Atherogenic index of plasma: A valuable novel index to distinguish patients with unstable atherogenic plaques

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Background: Plaque instability is a leading cause of morbidity and mortality in coronary artery disease (CAD) patients. Numerous efforts have been made to figure out and manage unstable plaques prior to major cardiovascular events incidence. The current study aims to assess the values of the atherogenic index of plasma (AIP) to detect unstable plaques. **Materials and Methods:** The current case-control study was conducted on 435 patients who underwent percutaneous coronary intervention due to chronic stable angina (stable plaques, n = 145) or acute coronary syndrome (unstable plaques, n = 290). The demographic, comorbidities, chronic medications, biochemical and hematological characteristics of the patients were entered into the study checklist. The baseline AIP was measured according to the formula of triglycerides/high-density lipoprotein logarithm. Binary logistic regression was applied to investigate the standalone association of AIP with plaque instability. Receiver operating curve (ROC) was depicted to determine a cut-off, specificity, and sensitivity of AIP in unstable plaques diagnosis. **Results:** AIP was an independent predictor for atherogenic plaque instability in both crude (odds ratio [OR]: 3.677, 95% confidence interval [CI]: 1.521–8.890; P = 0.004) and full-adjusted models (OR: 15, 95% CI: 2.77–81.157; P < 0.001). According to ROC curve, at cut-point level of 0.62, AIP had sensitivity and specificity of 89.70% and 34% to detect unstable plaques, respectively (area under the curve: 0.648, 95% CI: 0.601–0.692, P < 0.001). **Conclusion:** According to this study, at the threshold of 0.62, AIP as an independent biomarker associated with plaque instability can be considered a screening tool for patients at increased risk for adverse events due to unstable atherosclerotic plaques.

**Key words:** Acute coronary syndrome, atherogenic plaque, atherosclerosis, coronary artery disease, stable angina

INTRODUCTION

Cardiovascular disease (CVD) has turned into a public health concern responsible for approximately 18 million deaths globally. Moreover, over 71% of deaths in developing and low-income communities are attributed to coronary artery diseases (CADs).[¹,²] Atherogenesis, a lipid-driven chronic inflammatory disorder, is a critical principle in CAD pathogenesis. This phenomenon is responsible for intravascular plaques formation, rupture, and erosion, interrupting myocardium blood supply and leading to myocyte injury or death, known as an acute coronary syndrome (ACS).[³] Accordingly, since long ago, risk factors, including lipoprotein metabolism disorders, hypertension, diabetes mellitus (DM), physical inactivity, obesity, stress, and poverty, are well-known as the chronic proinflammatory conditions leading to CAD.[⁴-⁶] Nevertheless, to date, it is well-recognized that preventive approaches are the key point to combat CVD.[⁷]
To date, various indices have been recommended to assess the cardiovascular disease risk and initiate preventive medications. Therefore, scientists search for low-cost, quick, specific, non-invasive, and predictive tools to identify high-risk cases. In this regard, individual lipid risk factors including triglyceride (TG), total cholesterol (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and non-HDL have been proposed; however, later, it appeared that the constructed indices based on lipid profile are better predictors for CVD.[4]

The atherogenic index of plasma (AIP) is one of the indices calculated as the logarithm of TG/HDL. Epidemiological studies suggested that AIP was significantly associated with obesity, essential hypertension, DM, and other risk factors for CAD.[5,6] In recent years, AIP has been notified as a valuable marker for the prediction of atherogenicity and CAD.[7,8] Besides, strong evidence has suggested AIP as a superior marker than the other indices of a lipid profile to predict cardiovascular all-cause mortality.[9] Nevertheless, to the best of our knowledge, there is no assessment regarding the value of AIP for the determination of atherogenic plaque instability detected through coronary artery angiography, as a condition related to adverse outcomes in cardiovascular events. In other words, we consider AIP as a biomarker used to evaluate the severity of coronary artery involvement for making a decision to initiate or intensify protective treatments. Accordingly, the current study has been conducted to determine whether AIP is a valuable factor in distinguishing the patients with unstable atherogenic plaques.

**METHODS**

**Study population**
The current multi-centric cross-sectional study has been conducted on 435 patients admitted at the angiography/angioplasty departments of Baqiyatallah Hospital, affiliated with Baqiyatallah University of Medical Sciences and Shahid Chamran Heart Center, affiliated with Isfahan University of Medical Sciences, from November 2019 to May 2021.

The ethics committee of the clinical research center of Baqiyatallah University approved this study. The institutional ethical committee at Baqiyatallah University of Medical Sciences approved all study protocols (IR. BMSU. REC.1398.265). Accordingly, the patients were informed about the study protocol, reassured regarding the confidentiality of their personal information, and written informed consent taken from all participants before any intervention.

Indication for percutaneous coronary intervention (PCI) (angiography/angioplasty) due to chronic stable angina pectoris (according to clinical presentations and confirmed by detection of chronic plaques in PCI) or ACS, including unstable angina, non-ST elevated myocardial infarction or ST-elevated myocardial infarction diagnosed according to the European Society of Cardiology guidelines in 2015.[13] In over 18-year-old hemodynamically stable patients were determined as the inclusion criteria. Chronic stable angina pectoris diagnosis was made by the clinical presentations of episodes of chest discomfort, usually induced by physical activity or dealing with stress and relieved with rest, nitroglycerin administration, or both. Alterations in electrocardiography were not necessarily noted at the time of hospital admission.[14]

The exclusion criteria were coagulopathy, familial hypercholesterolemia, systemic inflammatory diseases, malignancies, renal and hepatic failure, severe valvular cardiac diseases, myocarditis, and cardiomyopathy.

The characteristics, including the degree of luminal stenosis (over 50%), presence of plaque calcification, complex lesions with plaque disruption and thrombosis, and coronary artery movement patterns (compression type for unstable plaques versus non-compression type), were applied to determine plaque instability.[15]

The patients who met the study criteria were entered into the study through convenience sampling and were assigned into two groups, including stable atherogenic plaque and unstable atherogenic plaques.

**Study design**
The on-admission blood samples were taken to assess complete blood count (CBC), urea, and creatinine. Although chronic stable angina (CSA) patients were included in the study according to their plaques in PCI, the on admission blood sampling is routinely done in our center.

Afterward, the coronary angiography examinations were performed using the Judkin technique via the radial or femoral artery. The angiography/angioplasty process was performed by a panel consisting of an interventional cardiology fellowship and a cardiologist specialist.

Following 12 h of fasting, another sample was obtained for the laboratory assessments, including total cholesterol (TC), TG, fasting blood sugar (FBS), HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C).

Eventually, on hospital discharge day, a physician examined the patients and completed the study checklist. The recruited items included age, gender, height, weight, smoking status, blood pressure, and medical regimens administered before angiography/angioplasty.
The medical regimens included antihypertensive agents (beta-blockers, diuretics, angiotensin convertase enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers), antiplatelet agents (aspirin and clopidogrel), and statins.

In addition, the patients’ left ventricular ejection fraction (LVEF) was measured at discharge through standard transthoracic echocardiography by a reference cardiologist. Cardiac dysfunction severity has been assessed according to LVEF and classified into four subsections of severe, moderate, mild, and normal as LVEF of <30%, 30 ≤LVEF ≤40%, 40 <LVEF <55% and ≥55%.

In order to minimize the potential inter-observer bias, all the blood samples were sent to the referral laboratory of Cardiovascular Research Institute, the coronary angiography/angioplasty, and LVEF assessments were done by a skilled fellowship of interventional cardiology.

**Measurements**

Hemoglobin, hematocrit, red cells distribution width, absolute leukocyte count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, and platelet count were extracted from the CBC. The neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) were measured by dividing absolute neutrophile and monocyte count by absolute lymphocyte count, respectively.

TC, TG, and FBS were determined enzymatically using an autoanalyzer (Eppendorf, Hamburg, Germany), and HDL-C was measured following precipitation of LDL-C and very low-density lipoprotein with dextran sulfate magnesium. The Friedwald equation was used to measure LDL-C for those with less than 400 mg/dl of TG, otherwise, it was measured using standard kits. The AIP was defined using the formula of TG to HDL logarithm.

Body mass index (BMI) was measured as weight (kg) divided by height squared (m^2) and divided into three subgroups of normal (19.5–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2). Arterial hypertension was concluded in patients with repeated systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg or both, or current use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose levels ≥126 mg/dL, postprandial blood glucose above 200 mg/dL on multiple measurements, hemoglobin A1C above 6.4% from the previous medical records, or current anti-diabetic medications. Dyslipidemia was considered as triglyceride >150 mg/dL, LDL >130 mg/dL, HDL <40 in males and <50 mg/dl in females or the use of lipid-lowering medication.

**Statistical analysis**

The obtained data were entered into the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23. Categorical data were presented in percentages, and absolute numbers, while the continuous ones were stated in mean, standard deviation, median and interquartile range. Primarily, the Kolmogorov–Smirnov test was applied to determine the normality of data distribution. Besides, skewness and kurtosis were assessed. If the data did not have a normal distribution, the Johnson transformation approach was applied to normalize the data distribution; otherwise, nonparametric tests were used. Chi-square test, Fisher’s exact test, or Mann–Whitney U-test (for nonnormal distributed data) was administered to compare the categorical data. The continuous data were compared using independent t-test. Multiple binary logistic regression analysis was applied to find the association between AIP and the plaque instability in crude and adjusted models. The dependent variable was considered as plaque stability. The crude model was presented as model 1. In model 2, the confounding effects of demographic characteristics (age and sex) were controlled. In model 3, adjustment was made for cardiac events risk factors (BMI, smoking, hypertension, DM, dyslipidemia, previous history of ischemic heart disease, and positive family history of ischemic heart disease). Medications including aspirin, clopidogrel, and statins were controlled in model 4. NLR and MLR were adjusted in model 5, and eventually, full adjustment was done in model 6. Odds ratios (ORs) were reported with the corresponding 95% confidence intervals (95% CIs). The receiver operating curve (ROC) was depicted to determine a cut-off value for AIP to predict plaque instability, and sensitivity, specificity, and area under the curve (AUC) were measured. P < 0.05 was considered as a significant level.

**RESULTS**

This study has been conducted on 435 patients with CAD, among which 145 were diagnosed with stable angina and 290 ones with ACS. The mean age of the studied population was 55.43 ± 10.74 years old, with the predominance of male gender (297 ones, 68.27%).

The proportion of male to female (P < 0.001) and smoking (P < 0.001) was remarkably higher in the patients with unstable plaques, while obesity/overweight (P = 0.026) was significantly more in the latter group. Detailed demographic, morbidity, and medical characteristics are presented in Table 1.

More severe cardiac dysfunction was found in those with unstable plaques (P < 0.001). The biochemical and hematological assessments revealed higher levels of...
AIP ($P < 0.001$), FBS ($P < 0.001$), NLR ($P < 0.001$) and MLR ($P = 0.010$) in the ACS group. Further information is presented in Table 2.

According to binary logistic regression assessment, AIP was an independent predictor for atherogenic plaque instability in both crude (OR: $3.677$, $95\%$ CI: $1.521$–$8.900$; $P = 0.004$) and full-adjusted models (OR: $15$, $95\%$ CI: $2.77$–$81.157$; $P = 0.002$). Further adjustments including demographic characteristics (OR: $6.134$, $95\%$ CI: $1.705$–$12.752$, $P = 0.003$), traditional cardiovascular risk factors (OR: $5.509$, $95\%$ CI: $1.670$–$18.176$, $P = 0.005$), taking preventive medications (OR: $3.937$, $95\%$ CI: $1.56$–$9.90$, $P = 0.004$) and NLR and MLR as the hematological factors (OR: $2.992$, $95\%$ CI: $1.066$–$8.393$, $P = 0.037$) revealed that AIP has a standalone role in distinguishing unstable plaques [Table 3].

ROC curve was depicted to determine a cut-off point for AIP in the differentiation of stable versus unstable atherogenic plaques. As shown in Figure 1, at cut-point level of 0.62, AIP had sensitivity, specificity, positive and negative predictive values of $89.7\%$, $34\%$, $40.4\%$, and $86.8\%$, respectively (AUC: $0.648$, $95\%$ CI: $0.60$–$0.69$, $P < 0.001$).

**DISCUSSION**

A rarity of knowledge is available regarding the role of AIP to determine atherogenesis progression. In this regard, the current study is among the limited ones assessing the role of AIP as a surrogate of small low-density lipoprotein particle size in the pathogenesis of ACS. According to our findings, AIP was a standalone index associated with the unstable atherogenic plaques leading to ACS, a condition of permanent myocyte injury. This associative outcome was achieved by controlling the patients’ demographic, medical, clinical, and paraclinical characteristics. Furthermore, at the cut-point of 0.62,


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Table 2: Clinical, biochemical, and hematological characteristics of the studied population

| Variable | Stable plaque (n=145) | Unstable plaque (n=290) | P |
|----------|-----------------------|-------------------------|---|
| Cardiac dysfunction severity | | | |
| LVEF<30 (severe) | 5 (5.7) | 55 (22.5) | <0.001* |
| 30≤LVEF≤40 (moderate) | 14 (15.9) | 86 (35.2) | |
| 40>LVEF≤55 (mild) | 39 (44.3) | 82 (33.6) | |
| LVEF≥55 (normal) | 30 (34.1) | 21 (8.6) | |

Biochemical parameters

| Variable | Stable plaque (n=145) | Unstable plaque (n=290) | P |
|----------|-----------------------|-------------------------|---|
| Triglyceride | 126.12±52.76 | 149.04±83.15 | 0.001* |
| Cholesterol | 163.52±37.65 | 169.23±44.96 | 0.190* |
| HDL | 46.66±10.49 | 42.12±9.03 | <0.001* |
| LDL | 88.48±27.08 | 98.03±36.33 | <0.001* |
| Atherogenic index of plasma | 0.40±0.22 | 0.51±0.23 | <0.001* |
| FBS | 98 (88, 110) | 116 (95,167.50) | <0.001* |
| Creatinine | 1.11±0.67 | 1.18±0.50 | 0.301* |
| Urea | 32.58±12.22 | 36.15±15.44 | 0.021* |

Hematological parameter

| Variable | Stable plaque (n=145) | Unstable plaque (n=290) | P |
|----------|-----------------------|-------------------------|---|
| Hemoglobin | 14.34±2.07 | 14.26±2.04 | 0.714* |
| Hematocrit | 40.71±5.40 | 41.88±5.13 | 0.038* |
| Leukocyte | 7500 (6225-8800) | 9400 (7400-11500) | <0.001** |
| Neutrophil absolute count | 4257.90 (3404.80-5212.50) | 6842.50 (4402.20-9229.50) | <0.001** |
| Monocyte absolute count | 367.20 (292.50-470.88) | 389.82 (281.40-524.08) | 0.725** |
| Lymphocyte absolute count | 2301 (1825.20-3078) | 1958.40 (1334-2389.60) | <0.001** |
| Platelet count | 220.73±65.27 | 207.19±60.01 | 0.043* |
| Red cells distribution width | 13.43±1.21 | 13.54±1.29 | 0.428* |
| Neutrophil-to-lymphocyte ratio | 1.70 (1.23-2.47) | 3.40 (1.82-6.78) | <0.001** |
| Monocyte-to-lymphocyte ratio | 0.15 (0.11-0.21) | 0.20 (0.14-0.29) | 0.010** |

Table 3: Binary logistic regression assessment of atherogenic index of plasma association with atherogenic plaque instability

| Models | OR | 95% CI | P |
|--------|----|-------|---|
| Lower | Upper | |
| Model 1 | 3.677 | 1.521 | 8.890 | 0.004 |
| Model 2 | 6.134 | 1.705 | 12.752 | 0.003 |
| Model 3 | 5.509 | 1.670 | 18.176 | 0.005 |
| Model 4 | 3.937 | 1.556 | 9.960 | 0.004 |
| Model 5 | 2.992 | 1.066 | 8.393 | 0.037 |
| Model 6 | 15.00 | 2.775 | 81.157 | 0.002 |

*Independent t-test, **Mann–Whitney U, *η, LVEF=Left ventricular ejection fraction; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; FBS=Fasting blood sugar

It is well-elucidated that chronic proinflammatory condition causes plaque progression and instability. Lipid deposition into the intima layer of the arteries is a key initial event in the development of atherosclerosis.[23] In addition to the mentioned points regarding the association of AIP with TG and HDL-C, accumulating evidence suggests that AIP is a substitute for small density LDL-C and is inversely related to the LDL-C particle size that is directly related to the formation of foam cells and the development of atherosclerosis.[29]

Accordingly, since long ago, LDL-C was considered one of the most critical risk factors for atherogenicity and plaque rupture. [30] Nevertheless, numerous cases with normal LDL-C presented atherosclerotic diseases, which ignited a theory regarding the crucial role of other lipoprotein particles. HDL-C is a particle that rules as the transporter of peripheral cholesterol to the liver and contains antioxidant enzymes such as paroxonase. [31] HDL-C is associated with anthropometric indices such as weight, BMI, waist and hip circumference, and metabolic indices, including glycemic state and triglycerides. [32] Besides, impaired HDL-C functionality has been notified in immune-inflammatory and autoimmune diseases. [33] The other particle involved in AIP is TG which is directly related to the serum levels of LDL-C. [34] In this regard, Norata et al. have presented that in

we found that AIP had 89.70% sensitivity, which shows the notifying value of this index to apply as a means of screening.

AIP is among the novel indices introduced as the marker of cardiovascular risk factors, including hypertension, DM, and metabolic syndrome, as well as the incidence of CVD events and even all-cause mortality due to CAD. [8][11,25-27]
addition to LDL-C particles, triglyceride-rich lipoproteins is another lipoprotein that independently predicts media-intima thickness and endothelial dysfunction.[33] Therefore, according to this logic, a rise in AIP accompanies an increase in the particles that are dramatically prone to oxidation, plaque, and foamy cell formation and, subsequently, rupture.[34]

One of the notifying findings of our study revealed that AIP was directly correlated with NLR, a combination of two independent inflammatory biomarkers. Neutrophils could reflect the ongoing nonspecific inflammation, and lymphocytes acted as markers of the regulatory pathway.[35] On the other hand, we found that independent of MLR and NLR, AIP was associated with plaque instability.

According to this sentence, the accumulation and deposition of monocytes and their derivatives in the arterial wall are leading cause of atherosclerosis progression. By the deposition of monocytes to the arterial wall, they will be transformed to macrophages which lead to activation and overproduction of proinflammatory cytokines, matrix metalloproteinases, and reactive oxidative species altogether have a substantial key role in the formation, exacerbation, and rupture of atherosclerotic plaques.[36,39] Furthermore, the superiority of MLR to NLR in the prediction of CAD severity and major adverse cardiac events incidence have been progressively presented.[40] Combining these facts made us hypothesize that AIP can be considered a marker linking hematological and lipid profile and an index measuring parameters associated with chronic inflammation; it is a better index for atherosclerosis.

Accordingly, we assumed that AIP could be applied as the biomarker to initiate or intensify the prophylactic remedies such as anti-platelet agents or statins. Therefore, a cut-off point of 0.62 was determined for AIP to differentiate unstable versus stable plaques with a significant sensitivity of 89.70%; however, the specificity was approximately 34% only. Based on our research, there is no other study assessing the value of AIP for plaque instability diagnosis. However, it should be pointed out that the low specificity of AIP may lead to overdiagnosis and unnecessary invasive approaches. Nevertheless, further studies with larger sample populations may help achieve more reliable outcomes.

The previous studies have presented wide ranges of cut-off points for AIP to distinguish CAD. Most of the studies presented AIP ≥0.21 as a high risk for CAD,[26,41,42] however, the cut-point of 0.29 by Mahfouz and colleagues in the population of Egyptians show the diversity of thresholds on different ethnicities.[43] Surprisingly, Wang and colleagues declared the cut point of 2.035 with the specificity of 61.8% and the sensitivity of 76.4% for CAD diagnosis.[27] In general, it seems that AIP, in addition to the other clinical and biomedical manifestations of plaque stability, can be administered as a screening biomarker to decide for intensified approaches for managing the patients prone to cardiovascular events. These considerable diversities may be attributed to the study design, sample population, and definitions for CAD or plaque instability.

Limitations and strengths

Presenting a cost-effective, noninvasive means to screen the high-risk patients for ACS is the most appreciable strength of this study; however, it is accompanied by notable limitations. The observational design and small sample population are the most significant limitations of this study. Furthermore, comparing ACS cases with the controls that have not developed CAD could better view AIP. In addition, failure to assess the patients’ dietary habits and physical activity is the significant restriction of this report that could remarkably affect the patients’ clinical and paraclinical outcomes. The latter limitation of this study that should not be underestimated is using angiography as the standard modality to determine plaque instability; because the included patients were those admitted with ACS undergone PCI.

Nevertheless, further studies using modalities such as computed tomography angiography or intravascular ultrasonography may provide more concise information. The fourth limitation of this study may be attributed to the adjustments. Despite all of the adjustments done in the analyses, it is still possible that unmeasured confounders interfere with a part of the associations between AIP and plaque stability.

CONCLUSION

Based on this study, at the threshold of 0.62, AIP as an independent biomarker associated with plaque instability can be considered a screening tool for the patients at increased risk for adverse events due to unstable atherosclerotic plaques. Although this outcome has been achieved for the first time, it aligns with the previous studies presenting the role of AIP in predicting CVD development. Further studies are strongly recommended.

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Conflicts of interest
There are no conflicts of interest.

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