ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

The atherogenic index of plasma and its impact on recanalization of chronic total occlusion

Authors: Jan-Erik Guelker, Alexander Bufe, Christian Blockhaus, Knut Kroeger, Thomas Rock, Ibrahim Akin, Michael Behnes, Kambis Mashayekhi

DOI: 10.5603/CJ.a2018.0064

Article type: Original articles

Submitted: 2018-03-14

Accepted: 2018-05-04

Published online: 2018-06-14

The atherogenic index of plasma and its impact on recanalization of chronic total **occlusion**

Short title: Atherogenic index of plasma and CTO

Jan-Erik Guelker[1, 2]*, Alexander Bufe[1, 2, 3]*, Christian Blockhaus[1, 2], Knut Kroeger[4], Thomas Rock[1, 2], Ibrahim Akin[5], Michael Behnes[5], Kambis Mashayekhi[6]

[1]Department of Cardiology, Heart Centre Niederrhein, Helios Clinic Krefeld, Krefeld, Germany

[2]Institute for Heart and Circulation Research, University Cologne, Germany

[3]University Witten/Herdecke, Witten, Germany

[4]Department of Angiology, Helios Clinic Krefeld, Krefeld, Germany

[5]First Department of Medicine, University Medical Centre Mannheim (UMM), Faculty of Medicine Mannheim, University of Heidelberg, Germany

[6]Division of Cardiology and Angiology II, University Heart Center Freiburg, Bad Krozingen, Bad Krozingen, Germany

**Contributed equally*

Address for correspondence: Jan-Erik Guelker, MD, Heartcentre Niederrhein, Department of Cardiology, Helios Clinic Krefeld, Lutherplatz 40, 47805 Krefeld, Germany, Institute for Heart and Circulation Research, University Cologne, Germany, tel: 0049-2151-32-4366, fax: 0049-2151-32-2026, e-mail: jan-erik.guelker@helios-gesundheit.de

Abstract

Background: The plasma-derived atherogenic index (AIP) is associated with an increasing risk for cardiovascular diseases. Whether an increased AIP may predict the complexity of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO), according to available research, has never been investigated before.

Methods: 317 patients were included prospectively and treated with PCI for at least one CTO between 2012 and 2017. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) plasma levels were measured 24 h before PCI. All patients were stratified into tertiles of AIP (defined as 0.11, 0.11–0.21, > 0.21) based on their TG/HDL-C (AIP) levels.

Results: Mean AIP of all patients undergoing CTO-PCI was 0.53 ± 0.29. The majority of patients were male (82.6%), and mean age was 61 ± 10.4 years. Increased AIP > 0.21 was associated with longer occlusion length (statistical trend p = 0.082) and stent routes (p = 0.022) and with a higher number of implanted stents (n > 4) (statistical trend p = 0.072). Success rates were similar in all AIP categories (p = 0.461). In-hospital PCI-related complications were rare and not statistically different (p = 0.852).

Conclusions: This study demonstrates for the first time that an increased AIP may predict the complexity of CTO-PCI and additionally may help to improve planning and quality of CTO-PCI.

Key words: atherogenic index, chronic total occlusion (CTO), coronary artery disease, percutaneous coronary intervention (PCI)

Introduction

Recanalization of chronic total occlusion (CTO) still remains a challenging procedure in interventional cardiology. A CTO of a coronary artery can be identified in up to 18% among patients with a clinical indication for coronary angiography. With the advent of novel recanalization techniques and emerging devices, percutaneous coronary intervention (PCI) has become promising leading treatment option for these patients [1–5].

The atherogenic index of plasma (AIP), the logarithm of molar ratio of triglyceridemia (TG) to high-density lipoprotein cholesterol (HDL-C) has been established as one marker to predict plasma atherogenicity and coronary artery disease (CAD) [8, 9]. Although some lipid variables were associated with the extent of CAD, the specific ratio of TG to HDL-C ratio showed the strongest association respectively. Variation of TG/HDL-C ratio may also be more associated with substantial alterations in metabolic indices predictive for increasing risk of ischemic heart disease compared to variation of low-density lipoprotein cholesterol (LDL-

C)/HDL-C ratio [10, 11]. Is has been shown recently that AIP may reveal highest sensitivity for predicting acute coronary events [23].

Within this context, this study assessed the association between AIP, as a major risk factor of CAD, and CTO and CTO-PCI, as a complex coronary intervention.

Methods

Between 2012 and 2017, a total of 317 patients undergoing CTO-PCI in a German high volume CTO center. All patients had a clinical indication for CTO-PCI and/or positive functional ischemia test assessed by magnetic resonance imaging (MRI) or stress-echocardiography in the territory of the occluded coronary artery.

All procedures were performed via femoral access using 7-french guiding catheters; in the majority of patients contralateral injections of contrast were performed to determine the length of the lesion and the existence and extent of collateral connections. Decisions to treat patients either by antegrade or retrograde CTO-PCI techniques was based on operator discretion. To prevent thrombembolic complications heparin was administered intravenously during CTO-PCI, guided by activated clotting time (> 300 s).

The J-CTO score, combining several parameters of CTO including the degree of calcification of lesion, bending > 45° in CTO segment, blunt proximal cap, length of occluded segment (> 20 mm) and a previously failed recanalization attempt, was calculated for all patients [21].

After PCI a dual antiplatelet therapy consisting of 100 mg of aspirin once daily indefinitely and 75 mg of clopidogrel once daily for at least 6 months was continued. Procedural success was defined as successful recanalization of CTO with a residual stenosis < 30% and restoration of thrombolysis in myocardial infarction (TIMI)-flow grade 3.

A composite safety endpoint summarizing severe complications such as all-cause mortality, vessel perforation, myocardial infarction (MI) and thrombembolic events was evaluated for all patients.

Triglycerides and HDL-C levels were measured after taking venous blood samples in EDTA tubes 24 h before the procedure. Analysis of plasma or serum total cholesterol (TC) and HDL was measured directly in serum while TG were measured enzymatically in serum or plasma [20]. TG/HDL-C was calculated as TG (mmol/L) divided by HDL-C (mmol/L). The patients were separately grouped into tertiles based on TG/HDL-C levels. It has been demonstrated before that an AIP value of under 0.11 is associated with low risk of cardiovascular disease (CVD); the values between 0.11 to 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively [8, 9].

Statistical analysis

The distribution of continuous variables is characterized by mean ± standard deviation, or median and minimum–maximum, the distribution of categorical variables by absolute and relative frequencies.

The Shapiro-Wilk test was used to test for normality of data. The differences of distributions of continuous variables between three AIP categories were tested with the Kruskal–Wallis Test (rejected normality) or F Test. Differences in distributions of categorical variables were tested using the Fisher exact test.

According to the exploratory character of analysis all p values were interpreted as descriptive measures rather than as definitive inferential measures.

Results

The overall procedural success rate was 86% which is in accordance with actual trials. The majority of the patients were male (82.6%), and the mean age was 61 ± 10.4 years. The mean AIP of all patients was 0.53 ± 0.29; male patients were younger than women (60.3 ± 10.2 years vs. 64.6 ± 10.7 years; $p < 0.005$). 92% of patients were already under medication with CSE inhibitors. No differences were found between patients with CSE inhibitor to those without CSE in this study population.

Figure 1 shows a disproportionate distribution of AIP categories in the present cohort. Only 5% of patients (n = 16) had a normal AIP level of < 0.11. Table 1 presents baseline characteristics of the patients studied, and are classified by AIP categories.

Patients with an AIP > 0.21 were more frequent male ($p = 0.075$) and had a higher body mass index (BMI) ($p = 0.023$). They also had a higher LDL-C ($p = 0.043$) and suffered more frequently from arterial hypertension ($p = 0.084$). There was an increase of frequency of diabetes mellitus (DM), BMI, smoking and family history of CAD alongside an increase in AIP. In summary, these cardiovascular risk factors were associated with a high AIP.

This increase was also seen for some peri-procedural characteristics as shown in Table 2.

A high AIP > 0.21 was associated with longest occlusions (statistical trend p = 0.082), the longest stent routes (p = 0.022; Table 1) and highest number of the implanted stents (n > 4) after successful recanalization (statistical trend p = 0.072) (Table 2). Although the J-CTO score — representing the complexity of the CTO lesion — was related to a high AIP (p = 0.015; Fig. 2), procedural variables such as amount of contrast medium, examination time and fluoroscopy time were independent of the extent of AIP.

A majority of patients suffered from a multi-vessel coronary disease; 38.8% had coronary 2-vessel disease and 32.2% coronary 3-vessel disease.

No differences in procedural success rates in different AIP categories was shown (p = 0.461). In-hospital, acute procedural complications were rare and showed no statistically significant difference (p = 0.852). They included mostly vascular complications such as a local hematoma at puncture site (n = 19) and one cardiac tamponade which could be treated with a pericardiocentesis without further consequences. No severe complications such as peri-procedural death or ST-elevation myocardial infarction occurred.

Discussion

Dyslipidemia is an established risk factor for CVD in the general population.

The AIP, which was first described by Dobiášová and Frohlich in 2001 [8], is a comprehensive lipid index, and a strong marker for predicting risk of CAD. In this retrospective study, we examined the association between AIP and patients with CTO and CTO recanalization, respectively. According to available research, no data are available in the current literature about this issue.

The present data emphasizes several important aspects. First, we did show that AIP may predict complexity of a CTO, evaluated by J-CTO score, including severe calcification, tortuosity, stump morphology and lesion length. Second, it could demonstrated that AIP is associated with peri-procedural characteristics such as number and length of stents after a successful recanalization. Third, it was confirmed that AIP is closely related to several cardiovascular risk factors including male gender.

These findings are in accordance with previous trials, showing a strong association between AIP, cardiovascular risk factors and severity of CAD [9, 11]. Therefore Niroumand et al. [9] has suggested that AIP could be used as a regular monitoring index of CAD in every day practice, while Wan et al. [12] proved that an elevated AIP is a powerful independent predictor of all-cause mortality and for subsequent CVD after coronary revascularization [12].

Lee et al. [13] confirmed prognostic relevance of AIP within a nationwide prospective cohort including more than 1,000 patients with a terminal renal failure. Furthermore Shimizu et al. [18] found a significant positive correlation between diabetes mellitus and AIP and as well as with carotid intima-media thickness (cIMT), progression and arterial stiffness.

An explanation may be the association of AIP with LDL-C particle size, insulin resistance and metabolic syndrome [8, 14–16]. Hermans et al. [17] demonstrated a relationship between AIP and vascular damage and an association with residual vascular risk, beta-cell function loss and microangiopathy in diabetic patients.

The present study observes that patients with a higher BMI revealed an increased AIP ($p = 0.023$). These findings are in agreement with previous data that proved close association between abnormalities of blood lipoproteins and habits of people, such as life style and eating habits [9, 25, 26].

Higher AIP correlates with a higher J-CTO Score, but failed to shown as a predictor for procedural success in CTO recanalization. Lemieux et al. [10] proved that in predicting CAD the AIP is superior to other indices like TC/HDL-C ratio and LDL-C/HDL-C ratio [10]. Furthermore Yildiz et al. [19] suggested that AIP might be a method which can be used for both diagnosis of subclinical atherosclerosis and in deceleration processes of its progression.

The fact that the AIP is associated with male gender in this study ($p = 0.075$) is in accordance with a large chinese cohort with over 430 patients which showed increased AIP being independently associated with coronary heart disease in Chinese males [24].

The AIP may be helpful to estimate the complexity of the procedure in advance and to make a decision on this basis. It is also easy to calculate and may be included in daily clinical practice. Unfortunately it could not demonstrated that this index can predict possible complications related to the complex coronary intervention of CTO-PCI. Gritzenko et al. [22] pointed out that AIP may be necessary to risk assessment before PCI and CABG. In a trial of 186 patients it was shown that this index can significantly predict re-stenosis after CABG and PCI.

Limitations oft he study

The present study is a retrospective analysis and all data are collected from a single-center. The results of this study may have been influenced by selection criteria, operator experience, and varying techniques used by operators. Furthermore, there was no data about the impact of long term follow-up of AIP in CTO patients. Another limitation may be that the matched and un-matched data used in this study were already collected. Thus, the analysis represents an observational character only.

Conclusions

The TG/HDL-C ratio may be an independent predictor for complexity of a CTO. Prospective evaluation of AIP as a determinant of the lesion may add adjunctive information for procedural planning of intervention.

Conflict of interest: Dr. Mashayekhi received consulting/speaker honoraria from Abbott Vascular, Asahi Intecc, Biotronik, Boston Scientific, Daiichi Sankyo, Nitiloop, Vascular Solution, Termuo. Jan-Erik Guelker: none. Alexander Bufe: none. Christian Blockhaus: none. Knut Kroeger: none. Heinrich Klues: none. Michael Behnes: none. Ibrahim Akin: none.

References

1. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol. 2012; 59(11): 991–997, doi: 10.1016/j.jacc.2011.12.007, indexed in Pubmed: 22402070.
2. Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. Eur Heart J. 2015; 36(45): 3189–3198, doi: 10.1093/eurheartj/ehv450, indexed in Pubmed: 26333367.
3. Bufe A, Haltern G, Dinh W, et al. Recanalisation of coronary chronic total occlusions with new techniques including the retrograde approach via collaterals. Neth Heart J. 2011; 19(4): 162–167, doi: 10.1007/s12471-011-0091-7, indexed in Pubmed: 22020996.
4. Galassi AR, Tomasello SD, Reifart N, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. EuroIntervention. 2011; 7(4): 472–479, doi: 10.4244/EIJV7I4A77, indexed in Pubmed: 21764666.
5. Stähli BE, Gebhard C, Gick M, et al. Impact of body mass index on long-term mortality in women and men undergoing percutaneous coronary intervention for chronic total occlusion. Int J Cardiol. 2016; 224: 305–309, doi: 10.1016/j.ijcard.2016.09.057, indexed in Pubmed: 27665402.
6. Yamamoto E, Natsuaki M, Morimoto T, et al. Long-term outcomes after percutaneous coronary intervention for chronic total occlusion (from the CREDO-Kyoto registry cohort-2). Am J Cardiol. 2013; 112(6): 767–774, doi: 10.1016/j.amjcard.2013.05.004, indexed in Pubmed: 23735646.
7. Suero JA, Marso SP, Jones PG, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. J Am Coll Cardiol. 2001; 38(2): 409–414, indexed in Pubmed: 11499731.
8. Dobiášová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate inapob-lipoprotein-depleted plasma (FERHDL). Clin Biochem. 2001; 34(7): 583–588, doi: 10.1016/s0009-9120(01)00263-6.
9. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, et al. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. Med J Islam Repub Iran. 2015; 29: 240, indexed in Pubmed: 26793631.

10. Lemieux I, Lamarche B, Couillard C, et al. Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: the Quebec Cardiovascular Study. Arch Intern Med. 2001; 161(22): 2685–2692, indexed in Pubmed: 11732933.

11. Lemos da Luz P, Favarato D, Faria-Neto Junior JR, et al. High ratio of triglycerides to hdl-cholesterol predicts extensive coronary disease. Clinics. 2008; 63(4), doi: 10.1590/s1807-59322008000400003.

12. Wan Ke, Zhao J, Huang H, 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; 10(4): e0123521, doi: 10.1371/journal.pone.0123521, indexed in Pubmed: 25880982.

13. Lee MiJ, Park JT, Han SH, 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; 12(5): e0177499, doi: 10.1371/journal.pone.0177499, indexed in Pubmed: 28549070.

14. McLaughlin T, Reaven G, Abbasi F, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? Am J Cardiol. 2005; 96(3): 399–404, doi: 10.1016/j.amjcard.2005.03.085, indexed in Pubmed: 16054467.

15. Hermans MP, Ahn SA, Rousseau MF. log(TG)/HDL-C is related to both residual cardiometabolic risk and β-cell function loss in type 2 diabetes males. Cardiovasc Diabetol. 2010; 9: 88, doi: 10.1186/1475-2840-9-88, indexed in Pubmed: 21156040.

16. Onat A, Can G, Kaya H, et al. "Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010; 4(2): 89–98, doi: 10.1016/j.jacl.2010.02.005, indexed in Pubmed: 21122635.

17. Hermans MP, Ahn SA, Rousseau MF. The atherogenic dyslipidemia ratio [log(TG)/HDL-C] is associated with residual vascular risk, beta-cell function loss and microangiopathy in type 2 diabetes females. Lipids Health Dis. 2012; 11: 132, doi: 10.1186/1476-511X-11-132, indexed in Pubmed: 23046637.

18. Shimizu Y, Nakazato M, Sekita T, 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): 491–495, doi: 10.1016/j.atherosclerosis.2013.03.021, indexed in Pubmed: 23601500.

19. Yildiz G, Duman A, Aydin H, 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, doi: 10.1111/hdi.12041, indexed in Pubmed: 23551383.

20. Cox RA, García-Palmieri MR. Cholesterol, Triglycerides, and Associated Lipoproteins. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd.

21. Morino Y, Abe M, Morimoto T, et al. J-CTO Registry Investigators. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interv. 2011; 4(2): 213–221, doi: 10.1016/j.jcin.2010.09.024, indexed in Pubmed: 21349461.

22. 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, doi: 10.1016/j.atherosclerosis.2015.04.1005.

23. Khazaál MS. Atherogenic Index of Plasma (AIP) as a parameter in predicting cardiovascular risk in males compared to the conventional dyslipidemic indices (cholesterol ratios). Karbala J Med. 2013; 6(1): 1506–11.

24. Ni W, Zhou Z, Liu T, et al. Gender-and lesion number-dependent difference in "atherogenic index of plasma" in Chinese people with coronary heart disease. Sci Rep. 2017; 7(1): 13207, doi: 10.1038/s41598-017-13267-6, indexed in Pubmed: 29038593.

25. Kanthe PS, Patil BS, Bagali Sh, et al. Atherogenic Index as a Predictor of Cardiovascular Risk among Women with Different Grades of Obesity. IJCRIMPH. 2012; 4(10): 1767–1774.

26. Flier JS. Biology of Obesity. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. eds. Harrison's Principles of Internal Medicine.17th ed. New York, NY : 462–464.

Table 1. Baseline and periprocedural characteristics of the study patients, classified by atherogenic index categories.

Variable	< 0.11	0.11–0.21	> 0.21	P
Number	16	20	281	
Age [years]*	62 (37–86)	61 (39–81)	61 (33–87)	0.870
Male gender	68.8% (11)	70.0% (14)	84.3% (237)	0.075
BMI [kg/m²]*	26.0 (21–39)	27.0 (19–35)	27.4 (17–45)	0.023
Diabetes mellitus	18.8% (3)	30.0% (6)	24.6% (69)	0.742
Smoking	25.0% (4)	30.0% (6)	46.6% (131)	0.101
COPD	6.3% (1)	15.0% (3)	7.1% (20)	0.377
LDL-C > 100 mg/dL	18.8% (3)	50.0% (10)	50.5% (142)	0.043
Hypertension	56.3% (9)	75.0% (15)	79.4% (223)	0.084
Family history of CAD	12.5% (2)	25.0% (5)	27.4% (77)	0.446
Prior MI	6.3% (1)	30.0% (6)	28.8% (81)	0.139
Prior CABG	12.5% (2)	0.0% (0)	13.2% (37)	0.245
Prior CTO-PCI attempt	37.5% (6)	35.0% (7)	49.8% (140)	0.325
Prior PCI	37.5% (6)	30.0% (6)	40.2% (113)	0.706
LVEF ≥ 40	93.8% (15)	100% (20)	97.5% (274)	0.403
Amount of contrast medium [mL]*	220.9 (90–500)	226.8 (90–600)	228.2 (70–600)	0.736
Examination time [min]*	108.4 (45–180)	95.3 (30–220)	110.9 (15–300)	0.110
Fluoroscopy time [min]*	37.4 (11–76)	34.9 (4–94)	37.6 (7–104)	0.476
Lenght of occlusion [mm]*	32.8 (15–70)	29.5 (15–70)	37.6 (10–100)	0.082
Stent diameter [mm]*	3.0 (2.5–3.5)	2.9 (2.5–3.5)	3.1 (2.25–4.0)	0.122
Lenght of stent [mm]	61.0 (23–119)	52.2 (18–104)	69.1 (12–157)	0.022

*Median (min–max); BMI — body mass index; CABG — coronary artery bypass graft surgery; CAD — coronary artery disease; COPD: chronic obstructive pulmonary disease; CTO — chronic total occlusion; LDL-C — low density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention

Table 2. Angiographic characetristics and procedural outcome, classified by median atherogenic index.

CTO — chronic total occlusion; J–CTO — japansese chronic total occlusion; LAD — left anterior descending; LCX — left circumflex; RCA — right coronary artery

Variable	N	Mean AIP	P
CTO in:			0.862
LAD	87	0.511	
LCX	32	0.564	
RCA	197	0.528	
Coronary vessel disease			0.535
1	93	0.522	
2	123	0.513	
3	102	0.556	
Blunt stump/no stump	215	0.536	0.483
Tortuosity > 90°	226	0.538	0.315
Severe calcification	248	0.538	0.208
J-CTO Score:			0.015
0	9	0.358	
1	28	0.366	
2	56	0.587	
3	77	0.539	
4	108	0.558	
5	39	0.502	
Retrograde approach	80	0.596	0.015
Drug eluting stents	270	0.525	0.662
Number of stents:			0.072
0	36	0.545	
1	53	0.424	
2	117	0.553	
3	77	0.531	
≥4	25	0.578	
Success	272	0.524	0.461
Complications	20	0.531	0.852

FIGURES LEGEND

Figure 1. Distribution of atherogenic index (AIP) categories.

Figure 2. Atherogenic index (AIP) in J-CTO score categories.

Figure 1: Distribution of AIP Categories

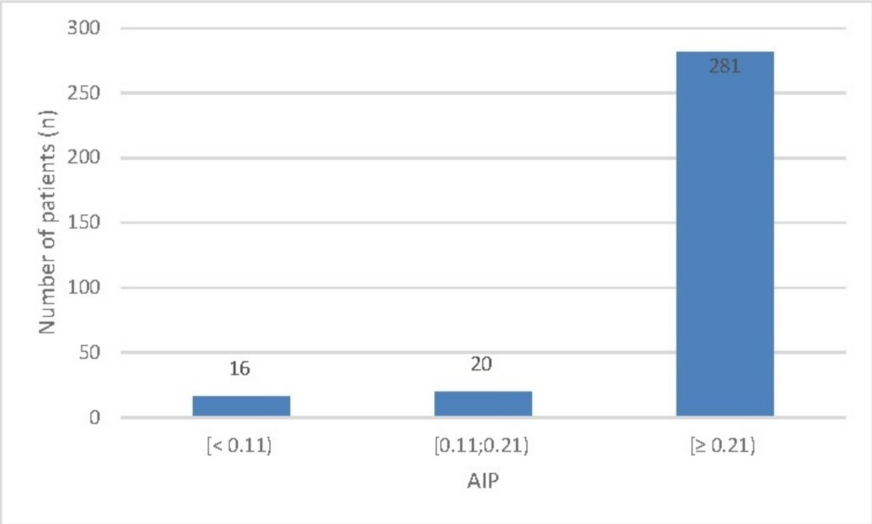

Figure 2: AIP in J-CTO Score Categories