Predictive value of calculated plasma osmolality and atherogenic index of plasma for chronic limb-threatening ischemia in lower extremity artery disease

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ABSTRACT

Objectives: Chronic limb-threatening ischemia (CLTI) is the end-stage form of lower extremity artery disease (LEAD) whose main reason is atherosclerosis. Plasma osmolality (PO) and plasma lipid levels affect the development and progression of atherosclerosis directly. The purpose of this study was to investigate the predictive effect of PO and atherogenic index of plasma (AIP) for the development of CLTI.
Methods: A total of 324 patients who were diagnosed with LEAD were analyzed retrospectively. The clinical stage of the disease was evaluated according to the Rutherford classification, and patients without CLTI were defined as "Group 1" and patients with CLTI as "Group 2".
Results: There were 248 patients (mean age 64.44 ± 9.05 years and 73.4% male) in Group 1, and 76 patients (mean age 66.62 ± 8.22 years and 76.3% male) in Group 2. In the multivariate regression analysis, CAD, PO, CRP and AIP were defined as independent predictive factors for the development of CLTI ($p = 0.015$, $p < 0.001$, $p = 0.007$, $p < 0.001$; respectively). ROC curve analysis showed that, PO cut-off value for CLTI development was 293.28 mOsm/kg (AUC: 0.821, $p < 0.001$) with 75% sensitivity and 74.2% specificity, and AIP cut-off value was 0.23 (AUC: 0.740, $p < 0.001$) with 67.1% sensitivity and 68.5% specificity.
Conclusions: The PO and AIP values in LEAD patients may be used as the new biomarkers of atherosclerosis progression, and therefore as predictive factors for the development of CLTI.
Keywords: Atherogenic index of plasma, chronic limb-threatening ischemia, osmolality, lower extremity artery disease

Peripheral artery disease (PAD) is a common disease with its main cause as atherosclerosis. Globally, more than 200 million adults live with PAD. PAD is more common in men and its incidence is increasing, especially in women over the age of 50. The most significant risk factors identified for PAD are diabetes mellitus, hypertension, hyperlipidemia, chronic renal disease and smoking [1, 2]. Lower extremity artery disease (LEAD) affects the lower extremity arteries and although it is mostly asymptomatic, patients often present with a hospital admission of intermittent claudication. The end-stage form of LEAD associated with high mortality and morbidity is chronic limb-threatening ischemia (CLTI). The diagnosis of CLTI is made clinically, and is characterized by ischemic resting pain, ulcerations and gangrene as a result of arterial blood flow insufficiency due to atherosclerosis progression [3].

Plasma osmolality (PO) is associated with the amount of minerals and particles dissolved in the blood. Since it is accepted as an indicator of body hydration, and since it affects endothelial cells, it has been associated with the prognosis of diseases [4, 5]. Fasting blood glucose, sodium (Na) and blood urea nitrogen (BUN) are the main components of PO; and seperate studies were conducted previously on the effects of each one on vascular diseases [6-8]. However, there are no studies in the literature regarding the effect of changes in PO calculated from these components on LEAD.

After understanding the role of plasma lipids in the pathogenesis of atherosclerosis, studies have been conducted to investigate the relationships between lipid profiles and LEAD. Low levels of high-density lipoprotein cholesterol (HDL-C) are among the strongest plasma lipid risk factors for LEAD. There is a relationship between triglyceride (TG) levels and LEAD progression [9]. In the Framingham Offspring Study, increased TG levels and decreased HDL-C levels were associated with increased LEAD risk [10]. In recent years, atherogenic index of plasma (AIP) has been identified as a new predictor of atherosclerosis. AIP is calculated with the logarithmic transformation of TG/HDL-C ratio [11]. Based on this information, we established the hypothesis that AIP could be a powerful biomarker for the development of CLTI.

It is important to know the predictors of CLTI development in patients diagnosed with LEAD, to detect them earlier, and to plan the treatment strategy early for these patients. For this reason, the purpose of this study was to investigate the relation between the development of CLTI and PO values and AIP values to predict the progression of atherosclerosis in patients with LEAD diagnosis, and to contribute to the preventability of atherosclerosis progression with more effective treatment and follow-up.

METHODS

A total of 324 patients diagnosed with LEAD between January 2018 and June 2020 admitting to our outpatient clinic were included in this study retrospectively, and study approved by local ethics committee (Adıyaman University Clinical Research Ethics Committee, 21.07.2020, 2020/7-3). The patient data were found from the patient files and the hospital registra-

tion system.

The LEAD diagnosis in our outpatient clinic is made with clinical examination of patients, ankle brachial systolic pressure index (ABI) measurement and color doppler ultrasonography [12]. Clinical stage evaluation of the disease is done according to the Rutherford classification. In the Rutherford Classification, asymptomatic patients are expressed as "Category 0", mild claudication presence is expressed as "Category 1", moderate claudication presence is expressed as "Category 2", severe claudication presence is expressed as "Category 3", presence of ischemic rest pain is expressed as "Category 4", presence of minor tissue loss presence is expressed as "Category 5", presence of major tissue loss is expressed as "Category 6" [13]. In recent years, "CLTI" definition has been used for category 4 and above in the Rutherford classification [3].

The patients who had a history of surgical or endovascular intervention with a diagnosis of LEAD, patients with acute limb ischemia, patients with diabetes mellitus diagnosis and using antidiabetic drugs, patients with chronic liver or renal disease, patients with known malignancy or systemic inflammatory disease, patients using steroid or statin group drug and patients with familial hyperlipidemia were excluded from the study. After applying these exclusion criteria, patients diagnosed with LEAD and in categories 0, 1, 2 and 3 according to the Rutherford classification were included in the study as "Group 1"; and the patients in categories 4, 5 and 6, that is, those who developed CLTI, were included in the study as "Group 2". The demographic data, comorbidities, and routine blood tests of the patients were evaluated.

Laboratory analysis and calculation of PO and AIP

The venous blood samples of patients diagnosed with LEAD were evaluated after 12 hours of fasting by taking blood from the antecubital vein into EDTA (ethylenediaminetetraacetic acid) tubes. The automatic analyzer (Abbott CELL-DYN Ruby; Illinois, USA) was used for complete blood count. Fasting blood glucose, creatinine, BUN, Na, HDL-C, TG, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and C-reactive protein (CRP) levels were analyzed with (Abbott 16000; Illinois, USA) automatic analyzer.

The following formula was used to calculate the

PO: Osmolality = (BUN / 2.8) + (Glucose / 18) + (2 × Na). And the normal PO value range was described as 275 - 295 mOsm/kg [14].

The following formula was used to calculate the AIP: AIP = log10 (TG / HDL-C). In this calculation, concentrations are expressed in mmol/L [11].

Statistical Analysis

The data were analyzed with SPSS 11.5 Program. As descriptive, mean ± standard deviation and median (minimum-maximum) values were used for quantitative variables, and number of patients (percent) was used for qualitative variables. Shapiro-Wilk test was used to test the normality distribution of the data. In terms of the quantitative variable, the difference between the two categories of qualitative variable categories was checked by Student-t test if the normal distribution assumptions were met; and if not by Mann-Whitney U test. When wanted to examine the relation between qualitative variables, the Chi-Square test was used. The Receiver Operating Characteristic (ROC) analysis was performed to find a method for determining the development of CLTI for the quantitative variable. The cut-off value for the quantitative variable was determined with the Youden Index. The univariate logistic regression and multivariate logistic

Table 1. Comparison of clinical and demographic characteristics of patient groups

Variables		Group 1 (n = 248)		Group 2 (n = 76)		p value
		Mean ± SD / n (%)	Median (Min-Max)	Mean ± SD / n (%)	Median (Min-Max)	
Age (years)		64.44 ± 9.05	65.00 (44.00-86.00)	66.62 ± 8.22	67.00 (45.00-85.00)	0.061[a]
Gender	Male	182 (73.4%)		58 (76.3%)		0.610[c]
	Female	66 (26.6%)		18 (23.7%)		
BMI (kg/m²)		25.84 ± 3.47	25.80 (18.60-34.60)	26.07 ± 2.63	26.40 (19.40-33.10)	0.542[a]
Hypertension		167 (67.3%)		54 (71.1%)		0.543[c]
CAD		106 (42.7%)		47 (61.8%)		**0.004[c]**
Atrial fibrillation		41 (16.5%)		13 (17.1%)		0.907[c]
CVD		74 (29.8%)		28 (36.8%)		0.250[c]
Current smoking		127 (51.2%)		43 (56.6%)		0.412[c]
COPD		55 (22.2%)		18 (23.7%)		0.783[c]
ABI		0.59 ± 0.12	0.57 (0.43-0.89)	0.36 ± 0.07	0.37 (0.19-0.48)	**< 0.001[a]**
Rutherford category						
	0	23 (9.3%)		0		**< 0.001[c]**
	1	73 (29.4%)		0		
	2	89 (35.9%)		0		
	3	63 (25.4%)		0		
	4	0		37 (48.7%)		
	5	0		28 (36.8%)		
	6	0		11 (14.5%)		

SD = Standard deviation, Min = Minimum, Max =Maximum; [a]Student-t test, [c]Chi-square test, BMI = Body mass index, CAD = Coronary artery disease, CVD = Cerebrovascular disease, COPD = Chronic obstructive pulmonary disease, ABI = Ankle brachial index

Table 2. Comparison of laboratory variables of patient groups

Variables	Group 1 (n = 248)		Group 2 (n = 76)		*p* value
	Mean ± SD / n (%)	Median (Min-Max)	Mean ± SD / n (%)	Median (Min-Max)	
Fasting blood glucose (mg/dL)	112.68 ± 23.95	112.00 (65.00-193.00)	121.97 ± 24.30	120.00 (74.00-182.00)	0.003[a]
Creatinine (mg/dL)	0.91 ± 0.30	0.86 (0.50-2.38)	0.90 ± 0.21	0.93 (0.70-2.21)	0.423[b]
Blood urea nitrogen (mg/dL)	20.96 ± 5.35	20.00 (11.00-37.00)	24.79 ± 6.94	24.50 (14.00-42.00)	< 0.001[a]
Sodium (mEq/L)	137.31 ± 3.22	137.00 (129.00-147.00)	140.91 ± 2.92	141.00 (133.00-145.00)	< 0.001[a]
PO (mOsm/kg)	288.36 ± 7.22	287.36 (272.38-312.54)	297.45 ± 6.78	297.32 (280.37-311.94)	< 0.001[a]
TC (mmol/L)	5.19 ± 0.61	5.28 (3.58-6.50)	5.16 ± 0.67	5.26 (3.65-6.72)	0.694[a]
TG (mmol/L)	1.66 ± 0.41	1.67 (0.78-2.89)	1.83 ± 0.42	1.85 (0.91-2.81)	0.002[a]
HDL-C (mmol/L)	1.13 ± 0.16	1.16 (0.80-1.45)	0.96 ± 0.10	0.93 (0.80-1.19)	< 0.001[a]
LDL-C (mmol/L)	3.29 ± 0.55	3.41 (2.02-4.40)	3.36 ± 0.58	3.48 (2.04-4.73)	0.372[a]
AIP	0.16 ± 0.14	0.17 (-0.26-0.55)	0.27 ± 0.11	0.28 (-0.02-0.54)	< 0.001[b]
C-reactive protein (mg/dL)	4.77 ± 2.95	3.56 (0.70-13.70)	5.84 ± 3.18	5.01 (1.02-12.80)	0.005[b]
Hemoglobin (g/dL)	13.34 ± 1.77	13.50 (9.20-16.90)	12.95 ± 1.80	12.75 (9.80-17.40)	0.094[a]
White blood cell (103/μL)	8.57 ± 2.26	8.42 (4.89-14.12)	8.84 ± 2.19	8.57 (5.14-14.85)	0.361[a]
Platelet (103/μL)	247.01 ± 64.69	238.50 (104.00-496.00)	237.34 ± 67.85	224.00 (129.00-479.00)	0.149[b]
Mean platelet volume (fL)	8.83 ± 1.18	8.77 (6.45-11.24)	9.27 ± 1.30	9.53 (6.26-11.35)	0.006[a]

SD = Standard deviation, Min = Minimum, Max =Maximum; [a]Student-t test, [b]Mann-Whitney U test, PO = Plasma osmolality, TC = Total cholesterol, TG = Triglyceride, HDL-C = High-density lipoprotein cholesterol, LDL-C = Low-density lipoprotein cholesterol, AIP = Atherogenic index of plasma

regression analyzes were performed to show risk factors for CLTI development. Statistical significance level was accepted as $p < 0.05$.

RESULTS

This study included 324 patients diagnosed with LEAD. There were 248 patients in Group 1 (mean age 64.44 ± 9.05 years; 73.4% male) and 76 patients in Group 2 (mean age 66.62 ± 8.22 years; 76.3% male). The mean ABI measurement of patients in Group 1 was 0.59 ± 0.11; and that of patients in Group 2 was 0.36 ± 0.08 ($p < 0.001$). No significant difference was found between the patient groups in terms of gender, age, body mass index, hypertension, atrial fibrillation, cerebrovascular disease, current smoking status, and chronic obstructive pulmonary disease. Patients in Group 2 had significantly higher concomitant coronary artery disease (CAD) compared to Group 1 (61.8% vs 42.7%, $p = 0.004$). The clinical and demographic characteristics of the patient groups are shown in Table 1.

When the laboratory variables of patient groups were compared, it was found that the values of Na, BUN, fasting blood glucose and PO were significantly higher in Group 2 ($p < 0.001$, $p < 0.001$, $p = 0.003$, $p < 0.001$; respectively). HDL-C value, which is one of the lipid profile variables, was significantly lower in

Group 2, while TG and AIP values were found to be high ($p < 0.001$, $p = 0.002$, $p < 0.001$; respectively). CRP and mean platelet volume (MPV) values were also found to be significantly higher in Group 2 ($p = 0.005$, $p = 0.006$; respectively) (Table 2).

When the results of univariate logistic regression analysis that was done to determine possible predictors of the development of CLTI were evaluated, CAD, PO, AIP, MPV and CRP variables were found to be significant risk factors, and these variables were included in the multivariate analysis (Table 3). And according to this analysis, CAD, PO, CRP and AIP variables were found to be independent predictive factors for the development of CLTI ($p = 0.015$, $p < 0.001$, $p = 0.007$, $p < 0.001$; respectively).

To determine the predictive effect of PO and AIP levels in the development of CLTI, ROC Curve analysis was done. The ideal cut-off value for calculated PO was 293.28 mOsm/kg (Area Under the Curve [AUC]: 0.821, $p < 0.001$) with 75% sensitivity and 74.2% specificity. The ideal cut-off value for AIP was 0.23 (AUC: 0.740, $p < 0.001$) with 67.1% sensitivity and 68.5% specificity (Fig. 1).

DISCUSSION

The relation between CLTI development and calculated PO values and AIP values was investigated in

Table 3. **Univariate and multivariate logistic regression analysis to determine predictors of the development of chronic limb-threatening ischemia**

Variables	Univariate analysis			Multivariate analysis		
	p value	OR	95% CI Lower-Upper	*p* value	OR	95% CI Lower-Upper
Age	0.062	1.028	0.999-1.059			
Gender (Male)	0.610	1.168	0.642-2.127			
CAD	**0.004**	2.171	1.282-3.677	**0.015**	2.245	1.171-4.304
Smoking	0.413	1.241	0.740-2.083			
PO	**< 0.001**	1.182	1.131-1.236	**< 0.001**	1.168	1.114-1.225
AIP	**< 0.001**	1406.004	120.477-16408.483	**< 0.001**	735.730	41.043-1188.634
CRP	**0.008**	1.115	1.028-1.208	**0.007**	1.156	1.040-1.285
MPV	**0.007**	1.352	1.087-1.680			

OR = Odds ratio, CI = Confidence interval, CAD = Coronary artery disease, PO = Plasma osmolality, AIP = Atherogenic index of plasma, CRP = C-Reactive protein, MPV = Mean platelet volume
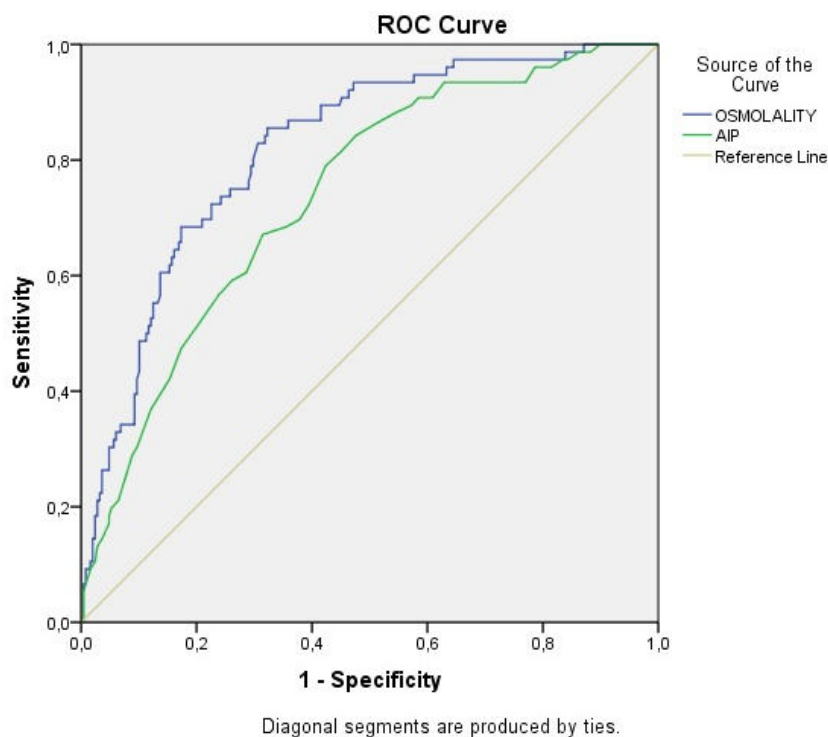
Fig. 1. ROC curve of calculated PO and AIP for predicting the development of chronic limb-threatening ischemia.

this retrospective study. We found that the increase in PO values and AIP values was related with the development of CLTI in patients with LEAD. In the multivariate logistic regression analysis, CAD, CRP, PO and AIP variables were found as independent predictive factors for CLTI development. In patients with LEAD diagnosis, it was found that having concomitant CAD increased the risk of developing CLTI by 2.245 times, one unit increase in CRP quantitative variable increased the risk of developing CLTI by 1.156 times, one unit increase of PO quantitative variable increased the risk of developing CLTI by 1.168 times, and 0.1 unit increase in AIP quantitative variable increased the risk of developing CLTI by 1.935 times. To the best of our knowledge, we determined for the first time in the literature with this study that the development of CLTI can be predicted with PO values and AIP values in patients with LEAD diagnosis.

CLTI is the end-stage of LEAD, and is related with high morbidity and mortality. It was reported that, major amputation rate was 30% and mortality rate was 25% in patients within 1 year after the development of CLTI [15]. Therefore, it is important to plan the treatment of LEAD patients before CLTI develops. In addition to medical treatments (antithrombotic, lipid-lowering, antihypertensive agents) and treatment approaches such as exercise, diet, smoking cessation, and preventive foot care applied in symptomatic LEAD patients, early revascularization options are also recommended for patients at high risk of developing CLTI [1, 3]. In recent years, many predictors of CLTI development have been identified in patients diagnosed with LEAD [16, 17]. Since atherosclerosis is the underlying cause of LEAD pathology, the identified predictors are focused on atherosclerosis, which is considered an inflammatory process.

Atherosclerosis is multifactorial and inflammation plays an important role in its patagonesis from its development to its progression. Plasma osmolality can be defined as the solite load in the body, and indicates body hydration. The increase in PO increases the inflammation and atherosclerosis progression in vascular endothelial cells by increasing the hemoconcentration [18, 19]. In their study of 315 patients, Rasouli *et al*. [4] reported that calculated PO, which is one of the markers of dehydration and hemoconcentration, showed correlations with CAD severity. In a study on 3748 acute coronary syndrome patients conducted by Tatlisu *et al*. [20], it was reported that PO at admission could be used to identify high-risk patients and is a predictor of in-hospital and long-term

mortality. Similar to these studies in the literature, statistically significant high PO values were found in patients who developed CLTI in our study (*p* < 0.001). In addition, PO has been found to be an independent predictor of CLTI development (odds ratio (OR): 1.168, 95% confidence interval (CI): 1.114-1.225, *p* < 0.001). It is known that diabetes mellitus is an important risk factor in LEAD etiology, increasing the risk of LEAD development by three-four times. It also accelerates the development of CLTI by increasing vascular inflammation and delaying the diagnosis and treatment of the disease with peripheral neuropathy effect [15]. In addition, since diabetes mellitus would increase PO alone, and reduce the reliability of the results of our study; patients with diabetes mellitus diagnosis and using antidiabetic drugs were not included in the study. Also, patients with chronic renal disease, which has close relations with atherosclerosis progression, and which might change PO with direct effect on plasma electrolyte values, were also excluded from the study [21].

Dyslipidemia causes the development and progression of atherosclerosis by affecting vascular endothelial cells. High TC and LDL-C levels are considered to be risk factors for LEAD, and low HDL-C levels were significantly associated with increased mortality and other cardiovascular complications in LEAD patients [22, 23]. Small dense LDL-C is the subfraction of LDL-C with high atherogenic potential, and increases in direct proportion with TG levels. For this reason, there is a strong relation between the increase in TG levels and atherosclerotic diseases [24]. Recently, AIP, which is calculated with the logarithmic transformation of plasma TG and HDL-C molar levels, has been described as a novel and powerful clinical biomarker for atherosclerotic diseases [11, 25]. In their prospective studies in which 2676 middle-aged individuals were included with a follow-up period of 7.8 years, Onat *et al*. [26] reported that AIP variable was an independent predictive factor for CAD. In the case-control study of 696 individuals conducted by Wu *et al*. [27], AIP was reported to be a strong predictive biomarker for CAD risk in women (OR: 3.290, 95% CI: 1.842-5.877, *p* < 0.001). In a meta-analysis summarizing the data related to AIP calculated in 8394 individuals, it was reported that the values -0.3 to 0.1 were associated with low, 0.1 to 0.24 were associated with medium and above 0.24 were associated with

high cardiovascular disease risk [28]. In our study, which included patients with LEAD diagnosis, statistically significant high AIP values were detected in patient group with CLTI, and AIP was detected as an independent predictive factor for CLTI development. The ideal AIP cut-off value for CLTI development was found as 0.23 with 67.1% sensitivity and 68.5% specificity.

In our study, statistically significant low HDL-C levels and high CRP levels were noted in patient group with CLTI (*p* < 0.001, *p* = 0.005; respectively). HDL-C is known as antiatherogenic lipoprotein due to its reverse cholesterol transport properties. Additionally, it has antioxidant and anti-inflammatory properties, and in particular, it inhibits vascular inflammation by inhibiting the expression of adhesion molecules from endothelial cells. For this reason, there is a negative correlation between HDL-C and CRP, which are inflammatory biomarkers [23]. It was also shown that there is a relation between elevation in CRP levels and the severity of atherosclerosis and LEAD [1]. Swastini *et al*. [29] investigated the relationship between CRP and atherosclerosis severity measured by ABI and doppler ultrasonography in 388 patients with dyslipidemia. They published that there was a important correlation between CRP levels and the severity of atherosclerosis. Barani *et al*. [30] associated CRP levels with 1-year mortality in CLTI patients. Based on our findings, we found that the CRP level is an independent predictive factor for CLTI development (OR: 1.156, 95% CI: 1.040-1.285, *p* = 0.007).

Atherosclerosis is a systemic disease, affecting many arteries simultaneously. Patients with LEAD diagnosis have concomitant CAD at a rate between 40% and 55% [15, 31]. It has been reported that the presence of CAD is an independent risk factor for mortality [32]. A total of 47.2% of the patients who were included in our study had concomitant CAD, and there were significantly higher CAD in patient group with CLTI. It was found that concomitant CAD in LEAD patients is an independent predictive factor for CLTI development (OR: 2.245, 95% CI: 1.171-4.304, *p* = 0.015).

Limitations

Our study had several limitations to consider. First of all, our study was single-centered, and was designed retrospectively. Patients who were diagnosed with

LEAD, that is, mostly symptomatic, with outpatient clinic application were included in our study. The rate of presence of symptoms in LEAD patients is 35% [33]. For this reason, studies that involve wider patient populations, including asymptomatic LEAD patients, should be planned to ensure that these two laboratory parameters we calculated to enter clinical use. In addition, stating the smoking status as only current smokers, not as pack years or former smokers, can be considered as another limitation of our study.

CONCLUSION

According to the data of our study, it was found that PO values and AIP values that are calculated simply from routine biochemical tests in patients with LEAD diagnosis were associated with the development of CLTI. Our analysis showed that CAD, PO, AIP and CRP are independent predictive factors for for CLTI development in patients with LEAD diagnosis. Since these patients may benefit from aggressive management of risk factors and intensified treatment options to prevent CLTI-related morbidity and mortality, we believe that identifying the high-risk population for the development of CLTI in patients with a diagnosis of LEAD is of great importance.

Authors' Contribution

Conflict of interest

Financing

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