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ORIGINAL RESEARCH

Serum LOXL2 is Elevated and an Independent Biomarker in Patients with Coronary Artery Disease

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Background: Arterial stiffness is associated with accelerated progression of atherosclerosis and plaque rupture. Lysyl oxidase-like 2 (LOXL2) plays a vital role in inflammatory responses, matrix deposition and arterial stiffness. This study assessed the correlation between the serum LOXL2 concentration and disease severity, inflammation, and endothelial dysfunction of coronary artery disease (CAD).

Methods: The study included 143 CAD patients and 150 non-CAD patients who underwent coronary angiography. Medical records, demographic and clinical baseline parameters were collected. Serum LOXL2 levels were measured using an ELISA kit.

Results: CAD patients had higher serum LOXL2 levels than non-CAD patients, and LOXL2 levels were associated with severity of coronary lesions. Serum LOXL2 level was positively correlated with low-density lipoprotein cholesterol (LDL-C) (r=0.161, P=0.054), systolic blood pressure (SBP) (r=0.175, P=0.036), high-sensitivity C-reactive protein (hs-CRP) (r=0.177, P=0.035), intima-media thickness (IMT) (r=0.190, P=0.023), and brachial-ankle pulse wave velocity (baPWV) (r=0.203, P=0.015), while negatively associated with high-density lipoprotein cholesterol (HDL-C) (r=−0.191, P=0.023) and flow-mediated dilation (FMD) (r=−0.183, P=0.028) in CAD patients. Multivariate logistic regression showed that LOXL2 is independently correlated with LDL-C (OR=3.380; 95% CI=1.258–9.082; P=0.016), hs-CRP (OR=10.988; 95% CI=1.962–61.532; P=0.006), TC (OR=2.229; 95% CI=1.005–4.944; P=0.049), IMT (OR=72.719; 95% CI=2.313–2286.008; P=0.015), and baPWV (OR=1.002; 95% CI=1.001–1.004; P=0.005) in CAD patients. The receiver operating characteristic (ROC) curve showed that the best cut-off for CAD as serum LOXL2 is 275.35 pg/mL, with sensitivity and specificity of 77.6% and 84%, respectively.

Conclusion: Our data demonstrated that LOXL2 could be a potential biomarker and independent risk factor for CAD patients.

Keywords: coronary artery disease, CAD, atherosclerosis, endothelial dysfunction, arterial stiffness, LXOL2

Introduction

Coronary artery disease (CAD), comprising stable angina and acute coronary syndromes, represents a constellation of critical illnesses responsible for an estimated 7 million fatalities worldwide annually.[1,2] The pathogenesis of CAD is multifaceted, involving interactions among various factors such as the accumulation of cholesterol-rich apolipoprotein B (ApoB) in the arterial intima, chronic inflammation, vascular endothelial dysfunction, and other elements that contribute to atherogenesis and the development of CAD.[3–5] Despite the implementation of appropriate lifestyle modifications, pharmacological treatments, and surgical procedures, the primary cardiovascular outcomes associated with CAD continue to yield suboptimal results.[6,7] Thus, there is an ongoing necessity to identify biomarkers capable of predicting the clinical prognosis of individuals with CAD.

The protein family known as lysyl oxidase consists of LOX and four lysyl oxidase-like proteins (LOXL1, LOXL2, LOXL3, and LOXL4). These proteins function as copper- and quinone-dependent amine oxidases.[8] The initial discovery attributed LOX to the enzymatic process of covalently crosslinking collagen and elastin within the extracellular matrix.[9] Several research studies have highlighted the role of LOXL2 in promoting tumor progression and fibrosis.[10,11] An

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imbalance in LOXL2 expression is closely linked to various fibrotic conditions, cardiovascular disorders, and malignancies.[12–14] A recent investigation delved into the association between LOXL2 and cardiac fibrosis in heart failure (HF) patients.[15] Their findings suggested that there could be a significant correlation between serum LOXL2 levels and CAD. Therefore, the current study aims to assess whether serum LOXL2 levels at baseline are associated with CAD's disease severity, inflammation, and endothelial dysfunction.

Patients and Methods

Study Population

In this study, we consecutively collected 143 CAD patients admitted to the Department of Cardiology in Shanghai Pudong Hospital between January 2022 and December 2023. All patients underwent coronary angiography and were diagnosed with CAD. We also selected 150 patients who underwent coronary angiography without CAD, with matched age and gender. Four experienced angiographers performed coronary angiography, two of whom evaluated the vessels. The severity of coronary lesions was evaluated by the number of significant coronary artery stenoses, and all 143 CAD patients were classified as vessels ≤ 2 (n = 98) or vessels > 2 (n = 45). We excluded subjects with infections, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), autoimmune diseases, liver diseases, renal failure, and malignancies in both non-CAD and CAD patients. The Research Ethics Committee of Shanghai Pudong Hospital approved this study protocol. All participants provided their written consent to participate in the study.

Data Collection

Clinical data were collected through inquiry with all subjects after admission, including demography (age, gender, history of smoking or alcohol intake), comorbidities (hypertension and diabetes mellitus), blood pressure, and laboratory tests. General biochemical indexes were obtained, including fasting blood sugar (FBS), white blood cell (WBC), high-sensitivity C-reactive protein (hs-CRP), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

Measurement of IMT

The carotid artery's IMT was measured by carotid ultrasound.[16] The ultrasound image was obtained from the posterior wall of the left and right carotid arteries. The measurements were repeated five times for each subject to get the mean carotid IMT.

Measurement of FMD

FMD was performed by measuring the brachial artery diameter at baseline and during reactive hyperemia to evaluate the endothelial function.[17] Patients were fasting for at least six hours. Patients were kept in the supine position for at least 15 min. An automated sphygmomanometer (Dinamap device) was placed in the forearm arm to monitor blood pressure and pulse at 5-min intervals. A standard blood pressure cuff measured the arterial pressure two inches below the antecubital fossa. After obtaining baseline images, reactive hyperemia was induced by inflating the cuff to 50 mm Hg above the SBP for 5 min. Images of the baseline and maximum diameters of the brachial artery were obtained.

Measurement of baPWV

BaPWV was used to measure the conduction velocity of the brachial-ankle pulse wave, and it reflects the compliance and elastic function of the vascular wall. The increase in baPWV demonstrates a decrease in arterial wall compliance and an increase in arterial wall stiffness. Patients were rested for a minimum of 5 min in the supine position, and their baPWV was measured and recorded using an automatic waveform analyzer (VP-1000; Omron, Tokyo, Japan). The cuffs were wrapped at the upper arm and ankle, and pressure waveforms were recorded at the brachial and tibial arteries. baPWV was calculated automatically by time-phased analysis, normalized to the distance between the upper arm and ankle.[18]

ELISA Detection of Serum LOXL2

Blood samples were collected within 24 hours of hospital admission, and serum was separated and stored at −80°C. Serum LOXL2 levels in non-CAD and CAD patients were measured by ELISA kit (DY2639-05, R&D Systems), and absorbance at 450 nm was measured with a microplate reader. LOXL2 concentrations were calculated according to the standard curve and expressed as pg/mL for each case.

Statistical Analysis

SPSS20.0 statistical software was used for data processing and figure plotting. Continuous variables are displayed as the mean ± standard deviation (SD) and analyzed using a *t*-test or Mann–Whitney *U*-test between two groups or ANOVA or Kruskal–Wallis test between three groups. Categorical variables are displayed as frequency (percentage) and analyzed using the chi-square test. The Pearson correlation test analyzed the correlation between LOXL2 and continuous variables. The ROC curve was made to determine the cut-off point of serum LOXL2 between the non-CAD and CAD. Univariate and multivariate logistic regression analyses assess the effect of serum LOXL2 on CAD, expressed as odds ratio (OR) and the 95% confidence interval (CI). $P<0.05$ was considered as a criterion for a significant difference.

Results

Baseline Characteristics of the Study Population

In the present study, we enrolled 293 patients, including 143 patients with confirmed CAD diagnosed through coronary angiography and 150 patients without CAD with matched age and gender. The baseline characteristics of the study population are described in Table 1. The mean age of the CAD patients was 62.48±8.68, and 55.9% of the participants were male. The baseline cohort showed significant increases in smoking, body mass index (BMI), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), hypertension,

Table 1 Baseline Characteristics of the Study Population

Parameters	Non-CAD (n=150)	CAD (n=143)	P value
Age (years)	62.20±9.22	62.48±8.68	0.793
Gender (male, %)	73 (48.7%)	80 (55.9%)	0.213
BMI (kg/m^2)	23.58±2.44	24.36±2.01	0.003
Smoking, n (%)	35 (23.3%)	52 (36.4%)	0.015
Drinking, n (%)	27 (18.0%)	32 (22.4%)	0.350
Hypertension, n (%)	56 (37.3%)	74 (51.7)	0.013
Diabetes mellitus, n (%)	32 (21.3%)	46 (32.2%)	0.036
SBP (mmHg)	127.63±6.71	129.94±6.07	0.002
FBS (mmol/L)	5.32±0.89	5.61±1.06	0.010
WBC ($10^9/L$)	5.80±1.27	6.22±1.30	0.005
hs-CRP (mg/L)	0.96±0.21	1.13±0.21	<0.001
TG (mmol/L)	1.44±0.20	1.50±0.23	0.018
TC (mmol/L)	4.41±0.40	4.77±0.48	<0.001
LDL-C (mmol/L)	2.52±0.37	2.90±0.42	<0.001
HDL-C (mmol/L)	1.03±0.22	1.07±0.21	<0.001
IMT (mm)	0.85±0.08	0.95±0.13	<0.001
FMD (%)	6.52±1.30	6.83±1.13	<0.001
baPWV (cm/s)	1478.05±193.90	1627.43±215.20	<0.001

Notes: Continuous variables are expressed as mean ± SD, and analyzed using *t* test or Wilcoxon-Mann–Whitney test. Categorical variables are expressed as frequency (percentage), and analyzed using the chi-square test.

Abbreviations: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; FBS, fasting blood sugar; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; FMD, flow-mediated dilation; baPWV, brachial-ankle pulse wave velocity.

diabetes mellitus, fasting blood sugar (FBS), white blood cell (WBC), high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), total cholesterol (TC), intima-media thickness (IMT), flow-mediated dilation (FMD), and brachial-ankle pulse wave velocity (baPWV) activity/levels for CAD patients compared to the non-CAD ($P < 0.05$).

Comparison of Serum LOXL2 Levels Between Non-CAD and CAD Patients

Mann–Whitney *U*-test compared the serum LOXL2 levels in CAD and non-CAD patients. As shown in Figure 1A, the serum LOXL2 concentration in CAD patients was significantly higher than in non-CAD patients (P<0.001). In addition, we carried out the Kruskal–Wallis test to evaluate the serum LOXL2 levels in CAD patients with different numbers of involved vessels. The results showed that those with more than two-vessel had a higher LOXL2 serum level than those with less than two or two-vessel (P<0.001); both groups had significantly higher serum levels of LOXL2 compared to the non-CAD group (P<0.001) (Figure 1B).

Correlation of LOXL2 Serum Levels with Clinical Indicators

Pearson correlation test was performed to evaluate any association between serum LOXL2 level with different clinical indicators, including IMT, FMD, and baPWV in CAD patients. The Pearson correlation analysis results revealed a significant positive correlation between LOXL2 levels with IMT (r=0.404, P<0.001), baPWV (r=0.350, P<0.001), while negatively correlated with FMD (r=−0.292, P<0.001) in CAD patients (Figure 2). In addition, serum LOXL2 level was positively correlated with LDL-C (r=0.161, P=0.054), SBP (r=0.175, P=0.036), hs-CRP (r=0.177, P=0.035), IMT (r=0.190, P=0.023), and baPWV (r=0.203, P=0.015), while negatively associated with HDL-C (r=−0.191, P=0.023) and FMD (r=−0.183, P=0.028) in CAD patients (Table 2). Moreover, no significant correlation was found between LOXL2 and the other variables presented.

Factors Associated with the Serum LOXL2 Levels in CAD Patients

To investigate the factors associated with serum LOXL2 levels in CAD patients, we initially conducted a univariate regression analysis to examine the relationship between serum LOXL2 and various variables. We found that serum LOXL2 was statistically associated with several parameters in CAD patients, including LDL-C (Odd Ratios [OR]=2.941; 95% Confidence Interval [CI]=1.003–8.619; P=0.049), HDL-C (OR=0.123; 95% CI=0.019–0.789; P=0.027), hs-CRP (OR=11.935; 95% CI=1.935–73.635; P=0.008), and baPWV (OR=1.003; 95% CI=1.001–1.005; P=0.005) (Table 3).

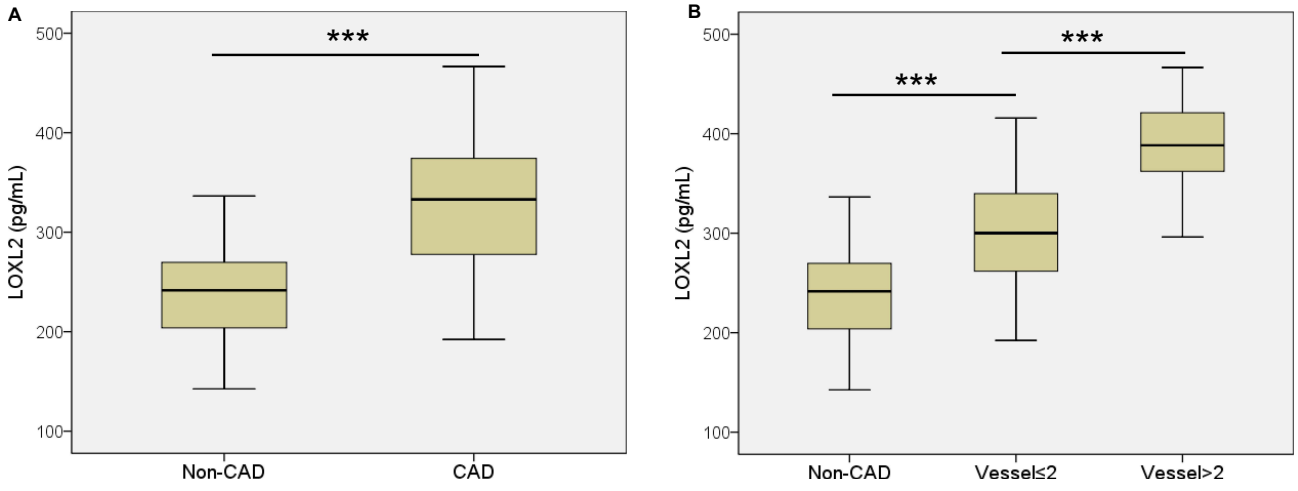

Figure 1 Comparison of serum LOXL2 levels in non-CAD and CAD patients. (**A**) Comparison of serum LOXL2 levels between the non-CAD and CAD groups. The serum LOXL2 concentration in CAD patients (n = 143) was significantly higher than that in non-CAD patients (n = 150). Mann–Whitney *U*-test was applied. (**B**) Comparison of serum LOXL2 levels in CAD patients with different number of involved vessels. Kruskal–Wallis test was applied. ***P<0.001.

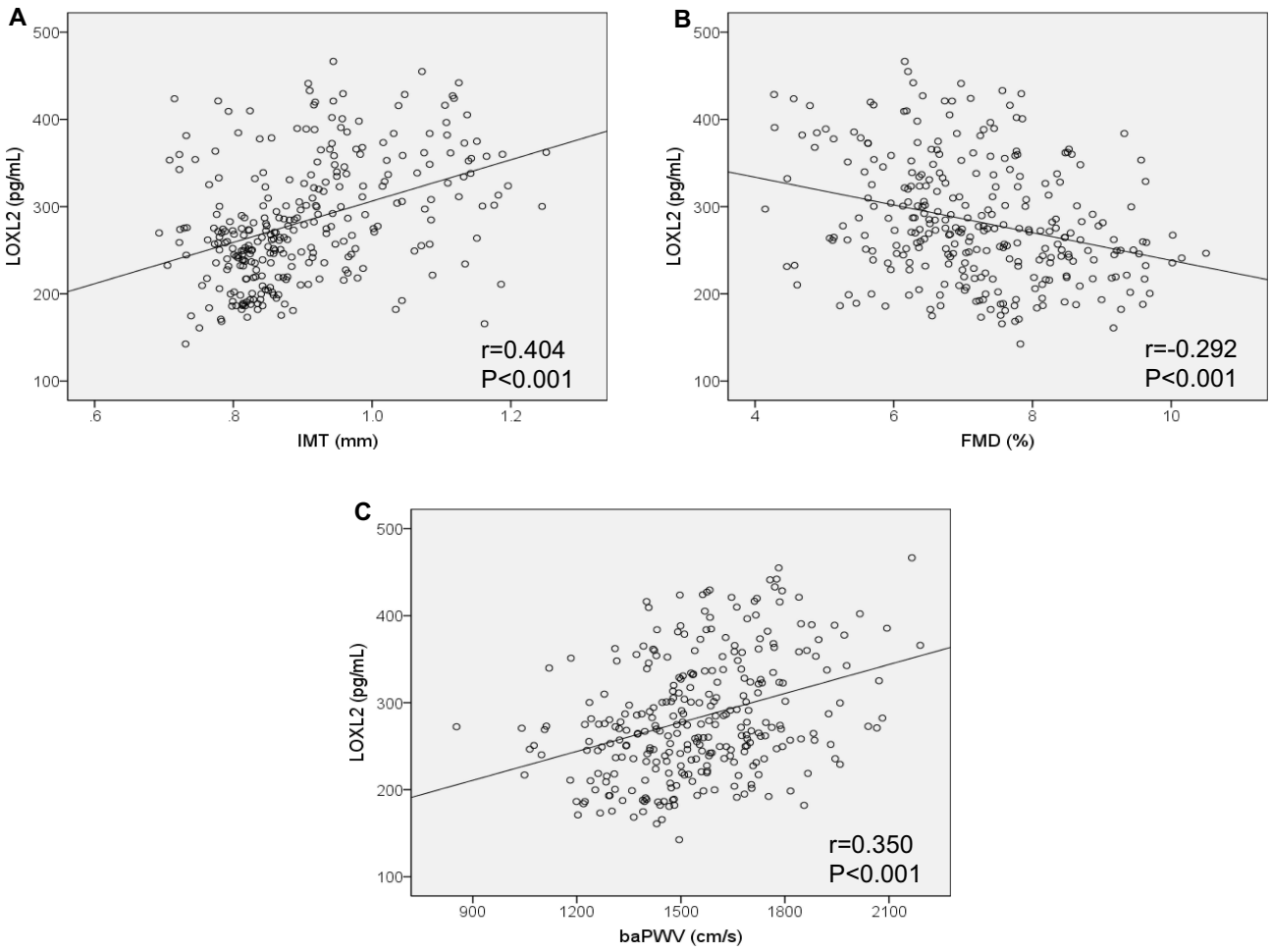

Figure 2 The correlation between serum LOXL2 and clinical indicators. Pearson correlation test was performed between LOXL2 with (**A**) IMT, (**B**) FMD, and (**C**) baPWV in all non-CAD and CAD patients.

Secondly, serum LOXL2 levels were investigated with different subgroups in CAD patients, including gender, smoking, drinking, hypertension, and diabetes mellitus. We found that for CAD patients, serum LOXL2 levels were associated with hypertension (P=0.042) (Figure 3).

Thirdly, we carried out a logistic multivariate regression analysis and found that serum LOXL2 levels were positively associated with LDL-C (OR=3.380; 95% CI=1.258–9.082; P=0.016), hs-CRP (OR=10.988; 95% CI=1.962–61.532; P=0.006), TC (OR=2.229; 95% CI=1.005–4.944; P=0.049), IMT (OR=72.719; 95% CI=2.313–2286.008; P=0.015), and baPWV (OR=1.002; 95% CI=1.001–1.004; P=0.005) (Table 4).

A cut-off value of serum LOXL2 (275.35 pg/mL) was determined based on the ROC curve analysis to differentiate between patients with and without CAD. This value demonstrated good sensitivity and specificity (77.6% and 84%, respectively). As shown in Figure 4, the area under the curve (AUC) was 0.885.

Discussion

Our study provides new insight into the role of serum LOXL2 levels in coronary artery disease. The present study showed that serum LOXL2 levels were elevated in the patients with CAD. Further studies have shown that levels of serum LOXL2 are associated with multiple cardiovascular risk factors in people with coronary artery disease. In CAD patients, serum LOXL2 levels were positively associated with hs-CRP, TC, LDL-C, IMT, and baPWV. The serum LOXL2 level is independently associated with CAD after adjusting the cut-off value of serum LOXL2 based on the ROC curve analysis. Therefore, our results demonstrated that serum LOXL2 level could be a potential biomarker for CAD.

Table 2 Correlation Between Serum LOXL2 and Clinical Indicators

Parameters	All Subjects (n=293)		Non-CAD (n=150)		CAD (n=143)	
	r	P	r	P	r	P
Age (years)	0.077	0.191	0.067	0.414	0.109	0.195
BMI (kg/m^2)	0.189	0.001	0.107	0.194	0.104	0.218
SBP (mmHg)	0.226	<0.001	0.118	0.151	0.175	0.036
FBS (mmol/L)	0.181	0.002	0.124	0.129	0.102	0.227
WBC (10^9/L)	0.207	<0.001	0.134	0.101	0.138	0.100
hs-CRP (mg/L)	0.350	<0.001	0.121	0.140	0.177	0.035
TG (mmol/L)	0.164	0.005	0.180	0.028	0.049	0.564
TC (mmol/L)	0.352	<0.001	0.169	0.039	0.134	0.109
LDL-C (mmol/L)	0.410	<0.001	0.230	0.005	0.161	0.054
HDL-C (mmol/L)	−0.319	<0.001	−0.041	0.622	−0.191	0.023
IMT (mm)	0.404	<0.001	0.214	0.009	0.190	0.023
FMD (%)	−0.292	<0.001	−0.131	0.111	−0.183	0.028
baPWV (cm/s)	0.350	<0.001	0.130	0.114	0.203	0.015

Notes: The correlation between serum LOXL2 and continuous variables was analyzed using the Pearson correlation test.

Table 3 Logistic Univariate Regression the Association of Independent Variables with CAD

Characteristics	Odds Ratio	95% Confidence Interval	P value
Age (years)	0.971	0.932–1.012	0.164
Gender (male, %)	0.991	0.459–2.141	0.982
BMI (kg/m^2)	1.021	0.865–1.206	0.804
Smoking, n (%)	1.020	0.448–2.321	0.963
Drinking, n (%)	1.047	0.378–2.899	0.930
Hypertension, n (%)	1.158	0.524–2.560	0.717
Diabetes mellitus, n (%)	1.152	0.476–2.784	0.754
SBP (mmHg)	0.981	0.922–1.044	0.549
FBS (mmol/L)	1.000	0.678–1.476	1.000
WBC (10^9/L)	1.004	0.751–1.342	0.981
hs-CRP (mg/L)	11.935	1.935–73.635	0.008
TG (mmol/L)	0.421	0.065–2.705	0.362
TC (mmol/L)	2.135	0.874–5.211	0.096
LDL-C (mmol/L)	2.941	1.003–8.619	0.049
HDL-C (mmol/L)	0.123	0.019–0.789	0.027
IMT (mm)	35.402	0.780–1606.937	0.067
FMD (%)	0.784	0.563–1.091	0.149
baPWV (cm/s)	1.003	1.001–1.005	0.005
LOXL2 (pg/mL)	1.024	1.014–1.033	<0.001

In the pathogenesis of atherosclerosis and its complications, inflammation plays a crucial role.[19] Currently, C-reactive protein (CRP) is used as the sole inflammatory biomarker employed in clinical practice for assessing and stratifying of cardiovascular risk. Elevated CRP levels typically signal a heightened likelihood of experiencing major cardiovascular events.[20,21] Nevertheless, it is worth noting that CRP originates in the liver and lacks specificity towards atherosclerosis; instead, an elevated CRP level signifies the presence of an acute phase response triggered by diverse inflammatory stimuli like infection, trauma, and allergies.[22] However, LOXL2 could be a suitable, clinically necessary biomarker that accurately reflects vascular inflammation in atherosclerosis. LOXL2 is a member of the lysyl oxidase (LOX) family,

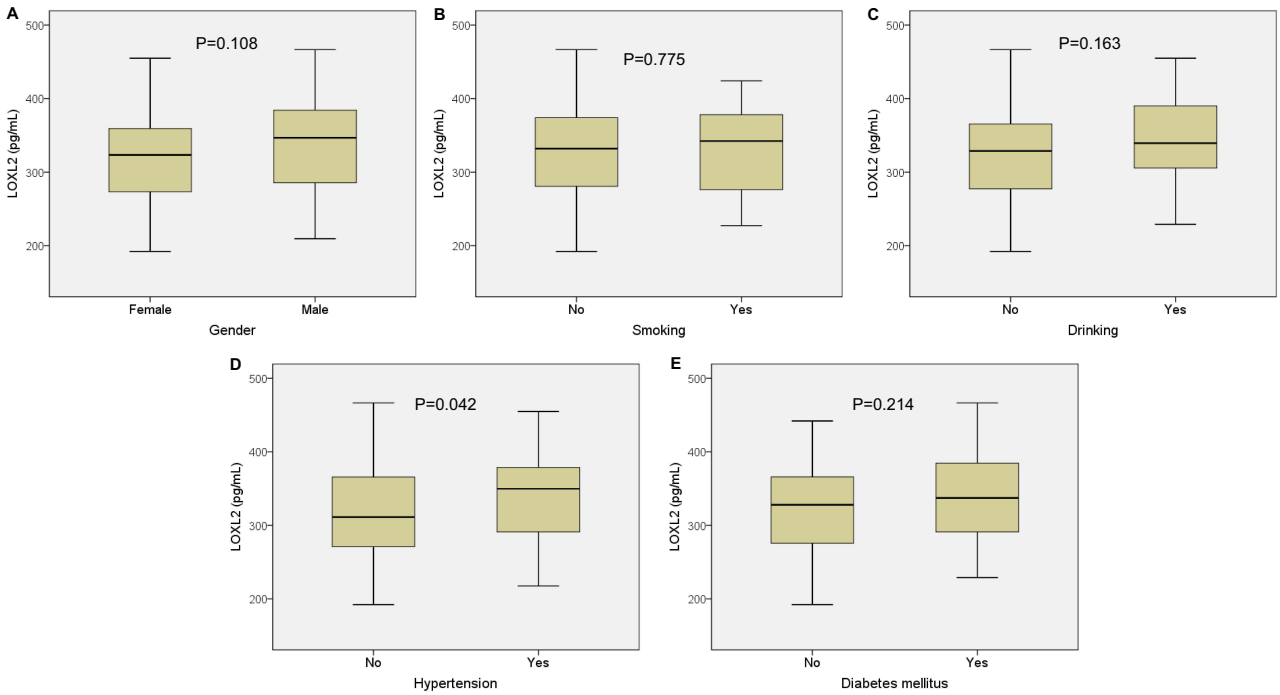

Figure 3 Serum LOXL2 in different subgroup in CAD patients. Serum LOXL2 was compared between subgroups dividing with (**A**) gender, (**B**) smoking, (**C**) drinking, (**D**) hypertension, and (**E**) diabetes mellitus in CAD patients.

exhibiting comparable functionality to LOX within the extracellular matrix through the facilitation of collagen and elastin crosslinking.[23,24] A correlation between LOXL2 levels and collagen crosslinking as well as cardiac dysfunction was indicated in a prior investigation.[25] Our present study evaluated its potential as a novel biomarker for CAD and non-CAD patients. We found that the serum LOXL2 levels were significantly associated with CAD. Thus, the serum LOXL2 levels could be a biomarker for CAD.

The lysyl oxidase protein family consists of LOX and four lysyl oxidase-like proteins (LOXL1, LOXL2, LOXL3, and LOXL4). These proteins depend on copper and quinone and are amine oxidases.[8] LOX was initially discovered to be responsible for the covalent binding of collagen and elastin in the extracellular matrix.[26] Several studies have shown that LOXL2 promotes tumor progression and fibrosis.[10,11] Dysregulation of LOXL2 is strongly related to fibrotic disorders, cardiovascular diseases, and cancers.[12–14] A recent study investigated the link between LOXL2 and cardiac fibrosis in heart failure (HF).[15] The researchers found that LOXL2 levels were higher in heart tissues and serum in patients with HF and that its levels were linked to cardiac dysfunction and HF biomarker levels.[25] In our study, there were no differences in age, gender, and drinking between CAD patients and non-CAD patients groups. However, serum LOXL2 levels were significantly associated with BMI, smoking, hypertension, diabetes mellitus, SBP, FBS, WBC, hs-CRP, TG, TC, LDL-C, HDL-C, IMT, FMD and baPWV in CAD patients (Table 1).

Table 4 Logistic Multivariate Regression the Association of Independent Variables with CAD

Characteristics	Odds Ratio	95% Confidence Interval	P value
LDL-C (mmol/L)	3.380	1.258–9.082	0.016
hs-CRP (mg/L)	10.988	1.962–61.532	0.006
TC (mmol/L)	2.229	1.005–4.944	0.049
IMT (mm)	72.719	2.313–2286.008	0.015
baPWV (cm/s)	1.002	1.001–1.004	0.005
LOXL2 (pg/mL)	1.024	1.016–1.033	<0.001

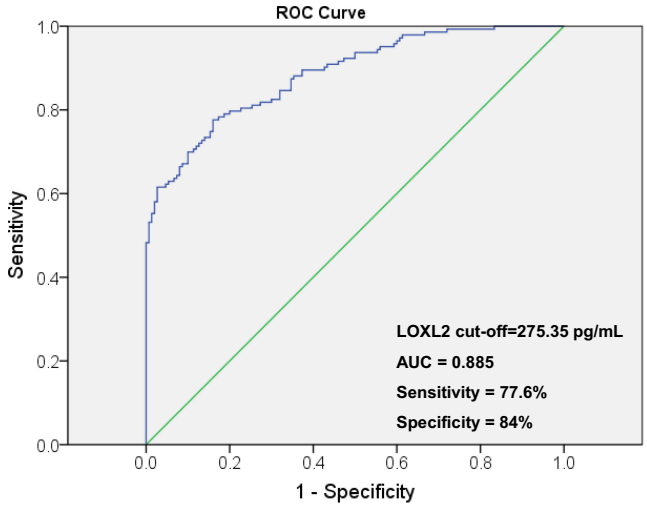

Figure 4 The cut-off value of serum LOXL2. The ROC curve was used to obtain the optimal cut-off value of serum LOXL2 that distinguishes the non-CAD subjects from CAD patients.

A Pearson correlation analysis was conducted to assess the potential relationship between serum LOXL2 levels and various clinical parameters, such as IMT, FMD, and baPWV, in patients with CAD. The findings of the Pearson correlation test demonstrated a statistically significant positive correlation between LOXL2 levels and IMT, FMD, and baPWV among CAD patients (Figure 2). Furthermore, the study identified a positive correlation between serum LOXL2 level and SBP, hs-CRP, LDL-C, IMT, and baPWV (Table 2).

To explore the factors related to serum LOXL2 levels in patients with coronary artery disease (CAD), an initial univariate regression analysis was performed to investigate the correlation between serum LOXL2 and various factors. Firstly, serum LOXL2 levels in various subgroups among CAD patients were examined, including gender, smoking, alcohol consumption, hypertension, and diabetes mellitus. An association between serum LOXL2 levels and hypertension in CAD patients was observed (Figure 3). Secondly, the investigation demonstrated a substantial correlation between serum LOXL2 levels and various parameters in patients diagnosed with CAD, including LDL-C, HDL-C, hs-CRP, and baPWV (Table 3). Thirdly, a logistic multivariate regression analysis was conducted, demonstrating a significant positive correlation between serum levels of LOXL2 and the parameters of LDL-C, hs-CRP, TC, IMT, and baPWV (Table 4). A particular threshold concentration of serum LOXL2 (275.35 pg/mL) was established via ROC curve analysis to differentiate between patients with CAD and those without. This delineated value demonstrated significant levels of sensitivity and specificity (77.6% and 84%, respectively). The evaluation of the area under the curve (AUC) produced a value of 0.885 (Figure 4).

Limitations

There are inevitably some limitations to this study. Our study had a small sample size and was conducted at a single healthcare center for patient enrollment. Therefore, large-scale research is required to validate our findings. Gene mutations, which are known to be correlated with serum LOXL2 levels, were not the subject of our data collection. Genetic factors may influence the expression and release of serum LOXL2, and our analysis may be limited if these factors are not considered. For further study, we will consider gene mutation subjects of data collection and conduct analysis. Finally, it is challenging to conclude a causal relationship between serum LOXL2 levels and CAD because of the cross-sectional design of our study.

Conclusion

In this research, we demonstrate that serum LOXl2 levels are increased in CAD patients and are related to several cardiovascular risk factors. We found that serum LOXL2 levels outperform established indications in detecting CAD. These results suggest that serum levels of LOXL2 could be a novel biomarker for coronary artery disease.

Ethics Approval and Consent to Participate

The Shanghai Pudong Hospital Ethics Committee (Shanghai Pudong Hospital Affiliated to Fudan University) approved (2023-MS-DS-14) this study. The authors implemented all standard protocols in accordance with the 1964 Declaration of Helsinki. All participants provided their written consent to participate in the study.

Disclosure

The author reports no conflicts of interest in this work.

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