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ARTICLE

Albumin to globulin ratio was associated with in-stent restenosis and revascularization events after percutaneous coronary intervention

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Abstract

In-stent restenosis is a common complication after percutaneous coronary intervention (PCI) for coronary heart disease requiring revascularization. We performed a retrospective analysis to assess the value of inflammatory biomarker albumin to globulin ratio (AGR) in clinical prognosis of PCI. In total, 992 patients with coronary heart disease who underwent the first drug-eluting stent implantation and re-examination angiography in our hospital were enrolled in this study. The AGR was measured. At mean follow-up of 11.2 ± 4 months, the in-stent restenosis (ISR) and revascularization events (including target lesion revascularization, target vessel revascularization, and revascularization of de novo lesions) occurred in 127 and 284 patients, respectively. Compared with the non-ISR or non-event group, AGR was significantly lower in the ISR group and the events group. Beyond that, albumin was significantly lower, whereas urea nitrogen, glucose, and Gensini score, as well as the proportions of a history of diabetes and peripheral vascular diseases were significantly higher in the ISR group and the events group. Age, heart rate, white blood cell, neutrophils, lymphocyte, monocyte, and incidence of ischemic stroke were significantly higher in the events group. Multivariate Cox regression analysis showed that AGR was independently associated with ISR ($p = 0.032$) and events ($p = 0.024$). Besides, Kaplan-Meier analysis indicated that the higher quartile of AGR had a lower rate of ISR ($p = 0.038$) and events ($p \leq 0.001$). Finally, the receiver operating characteristic curve for AGR in diagnosing ISR and events indicated that the area under the curve were 0.56 and 0.57, respectively. Therefore, AGR is one of the most important factors that independently associate with the ISR and revascularization events after PCI.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Albumin to globulin ratio (AGR) is regarded as an inflammatory biomarker and demonstrates a promising clinical role in various diseases. However, there are limited data suggesting it may serve as a biomarker of clinical outcomes, including in-stent restenosis (ISR) and revascularization events, in patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI).

WHAT QUESTION DID THIS STUDY ADDRESS?

We sought to perform this analysis to assess the value of inflammatory biomarker AGR in the clinical prognosis of PCI.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Compared with the non-ISR and non-event groups, AGR was significantly lower both in the ISR and revascularization events groups. Further, AGR was independently associated with ISR and revascularization events after PCI in patients with CHD.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Measures should be taken based on the level of AGR in time. Besides, albumin supplementation or decreasing globulin levels may help to improve the occurrence of adverse events, including ISR.

INTRODUCTION

Percutaneous coronary intervention (PCI) has been thought of as a tremendous advance in the treatment of coronary heart disease (CHD). Traditional PCI only used the balloon to open narrow coronary vessels, usually leading to a high risk of restenosis after surgery. Next came the first-generation of bare-metal stents (BMS), which greatly decreased the restenosis rate. Currently, the second-generation drug-eluting stent (DES) has become the main method in treating CHD, which greatly benefits patients but still fails to completely solve the puzzle of in-stent restenosis (ISR).[1] Therefore, it is of great significance to explore new ways to inhibit ISR.

Previous researches have proved that CHD is a form of chronic inflammatory disease.[2] Among the increasing evidence, inflammation was further confirmed to play a vital role in the development and progression of ISR.[3] Recently, some studies revealed the potential function of inflammatory markers, including TREM-1, C1q/TNF-related protein (CTRP), TLR3, and TLR4 in predicting ISR.[4–6] More than that, the ratio of platelet-to-lymphocyte, which was an inflammation-related indicator, could provide the basis for assessing the inflammatory status and predicting the possibility of ISR.[7]

More and more results indicated that the albumin to globulin ratio (AGR), a serum inflammatory marker, could construct a close relationship with inflammatory diseases, such as cancer[8,9] and CHD.[10] However, there is limited information explaining comprehensively the function of AGR in ISR. In our study, we focused on the impact of peri-operative period AGR on the occurrence of ISR and revascularization events after DES implantation.

METHODS

Study populations

This study was a retrospective observational study. A total of 1270 patients with CHD who received DES implantation for the first time and follow-up angiography in our hospital from July 2013 to February 2019 were retrospectively reviewed for relevant medical records. Of them, 180 patients were excluded because the follow-up time was either less than 5 months or more than 24 months and 14 patients were excluded due to the lack of laboratory results. The range between two angiographies was from 5 months to 24 months and the average was 11.2 ± 4 months. Patients were excluded from the study if they met the following criteria: history of autoimmune diseases, systemic diseases, malignant tumors, acute infection, severe hepatorenal insufficiency, a history of coronary artery bypass grafting or PCI, and severe valvular heart disease. Finally, 992 patients were enrolled in the study. Our study protocol was approved by the ethics committee of Zhongda Hospital.

Study procedures

All the coronary interventions were performed by experienced cardiologists in accordance with the guidelines.[11] After PCI, all the patients were given standardized treatment, including dual antiplatelet therapy, statin, and other cardiovascular-related drugs. All laboratory data were collected at the first time after hospital admission, including routine blood test (white blood cell, red blood cell, platelet, neutrophils, monocyte, lymphocyte, eosinophil, basophil, mean platelet volume, platelet distribution width, and red blood cell distribution width), fibrinolytic function (prothrombin time, activated partial thromboplastin time, International Normalized Ratio [INR], and D-dimer), and biochemical indicators (total protein, albumin, globulin, prealbumin, creatinine, urea nitrogen, alanine aminotransferase, aspartate transaminase, total bilirubin, direct bilirubin, uric acid, glucose, cholesterol, and triglyceride). The value of AGR was calculated by dividing albumin concentration by globulin concentration. Clinical values, such as body mass index (BMI), current smoking and drinking, hypertension, diabetes, hyperlipidemia, atrial fibrillation, stroke, and peripheral vascular disease history were also collected. BMI was calculated using the formula weight (kg)/height $(m)^2$. Current smoking and drinking were defined as smoking and alcohol consumption within 1 year before the first hospitalization. To assess the severity of coronary lesions in patients, we calculated the coronary stenosis score Gensini for each patient. The Gensini score was computed according to previously described methods.[12]

Follow-up was carried out between 5 and 24 months after stent implantation. ISR was defined as more than 50% restenosis in or adjacent to the implanted stent(s) (less than 5 mm). Revascularization events was defined as target lesion revascularization (TLR), target vessel revascularization (TVR), and de novo revascularization. TLR was defined as repeated PCI treatment within the target lesion stent or edge 5 mm. TVR was defined as PCI in the target lesion coronary vessel outside the stent. De novo revascularization was defined as the revascularization of other coronary vessels.

Statistical analysis

All data were analyzed by using SPSS 22.0 and GraphPad Prism 8. Continuous variables are presented in the form of mean ± standard deviation. The *t*-test was used for comparison between the two groups and analysis of variance (ANOVA) was used to compare differences between more than two groups. Categorical variables are presented as numbers and percentages and were compared using the chi-square test. Univariate or multivariate (method: forward LR) Cox proportional hazard model analysis was used to determine which variables are independent risk factors for ISR and events. Those recognized risk factors for CHD or factors with significant differences between ISR or events group and the control group were included in the analysis. The results are presented in the form of hazard ratio (HR), 95% confidence interval (CI), and *p* value. Patients were divided into quartiles according to AGR. Kaplan-Meier analysis was used to deeply explore the relationship between AGR and ISR events. The receiver operating characteristic (ROC) curve was also plotted to evaluate the role of AGR in diagnosing the occurrence of ISR and events. Any *p* value less than 0.05 was considered to have statistical significance.

RESULTS

Patients who received second-generation DES stent implantation for the first time in our hospital and follow-up angiography were enrolled in our study. In the end, 992 patients (men: 690/992, 70%; mean age: 63.4 ± 10.7 years) were selected. These patients were divided into the ISR group ($n = 127$) and the non-ISR group ($n = 865$), as well as the events group ($n = 284$) and the non-event group ($n = 708$). The basic characteristics of patients are shown in Tables 1 and 2. Compared with the non-ISR group and non-event group, both the ISR and events group had lower levels of AGR and albumin. The average level of urea nitrogen, glucose, and Gensini score, as well as the proportions of diabetes and peripheral vascular diseases history, were higher in the ISR and events group compared with their corresponding control groups. Beyond that, average age, heart rate, white blood cell, neutrophils, lymphocyte, and monocyte, as well as history of ischemic stroke were only significantly higher in the events group than in the non-event group.

To further determine the role of AGR in ISR and events, we performed univariate and multivariate Cox proportional hazard model analyses (Tables 3 and 4), and found that AGR (HR: 0.551, 95% CI: 0.320–0.950, $p = 0.032$), glucose (HR: 1.094, 95% CI: 1.038–1.153, $p = 0.001$) were risk factors of ISR. AGR (HR: 0.640, 95% CI: 0.435–0.943, $p = 0.024$) and glucose (HR: 1.076, 95% CI: 1.036–1.119, $p \leq 0.001$) were also independent risk factors of events. Besides, age (HR: 1.020, 95% CI: 1.008–1.033, $p = 0.002$), heart rate (HR: 1.010, 95% CI: 1.001–1.020, $p = 0.038$), and white blood cells (HR: 1.048, 95% CI: 1.002–1.096, $p = 0.041$) were independently associated with events, not ISR.

Next, we divided all the 992 patients into four groups according to the quartile of AGR. As shown in Table 5, the

TABLE 1 Clinical characteristic of the patients

Variables	Non-ISR ($n = 865$)	ISR ($n = 127$)	p value	Non-event ($n = 708$)	Events ($n = 284$)	p value
Men, n (%)	598 (69.1)	92 (72.4)	0.449	494 (69.8)	196 (69)	0.814
Age	63.17 ± 10.82	64.65 ± 9.99	0.147	62.73 ± 10.8	64.92 ± 10.38	0.004
BMI	25.31 ± 3.36	25.56 ± 3.25	0.455	25.31 ± 3.25	25.44 ± 3.58	0.622
Current smoking, n (%)	320 (37)	51 (40.2)	0.491	267 (37.7)	104 (36.6)	0.748
Current drinking, n (%)	129 (14.9)	14 (11)	0.244	105 (14.8)	38 (13.4)	0.557
Hyperlipemia, n (%)	79 (9.1)	9 (7)	0.449	67 (9.5)	21 (7.4)	0.3
Hypertension, n (%)	638 (73.8)	89 (70.1)	0.382	519 (73.3)	208 (73.2)	0.983
Diabetes, n (%)	232 (26.8)	58 (45.7)	≤0.001	176 (24.9)	114 (40.1)	≤0.001
Atrial fibrillation, n (%)	51 (5.9)	7 (5.5)	0.863	38 (5.4)	20 (7)	0.309
Stroke, n (%)	160 (18.5)	24 (18.9)	0.914	118 (16.7)	66 (23.2)	0.016
Peripheral vascular diseases, n (%)	31 (3.6)	11 (8.7)	0.008	24 (3.4)	18 (6.3)	0.037
COPD, n (%)	14 (1.6)	0 (0)	0.298	10 (1.4)	4 (1.4)	1

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ISR, in-stent restenosis.

range of AGR in each group was 0.675–1.374, 1.375–1.583, 1.584–1.826, and 1.827–3 separately. The incidence rate of ISR in the four groups declined gradually, and, in turn: 16.94%, 12.85%, 12.05%, and 9.35% ($p = 0.088$) whereas that of events also decreased from 37.5% to 28.51% to 24.5% and to 23.98% ($p = 0.003$).

We also performed Kaplan-Meier curve analysis based on quartiles of AGR to deeply explore the relationship between AGR with ISR, as well as with events. The results shown in Figure 1 indicated that the risk of ISR ($p = 0.038$) and events ($p \leq 0.001$) were significantly higher in patients with lower AGR values.

Finally, to evaluate the diagnostic value of AGR for diagnosing the ISR and events, we performed ROC curve analysis and found that the area under the curve (AUC) value was 0.56 for ISR and was 0.57 for events (Figure 2).

DISCUSSION

In this study, we found that AGR is a risk factor independently associated with ISR and revascularization events in patients with CHD. Patients with CHD with higher AGR may be confronted with a lower incidence of ISR and events. The present research is the first to report the relationship between AGR and ISR or revascularization events after stent implantation.

CHD is one of the leading causes of mortality around the world.[13] PCI has been widely used in the treatment of CHD when vascular stenosis is serious.[14] With the development of technology, instruments for PCI ranged from balloon to first-generation BMS, then to second-generation DES.[15] Although this progress has led to a lower rate of coronary restenosis, ISR remains a major clinical problem in cardiac interventional surgery.[16] According to statistics, the average time of ISR occurrence in patients with CHD after PCI is more than 12 months.[17] The mechanism of ISR is very complex. ISR in patients who undergo BMS implantation usually results from intimal injury and subsequently neointimal formation, whereas ISR in DES is mainly due to inflammation.[18] Revascularization events are another common cardiovascular event after PCI with BMS implantation or DES implantation.[19] As is known, inflammatory response and neointimal formation are major risk factors for revascularization.[20]

Atherosclerosis is recognized as a chronic inflammatory disease, which is the most important pathological basis of CHD.[21] A variety of inflammatory biomarkers have been discovered to be closely associated with CHD. Recently, lymphocyte-to-monocyte ratio, which is a novel inflammatory marker, has been found to be independently associated with ISR in patients with CHD after BMS implantation.[22] Both neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio, which represent the inflammatory status, were independent risk factors of ISR for chronic total occlusion coronary lesions after DES implantation.[23] In addition, NLR has been suggested to predict ISR after carotid angioplasty and stenting.[24] Therefore, inflammatory biomarkers have important predictive value in the occurrence of ISR.

The AGR is obtained by dividing albumin by globulin. As a recognized marker of inflammation, AGR has been widely used in the judgment of cancer prognosis, such as diffuse large B cell lymphoma,[25] esophageal cancer,[9] colon cancer,[26] clear cell renal cell carcinoma,[27] and non-small

TABLE 2 Laboratory characteristic of the patients

Variables	Non-ISR ($n = 865$)	ISR ($n = 127$)	p value	Non-event ($n = 708$)	Events ($n = 284$)	p value
Systolic pressure, mm Hg	134.8 ± 19.2	131.43 ± 18.75	0.065	133.85 ± 19.03	135.65 ± 19.57	0.182
Diastolic pressure, mm Hg	79.17 ± 12.08	77.86 ± 9.76	0.174	79.11 ± 11.98	78.71 ± 11.39	0.632
Heart rate, per min	74.87 ± 12.76	76.76 ± 14.16	0.125	74.37 ± 11.9	76.99 ± 15.14	0.009
White blood cell, $\times 10^9$/L	7.54 ± 2.82	7.82 ± 3	0.296	7.45 ± 2.85	7.88 ± 2.81	0.031
Red blood cell, $\times 10^{12}$/L	4.62 ± 0.52	4.6 ± 0.6	0.62	4.63 ± 0.52	4.59 ± 0.56	0.208
Platelet, $\times 10^9$/L	198.44 ± 52.34	200.94 ± 62.7	0.627	198.88 ± 53.23	198.46 ± 55.12	0.913
Neutrophils, $\times 10^9$/L	5.34 ± 2.71	5.6 ± 2.77	0.312	5.23 ± 2.7	5.74 ± 2.73	0.008
Lymphocyte, $\times 10^9$/L	1.66 ± 0.68	1.65 ± 0.64	0.924	1.69 ± 0.69	1.59 ± 0.63	0.04
Monocyte, $\times 10^9$/L	0.4 ± 0.18	0.43 ± 0.21	0.104	0.4 ± 0.18	0.42 ± 0.19	0.035
Eosinophil, $\times 10^9$/L	0.12 ± 0.13	0.1 ± 0.09	0.151	0.12 ± 0.13	0.11 ± 0.12	0.349
Basophil, $\times 10^9$/L	0.02 ± 0.02	0.02 ± 0.02	0.249	0.02 ± 0.02	0.02 ± 0.02	0.079
MPV, fL	10.56 ± 1.31	10.78 ± 1.32	0.074	10.58 ± 1.32	10.61 ± 1.29	0.714
PDW, fL	15.02 ± 3.05	15.02 ± 3.26	0.998	14.94 ± 2.85	15.21 ± 3.57	0.203
RDW CV, %	13.02 ± 0.91	12.98 ± 0.68	0.626	13.00 ± 0.86	13.04 ± 0.94	0.53
RDW SD, fL	42.48 ± 3.39	42.15 ± 3.26	0.314	42.46 ± 3.32	42.37 ± 3.53	0.71
PT, S	11.27 ± 3.77	11.32 ± 1.63	0.898	11.33 ± 3.89	11.16 ± 2.64	0.507
APTT, S	35.04 ± 21.26	33.95 ± 20.07	0.611	34.85 ± 20.45	35.06 ± 22.76	0.894
INR	1.06 ± 0.35	1.05 ± 0.13	0.931	1.06 ± 0.36	1.04 ± 0.25	0.405
D-Dimer, ug/L	246.14 ± 2053.32	177.42 ± 169.24	0.722	243.06 ± 2253.65	225.03 ± 539.76	0.897
TG, mmol/L	1.93 ± 1.63	1.75 ± 1.42	0.244	1.94 ± 1.72	1.81 ± 1.3	0.229
TC, mmol/L	4.62 ± 1.26	4.45 ± 1.08	0.152	4.6 ± 1.24	4.59 ± 1.24	0.912
HDL, mmol/L	1.13 ± 0.26	1.11 ± 0.23	0.352	1.13 ± 0.26	1.13 ± 0.25	0.787
LDL, mmol/L	2.82 ± 0.9	2.71 ± 0.79	0.191	2.81 ± 0.89	2.8 ± 0.87	0.811
ApoA1, g/L	1.05 ± 0.23	1.04 ± 0.24	0.508	1.05 ± 0.23	1.05 ± 0.24	0.91
ApoB, g/L	0.82 ± 0.22	0.8 ± 0.22	0.439	0.81 ± 0.22	0.82 ± 0.22	0.891
Lipoprotein a, mg/L	296.58 ± 249.43	341.26 ± 314.12	0.133	297.14 ± 255.29	315.09 ± 267.35	0.33
Total protein, g/L	64.88 ± 6.21	64.58 ± 6.83	0.618	64.98 ± 6.12	64.49 ± 6.7	0.272
Albumin, g/L	39.7 ± 4.44	38.85 ± 5.05	0.048	39.91 ± 4.26	38.81 ± 5.06	0.001
Globulin, g/L	25.18 ± 4.51	25.73 ± 4.44	0.195	25.07 ± 4.47	25.68 ± 4.55	0.052
Prealbumin, g/L	0.35 ± 1.95	0.96 ± 4.78	0.165	0.4 ± 2.26	0.48 ± 3.03	0.671
Creatinine, umol/L	85.21 ± 22.05	88.28 ± 23.29	0.148	84.67 ± 20.31	87.93 ± 26.28	0.061
Urea nitrogen, mmol/L	5.56 ± 1.81	5.97 ± 2.34	0.023	5.5 ± 1.77	5.89 ± 2.13	0.007
ALT, U/L	31.32 ± 33.88	31.38 ± 25.26	0.985	31.32 ± 35.07	31.33 ± 26.74	0.997
AST, U/L	53.65 ± 90.23	63.14 ± 91.49	0.27	54.73 ± 95.95	55.21 ± 74.92	0.94
Total bilirubin, umol/L	12.78 ± 5.97	13.04 ± 5.42	0.651	12.79 ± 5.87	12.88 ± 6.01	0.835
Direct bilirubin, umol/L	3.53 ± 2.12	3.87 ± 2.2	0.097	3.55 ± 2.21	3.65 ± 1.94	0.48
Uric acid, umol/L	335.57 ± 95.36	338.32 ± 97.41	0.762	337.16 ± 94.52	332.82 ± 98.28	0.518
Glucose, mmol/L	6.52 ± 2.56	7.23 ± 2.82	0.004	6.37 ± 2.25	7.22 ± 3.26	≤0.001
Gensini score	44.11 ± 31.86	51.04 ± 32.65	0.023	39.82 ± 29.7	57.91 ± 33.98	≤0.001
AGR	1.63 ± 0.35	1.56 ± 0.35	0.029	1.64 ± 0.35	1.56 ± 0.34	≤0.001

Abbreviations: AGR, albumin-to-globulin ratio; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; HDL-C, high density lipoprotein cholesterol; INR, International Normalized Ratio; LDL-C, low density lipoprotein cholesterol; MPV, mean platelet volume; PDW, platelet distribution width; PT, prothrombin time; RDW, red blood cell distribution width; TC, total cholesterol; TG, triglyceride.

TABLE 3 Cox proportional hazard model Analysis of Predicting Risk Factors of ISR

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Male	1.166	0.790–1.721	0.439			
Age	1.012	0.996–1.029	0.144			
Current smoking	1.157	0.811–1.650	0.421			
Hypertension	0.842	0.576–1.231	0.374			
BMI	1.020	0.968–1.076	0.455			
White blood cell	1.033	0.975–1.094	0.272			
MPV	1.132	0.992–1.291	0.066			
Creatinine	1.005	0.998–1.012	0.243			
Urea nitrogen	1.09	1.012–1.175	0.023			
Direct bilirubin	1.055	0.989–1.125	0.105			
TC	0.900	0.774–1.046	0.170			
Glucose	1.073	1.022–1.127	0.004	1.094	1.038–1.153	0.001
AGR	0.538	0.320–0.906	0.020	0.551	0.320–0.950	0.032

Abbreviations: AGR, albumin-to-globulin ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ISR, in-stent restenosis; MPV, mean platelet volume; TC, triglyceride.

TABLE 4 Cox proportional hazard model analysis of predicting risk factors of events

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Male	0.978	0.760–1.258	0.862			
Age	1.016	1.005–1.028	0.004	1.020	1.008–1.033	0.002
Current smoking	0.962	0.756–1.224	0.752			
Hypertension	0.998	0.767–1.298	0.987			
BMI	1.007	0.970–1.045	0.725			
Heart rate	1.013	1.004–1.021	0.003	1.010	1.001–1.020	0.038
White blood cell	1.045	1.007–1.085	0.019	1.048	1.002–1.096	0.041
MPV	1.018	0.932–1.113	0.692			
Creatinine	1.006	1.001–1.011	0.020			
Urea nitrogen	1.085	1.032–1.142	0.001			
Direct bilirubin	1.016	0.966–1.068	0.542			
TC	0.995	0.905–1.094	0.910			
Glucose	1.084	1.049–1.119	≤0.001	1.076	1.036–1.119	≤0.001
AGR	0.512	0.361–0.728	≤0.001	0.640	0.435–0.943	0.024

Abbreviations: AGR, albumin-to-globulin ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ISR, in-stent restenosis; MPV, mean platelet volume; TC, triglyceride.

TABLE 5 Analysis in relation with AGR quartiles

	Patient groups in relation with AGR quartiles				
	Group A	Group B	Group C	Group D	*p*
Patients, *n*	248	249	249	246	
AGR, min–max	0.675–1.374	1.375–1.583	1.584–1.826	1.827–3	≤0.001
AGR, mean ± SD	1.21 ± 0.14	1.48 ± 0.06	1.70 ± 0.07	2.09 ± 0.23	≤0.001
ISR, *n* (%)	42 (16.94)	32 (12.85)	30 (12.05)	23 (9.35)	0.088
Event, *n* (%)	93 (37.5)	71 (28.51)	61 (24.5)	59 (23.98)	0.003

Abbreviations: AGR, albumin-to-globulin ratio; ISR, in-stent restenosis.

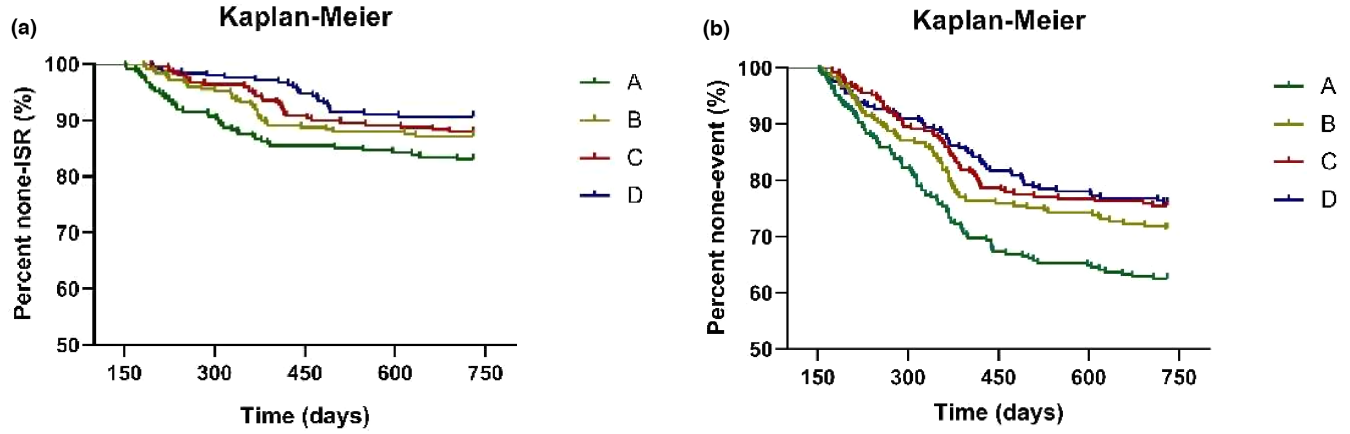

FIGURE 1 The Kaplan-Meier estimate curve of ISR and events in relation to AGR quartiles. Green represents group A, yellow represents group B, red represents group C, and blue represents group D. As shown, the lower the AGR level, the higher the incidence of ISR (a) and events (b). AGR, albumin-to-globulin ratio; ISR, in-stent restenosis

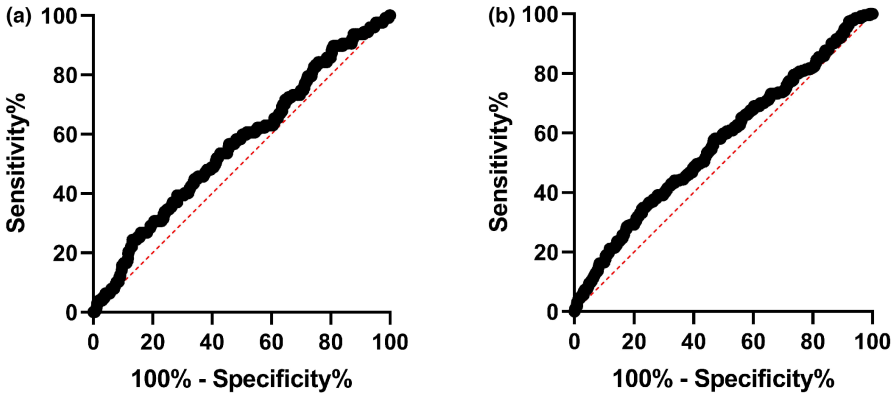

FIGURE 2 The ROC curve analysis of AGR in diagnosing the ISR and events. The red dotted line is the reference line. According to the ROC curve, the AUC for ISR is 0.56 (a) and for events is 0.57 (b). AGR, albumin-to-globulin ratio; AUC, area under the curve; ISR, in-stent restenosis; ROC, receiver operating characteristic

cell lung cancer.[28] Besides, in the nervous system, AGR is considered to be one of the important anticognitive decline factors.[29] In circulatory diseases, lower AGR was closely related to the occurrence of malignant cardiovascular and cerebrovascular events[30] and mortality in patients with heart failure with reduced ejection fraction.[31] However, whether the AGR could be used in the prediction of ISR was still unknown. Therefore, we performed a retrospective study enrolling patients with CHD who underwent their first DES implantation and underwent follow-up angiography in the following 5–24 months.

In the present research, AGR was significantly lower in the ISR group compared with the non-ISR group. AGR was also lower in the events group compared with the non-event group, indicating a role of AGR in anti-atherosclerosis progression. Multivariate Cox regression analysis showed that AGR and diabetes history were both independent risk factors of ISR and events in patients with CHD. We further divided the patients into four groups according to AGR quartiles and performed Kaplan-Meier curve analysis to reveal the relationship among AGR and ISR or events. As shown in the results, patients in the highest quartile of AGR had the lowest rate of ISR and revascularization events, which indicated a protective biomarker of AGR in patients with CHD after percutaneous coronary stent implantation. However, the ROC analysis indicated that AGR was not a valuable biomarker in diagnosing the occurrence of ISR and revascularization events due to the lack of predictiveness. The possible reason why AGR has a role in Kaplan-Meier curve but not in ROC analysis is because ROC was analyzed based only on whether ISR or events occurred, and the Kaplan-Meier curve was analyzed not only based on whether ISR and events occurred, but also on the occurrence time of the ISR and events.

We speculate that AGR mainly decreases the risk of ISR and events through anti-oxidant reaction and anti-inflammatory response. Albumin and globulin are the main components of protein in human plasm.[10] As the most abundant plasma protein component, albumin protects the vascular wall by playing an antioxidant role against oxidative damage of vascular endothelium,[32] therefore inhibiting the progress of atherosclerosis. Globulin is the main executor of immune function, and the immune system was closely connected with the development of atherosclerosis.[33] Wang et al. found[10] that albumin and

globulin were both independently associated with CHD. Therefore, albumin and globulin may also participate in the progression of ISR.

Although our research shows the relationship among AGR with ISR and events, there are still some limitations in our study. First, the study was designed in a retrospective, single-center way. Second, this study was unable to collect indicators including stent diameter and length for analysis. Third, most patients had no test results for inflammatory factors, such as C reactive protein (CRP), and interleukin-6 (IL-6).

CONCLUSION

In conclusion, our study showed that AGR, an inflammation biomarker, appears to be independently associated with ISR and revascularization events after PCI in patients with CHD. As a clinically accessible indicator, AGR may help cardiologists to more easily judge the prognosis of patients after PCI. Before clinical application, large, multicenter, prospective studies need to be conducted to determine the value of AGR.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.Z. wrote the manuscript. G.S.M. and Y.J.L. designed the research. R.Z., Z.X.T., J.G., Z.J.J., and M.M.Y. performed the research. R.Z., Z.X.T., and J.G. analyzed the data.

REFERENCES

1. Alraies MC, Darmoch F, Tummala R, Waksman R. Diagnosis and management challenges of in-stent restenosis in coronary arteries. *World J Cardiol*. 2017;9:640-651.
2. Soeki T, Sata M. Inflammatory biomarkers and atherosclerosis. *Int Heart J*. 2016;57:134-139.
3. Niccoli G, Montone RA, Sabato V, Crea F. Role of allergic inflammatory cells in coronary artery disease. *Circulation*. 2018;138:1736-1748.
4. Wang F, Li C, Ding FH, et al. Increased serum TREM-1 level is associated with in-stent restenosis, and activation of TREM-1 promotes inflammation, proliferation and migration in vascular smooth muscle cells. *Atherosclerosis*. 2017;267:10-18.
5. Shen Y, Li C, Zhang RY, et al. Association of increased serum CTRP5 levels with in-stent restenosis after coronary drug-eluting stent implantation: CTRP5 promoting inflammation, migration and proliferation in vascular smooth muscle cells. *Int J Cardiol*. 2017;228:129-136.
6. Liang S, Aiqun M, Jiwu L, Ping Z. TLR3 and TLR4 as potential clinical biomarkers for in-stent restenosis in drug-eluting stents patients. *Immunol Res*. 2016;64:424-430.
7. Yılmaz S, Sen F, Ünal S, et al. Usefulness of the platelet-to-lymphocyte ratio in predicting bare-metal stent restenosis. *Scand Cardiovasc J*. 2015;49:39-44.
8. He X, Guo S, Chen D, et al. Preoperative albumin to globulin ratio (AGR) as prognostic factor in renal cell carcinoma. *J Cancer*. 2017;8:258-265.
9. Oki S, Toiyama Y, Okugawa Y, et al. Clinical burden of preoperative albumin-globulin ratio in esophageal cancer patients. *Am J Surg*. 2017;214:891-898.
10. Wang M, Liu J, Ma C, et al. Synergistic association of serum albumin and globulin with coronary heart disease. *J Atheroscler Thromb*. 2012;19:619-632.
11. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2012;79:453-495.
12. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol*. 1983;51:606.
13. Richards SH, Anderson L, Jenkinson CE, et al. Psychological interventions for coronary heart disease. *Cochrane Database System Rev*. 2017;4:cd002902.
14. Al-Lamee R, Thompson D, Dehbi H-M, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet (London, England)*. 2018;391:31-40.
15. Bhatt DL. Percutaneous coronary intervention in 2018. *JAMA*. 2018;319:2127-2128.
16. Gonzalo N, Ryan N, Escaned J. New light on second-generation drug-eluting stent restenosis. *EuroIntervention*. 2017;13:265-266.
17. Lee MS, Banka G. In-stent restenosis. *Interventional Cardiol Clin*. 2016;5:211-220.
18. Kokkinidis DG, Waldo SW, Armstrong EJ. Treatment of coronary artery in-stent restenosis. *Expert Rev Cardiovasc Ther*. 2017;15:191-202.
19. Desrosiers KP, Brown JR, Langner CA, et al. Extended outcomes of complex coronary disease in the drug eluting stent era. *Cardiol Res*. 2011;2:97-105.
20. Okura H, Takagi T, Yoshida K. Therapies targeting inflammation after stent implantation. *Curr Vasc Pharmacol*. 2013;11:399-406.
21. Golia E, Limongelli G, Natale F, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. *Curr Atherosclerosis Rep*. 2014;16:435.
22. Murat SN, Yarlioglues M, Celik IE, et al. The relationship between lymphocyte-to-monocyte ratio and bare-metal stent in-stent restenosis in patients with stable coronary artery disease. *Clin Appl Thromb Hemost*. 2017;23:235-240.
23. Li C, Shen YI, Xu R, et al. Evaluation of preprocedural laboratory parameters as predictors of drug-eluting stent restenosis in coronary chronic total occlusion lesions. *Angiology*. 2019;70:272-278.
24. Dai Z, Li R, Zhao N. Neutrophil to lymphocyte ratio as a predictor of restenosis after angioplasty and stenting for asymptomatic carotid stenosis. *Angiology*. 2019;70:160-165.
25. Yue W, Liu B, Gao L, et al. The pretreatment albumin to globulin ratio as a significant predictor in patients with diffuse large B cell lymphoma. *Clin Chim Acta* 2018;485:316-322.
26. Fujikawa H, Toiyama Y, Inoue Y, et al. Prognostic impact of preoperative albumin-to-globulin ratio in patients with colon

cancer undergoing surgery with curative intent. *Anticancer Res*. 2017;37:1335-1342.
27. Koparal MY, Polat F, Cetin S, Bulut EC, Sozen TS. Prognostic role of preoperative albumin to globulin ratio in predicting survival of clear cell renal cell carcinoma. *Int Braz J Urol*. 2018;44:933-946.
28. Park S, Park S, Lee S-H, et al. Pretreatment albumin-to-globulin ratio as a predictive marker for tyrosine kinase inhibitor in non-small cell lung cancer. *Cancer Biomarkers*. 2016;16:425-433.
29. Koyama T, Kuriyama N, Ozaki E, et al. Serum albumin to globulin ratio is related to cognitive decline via reflection of homeostasis: a nested case-control study. *BMC Neurol*. 2016;16:253.
30. Beamer N, Coull BM, Sexton G, et al. Fibrinogen and the albumin-globulin ratio in recurrent stroke. *Stroke*. 1993;24:1133-1139.
31. Niedziela JT, Hudzik B, Szygula-Jurkiewicz B, et al. Albumin-to-globulin ratio as an independent predictor of mortality in chronic heart failure. *Biomarkers Med*. 2018;12:749-757.
32. Anraku M, Chuang VT, Maruyama T, Otagiri M. Redox properties of serum albumin. *Biochem Biophys Acta*. 2013;1830:5465-5472.
33. Sanjadi M, Rezvanie Sichanie Z, Totonchi H, et al. Atherosclerosis and autoimmunity: a growing relationship. *Int J Rheum Dis*. 2018;21:908-921.

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