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Original Article

Prevalence and predictors of lower extremity atherosclerotic disease amongst high-risk patients using ankle brachial index

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ABSTRACT

Introduction: The prevalence of lower extremity artery disease (LEAD) continues to increase worldwide. This is expected to translate into logarithmic rise in lower-limb amputations especially in the developing world. Majority of patients suffering from LEAD remain asymptomatic until late and are vulnerable to limb-threatening complications unless actively screened and treated.
Methods: This was a prospective, single-center, observational study to determine the prevalence and predictors of LEAD. Patients with known atherosclerotic vascular disease (but not known LEAD) or those at risk were enrolled. All underwent ankle brachial index (ABI) measurement as per the standard protocol. A threshold of ABI $\leq$0.90 was taken to diagnose LEAD.
Results: A total of 1000 patients were enrolled. The mean age of the group was 61.4 $\pm$ 10.0 years and the prevalence of LEAD was 10.2%. Amongst those who had LEAD, the majority of patients (69.6%) had no symptoms. The prevalence of LEAD in diabetic population in our study was 13.2% and it was 30.9% in coronary artery disease patients . Factors independently linked to LEAD on regression analysis included advanced age, presence of diabetes, smoking history, lower serum HDL and a lower ejection fraction.
Conclusions: The vast majority of patients suffering from LEAD are asymptomatic. Early diagnoses and institution of appropriate medical and physical therapy can prevent excess morbidity and mortality due to LEAD. Factors independently linked to LEAD are advanced age, presence of diabetes, smoking history, lower serum HDL and a lower ejection fraction. The presence of either of these should signal undertaking of appropriate steps to unmask underlying LEAD.

1. Introduction

Lower extremity artery disease (LEAD) refers to atherosclerotic disease involving the arterial system of the lower limbs starting from common iliac arteries till the dorsalis pedis and posterior tibial arteries. Despite the progress in disease management, the prevalence of LEAD continues to increase worldwide[1,2]. The increasing prevalence worldwide largely stems from the steep rise in disease prevalence in the low/middle income countries (LMIC) where around 70% of all patients of LEAD reside. Coupled with increasing number of individuals with cardiovascular disease risk factors (CVDRFs) especially at a younger age in India, the same is expected to translate into an increased number of lower limb amputations in the coming years[1,3–8]. Early recognition and treatment initiation seems to be the most cost-effective and handsome option in our country given the limited resources.

LEAD confers a 4-fold increased risk of a major adverse cardiac and cerebrovascular event (MACCE) even in asymptomatic patients. At 5 years, one in five will have a MACCE event and around 15% will die[1,5,9]. The risk factors for LEAD are similar to atherosclerotic

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process elsewhere and include diabetes, smoking, hypertension, chronic kidney disease and dyslipidemia[6]. An important observation from epidemiological studies is that more than 50% of all patients suffering from LEAD remain asymptomatic and are vulnerable to acute and chronic complications unless actively screened and treated. Functional testing however, is markedly reduced even in asymptomatic patients. Less than 25% of LEAD patients present with classical claudication[1,4,5]. The prevalence increases with advancing age and is around 10–40% in high-risk population in the west[1,10]. The reason for the wide range is the variable selection criteria as well as the differences in LEAD definition in the prior studies. The data from India with respect to the prevalence of LEAD in high-risk individuals is scarce and limited by the small sample size. Unfavorable genetics and early onset of aggressive atherosclerotic disease makes Indian population vulnerable to develop advanced LEAD if not diagnosed early[1,6]. Hence, we conducted this study to look into the prevalence and predictors of LEAD amongst high-risk patients using ankle brachial index (ABI).

2. Methods

2.1. Study design and participants

This was a prospective, single-center, observational study enrolling patients aged 18 years or more. The study was conducted over a period of 9 months from July 2019 to March 2020. All patients attending the outpatient department (OPD) or being admitted were screened for eligibility. Eligible candidates fulfilling the selection criteria underwent detailed history taking and clinical examination. All individuals underwent basic blood investigations to look for the presence of underlying diabetes, renal dysfunction or dyslipidemia. A total 1000 patients were recruited in the study and all underwent ABI measurement as per the standard protocol.

2.2. Selection criteria

Patients with known atherosclerotic vascular disease in the form of either coronary artery disease and/or cerebrovascular disease or having symptoms of the same (but not known LEAD) were recruited. In addition, patients without known atherosclerotic vascular disease, but who were otherwise at risk were also enrolled. The detailed selection criteria were as follows: -

2.3. Inclusion criteria

A) Patients with known atherosclerotic vascular disease or having symptoms suggestive of the same: -
   i. Prior history of coronary artery disease in the form of acute or chronic coronary syndrome or having underwent percutaneous intervention or coronary artery bypass surgery
   ii. Prior history of cerebrovascular disease in the form of stroke or transient ischemic attacks or radiological evidence of the same
   iii. Past or current symptoms of stable or unstable angina

B) Patients without atherosclerotic vascular disease or symptoms but having risk factors that predispose them to develop the same. Patients having two or more of the following risk factors were recruited: -
   i. Diabetes mellitus
   ii. Hypertension (blood pressure >140/90 or already on antihypertensive drugs)
   iii. Obesity with body mass index >25 kg/m^2
   iv. Smoking (active or past)
   v. Dyslipidemia defined as any of the following: -
      a. Total cholesterol >200 mg/dl
      b. Triglycerides >150 mg/dl
      c. Triglyceride/HDL ratio >4.5
      d. Already on statin for dyslipidemia

2.4. Exclusion criteria

i. Past history of LEAD in the form of limb ulceration, non-healing wounds, past interventions or surgical bypass or past lower limb amputation
ii. Current signs or symptoms of acute limb ischemia
iii. Buerger's disease
iv. Vasculitis like Takayasu or giant cell arteritis
v. Prior trauma or irradiation injury to lower limbs
vi. Not willing to participate in the study

2.5. ABI measurement

ABI represents the ratio of the systolic blood pressure measured at the ankle to the systolic pressure measured at the brachial artery. A threshold of ABI $\leq$0.90 has reported to be >90% sensitive and specific in detecting LEAD compared with angiography. Over the years, ABI has emerged as an indirect marker of systemic atherosclerosis. It also serves as a potential marker for future MACCE events. A lower ABI is associated with many CVDRFs including hypertension, diabetes mellitus, dyslipidemia, smoking history. Evidence suggests that there is significant variation at multiple levels while recording ABI leading to discrepant findings. Following a standardized protocol while taking ABI measurement is necessary as an incorrectly measured ABI can have significant impact on diagnoses and patient management.

The protocol used for ABI measurement in the study was adapted from the article by Aboyans et al[11] is tabulated in Table 1.

All patients who had an ABI $\leq$0.9 underwent screening duplex scanning to rule out diseases other than atherosclerosis as a cause of abnormal ABI. According patients with burgers disease were all excluded. A total of 34 such patients whose duplex suggested the presence of diffuse bilateral occlusion of posterior tibial, peroneal or anterior tibial arteries in the presence of patent larger arteries including popliteal, femoral and iliac arteries and no evidence of atherosclerosis in either of these arteries. These were consistent with a buerger's disease and hence were excluded.

2.6. Ethical justification

The study involved screening of high-risk patients for LEAD using ABI to determine the prevalence and predictors of LEAD in our population. The ABI measurements were performed by trained personnel (2 doctors) at no additional cost to the patient. It took 30 min for each participant to be screened for LEAD. Written informed consent was taken from all participants prior to enrolment. The study protocol conformed to the ethical guidelines of the recent declaration of Helsinki updated in October 2013 and was reviewed and cleared by the ethical committee of the institute (ref No. BFUHS/2K19p-TH/10722).

2.7. Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, IL, United States). Variables were presented as mean ± SD or median (IQR). Variable were checked for outliers and normalcy using the Shapiro–Wilk

Table 1
Standardized protocol used for ABI measurement in the study.

Patient setting	• At rest for 5–10 min • Supine • Head and heel supported • Pleasant room temperature (19–22 °C) • Not smoked for last 2 h
Cuff specifications	• Choose according to limb size • Cuff width around 40% of limb circumference
Pressure measurement	• Patient to remain still during recording • Place the lower edge of ankle cuff 2 cm above medial malleolus • Cover any open wound on the limb with sterile dressing
Doppler recording	• 8–10 MHz doppler probe with gel applied over it • Turn on the probe and place at an angle of 45-60° angle • Move probe until clearest signals audible • Inflate cuff 20 mm Hg above the level of signal disappearance • Deflate slowly to detect the systolic pressure • Avoid >300 mm Hg inflation • Brachial blood flow also measured using the doppler • Divide the higher or posterior tibial or dorsalis pedis artery pressure with arm pressure to determine ABI • Perform ABI on the other limb
Sequence	• Use clockwise or counter clockwise sequence • Maintain consistency in measurement by using same sequence of limb measurement • Repeat ABI measurement at the end of sequence • Average of 2 ABI recording be done to nullify any white coat effect • However, if > 10 mm difference in first arm BP, discard the 1st ABI reading and use only 2nd as the final ABI

Abbreviations: ABI: ankle-brachial index; BP: blood pressure.

test. Continuous variables with normal distribution were compared with the independent samples Student's *t*-test and those with non-normal distribution with the Mann–Whitney *U* test. Comparison between categorical variables was done using chi-square test or Fisher's exact test. Subsequently, variables significantly associated with LEAD on univariate analysis were included in a multivariable regression analysis to identify independent predictors of LEAD. A two-sided p-value <0.05 was considered to be significant for all variables.

3. Results

A total of 1000 consecutive patients visiting OPD or being admitted in the cardiac centre of the institute were recruited. Amongst them 441 (44.1%) patients were from the OPD and 559 (55.9%) were admitted patients. The mean age of the group was 61.4 ± 10.0 years with 73.7% of all patients being males. The baseline characteristics of the study population are shown in Table 2. The study population comprised of a high-risk group with 635 (63.5%) patients suffering from diabetes. A total of 598 individuals had known coronary artery anatomy on angiography. Angiographically proven coronary artery disease was present in 392 (39.2%) of the cohort. Anaemia defined as haemoglobin <12 gm/dL in females and <13 gm/dL in males was present in 421 (42.1%) patients.

3.1. Prevalence of LEAD

The prevalence of LEAD (defined as an ABI ≤0.9) in the study cohort was 10.2%. Amongst those who had LEAD, the ABI was 0.8–0.9 in 41 (40.2%) and 0.5–0.8 in 56 (54.9%) cases representing mild and moderate LEAD respectively. Only 5 (4.9%) had an ABI <0.5 representing severe LEAD. The prevalence of LEAD was 30.9% in patients with coexistent coronary artery disease (CAD).

Amongst individual risk factors, the prevalence of LEAD was maximum in smokers (24.7%) and diabetics (13.3%) followed by dyslipidaemia (11.0%) and hypertension (10.2%) (Table 3). These 4 principal risk factors when coexisted together, increased an individual's odds of developing LEAD multi-fold. Accordingly, an individual with only one of these risk factors had a 5.9% risk of developing LEAD and someone who had all 4 of these risk factors had a 33.3% chances of having LEAD. Exertional leg symptoms were enquired using the Edinburgh Claudication Questionnaire (ECQ) and was graded as either definite claudication, atypical claudication and no claudication. Amongst those who had LEAD, the majority of patients (69.6%) had no symptoms, and only a fraction of patients

Table 2
Baseline characteristics of the study population.

Baseline characteristic of patients (n = 1000)	Results
Age (years) ±SD	61.4 ± 10
Height (cm) ±SD	168 ± 7
Sex	
• Males	737 (73.7%)
• Females	263 (26.3%)
BMI (kg/m^2) ±SD	26.37 ± 3.94
Overweight and obesity (>25 kg/m^2)	641 (64.1%)
Lipid profile (mg/dl)	
• Total cholesterol	• 157.5 ± 52.7
• High density cholesterol (HDL)	• 38.6 ± 16.4
• Low density cholesterol (LDL)	• 89.4 ± 35.3
• Triglycerides	• 152.5 ± 110.4
Dyslipidaemia, n (%)	
• Total cholesterol >200 mg/dl	• 206 (20.6%)
• High density cholesterol (HDL) < 40 mg/dl for males and <50 mg/dl for females	• 567 (56.7%)
• Triglycerides >150 mg/dl	• 457 (45.7%)
• Triglyceride/HDL ratio >4.5	• 300 (30%)
Diabetics, n (%)	635 (63.5%)
Hypertension, n (%)	620 (62%)
Coronary artery disease, n (%) (Angiographically proven)	392 (39.2%)
• SVD	• 119 (11.9%)
• DVD	• 113 (11.3%)
• TVD	• 160 (16.0%)
Past cerebrovascular accident, n (%)	19 (1.9%)
Chronic kidney disease, n (%)	65 (6.5%)
Smoking, n (%)	117 (11.7%)
Alcohol abuse, n (%)	187 (18.7%)
Substance misuse, n (%)	90 (9%)
Anaemia, n (%)	421 (42.1%)
Ejection fraction (%)	43 ± 12

Abbreviations: BMI: body mass index. SVD: single vessel disease, DVD: Double vessel disease, TVD: Triple vessel disease.

Table 3
Prevalence of LEAD across various comorbidities.

Prevalence of LEAD across various comorbidities	
Overweight and obesity (>25 kg/m^2)	
Outpatient department	7.5%
Admitted patients	12.3%
Dyslipidaemia, (%) Overall	11%
• Total cholesterol >200 mg/dl	• 8.2%
• High density cholesterol (HDL) < 40 mg/dl for males and <50 mg/dl for females	• 12.7%
• Triglycerides >150 mg/dl	• 8.0%
• Triglyceride/HDL ratio >4.5	• 16.7%
Diabetics, (%)	13.3%
Hypertension, (%)	10.2%
Coronary artery disease, (%)	30.9%
Smoking, (%)	24.7%

had atypical claudication (9.8%) or typical claudication (20.6%) upon detailed enquiry.

3.2. Predictors of LEAD

Various demographical, risk factors, laboratory parameters, echocardiographic parameters were evaluated for their association with LEAD (Table 4). LEAD was more prevalent amongst those admitted patients compared to those who visited the OPD ($p = 0.01$). Other parameters having a significant association with LEAD on univariate analysis included the older age, diabetes, chronic kidney disease, past history of cerebrovascular accident (CVA), current or past smoking history, a lower HDL, elevated triglycerides, a triglyceride/HDL >4.5, a lower ejection fraction on echocardiogram, a lower serum haemoglobin and an elevated serum urea. Coronary artery disease was more common amongst the patients who had LEAD, however it was not statistically significant ($p = 0.19$).

Multivariate analysis was performed on variables found to have a significant association with LEAD in the univariate analysis (Table 5). Factors independently linked to LEAD on regression analysis included advanced age (OR: 1.03, 95% CI: 1.00–1.05; $p = 0.025$), presence of diabetes (OR: 2.68, 95% CI: 1.49–4.70; $p = 0.001$), past or current smoking history (OR: 4.64, 95% CI: 2.72–7.91; $p < 0.001$), lower serum HDL (OR: 0.97, 95% CI: 0.94–0.99; $p = 0.015$) and a lower ejection fraction (OR: 0.97, 95% CI: 0.95–0.99; $p = 0.001$).

Table 5
Predictors of LEAD (multivariate analysis).

	Odds Ratio	CI (95%)		
		Lower	Upper	p-value
Age	1.03	1.00	1.05	**0.025**
Diabetes	2.68	1.49	4.70	**0.001**
Smoking	4.64	2.72	7.91	**0.000**
Cerebrovascular accident	2.60	0.85	7.92	0.092
Chronic Kidney disease	0.73	0.30	1.77	0.482
Elevated TGs	1.00	1.00	1.00	0.731
Low HDL	0.97	0.94	0.99	**0.015**
Elevated TG/HDL >4.5	0.98	0.85	1.14	0.831
Ejection fraction	0.97	0.95	0.99	**0.001**
Hemoglobin	0.92	0.82	1.03	0.149
Urea	1.00	1.00	1.01	0.501

Abbreviation: LEAD: lower extremity atherosclerotic disease; HDL: high-density lipoprotein; TGs: triglycerides.

Table 4
Demographic, echocardiographic and laboratory parameters affecting LEAD.

Variable	LEAD (n = 102) ABI <0.9	No LEAD (n = 898) ABI >0.9	P- value
Patient profile			**0.01**
• OPD	33 (32.4%)	408 (45.4%)	
• Admitted	69 (67.6%)	490 (54.6%)	
Age, years, mean (±SD)	64.3 (±8.7)	61.2 (±10.2)	**0.003**
BMI, (kg/m^2) mean ± (SD)	26.5 ± 3.3	26.3 ± 4.0	0.68
Sex, n (%)			0.36
Male	79 (77.5%)	658 (73.3%)	
Female	23 (22.5%)	240 (26.7%)	
Diabetes, n (%)	85 (83.3%)	550 (61.2%)	**0.001**
Hypertension, n (%)	66 (64.7%)	554 (61.7%)	0.52
CAD, n (%) (overall)	84 (82.4%)	689 (76.7%)	0.19
CAD, n (%) (angiographically proven)			0.12
• SVD	• 18 (17.6%)	• 101 (11.2%)	
• DVD	• 17 (16.6%)	• 96 (10.6%)	
• TVD	• 20 (19.6%)	• 140 (15.5%)	
CKD, n (%)	12 (11.8%)	53 (5.9%)	**0.02**
CVA, n (%)	5 (4.9%)	14 (1.6%)	**0.036**
• Total cholesterol >200 mg/dL	17 (16.70%)	189 (21%)	0.3
• Low HDL	23 (22.5%)	544 (60.6%)	**0.04**
• Elevated TGs	37 (36.3%)	420 (46.8%)	**0.001**
• TGs/HDL ratio >4.5	43 (42.2%)	257 (26.8%)	**0.006**
Smoking, n (%)	29 (28.4%)	88 (9.8%)	**0.001**
Alcohol intake, n (%)	20 (19.6%)	167 (18.6%)	0.8
Echocardiographic parameters			
LVEF, %, mean ± (SD)	39.3 ± 12.1	44.2 ± 12.3	**0.001**
Laboratory parameters			
Mean Hemoglobin (gm/dL ± SD)	11.8 ± 2.4	12.6 ± 2.0	**0.001**
Mean Platelet count (lacs/dL SD)	2.5 ± 0.9	2.3 ± 0.8	0.14
Mean creatinine mg/dL ± SD)	1.3 ± 0.9	1.2 ± 0.4	0.61
Mean urea mg/dL ± SD)	53.6 ± 43.0	40.94 ± 29.6	**<0.001**
HbA1c ± SD)	7.5 ± 1.3	7.3 ± 1.1	0.25

Abbreviation: LEAD: lower extremity atherosclerotic disease; OPD: outpatient department; BMI; body mass index, LVEF; left-ventricular ejection-fraction, CAD; coronary artery disease, CKD: chronic kidney disease; CVA: cerebrovascular accident; HDL: high-density lipoprotein; TGs: triglycerides. SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease.

4. Discussion

LEAD is the 3rd leading cause of atherosclerotic comorbidity following CAD and CVA[1,2]. However, despite its prevalence and its adverse clinical impact, it remains understudied and underappreciated compared to CAD and CVA. The lack of awareness has translated into underdiagnoses and undertreatment of LEAD worldwide[5,12,13]. The most common reason for underappreciation of this entity remains the poor availability of tools used for assessing ABI, which is regarded as the first-line diagnostic modality for LEAD[13]. Other common reasons for the lack of awareness is the general notion that LEAD carries less morbidity and mortality compared to CAD and CVA. Despite this popular belief, recent pool of evidence points towards the strong association of LEAD with mortality and future MACCE events[1,5,9,10]. Besides the MACCE events, LEAD significantly impairs the quality of life. The LMICs are particularly vulnerable to the devastating effects of LEAD given the lack of awareness, limited availability of diagnostic tools and poor health care infrastructure. The prevalence of LEAD and its complications are expected to rise exponentially in these parts of the world with attended significant impact on overall morbidity and mortality[1,2,6,7,14].

The index study was conducted to determine the prevalence and predictors of LEAD amongst individuals with CVDRFs in a tertiary care centre in Northern India. Data on prevalence of LEAD in Indian subcontinent is scant and largely limited to small observational studies. The prevalence of LEAD in our study was around 10.2%. Prior studies from India which primarily included diabetic and CAD patients were those by Saran et al and Agarwal et al. The prevalence of LEAD in these studies was 7.7% and 14.3% respectively, which was comparable to our data[15,16]. However, these studies were limited by the small sample size with only around 200 participants recruited. In contrast, in the study by Krishan et al the prevalence of LEAD in elderly population with CVDRFs was much higher at 26.7%[17]. The higher prevalence in their study stems from the patient selection with a much higher mean patient age and higher prevalence of CVDRFs compared to other Indian studies. This is understandable as the prevalence of LEAD increases with increasing number of CVDRFs. The worldwide prevalence of LEAD is around 12% at 70 years and is higher in the western population compared to LMICs. Estimated prevalence of LEAD in LMICs is lower compared to the west and is around 8%[1,5,6,18]. Our study shows the narrowing of this gap and reflects the increased burden of atherosclerotic diseases in the Indian subcontinent owing to unfavourable genetics and unhealthy lifestyle.

A common theme among most of the data pertaining to LEAD is the fact that majority of patients diagnosed by ABI are asymptomatic. In general, less than 1/4th patients suffering from LEAD have typical claudication[1,5,11]. The same was mirrored in our study and only around 20% had typical claudication as per the ECQ. The clinical impact of this finding is huge as at the time of symptom onset the disease is invariably advanced and irreversible which leads to significant morbidity. The early identification of LEAD can lead to early institution of preventive medical and physical therapy and translate into a meaningful positive impact on clinical outcomes.

The key to success remains the identification of this high-risk population who will benefit the most from screening for LEAD. The traditional risk factors linked to LEAD in prior studies included diabetes, smoking, hypertension and dyslipidaemia[1,19,20]. Recent research also points towards sedentary lifestyle and obesity being linked to LEAD. Nonconventional risk factors include elevated inflammatory markers including HsCRP, IL-6 and fibrinogen[19,20]. In our study the factors independently linked to LEAD were advanced age, presence of diabetes, past or current smoking history, lower serum HDL and a lower ejection fraction.

While advanced age, diabetes, and smoking are well established risk factors for LEAD, the association between low HDL and a lower EF with LEAD has not been clearly defined beforehand. The link between a low HDL and incidence of LEAD has been known for 2 decades following the results of Framingham Offspring study which showed that for every 5 mg/dL decrease in HDL, the risk of LEAD increased by 10%[21]. Despite the evidence, serum LDL remained the prime target for research, treatment and prognostication amongst LEAD patients just like other forms of atherosclerotic vascular disease. The association between a lower serum HDL (which represents the cholesterol efflux capacity in an individual) and atherosclerotic cardioavscular disease has recently gained acceptance following larger studies. Evidence points towards the inverse relationship between HDL levels and presence of LEAD and irrespective of other risk factors. Further a lower HDL increases the odds of MACCE in an individual having LEAD[22,23]. Targeting lower HDL via pharmacological and non-pharmacological is now increasingly being realized as important domain in the arsenal for managing atherosclerotic vascular disease. The association of lower left ventricular EF with LEAD does not appear to be a direct causal relationship. LEAD is commonly associated with underlying CAD in over 1/3rd patients. Underlying left ventricular dysfunction may represent a more severe CAD which is more likely to be associated with LEAD. Recent research points towards significantly worse outcomes in CAD patients having concomitant LEAD with increased odds of heart failure, left ventricular dysfunction and overall MACCE than CAD occuring without coexistent LEAD[24].

While there are obvious strength of the study in regards to large sample size and prospective study design. Meticulous data collection was ensured by following the standardised ABI measurement protocol. However, there were certain limitations in our study which needs to be mentioned. This was a single-centre study from a tertiary care centre and hence cannot be generalized to entire population. The patient population were all attending cardiology services and hence the prevalence of atherosclerotic vascular disease is expected to be higher than those attending other speciality clinics or inpatient services. Absence of a validation cohort limits the generalizability of our findings.

5. Conclusions

The vast majority of patients suffering from LEAD are asymptomatic. Early diagnoses and institution of appropriate medical and physical therapy can prevent excess morbidity and mortality due to LEAD. ABI is a simple tool that can be effectively used to identify coexistent LEAD in high-risk patients. The prevalence of LEAD in our cohort was 10.2%. Factors independently linked to LEAD were advanced age, presence of diabetes, past or current smoking history, lower serum HDL and a lower ejection fraction. The presence of either of these should signal undertaking of appropriate steps to unmask underlying LEAD.

Declarations

Ethics approval and consent to participate

The study protocol conformed to the ethical guidelines of the recent declaration of Helsinki updated in October 2013 and was reviewed and cleared by the ethical committee of the institute (ref No. BFUHS/2K19p-TH/10722).

Consent for publication

Written informed consent was obtained directly from the patients for inclusion in this study.

Availability of data and materials

All data and materials will be upload as per the needs of the editor/reviewer or the readers as per their request.

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Authors' contributions

Equal contributions.

Declaration of competing interest

None.

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