically significant.

Results

From June 2019 to January 2020, a total of 878 participants were enrolled in this clinical study, with 177 in the hSS group and 701 in the lSS group. The median SYNTAX score for all participants was 10.50 (P25–P75: 4.00–19.00). The distribution of coronary artery lesions was as follows: 29.5% (259/878) had single-vessel disease, 25.1% (220/878) had double-vessel disease, 31.8% (279/878) had triple-vessel disease, and 8.2% (72/878) had left-main artery disease. Additionally, on coronary angiography, 5.4% (48/878) of patients had less than 50% diameter stenosis.

Fundus hemorrhage was identified in 91 patients, representing an incidence rate of 10.36% (95% CI: 8.35%–12.38%) (Table 1). The incidence of fundus hemorrhage was significantly higher in the hSS group (21.47%) compared to the lSS group (7.56%), with a statistically significant difference between the two groups ($p < 0.001$). There were no significant differences between the hSS and lSS groups in terms of gender, age, smoking history, hyperlipidemia, history of stroke, aspirin use, eGFR, total cholesterol, LDL-C, or HDL-C ($p > 0.05$). However, there were significant differences between the two groups in terms of fundus hemorrhage events, BMI, and diabetes history ($p < 0.05$) (Table 1).

Multivariate logistic regression analysis identified a history of type 2 diabetes, BMI, fundus hemorrhage, and LDL-C as factors associated with a high SYNTAX score, while a history of hypertension and total cholesterol levels were associated with low SYNTAX score (Table 2).

Logistic regression analysis was performed using the SYNTAX score as a binary dependent variable, and the variables with significance from Table 2 were included as independent variables. A backward logistic regression (LR) method was applied to screen variables, with inclusion and exclusion criteria of 0.10 and 0.05, respectively. The results demonstrated that fundus hemorrhage remained significantly associated with a high SYNTAX score (odds ratio (OR) = 3.340, 95% CI = 2.106–5.296, $p < 0.001$) (Table 3).

Table 1. Comparison of clinical characteristics between hSS group and lSS group.

Factor	SYNTAX score ≤22 (n = 701)	SYNTAX score ≥23 (n = 177)	*p*-value [d]	Statistics
Age, years	60.35 ± 9.89	59.43 ± 10.75	0.278 [a]	1.085
Male, n (%)	503 (71.75)	139 (78.53)	0.069 [b]	3.302
Fundus hemorrhage, n (%)	53 (7.56)	38 (21.47)	<**0.001** [b]	29.425
BMI	25.56 (23.66–27.77)	26.23 (23.93–28.34)	**0.030** [c]	–2.164
Smoking	299 (42.65)	86 (48.59)	0.155 [b]	2.021
History of type 2 diabetes, n (%)	231 (32.95)	80 (45.20)	**0.002** [b]	9.263
History of hypertension, n (%)	417 (59.49)	101 (57.06)	0.558 [b]	0.343
History of hyperlipidemia	327 (46.65)	82 (46.33)	0.939 [b]	0.006
History of stroke	42 (5.99)	10 (5.65)	0.863 [b]	0.030
Medication history of aspirin, n (%)	599 (85.45)	158 (89.27)	0.188 [b]	1.732
Medication history of clopidogrel, n (%)	344 (49.07)	90 (50.85)	0.673 [b]	0.178
Medication history of ticagrelor, n (%)	111 (15.83)	20 (11.30)	0.130 [b]	2.290
Medication history of antidiabetic drugs	167 (23.82)	53 (29.94)	0.093 [b]	2.819
Medication history of antihypertensive drugs	176 (25.11)	49 (27.68)	0.483 [b]	0.492
Medication history of statins	586 (83.59)	157 (88.70)	0.092 [b]	2.831
eGFR (mL/min/1.73 m^2)	95.60 (85.05–102.40)	96.10 (85.05–103.05)	0.951 [c]	–0.061
Total cholesterol (mg/dL)	143.08 (119.88–170.15)	139.21 (119.88–168.21)	0.545 [c]	–0.605
LDL-C (mg/dL)	81.21 (65.74–104.41)	85.07 (65.74–104.41)	0.528 [c]	–0.631
HDL-C (mg/dL)	38.67 (34.80–46.40)	42.54 (34.80–50.27)	0.143 [c]	–1.463
GHb (%)	5.60 (5.00–6.85)	5.90 (5.10–7.30)	0.058 [c]	–1.899

Note: Data are presented as median (25th percentile, 75th percentile). [a] *t*-test; [b] Chi-square test; [c] Rank sum test; [d] Bold indicates $p < 0.05$. BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; GHb, glycosylated hemoglobin; hSS, high SYNTAX score; lSS, low SYNTAX score.

Discussion

Fundus hemorrhage can be easily detected during ophthalmological examination, making it valuable for diagnosing major eye diseases (Zhou et al, 2019). A previous study has suggested that anticoagulation or antiplatelet therapy may exacerbate fundus hemorrhage in patients with pre-existing retinal conditions (Kuhli-Hattenbach et al, 2010). Therefore, careful monitoring of retinal health is essential for patients with CHD undergoing long-term antiplatelet therapy. In clinical practice, the use of dual antiplatelet and anticoagulant therapy during the perioperative period of CAG may increase the risk of fundus hemorrhage. Due to concerns about worsening retinal hemorrhages, cardiovascular specialists may hesitate to perform CAG in such patients. Consequently, limited data exist on the degree of coronary lesions in patients with retinal hemorrhage or the incidence of fundus hemorrhage in patients with CHD.

A large cohort study of 3417 individuals over 59 years identified 432 cases of fundus hemorrhage, representing an incidence rate of 12.7% (95% CI: 11.7–13.7) (Zhou et al, 2019). Of these, 36.7% were associated with diabetic retinopathy and 1.9% with hypertensive retinopathy (Zhou et al, 2019). Another study involving 11,644 participants showed that traditional arteriosclerosis risk factors, such as hypertension, elevated BMI, and smoking, were also risk factors for fundus hemorrhage (Umesawa et al, 2016). Therefore, retinal conditions such as fundus hemorrhage may be associated with the pathophysiological processes underlying CHD (van Hecke et al, 2005).

Another study demonstrated that hypertensive retinopathy, retinal artery stenosis, and other forms of retinopathy could predict CHD (Wong and Mitchell, 2004; Wong et al, 2002). Kralev et al (2010) compared patients with ACS and those with stable CHD, finding a higher incidence of fundus hemorrhage in the ACS. Although these authors suggested an association between retinal hemorrhage and ACS, they did not examine the degree of coronary lesions in these patients. Cheng et al (2018) reported that fundus hemorrhage was associated with a higher Leaman score, indicating more severe CHD. However, the Leaman score is not widely used in clinical practice. The American College of Cardiology/American Heart Association Joint Committee (ACC/AHA) 2021 guidelines for coronary artery revascularization recommend using the SYNTAX score to quantify coronary lesions and evaluate the long-term prognosis in CHD patients (Lawton et al, 2022).

In the present study, we utilized the SYNTAX score to quantitatively assess coronary lesion severity. Our findings indicate that fundus hemorrhage is associated with an increased SYNTAX score, a result confirmed by multivariate logistic regression analysis. These findings suggest a potential association between retinal hemorrhage and the severity of coronary artery disease. Fundus photography may serve as a supplementary tool to assess CHD severity, though not as an independent predictor. Further in-depth research is required to validate these findings.

Asymptomatic myocardial ischemia is prevalent in diabetic patients, with a clinical study detecting it in 20%–30% of cases using myocardial perfusion imaging and as high as 50% in autopsy reports (Choi et al, 2020). Since asymptomatic

Table 2. Multivariate logistic regression analysis of clinical factors affecting SYNTAX score.

Factor	β coefficient	SE	Wald χ^2	OR (95% CI)	p-value [a]
Age, (years)	–0.004	0.011	0.123	0.996 (0.976–1.017)	0.725
Male, n (%)	0.212	0.241	0.773	1.236 (0.771–1.982)	0.379
Fundus hemorrhage, n (%)	1.010	0.262	14.857	2.745 (1.643–4.586)	**<0.001**
BMI	0.061	0.026	5.510	1.063 (1.010–1.119)	**0.019**
Smoking	0.077	0.198	0.150	1.080 (0.733–1.591)	0.699
History of type 2 diabetes, n (%)	0.610	0.282	4.672	1.841 (1.059–3.203)	**0.031**
History of hypertension, n (%)	–0.913	0.415	4.827	0.401 (0.178–0.906)	**0.028**
History of hyperlipidemia	–0.163	0.187	0.761	0.850 (0.589–1.225)	0.383
History of stroke	–0.043	0.384	0.012	0.958 (0.451–2.034)	0.911
Medication history of aspirin, n (%)	0.448	0.332	1.816	1.565 (0.816–3.000)	0.178
Medication history of clopidogrel, n (%)	0.366	0.392	0.871	1.441 (0.669–3.105)	0.351
Medication history of ticagrelor, n (%)	–0.288	0.309	0.867	0.750 (0.409–1.374)	0.352
Medication history of antidiabetic drugs	–0.328	0.287	1.305	0.720 (0.410–1.265)	0.253
Medication history of antihypertensive drugs	0.367	0.248	2.200	1.444 (0.889–2.345)	0.138
Medication history of statins	0.469	0.304	2.391	1.599 (0.882–2.898)	0.122
eGFR (mL/min/1.73 m^2)	–0.003	0.006	0.311	0.997 (0.986–1.008)	0.577
Total cholesterol (mg/dL)	–0.012	0.005	4.880	0.988 (0.978–0.999)	**0.027**
LDL-C (mg/dL)	0.014	0.006	5.040	1.014 (1.002–1.026)	**0.025**
HDL-C (mg/dL)	0.008	0.007	1.251	1.008 (0.994–1.023)	0.263
GHb (%)	–0.031	0.044	0.500	0.969 (0.889–1.057)	0.479

Note: Data are presented as median (25th percentile, 75th percentile). [a] Bold indicates $p < 0.05$. BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; GHb, glycosylated hemoglobin; SE, standard error; OR, odds ratio; CI, confidence interval.

myocardial ischemia often lacks typical risk factors such as hyperlipidemia and hypertension, identifying CHD (including obstructive CHD and ischemia with non-obstructive CHD) in diabetic patients remains a challenge for cardiovascular clinicians (Bairey Merz et al, 2017; Scognamiglio et al, 2006). The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" do not recommend routine screening in diabetic patients without cardiovascular symptoms but suggest screening in patients with stroke, transient ischemic attack, carotid murmur, peripheral arterial disease, and abnormal ECG findings (American Diabetes Association Professional Practice Committee, 2022). Our research suggests that fundus hemorrhage is associated with more severe coronary lesions, and we propose a simple screening strategy for asymptomatic CHD in diabetic patients. Notably, fundus photography could be used as an initial step, and patients with fundus hemorrhages could undergo further evaluation for CHD.

In a cohort study by Zhou et al (2019), 36.7% of fundus hemorrhages were associated with diabetic retinopathy, and 1.9% with hypertensive retinopathy; in our study, 79.12% (72/91) of patients with fundus hemorrhage had diabetes. This suggests that the association between fundus hemorrhage and high SYNTAX scores may be influenced by diabetes. However, multivariate logistic regression did not

Table 3. Results of multivariate logistic regression analysis (variables screened by backward LR method).

Factor	β coefficient	SE	Wald χ^2	OR (95% CI)	p-value [a]
Fundus hemorrhage	1.206	0.235	26.282	3.340 (2.106–5.296)	**<0.001**
BMI	0.060	0.024	6.062	1.062 (1.012–1.113)	**0.014**
Total cholesterol (mg/dL)	–0.012	0.005	5.015	0.988 (0.978–0.999)	**0.025**
LDL-C (mg/dL)	0.012	0.006	4.193	1.012 (1.001–1.024)	**0.041**

Note: Data are presented as median (25th percentile, 75th percentile). [a] Bold indicates $p < 0.05$.
Abbreviations: LR, logistic regression; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; SE, standard error; OR, odds ratio; CI, confidence interval.

identify diabetes as a significant independent factor after adjustment. Similarly, Wang et al (2021) analyzed data from 2253 patients with CHD and 134 without, finding through multivariate logistic regression analysis that diabetes was not an independent predictor of high SYNTAX scores. The duration of diabetes, treatment compliance, and type of diabetes medication may influence the development of microvascular and macrovascular complications, with fundus hemorrhage being a microvascular complication, potentially synchronizing with coronary complications.

A limitation of this study is the high-risk profile of the included subjects, as most were hospitalized due to angina, while a smaller subset was admitted following abnormal ECG or echocardiographic findings or coronary computed tomography angiography. Prior to fundus photography, aspirin use was recorded in 85.45% of the lSS group and 89.27% of the hSS group, while clopidogrel use was observed in 49.07% of the lSS group and 50.85% of the hSS group. Whether antiplatelet agents like aspirin and clopidogrel increase the incidence of fundus hemorrhage was not determined in this research, and further research is warranted to address this clinically significant question.

Among the patients in this study, 35.4% (311/878) were diagnosed with type 2 diabetes, and fundus hemorrhage was observed in 91 patients (incidence: 10.36%, 95% CI: 8.35%–12.38%) (Table 1). However, we did not diagnose or stage diabetic retinopathy among diabetic patients. At enrollment, ophthalmologists did not collect the medical history or conduct detailed eye examinations specific to diabetic retinopathy, precluding retrospective diagnosis or staging based on fundus photography alone. In our study, the primary objective during the study design phase was to identify simple retinal markers, such as hemorrhage, to assist in screening for severe coronary artery disease, although this narrowed focus and lack of attention to other retinal conditions constitute a notable limitation of this study.

GLP-1 receptor agonists (GLP-1 RAs) are known to enhance glycemic control and reduce adverse cardiovascular events (Verma et al, 2020). However, they may also increase the risk of worsening diabetic retinopathy (Eleftheriadou et al, 2024). In this study, we recorded whether patients had been receiving hypoglycemic therapy at enrollment, though we did not document specific drugs used, including GLP-1 RAs. In future studies, we intend to further examine the impact of GLP-1 RAs on

coronary outcomes in patients with diabetes and CHD, and their impact on diabetic retinopathy.

Additionally, the potential of fundus hemorrhage as a predictor of major adverse cardiovascular events (MACE) during follow-ups could add significant clinical value to our findings. All study participants underwent regular follow-up, and MACE events, including non-fatal ACS, acute heart failure, non-fatal stroke, and death, were meticulously recorded. Two trained attending physicians conducted follow-ups every six months, either in person or by phone, until May 2022. The follow-up data are currently being organized and analyzed.

Another notable limitation of this study is that the SYNTAX score, used to evaluate the degree of coronary artery disease in epicardial and major arteries, does not account for coronary microcirculation. Arbel et al (2014) have suggested that the SCF phenomenon, observed in angiographically normal coronaries, may result from microvascular and endothelial dysfunctions. SCF is associated with high retinal arterial blood flow in patients with normal coronary arteries. Based on these findings, it is inferred that coronary artery microcirculation disorders may be related to changes in fundus artery blood flow. Additionally, research on central serous retinopathy suggests that corticosteroids and the symptomatic system may play pivotal roles in the disease by increasing microvascular resistance and tone (Koç et al, 2013). These studies support the hypothesis that retinal anomalies may reflect coronary microvascular disturbances. Therefore, further research is needed to clarify the potential role of fundus photography in predicting coronary microvascular disease.

While coronary artery disease is not limited to epicardial vessels, our study only employed the SYNTAX scores to quantify coronary lesions, which presents a limitation. Nevertheless, our research contributes meaningfully to the current knowledge system by exploring a potential association between retinal hemorrhage and the severity of coronary artery disease. Future studies are essential to evaluate the clinical utility and cost-effectiveness of incorporating fundus photography into routine coronary artery disease evaluation.

Conclusion

Fundus hemorrhage, a common ocular condition in older adults, was shown to correlate with higher SYNTAX scores in this study. Multivariate logistic regression analysis also indicated a significant association between fundus hemorrhage and elevated SYNTAX scores. As a microvascular complication, fundus hemorrhage, especially in cases involving diabetes and hypertension, may be synchronized with coronary complications. A critical limitation of this study is that coronary artery disease affects epicardial and microvascular domains, yet we solely relied on the SYNTAX scores to quantify coronary artery involvement. Thus, further in-depth and rigorous research is needed to validate and expand upon these findings.

Key Points

- Fundus hemorrhage is prevalent, particularly in the elderly.
- Limited data exists on fundus hemorrhage incidence among high-risk CHD patients with fundus hemorrhage.
- Fundus hemorrhage showed a significant association with elevated SYNTAX scores.
- Fundus hemorrhage may serve as a potential predictor of severe coronary lesions in clinical practice.

Availability of Data and Materials

The corresponding author will provide the data that underpin the study's conclusions with a reasonable application.

Author Contributions

YJZ and XG designed the study. XG, XLL, TNS, XXG, HYH, and YJZ conducted the study. XG and TNS collected and analysed the data. XLL participated in drafting the manuscript, and all authors contributed to the critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study has been approved by the Institutional Ethics Committee of Beijing Anzhen Hospital (AZ20190514). Patients were aware of the purpose and significance and signed an informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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