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ORIGINAL RESEARCH

Serum Angptl2 and CyPA Levels in Acute Myocardial Infarction and In-Stent Restenosis After Percutaneous Coronary Intervention: A Single-Center Retrospective Case-Control Study

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Purpose: To explore the association between angiopoietin-like protein 2 (Angptl2) and cyclophilin A (CyPA) with acute myocardial infarction (AMI) and the occurrence of in-stent restenosis (ISR) after percutaneous coronary intervention (PCI).

Patients and Methods: A single-center retrospective research was conducted. Clinical data from 146 AMI patients who underwent PCI at our hospital were analyzed and designated as the AMI group. Additionally, 56 healthy individuals who underwent medical check-ups during the same period were enrolled as the Control group. Serum levels of Angptl2 and CyPA were compared between the AMI and control groups. Furthermore, based on the presence or absence of in-stent restenosis (ISR) during the follow-up period, the AMI patients were further divided into ISR and NISR groups. *Logistic* regression analysis was utilized to ascertain the risk factors influencing ISR after PCI in AMI patients. The diagnostic value of serum Angptl2 and CyPA for ISR after PCI was assessed using the receiver operating characteristic (ROC) curve.

Results: Compared with the Control group, the AMI group exhibited significantly elevated levels of Angptl2 and CyPA ($P<0.05$). *Logistic* regression analysis identified serum Angptl2 and CyPA are risk factors for occurrence of ISR after PCI in AMI patients. Additionally, the ROC curve analysis demonstrated that the combined use of serum Angptl2 and CyPA achieved an area under the curve (AUC) of 0.895 for predicting ISR in AMI patients after PCI.

Conclusion: Elevated serum levels of Angptl2 and CyPA in AMI patients who developed ISR after PCI suggest that these biomarkers may serve as potential risk indicators for predicting ISR following PCI.

Keywords: angiopoietin-like protein 2, cyclophilin A, acute myocardial infarction, in-stent restenosis, percutaneous coronary intervention

Introduction

Acute myocardial infarction (AMI) is one of the leading causes of cardiovascular mortality worldwide. Its pathogenesis is primarily associated with the rupture of atherosclerotic plaques in the coronary arteries, followed by platelet aggregation and thrombus formation. These events lead to a sudden and significant reduction or complete cessation of coronary blood flow, resulting in myocardial injury and necrosis due to ischemia and hypoxia.[1] The current treatment for myocardial infarction is percutaneous coronary intervention (PCI), but some patients may still experience in-stent restenosis (ISR) after undergoing PCI, which affects the quality of life of AMI patients.[2,3] Therefore, it is necessary to identify effective diagnostic markers for AMI and ISR after PCI. In recent years, with the in-depth investigation into the pathophysiological mechanisms of AMI and ISR, inflammatory responses have been identified as a critical factor in these pathological processes. Angiopoietin-like protein 2 (Angptl2) is a secretory glycoprotein that serves as a crucial inflammatory mediator, primarily originating from sources such as visceral adipose tissue, endothelial cells, and

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macrophages. It possesses pro-inflammatory properties and is closely associated with atherosclerosis and cardiovascular diseases.[4,5] Studies have demonstrated that serum levels of Angptl2 are elevated in patients with acute coronary syndrome, suggesting its potential utility as a biomarker for assessing the risk of developing acute coronary syndrome.[6] Cyclophilin A (CyPA), a molecular chaperone protein, is primarily expressed in various cell types, including vascular smooth muscle cells, endothelial cells, and cardiac fibroblasts. It can be secreted extracellularly in response to stimulation by reactive oxygen species. This protein significantly impacts cardiovascular inflammation, myocardial ischemia, and reperfusion injury processes and can accelerate the progression of coronary atherosclerosis.[7–9] Currently, there is a scarcity of research examining the relationship between serum Angptl2, CyPA, and AMI and ISR in AMI patients after PCI. Therefore, we conducted a single-center retrospective case-control study. This study aimed to determine the serum levels of Angptl2 and CyPA in AMI patients following PCI and to analyze the relationship between these biomarkers and the occurrence of ISR. We hope that our findings will provide new insights and potential biomarkers for the early identification of high-risk AMI patients and for optimizing post-PCI management in clinical practice.

Materials and Methods

Research Subjects

This single-center retrospective case-control study aimed to investigate the differences in serum Angptl2 and CyPA levels between AMI patients and healthy controls, as well as to follow up on the occurrence of ISR after PCI in AMI patients. Previous studies have shown that the incidence of ISR within one year after PCI for AMI is approximately 10%.[10,11] In this study, we set the error margin not to exceed 4.5% (ie, the upper and lower limits of the confidence interval differ by 9%). Using PASS 15.0 software and setting 1-α=0.9 (two-sided test), we calculated that a total of 142 participants would be required to ensure the scientific rigor of the study design.

The subjects of this study were hospitalized patients diagnosed with AMI at Zhejiang Provincial People's Hospital Bijie Hospital from March 2022 to March 2023, as identified in the electronic medical record system. Inclusion Criteria: (1) Patients diagnosed with AMI, including both ST-segment Elevation Myocardial Infarction (STEMI) and Non-ST-segment Elevation Myocardial Infarction (NSTEMI), the diagnostic criteria includes elevated cardiac biomarkers (eg, cTnI) above the 99th percentile upper reference limit, along with at least one of the following: ischemic symptoms, new ischemic ECG changes, pathological Q waves, imaging evidence of new viable myocardial loss, or coronary thrombus on angiography;[12,13] (2) Patients who successfully underwent PCI with stent placement at our hospital; (3) Patients experiencing their first episode of AMI, with normal cardiac function prior to the onset of the disease, and admitted within 24 hours; (4) Patients with complete follow-up records. Exclusion Criteria: (1) Patients who underwent stent implantation for other reasons, such as unstable angina or stable coronary artery disease; (2) Patients with severe infections; (3) Patients with impaired liver, kidney, or lung function; (4) Patients with a history of malignant tumors, hematological diseases, autoimmune diseases, or recent severe bleeding history; (5) Patients who had been taking antiplatelet drugs for a long time before admission were excluded to minimize potential confounding effects of pre-existing antiplatelet therapy on the study outcomes, ensuring a more homogeneous study population and enhancing the accuracy of the results; (6) Patients who had undergone surgery due to major trauma in the recent past; (7) Patients who refused to take aspirin and clopidogrel; (8) Patients with incomplete clinical data. A total of 146 patients diagnosed and treated with PCI were selected for this study (AMI group). Additionally, a control group comprising 56 individuals who underwent a health examination at our hospital during the corresponding period was selected for comparison, with no statistically significant differences in gender and age compared with the AMI group.

All AMI patients received standard treatment at our hospital, taking oral aspirin enteric-coated tablets (Jiangxi Xin Ganjiang Pharmaceutical Co., Ltd., National Drug Approval Number H36021440) and clopidogrel sulfate tablets (Yangtze River Pharmaceutical Group Guangzhou Hairui Pharmaceutical Co., Ltd., National Drug Approval Number H20213479) each 300 mg, once daily. PCI was performed by experienced interventional physicians, followed by daily administration of aspirin 75–100 mg, clopidogrel 75 mg, once daily, with a minimum of one year of medication adherence.

Research Methods

Collection of Basic Information

Basic information of the subjects in each group was collected through medical records or physical examination data, including age, gender, BMI, drinking history, diabetes history, smoking history, and hypertension history.

Laboratory Testing Indicators

For AMI patients, 5 mL of peripheral venous blood was collected in the early morning following an overnight fast before the preparation for PCI. During the health examination, 5 mL of peripheral venous blood was collected from the control group. The blood samples were allowed to coagulate at room temperature and subsequently centrifuged at 2500×g for 20 minutes to isolate the serum. The obtained serum was stored at −80°C in a freezer for further use.

Enzyme-linked immunosorbent assay (ELISA) methodology was employed to quantify the levels of cardiac troponin I (cTnI), myoglobin (Mb), serum Angptl2, and CyPA in the serum.

Employing a high-throughput automated biochemistry analyzer, along with its requisite reagents, we determined the serum concentrations of total cholesterol (TC), fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in the collected samples.

Evaluation Criteria for ISR and Grouping

Patients were followed up for 12 months after PCI via a combination of outpatient visits and telephone contact. During the follow-up period, patients who developed angina symptoms underwent immediate coronary angiography. Asymptomatic patients with high-risk features (eg, diabetes mellitus, multivessel disease, or a history of high-risk PCI) underwent non-invasive imaging tests, such as coronary computed tomography angiography (CTA) and myocardial enzyme tests, to evaluate potential asymptomatic ISR. The definition and evaluation criteria for ISR are:[14] recurrent diameter stenosis of more than 50% of the angiographic vessel diameter in the stented segment. Based on the occurrence of ISR, subjects were divided into the ISR group (n=21 cases) and the NISR group (n=125 cases).

Statistical Analysis

The data collected in this study underwent processing through SPSS version 26.0. To determine the normality of the quantitative data, the Kolmogorov–Smirnov test was employed. For quantitative data that adhered to a normal distribution, they were presented using the mean ± standard deviation ($\bar{x}$±s) notation, and group comparisons were performed using the *t*-test. For quantitative data that did not conform to a normal distribution, they were expressed as the *M (P25, P75)* and were analyzed using the Mann–Whitney U non-parametric test. Categorical data were presented as cases or percentages (%), and differences between groups were analyzed using the chi-square ($\chi 2$) test. *Pearson* correlation analysis was used to explore the correlation between serum levels of Angptl2 and CyPA with cTnI and Mb levels. *Logistic* regression analysis was employed to identify risk factors affecting AMI and ISR occurrence after PCI with stent implantation. The efficacy of serum Angptl2 and CyPA as diagnostic markers for the detection of ISR following PCI with stenting was assessed utilizing the receiver operating characteristic (*ROC*) curve analysis. Statistical significance was set at a p-value of less than 0.05.

Results

Comparison of General Information Between the Control Group and the AMI Group

No statistically significant differences were observed between the Control group and the AMI group in terms of gender, age, BMI, smoking history, history of alcohol abuse, hypertension, diabetes, levels of FPG, TG, TC, LDL-C, and HDL-C ($P > 0.05$). Compared to the Control group, the AMI group had higher levels of cTnI and Mb before PCI ($P < 0.05$), as shown in Table 1.

Comparison of Serum Angptl2 and CyPA Levels Between the Control Group and the AMI Group

Compared to the Control group, patients in the AMI group had increased serum levels of Angptl2 and CyPA before the procedure ($P < 0.05$), as shown in Figure 1.

Table 1 General Information Comparison Between Control Group and AMI Group

Indicator	Control Group (n=56)	AMI Group (n=146)	t/χ^2	*P*
Gender			0.008*	0.927
Male (cases/%)	33	85		
Female (cases/%)	23	61		
Age ($\bar{x}$±s, years)	56.14±8.74	57.21±9.23	0.748	0.455
BMI ($\bar{x}$±s, kg/m^2)	23.12±2.31	23.34±2.41	0.587	0.558
Smoking history (cases/%)	30 (53.57)	62 (42.47)	2.013*	0.156
Drinking history (cases/%)	31 (55.36)	60 (41.10)	3.325*	0.068
Hypertension (cases/%)	30 (53.57)	59 (40.41)	2.844*	0.092
Diabetes (cases/%)	32 (57.14)	64 (43.84)	2.874*	0.090
FPG ($\bar{x}$±s, mmol/L)	5.68±1.31	6.01±1.57	1.397	0.164
TG ($\bar{x}$±s, mmol/L)	4.62±1.42	4.86±1.21	1.201	0.231
TC ($\bar{x}$±s, mmol/L)	4.21±1.12	4.51±1.36	1.470	0.143
LDL-C ($\bar{x}$±s, mmol/L)	2.42±0.51	2.62±0.69	1.971	0.050
HDL-C ($\bar{x}$±s, mmol/L)	1.23±0.54	1.33±0.28	1.719	0.087
cTnI ($\bar{x}$±s, pg/mL)	195.91±47.48	383.80±98.48	13.67	<0.0001
Mb ($\bar{x}$±s, ng/mL)	26.13±6.34	51.11±13.09	13.66	<0.0001

Note: *is the *t*-value.

Logistic Regression Analysis of Risk Factors Affecting AMI

Using the presence or absence of AMI as the dependent variable (Yes = 1, No = 0), and serum levels of Angptl2, CyPA, cTnI, and Mb prior to PCI surgery among AMI patients as independent variables, a *Logistic* regression analysis was conducted. The results indicated that serum levels of Angptl2 and CyPA were significant risk factors for AMI (P<0.05), as presented in Table 2.

Correlation Between Serum Angptl2, CyPA, and cTnI, Mb

Pearson correlation analysis revealed a statistically significant positive correlation between the serum levels of angiopoietin-like Angptl2, CyPA, and cTnI, Mb prior to PCI surgery among AMI patients (P<0.05), as depicted in Figure 2.

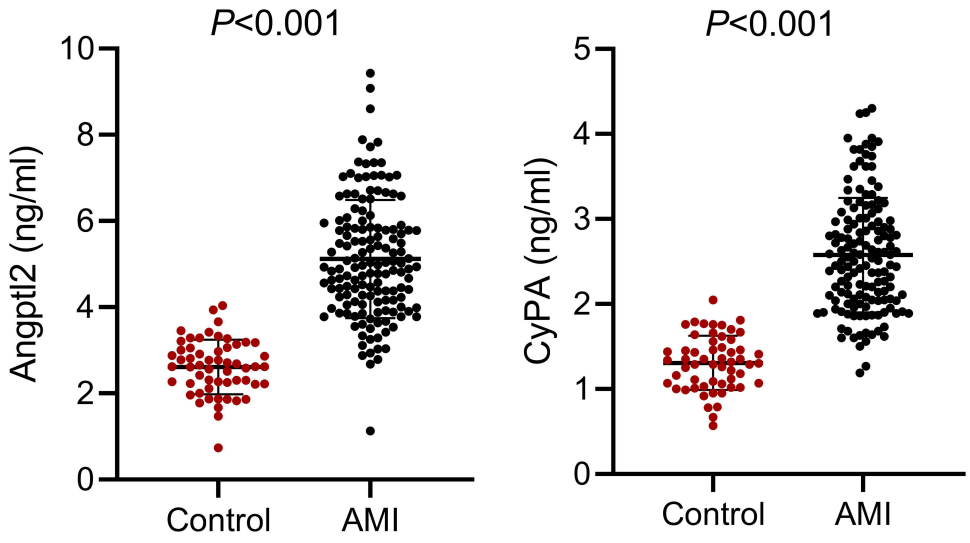

Figure 1 Comparison of serum Angptl2 and CyPA levels between Control group and AMI group.

Table 2 Logistic Regression Analysis of Risk Factors Affecting AMI

Indicator	*β*	*S.E*	*Z*	*P*	*OR*	*95% CI*
angptl2	2.54	1.01	2.51	0.012	12.65	2.395–157.5
CyPA	6.37	2.87	2.22	0.026	581.6	5.741–739235
cTnI	0.03	0.02	1.96	0.050	1.03	1.004–1.078
Mb	0.15	0.09	1.69	0.090	1.17	0.997–1.446

Comparison of Serum Angptl2 and CyPA Levels Between ISR and NISR Groups

During the 1-year follow-up period subsequent to PCI surgery among patients with AMI, patients were categorized into two groups based on the incidence of ISR: ISR and NISR. Prior to hospital discharge, the ISR group demonstrated statistically significant elevations in serum concentrations of Angptl2, CyPA, cTnI, and Mb compared to the NISR group (all $P<0.05$), as illustrated in Table 3.

Influencing Factors of ISR After PCI

The findings from the multivariate Logistic regression analysis indicated that pre-discharge serum concentrations of Angptl2, cTnI, CyPA, and Mb in patients with AMI were statistically significant predictors of ISR following PCI ($P<0.05$), as presented in Table 4. The diagnostic results for multicollinearity indicated that the variance inflation factors (VIFs) for all variables were <5, suggesting the absence of multicollinearity among the independent variables. The Durbin-Watson value was 1.380, indicating no significant autocorrelation among the residuals. The model demonstrated good fit and statistical significance, with an adjusted $R^2=0.681$, F=78.530, and $P<0.001$ (Table 5 and Figure 3).

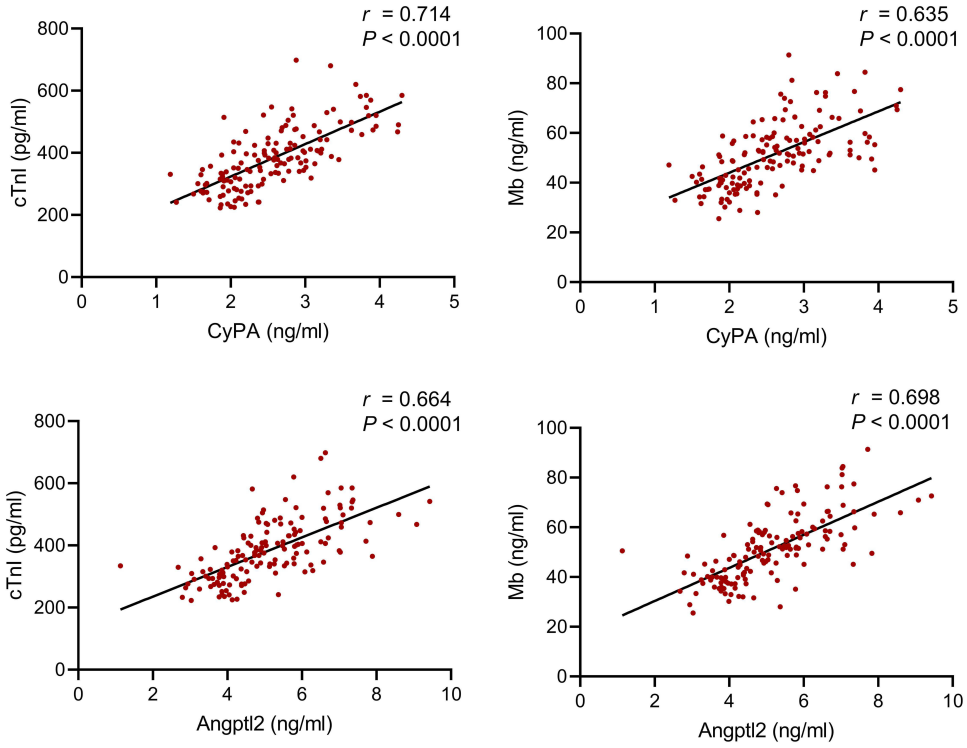

Figure 2 Correlation between Serum Angptl2, CyPA, and cTnI, Mb.

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Table 3 Comparison of Serum angptl2 and CyPA Levels Between ISR and NISR Groups

Indicator	ISR Group (n=21)	NISR Group (n=125)	*P*
angptl2 ($\bar{x}$±s, ng/mL)	5.87±1.18	4.54±1.14	<0.0001
CyPA ($\bar{x}$±s, ng/mL)	3.03±0.61	2.23±0.49	<0.0001
cTnI ($\bar{x}$±s, pg/mL)	455.28±84.58	326.44±63.27	<0.0001
Mb ($\bar{x}$±s, ng/mL)	60.30±11.49	44.21±9.57	<0.0001

Table 4 Analysis of Influencing Factors for ISR After PCI

Indicator	*β*	*S.E*	*Z*	*P*	*OR*	*95% CI*
angptl2	1.459	0.410	3.56	<0.001	4.303	2.161–11.33
CyPA	2.782	0.847	3.28	<0.001	16.15	3.824–116.6
cTnI	0.022	0.008	2.94	0.003	1.022	1.010–1.040
Mb	0.216	0.058	3.75	<0.001	1.241	1.126–1.416

Table 5 Multicollinearity Diagnosis Results for Factors Associated with ISR After PCI

Indicator	*β*	Standardized *β*	t	*P*	Tolerance	VIFs
angptl2	0.110	0.293	5.933	<0.001	0.903	1.108
CyPA	0.192	0.259	4.722	<0.001	0.732	1.366
cTnI	0.002	0.313	5.329	<0.001	0.638	1.568
Mb	0.011	0.300	5.472	<0.001	0.729	1.371

Predictive Value of Pre-Discharge Serum Angptl2 and CyPA for ISR After PCI in AMI Patients

The *ROC* curve analysis revealed that the sensitivity of pre-discharge serum Angptl2, CyPA, and their combination in predicting ISR after PCI were 56.06%, 80.3%, and 88.75%, respectively, with specificities of 87.5%, 78.75%, and 77.27%, respectively. The AUC values were 0.790, 0.851, and 0.895, respectively, as depicted in Figure 4.

Discussion

AMI refers to myocardial necrosis caused by sustained ischemia and hypoxia of myocardial cells, commonly manifesting as retrosternal pain and associated with poor prognosis.[15] PCI is the preferred treatment for AMI, as it rapidly recanalizes blood vessels, restoring blood flow to myocardial cells and reducing the incidence of cardiovascular events and mortality among myocardial infarction patients. However, a subset of patients still experience ISR after PCI, impacting the quality of life for AMI patients.[16–18] The development of new coronary atherosclerosis is a significant contributor to ISR. Coronary angiography serves as the standard for assessing ISR after PCI, yet the confirmation of ISR through coronary angiography often occurs after the optimal treatment window.[19] Therefore, identifying factors associated with ISR after PCI in AMI patients and developing effective diagnostic methods for ISR are crucial for preventing ISR, thereby enhancing the quality of life for AMI patients.

Serum Angptl2, a member of the angptl family, is secreted by vascular endothelial cells and possesses pro-inflammatory properties and the ability to promote intimal thickening of blood vessels. It can elicit inflammatory responses by recruiting leukocytes to sites of inflammation, enhancing vascular permeability, in patients with AMI, this inflammatory response exacerbates myocardial cell injury, leading to intimal hyperplasia and ISR. It can also modulate the activity of other Angptl family members, thereby affecting endothelial cell integrity and resulting in endothelial dysfunction. This dysfunction is an important pathophysiological basis for the development of both AMI and

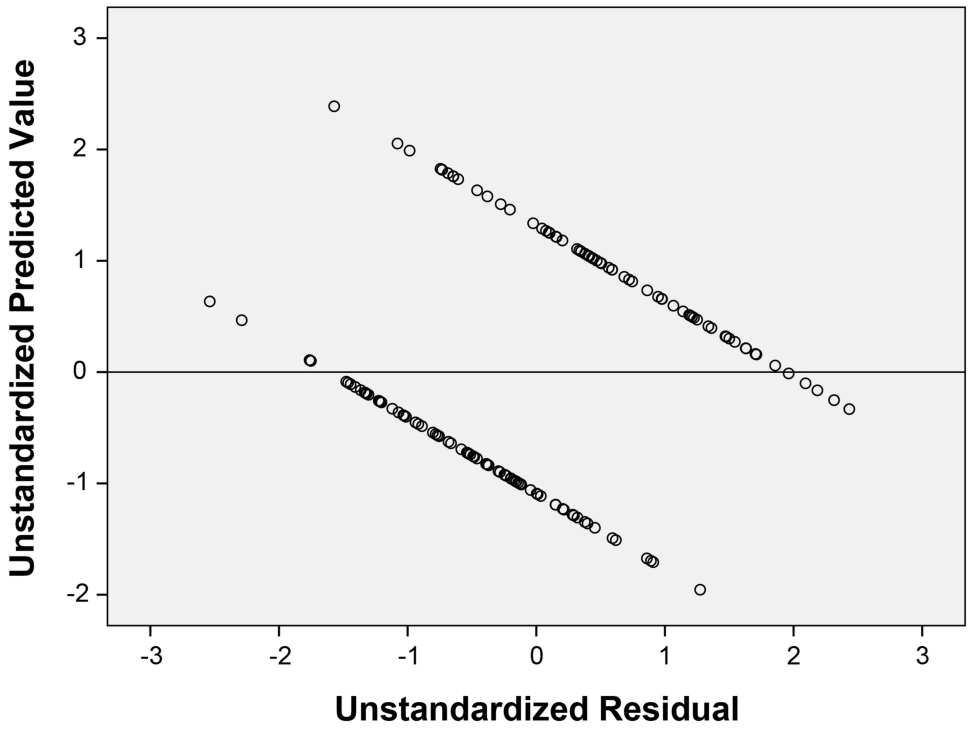

Figure 3 Residual plot of the Logistic regression analysis.

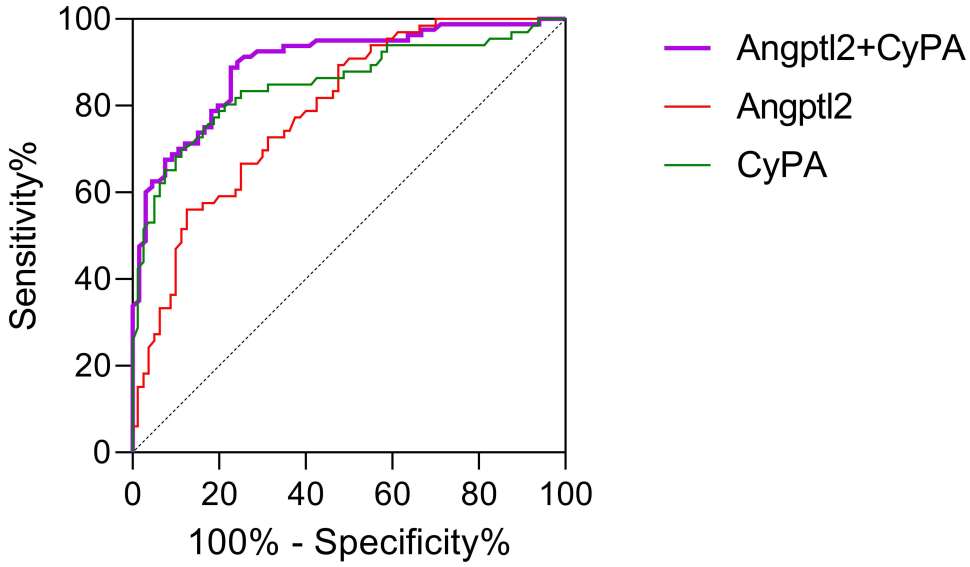

Figure 4 Predictive Value of Serum Angptl2 and CyPA for ISR after PCI.

ISR.[20] Previous research[6] has demonstrated that serum Angptl2 is highly expressed in individuals with acute coronary syndrome and exhibits a close association with thrombus formation, with elevated levels also noted in patients with AMI. However, the relationship between serum Angptl2 and ISR after PCI in AMI patients remains unclear. In this study, we observed a significant increase in serum Angptl2 levels prior to PCI treatment in AMI patients. Further analysis revealed that AMI patients who developed ISR after PCI had higher serum Angptl2 concentrations measured before discharge compared to those without ISR. We speculate that high levels of Angptl2 may exacerbate inflammatory responses in the body, weaken the stability of vascular structures, induce injury to vascular walls, and accelerate the progression of

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atherosclerosis and neovascularization. These alterations in pathophysiology may ultimately contribute to the onset of ISR in patients with AMI after undergoing PCI.

Serum CyPA is a key role in vascular remodeling, significantly contributing to the onset and advancement of atherosclerosis through the facilitation of smooth muscle cell migration and the modulation of gene expression associated with vascular endothelial function.[7,21] Wei Yuan et al found that CyPA can exacerbate the migration and proliferation of vascular smooth muscle cells, leading to increased intimal hyperplasia and subsequent gradual narrowing of the vascular lumen.[22] Additionally, CyPA can further exacerbate the inflammatory response by enhancing the inflammatory activity of monocytes and macrophages within atherosclerotic plaques.[23,24] In this study, both pre-PCI serum CyPA levels in AMI patients and pre-discharge CyPA levels in the ISR group were higher than those in healthy controls and the NISR group, indicating that elevated serum CyPA levels are associated with AMI and ISR after PCI. Logistic regression analysis revealed that elevated serum Angptl2 and CyPA levels are risk factors for AMI and ISR after PCI, suggesting that these biomarkers not only contribute to the risk of AMI but also increase the risk of restenosis after PCI in AMI patients. Therefore, we speculate that serum Angptl2 and CyPA may initiate inflammatory responses by recruiting inflammatory factors, stimulate intimal hyperplasia, and participate in the formation of atherosclerotic plaques, leading to luminal stenosis.[25,26] Further ROC curve analysis revealed that serum Angptl2 and CyPA can serve as predictive indicators for ISR in AMI patients following PCI, with a more significant predictive effect when used in combination, suggesting that serum Angptl2 and CyPA may act through distinct pathophysiological mechanisms in the context of AMI and ISR, thereby contributing synergistically to the exacerbation of both conditions, these findings provide a novel biomarker combination for the early identification of high-risk patients in clinical practice.

cTnI and Mb are commonly used as myocardial injury markers, with their levels positively correlated with myocardial damage.[27] The findings of this study indicated that serum levels of angptl, CyPA, cTnI, and Mb were all elevated in the AMI group prior to PCI treatment. Pearson correlation analysis revealed a positive correlation between serum angptl, CyPA, and the levels of cTnI and Mb, confirming the high expression of angptl, CyPA, cTnI, and Mb in AMI patients. Additionally, as serum angptl and CyPA levels increased, the levels of myocardial markers also rose. This phenomenon may be attributed to the presence of ruptured plaques and impaired vascular endothelial cell function in AMI patients, which stimulate the release of inflammatory factors.[28,29] Serum Angptl2 and CyPA may exacerbate inflammatory responses, leading to more severe cardiac dysfunction, as evidenced by the increasing trends in cTnI, Myoglobin, and CK-MB, this further intensifies the pathophysiological processes of AMI, potentially contributing to adverse outcomes.

In summary, elevated serum levels of Angptl2 and CyPA in AMI patients who develop ISR after PCI can serve as predictors of ISR occurrence. However, the sample size of this study was relatively limited. Future research could consider enlarging the sample size and incorporating multiple time points for detecting serum Angptl2 and CyPA levels to further explore the relationship between their levels and the incidence of ISR after PCI.

Conclusion

Elevated serum levels of Angptl2 and CyPA in AMI patients who developed ISR after PCI suggest that these biomarkers may serve as potential risk indicators for predicting ISR following PCI. Given the complex pathophysiology of ISR, which involves inflammation, neointimal hyperplasia, and vascular remodeling, the identification of such biomarkers could provide valuable insights into the underlying mechanisms. Furthermore, these biomarkers may facilitate early risk stratification and guide more aggressive management strategies for high-risk patients, potentially improving outcomes after PCI.

Abbreviations

Angptl2, angiopoietin-like protein 2; CyPA, cyclophilin A; AMI, acute myocardial infarction; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; cTnI, cardiac troponin I; Mb, myoglobin; ROC, receiver operating characteristic; AUC, area under the curve; ELISA, Enzyme-linked immunosorbent assay; TC, total cholesterol; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the ethics committee of Zhejiang Provincial People's Hospital Bijie Hospital (Approval Number: 2024-10-8), informed consent was waived due to the anonymization of the data.

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Disclosure

The author(s) report no conflicts of interest in this work.

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