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Original Research Article

THE ATHEROGENIC INDEX OF PLASMA (AIP) IS A PREDICTOR FOR THE SEVERITY AND OUTCOME IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Abstract

Introduction: The atherogenic index of plasma (AIP) is a cost-effective alternative to measuring small dense LDL particles and can be used as a reliable indicator for CAD prevention. Recent research suggests that AIP may be a marker for evaluating CAD severity. The main aim of this study was to investigate the association between AIP and CAD severity.

Materials and Methods: This retrospective observational study was conducted among 120 patients of acute coronary syndrome (ACS). Socio demographic data, risk factors for CAD, laboratory parameters were recorded in predesigned proforma. AIP was calculated by using the following formula AIP=Log 10(TG/HDLc). Follow-up data of all patients for 12 months for major adverse cardiovascular events (MACEs) was noted from hospital records.

Result: Old age, obesity, and hyperlipidemia were more common in the high AIP group (p=0.04, 0.02, 0.008 respectively). The SYNTAX score was also significantly higher in the high AIP group (24.3 ± 12.47) compared to the low AIP group (16.23 ± 10.97, p=0.001). MACEs occurred more frequently in the high AIP group (33.3%) compared to the low AIP group (16.7%, p=0.03). Hyperlipidemia, high AIP, LDL-C, age, and BMI were independent predictors of a SYNTAX score ≥23 (OR=2.24, 1.85, 1.65, 1.21, and 1.17 respectively, all p-values < 0.05).

Conclusion: AIP serves as a valuable indicator of atherogenic dyslipidemia, as it doesn't require additional costs. It could serve as independent predictive factors for CAD severity.

Keywords: Acute coronary syndrome, atherogenic index of plasma, hyperlipidemia, major adverse cardiovascular events (MACE), SYNTAX score

Introduction

Coronary artery disease (CAD) is a widespread disease and a major contributor to global mortality rates.[1] Acute coronary syndrome (ACS) represents the most severe form of CAD, including unstable angina, NSTEMI, and STEMI.[2,3]

To enhance cardiac risk assessment and improve preventive and therapeutic approaches, researchers have explored various biomarkers associated with CAD risk, such as C-reactive

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protein, lipoprotein-associated phospholipase A2, and fibrinogen.[4] Among these, abnormalities in lipoprotein metabolism, particularly elevated LDL-C, play a significant role in ACS development. While current guidelines prioritize reducing LDL-C levels in lipid-lowering interventions for ACS patients[5], some individuals, despite achieving optimal LDL-C levels through medication, remain at a higher risk of recurrent cardiovascular events.[6] This suggests that focusing solely on LDL-C may not be sufficient. It's important to note that LDL-C comprises particles with different sizes, densities, and properties. Studies have demonstrated that smaller, denser particles are more prone to oxidation and possess a higher atherogenic potential.[7]

The atherogenic index of plasma (AIP) is a novel biomarker consisting of the logarithmically transformed ratio of triglycerides to high-density lipoprotein (HDL)-cholesterol in molar concentrations.[4] It provides insights into the size of HDL and LDL particles and the fractional esterification rate of HDL cholesterol. Interestingly, AIP is inversely proportional to the diameter of LDL particles, indirectly indicating levels of small dense LDL.[8] Research by Gentile et al. has shown a stronger association between small dense LDL particles and premature atherosclerosis compared to large LDL particles.[9] However, measuring small dense LDL particles can be complex and costly. As a cost-effective alternative, AIP serves as a reliable indicator for CAD, assisting in its prevention.[8]
The SYNTAX score (SS) is used to assess the severity of coronary stenosis.[10] A recent study found that AIP not only predicts CAD but also has a positive correlation with a high SYNTAX score, suggesting its potential as a marker for evaluating CAD severity.[8] However, more research is needed to establish the relationship between AIP and SS. The main aim of this study was to investigate the association between AIP and the severity of CAD.

MATERIALS AND METHODS

This retrospective observational study was conducted among 160 patients of ACS who underwent coronary angiography (CA) in tertiary care hospital, Gujarat during January 2021 and December 2022.

Inclusion criteria: Patients diagnosed with ACS (STEMI, NSTEMI, UA) with age >18 years were included in this study

Exclusion criteria:

- Patients with a history of previous myocardial infarction, prior stent placement, or bypass grafting
- Patients on a statin and triglyceride-lowering medication.
- Patients with heart failure, malignancy, severe renal insufficiency, nephrotic syndrome, myocarditis, infectious endocarditis, active infection, and systemic diseases.
- Viral infections like Human Immuno Deficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), COVID-19
- Incomplete follow up data

Of this study population, 40 patients were fit to exclusion criteria. The remaining 120 patients met the inclusion criteria for the study. Our study was conducted after the approval from institutional ethics committee and informed consent was obtained from all patients.
Socio demographic data and clinical data including medical history, laboratory parameters were recorded in predesigned proforma. Risk factors for CAD comprised of cigarette smoking, hyperlipidemia [total cholesterol (TC) levels $\geq$ 200 mg/dl], family history of CAD (first-degree

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relatives before the age of 55 in men and 65 years in women), hypertension (systolic blood pressure ≥140 and/or diastolic ≥90 mmHg or on anti-hypertensive treatment), DM (FBG ≥ 126 mg/dl or 2-h serum glucose of the oral glucose tolerance test ≥ 200 mg/dl or the use of anti-diabetic medication) were noted.

Biochemical parameters such as TC, TG, LDL-c, HDL-c, fasting blood glucose, creatinine, troponin-I and C-reactive protein (CRP) were measured by utilizing the standard methods. AIP was calculated by using the following formula AIP=Log 10(TG/HDLc). Patients were divided into the two groups: low risk (≤ 0.21) and high risk (> 0.21).[8]

ACS population consisted of NSTE-ACS and STE-ACS. CA was performed by standard Judkins techniques *via* radial or femoral approach. All the coronary angiograms were recorded on compact disks (DICOM format). In need, PCI was carried out by using standard techniques. CAD was determined on the quantitative CA as coronary stenosis ≥50% luminal diameter narrowing. ACS group was classified according to 1-, 2- or 3-vessel disease. The number of vessels with coronary artery lesion was calculated by counting the major coronary artery stenosis ≥50%, including the left main (LM), left anterior descending (LAD), left circumflex (LCX), right coronary artery (RCA), and main branches (diagonal, etc.) bigger than 1.5 mm. For all coronary lesions with >50% diameter stenosis in a vessel >1.5 mm, SYNTAX score calculator 2.28 (available at: www.syntaxscore.com) was used to determine the SYNTAX score.

Follow-up data of all patients for 12 months for major adverse cardiovascular events (MACEs) was noted from hospital records. MACEs were defined as cardiac death, nonfatal myocardial infarction, target vessel revascularization (TVR), congestive heart failure (CHF), and nonfatal stroke. Cardiac death was considered as death primarily due to acute myocardial infarction (MI), CHF, and malignant arrhythmia.

Statistical Analysis: Data was entered in Microsoft excel 2016 and analysed using SPSS for Windows version 21.0. Quantitative data was displayed with mean and standard deviation. Qualitative data was displayed in frequency and percentage (%). The $\chi 2$ or Fisher's Exact tests were used in the comparison of qualitative data between groups. Independent T test was used to compare qualitative data between groups. Independent risk factor for SYNTAX score ≥23 were evaluated by binary logistic regression analysis with enter method. This result was described as Odds ratio with 95% confidence interval (CI). The p-value less than 0.05 was considered as a statistically significant.

RESULT

AIP was divided into three groups low risk (≤ 0.21) and high risk (> 0.21). Out of 120 ACS patients, 48 (40.0%) patients had low AIP and 72 (60.0%) patients had high AIP.

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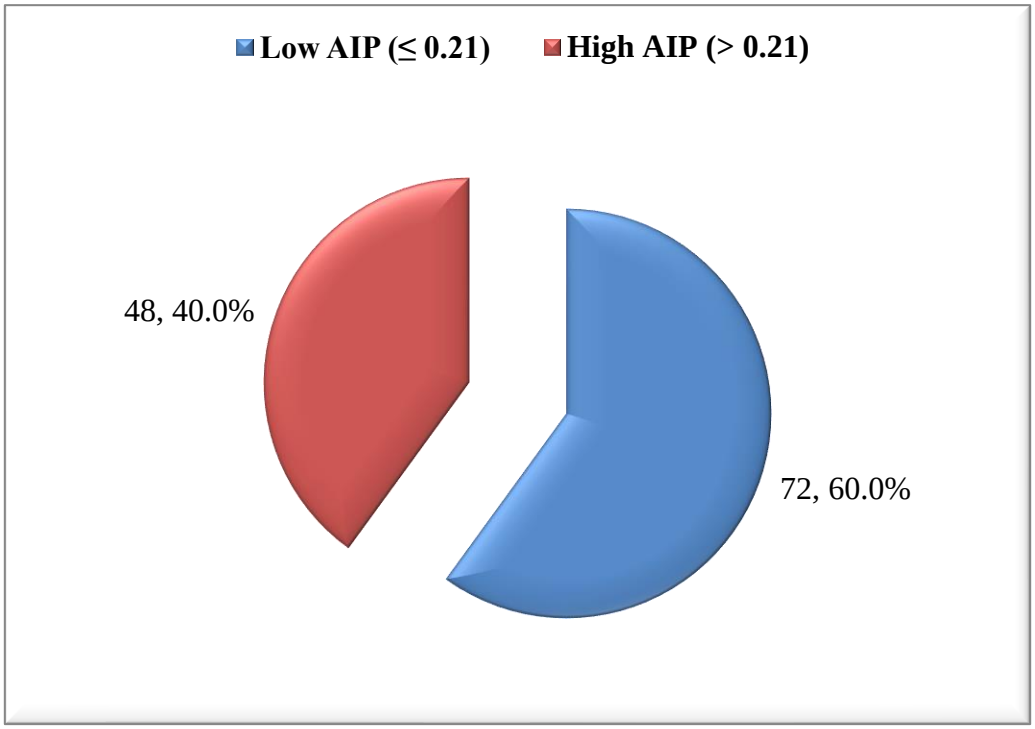

Figure 1: Distribution of ACS patients according to AIP

Table 1: Comparison of socio demographic characteristic of between two groups

Characteristics	Low AIP (≤ 0.21) (n-72)	High AIP (> 0.21) (n-48)	Total (n-120)	p value
Age	58.51 ± 11.00	64.01 ± 12.24	60.59 ± 12.44	**0.04**
Gender [male (%)]	49 (68.1%)	37 (77.1%)	86 (71.7%)	0.81
BMI, kg/m²	25.7 ± 3.5	28.1 ± 3.3	26.9 ± 3.7	**0.02**
WHR	0.94 ± 0.07	0.98 ± 0.05	0.96 ± 0.09	**0.02**
Obesity	5 (6.9%)	10 (20.8%)	15 (12.5%)	**0.02**
Smoker	25 (34.7%)	18 (37.5%)	43 (35.8%)	0.75
Diabetes mellitus	23 (31.9%)	19 (39.6%)	42 (35%)	0.39
Hypertension	25 (34.7%)	20 (41.7%)	45 (37.5%)	0.44
Hyperlipidaemia	19 (26.4%)	24 (50%)	43 (35.8%)	**0.008**
Family history	9 (12.5%)	9 (18.8%)	18 (15%)	0.34

The demographic and angiographic characteristics of ACS groups based on AIP subgroups are shown in Table 1. Mean age in ACS patients with high AIP group (64.01 ± 12.24) was significantly higher as compared to low AIP group (58.51 ± 11.00, p – 0.04). BMI in ACS patients with high AIP group was 28.1 ± 3.3, which was significantly higher than low AIP group (25.7 ± 3.5, p – 0.02). Prevalence of obesity was also higher in ACS patients with high AIP group (20.8%) than low AIP group (6.9%, p – 0.02). Out of 48 patients with high AIP group, 24 patients (50.0%) had Hyperlipidaemia. However, 19 patients of low AIP group had Hyperlipidaemia. This difference was statistically significant (p-**0.008)**. Smoker, DM, hypertension and family history were more common in the high AIP group, but it could not reach statistical significance (p=0.75, 0.39, 0.44, 0.34 respectively).

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Table 2: Comparison of lipid profile between two groups

Lipid profile	Low AIP (≤ 0.21) (n-72)	High AIP (> 0.21) (n-48)	Total (n-120)	p value
TC (mg/dL)	182.56 ± 50.5	187.23 ± 56.72	186.12 ± 45.32	0.08
TG (mg/dL)	142.31 ± 92.32	177.35 ± 94.97	154.34 ± 90.56	**0.03**
HDL-C (mg/dL)	45.02 ±11.34	38.07 ± 12.56	41.34 ± 15.34	**0.01**
LDL-C (mg/dL)	112.34 ± 34.45	128.58 ± 42.45	120.47 ± 56.32	**0.03**
Creatinine (mg/dL)	0.89 ± 0.12	0.93 ± 0.34	0.90 ± 0.11	0.12
CRP (mg/dL)	4.23 ± 3.57	4.47 ± 6.89	4.45 ± 6.54	0.23

TG was 177.35 ± 94.97 in high AIP group and 142.31 ± 92.32 mg/dL in low AIP group. This difference was statistically significant (p-0.03). Similarly LDL-C was also significantly higher in high AIP group (128.58 ± 42.45 mg/dL) than low AIP group (112.34 ± 34.45 mg/dL, p - 0.03).

Table 3: Comparison of ACS characteristics between two groups

ACS characteristics	Low AIP (≤ 0.21) (n-72)	High AIP (> 0.21) (n-48)	Total (n-120)	p value
Angiographic findings				
SVD	38 (52.8%)	14 (29.2%)	52 (43.3%)	**0.008**
DVD	22 (30.6%)	15 (31.3%)	37 (30.8%)	
TVD	12 (16.7%)	19 (39.6%)	31 (25.8%)	
Type of ACS				
STE	39 (54.2%)	26 (54.2%)	65 (54.2%)	0.90
NSTE	33 (45.8%)	22 (45.8%)	55 (45.8%)	
LVEF (%)	11 (15.3%)	7 (14.6%)	18 (15%)	0.91
Syntax score	16.23 ± 10.97	24.3 ± 12.47	19.21 ± 11.23	**0.01**
Treatment				
CABG	7 (9.7%)	5 (10.4%)	12 (10%)	0.80
PCI and CABG	3 (4.2%)	4 (8.3%)	7 (5.8%)	
Medical	2 (2.8%)	1 (2.1%)	3 (2.5%)	
Only PCI	60 (83.3%)	38 (79.2%)	98 (81.7%)	

The three-vessel disease was more common in the high AIP group as compared to low AIP group (39.6% v/s 16.7% respectively), while single vessel disease was more common in the low AIP group (52.8%) than high AIP group (29.2%, p – 0.008). The SYNTAX score of the high AIP group was significantly higher (24.3 ± 12.47) than the score of the low AIP group (16.23 ± 10.97, p - 0.001). There was no significant difference between the two groups in terms of the ACS type (p - 0.90). LVEF was also not significantly different between two groups (p - 0.91). Both CABG and PCI treatment were performed more in the high AIP group (10.4% and

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8.3% respectively) than low AIP group (9.7% and 4.2% respectively) but statistically not significant (p -0.80).

Table 4: Comparison of complications between two groups

Complication	Low AIP (≤ 0.21) (n-72)	High AIP (> 0.21) (n-48)	Total (n-120)	p value
In hospital mortality	1 (1.4%)	5 (10.4%)	6 (5.0%)	**0.02**
MACE	12 (16.7%)	16 (33.3%)	28 (23.3%)	**0.03**
Non fatal MI	4 (5.6%)	6 (12.5%)	10 (8.33%)	0.17
TVR	7 (9.7%)	8 (16.7%)	15 (12.5%)	0.25
Non fatav CVE	1 (1.4%)	1 (2.1%)	2 (1.67%)	0.77
CHF	4 (5.6%)	6 (12.5%)	10 (8.33%)	0.17

In-hospital mortality of the study population was found to be 5.0%. In-hospital mortality was higher in the high AIP group (1.4% *vs.*10.4%, *p*-0.02). MACEs occurred in 33.3% in the high AIP group and 16.7% in the low AIP group (*p*-0.03). While there was no difference for both groups in terms of non-fatal CVE (*p*-0.77), non-fatal MI (*p*-0.17), TVR (*p*-0.25) and CHF (*p*-0.17).

Table 5: Logistic regression analysis showing the predictors of the SYNTAX ≥23.

Variables	OR (95% CI)	p value
Age	1.21 (1.01-1.32)	**0.04**
BMI, kg/m²	1.17 (1.07-1.24)	**0.02**
Smoking	1.01 (0.63-1.64)	0.16
Diabetes	0.78 (0.54-189)	0.35
Hypertension	0.702 (0.45-1.19)	0.58
Hyperlipidaemia	2.24 (1.46-3.78)	< **0.001**
Family history	1.23 (0.62-1.89)	0.43
TG (mg/dL)	1.63 (0.28-1.76)	0.87
LDL-C (mg/dL)	1.65 (1.23-2.86)	**0.01**
LVEF (%)	0.54 (0.11-1.02)	0.74
AIP	1.85 (1.24-2.96)	< **0.001**
Constant	-6.56	< **0.001**

We performed multiple logistic regression analyses for the SYNTAX ≥23 score predictors. Hyperlipidaemia (OR=2.24; 95% CI: 1.46-3.78; $p < 0.001$), High AIP (OR=1.85; 95% CI: 1.24-2.96; $p < 0.001$), LDL-C (OR=1.65; 95% CI: 1.23-2.86; $p < 0.001$), age (OR=1.21; 95% CI: 1.01-1.32; p - 0.04), and BMI (OR=1.17; 95% CI: 1.07-1.24; p - 0.02) were found to be independent predictors of SYNTAX score ≥23 after multiple logistic regression analysis.

DISCUSSION

Dyslipidaemia, a well-known cardiovascular risk factor, plays a pivotal role in the occurrence and progression of coronary artery disease (CAD).[11] Elevated triglyceride (TG) levels and reduced high-density lipoprotein (HDL) levels have been strongly correlated with cardiovascular disease. To assess CAD risk, researchers have explored the atherogenic index of plasma (AIP), which is calculated as the logarithmic transformation of TG/HDL. Studies

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have shown that AIP is associated with the incidence of CVD and is inversely related to LDL particle diameter. Moreover, AIP can serve as a surrogate marker for small dense LDL (sdLDL) particles, which are also implicated in CVD.[12] Therefore, utilizing AIP as a predictor of CAD risk appears to be a more rational approach

In our study, we found that the high AIP group had a higher prevalence of certain factors compared to the low AIP group. Old age, obesity, and hyperlipidemia were more common in the high AIP group (p=0.04, 0.02, 0.008 respectively). We also observed a higher proportion of smokers, individuals with diabetes (DM), hypertension, and family history in the high AIP group, although these differences did not reach statistical significance (p=0.75, 0.39, 0.44, 0.34 respectively). In a study by Ozen Y et al.[13], they also found that the high AIP group had a significantly higher BMI (p=0.015), and hyperlipidemia and family history were significantly more prevalent in this group (p<0.001, p=0.005 respectively). Although DM was more common in the high AIP group, it did not reach statistical significance (p=0.067). The high AIP group had higher levels of glucose and triglycerides (TG), while their high-density lipoprotein cholesterol (HDL-c) levels were lower. Similarly, Wang et al.[14] reported that patients in the high AIP group were older, more likely to be smokers, and had a higher prevalence of dyslipidemia, previous myocardial infarction (MI), and previous stroke. They also had higher BMI, total cholesterol (TC), TG, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and uric acid levels. Additionally, they more frequently used oral hypoglycemic agents (p < 0.05). Numerous studies have consistently shown that AIP is strongly associated with various cardiovascular risk factors such as BMI, visceral fat, TG, and glucose levels.[15,16] AIP has been closely linked to obesity, hypertension, DM, insulin resistance, and metabolic syndrome.[17] These findings highlight the importance of considering AIP as a valuable marker for assessing cardiovascular risk factors.

In the present study, the three-vessel disease was more common in the high AIP group as compared to low AIP group (39.6% v/s 16.7% respectively, p – 0.008).The SYNTAX score was also significantly higher in the high AIP group (24.3 ± 12.47) compared to the low AIP group (16.23 ± 10.97, p=0.001). We didn't observe any significant differences between the two groups in terms of ACS type, LVEF, and treatment type (p=0.90, 0.91, 0.80 respectively). In a study by Ozen Y et al.[13], they also found that three-vessel disease was more common in the high AIP group (40.5% vs. 27.2%, p=0.01). The SYNTAX score was significantly higher in the high AIP group (23.5 ± 12.0) compared to the low AIP group (15.0 ± 10.0, p<0.001). Both PCI and CABG treatments were performed more frequently in the high AIP group. These findings emphasize the association between AIP and the severity of coronary artery disease
In our study, we observed a higher in-hospital mortality rate in the high AIP group compared to the low AIP group (1.4% vs. 10.4%, p=0.02). Additionally, MACEs occurred more frequently in the high AIP group (33.3%) compared to the low AIP group (16.7%, p=0.03). After conducting multiple logistic regression analysis, we identified several independent predictors of a SYNTAX score ≥23. Hyperlipidemia, high AIP, LDL-C, age, and BMI were independent predictors of a SYNTAX score ≥23 (OR=2.24, 1.85, 1.65, 1.21, and 1.17 respectively, all p-values < 0.05). In a study by Ozen Y et al.[13], they also found a higher in-hospital mortality rate in the high AIP group (1.1% vs. 4.7%, p=0.022). MACEs were more prevalent in the high AIP group (34.1%) compared to the low AIP group (15.1%, p<0.001). High AIP was identified as an independent predictor of a SYNTAX score ≥23 (OR=1.378, 95% CI: 1.106-1.716, p=0.004).

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In the study conducted by Wang et al.[14], they found a significant association between high AIP levels and an increased risk of MACCE compared to low AIP levels (HR 1.66, 95% CI 1.08–2.55). The high AIP group also had a significantly higher risk of unplanned repeat revascularization compared to the low AIP group (HR 1.74, 95% CI 1.06–2.87). LI Y et al.[18] observed a positive correlation between AIP and the severity of CAD, even after adjusting for various confounders. Another observational study showed a strong correlation between AIP and the severity of CAD.[19] Additionally, AIP was found to be significantly related to the progression of coronary artery calcification in Korean adults without CVD.[20] Furthermore, an increased AIP was shown to predict the complexity of percutaneous coronary intervention in chronic total occlusion patients and improve therapeutic intervention.[21] Lastly, a previous study suggested that AIP and SYNTAX scores were positively correlated and could be used to predict the severity of CAD.[8]

CONCLUSION

Elevated AIP levels have been found to be associated with an increased risk of MACE and higher SYNTAX scores in patients with ACS. AIP serves as a valuable indicator of atherogenic dyslipidemia, as it doesn't require additional costs and its calculations are not complicated. AIP could serve as independent predictive factors for CAD severity.

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