

Atherogenic Index of Plasma and the Risk of In-Stent Restenosis in Patients with Acute Coronary Syndrome beyond the Traditional Risk Factors

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Aim: Recently, the atherogenic index of plasma (AIP) has been proposed as a novel, reliable plasma atherogenicity marker. This study aimed to investigate the association of AIP with the risk of in-stent restenosis (ISR) in patients with acute coronary syndrome (ACS).

Methods: This study retrospectively enrolled patients with ACS followed by angiography within 6 to 18 months after successful percutaneous coronary intervention (PCI) with a drug-eluting stent (DES). And the participants were divided into ISR or non-ISR groups based on the angiographic follow-up results. AIP was defined as the base 10 logarithm of the ratio of serum triglyceride (mmol/L) to high-density lipoprotein cholesterol (mmol/L).

Results: This study recruited 1319 patients with ACS, 199 of which had ISR. Compared with the non-ISR group, patients in the ISR group had higher level of AIP (0.199 ± 0.290 vs 0.131 ± 0.282 , $p=0.002$). In the multiple logistic regression analysis, AIP was an independent risk factor for DES-ISR (OR=2.100, 95% CI 1.134 to 3.891, $p=0.018$). When we modulated AIP as a categorical variable, the risk of DES-ISR increased in quartile 4 compared to quartile 1 (OR=1.713, 95% CI 1.040 to 2.822, $p=0.034$). Furthermore, this association remains stable in various subgroups. Unexpectedly, the subgroup analysis suggested AIP and DES-ISR had a stronger positive association in individuals with low-density lipoprotein cholesterol (LDL-C) < 1.8 mmol/L.

Conclusions: AIP and the risk of DES-ISR were positively and independently correlated in patients with ACS, especially in those with an LDL-C < 1.8 mmol/L.

Key words: Atherogenic index of plasma, Drug-eluting stent, In-stent restenosis, Acute coronary syndrome, Low-density lipoprotein cholesterol

Introduction

Despite advances in the primary and secondary prevention of cardiovascular disease in recent years, the morbidity and mortality of atherosclerotic cardiovascular diseases (ASCVDs) remain high in contemporary society^{1, 2}. Atherogenic dyslipidemia, characterized by reduced concentration of high-density lipoprotein cholesterol (HDL-C), increased circulating triglyceride (TG), and high small dense

low-density lipoprotein (sdLDL) with normal low-density lipoprotein cholesterol (LDL-C), was considered a substantial residual risk for ASCVDs and may account for it³⁻⁶.

The atherogenic index of plasma (AIP), determined with formula $\log_{10}(\text{TG}/\text{HDL-C})$ and associated with lipoprotein particle size, could reflect the main atherogenic dyslipidemia characteristics and regarded as a plasma atherogenicity marker⁷⁻⁹. According to previous studies, AIP was associated with various

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risk factors for ASCVD, such as insulin resistance, abdominal obesity, diabetes mellitus (DM), and metabolic syndrome¹⁰⁻¹³. Meanwhile, mounting evidence associated AIP with the prevalence and severity of coronary artery disease (CAD)^{10, 14}. AIP was an independent risk factor for the rapid progress of coronary atherosclerosis^{15, 16}. Furthermore, recent evidence also demonstrated AIP was associated with a worse prognosis and could serve as a biomarker to predict long-term prognoses in patients with acute coronary syndrome (ACS)^{17, 18}.

However, to the best of our knowledge, no prior studies have been designed to evaluate the association between AIP and in-stent restenosis (ISR), which remains as the primary cause of percutaneous coronary intervention (PCI) failure even in the era of drug-eluting stents (DES)¹⁹.

Aim

To fill this knowledge gap and provide a novel promising way to prevent ISR, we aim to assess the correlation of AIP with ISR in patients with ACS after DES implantation.

Methods

Study Population

In this single-center, retrospective, and observational study, we consecutively screened the patients with ACS admitted for PCI in Beijing AnZhen Hospital, Capital Medical University, from January 2018 to August 2020. The main inclusion criteria were: (1) culprit lesions in native coronary artery treated successfully by PCI (successful PCI was defined as the recanalization of lesion with thrombolysis in myocardial infarction grade 3 and residual stenosis <10%); (2) patients followed by coronary angiography within 6 to 18 months after successful PCI. We also excluded patients according to the following criteria: (1) age <18 years; (2) previous history of coronary artery bypass grafting (CABG); (3) target lesion only treated by PCI with a bare metal stent or percutaneous transluminal coronary angioplasty (PTCA); (4) those with severe dysfunction in liver, renal, or thyroid; (5) cancer, acute/chronic inflammatory disease, and patients without completed baseline data. The Ethics Committee of Beijing AnZhen Hospital, Capital Medical University approved this study, which strictly complied with the Declaration of Helsinki. Meanwhile, all the patients provided informed consent.

Procedure and Periprocedural Management

Diagnostic coronary angiography, PCI, and periprocedural management were all implemented according to current guidelines²⁰. All patients enrolled received a loading dose of aspirin plus clopidogrel or ticagrelor before the intervention. Additionally, unfractionated heparin (70–100 U/Kg, with additional boluses if required) was also administered at the beginning/during the PCI to maintain the activated clotting time >250 s. Most importantly, the PCI was performed by experienced interventional cardiologists using 6F or 7 F (1F=0.33 mm) guiding catheter mainly with radial access. And the application of intracoronary imaging techniques, the type of DES, and the size of stents were all left to the operator's discretion.

Data Collection and Definitions

A trained physician, blinded to the study objective, collected the participants' demographic and clinical characteristics, including age, gender, height, weight, admission blood pressure, medical history, cardiac function, laboratory parameters, procedural details, and medication used at discharge, with a dedicated case report form. Noteworthy, venous blood samples were obtained after patients fasted overnight (>8 h). Common hematology and biochemical parameters, including high sensitivity C-reactive protein (Hs-CRP), glycosylated hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), and lipid profile, were all determined in center laboratory of Beijing AnZhen Hospital.

In line with previous studies⁹, AIP in the present study was calculated with the formula $\text{Log}_{10}(\text{TG}/\text{HDL-C})$. Body mass index (BMI) was computed as weight (Kg) divided by height squared (m). Hypertension and DM were ascertained based on self-report of physician's diagnosis, which complied with criteria from current guidelines^{21, 22}, and/or active therapy with medications. Hypercholesterolemia was defined as LDL-C >4.14 mmol/L, and/or total cholesterol (TC) >6.22 mmol/L, or active therapy with lipid-lowering drugs. The SYNTAX and Gensini scores, which evaluate coronary disease severity, were calculated by 2 independent intervention cardiologists blinded to the participant's information.

Follow-Up Angiography and Evaluation of ISR

The patients recruited were followed up by coronary angiography at 6 to 18 months after DES implantation. The ISR was defined as a lumen diameter stenosis $\geq 50\%$ occurred at the segment inside the stent or involving its 5 mm-edges. The 2 independent intervention cardiologists were

responsible for interpreting follow-up angiography and further dividing the participants into ISR or non-ISR groups. The disagreements encountered were resolved by a discussion with senior researcher.

Statistical Analysis

Continuous variables with a normal distribution were expressed as mean \pm standard deviation, and those with skewed distribution were summarized as median with interquartile ranges. The difference in continuous variables between the ISR group and non-ISR group was examined by the Student's *t* test or Mann–Whitney *U*-test, which depends on normality of data distribution. Meanwhile, categorical variables were presented as numbers (percentage) and compared by the Pearson chi-square test or Fisher's exact test. We also performed the Pearson correlation test and Spearman's rank correlation test to evaluate the correlation between AIP and traditional cardiometabolic risk factors.

Subsequently, the determinants of DES-ISR were explored by us using univariate logistic regression analysis. Variables showed $p < 0.1$ in univariate analysis and those judged to be of clinical significance were purposefully introduced into the following multivariate logistic regression analysis models. Model 1 included age, sex, and BMI. Model 2 consisted of variables in Model 1 and systolic blood pressure, hypertension, previous PCI, Hs-CRP, platelet count, HbA1c, TC, and left ventricular ejection fraction. Model 3 was used to adjust confounders in Model 2 and SYNTAX score, target in multivessel, target in the left anterior descending artery (LAD), target in right coronary artery, multiple stents (≥ 2), DES-sirolimus, minimal stent diameter ≤ 3 mm, intracoronary imaging technique, and follow-up time. Model 4, as the fully adjusted model, was established to adjust variables in Model 3 and the medical therapy with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), insulin, and other hypoglycemic agents.

All the statistical analyses involved in the present study were performed using SPSS 20.0 (IBM, Armonk, New York), and a two-sided $p < 0.05$ was regarded as statistically significant.

Results

Baseline Characteristics

A total of 1319 patients (84.7% were diagnosed as unstable angina) who were followed up by coronary angiography at 11.11 ± 3.04 months after successful PCI were enrolled for the final analysis. As shown in **Table 1**, the average age of the study population was

58.40 ± 9.47 years, and 77.7% of participants were men. The percentages of current smokers, hypertension, DM, and previous PCI were 35.3%, 65.1%, 36.1%, and 17.5%, respectively. Meanwhile, more than half of the participants underwent PCI for LAD and implanted multiple stents (≥ 2).

Later, the study population was divided into ISR and non-ISR groups. As demonstrated in **Table 1**, the prevalence of hypertension, DM, and previous PCI; serum Hs-CRP, TG, and HbA1c; SYNTAX score and Gensini score were all higher in the ISR group than the non-ISR group. Furthermore, the patients in the ISR group were more likely to undergo PCI for multivessel and implant multiple stents. However, the patients in the ISR group had lower serum HDL-C and were less likely to take intracoronary imaging techniques.

Correlation between AIP and Cardiometabolic Risk Factors

The distribution of AIP is normal, and the mean AIP of the study population was 0.14 ± 0.28 . As shown in **Table 2**, AIP correlated positively with various cardiometabolic risk factors, including BMI, DBP, DM, current smoker, Hs-CRP, uric acid, TG, LDL-C, TC, and HbA1c. However, AIP has negative association with age ($r = -0.232$, $p < 0.001$) and HDL-C ($r = -0.606$, $p < 0.001$).

The Association between DES-ISR and AIP

First of all, we compared the difference in AIP between the ISR and non-ISR groups. As presented in **Fig. 1A**, serum AIP level was significantly higher in patients with ISR than those without (0.199 ± 0.290 vs. 0.131 ± 0.282 , $p = 0.002$). Subsequently, we stratified the patients recruited into 4 groups according to the quartile (Q) of AIP (Q1(AIP ≤ -0.042), Q2($-0.042 < \text{AIP} \leq 0.136$), Q3($0.136 < \text{AIP} \leq 0.305$), Q4(AIP > 0.305)) and investigated the incidence of DES-ISR according to the quartiles of AIP. As presented in **Fig. 1B**, the incidences of DES-ISR according to the quartile of baseline AIP were 10.6%, 15.8%, 16.1%, and 18.0%, respectively. And the trend was marginally significant ($p = 0.051$).

Association of AIP with the Risk of DES-ISR in Logistic Regression Analysis

As a continuous variable, AIP was associated with the increased risk of DES-ISR (OR = 2.284, 95% CI 1.355 to 3.849, $p = 0.002$) in the univariate logistic regression analysis.

Multivariate logistic regression analysis models were established to avoid the interference of confounding risk factors (**Table 3**). As presented in

Table 1. Baseline characteristics of the study population

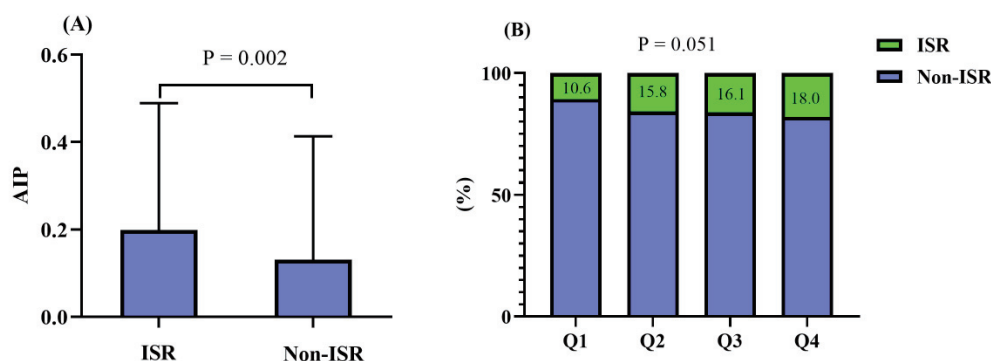
Variables	Total (n = 1319)	ISR group (n = 199)	Non-ISR group (n = 1120)	P-value
Demographics				
Age, years	58.40 ± 9.47	58.96 ± 10.00	58.30 ± 9.37	0.368
Male, n (%)	1025 (77.7)	158 (79.4)	867 (77.4)	0.535
BMI, Kg/m ²	25.92 ± 3.24	26.05 ± 2.84	25.90 ± 3.30	0.552
SBP, mmHg	129.13 ± 17.34	131.11 ± 17.83	128.78 ± 17.23	0.081
DBP, mmHg	76.42 ± 11.20	75.63 ± 11.87	76.56 ± 11.08	0.281
Diagnosis, n (%)				0.792
UA	1117 (84.7)	167 (83.9)	950 (84.8)	
NSTEMI	98 (7.4)	14 (7.0)	84 (7.5)	
STEMI	104 (7.9)	18 (9.0)	86 (7.7)	
Medical History, n (%)				
Current smoker	466 (35.3)	74 (37.2)	392 (35.0)	0.552
Hypertension	859 (65.1)	142 (71.4)	717 (64.0)	0.045
Diabetes mellitus	476 (36.1)	97 (48.7)	379 (33.8)	<0.001
Hypercholesterolemia	514 (39.0)	77 (38.7)	437 (39.0)	0.931
Stroke	107 (8.1)	20 (10.1)	87 (7.8)	0.277
Previous PCI	231 (17.5)	55 (27.6)	176 (15.7)	<0.001
Cardiac Function				
LVEF, %	62.14 ± 6.91	61.28 ± 7.91	62.29 ± 6.71	0.090
Laboratory Results				
Hs-CRP, mg/L	1.45 (0.57,4.12)	2.23 (0.72, 5.26)	1.33 (0.55, 3.89)	<0.001
Platelet, 10 ⁹ /L	223.99 ± 56.17	231.13 ± 62.71	222.72 ± 54.87	0.077
Hemoglobin, g/L	144.24 ± 14.88	145.47 ± 15.24	144.03 ± 14.81	0.209
Uric acid, umol/L	345.36 ± 84.40	339.84 ± 75.49	346.34 ± 85.88	0.275
Triglyceride, mmol/L	1.40 (1.03, 1.96)	1.52 (1.14, 2.05)	1.38 (1.01, 1.94)	0.011
LDL-C, mmol/L	2.45 ± 0.89	2.52 ± 0.97	2.44 ± 0.88	0.241
HDL-C, mmol/L	1.07 ± 0.24	1.03 ± 0.23	1.07 ± 0.24	0.017
TC, mmol/L	4.12 ± 1.16	4.26 ± 1.45	4.10 ± 1.09	0.140
HbA1c, %	6.55 ± 1.35	7.14 ± 1.63	6.44 ± 1.27	<0.001
eGFR, ml/min/1.73m ²	96.21 ± 14.88	96.20 ± 15.31	96.21 ± 14.81	0.991
Intervention, n (%)				
Gensini score	40.00 (25.00,62.00)	47.00 (29.00,72.00)	40.00 (24.00,60.00)	0.001
SYNTAX score	13.00 (8.50, 18.00)	13.00 (9.00,21.00)	12.00 (8.00,18.00)	0.024
No. of target vessel				
One	989 (75.0)	132 (66.3)	857 (76.5)	
Multivessel	330 (25.0)	67 (33.7)	263 (23.5)	
Target in LM	66 (5.0)	11 (5.5)	55 (4.9)	0.713
Target in LAD	743 (56.3)	123 (61.8)	620 (55.4)	0.091
Target in LCX	356 (27.0)	54 (27.1)	302 (27.0)	0.960
Target in RCA	544 (41.2)	100(50.3)	444 (39.6)	0.005
DES-sirolimus	707 (53.6)	121 (60.8)	586 (52.3)	0.027
DES-zotarolimus	285 (21.6)	46 (23.1)	239 (21.3)	0.575
DES-everolimus	517 (39.2)	75 (37.7)	442 (39.5)	0.636
Intracoronary imagine	88 (6.7)	7 (3.5)	81 (7.2)	0.053
Multiple Stents (≥ 2)	667 (50.6)	118 (59.3)	549 (49.0)	0.008
Minimal stent diameter ≤ 3 mm	1057 (80.1)	170 (85.4)	887 (79.2)	0.042
Follow up time, months	11.11 ± 3.04	10.62 ± 3.02	11.19 ± 3.04	0.015
Medication used after discharge, n (%)				
Aspirin	1319 (100.0)	199 (100.0)	1120 (100.0)	>0.999
Clopidogrel/Ticagrelor	1319 (100.0)	199 (100.0)	1120 (100.0)	>0.999
Statin	1316 (99.8)	199 (100.0)	1117 (99.7)	0.465
β-block	924 (70.1)	143 (71.9)	781 (69.7)	0.546
ACEI/ARB	614 (46.6)	107 (53.8)	507 (45.3)	0.027
Insulin	150 (11.4)	38 (19.1)	112 (10.0)	<0.001
Other hypoglycemic agents	377 (28.6)	78 (39.2)	299 (26.7)	<0.001

ISR, in-stent restenosis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; HbA1c, glycosylated hemoglobin A1c; eGFR, estimated glomerular filtration rate; LM, left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stents; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

Table 2. Association between AIP and cardiometabolic risk factors

Variables	Correlation coefficient (r)	P-value
Age	-0.232	<0.001
BMI	0.224	<0.001
DBP	0.090	0.001
DM	0.078	0.004
Current smoker	0.146	<0.001
Hs-CRP	0.124	<0.001
Hemoglobin	0.182	<0.001
Uric acid	0.242	<0.001
Triglyceride	0.933	<0.001
LDL-C	0.093	0.001
HDL-C	-0.606	<0.001
TC	0.233	<0.001
HbA1c	0.120	<0.001

AIP, atherogenic index of plasma; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; Hs-CRP, high sensitivity-C reactive protein; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; HbA1c, glycosylated hemoglobin A1c.

**Fig. 1.**

Comparison in the level of AIP between ISR and non-ISR group (A), and the incidence of ISR according to the quartiles (Q) of AIP (B). AIP, atherogenic index of plasma; ISR, in-stent restenosis.

Table 3. Multiple logistic regression analysis Models for evaluating the association between AIP and the risk of DES-ISR

Models	OR	95% CI	P-value
Model 1	2.498	1.449 to 4.309	0.001
Model 2	1.958	1.079 to 3.555	0.027
Model 3	2.064	1.117 to 3.815	0.021
Model 4	2.100	1.134 to 3.891	0.018

Model 1: adjusted for age, sex, BMI;

Model 2: adjusted for confounders in Model 1 plus SBP, hypertension, previous PCI, Hs-CRP, platelet count, HbA1c, TC, and LVEF;

Model 3: adjusted for confounders in Model 2 plus SYNTAX score, target in multivessel, target in LAD, target in RCA, multiple stents (≥ 2), DES-sirolimus, minimal stent diameter ≤ 3 mm, intracoronary imaging technique, and follow-up time;

Model 4: adjusted for confounders in Model 3 plus therapy with ACEI/ARB, insulin, and other hypoglycemic agents.

AIP, atherogenic index of plasma; DES, drug-eluting stent; ISR, in-stent restenosis; BMI, body mass index; SBP, systolic blood pressure; PCI, percutaneous coronary intervention; Hs-CRP, high sensitivity-C reactive protein; HbA1c, glycosylated hemoglobin A1c; TC, total cholesterol; LVEF, left ventricular ejection fraction; LAD, left anterior descending artery; RCA, right coronary artery; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

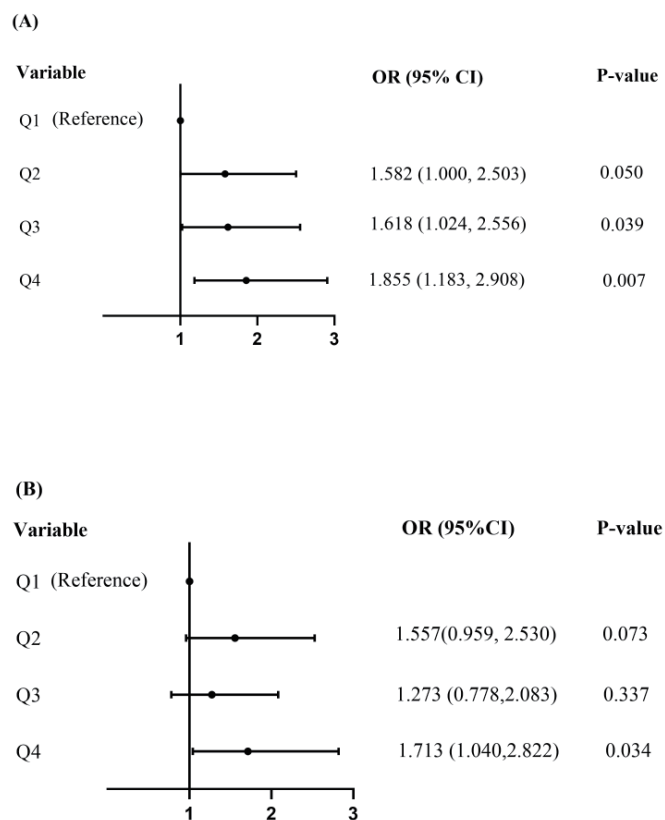


Fig. 2.

Forest plot of the risk of ISR according to quartiles (Q) of AIP in unadjusted Model (A), and the fully adjusted Model (B). ISR, in-stent restenosis; AIP, atherogenic index of plasma.

Table 3, AIP remained independently associated with the elevated risk of DES-ISR (OR=2.100, 95% CI 1.134 to 3.891, $p=0.018$) after fully adjusted the confounding risk factors with Model 4. And the optimal AIP cutoff point for DES-ISR was -0.037 (sensitivity: 81.9%, specificity:27.5%, area under curve: 0.557 (0.516 to 0.599), $p=0.0072$).

To further evaluate the association between AIP and DES-ISR risk in patients with ACS, we also modulated AIP as a categorical variable. In univariate analyses (**Fig. 2A**), the ORs (95% CI) for Q2, Q3, and Q4 were 1.582 (1.000, 2.503), 1.618 (1.024, 2.556), and 1.855(1.183, 2.908), respectively. After fully adjusting for traditional clinical risks with a multiple logistic regression analysis model, the incidence of DES-ISR increased significantly in Q4 compared to the reference Q1(OR=1.713, 95 % CI 1.040 to 2.822, $p=0.034$, **Fig. 2B**).

Association of AIP with the Risk of DES-ISR in Different Subgroups

The independent association of AIP with the incidence of DES-ISR was further assessed by us in the different subgroups of study population. As

presented in **Fig. 3**, the association was still persisted in the subgroups of male (OR=2.382, 95% CI 1.192 to 4.761, $p=0.014$), age < 65 years (OR=2.292, 95% CI 1.130 to 4.649, $p=0.022$), BMI<25 kg/m² (OR=3.012, 95%CI 1.162 to 7.811, $p=0.023$), DM (OR=3.115, 95%CI 1.271 to 7.636, $p=0.013$), and LDL-C < 1.8 mmol/L (OR=3.116, 95% CI 1.157 to 8.396, $p=0.025$) after fully adjusting the confounding variables. Furthermore, this trend was also observed by us in the subgroup of current smoker as well as non-current smoker ($p<0.1$).

Discussion

In the present study, we evaluated the association between AIP and ISR incidence after successful DES-based PCI for the first time. And the major findings were listed as follows: (1) AIP, as a comprehensive lipid parameter, was associated with various cardiometabolic risk factors; (2) AIP, either as a continuous or categorical variable, was an independent predictor of DES-ISR in patients with ACS; (3) Furthermore, the independent predictive effect of AIP on the risk of DES-ISR was also reflected in the

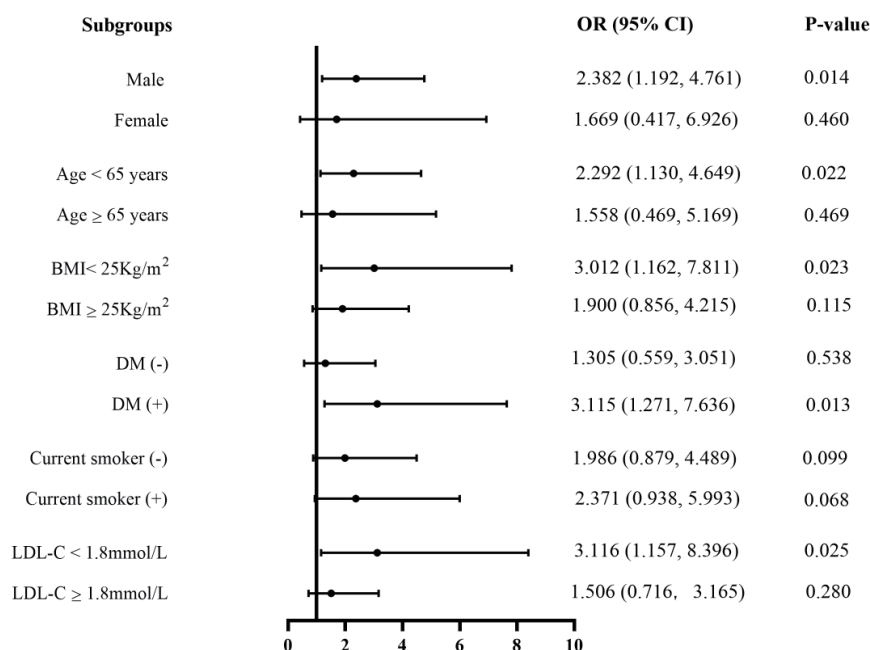


Fig. 3.

Forest plot for the subgroup analysis of the effect size of AIP on the incidence of ISR in our cohort study. AIP, atherogenic index of plasma; ISR, in-stent restenosis; BMI, body mass index; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

subgroups of male, age < 65 years, BMI < 25 kg/m², DM, and LDL-C < 1.8 mmol/L.

ASCVDs remains the leading cause of morbidity and mortality for patients worldwide, despite great advances in management strategies to lessen ASCVDs risk factors^{1, 2}). A major reason is atherogenic dyslipidemia, consisting of reduced serum HDL-C and increased TG-rich lipoproteins as well as sdLDL^{5, 6}). Notably, therapy with statins alone fails to correct it adequately, and a single lipid parameter commonly used in the clinical practice at present cannot fully reflect this specific dyslipidemia²³). The triglyceride-based indices AIP, calculated with the formula $\log_{10}(\text{TG}/\text{HDL-C})$ and could act as a surrogate marker of sdLDL, may serve as a more useful and comprehensive parameter to reflect plasma atherogenicity⁷⁻⁹). A higher AIP level was also associated with an increasingly atherogenic lipid phenotype and cholesterol esterification rate^{8, 9}). Moreover, our present study and prior studies suggested AIP was relevant to various cardiometabolic risk factors¹⁰⁻¹²).

Currently, the link between AIP and ASCVD has been well established in previous epidemiological studies as well. Zhou *et al.*, Wang *et al.*, and Shanker *et al.* reported AIP was an independent and powerful predictor for the presence of CAD, and adding it with family history to traditional risk factors models could improve predictive accuracy for CAD^{10, 14, 24}). Meanwhile, recent evidence also confirmed that AIP

was independently and strongly associated with the risk of CAD in special populations such as very young adults and postmenopausal women, who usually had the unique risk factor profile^{25, 26}). Furthermore, mounting evidence suggests AIP may serve as an independent predictor for arterial stiffness, coronary artery calcification progression, and the rapid progression of coronary plaque, all of which were powerful predictors of adverse cardiac events^{15, 27, 28}). Most importantly, Qin *et al.* and Ma *et al.* demonstrated that increased AIP upon admission correlated positively with the worse long-term prognosis in patients after PCI. The effects were independent of LDL-C level^{17, 18}). Extending those prior studies, our present study indicated the AIP is strongly related to the prevalence of ISR beyond the traditional risk factors in patients with ACS after DES-based PCI. This result suggests optimizing the lipid management according to AIP may be a promising way to prevent ISR in the future. However, the predictive ability of AIP for DES-ISR was mild, with the cutoff point -0.037 in this study. Considering this study's limitations, future studies are required to identify a more accurate reference value of AIP for clinical guidance.

According to previous studies, gender-specific associations existed between AIP and cardiovascular disorder^{12, 25}). Consistent with those studies, our subgroup analysis also confirmed the gender difference

and revealed the incidence of ISR increased with AIP elevated in men while not in women. Unexpectedly, our subgroup analysis also revealed that AIP was more closely associated with the DES-ISR in patients LDL-C <1.8 mmol/L, which prior studies have not reported. Although the exact reasons underlying this phenomenon remain unclear, further strengthening lipid management based on AIP value in patients with LDL-C <1.8 mmol/l may substantially reduce the residual risk for DES-ISR.

Although the potential mechanisms underlying AIP and DES-ISR were unknown at present, several possible explanations were listed according to previous studies. First, this study and prior studies all suggested AIP correlates positively with various metabolic disorders such as insulin resistance, DM, hyperglycemia, and hyperuricemia^{10, 11}), all of which were well-established risk factors for ISR²⁹⁻³¹). Second, remnant-lipoprotein cholesterol, as a risk factor for the occurrence and development of ISR^{32, 33}), is usually increased with increasing AIP levels^{8, 10}). Last but not least, AIP is a surrogate marker of sdLDL, which is one of the LDL subfractions with increased proinflammatory and proatherogenic action^{9, 34}). The clinical trial also reported an association between sdLDL and ISR incidence based on population³⁵).

Limitations

First, this retrospective cohort study fails to control all of the potential confounding factors and cannot provide a definite causal relationship between AIP and DES-ISR. Second, the present study only enrolled subjects who took follow-up angiography within 6 to 18 months after PCI, which may cause select bias. Third, this study was mainly based on the Chinese population, which means our present findings may not generalize to other ethnic groups. Finally, our present study only assessed the association of baseline AIP with the risk of ISR, failing to evaluate the effect of consecutive change in AIP during follow-up on ISR incidence. Therefore, future prospective, multicenter studies are needed to determine the association between them.

Conclusions

Based on our cohort study's findings, the increased AIP level was independently associated higher risk of ISR in patients with ACS during the intermediate-term follow-up. And this association was much stronger in those with LDL-C <1.8 mmol/L. These results suggest optimizing the lipid management based on AIP may be a promising way to prevent ISR.

To further confirm our findings, multicenter, randomized, and prospective studies were necessary.

List of Abbreviation

ASCVDs, atherosclerotic cardiovascular diseases; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; sdLDL, small dense low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; AIP, atherogenic index of plasma; DM, diabetes mellitus; CAD, coronary artery disease; ACS, acute coronary syndrome; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; DES, drug-eluting stent; TIMI, thrombolysis in myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; Hs-CRP, high sensitivity-C reactive protein; HbA1c, glycosylated hemoglobin A1c; eGFR, estimated glomerular filtration rate; BMI, body mass index; TC, total cholesterol; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; LAD, left anterior descending artery; RCA, right coronary artery; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; TRLs, TG-rich lipoproteins.

Declaration

Ethics approval and Consent to Participate

The present study was approved by the Ethics Committee of Beijing AnZhen Hospital, Capital Medical University and was performed in line with Declaration of Helsinki. Meanwhile, all the patients included were informed and consent to participate.

Consent for Publication

Not applicable.

Availability of Data and Materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contribution

YZ was responsible for the data analysis and manuscript writing; MLC, KSL, AG, XYK, and YL contributed to the data collection; HYH and HL reviewed and revised this manuscript carefully.

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