

Retinal artery lesions and long-term outcome in Chinese patients with acute coronary syndrome

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Abstract

Objective To investigate the relationship between staging of retinal artery lesions and the prognosis of acute coronary syndrome (ACS) in a Chinese population.

Methods A total of 436 Chinese patients with ACS underwent coronary angiography and the eyes fundus examinations. All the patients were divided into three groups: group 1, no retinal artery lesions ($n = 111$); group 2, retinal artery lesions of < Stage 2 (Stage 1—a broadening of the light reflex from the artery can be seen, with minimal or no arteriovenous compression; $n = 135$); and group 3, retinal artery lesions of \geq Stage 2 (Stage 2—the changes similar to those in Stage 1, but more prominent, Stage 3—the arteries have a ‘copper wire’ appearance and this is much more arteriovenous compression, and Stage 4—the arteries have a ‘silver wire’ appearance and the arteriovenous crossing changes are more severe; $n = 190$). The endpoints were main adverse cardiovascular and cerebrovascular events (MACCE), including all-cause death, myocardial infarction (MI), and stroke after 3–6 years of follow-up.

Results There was no significant differences of the baseline data among the three groups. After 3–6 years of follow-up, we found that patients of group 3 had more MACCE and death than those of the group 1 or group 2. Cox regression analysis found that factors related to the prognosis of ACS was staging of retinal artery lesions ($P < 0.05$) in addition to traditional risk factors such as age, gender, diabetes, hypertension, and hypercholesterolemia.

Conclusion Staging of retinal artery lesions plays an important role in the long-term outcome of patients with ACS.

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Introduction

Despite improvements in diagnosis and therapy over the last few decades, mortality of patients with acute coronary syndrome (ACS) is still high. In the recent 10 years, a large percentage of patients post ACS continue to experience cardiac events with high long-term mortality rates and overall suboptimal medical management such as blood pressure control, statins administration, glycemic control, and percutaneous coronary intervention.¹ It indicates that there are still some residual cardiovascular risk factors that we did not find yet.

The present studies showed that the retinal artery lesions had a relationship with the coronary artery lesions based on the results of coronary angiography.^{2–4} Kim *et al*⁵ and Wang *et al*⁶ found that the retinal artery lesions of \geq Stage 2 (including Stage 2—a broadening of the light reflex from the artery can be seen, but more prominent, Stage 3—the arteries have a ‘copper wire’ appearance and this is much more arteriovenous compression, and Stage 4—the arteries have a ‘silver wire’ appearance and the arteriovenous crossing changes are more severe) classified according to Scheie⁷ had a close correlation with ACS. However, there is little information about the correlation of retinal artery lesion with the long-term outcome of ACS.

The aim of this study was to explore the relationship of retinal artery lesions with the main adverse cardiovascular and cerebrovascular events (MACCE) after 3–6 years of follow-up in the patients with ACS.

Methods

Study population

This study was a retrospective analysis in a single-site center. A total of 472 patients with ACS who underwent coronary angiography

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and percutaneous coronary intervention at the Beijing Mentougou District Hospital from 1 July 2006 to 31 August 2009 were enrolled. The endpoints were analyzed in 436 patients were analyzed because 36 of them were lost to follow-up after 3 to 6 years. All the subjects were divided into three groups based on the retinal artery examination according to Scheie:⁷ group 1, no retinal artery lesions ($n = 111$); group 2, retinal artery lesions of $< \text{Stage 2}$ ($n = 135$); and group 3, retinal artery lesions of $\geq \text{Stage 2}$ ($n = 190$). Patients were excluded from the study if they had heart failure, malignancies, renal insufficiency (creatinine $> 133 \mu\text{mol/l}$), liver disease, stroke, and severe lung disease. All the subjects underwent the following examinations, such as past history, physical examination, blood routine, glucose, lipids, liver and kidney function, electrolyte, electrocardiogram, chest X-rays, and echocardiography examination.

Assessment of retinal artery lesions

The eye fundus examination was carried out in all patients by direct ophthalmoscopy performed after pupil dilation. The severity of atherosclerotic lesions was classified according to Scheie⁷ and evaluated by the same ophthalmologist who was trained. In Stage 1, a broadening of the light reflex from the artery can be seen, with minimal or no arteriovenous compression. This was the earliest sign of retinal artery atherosclerosis. In Stage 2, the changes were similar to those in Stage 1, but more prominent. In Stage 3, the arteries have a 'copper wire' appearance and this is much more arteriovenous compression. These are serious atherosclerotic changes of the retinal arteries. In Stage 4, the arteries have a 'silver wire' appearance and the arteriovenous crossing changes are more severe. This is the most severe form of atherosclerosis of the retinal arteries. In addition, we found that the retinal artery lesion over Stage 2 had good specificity and sensitivity according to the area under the ROC curve. Therefore, the retinal artery atherosclerosis greater than or equal to Stage 2 was defined as a grouping criteria.

Coronary angiography

Coronary angiography was performed in all patients using a standard Judkins technique.⁸ The degree of diameter stenosis (%) was evaluated by two observers who were blinded to the information regarding retinal artery lesions. The percentage of luminal diameter stenosis was evaluated by quantitative coronary analysis in each segment, and CAD was defined as the presence of a greater than 50% narrowing in diameter for each of the three main coronary vessels (left anterior descending

coronary artery, left circumflex coronary artery, and right coronary artery). The total number of patients was divided into three severity grading according to the coronary angiography result: single vessel lesion, double vessels lesion, and multiple vessels lesion.

Follow-up visits and ethical statements

All patients were followed up for 3–6 years at an outpatient clinic after hospital discharge. Follow-up was scheduled once every 3 months after discharge by a cardiologist and until the end of the study on 31 August 2012. Primary endpoints included all-cause mortality and the occurrence of MI, stent thrombosis, and target vessel revascularization. The composite endpoints were defined as major adverse cardiac and cerebrovascular events (MACCE), namely death, MI, and stroke. Clinical follow-up was carried out through patient visits, telephone interviews, and medical record reviews. Independent research personnel entered the data and an independent committee adjudicated clinical events. There was a 7.63% lost rate after 3–6 years of follow-up. This study was approved by the Ethics Committee of Beijing Mentougou District Hospital. Informed consent was obtained for all the participants and signed by themselves.

Statistical analysis

Baseline characteristics of patients were presented as the means \pm standard deviation and compared using ANOVA for continuous variables and the chi-squared test was used for non-continuous variables. Kaplan-Meier curves were calculated for visualizing overall survival as well as freedom from MACCE and death for patients among three groups. A long-rank test was performed to compare three curves. Cox regression analysis was performed to assess the independent predictors of outcome. P value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software (version 13.0).

Results

The baseline data between the groups

There were significant differences in the outcome of coronary artery lesion, MACCE, and death among the three groups ($P < 0.001$, $P = 0.006$, $P = 0.019$, respectively; Table 1). There was no significant difference in other outcome among three groups ($P > 0.05$; Table 1).

Table 1 Baseline characteristics of the 436 patients

Characteristic	Group 1 (n = 111)	Group 2		P value	P value
		Stage <2 (n = 135)	Stage ≥2 (n = 190)		
Male, n (%)	37 (33.3)	53 (39.3)	77 (40.5)	0.694	0.092
Mean age ± SD (years)	60.1 ± 10.1	60.7 ± 11.4	61.2 ± 11.2	0.688	0.679
Mean BMI ± SD (kg/m ²)	24.7 ± 3.35	25.0 ± 3.51	25.6 ± 4.00	0.124	0.061
Hypertension, n (%)	95 (85.6)	115 (85.2)	153 (80.5)	0.587	0.209
Hypercholesterolemia, n (%)	55 (49.5)	64 (47.4)	75 (39.5)	0.077	0.310
Diabetes, n (%)	36 (32.4)	47 (34.8)	61 (32.1)	0.723	0.884
Smoking, n (%)	66 (59.5)	84 (62.2)	96 (50.5)	0.076	0.191
Mean LDL-C ± SD (mmol/l)	2.8 ± 0.76	2.8 ± 0.72	2.8 ± 0.82	0.530	0.809
AMI, n (%)	46 (41.4)	56 (41.5)	89 (46.8)	0.152	0.296
UAP, n (%)	65 (58.6)	79 (58.5)	101 (53.2)	0.152	0.296
Coronary artery lesion, n (%)				0.707	0.001
Single vessel lesion	45 (39.8)	29 (22.4)	34 (18.8)		
Double vessels lesion	45 (39.8)	46 (34.0)	68 (35.6)		
Multiple vessels lesion	21 (20.4)	60 (43.6)	88 (45.6)		
Drug administration, n (%)					
statins	111 (100.0)	132 (98.0)	188 (99.0)	0.415	0.262
aspirin	108 (97.6)	131 (97.3)	188 (99.0)	0.219	0.446
clopidogrel	107 (96.7)	132 (98.0)	188 (99.0)	0.415	0.348
ACEI/ARB	71 (76.4)	112 (83.0)	159 (83.7)	0.868	0.228
β-blocker	97 (87.0)	119 (88.4)	168 (88.6)	0.959	0.900
MACCE, n (%)	7 (6.3)	8 (5.9)	29 (15.3)	0.006	0.007
Death, n (%)	3 (2.7)	4 (3.0)	16 (8.4)	0.030	0.035

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin II receptor blockers; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; MACCE, main adverse cardiovascular and cerebrovascular events; SD, standard deviation; UAP, unstable angina pectoris.

Comparison of the prevalence of MACCE, MI, revascularization, death, and stroke among the three groups

There were significant differences in the prevalence rate of MACCE and death among the three groups (6.3 vs 5.9 vs 15.3%, $P = 0.007$; 2.7 vs 3.0 vs 8.4%, $P = 0.035$; respectively. Figure 1). There was no significant difference in the prevalence rate of MI, revascularization, and stroke among three groups (1.8 vs 1.5 vs 3.2%, $P = 0.563$; 0.9 vs 0.7 vs 1.6%, $P = 0.753$; 0.9 vs 0.7 vs 2.1%, $P = 0.514$. Figure 1).

Comparison of the MACCE and mortality among three groups

Group 3 had more MACCE than those of group 1 and group 2 (15.3 vs 6.3%, $P = 0.007$; 15.3 vs 5.9%, $P = 0.006$). The patients of group 1 had no more MACCE than those of Stage <2 group (6.5 vs 5.9%, $P = 0.921$). This effect was confirmed by their survival, Kaplan-Meier analysis (Figure 2). The patients of group 3 had more mortality than those of group 1 and group 2 (8.4 vs 2.7%, $P = 0.032$; 8.4 vs 3.0%, $P = 0.030$). The patients of group 1 had no more mortality than those of Stage <2 group (2.7 vs 3.0%, $P = 0.927$). This effect was confirmed by their survival, Kaplan-Meier analysis (Figure 3).

Multi-factorial analysis using the Cox proportional hazard model in patients with MACCE

In the multivariate Cox regression model, after adjusting for other important covariates, Stage ≥2 remained an independent predictor for MACCE with a risk ratio of 2.443, with 95% confidence interval: 1.108–5.388, $P = 0.027$ (see Table 2).

Discussion

Retina was the only place in the body where microvascular damage can be observed directly. Retinal artery lesion was a chronic vascular lesion, which was of aging performance in the whole vascular system. Atherosclerotic changes in the retinal arteries were characterized by thickening of the arterial wall and lipid deposition in the intima. Retinal artery microvascular abnormalities and the development and prognosis of cardiovascular and cerebrovascular disease were closely related. In the ARIC Study, smaller retinal arteriole-to-venule ratio was reported to be associated with an increased risk of stroke, especially cerebral infarction.⁹ This association was confirmed in the Cardiovascular Health Study.¹⁰ Retinal vascular caliber and coronary heart disease (CHD) studies suggested that retinal vascular caliber predicts CHD more strongly in

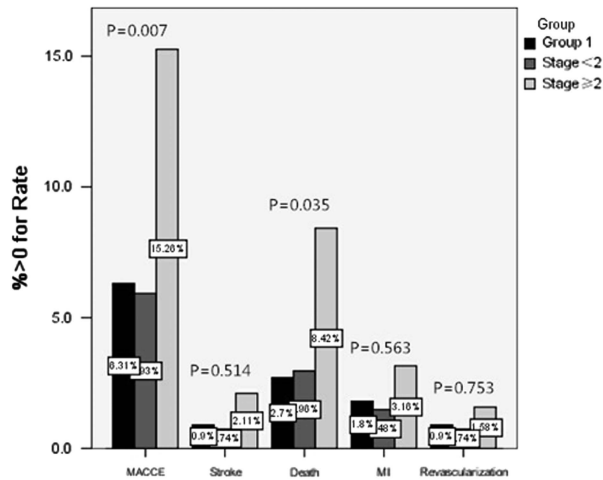


Figure 1 Comparison of the prevalence rate of MACCE, stroke, death, MI, and revascularization among three groups.

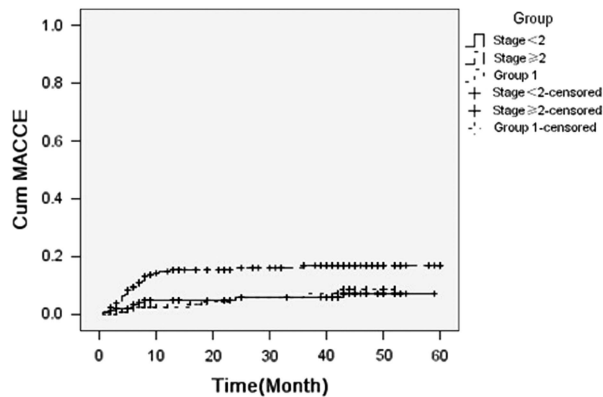


Figure 2 Comparison of three Kaplan-Meier curves as a function of time to the MACCE in Group 1, Stage <2, and Stage ≥2 (Wilcoxon-Gehan test, $F=13.93$, $P=0.001$; Cox's F test = 11.57, $P=0.003$).

women than men, possibly reflecting the greater contribution of microvascular disease to CHD development.¹¹ In combined analysis of the Blue Mountains Eye Study and the Beaver Dam Eye Study, smaller arterioles and larger venules were associated with a 20–30% increased risk of CHD mortality independent of cardiovascular risk factors.¹² In another meta-analysis including 22 159 participants, McGeehan *et al*¹³ found that retinal vessel caliber changes of both wider venules and narrower arterioles were associated with an increased risk for CHD.

The retinal artery atherosclerosis degree was closely related to ACS recurrence of MACCE from this study. It seemed that the early detection of retinal artery atherosclerosis had a directed significance to the long-term outcome of patients with ACS. With the increase in severity of retinal artery atherosclerosis, MACCE was more likely to occur.

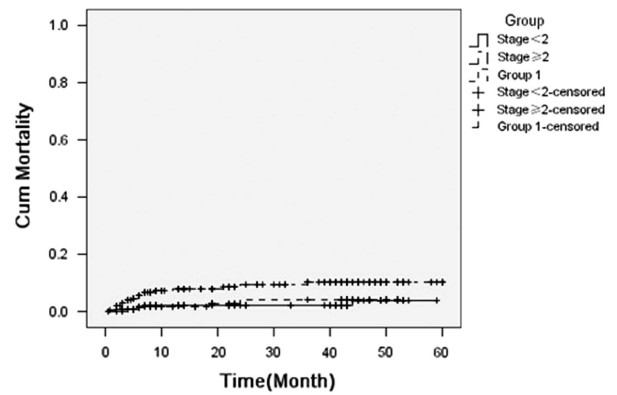


Figure 3 Comparison of three Kaplan-Meier curves as a function of time to the cumulative mortality in Group 1, Stage <2, and Stage ≥2 (Wilcoxon-Gehan test, $F=2.77$, $P=0.251$; Cox's F test = 3.176, $P=0.204$).

Table 2 Cox regression analysis in patients with MACCE

Category	RR	95% CI	P value
Female	0.646	0.335–1.247	0.193
Age (years)	0.989	0.964–1.014	0.381
Hypertension	1.064	0.544–2.084	0.856
Hypercholesterolemia	1.796	0.939–3.332	0.078
Diabetes	0.583	0.284–1.195	0.140
Smoking	1.075	0.555–2.082	0.830
Multiple vessels lesion	1.838	0.826–4.088	0.136
Stage ≥2	2.443	1.108–5.388	0.027
LDL-C (mmol/l)	0.690	0.465–1.022	0.064
BMI (kg/m ²)	0.953	0.885–1.026	0.204

Abbreviations: BMI, body mass index; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; MACCE, main adverse cardiovascular and cerebrovascular events; RR, risk ratio.

Retinal artery atherosclerosis was the marker for the body where microvascular damage happened. It was the result of multiple risk factors of hypertension, diabetes mellitus, and hyperlipidemia. The study found that there was no significant difference in hypertension, diabetes mellitus, and hyperlipidemia among the three groups because the study did not consider the duration of the risk factors. Retinal artery lesions often indicate a wide atherosclerosis in the vascular of the whole body. Wang *et al*⁶ found that retinal artery lesions of ≥Stage 2 had a significant correlation with the large artery atherosclerosis and those patients who had a retinal artery lesions often had severe coronary artery lesions. Wieberdink *et al*¹⁴ found that retinal artery lesion had correlation with the cerebral and renal artery lesions. This study found that the retinal artery also had a close correlation with coronary artery lesions, and the patients with retinal artery lesions of ≥Stage 2 had higher risk to catch MACCE than those who with retinal artery lesions of <Stage 2, which indicated that retinal artery lesions may be the indicators of coronary lesions. It is

recommended that the patients with ACS had better to take the examination of retinal artery.

The present study showed that the incidences of stroke, MI, and revascularization were not significantly different among the groups. Comparison of three Kaplan-Meier curves as a function of time to the cumulative mortality in Group 1, Stage <2, and Stage \geq 2 (Wilcoxon-Gehan test, $F = 2.77$, $P = 0.251$; Cox's F test = 3.176, $P = 0.204$; Figure 3) proved difference among three groups. Retinal artery atherosclerosis^{9,12} had been shown to predict clinical cardiovascular and cerebrovascular outcomes.

It was increasingly recognized that abnormalities of the microvasculature played an important role in the development and consequences of cardiovascular disease (CVD).^{15,16} From a theoretical standpoint, the design of the microvascular network was important in determining the delivery of nutrients and oxygen with maximal efficiency.¹⁷ Angiogenesis and increased flow in the retina was also associated with the degree of bending of the fundus artery,¹⁸ and significant alterations in retinal bifurcation geometry have been shown to be associated with age, hypertension, and peripheral vascular disease.^{19,20} We suggest that evaluation of the retinal microvasculature may be a useful predictor of target organ damage and cardiovascular risk. However, we advise cautious interpretation of the study findings, because we cannot assume a perfect correlation of structural microvascular changes in the retina with coronary or cerebral microvascular disease. Although some of the histopathologic features of retinal abnormalities (arteriolar narrowing, intimal thickening, and medial hyalinization) are also seen in histological studies of patients with coronary microvascular disease, there are also significant differences in the anatomy and physiology of the retinal microcirculation and the circulation in the heart and brain.²¹

Conclusions

After 3–6 years of follow-up, the retinal artery atherosclerosis degree was closely related to ACS recurrence of MACCE. Patients with ACS and retinal artery atherosclerosis of \geq Stage 2 had excellent and significantly better prognosis for MACCE after follow-up compared with patients with retinal artery atherosclerosis of <Stage 2. After eliminating the other factors influencing the prognosis of ACS, retinal artery atherosclerosis of \geq Stage 2 of ACS patients with recurrence of MACCE was increased.

Study limitations

Our study has some limitations that should be considered. First, the study was a consecutive but

retrospective observational analysis from a single-center and the duration of risk factors such as hypertension and diabetes was not considered, which could produce potential biased results. Second, the fundus examination was undertaken only with a direct ophthalmoscope by one clinician, which means peripheral lesions could have been missed and could produce potential bias. Examination with slit-lamp biomicroscopy and indirect ophthalmoscopy would have improved the assessment. Even so, our findings also have some value.

Summary

What was known before

- Some studies showed that the retinal artery lesions had a relationship with the coronary artery lesions but none of them described the affection of retinal artery lesions to the long-term outcome of ACS.

What this study adds

- The aim of this study was to explore the relationship of retinal artery lesions with the main adverse cardiovascular and cerebrovascular events (MACCE) after 3–6 years of follow-up in the patients with ACS.

Conflict of interest

The authors declare no conflict of interest.

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