Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Atherogenic Index of plasma as feasible biomarker (Index) for plaque instability: An observational cross-sectional study in tertiary care hospital in North India

Ashish Bajpai
All India Institute Medical Science (AIIMS)
Rabari Kamlesh
kamleshrabari225@gmail.com

All India Institute Medical Science (AIIMS)
Barun Kumar
All India Institute Medical Science (AIIMS)
Anissa Atif Mirza
All India Institute Medical Science (AIIMS)
Navita Sharma
All India Institute Medical Science (AIIMS)

Research Article

Keywords: Coronary artery disease, Atherogenic index of plasma, Atherogenic plaque

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11765680/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Atherogenic Index of plasma as feasible biomarker (Index) for plaque instability: An observational cross-sectional study in tertiary care hospital in North India

Ashish Bajpai[1], Rabari Kamlesh[1], Barun kumar[2], Anissa Atif Mirza[1], Navita Sharma[1]

1. Department of Biochemistry, All India Institute Medical Science (AIIMS), Rishikesh, Uttarakhand, India
2. Department of Cardiology, All India Institute Medical Science (AIIMS), Rishikesh, Uttarakhand, India

***Corresponding author:** Rabari Kamlesh[1]
Email id: kamleshrabari225@gmail.com
Orchid ID: 0000000160623240

ABSTRACT

Background: Cardiovascular Diseases are the root cause of fatality globally which is responsible for vast number of deaths. Atherosclerosis has a progressive core from stable to unstable plaque which leads to the morbidity and mortality. There are various biomarkers to identify this unstable plaque but still search for biomarker is in this field required to identify the simple and economical biomarker so we have done study on Atherogenic Index of plasma (AIP) as biomarker of plaque instablility.

Methods: We conducted study on total 150 coronary artery disease (CAD) patients 75 of each group (stable and unstable atherogenic plaque). Biochemical parameters analyse by using Fully automated clinical chemistry analyzer (Backman Coulter). AIP calculated by using formula log(TG/HDL). The receiver operating characteristic (ROC) analysis was used to find the sensitivity, specificity, and area under the curve (AUC).

Results: A cutoff point for AIP in distinguishing between stable and unstable atherogenic plaques was established using a ROC curve, which shows 93% sensitivity and 0.668 AUC.

Conclusion: Based on this study, AIP is an independent biomarker for plaque instability. It is cost effective and can done routinely.

Keywords: Coronary artery disease, Atherogenic index of plasma, Atherogenic plaque.

1. INTRODUCTION

Coronary artery disease (CAD) refers to a condition when the cardiac muscle does not receive sufficient blood or oxygen [1].

Cardiovascular diseases (CVDs) are the root cause of fatality globally and are responsible for a vast number of deaths. CAD accounts for approximately 32.7% of all CVD cases globally. In 2021, CVD was responsible for nearly 19.41 million deaths, which is close to one-third of all deaths worldwide [2]. In India, among people with diabetes, approximately 21.4% have CAD, while approximately 11% of those without diabetes have CAD [3].

Atherosclerosis is primarily responsible for CAD, which occurs when fatty deposits build up in the arteries, narrowing them and restricting blood flow. Initially, a "fatty streak" forms because lipid-filled cells called foam cells accumulate under the subendothelial space. If the endothelial lining is damaged, monocytes migrate into this space, turn into macrophages, and ingest bad cholesterol called low-density lipoprotein (LDL), which elevates foam cell formation [1]. Activated T lymphocytes subsequently release cytokines, promoting further inflammation and the recruitment of smooth muscle cells, which also ingest LDL and collagen, leading to the formation of more foam cells and the development of plaques [4].

Over time, these plaques can either expand or become stable. A stable plaque forms a fibrous cap and may become calcified. Even if it is stable, it might not significantly obstruct blood flow at rest but can cause angina during physical activity due to increased myocardial demand. For angina to occur at rest, the lesion must be at least 90% stenosed [1]. If the atherosclerotic plaque ruptures, it can expose thrombogenic material, promoting clot formation that can obstruct coronary blood flow, giving rise to ACS “acute coronary syndrome”, manifesting as unstable angina; NSTEMI “non-ST-elevation myocardial infarction”; or STEMI “ST-elevation myocardial infarction”, which, in severe cases, progress to myocardial infraction (MI) or sudden cardiac death [1,4].

Several variables increase the risk of CAD, such as elevated cholesterol and LDL, hypertension, low HDL (high-density lipoprotein) levels, tobacco use, diabetes mellitus, obesity, physical inactivity, and advanced age, and can be managed to prevent or slow plaque build-up [5]. Among all modifiable risk factors, hypertension remains the most widespread contributor to the onset of atherosclerosis [6]

A key risk factor for both CAD and stroke is dyslipidemia [7]. Abnormal blood lipid levels are referred to as dyslipidemia. Although dyslipidemia typically shows no symptoms, it can be identified with a blood test that measures various lipid levels [8].

Unstable plaques are associated with high morbidity and mortality, so early identification is needed to prevent death.

A study revealed genes associated with unstable plaques and 1,139 differentially expressed genes (DEGs). Compared with stable plaques, unstable plaques presented increased expression of 600 genes and decreased expression of 539 genes.

In unstable plaques, genes associated with fatty acid transport, such as “CD36 and APOE”; genes involved in inflammatory processes, including “MMP9, CTSL, and IFI30”; and antigen presentation genes, including “CD74, B2M, and HLA-DRA”, were increased.

On the other hand, the expression of genes responsible for smooth muscle tightening, such as “TAGLN, ACAT2, MYH10, and MYH11”, were decreased. Additionally, “CD68, PAM, and IGFBP6” emerged as supplementary indicators for identifying unstable atherosclerotic plaques early. M1 macrophages were found to be significant contributors to the formation of these unstable plaques through bioinformatics analysis and machine learning algorithms [9].

Myeloperoxidase (MPO) is a prognostic marker for atherosclerotic CVD [10].

Myeloid-derived protein 8 (Mrp-8) and Mrp-8/14 are linked to plaques, which are more likely to rupture [11].

Elevated PTX3 concentrations indicate the progression of CAD. PCSK9 “Proprotein convertase subtilisin/kexin type 9”, which influences the LDL receptor in the liver, also has a positive connection with PTX3, supporting its use in assessing atherosclerosis. It is known that High-sensitivity C-reactive protein is a biomarker for persistent inflammation [12].

Lp-PLA2- “lipoprotein-associated phospholipase A2” is recognized as a marker of inflammation in atherosclerotic plaques [13].

Researchers continue to look for tools that are cost-effective, fast, precise, and non-invasive, and can predict the risk for high-risk patients.

High triglyceride and reduced HDL concentrations act as independent indicators of CHD “coronary heart disease” [14].

The AIP or “atherogenic index of plasma”, established in 2001, It is determined by calculating the logarithm of the ratio of triglycerides (TGs) to HDL cholesterol using molar concentrations [15].

$$AIP = \log (TG/HDL\text{-}C)$$

The AIP helps evaluate the progression of atherosclerosis and has shown potential as an alternative marker for sdLDL [16]. According to research, the AIP is a reliable and powerful biomarker for estimating the severity of CAD [17].

2. MATERIALS AND METHODS

Study setting: This research was carried out in the Department of Biochemistry in collaboration with the Cardiology Department at the All India Institute of Medical Sciences, Rishikesh, Uttarakhand. Institutional ethical approval was obtained prior to data collection, and the study adhered to National Ethical Guidelines.

Study Design: Observational cross-sectional study conducted in a hospital setting

Study duration: 15 months

Sample size: G*Power (3.1.9.4) software was used to calculate the sample size, referencing a study by Khosravi et al. from 2022. The total sample size was 62 (Odds ratio-3.67; α error – 0.05; power – 0.95).

However, we conducted this study with a total of 150 patients (figure-1)

Stable plaque group- 75 sample

Unstable plaque group-75 sample

Total sample size -150

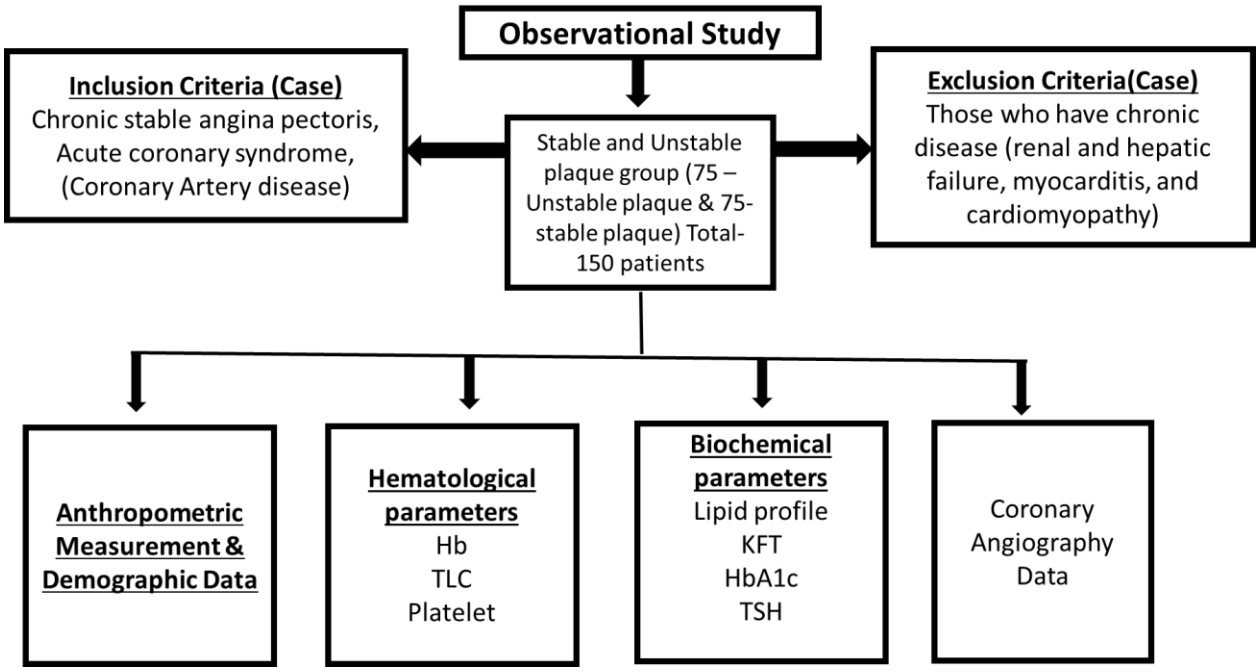


Figure 1. Flow chart of method. "Note-, Hb-Haemoglobin, KFT-Kidney Function Test, TSH-Thyroid Stimulating Hormone, TLC-Total leuckocyte count"

Inclusion criteria:

Study subjects: According to the 2015 guidelines of the European Society of Cardiology, we recruited patients who were attending cardiology outpatient departments and had ACS, such as unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction, as well as patients who had stable angina for a long period of time on the basis of their symptom patterns.

Exclusion criteria:

We had excluded patients who had coagulopathy, familial hypercholesterolemia, systemic inflammatory diseases, malignancies, renal and hepatic failure, severe valvular cardiac diseases, myocarditis, or cardiomyopathy.

Using convenience sampling, we enrolled patients who satisfied the inclusion criteria for this study. According to their clinical findings, participants were assigned to two categories: individuals with stable and unstable atherogenic plaques. A diagnosis of chronic stable angina pectoris resulted from the patient's presentation of episodes of chest pain, which were often caused on by physical activity or emotional stress and resolved by rest or nitroglycerin delivery. The unstable plaque group included participants who, according to the 2015 recommendations of the European Cardiology Society, presented with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction [17].

Data collection:

After obtaining signed informed consent (confirmed by a witness) was obtained, baseline demographic and anthropometric data were collected. Biochemical parameters: (lipid profile) Patient data of were collected from patient records, and the results were used for our study.

Biochemical parameters: Lipid profiling was performed via the following methods: Total Cholesterol by CHOD-PAP method; LDL-Cholesterol by LDL-C Select FS(Direct LDL Cholesterol)-homogenous method without centrifugation and HDL-Cholesterol by HDL-C direct FS- homogenous method without centrifugation and TG production via the GPO Method with the DiaSys Reagent in a fully automated clinical chemistry analyzer (Backman Coulter).

Implication:

Statistical data analysis

We utilized the SPSS 22.0 software suite to look at all the data we had. The Kolmogorov–Smirnov test was used to determine whether the distributions of continuous variables were normal. For continuous variables that followed a normal distribution, the data are presented as means ± standard deviations (SDs). Independent sample t-tests were utilized to assess disparities between two groups. In other cases, the Mann–Whitney test was used to compare data, and the findings are shown as medians with interquartile ranges (IQRs). Receiver operating characteristic (ROC) analysis was used to determine the sensitivity, specificity, and area under the curve (AUC). The ROC curve was then plotted to obtain the AIP cutoff level for identifying plaque instability. Statistical significance was defined as $p < 0.05$.

3. RESULT

The study involved 150 patients diagnosed with CAD, of whom 75 had stable angina and the remaining 75 presented with unstable angina. Predominance of male gender with the studied population having a mean age of 56.40 ± 10.15 years. Unstable plaque associated with slightly older age as compare to stable plaque.

The proportion of male to female is approximately equal in both groups, and smoking was notably more common among patients with stable plaques. Detailed demographic characteristics are presented in Table 1.

Variable	**Stable plaque (n=75)**	**Unstable plaque (n=75)**
Demographic characteristics		
1. Age (years)	55.64 ± 9.68	58.41 ± 10.47
2. Gender		
Male	56	57
Female	19	18
3. BMI (kg/m^2)	23.73 [22.10-27.23]	24.45 [22.49-27.60]
4. History of smoking	31	23
5. History of alcohol	13	09
COMORBIDITIES		
1) History of DM	32	34
2) History of HTN	34	34

Table 1. Shows demographic data of patients of both groups along with their history. "Note- BMI-Body Mass Index, DM-Diabetes mellitus, HTN-Hypertension"

Table 2. shows biochemical and haematological parameters of both stable and unstable plaque groups along with their significance level. In all these biochemical parameters AIP($p<0.001$) shows highly significant difference and some other biochemical parameters also shows significant difference, Triglyceride($p=0.022$), HDL($p=0.009$), Urea($p=0.037$) and In haematological parameters TLC($p=0.021$) shows significant difference.

Variable	Stable plaque (n=75)	Unstable plaque (n=75)	p-value
BIOCHEMICAL PARAMETERS			
Triglyceride (mg/dl)	113[80-146]	133 [97-168]	0.022
Cholesterol (mg/dl)	144 [115-180]	153 [121-195]	0.319
HDL (mg/dl)	42 [35-52]	38 [32-43]	0.009
LDL (mg/dl)	83 [55-103]	86 [59-120]	0.258
Hba1c (%)	6.2 [5.9-7.5]	6.2 [5.8-7.0]	0.538
Urea (mg/dl)	27 [21-34]	31 [24-41]	0.037
Creatinine (mg/dl)	1.01 [0.85-1.14]	1.02 [0.90-1.30]	0.167
TSH (mciu/ml)	1.54 [0.83-2.70]	1.70 [1.25-2.86]	0.194
Uric acid (mg/dl)	5.96 ± 1.68	5.72 ± 1.56	0.855
Atherogenic index of plasma	0.44 [0.27-0.56]	0.52 [0.40-0.67]	<0.001
HEMATOLOGICAL PARAMETERS			
HEMOGLOBIN (gram/dl)	12.7 [11.6-13.6]	13.2 [11.9-13.9]	0.108
TLC (per Ul)	7150 [5940-9090]	8530 [7230-10000]	0.021
PLT (10^3 /ul)	195.23 ± 77.19	214.96 ± 82.93	0.590

Table 2. Shows the laboratory parameters (biochemical and hematological) of both groups with associated statistical significance. "Note- LDL-Low density lipoprotein, HDL- High density lipoprotein, TSH-Thyroid Stimulating Hormone, TLC-Total leuckocyte count, PLT-Platelet".

AIP is distinguishing between stable and unstable atherogenic plaques was established using a ROC curve, which shows 0.668 AUC. Cut off point for AIP is 0.322, having sensitivity and specificity 93.3% and 36% respectively. (Figure 2)

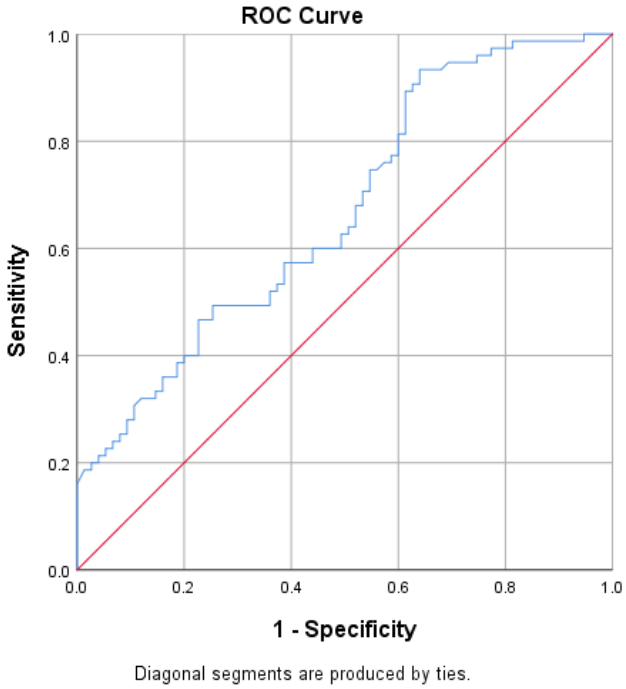


Figure 2. ROC curve drawn between stable and unstable group which shows 0.668 AUC (Area under curve).

4. DISCUSSION

In recent years, CAD has shown high morbidity and mortality worldwide.

The AIP has been studied as a potential indicator of plaque vulnerability and the degree of CAD. Several investigations have examined the usefulness of AIP in evaluating CAD.

Zhou et al. performed a study that showed how AIP predicts the severity of CAD among individuals with type 2 diabetes, with the ROC analysis yielding an AUC value of 0.631, further suggesting AIP can be considered the best biomarker for CAD severity [18].

Kurklu et al. found that AIP serves as a useful indicator for estimating cardiovascular risk among individuals diagnosed with stable angina pectoris [19].

Mirzadeh et al. also found that AIP can be used to predict CAD [20].

A study was conducted to check whether AIP linked to severity of CAD in different glucose metabolic state which shows AIP is linked with severity of CAD only in pre diabetic not in other two groups (Normal glucose regulation and Diabetes mellitus) [21].

Jesrani et al. conducted their study in India and found that the extent of CAD among MI patients showed a positive association with AIP [22].

Another study shows, AIP is not superior to the conventional blood lipid parameters, like LDL-C, but it acts as an independent predictor of CAD in individuals of middle age [23].

The investigation led by You FF indicates a no clear connection between raised AIP and the risk of overall or cardiovascular mortality [24].

Khosravi et al. conducted a study in Iran on plaque instability, and their results show AIP is a feasible biomarker. Their ROC curve showed an AUC of 0.648, indicating that AIP can be a better biomarker for plaque instability [25].

AIP is higher in groups with unstable atherogenic plaques because the lipid abnormalities low HDL and high triglycerides create an environment that is favourable to oxidative damage, inflammation, and decreased plaque integrity, all of which raise the risk of plaque rupture and serious adverse cardiovascular events [26].

5. LIMITATIONS

1. Small sample size due to limited time frame
2. Group based on clinical presentation only
3. Hospital based population

6. CONCLUSION

The results indicate that AIP serves as an independent indicator for unstable plaque and can be used as a screening tool. AIP could help to predict cardiovascular diseases. It is cost effective and can routinely done.

DECLARATIONS

1. **Funding:** Not applicable
2. **Conflict of Interest:** No conflict of interest from all authors
3. **Ethics Approval:** Yes
4. **Consent to participate:** yes
5. **Written Consent for publication:** Not applicable
6. **Availability of data and material:** yes
7. **Code availability:** Not applicable
8. **Author contribution:**

Rabari Kamlesh Karshan: Gave ideas, formulation of subtopics, critical reviewed, and final approval of this article.

Ashish Bajpai: Drafted the primary manuscript and performed data collection, analysis and interpretation, as well as preparing all figures and tables.

Navita Sharma: literature search and review this article and formatting the references.

Barun kumar: Clinical guidance and critical reviewed of this article.

Anissa Atif Mirza: Clinical guidance and critical reviewed of this article.

REFERENCES:

1. Shahjehan RD, Bhutta BS (2024). Coronary Artery Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
2. GENEVA (2023). Deaths from cardiovascular disease surged 60% globally over the last 30 years: Report. World Heart Federation.
3. Falk E. Pathogenesis of atherosclerosis (2006). J Am Coll Cardiol. 47(8 Suppl):C7-12.
4. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al (2022). Pathophysiology of Atherosclerosis. Int J Mol Sci 23(6):3346.
5. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H (2014). Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med 5(8):927-46. PMID: 25489440; PMCID: PMC4258672.
6. Poznyak AV, Sadykhov NK, Kartuesov AG, Borisov EE, Melnichenko AA, Grechko AV, et al (2022). Hypertension as a risk factor for atherosclerosis: Cardiovascular risk assessment. Front Cardiovasc Med 9:959285.
7. Arvanitis M, Lowenstein CJ (2023). Dyslipidemia. Ann Intern Med. 176(6):ITC81-ITC96.
8. Pappan N, Awosika AO, Rehman A (2024) Dyslipidemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
9. Wang J, Kang Z, Liu Y, Li Z, Liu Y, Liu J (2022). Identification of immune cell infiltration and diagnostic biomarkers in unstable atherosclerotic plaques by integrated bioinformatics analysis and machine learning. Front Immunol 13:956078.
10. Nicholls SJ, Hazen SL (2005). Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 25(6):1102-11.
11. Ionita MG, Vink A, Dijke IE, Laman JD, Peeters W, van der Kraak PH, et al (2009). High levels of myeloid-related protein 14 in human atherosclerotic plaques correlate with the characteristics of rupture-prone lesions. Arterioscler Thromb Vasc Biol 29(8):1220-7.
12. Bordeianu G, Mitu I, Stanescu RS, Ciobanu CP, Petrescu-Danila E, Marculescu AD, et al (2022). Circulating Biomarkers for Laboratory Diagnostics of Atherosclerosis-Literature Review. Diagnostics (Basel) 12(12):3141.
13. Sertić J, Skorić B, Lovrić J, Bozina T, Reiner Z (2010). [Does Lp-PLA2 determination help predict atherosclerosis and cardiocerebrovascular disease?]. Acta Med Croatica. 64(4):237–45.
14. Ulloque-Badaracco JR, Hernandez-Bustamante EA, Alarcon-Braga EA, Mosquera-Rojas MD, Campos-Aspajo A, Salazar-Valdivia FE, et al (2022). Atherogenic index of plasma and coronary artery disease: A systematic review. Open Med (Wars) 17(1):1915-1926.
15. Cai G, Shi G, Xue S, Lu W (2017). The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine (Baltimore) 96(37):e8058.
16. Liu Y, Feng X, Yang J, Zhai G, Zhang B, Guo Q, et al (2023). The relation between atherogenic index of plasma and cardiovascular outcomes in prediabetic individuals with unstable angina pectoris. BMC Endocr Disord 23(1):187.

17. Kim SH, Cho YK, Kim YJ, Jung CH, Lee WJ, Park JY, et al (2022). Association of the atherogenic index of plasma with cardiovascular risk beyond the traditional risk factors: a nationwide population-based cohort study. Cardiovasc Diabetol 21(1):81.
18. Zhou K, Qin Z, Tian J, Cui K, Yan Y, Lyu S (2021). The Atherogenic Index of Plasma: A Powerful and Reliable Predictor for Coronary Artery Disease in Patients With Type 2 Diabetes. *Angiology* 72(10):934-941.
19. Kurklu, H.A.; Tan, T.S.; Ozyuncu, N.; Baskovski, E.; Ozdol, C (2023). Atherogenic Index of Plasma Predicts Obstructive Coronary Artery Disease in Patients with Stable Angina Pectoris. Diagnostics(Basel) 13(20);3249.
20. Mirzadeh M, Nikparvar M, Rafati S, Kheirandish M, Azarbad A, Sheybani-Arani M, et al (2024). Atherogenic index of plasma as a predictor of coronary artery disease: a cohort study in south of Iran. Egypt Heart J 76(1):65.
21. Jin K, Ma Z, Zhao C, Zhou X, Xu H, Li D, et al (2025). The correlation between the atherogenic index of plasma and the severity of coronary artery disease in acute myocardial infarction patients under different glucose metabolic states. Sci Rep 15(1):6128.
22. Jesrani G, Shekhawat D S, Mittal G (2024). Correlation of Atherogenic Index of Plasma with Coronary Artery Disease in Myocardial Infarction Patients: An Observational Study from NorthIndia. International Journal of Pharmaceutical and Clinical Research. 16(2):1303–7
23. Hong L, Han Y, Deng C, Chen A (2022). Correlation between atherogenic index of plasma and coronary artery disease in males of different ages: a retrospective study. BMC Cardiovasc Disord 22(1):440.
24. You FF, Gao J, Gao YN, Li ZH, Shen D, Zhong WF, et al (2024). Association between atherogenic index of plasma and all-cause mortality and specific-mortality: a nationwide population-based cohort study. Cardiovasc Diabetol 23(1):276.
25. Khosravi A, Sadeghi M, Farsani ES, Danesh M, Heshmat-Ghahdarijani K, Roohafza H, et al (2022). Atherogenic index of plasma: A valuable novel index to distinguish patients with unstable atherogenic plaques. J Res Med Sci 27:45.

26. Wu S, Gao Y, Liu W, Wang R, Ma Q, Sun J, et al (2024) The relationship between atherogenic index of plasma and plaque vulnerabilities: an optical coherence tomography study. Cardiovasc Diabetol. 23(1):442.