J Surg Med. 2021;5(10):1037-1040.
DOI: 10.28982/josam.1005712

Journal of Surgery and Medicine
e-ISSN=2602-2079

The relationship between atherogenic index and coronary collateral circulation

Cihan Aydın [1], Mustafa Abanoz [2]

[1] Department of Cardiology, Faculty of Medicine Namık Kemal University, Namık Kemal Kampüs Street, Tekirdag, Turkey
[2] University of Health Sciences, Mehmet Akif İnan Training and Research Hospital, Department of Cardiovascular Surgery, Karaköprü, Şanlıurfa, Turkey

ORCID ID of the author(s)

CA: 0000-0002-1401-5727
MA: 0000-0003-1821-1706

Corresponding Author
Cihan Aydın
Department of Cardiology, Faculty of Medicine Namık Kemal University, Namık Kemal Kampüs Street, Tekirdag, Turkey
E-mail: drcihanaydin@hotmail.com

Ethics Committee Approval
Faculty of Medicine Namık Kemal University Clinical Research Ethics Board, Date: 27.08.2020, Number: 2020.180.07.13
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 October 24

Abstract

Background/Aim: The atherogenic index of plasma (AIP) is a simple and useful biomarker that can predict plasma atherogenicity and coronary artery disease (CAD). Previous studies showed a relationship between AIP with CAD. Therefore, we researched the relationship between the AIP and coronary collateral circulation (CCC) in patients with chronic coronary total occlusion (CTO).
Methods: Three hundred and twenty patients who underwent coronary angiography with the diagnosis of stable or unstable angina pectoris between 2015 and 2019 and who had CTO in at least one coronary artery were included in this retrospective study. The AIP was calculated as the logarithm of [Triglyceride (mg/dL) / high-density lipoprotein cholesterol (mg/dL)]. CCC was graded per the Rentrop grading system in patients with CTO after coronary angiography. Rentrop grades were as follows: 0-1: Low-grade (Group 1) CCC, 2-3: High-grade CCC (Group 2).
Results: There were 170 and 150 patients in Groups 1 and 2, respectively, with the mean ages of 63.5 (9.5) years and 61.1 (10.1) years. Mean body mass index, left ventricular ejection fraction, the rate of hypertension, and smoking were similar between the two groups. The rate of diabetes mellitus (DM) was higher in Group 1 (P=0.006). Multivariate analysis showed that AIP (OR: 4.357, CI 95%: 2.741-6.335, P<0.001) and DM (OR: 0.893, CI 95%: 0.826-0.966, P=0.015) were independent predictors of poor CCC.
Conclusion: In our study, we found that a high AIP is related to poor coronary collateral circulation.

Keywords: Cholesterol, Coronary arteries, Atherosclerosis, Collateral circulation

How to cite: Aydın C, Abanoz M. The relationship between the atherogenic index and coronary collateral circulation. J Surg Med. 2021;5(10):1037-1040.

Introduction

Cardiovascular diseases are among the most important causes of mortality and morbidity. Chronic coronary total occlusion (CTO) is the almost complete obstruction of a coronary artery for more than three months. Major adverse cardiovascular events are observed more frequently in CTO patients. CTO is detected in approximately 20% of patients during coronary angiography [1]. Despite new techniques and devices, recanalization of CTO is difficult and complication rates are high during the procedure. The procedure is unsuccessful in almost 20-35% of patients with CTO [2].

When a coronary artery is completely occluded, collateral vessels progressively dilate and begin to transport blood to the ischemic or infarcted area. The presence of coronary collateral circulation (CCC) is important to avoid damage to the ventricle during infarction. The mechanism of CCC varies in each patient, and vascular growth factors, various mediators, and immune system cells are involved [3]. Improved collateral circulation is important in terms of long-term adverse cardiovascular events.

As known, dyslipidemia is one of the prominent risk factors responsible for the pathogenesis of atherosclerosis in coronary artery disease (CAD). Although low-density lipoprotein cholesterol (LDL-C) is blamed in ischemic heart diseases, there are also new markers to show the presence of CAD. The atherogenic index of plasma (AIP) can be a simple, valuable marker for predicting the severity of CAD and the grade of CCC. The AIP is the logarithm of the TG to HDL-C ratio. Previous studies reported AIP to have a high sensitivity in predicting acute coronary events [4]. Also, it was shown that AIP is a powerful and independent predictor of cardiovascular diseases [5, 6].

The relationship between CCC and AIP in patients with CTO has not been studied. This study aimed to research the relationship between the AIP and CCC.

Materials and methods

Study population

The patients who visited the emergency department of our hospital with the complaint of chest pain and underwent angiography with the diagnosis of acute coronary syndrome (ACS) between June 2015 and November 2019 were included in this retrospective study. Consecutive 350 patients diagnosed with CTO during the angiography procedure were divided into two groups per the Rentrop classification. Rentrop grades were defined as low-grade CCC (0-1) and high-grade CCC (2-3). The total occlusion of the coronary artery with thrombolysis in myocardial infarction (TIMI) grade 0 flow for more than three months was considered CTO. These findings were obtained by examining the patient's history and previous angiography reports. The study was carried out per the Helsinki declaration and approval was obtained from the Ethics Committee of Tekirdag Namık Kemal University Hospital (Date: 27.08.2020, Number: 2020.180.07.13).

Patients with severe liver or renal insufficiency (serum creatinine>2mg/dl), elevated triglyceride levels (≥400mg/dl), active infection, and malignancy, and those taking triglyceride-lowering medications were excluded from the study. After exclusion criteria were implemented, 320 consecutive patients with ACS were included. Data about the patients' basic clinical characteristics (age, sex, medical history, body mass index, smoking status, etc.) were obtained by examining the hospital database.

Fasting blood samples were obtained from all patients 12 hours before the procedure and analyzed by an automated biochemical analyzer. Blood pressure was measured three times using an automatic blood pressure (BP) monitor, with the arm placed at the heart level after a 10-minute rest period, and an average of three measurements was obtained. Patients with an average of these three measurements >140/90 mmHg or those under antihypertensive medication were considered hypertensive. Diabetes mellitus was determined by a fasting plasma glucose level of ≥ 7.0 mmol/L (126 mg/dL), or a glycated hemoglobin A1c of ≥ 6,5%. Those using antidiabetic drugs were also considered to have DM. Hyperlipidemia was determined as being on lipid-lowering therapy or having a total cholesterol level above 220 mg/dl. Dyslipidemia was defined as having LDL-C≥160 mg/dL or total cholesterol≥220 mg/dl or HDL-C<40 mg/dl or TG≥200 mg/dl or a history of taking lipid-lowering therapy. The AIP was calculated by the logarithmic transformation of the ratio of TG and HDL-C concentrations: $\log_{10}$ [TG (mg/dl)/HDL-C (mg/dl)].

Coronary angiography

Coronary Angiography was performed using a standard Judkins' technique through the right femoral artery in standard projections, after informed consent was obtained from each patient by an experienced team of cardiologists. Two independent cardiologists were blinded to the groups when interpreting the coronary angiograms of the patients. CCC was assessed per the Rentrop classification as mentioned in previous studies [3], and the patients were divided into two groups accordingly: Group 1 (Grade 0 and 1) and Group 2 (Grade 2 and 3).

Statistical analysis

SPSS 22.0 statistical software (SPSS Inc, Chicago, IL) program was used for statistical analysis. Continuous variables were reported as mean (standard deviation) for normally distributed data or median (minimum-maximum) for non-normally distributed data. Categorical variables were expressed as percentage and compared with the Chi-square or the Fischer's exact test. The conformation of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Two groups were compared with an independent-samples t-test for normally distributed continuous data. Non-normally distributed data were compared with the Mann-Whitney U test. Receiver-operating characteristic analyses (ROC) were used to obtain the cut-off values of AIP for CCC prediction. Multivariate logistic regression analysis was used to identify the independent predictors of poor CCC. A *P*-value of <0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics and the laboratory results of the patients. In Group 1, there were 170 patients with a mean age of 63.5 (9.5) years and in Group 2, there were 150 patients with a mean age of 61.1 (10.1) years.

The mean body mass index, left ventricular ejection fraction, age, the rate of hypertension, and smoking were similar between the two groups. The rate of diabetic patients was higher in Group 1 (P=0.006). There was no difference between the two groups in terms of medical treatment. The vessels with chronic total occlusion, and the number of vessels with CAD were similar in both groups. Laboratory parameters of the two groups were similar except for triglyceride, AIP, and lipid parameters. Triglyceride, LDL-C, AIP, and total cholesterol were higher, while HDL-C levels were lower in Group 1 (P<0.001 for all values) (Table 1).

Table 1: Baseline characteristics and laboratory parameters of the patients

Variables	Group 1 (n=170)	Group 2 (n=150)	Total (n=320)	*P*-value
Age (years)	63.5 (9.5)	61.1 (10,1)	62.2 (9.6)	0.941†
Male, n (%)	110(83.3%)	152(80.9%)	262(81.9%)	0.578#
Female, n (%)	22(16.7%)	36(19.1%)	58(18.1%)	0.572#
Hypertension, n (%)	67(50.8%)	109(58%)	176(55%)	0.208#
Smokers, n (%)	83(62.9%)	103(54.8%)	186(58.1%)	0.147#
Diabetes mellitus, n (%)	65(49.2%)	64(34%)	129(40.3%)	0.006#
Body mass index (kg/m^2)	27.9 (3.9)	27.9 (4.4)	27.9 (4.58)	0.984†
Ejection fraction %	45.8 (11.5)	49.9 (12)	49.77 (10.5)	0.052†
Vessel with chronic total occlusion				
LAD, n (%)	89(67.4%)	131(69.7%)	220(68.8%)	0.880#
Cx, n (%)	37(28%)	50(26.6%)	87(27.2%)	0.880#
RCA, n (%)	6(4.5%)	7(3.7%)	13(4.1%)	0.880#
Medical Treatment				
Beta blocker, n (%)	87(65.9%)	108(57.4%)	195(60.9%)	0.128#
Ca–channel blocker, n (%)	12(9.1%)	19(10.1%)	31(9.7%)	0.764#
ACE-I, n (%)	66(50%)	100(53.2%)	166(51.9%)	0.571#
Diuretic, n (%)	13(9.8%)	25(13.3%)	38(11.9%)	0.349#
Acetyl salicylic acid, n (%)	89(67.4%)	116(61.7%)	205(64.1%)	0.291#
Clopidogrel, n (%)	13(9.8%)	15(8%)	28(8.8%)	0.561#
Oral antidiabetic %	34(25.8%)	40(21.3%)	74(23.1%)	0.345#
Insulin%	27(20.5%)	36(19.1%)	63(19.7%)	0.776#
Statin %	83(62.9%)	117(62.2%)	200(62.5%)	0.902#
Number of vessels with coronary artery disease				
One vessel	29(21.9%)	33(17.6%)	62(19.4%)	0.672#
Two vessel	87(65.9%)	132(70.2%)	219(68.4%)	0.672#
Three vessel	17(12.9%)	22(11.7%)	39(12.2%)	0.672#
Laboratory parameters				
Hemoglobin(g/dl)	13.8 (1.23)	13.7 (1.36)	13.5 (1.43)	0.593†
BUN(mg/dl)	18.21(11-46)	15.41(6-40)	17.44(6-46)	0.407*
Creatinine (mg/dl)	1(0.75-1.7)	0.9(0.3-1.7)	0.9(0.3-1.7)	0.421*
Total cholesterol (mg/dl)	248.2 (33.3)	205 (41.1)	213.27 (46.8)	<0.001†
HDL-C (mg/dl)	32(21-50)	48(26-71)	43.65(18-83)	<0.001*
LDL-C (mg/dl)	171.29 (28.9)	128.25 (38.9)	133.8 (43.8)	<0.001†
Triglyceride(mg/dl)	182.35 (75.3)	111.14 (21.9)	145.48 (67.3)	<0.001†
WBC (×10^3/µL)	7.88 (2.31)	8.34 (2.19)	8.04 (2.23)	0.365†
Neutrophil (×10^3/µL)	4.81 (1.64)	5.03 (2.09)	4.8 (1.89)	0.596†
Lymphocyte(×10^3/µL)	2.21 (0.92)	2.24 (0.86)	2.17 (0.89)	0.992†
Monocyte (×10^3/µL)	0.54(0.3-1.44)	0.59(0.28-2)	0.57(0.27-2)	0.383*
MPV, fl	8.37 (1.13)	8.04 (1.15)	8.20 (1.13)	0.056†
Platelet (×10^3/µL)	279.4 (81.6)	279.8 (62.1)	276.7 (69.4)	0.963†
GFR, ml/dk/1.73 m^2	82.03 (14.9)	84.46 (17.03)	81.83 (17.16)	0.928†
AIP	0.74 (1.17)	0.35 (0.11)	0.5 (0.24)	<0.001†

ACE-I; Angiotensin-converting enzyme inhibitors, LAD; Left anterior descending coronary artery, Cx; Circumflex coronary artery, RCA; Right coronary artery, BUN: Blood urea nitrogen, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein cholesterol, WBC: White blood cell count, MPV: Mean platelet volume, GFR: Glomerular filtration rate, AIP: Atherogenic index of plasma. #Chi- square test (percentage), *Mann Whitney U (median, minimum-maximum), † Student's t-test (mean (standard deviation))

Logistic regression analysis was executed to predict poor CCC predictors (Table 2). In univariate analysis, total cholesterol (OR [odds ratio]: 0.978, 95% CI [confidence interval]: 0.972-0.985, P<0.001), LDL-C (OR: 0.954, 95% CI: 0.871-0.985, P<0.001), triglyceride (OR: 3.712, 95% CI: 2.429-4.396, P<0.001), low HDL-C (OR: 0.875, 95% CI: 0.673-0.947, P<0.001) AIP (OR: 5.641, 95% CI: 3.556-6.748, P<0.001) and DM (OR: 0.535, 95% CI: 0.338-0.839, P=0.007) were found to be significantly correlated with poor CCC. Multivariate analysis revealed that AIP (OR: 4.357, CI 95%: 2.741-6.335, P<0.001) and DM (OR: 0.893, CI 95%: 0.826-0.966, P=0.015) were independent predictors for poor CCC.

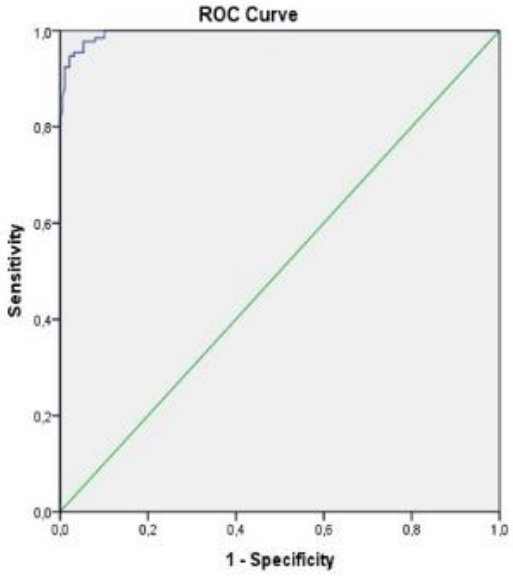
The result of the ROC analysis for the AIP to predict a low degree of coronary collateral circulation was as follows: Cut-off: ≥0.51, AUC: 0.995 and 95% CI: 0.991-0.999 with 95.5% sensitivity and 93% specificity (Figure 1).

Table 2: Univariate and multivariate logistic regression analysis of variables related to poor coronary collateral circulation

Variables	Univariate analysis Odd ratio (95% Confidence interval)	*P*-value	Multivariate analysis Odd ratio (95% Confidence interval)	*P*-value
Total cholesterol (mg/dl)	0.978(0.972-0.985)	<0.001	0.968(0.880-1.065)	0.532
LDL-C (mg/dl)	0.954 (0.871-0.985)	<0.001	1.033(0.944-1.131)	0.454
Triglyceride(mg/dl)	3.712 (2.429- 4.396)	<0.001	---	---
HDL-C (mg/dl)	0.875 (0.673-0.947)	<0.001	---	---
AIP	5.641 (3.556-6.748)	<0.001	4.357 (2.741-6.325)	<0.001
Ejection fraction, %	1.389 (0.681- 1.454)	0.058	--	--
Diabetes mellitus, n	0.535 (0.338-0.839)	0.007	0.893 (0.826-0.966)	0.015
Smoking, n	0.715 (0.454-1.128)	0.149	---	---

LDL: Low-density lipoprotein cholesterol, HDL: High density lipoprotein-cholesterol, AIP: Atherogenic index of plasma

Figure 1: ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for atherogenic index for predicting low coronary collateral circulation grade. (Cut off: 0.51, AUC: 0.995, 95% CI: 0.991- 0.999, P<0.001, 95.5% sensitivity and 93% specificity)



Discussion

Dyslipidemia is the classic risk factor for cardiovascular disease. High triglyceride levels cause both atherogenesis and thrombogenesis. The lipolytic products of triglycerides, which are involved in the pathogenesis of atherosclerosis, activate many proinflammatory, procoagulant, and proapoptotic signaling pathways. AIP is an indirect indicator of small particulate LDL-C. Atherogenic dyslipidemia is defined as a rise in blood TG and LDL-C levels and a decline in HDL-C levels. In previous studies, AIP was associated with LDL-C, HDL-C, and very-low-density lipoprotein (VLDL) particle size [7].

We examined the relationship between the CCC and AIP in patients with ACS who underwent coronary angiography procedures. AIP, as defined by Dobiášová and Frohlich, is an important marker in predicting cardiovascular diseases. Recent CTO studies have reported that AIP correlates with the J-CTO scoring system in predicting the complexity of the lesion [8]. Wan et al. demonstrated that a high AIP is an independent predictor of all-cause mortality in their study [9]. In a prospective cohort including more than 1,000 patients with terminal renal failure, Lee et al. reported the prognostic value of AIP [10]. In various studies, a positive correlation was observed between AIP and diabetes mellitus, arterial stiffness, carotid intima-media thickness [11]. It has also been stated in various studies that AIP can be used in risk assessment before percutaneous coronary intervention (PCI) and coronary artery

bypass grafting (CABG) [12]. In another study, it was demonstrated that AIP could predict restenosis after PCI or CABG [13].

Although many indexes can be used to predict CAD, Lemieux et al. reported that AIP is superior to other indexes such as total cholesterol/HDL-C ratio and LDL-C/HDL-C ratio in CAD estimation [14]. A large Chinese cohort study with over 430 patients showed that increased AIP was independently related to CAD in Chinese males [15]. In a previous study that enrolled 1437 patients without CAD and 2253 patients with CAD, a positive correlation was found between the AIP and SYNTAX score [16]. In another prospective study in which the patients were followed for 4.2 years, a linear relationship was found between AIP and coronary artery calcification progression [15]. In a different study involving 1131 patients newly diagnosed with CAD, AIP was associated with the GRACE score, which predicts major cardiac adverse events [17]. The relationship between AIP and atherosclerosis has been shown in previous studies. We also showed a relationship between AIP and CTO in this study.

Impaired ischemia-induced angiogenesis is the cause of frequent diabetic vascular complications. Angiogenesis is the formation of a new vascular network from the existing main vessels to re-oxygenate the ischemic region. The main underlying cause of diabetic vascular complications is impaired angiogenesis due to ischemia [18]. DM was shown as an independent predictor of poor CCC in a recent study by Chen et al., which included 128 CTO patients [19]. In our study, DM was also an independent predictor of poor CCC.

The most important limitation of our study is that it was conducted with a small group of patients in a single center. In addition, the present study is retrospective, all of which reduce its power. Findings may not be inclusive for other demographic groups. The AIP was calculated only once at admission. Calculating the changes in the AIP during the follow-up period may be better in predicting the prognosis. Further large-scale and multi-center prospective studies are required to validate our results.

Conclusion

In summary, we found that high AIP levels are related to poor collateral circulation in patients with CTO. A high AIP is an important predictor of a low CCC grade. AIP may be a useful marker for prognosis in patients with ACS who underwent percutaneous coronary intervention. It can guide in patient selection for an intervention in CTO.

References

1. Råmunddal T, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, et al. Chronic total occlusions in Sweden--a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). PLoS One. 2014;9(8):e103850.
2. Stojkovic S, Juricic S, Dobric M, Nedeljkovic MA, Vukcevic V, Orlic D, et al. Improved Propensity-Score Matched Long-Term Clinical Outcomes in Patients with Successful Percutaneous Coronary Interventions of Coronary Chronic Total Occlusion. Int Heart J. 2018 Jul 31;59(4):719-26.
3. Hakimzadeh N, Verberne HJ, Siebes M, Piek JJ. The future of collateral artery research. Curr Cardiol Rev. 2014 Feb;10(1):73-86.
4. Ma X, Sun Y, Cheng Y, Shen H, Gao F, Qi J, Yet al. Prognostic impact of the atherogenic index of plasma in type 2 diabetes mellitus patients with acute coronary syndrome undergoing percutaneous coronary intervention. Lipids Health Dis. 2020 Nov 16;19(1):240.
5. Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine (Baltimore). 2017;96(37):e8058.
6. Mesut E, Cihan A, Orhan G. Is it possible to predict the complexity of peripheral artery disease with atherogenic index? Vascular. 2020;28(5):513-9.
7. Hernández-Reyes A, Vidal Á, Moreno-Ortega A, Cámara-Martos F, Moreno-Rojas R. Waist Circumference as a Preventive Tool of Atherogenic Dyslipidemia and Obesity-Associated Cardiovascular Risk in Young Adults Males: A Cross-Sectional Pilot Study. Diagnostics (Basel). 2020 Dec 2;10(12):1033.
8. Guelker JE, Bufe A, Blockhaus C, Kroeger K, Rock T, Akin I, Behnes M, Mashayekhi K. The atherogenic index of plasma and its impact on recanalization of chronic total occlusion. Cardiol J. 2020;27(6):756-61.
9. Wan K, Zhao J, Huang H, Zhang Q, Chen X, Zeng Z, et al. The association between triglyceride/high-density lipoprotein cholesterol ratio and all-cause mortality in acute coronary syndrome after coronary revascularization. PLoS One. 2015 Apr 16;10(4):e0123521.
10. Lee MJ, Park JT, Han SH, Kim YL, Kim YS, Yang CW, et al. The atherogenic index of plasma and the risk of mortality in incident dialysis patients: Results from a nationwide prospective cohort in Korea. PLoS One. 2017 May 26;12(5):e0177499.
11. Shimizu Y, Nakazato M, Sekita T, Kadota K, Yamasaki H, Takamura N, et al. Association of arterial stiffness and diabetes with triglycerides-to-HDL cholesterol ratio for Japanese men: the Nagasaki Islands Study. Atherosclerosis. 2013;228(2):491-5.
12. Gritzenko O, Chumakova G, Veselovskaya N. Atherogenic indexes as predictors of stenotic complication after percutaneous coronary interventions or coronary artery bypass graft. Atherosclerosis. 2015;241(1):e212.
13. Yildiz G, Duman A, Aydin H, Yilmaz A, Hür E, Mağden K, et al. Evaluation of association between atherogenic index of plasma and intima-media thickness of the carotid artery for subclinic atherosclerosis in patients on maintenance hemodialysis. Hemodial Int. 2013;17(3):397-405.
14. Ni W, Zhou Z, Liu T, Wang H, Deng J, Liu X, et al. Gender-and lesion number-dependent difference in "atherogenic index of plasma" in Chinese people with coronary heart disease. Sci Rep. 2017 Oct 16;7(1):13207.
15. Wang L, Chen F, Xiaoqi C, Yujun C, Zijie L. Atherogenic Index of Plasma Is an Independent Risk Factor for Coronary Artery Disease and a Higher SYNTAX Score. Angiology. 2021 Feb;72(2):181-6.
16. Nam JS, Kim MK, Nam JY, Park K, Kang S, Ahn CW, et al. Association between atherogenic index of plasma and coronary artery calcification progression in Korean adults. Lipids Health Dis. 2020 Jul 2;19(1):157.
17. Liu T, Liu J, Wu Z, Lv Y, Li W. Predictive value of the atherogenic index of plasma for chronic total occlusion before coronary angiography. Clin Cardiol. 2021 Apr;44(4):518-25.
18. Kartono T, Mallapasi MN, Mulawardi MM, Laidding SR, Aminyoto M, Prihantono P. Correlation of HDL cholesterol serum and Wagner's severity level of diabetic foot ulcers. Int J Res Med Sci 2017;5:5129-34.
19. Chen X, Lin Y, Tian L, Wang Z. Correlation between ischemia-modified albumin level and coronary collateral circulation. BMC Cardiovasc Disord. 2020 Jul 8;20(1):326.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.