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High Atherogenic Index of Plasma (AIP) as a Predictor of Poor Coronary Collateral Circulation (CCC) in Patients with Chronic Total Occlusion (CTO)

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ABSTRACT

Background: Chronic Total Occlusion (CTO) of the coronary arteries is a condition where the coronary vessels are completely or nearly obstructed for over three months, indicated by angiographic opacity in the distal vessel through collateral circulation. These collaterals form in response to chronic ischemia. The Atherogenic Index of Plasma (AIP) measures the balance between pro-atherogenic and anti-atherogenic lipoproteins in the blood. AIP is a strong predictor of atherosclerosis and cardiovascular risk factors. ***Methods:*** This study is an observational analytic study with a retrospective cohort design. The target population in this study is all patients with Chronic Total Occlusion (CTO). Data were collected from patient medical records. All subjects underwent AIP calculation and CCC degree assessment. Data analysis was conducted using SPSS version 26, including bivariate and multivariate analyses. ***Results:*** The study sample consisted of 94 subjects. The ROC analysis resulted in an area under the curve (AUC) of 0.660 (95% CI 0.550-0.770; p=0.008), with a sensitivity of 87.5% and a specificity of 42.6%, and an AIP cut-off value of 0.205. A high AIP value of ≥0.205 significantly increased the risk of poor CCC occurrence in CTO patients by 2.97 times (95% CI 1.30-6.78; p=0.002). Multivariate analysis showed that the most influential factor for poor CCC was high AIP with an HR of 3.676 (95% CI 1.306-10.350; p=0.014). ***Conclusion:*** A high Atherogenic Index of Plasma (AIP) is a predictor of poor Coronary Collateral Circulation (CCC) in patients with Chronic Total Occlusion (CTO) at our centre.

Keywords: atherogenic index of plasma; coronary collateral circulation; chronic total occlusion; heart disease; pro-atherogenic and anti-atherogenic lipoproteins.

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide, accounting for 32% of global deaths, with 85% of these due to heart attacks [1]. In Indonesia, Coronary Heart Disease (CHD) prevalence is 1.5%, with 1.25 million CHD-related deaths in 2020[2]. Chronic Total Occlusion (CTO) of the coronary arteries, persisting for over three months, is a significant challenge in interventional cardiology, with prevalence rates between 30% and 50% [3].

Coronary Collateral Circulation (CCC) develops in response to chronic ischemia to maintain tissue perfusion. Well-developed CCC is linked to better prognosis and higher procedural success in CHD patients [3]. However, dyslipidemia, characterized by abnormal levels of lipoproteins, can impede CCC formation. The Atherogenic Index of Plasma (AIP), a measure of dyslipidemia, is a strong predictor of cardiovascular risk and atherosclerosis [4].

High AIP negatively correlates with CCC development, suggesting that effective management of lipid levels could improve CCC outcomes [5]. Evaluating AIP, which is derived from widely available lipid profile tests, offers a simple and affordable method for predicting CCC development, making it accessible for use in various healthcare settings [7]. Thus, researchers aim to validate the relationship between AIP and CCC in Chronic Total Occlusion (CTO) patients at our centre to provide insights that could enhance the management and treatment of cardiovascular disease.

METHOD

This study is an analytical observational research using a retrospective cohort design. The research was conducted at Prof. Dr. I. G. N. G. Ngoerah General Hospital, Denpasar, Bali, Indonesia. It collects data from patients with coronary artery disease (CAD) who were found to have chronic total occlusion (CTO) from

March 2023 until March 2024. For these CTO patients, AIP values at the initial visit to the Cardiology Clinic at Prof. Dr. IGNG Ngoerah Hospital will be collected through medical records. Subsequently, the angiographic results in the medical records will be traced for the evaluation of the Coronary Collateral Circulation (CCC) degree.

Inclusion criteria: Patients with stable CAD aged ≥18 years and patients with CTO based on angiographic examination results. Exclusion criteria: 1) Incomplete medical record data, especially related to characteristics and lipid profiles; 2) Patients with a confirmed history of Coronary Artery Bypass Graft (CABG) through medical records; 3) Patients with a history of severe renal failure and liver failure confirmed through medical records; 4) Patients with severe infection or sepsis; 5) Pregnant patients; 6) Patients with malignancy; 7) Patients with autoimmune diseases. The sampling technique used in this study is non-probability sampling with consecutive sampling. This study's data consists of secondary data obtained from the available medical records.

Triglyceride and HDL-C levels of the patients were measured using the Glycerol Phosphate Oxidase (GPO-PAP) method in the Clinical Pathology Laboratory at RSUP Prof. Dr. I.G.N.G Ngoerah using the Alinity ci-series device. The examination utilized venous blood samples from patients who had fasted for approximately 8 hours. The researcher will extract data from the laboratory results recorded in the available medical records. The calculation will then be performed using the formula [Log10(TG/HDL-C)].

The degree of CCC is assessed based on coronary angiographic examination results conducted at the Integrated Cardiology Services cath-lab at Prof. Dr. I.G.N.G Ngoerah Hospital and classified according to the Rentrop classification.

The researcher will collect data from the available medical record readings.

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26, including descriptive analysis, Receiver Operating Characteristic (ROC) curve analysis, proportion comparison analysis, and Relative Risk (RR) analysis. Statistical tests used are the Chi-Square test and Cox Regression analysis.

RESULT

Characteristic data in Table 1 shows: that the average age of the sample involved in the study was 60.22±9.59 years, with the majority being male (76 subjects, 80.9%). A total of 45 subjects (47.9%) were obese, and 69 subjects (73.4%) were smokers. Family history was noted in 9 subjects (9.6%). Comorbid conditions included hypertension in 63 subjects (67.0%), renal failure in 45 subjects (47.9%), and diabetes mellitus in 34 subjects (36.2%). The majority of angina incidents had occurred more than 3 months prior in 64 subjects (68.1%). The mean total cholesterol was 163.20±45.02 mg/dL, HDL was 37.97±9.75 mg/dL, LDL was 110.60±39.96 mg/dL, triglycerides (TG) were 121.73±76.44 mg/dL, and the mean AIP was 0.45±0.29. The high AIP group had a mean of 0.57±0.25, while the low AIP group had a mean of 0.13±0.52. The most common location for CTO lesions was the left anterior descending artery (LAD) in 45 subjects (47.9%). The most common Rentrop classification was Rentrop 3 in 43 subjects (45.7%); high AIP cases were mostly classified as Rentrop 1 (34 subjects, 51.5%), whereas low AIP cases were mostly classified as Rentrop 3 (23 subjects, 82.1%). The majority of CAD cases involved three-vessel disease (CAD3VD) in 66 subjects (70.2%). The majority of subjects had an LVEF of more than 40% (60 subjects, 63.8%).

TABLE 1: Basic characteristics of the research sample.

Basic Characteristics	High AIP (≥0.205) (n=66)	Low AIP (<0.205) (n=28)	Total (n=94)
Age, mean±standard deviation	59.83±10.27	61.14 ± 7.83	60.22±9.59
> 50 years	52 (78.8)	26 (92.9)	78 (83.0)
≤ 50 years	14 (21.2)	2 (7.1)	16 (17.0)
Gender			
Male, n (%)	55 (83.3)	21 (75.0)	76 (80.9)
Female, n(%)	11 (16.7)	7 (25.0)	18 (19.1)
Body mass index, mean ± standard deviation	25.25±3.57	24.77±3.90	25.11 ± 3.66
Obesity, n (%)	35 (53.0)	10 (35.7)	45 (47.9)
Smoking, n (%)	50 (75.8)	19 (66.9)	69 (73.4)
Family history, n(%)	7 (10.6)	2 (7.1)	9 (9.6)
Comorbidities, n (%)	58 (87.9)	24 (85.7)	82 (87.2)
Hypertension, n (%)	47 (71.2)	16 (57.1)	63 (67.0)
Kidney disorders, n(%)	31 (47.0)	14 (50.0)	45 (47.9)
Diabetes mellitus, n(%)	24 (36.4)	10 (35.7)	34 (36.2)
Duration of Angina			
> 3 months	42 (63.6)	22 (78.6)	64 (68.1)

Basic Characteristics	High AIP (≥0.205) (n=66)	Low AIP (<0.205) (n=28)	Total (n=94)
≤3 months	24 (36.4)	6 (21.4)	30 (31.9)
Total cholesterol, mean±standard deviation (mg/dL)	167.94 ± 46.78	152.04±39.09	163.20 ± 45.02
HDL, mean±standard deviation (mg/dL)	34.80±8.46	45.43±8.52	37.97±9.75
LDL, mean±standard deviation (mg/dL)	115.76 ± 41.16	98.43±34.68	110.60 ± 39.96
TG, mean±standard deviation (mg/dL)	146.05 ± 79.15	64.43 ± 13.95	121.73±76.44
AIP, mean±standard deviation	0.57±0.25	0.13±0.52	0.45±0.29
CTO Location			
LAD	31 (47.0)	14 (50.0)	45 (47.9)
LCx	22 (33.3)	8 (28.6)	30 (31.9)
RCA	30 (45.5)	11 (39.3)	41 (43.6)
Rentrop			
1	35 (53.0)	5 (17.9)	40 (42.6)
2	11 (16.7)	0 (0)	11 (11.7)
3	20 (30.3)	23 (82.1)	43 (45.7)
Number of blood vessels with CAD			
1	6 (9.1)	1 (3.6)	7 (7.4)
2	17 (25.8)	4 (14.3)	21 (22.3)
3	43 (65.2)	23 (82.1)	66 (70.2)
Left Ventricle Ejection Fraction(LVEF), mean±standard deviation	42.13±13.12	48.64±13.12	44.07±13.58
EF >40%, n (%)	39 (59.1)	21 (75.0)	60 (63.8)
EF ≤40%, n (%)	27 (40.9)	7 (25.0)	34 (36.2)
Medications			
Statins	100 (100)	100 (100)	100 (100)
Simvastatin, n (%)	30 (45.4)	9 (32.1)	39 (41.5)
20 mg	5 (16.7)	2 (22.2)	7 (17.9)
40 mg	25 (83.3)	7 (77.8)	32 (32.1)
Atorvastatin, n (%)	36 (54.5)	19 (67.9)	55 (58.5)
20 mg	10 (27.8)	6 (31.6)	16 (29.1)
40 mg	26 (72.2)	13 (68.4)	39 (70.9)
Duration of statin use			
≥ 3 months	39 (59.1)	19 (67.9)	58 (61.7)
< 3 months	27 (40.9)	9 (32.1)	36 (38.3)
Acetosal	65 (98.5)	27 (96.4)	92 (97.9)
Clopidogrel	64 (97.0)	24 (85.7)	88 (93.6)
Anti-hypertension			
ACE-I, ARB, ARNI	63 (95.5)	27 (96.4)	90 (95.7)
Beta-blockers	66 (100)	27 (96.4)	93 (98.9)
Calcium channel blockers	22 (33.3)	12 (42.9)	34 (36.2)
Diuretic	31 (47.0)	15 (53.6)	46 (48.9)
Diabetes treatment	23 (34.8)	9 (32.1)	32 (34.1)
Insulin	17 (25.8)	7 (25.0)	24 (25.5)
OAD	6 (9.4)	2 (6.7)	8 (8.5)
Nitrate	26 (39.4)	9 (32.1)	35 (37.2)
MRA	36 (54.5)	16 (57.1)	52 (55.3)

All numerical data are presented as mean±standard deviation.
Categorical data are presented as frequencies (%).
ACEi, ACE-inhibitor; AIP: A*thermogenic plasma index*; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor*neprilysin inhibitor*; CTO: Chronic total occlusion; EF: Ejection Fraction; HDL: High-density cholesterol; LAD: left anterior descending; LCx: Left Circumflex; LDL: Low-density lipoprotein; MRA: Mineralocorticoid receptor antagonist: OAD: Antidiabetic drug; RCA: Right coronary artery: TG: Triglyceride.

ROC curve analysis was performed to determine the AIP threshold that could influence poor CCC formation. The ROC curve results are displayed in Figure 1.

The ROC analysis yielded an area under the curve (AUC) of 0.660 (95% CI 0.550-0.770; p=0.008), with a sensitivity of 87.5% and specificity of 42.6% at an AIP threshold of 0.205.

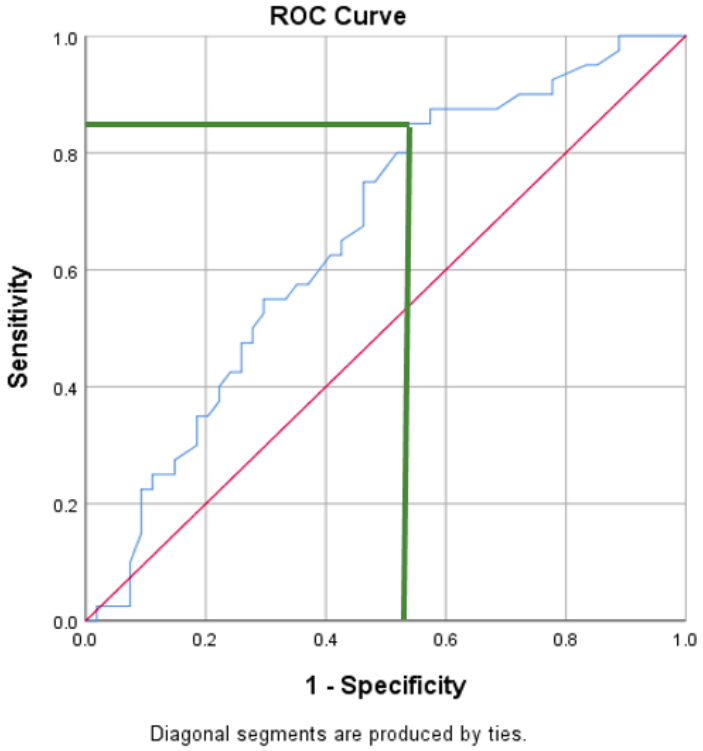

FIGURE 1: ROC curve.

Bivariate analysis was conducted to examine the association between high AIP (≥ 0.205) and poor CCC formation, as well as the relative risk (RR) (Table 2). The bivariate analysis results are shown in Table 2, indicating that high AIP in CTO patients is associated with a higher frequency of poor CCC formation compared to low AIP (53.0% vs. 17.9%; p=0.002). Patients with high AIP (≥0.205) had a significantly higher risk (2.97 times) of experiencing poor CCC formation in CTO patients (95% CI 1.30-6.78; p=0.002).

TABLE 2: Risk of bad CCC formation at high AIP values compared to low AIP values.

Variable	Formation of the CCC		RR	IK 95%	p-value
	Poor (n=40)	Good (n=54)			
High AIP ≥ 0.205	35 (53.0%)	31 (47.0%)	2.97	1.30-6.78	0.002*
Low AIP < 0.205	5 (17.9%)	23 (82.1%)			

*Chi-square test is significant
AIP: Atherogenic plasma index: CCC: Coronary collateral circulation

Bivariate analysis was also performed to evaluate the relationship between control factors, confounding factors, and CCC formation in CTO patients, as presented in Table 3. This analysis showed that age, gender, obesity, smoking, family history, comorbid conditions, duration of angina, CTO location, number of vessels, LVEF, and medication use did not influence poor CCC formation in CTO patients.

TABLE 3: Characteristics of the risk of poor CCC formation in confounding and control variables.

Variable		Formation of the CCC		RR	IK 95%	p-value*
		Poor (n=40)	Good (n=54)			
Age	> 50 years	31 (39.7)	47 (60.3)	0.71	0.42-1.18	0.224
	≤ 50 years	9 (56.3)	7 (43.8)			
Gender	Man	33 (43.4)	43 (56.6)	1.12	0.59-2.10	0.727
	Woman	7 (38.9)	11 (61.1)			
Obesity	Yes	21 (46.7)	24 (53.3)	1.20	0.75-1.93	0.440
	No	19 (38.8)	30 (61.2)			
Smoke	Yes	31 (44.9)	38 (55.1)	1.25	0.70-2.23	0.439
	No	9 (36.0)	16 (64.0)			
Family History	Yes	4 (44.4)	5 (55.6)	1.05	0.48-2.27	0.904
	No	36 (42.4)	49 (57.6)			

Variable		Formation of the CCC		RR	IK 95%	p-value*
		Poor (n=40)	Good (n=54)			
Comorbidities						
Hypertension	Yes	27 (42.9)	36 (57.1)	1.02	0.62-1.69	0.932
	No	13 (41.9)	18 (58.1)			
Diabetes mellitus	Yes	15 (44.1)	19 (55.9)	1.06	0.65-1.71	0.817
	No	25 (41.7)	35 (58.3)			
Kidney disorders	Yes	20 (44.4)	25 (55.6)	1.09	0.68-1.74	0.722
	No	20 (40.8)	29 (59.2)			
Duration of Angina	> 3 months	27 (42.2)	37 (57.8)	0.97	0.59-1.61	0.917
	≤3 months	13 (43.3)	17 (56.7)			
Total cholesterol	> 200 mg/dl	7 (41.2)	10 (58.8)	0.96	0.51-1.79	0.899
	≤ 200 mg/dl	33 (42.9)	44 (57.1)			
LDL	> 100 mg/dl	24 (49.0)	25 (51.0)	1.38	0.85-2.24	0.189
	≤ 100 mg/dl	16 (16.0)	29 (64.4)			
HDL	≤ 50 mg/dl	34 (43.6)	44 (56.4)	1.16	0.58-2.22	0.654
	> 50 mg/dl	6 (37.5)	10 (62.5)			
TG	> 150 mg/dl	15 (44.1)	19 (55.9)	1.06	0.65-1.71	0.817
	≤ 150 mg/dl	25 (41.7))	35 (58.3)			
CTO Location						
LAD	Yes	18 (40.0)	27 (60.0)	0.89	0.55-1.43	0.631
	No	22 (44.9)	27 (55.1)			
LCx	Yes	12 (40.0)	18 (60.0)	0.91	0.54-1.53	0.732
	No	28 (43.8)	36 (56.3)			
RCA	Yes	22 (53.7)	19 (46.3)	1.58	0.99-2.53	0.055
	No	18 (34.0)	35 (66.0)			
LVEF	> 40%	24 (40.0)	36 (60.0)	0.85	0.53-1.36	0.506
	≤ 40%	16 (47.1)	18 (52.9)			
Number of vessels	Multiple	37 (42.5)	50 (57.5)	0.99	0.41-2.41	0.987
	Single	3 (42.9)	4 (57.1)			
Statins	Atorvastatin	24 (43.6)	31 (56.4)	0.94	0.58-1.52	0.801
	Simvastatin	16 (41.0)	23 (59.0)			
Duration of statin use	≥3 months	25 (43.1)	33 (56.9)	1.03	0.63-1.68	0.891
	<3 months	15 (41.7)	21 (58.3)			
Intensity of statin use	Tall	18 (46.2)	21 (53.8)	1.15	0.72-1.84	0.552
	Currently	22 (40.0)	33 (60.0)			
Acetosal	Yes	39 (42.4)	53 (57.6)	0.84	0.21-3.46	0.830
	No	1 (50.0)	1 (50.0)			
Clopidogrel	Yes	38 (43.2)	50 (56.8)	1.30	0.41-4.11	0.637
	No	2 (40.0)	4 (60.0)			
ACE/ARB/ARNI	Yes	37 (41.1)	53 (58.9)	0.54	0.29-1.01	0.180
	No	3 (75.0)	1 (25.0)			
Beta-blockers	Yes	39 (97.5)	54 (100)	-	-	0.243
	No	1 (2.5)	0 (0)			
CCB	Yes	11 (32.4)	23 (67.6)	0.69	0.38-1.16	0.132
	No	29 (48.3)	31 (51.7)			
Diuretic	Yes	22 (47.8)	24 (52.2)	1.27	0.79-2.04	0.311
	No	18 (37.5)	30 (62.5)			
Insulin	Yes	9 (37.5)	15 (62.5)	0.85	0.47-1.51	0.562
	No	31 (44.3)	39 (55.7)			
OAD	Yes	4 (50.0)	4 (50.0)	1.19	0.57-2.49	0.656
	No	36 (41.9)	50 (58.1)			
Nitrate	Yes	11 (31.4)	24 (68.6)	0.64	0.36-1.11	0.093
	No	29 (49.2)	30 (50.8)			
MRA	Yes	22 (42.3)	30 (57.7)	0.98	0.62-1.58	0.957
	No	18 (42.9)	24 (57.1)			

*UJji Chi-square
ACE-I: ACE-inhibitor; AIP: A*thermogenic plasma index*;ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor*neprilysin inhibitor*; CCB: Calcium canal blocker; CTO: Chronic total occlusion;EF: Ejection Fraction; HDL: High-density cholesterol; LAD: left anterior descending; LCx: Left Circumflex; LDL: Low-density lipoprotein; MRA: Mineralocorticoid receptor antagonist: OAD: Antidiabetic drug; RCA: Right coronary artery: TG: Triglyceride

Multivariate analysis was used to identify independent risk factors predicting poor CCC formation in CTO patients. All variables with no multicollinearity and p<0.25 in the bivariate analysis were included in the multivariate analysis.

The multivariate analysis was conducted and revealed that high AIP is a significant independent predictor of poor CCC formation in CTO patients (HR 3.676; 95% CI 1.306-10.350; p=0.014) (Table 4).

TABLE 4: Cox Regression Test Results Using the Backward LR Method.

Variable	HR	IK95%		p-value
		Lower limit	Upper limit	
Step 1				
AIP	3,265	1,129	9,444	0.029
LDL	1,182	0.604	2,313	0.626
RCA	1,343	0.708	2,545	0.367
ACE/ARB/ARNI	0.488	0.146	1,637	0.246
CCB	0.824	0.399	1,703	0.602
Nitrate	0.641	0.307	1,337	0.235
Beta-blockers	0.199	0.021	1,918	0.163
Step 5				
AIP	3,676	1,306	10,350	0.014*
Nitrate	0.620	0.309	1,246	0.179
Beta-blockers	0.170	0.019	1,527	0.114

*Cox regression test
AIP: Atherogenic plasma index; ARB: Angiotensin Receptor Blocker; ARNI, Angiotensin receptor; CCB: Calcium canal blocker; RCA: Right *coronary arteries.*

DISCUSSION

Chronic Total Occlusion (CTO) describes the total or near-total occlusion of coronary arteries due to atherosclerotic disease, with an estimated occlusion duration of ≥ 3 months [8]. The prevalence of CTO in patients with coronary artery disease varies between 20-30%. Age is associated with an increased incidence of CTO. Older age affects the level of clinical improvement and lesion extent in patients.

The occurrence of CTO is related to the continuous formation of CCC. CCC are collateral vessels that create alternative pathways to bypass occlusions in the coronary arteries. Collateral vessels connect areas of the heart that still receive blood flow with the chronically blocked arteries. Thus, they help deliver blood to the heart, partially compensating for the blocked arteries and usually protecting against heart attacks. Therefore, although CTO obstructs direct blood flow through the coronary arteries, collateral vessels form alternative pathways to help supply blood to the heart [13].

In normal individuals, coronary collateral circulation is often not visualized in angiography due to its small size. Fulton et al. explained that the normal collateral size, without CAD, ranges from 10–200 micrometers, and with CAD, the diameter increases to 100–800 micrometers. When collateral circulation takes over, vascular structural size growth occurs alongside a reduction in the number of collateral arteries called pruning.

Smaller vessels must enlarge to accommodate increased blood flow, reducing vascular resistance through this pruning process [13,16].

Enlarged collateral vessels can continue accommodating normal blood flow for months or even years. However, as age increases, the development of collateral vessels gradually tends to decrease. This process, called rarefaction, is more likely in individuals with cardiovascular diseases [7]. When collateral vessels shrink, their function is impaired, leading to angina symptoms when blood flow is obstructed in the main vessels. In a study by Guzel et al. (2021), the average age of subjects in both the good and poor collateral groups was over 60 years, with no significant difference (60.70±10.85 and 62.86±11.40 years) [5]. Multivariate analysis showed no significant effect of age on CCC development (OR 1.008, 95% CI 0.987-1.029, p=0.470), indicating a high incidence of CTO in older age despite no association with poor CCC possibly due to the body's compensatory mechanisms maintaining hemodynamics [5].

Hypertension is a significant risk factor for obstructive coronary artery disease. It can cause endothelial dysfunction, impairing coronary collateral formation. Endothelial dysfunction is characterized by reduced NO production and increased oxidative stress, crucial for maintaining endothelial integrity and promoting vasodilation.

Hypertension can increase shear stress, initially promoting endothelial activation and angiogenesis, but chronic hypertension can lead to maladaptive vascular remodeling, impairing collateral growth. In this study, hypertension was the most common comorbidity (67.0%), higher than kidney disease or diabetes. Although hypertension was more common in CTO, it was not associated with poor CCC (RR 1.02, 95% CI 0.62-1.69, p=0.932), consistent with Aydin & Abanoz (2021), where 55% of CTO patients had hypertension without poor CCC association (p=0.208) [7]. Pei J et al. (2021) also found no effect of hypertension on CCC development (OR = 0.94, 95% CI: 0.75–1.17, p = 0.564), possibly due to comprehensive management of comorbidities. Microvascular rarefaction, a phenomenon in hypertension patients, is an early abnormality from long-term high blood pressure, though its detailed mechanism remains unclear [25]. Recent clinical studies show long-term hypertension management can prevent microvascular rarefaction in hypertensive patients.

Diabetes mellitus (DM) is a major cardiovascular disease risk factor linked to more extensive and progressive atherosclerosis compared to non-DM patients. DM significantly affects CTO (p = 0.032, and p < 0.001) [10]. 46.8% of CTO patients had DM[17]. A Canadian multicenter study found a 34% DM incidence in CTO patients [27]. Guzel et al. (2021) found a significant difference in DM incidence between poor (45.3%) and good CCC (25.1%) groups (p<0.000) [5]. Aydin & Abanoz (2021) found poorer CCC in DM patients compared to non-DM (49.2% vs 34%, p=0.006) [7]. Multivariate analysis confirmed DM as an independent predictor of poor CCC (OR: 0.893, 95% CI: 0.826-0.966, P=0.015). Our study found no effect of DM on CCC development (RR 1.06, 95% CI 0.65-1.71, p=0.817), possibly due to the small number of DM patients with poor CCC (15 subjects) compared to those with good CCC (19 subjects), and the fact that most DM patients were on insulin or antidiabetic drugs.

Angina pectoris is a clinical correlate of myocardial ischemia. Although the presence or absence of symptoms before an occlusive event has been studied, angina pectoris duration has not been considered. Julliere Y et al. (1990) considered angina duration before myocardial infarction or coronary angiography. Angina pectoris duration may parallel disease progression and represent the time for CCC development before coronary occlusion [30]. This study showed that angina pectoris duration is associated with better collateral vessel development, improving LV function after coronary occlusion in CAD1VD. However, some patients with good CCC and myocardial function had no prior angina symptoms or similar angina pectoris duration to those with poor CCC. Ischemic stimulus triggering collateral development might occur unnoticed, indicating a potential role of silent ischemia. In this study, most angina cases lasted > 3 months in 64 subjects (68.1%), with more patients having good CCC (37, 57.8%) than poor CCC (27, 42.2%).

This aligns with epidemiological data showing the highest CTO incidence in subjects with angina symptoms > 3 months [12]. Angina duration did not affect poor CCC formation (RR 0.97; 95% CI 0.59-1.61; p=0.917), possibly due to CCC development occurring approximately 4 weeks after angina onset. Newly developed CCC is visible in angiography within ±10 days of persistent occlusion but not fully developed, with further functional maturation in 12 weeks [14].

Dyslipidemia has the highest incidence in CTO. In Surya's (2017) study, most CTO patients had dyslipidemia (95.7%) [31]. The European CTO registry reported dyslipidemia as the most common risk factor (74.9%) [32]. HDL is known for its anti-atherogenic properties and ability to reverse cholesterol transport from artery walls, specifically from lipid-rich macrophages. HDL also has anti-inflammatory, antioxidant, and antithrombotic functions [26,37]. Experimental studies show that HDL-C improves coronary artery blood flow through NO-mediated vasodilation [38]. These findings suggest that HDL cholesterol may positively influence CCC development by enhancing NO effects. Low HDL-C is an independent risk factor for endothelial dysfunction in healthy individuals without additional cardiovascular risk factors [39]. Thus, patients with poor CCC may have low HDL cholesterol levels.

This study found more subjects with low HDL in the good CCC group than in the poor CCC group (56.4% vs. 43.6%), and low HDL did not affect poor CCC formation (RR 1.16; 95% CI 0.58-2.22; p=0.654). Similarly, total cholesterol, LDL, and TG levels did not affect poor CCC formation. Guzel et al. (2021) reported that although HDL levels were higher in the good CCC group, the difference was not statistically significant (p=0.397) [5]. Aydin & Abanoz (2021) found that while univariate analysis showed lipid profile parameters (total cholesterol, LDL, TG, HDL) significantly correlated with poor CCC, multivariate analysis did not find them as independent predictors of poor CCC [7]. Li Y et al. (2023) also found that LDL did not affect CCC formation (p=0.287) [40]. This study found that traditional cardiovascular risk factors were not associated with poor CCC formation, possibly due to the sample size aimed at proving the influence of high AIP on CCC development. Therefore, the effect size for proving other cardiac risk factors might be smaller.

This study found that high AIP (≥0.205) significantly increased the risk of poor CCC in CTO patients by 2.97 times (95% CI 1.30-6.78; p=0.002). Multivariate analysis showed that high AIP was the most influential factor for poor CCC (HR 3.676, 95% CI 1.306-10.350; p=0.014). Wang et al. (2021) also found high AIP to be a predictor of poor CCC (p<0.001) [41]. Other studies reported a high AIP sensitivity threshold > 0.21 with 84% sensitivity (76%-89%) and 99% specificity, compared to TC/HDL ratio [sensitivity 68% (61-75%); specificity 98%], HDL/LDL ratio [sensitivity 73% (65-80%); specificity 99%], and LDL/HDL ratio [sensitivity 76% (68-82%); specificity 99% [42].

This study found an AUC of 0.660 (95% CI 0.550-0.770; p=0.008), with 87.5% sensitivity and 42.6% specificity at a 0.205 cutoff value. Guzel's study found AIP values of 0.63±0.25 vs. 0.48±0.25 (p<0.001) in poor vs. good CCC groups, with a correlation of -0.299 and p=0.000 [5]. ROC analysis revealed a relationship between poor collateral formation and the atherogenic plasma index, with 64.7% sensitivity and 66.2% specificity using a 0.58 cutoff for AIP. Aydin & Abanoz (2021) found a ROC analysis results for AIP predicting CCC degree with a cutoff of ≥0.51, AUC of 0.995 (95% CI 0.991-0.999), 95.5% sensitivity, and 93% specificity [7]. Li Y et al. (2023) found ROC analysis results with a 0.12 cutoff, AUC of 0.597 (95% CI 0.991-0.999; p=0.002), 92.2% sensitivity, and 19.4% specificity [40].

First described by Dobiášová & Frohlich (2001), AIP is a comprehensive lipid index and a strong marker for predicting CAD risk. Niroumand et al. suggested that AIP can be used as a routine monitoring index for CAD in daily practice [43]. Recent studies have shown AIP's significant value in assessing the severity of coronary syndromes. Other research has found a significant relationship between AIP and coronary artery calcification progression [45].

AIP is independently associated with CTO occurrence and can predict CTO presence and disease severity, with significantly increased AIP values in the CTO group compared to the non-CTO group [46]. Good CCC can positively impact clinical and functional outcomes in CTO patients. Several studies have shown that CCC formation and development can play an important role in reducing mortality, myocardial infarction recurrence, MACE, and overall patient prognosis [46].

The underlying mechanisms linking AIP and CCC are not fully understood. However, AIP is believed to influence CCC development by increasing inflammation, oxidative stress, and endothelial dysfunction due to dyslipidemia, disrupting collateral vessel growth and function. AIP indirectly reflects sdLDL-C particle size. Compared to LDL-C, sdLDL is more likely to invade and deposit in arteries and easily oxidize into oxidized LDL (ox-LDL), accelerating atherosclerosis [47]. Numerous studies have shown that sdLDL-C has greater atherogenic potential than other LDL subfractions, and sdLDL-C ratio is a better predictor of cardiovascular disease than LDL-C (Higashi, 2023). SdLDL-C's strong atherosclerotic effect is due to its small particle diameter and strong affinity with arterial intima proteoglycans. This lipid type is easily modified by oxidation, and has low receptor affinity, slow clearance, and long retention time. Thus, AIP may be a better index for assessing cardiovascular disease risk [48]. Multivariate analysis in this study also found high AIP as the only independent factor associated with poor CCC. Additionally, AIP can be an alternative screening tool when all atherogenic parameters are normal.

The 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. Calculating the changes in the AIP during the longer 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

Atherogenic Index of Plasma (AIP) is a strong predictor of poor Coronary Collateral Circulation (CCC) formation in Chronic Total Occlusion (CTO) patients at RSUP Prof. Dr. I.G.N.G. Ngoerah.

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Declarations

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