ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2023, Volume 12, Number 2: 1175-1180
P-ISSN.2089-1180, E-ISSN: 2302-2914

LOX-1 rs1050283 TT genotype is associated with the severity of peripheral artery disease: a cross-sectional study in Mataram, Indonesia

Yanna Indrayana[1,2*], Irawan Yusuf[3], Agussalim Bukhari[3], Idar Mappangara[3], Herpan Syafii Harahap[2]

[1]Doctoral Program, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
[2]Faculty of Medicine, Universitas Mataram, Mataram, Indonesia;
[3]Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;

*Corresponding author:
Yanna Indrayana;
Doctoral Program, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
yannaindrayana@unram.ac.id

Received: 2023-02-28
Accepted: 2023-03-26
Published: 2023-04-12

ABSTRACT

Background: Peripheral arterial disease (PAD) is an important consequence of atherosclerosis commonly determined based on the results of ankle-brachial index (ABI) measurements. Due to its limitations, the search for potential predictors of PAD severity is ongoing. Serum soluble Lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) levels and LOX-1 polymorphism rs1050283 are candidates for predictors of PAD severity. This study aimed to investigate the association between the LOX-1 rs1050283 TT genotype and the severity of PAD.

Methods: This cross-sectional study involved PAD patients recruited consecutively. The patients were genotyped for rs1050283 (3′ UTR C>T) LOX-1 single nucleotide polymorphism using the sequencing method. Serum sLOX-1 levels were measured using ELISA. Data on ABI were collected, and the patients were categorized into mild and moderate to severe PAD groups.

Results: A total of 66 PAD patients with a mean age of 58.9 years participated in this study, which consisted of 45 patients with mild PAD and 21 patients with moderate to severe PAD. Multivariate logistic regression analysis showed that the TT genotype was associated with PAD severity compared to those with the CC genotype (odds ratio (OR): 15.0, 95% confidence intervals (CI): 1.1 – 209.0), while higher serum sLOX-1 levels were not. PAD severity was also associated with increasing age (OR: 5.7, 95% CI: 1.3 – 25.7) and male gender (OR: 6.0, 95% CI: 1.1 – 32.2).

Conclusion: TT genotype of LOX-1 rs1050283 polymorphism was associated with PAD severity, whereas higher serum sLOX-1 levels were not. In addition, increasing age and male gender were also associated with PAD severity.

Keywords: Ankle-brachial index, atherosclerotic diseases, LOX-1 rs1050283 polymorphism, peripheral artery disease, serum sLOX-1 levels.

Cite This Article: Indrayana, Y., Yusuf, I., Bukhari, A., Mappangara, I., Harahap, H.S. 2023. The relationship of the use of masks with the event of maskne on Universitas Sumatera Utara Hospital healthcare workers during the COVID-19 pandemic. *Bali Medical Journal* 12(2): 1175-1180. DOI: 10.15562/bmj.v12i2.4221

INTRODUCTION

Peripheral arterial disease (PAD) is an important consequence of the progressive development of atherosclerosis. The prevalence is quite high, namely 5.6% in the general population at any point of age and becomes higher in the elderly group.[1] Since >50% of PAD is asymptomatic, this disease is often underdiagnosed and undertreated in primary care.[2] However, this disease remains a major health problem since it is associated with an increased risk of cardiovascular disease morbidity and mortality and reduced patient functional capacity resulting in an increased economic and health burden for the patient's family and the existing public health care system.[3] In fact, simple detection and optimal early intervention in PAD can prevent patients from further complications from PAD and thus can reduce the economic and health burden associated with this disease.

In clinical practice, the diagnosis of PAD can be determined based on the results of ankle-brachial index (ABI) measurements. An ABI value of <0.9 indicates a sensitivity of 90% and a specificity of 80% for the diagnosis of PAD, which refers to the occurrence of a stenosis of 50% of the arterial diameter.[4] Thus, this ABI value still has limitations that may result in PAD being under-recognized in clinical practice. Therefore, a number of studies have been conducted to identify blood biomarkers that might be helpful in screening for PAD and determining the severity of PAD. One of the biomarkers currently being extensively studied in relation to the diagnosis and determination of the prognosis of atherosclerotic diseases is Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1). LOX-1, a scavenger receptor that mediates the binding of oxidized LDL (ox-LDL) to the endothelial cell surface, plays an important role in downstream pathways of the atherosclerotic process, including endothelial dysfunction, atherosclerosis progression, plaque instability, and thrombogenesis.[5] Previous studies have shown that serum soluble LOX-1 (sLOX-1) levels are associated with the presence and severity of coronary artery disease (CAD), a type of atherosclerotic disease other than PAD.[6,7] A previous study also showed that serum sLOX-1 levels could

be used as a novel biomarker for PAD in patients with type 2 diabetes mellitus.[8]

Serum sLOX-1 levels in atherosclerotic diseases, including PAD, are influenced by several factors, including the presence of vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity), the treatment received to control identified vascular risk factors, and genetic factors. One of the genetic factors considered to have a significant role in determining LOX-1 expression and thus influencing serum sLOX-1 levels is the presence of the LOX-1 rs1050283 polymorphism.[9–11] To our knowledge, the relationship between the LOX-1 rs1050283 polymorphism and serum sLOX-1 levels and the severity of PAD in the general population is not currently established.

This study aimed to investigate the relationship between the LOX-1 rs1050283 polymorphism and serum sLOX-1 levels in a subpopulation of PAD patients in Mataram, Indonesia.

METHODS

Subjects and Study Design

This was a cross-sectional study involving subjects with PAD recruited consecutively in Internal Medicine and Cardiology outpatient clinics in Siti Hajar Hospital, Mataram, from May to July 2019. The inclusion criteria of the subjects were: (1) ABI 0.9 or less, (2) aged > 30 years old, and (3) voluntary participated. The exclusion criteria of the subjects were: (1) prior history of coronary artery disease or stroke, (2) severe renal or hepatic impairment. This study was conducted after obtaining ethical approval from Health Research Ethics Committee, Faculty of Medicine, Universitas Mataram (number 019/UN18.F7/ETIK/2022). All subjects provided written informed consent before their participation.

Data Collection

Sociodemographic and clinical data collected in this study were age, sex, occupation, hypertension, diabetes mellitus, dyslipidemia, smoking status, overweight/obesity, central obesity, and grade of PAD. Data on age was expressed as years and then categorized into <60 years and ≥60 years; data on sex was categorized into male and female; and data on occupation was categorized as employed and unemployed. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or receiving antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL and/or HbA1c ≥6.5% and/or receiving antidiabetic drugs. Dyslipidemia was defined as serum low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL and/or triglycerides ≥150 mg/dL and/or current treatment with lipid-lowering drugs. Data on overweight/obesity was obtained by measuring body mass index (BMI), i.e., by dividing body weight in kilograms by the square of height in meters. Using the BMI cut-off value of 25 kg/m^2, the subjects were categorized as overweight/obese (BMI ≥25 kg/m^2) and normoweight (BMI <25 kg/m^2). Data on central obesity were obtained by measuring the waist-to-hip ratio (WHR) of the subjects, and they were categorized as having central obesity if they had a WHR ≥ 0.90 for males and ≥0.85 for females.

The grade of PAD was determined based on the results of the patient's ABI measurement. ABI was measured using handheld vascular Doppler Bestman BF-520T. Measurement protocols for the determination of ABI have been described in a previous study.[12] ABI was calculated as a ratio of the highest ankle systolic blood pressure in both ankles to the highest brachial systolic blood pressure in both arms of the subjects. The ABI <0.90 was diagnostic for PAD, and using the ABI cut-off value of 0.80, the subjects were categorized into patients with mild PAD (ABI 0.80 – 0.90) and those with moderate to severe PAD (ABI <0.80).

Serum sLOX-1 level measurement

A total of 5 milliliters of fasting peripheral venous blood samples were obtained from each subject and distributed into two tubes. Half of the blood samples from each patient were collected in a tube containing EDTA and stored at -80°C until used for the genotyping process. The other half of the blood samples are placed in a coagulation tube and centrifuged to collect the serum. The serum obtained was then placed in an eppendorf tube and stored at -80°C for further testing. The serum sLOX-1 levels were examined at the Laboratory of Immunology, Faculty of Mathematics and Natural Sciences, University of Mataram, using CUSABIO Human Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 (sLOX-1) ELISA Kit (Catalog No. CSB-E13567h). Data on serum sLOX-1 levels was expressed in pg/mL. Using the cut-off value obtained from a receiver operating characteristic (ROC) curve analysis, serum sLOX-1 levels were categorized into higher and lower.

Genotyping

Genomic DNA extraction was performed using a Blood DNA Preparation Kit from Jena Bioscience. PCR was performed with Labcycler Sensoquest. Genotyping of LOX-1 rs1050283 polymorphism was performed by modifying the method as described in a previous study.[9] Using primer pairs: Forward primer 5'-ATTTGAAGGCTCTGGAAG-3'; Reverse primer 5-TTCTTGATTTCGG AATGG-3' resulting in a 471 bp fragment amplified. The PCR reaction was performed with the following conditions: PCR reactions in total volume 25 µl contain 12.5 µl Go Tag Green Master Mix, 2x Primer forward (µl (10 µM), primer reverse 1.25 µl (10 µM), DNA template 1 µl, Nuclease Free Water 8 µl (up to 25 µl). The PCR amplification condition is described as follows: a denaturation step at 95°C for 5 min, followed by 37 cycles of denaturation at 95°C for 30 sec, annealing at 43°C for 45 sec, extension at 72°C for 30 sec, and final incubation at 72°C for 10 min. These processes were conducted at the Laboratory of Immunology, Faculty of Mathematics and Natural Sciences, University of Mataram. Genotyping analysis by sequencing method was performed by Apical Scientific Malaysia (sequencing results are shown in Figure 1).

Statistical analysis

The sociodemographic and clinical data of the subjects were presented as mean value ± standard deviation (SD) for continuous variables and frequency (%) for categorical variables. The significant difference in the mean of serum sLOX-1 levels among genotypes of LOX-1 gene groups, i.e., TT

vs. CC and CT vs. CC, was analyzed using the Mann-Whitney test. The crude odds ratios (OR) with 95% confidence interval (CI) of LOX-1gene polymorphism and serum sLOX-1 levels associated with the grade of PAD were examined using bivariate analysis. The contribution of LOX-1 gene polymorphism and serum sLOX-1 levels to a grade of PAD were examined using multivariate logistic regression analysis after controlling socio-demographic variables (age, gender, and occupation) for Model 1, plus identified vascular risk factors (hypertension, diabetes, cigarette smoking, dyslipidemia, overweight/obesity, and central obesity) for Model 2 and reported as adjusted OR with 95%CI. The analysis was performed using SPSS 26.0 statistical software, and statistical significance was set at $p<0.05$.

RESULTS

This cross-sectional study involved 66 subjects with PAD confirmed by ABI ≤ 0.9. Table 1 shows the characteristics of the subjects. The mean age of the subjects was 58.9 years, with relatively comparable proportions between subjects aged ≥60 years and <60 years. Most of the subjects were female and unemployed. Hypertension, diabetes mellitus, dyslipidemia, overweight/obesity, and central obesity were the most commonly identified vascular risk factors, whereas cigarette smoking was not. Most importantly, the frequency of LOX-1 gene polymorphism was 39.4% consisting of 7.6% TT genotype and 31.8% CT genotype.

The results of DNA sequencing confirmed the presence of LOX-1 rs1050283 polymorphism (Figure 1). The frequency of subjects with mild PAD was higher than those with moderate to severe PAD. After performing ROC curve analysis, this study shows that the cut-off value of serum sLOX-1 level was 59.26 pg/mL with the AUC 0.579. Using this cut-off value, most subjects had higher serum sLOX-1 levels.

Table 2 presents the result of the Mann-Whitney test in examining the significant difference in the mean of serum sLOX-1 levels among genotypes of LOX-1 gene groups, i.e., TT vs. CC and CT vs. CC. The results showed that there was a significant difference in mean serum sLOX-1 levels in TT vs. CC (101.25±62.87 vs. 57.19±52.11, p = 0.042) and CT vs. CC (79.99±11.52 vs. 57.19±52.11, p = 0.028).

Table 1. Characteristics of the subjects (n = 66).

Variables	Mean ± SD, unless otherwise stated
Age in years, mean ± SD	58.89±10.26
Age groups, n (%)	
≥60 years	32 (48.5)
<60 years	34 (51.5)
Gender, n (%)	
Male	16 (24.2)
Female	50 (75.8)
Occupation, n (%)	
Employed	8 (12.1)
Unemployed	58 (87.9)
Cigarette smoking, n (%)	
Yes	3 (4.5)
No	63 (95.5)
Hypertension, n (%)	
Yes	55 (83.3)
No	11 (16.7)
Diabetes mellitus, n (%)	
Yes	46 (69.7)
No	20 (30.3)
Dyslipidemia, n (%)	
Yes	50 (75.8)
No	16 (24.2)
Overweight/obese, n (%)	
Yes (BMI ≥25 kg/m^2)	40 (60.6)
No (BMI <25 kg/m^2)	26 (39.4)
Central obesity, n (%)	
Yes	50 (75.8)
No	16 (24.2)
ABI, mean ± SD	0.80±0.09
Grade of PAD, n (%)	
Moderate to severe (ABI <0.80)	21 (31.8)
Mild (ABI 0.80 – 0.90)	45 (69.2)
Serum sLOX-1 levels in pg/mL, mean ± SD	67.79±54.16
Serum sLOX-1 levels groups, n (%)	
Higher (≥59.26 pg/mL)	51 (77.3)
Lower (<59.26 pg/mL)	15 (22.7)
Genotypes, n (%)	
TT	5 (7.6)
CT	21 (31.8)
CC	40 (60.6)

Notes: SD: standard deviation, BMI: body mass index, ABI: ankle-brachial index, PAD: peripheral artery disease, sLOX-1: soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1.

Table 3 presents the bivariate analysis results in investigating the association between the LOX-1 rs1050283 polymorphism and serum sLOX-1 levels and the frequency of moderate to severe PAD. There was no significant association between LOX-1 rs1050283 genotypes and serum sLOX-1 levels with grade of PAD (p >0.05).

Table 4 presents a multivariate logistic regression analysis examining whether LOX-1 gene polymorphism and serum sLOX-1 levels increased the frequency of moderate to severe PAD after adjustment by controlling for other independent variables. In Model 1, LOX-1 gene polymorphism and higher serum

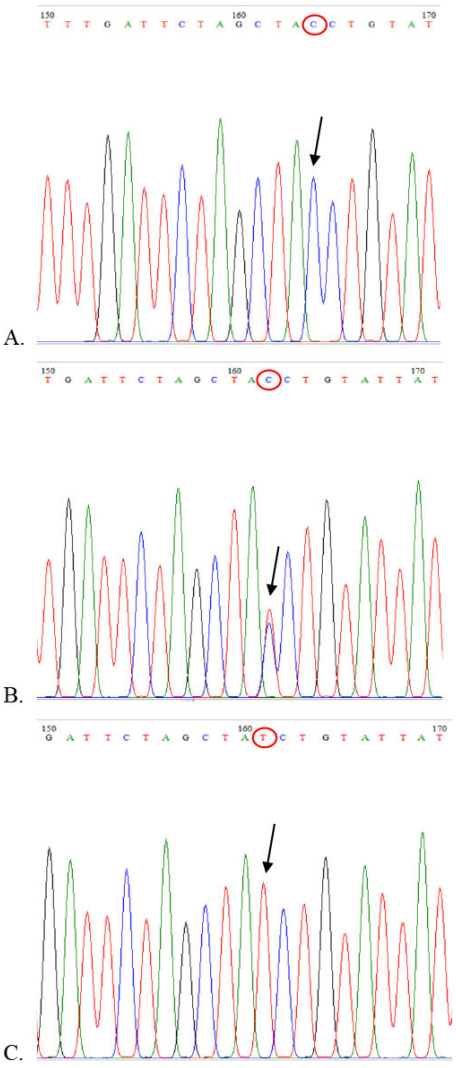

Figure 1. The results of DNA sequencing of rs1050283 polymorphism of 3'UTR LOX-1 gene (C>T) were presented using the BioEdit computer program. A. DNA sequence of CC genotype. B. DNA sequence of CT genotype. C. DNA sequence of TT genotype. LOX-1: Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1.

Table 2. **Bivariate analysis examining the significant difference in the mean of serum sLOX-1 levels among genotypes of LOX-1 gene groups (n = 66).**

Genotypes	n	Serum sLOX-1 levels in pg/mL, mean ± SD	p-value (compared with CC genotype)
TT	5	101.25±62.87	0.042
CT	21	79.99±11.52	0.028
CC	40	57.19±52.11	reference

Notes: Mann-Whitney test, significant if p <0.05)

Table 3. **Bivariate analysis examining the association between LOX-1 gene polymorphism and serum sLOX-1 levels and grade of PAD (n = 66).**

Variables	Grade of PAD		OR (95% CI)	p-value
	Mild (n = 45)	Moderate to severe (n = 21)		
Genotypes, n (%)				
TT	2 (40.0)	3 (60.0)	3.8 (0.5 – 28.4)	0.201
CT	15 (71.4)	6 (28.6)	3.5 (0.5 – 23.7)	0.199
CC	28 (70.0)	12 (30.0)	Reference	
Serum sLOX-1 levels, n (%)				
Higher	19 (61.3)	12 (38.7)	1.8 (0.6 – 5.2)	0.260
Lower	26 (74.3)	9 (25.7)	Reference	

Notes: PAD: peripheral artery disease, OR: odds ratio, CI: confidence intervals, sLOX-1: soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1.

Table 4. **Multivariate logistic regression analysis examining the association of LOX-1 gene polymorphism and serum sLOX-1 levels and frequency of moderate to severe PAD after adjustment with other independent variables (n = 66).**

Independent variables	OR	95% CI	p-value
Model 1			
LOX-1 gene polymorphism, TT genotype	10.0	1.0 – 103.1	0.052
LOX-1 gene polymorphism, CT genotype	4.4	0.5 – 37.5	0.177
Higher serum sLOX-1 levels	2.6	0.7 – 9.4	0.138
Increasing age	3.9	1.0 – 14.6	0.044*
Male gender	4.9	1.0 – 22.9	0.043*
Unemployed	3.3	0.3 – 32.3	0.311
Model 2			
LOX-1 gene polymorphism, TT genotype	15.0	1.1 – 209.0	0.044*
LOX-1 gene polymorphism, CT genotype	4.4	0.4 – 47.4	0.215
Higher serum sLOX-1 levels	2.7	0.6 – 11.3	0.178
Increasing age	5.7	1.3 – 25.7	0.022*
Male gender	6.0	1.1 – 32.2	0.037*
Unemployed	7.8	0.4 – 134.1	0.157
Hypertension	4.4	0.7 – 29.4	0.122
Diabetes mellitus	1.3	0.3 – 5.5	0.678
Cigarette smoking	9.5	0.2 – 404.0	0.238
Dyslipidemia	2.4	0.5 – 13.0	0.295
Overweight/obesity	1.3	0.3 – 5.2	0.723
Central obesity	1.2	0.2 – 6.9	0.801

Notes: OR: odds ratio, CI: confidence intervals, *significant association (p <0.05). Model 1: adjusted for serum sLOX-1 levels, age, sex, and occupation; Model 2: Model 1 plus identified vascular risk factors (hypertension, diabetes, cigarette smoking, dyslipidemia, overweight/obesity, and central obesity).

sLOX-1 levels were not associated with moderate to severe PAD frequency. However, in Model 2, after controlling for all independent variables (socio-demographic and identified vascular risk factors), subjects with TT genotype were 15.0 times more likely to have moderate to severe PAD compared to those with CC genotype (OR: 15.0, 95% CI: 1.1 – 209.0, p = 0.044), while higher serum sLOX-1 level was not. Still in Model 2, the frequency of subjects with moderate to severe PAD was also increased by increasing age (OR:5.7, 95% CI: 1.3 – 25.7, p = 0.022) and male gender (OR: 6.0, 95% CI: 1.1 – 32.2, p = 0.037).

DISCUSSION

This study investigated the association between LOX-1 rs1050283 polymorphism and serum sLOX-1 levels and the severity of PAD in sub-population patients in Mataram, Indonesia. This study showed that TT genotype of LOX-1 gene polymorphism was associated with the high frequency of moderate to severe PAD, whereas CT genotype was not. To our knowledge, this was the first global study examining these associations. A previous study examined the association between LOX-1 gene polymorphisms, including rs1050283 polymorphism, and the risk of coronary artery disease (CAD) in the North Indian population and the results showed that TT genotype but not CT genotype increases the risk of CAD.[13] Since CAD and PAD share the same pathogenesis and risk factors, the equivalence of that study's results with the present study's findings is still relevant. The presence of the LOX-1 rs1050283 TT genotype is associated with increased progression of systemic atherosclerosis, either through increased atherogenic activity of LOX-1 or decreased anti-atherogenic activity of LOXIN.[14] Since systemic atherosclerosis is the main pathology of the arterial wall that underlies the development of PAD, it is rational if the presence of the LOX-1 polymorphism of the TT genotype can also determine the severity of PAD.[15]

This study also demonstrated that both TT and CT genotypes of LOX-1 rs1050283 polymorphism were associated with serum sLOX-1 levels. Currently, no similar studies have been conducted on subjects with PAD. Two previous studies that examined the relationship between these two variables in two different medical conditions (renal hypertension and ischemic stroke) known to have the same pathophysiological basis as PAD, namely as a complication of systemic atherosclerosis, showed similar results from the present study.[9,10] Theoretically, the presence of LOX-1 rs1050283 polymorphism, especially TT genotype, will increase the expression of endothelial LOX-1 and serum sLOX-1 levels. Since LOX-1 is the main receptor for oxidized low-density lipoprotein (ox-LDL) and the interaction between LOX-1 and ox-LDL activates the initiation and progression of atherosclerotic lesions in the arterial wall, the increase of serum sLOX-1 levels is associated with the progression of the atherosclerosis-related disease, including PAD.[16]

However, this study showed that serum sLOX-1 levels were not associated with the increased risk of moderate to severe PAD. The results of this study were not in accordance with the results of a previous study conducted by Fukui et al.[8] demonstrating that serum sLOX-1 levels were independently associated with PAD. These results also imply that although it is associated with the presence of the LOX-1 rs1050803 polymorphism, increased serum sLOX-1 levels are not necessarily related to the severity of PAD. The difference in the results of this study with a previous study may be due to differences in methods, ethnicity of subjects, and frequency of identified vascular risk factors in the subjects. In addition, since expression of LOX-1 is upregulated by vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and obesity, better or poorer control status for the identified vascular risk factors also determines this difference in results.[14,16,17]

In addition, this study also revealed that increasing age was associated with the frequency of moderate to severe PAD. This finding was in line with the results of the previous study. Savji et al.[18] examined the association between increasing age and vascular disease in different artery territories, including PAD. The results demonstrated that increasing age was associated with the increased frequency of PAD. Selvin et al.[19] examined the prevalence of and risk factors for PAD in the United States, and the results showed that the frequency of PAD in subjects aged ≥70 years is significantly higher compared to those aged 40 to 49 years, 14.5% vs. 1%, respectively. Increasing age is known as one of the strongest risk factors of all atherosclerotic diseases, including PAD.[1] Increasing age theoretically promotes cellular senescence of the arterial wall and epigenetic modification-induced upregulation of pathologic genes that result in a series of pathologic processes in the atherosclerotic arterial wall, including DNA damage, and progression of arterial atherosclerotic plaque.[20]

This study also demonstrated that the male gender was associated with moderate to severe PAD frequency. Regarding this association, the previous study showed conflicting results. This finding was in line with the results of a previous study conducted by Aday et al.[21] However, a previous study conducted by Selvin et al.[19] showed no significant difference in the frequency of PAD between males and females. The hormonal factor might play a role in the sex difference in PAD. Theoretically, the male hormone testosterone increases the risk for PAD by promoting the development of atherosclerotic plaques in the artery walls, whereas the female hormone estrogen is protective against atherosclerosis.[22] However, in the postmenopausal period, the risk for women to develop PAD increases due to the loss of the protective effect of estrogen during this period.[23] Therefore, variations in research findings regarding the relationship between gender and frequency for the severity of PAD may be due to variations in the age characteristics of the subjects studied.

This study has several limitations. First, this study used a small sample size that can affect the study results. The small sample of this study was due to the small number of participants who met the inclusion criteria and limited funding. Second, this study used a cross-sectional design so that analysis of the causal relationship between the LOX-1 rs1050283 polymorphism and serum sLOX-1 levels and the severity of PAD could not be carried out. Since the role of LOX-1 rs1050283 polymorphism and serum sLOX-1 levels in the progression of atherosclerosis occurs through a series of chronic pathological processes, cohort studies are needed to prove LOX-1 rs1050283 polymorphism and serum sLOX-1 levels in the development of atherosclerosis-related diseases, including PAD. Nevertheless, due to the scarcity of the previous study, the results of this study contribute to adding the previous study related to the role of LOX-1 in increasing the severity of PAD.

CONCLUSION

This study revealed that TT genotype of LOX-1 rs1050283 polymorphism was associated with the severity of PAD after

adjusting for the sociodemographic and clinical characteristics of the subjects. However, although higher serum sLOX-1 levels were associated with the presence of the LOX-1 rs1050283 polymorphism, higher serum levels of this protein were not associated with the severity of PAD. In addition, increasing age and male gender were also associated with the severity of PAD.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

FUNDING

The authors are responsible for all research funding without obtaining financial support from any source.

ETHICAL CONSIDERATION

The ethical approval was from Ethical Committee for Health Research, Faculty of Medicine, University of Mataram (Register number: 019/UN18.F7/ETIK/2022).

AUTHOR CONTRIBUTION

Yanna Indrayana (YI), Irawan Yusuf (IY), Agussalim Bukhari (AB), Idar Mappangara (IM), and Herpan Syafii Harahap (HS) conceptualized the study. YI, IY, AB, IM, HS designed the study. YI, HS drafted the manuscript. All authors analyzed and interpreted the study results and revised the manuscript.

REFERENCES

1. Aday AW, Matsushita K. Epidemiology of Peripheral Artery Disease and Polyvascular Disease. Circ Res. 2021;128(12):1818–32. https://doi.org/10.1161/CIRCRESAHA.121.318535
2. Shu J, Santulli G. Update on peripheral artery disease: Epidemiology and evidence-based facts. Atherosclerosis. 2018;275:379–81. https://doi.org/10.1016/j.atherosclerosis.2018.05.033
3. Lin J, Chen Y, Jiang N, Li Z, Xu S. Burden of peripheral artery disease and its attributable risk factors in 204 countries and territories from 1990 to 2019. Front Cardiovasc Med. 2022;9:868370. https://doi.org/10.3389/fcvm.2022.868370
4. Pabon M, Cheng S, Altin SE, Sethi SS, Nelson MD, Moreau KL, et al. Sex Differences in Peripheral Artery Disease. Circ Res. 2022;130:496–511. https://doi.org/10.1161/CIRCRESAHA.121.320702
5. Barreto J, Karathanasis SK, Remaley A, Sposito AC. Role of LOX-1 (Lectin-like oxidized low-density lipoprotein receptor 1) as a cardiovascular risk predictor: mechanistic insight and potential clinical use. Arterioscler Thromb Vasc Biol. 2021;41(1):153–66. https://doi.org/10.1161/ATVBAHA.120.315421
6. Li B, Zhang L, Yang X, Liu X, Ren Y. Serum sLOX-1 levels are associated with the presence and severity of angiographic coronary artery disease in patients with metabolic syndrome. Clin Investig Med. 2010;33(6):E398–404. https://doi.org/10.25011/cim.v33i6.14591
7. Kumar S, Ali W, Mishra S, Pradhan A, Sethi R, Kushwaha R, et al. Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1): A diagnostic indicator across the spectrum of acute coronary syndrome. J Clin Med. 2021;10:5567. https://doi.org/10.3390/jcm10235567
8. Fukui M, Tanaka M, Senmaru T, Nakanishi M, Mukai J, Ohki M, et al. LOX-1 is a novel marker for peripheral artery disease in patients with type 2 diabetes. Metabolism. 2013;62(7):935–8. http://dx.doi.org/10.1016/j.metabol.2013.01.018
9. Sun Y, Zhang H. The association of LOX-1 rs1050283 polymorphism with renal hypertension susceptibility in a Chinese population. Int J Clin Exp Pathol. 2017;10(2):1667–74.
10. Guo X, Xiang Y, Yang H, Yu L, Peng X, Guo R. Association of the lox-1 rs1050283 polymorphism with risk for atherosclerotic cerebral infarction and its effect on slox-1 and lox-1 expression in a chinese population. J Atheroscler Thromb. 2017;24(6):572–82. https://doi.org/10.5551/jat.36327
11. Salehipour P, Rezagholizadeh F, Mahdiannasser M, Kazerani R, Modarressi MH. Association of OLR1 gene polymorphisms with the risk of coronary artery disease: A systematic review and meta-analysis. Hear Lung. 2021;50:334–43. https://doi.org/10.1016/j.hrtlng.2021.01.015
12. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the Ankle-Brachial Index: A scientific statement from the American Heart Association. Circulation. 2012;126:2890–909. https://doi.org/10.1161/CIR.0b013e318276fbcb
13. Kaur N, Singh J, Reddy S. The LOX1 gene polymorphisms and coronary artery disease in North Indian population. Arch Clin Biomed Res. 2019;3(2):21–35.
14. Pothineni NVK, Karathanasis SK, Ding Z, Arulandu A, Varughese KI, Mehta JL. LOX-1 in atherosclerosis and myocardial ischemia: biology, genetics, and modulation. J Am Coll Cardiol. 2017;69(22):2759–68. https://doi.org/10.1016/j.jacc.2017.04.010
15. Bonaca MP, Hamburg NM, Creager MA. Contemporary medical management of peripheral artery disease. Circ Res. 2021;128:1868–84. https://doi.org/10.1161/CIRCRESAHA.121.318258
16. Pirillo A, Catapano AL. Soluble lectin-like oxidized low density lipoprotein receptor-1 as a biochemical marker for atherosclerosis-related diseases. Dis Markers. 2013;35(5):413–8. https://doi.org/10.1155/2013/716325
17. Komiyama M, Wada H, Ono K, Yamakage H, Satoh-Asahara N, Shimada S, et al. Smoking cessation reduces the lectin-like low-density lipoprotein receptor index, an independent cardiovascular risk marker of vascular inflammation. Heart Vessels. 2018;33:9–16. https://doi.org/10.1007/s00380-017-1026-z
18. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, et al. Association between advanced age and vascular disease in different arterial territories: A population database of over 3.6 million subjects. J Am Coll Cardiol. 2013;61(16):1736–43. http://dx.doi.org/10.1016/j.jacc.2013.01.054
19. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: Results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004;110(6):738–43. https://doi.org/10.1161/01.CIR.0000137913.26087.F0
20. Wang JC, Bennett M. Aging and atherosclerosis: Mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circ Res. 2012;111(2):245–59. https://doi.org/10.1161/CIRCRESAHA.111.261388
21. Aday AW, Duncan MS, Patterson O V., Duvall SL, Alba PR, Alcorn CW, et al. Association of sex and race with incident peripheral artery disease among veterans with normal Ankle-Brachial Indices. JAMA Netw Open. 2022;5(11):e2240188. https://doi.org/10.1161/CIRCRESAHA.111.261388
22. Gao S, Geng YJ. LOX-1: A male hormone-regulated scavenger receptor for atherosclerosis. Vascul Pharmacol. 2013;59:138–43. http://dx.doi.org/10.1016/j.vph.2013.10.003
23. Buso G, Darioli R, Calanca L, Depairon M, Schwitter J, Mazzolai L, et al. In postmenopausal women, lower limb peripheral arterial disease, assessed by ankle-brachial index, may be a strong predictor of cardiovascular risk. Eur J Intern Med. 2022;99:63–9. https://doi.org/10.1016/j.ejim.2022.02.002