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Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 as a diagnostic marker for acute ST-elevation myocardial infarction

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Abstract

Introduction: *ST-elevation myocardial infarction (STEMI) is a major cause of mortality and morbidity worldwide, but fast and reliable diagnosis can reduce mortality. Therefore, this study aimed to assess the diagnostic value of serum soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) among patients with acute STEMI, and also its importance to monitor the response to percutaneous coronary intervention (PCI). A total of 30 healthy subjects and 150 acute STEMI patients treated by PCI were enrolled into our study. Besides the routine lab work, serum sLOX-1 level was measured using a commercial ELISA kit.*

Results: *Our results revealed the increased serum sLOX-1 level among patients with acute STEMI (112.79 ± 10.76) than controls (47.75 ± 12.87). After the treatment of acute STEMI patients with the primary PCI, the level of serum sLOX-1 was not sigificantly decreased either after 12 hrs (111.04 ± 11.06) or 48 hrs (110.31 ± 11.24) from PCI management. Our results also showed that serum sLOX-1 level was positively correlated with cholesterol, LDL, troponin I, CK-MB, CRP, TG, and VLDL. Results obtained from ROC curve analysis showed that serum sLOX-1 is an excellent biomarker for acute STEMI disease, its AUC is one with 100% sensitivity and specificity.*

Conclusions: *Finally, from these results, we can conclude that LOX-1 has a crucial role in the pathogenesis of acute STEMI; also, serum sLOX-1 could be a good diagnostic clinical biomarker for the detection of acute STEMI disease and to monitor the response to PCI.*

Key **words:** acute coronary syndrome (ACS), coronary heart disease, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), percutaneous coronary intervention (PCI), myocardial infarction (MI), ST-elevation myocardial infarction (STEMI)

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Introduction

Acute coronary syndrome (ACS) is a type of coronary heart disease and refers to a spectrum of conditions that range from non-ST elevation myocardial infarction (NSTEMI), and unstable angina to ST-elevation myocardial infarction (STEMI) [1]. ACS is considered a major cause of mortality and morbidity and accounts for more than 2.5 million hospitalizations annually worldwide [2]. An acute ST-elevation myocardial infarction (STEMI) is a disease in which myocardial injury or necrosis is caused by transmural myocardial ischemia.

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The current 2018 clinical definition of myocardial infarction (MI) needs myocardial ischemic injury confirmation by abnormal cardiac biomarkers associated with ECG changes and chest pain [3]. The management of ACS patients is a global challenge to clinicians and healthcare systems [4]. Percutaneous coronary intervention (PCI) with a coronary stent is considered as a major standard-of-care procedure in the manipulation of angina or ACS worldwide [5].

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) belongs to class E scavenger transmembrane receptor that mainly binds oxidized low-density lipoprotein (ox-LDL) [6]. It is 50-kDa glycoproteins consisting of 4 domains: a short N-terminal cytoplasmic domain, a transmembrane domain, a neck domain, and a lectin-like extracellular C-terminal domain which binds with OxLDL [7]. The extracellular domain of LOX-1 proteolytically cleaved generating soluble LOX-1 (sLOX-1) which released into the bloodstream reflecting the expression of LOX-1 [8]. It was found that sLOX-1 was elevated in acute coronary syndromes and stable coronary disease in which sLOX-1 can distinguish the disease severity and monitor response to treatment [9].

Therefore, this is a case-control study aimed to assess the importance of the use of sLOX-1 as a diagnostic maker and also its importance to monitor the response to PCI with a coronary stent in acute STEMI patients.

Material and methods

Ethics statement

The current study was approved by the ethics committees of El-Demerdash Hospital, Faculty of Medicine, Ain Shams University. Informed consent were obtained from all patients. All procedures performed in this study were in accordance with the ethical standards of the ethics committees of the Faculty of Medicine, Ain Shams University, and also Helsinki Declaration.

Human subjects

The current study was conducted on 30 healthy controls and 150 patients with acute STEMI treated by PCI. All patients were successfully revascularized achieving normal coronary blood flow during the PCI procedure. All study subjects were investigated for age, gender, body mass index (BMI), and blood pressure. Laboratory tests were conducted at admission, including blood levels of random blood sugar (RBS), C-reactive protein (CRP), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and very low-density lipoprotein cholesterol (VLDL) levels in all study subjects. Blood samples were collected before the PCI procedure (zero time), and repeated after 12, and 48 hours from PCI for all patients.

Measurement of sLOX-1

Serum sLOX-1 concentration was measured using Human sLOX-1 ELISA Kit (cat# E1424Hu) (BIOTECH, Inc., China) according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using SPSS software (version 20.0; SPSS Inc., Chicago, Illinois, USA), and Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Comparison between estimated parameters was done by means of independent-samples T-test. Pearson's correlation coefficient was used to determine significant correlations of sLOX-1 and other clinical parameters. The Receiver Operating Characteristic curve (ROC curve) was used to calculate the area under the curve (AUC) of serum sLOX-1 in order to evaluate its sensitivity and specificity as a biomarker for the detection of acute ST-elevation myocardial infarction. The criterion for significance was $p<0.05$.

Results

Demographic and biochemical data of acute STEMI patients

The current study included 150 acute STEMI patients treated with PCI; 92 male and 58 female; with mean age 48.40 ± 10.82 years; the clinical and biological data of healthy subjects and acute STEMI patients are summarized in Table 1.

Data obtained from laboratory routine work of acute STEMI patients revealed a highly significantly ($P < 0.001$) increase in blood pressure (systolic and diastolic) and the serum levels of Troponin I, LDH, AST, CK-Total, CK-MB, CRP, RBD, cholesterol, TG, HDL, LDL, and VLDL when compared to controls; as shown in Table 1.

Serum level of sLOX-1 in acute STEMI patients

As depicted from Figure 1A, the level of serum sLOX-1 was found to be highly significantly ($P < 0.001$) increased in acute STEMI patients (112.79 ± 10.76) when compared to the control group (47.75 ± 12.87).

Also, the level of serum sLOX-1 was measured after 12hrs and 48hrs from PCI to assess its impor-

Table 1. Clinicopathological characteristics of acute STEMI patients and controls

Group Parameter	Control group (n = 30) Mean ± SD	Patients Group (n = 150) Mean ± SD	p-value
Gender Female Male	 12 (40.0%) 18 (60.0%)	 58 (38.7%) 92 (61.3%)	0.913
Age (years)	46.80 ± 6.69	48.40 ± 10.82	0.192
BMI [wt/(ht) ^ 2]	22.50 ± 1.96	24.24 ± 3.07	0.254
Blood pressure [mm Hg] Systolic Diastolic	 116.50 ± 6.90 75.00 ± 6.88	 168.69 ± 7.95 95.28 ± 3.39	 <0.001** <0.001**
Troponin I [ng/ml]	0.02 ± 0.01	0.55 ± 0.76	< 0.001**
LDH [U/L]	91.70 ± 11.97	566.76 ± 121.07	< 0.001**
AST [U/L]	21.75 ± 7.00	41.80 ± 20.09	< 0.001**
CK-total [U/L]	69.25 ± 16.56	322.59 ± 209.65	< 0.001**
CK-MB [U/L]	13.40 ± 4.38	54.98 ± 26.57	< 0.001**
CRP [mg/dl]	3.21 ± 1.45	11.52 ± 10.27	< 0.001**
RBS [mg/dl]	87.85 ± 11.72	190.07 ± 94.05	< 0.001**
Cholesterol [mg/dl]	153.28 ± 19.10	200.93 ± 35.73	< 0.001**
TG [mg/dl]	87.70 ± 10.21	157.48 ± 51.63	< 0.001**
HDL [mg/dl]	50.92 ± 4.69	43.46 ± 5.98	< 0.001**
LDL [mg/dl]	84.82 ± 21.98	125.98 ± 34.68	< 0.001**
VLDL [mg/dl]	17.54 ± 2.04	31.49 ± 10.33	< 0.001**

* Significant at p-value < 0.05
** Highly significant at p-value < 0.001

Table 2. Area under the curve (AUC), cut-off value, sensitivity and specificity of serum sLOX-1, and other parameters in acute STEMI patients

	sLOX-1 [pg/ml]	Troponin [ng/ml]	LDH [U/L]	AST [U/L]	CK-Total [U/L]	CK-MB [U/L]	CPR [mg/dl]
AUC	1	1	1	0.81	1	1	0.91
Cut-off value	78.92	0.065	234	25.9	96	21.98	4.25
Asymptotic Sig.	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**
Sensitivity	100%	100%	100%	71.1%	100%	100%	81.6%
Specificity	100%	100%	100%	76.2%	100%	100%	71.4%

* Significant at p-value < 0.05
** Highly significant at p-value < 0.001

tance to monitor the response to PCI. Our results revealed that serum sLOX-1 is not significantly decreased ($P > 0.05$) either after 12 hrs (111.04 ± 11.06) or 48 hrs (110.31 ± 11.24) when compared with zero time (112.79 ± 10.76); as shown in Figure 1B.

Correlation of serum sLOX-1 level with clinical variables in acute STEMI patients

The correlation matrix of serum sLOX-1 with the different clinical parameters in this study was assessed. Our results revealed that the level of serum sLOX-1 had

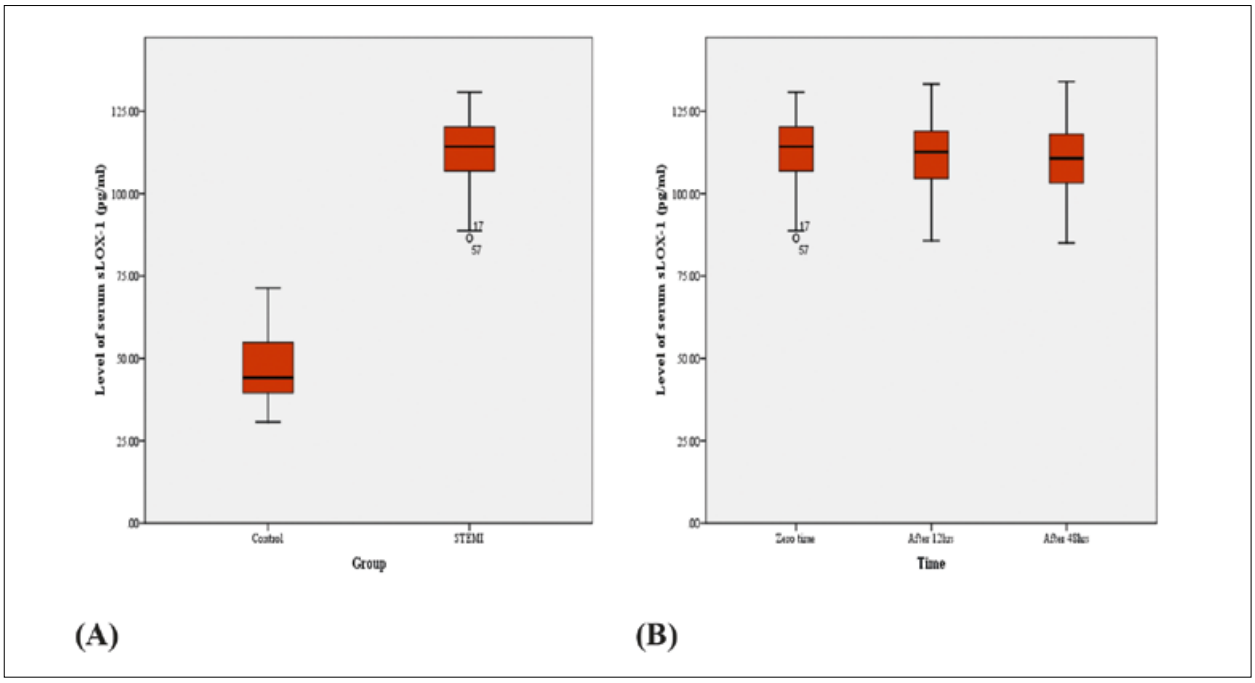

Figure 1. The level of serum sLOX-1 in: (A) acute STEMI patients and controls; (B) acute STEMI patients before and after 12 or 48 hours from PCI

highly significant positive correlations ($P < 0.001$) with cholesterol and LDL serum levels; while it had significant positive correlations ($P < 0.05$) with troponin I, CK-MB, CRP, TG, and VLDL; as shown in Figure 2 (A–G).

Receiver operating characteristic (ROC) curves analysis

To evaluate the sensitivity and specificity of the serum sLOX-1 level as a marker for the detection of acute STEMI disease, ROC curve analysis was done. Our results showed that AUC for sLOX-1 is 1 with 100% sensitivity and specificity, as shown in Table 2 and Figure 3.

Discussion

Worldwide, MI is the main cause of mortality and morbidity, but fast and reliable diagnosis can reduce mortality [10]. Therefore, this study aimed to assess the diagnostic value of serum sLOX-1 among patients with acute STEMI, and also its importance to monitoring the response to PCI.

Results of the current study revealed that the level of serum sLOX-1 was significantly increased in acute STEMI patients when compared with healthy subjects, which indicates that sLOX-1 may play a crucial role in the pathogenesis of acute STEMI disease. These results are consistent with Mehta et al. [11] who reported that LOX-1 is a critical player in the development of atherosclerosis and related disorders, and also with Caglar et al. [12] who found that sLOX-1 levels were associated with coronary slow flow phenomenon which linked with myocardial ischemia, myocardial infarction, life-threatening arrhythmias, sudden cardiac death and increased cardiovascular mortality similar to coronary artery disease (CAD). This is in addition to Takanabe-Mori et al. [13] who found that LOX-1 had an important role in vascular inflammation in current smokers. There is a multicenter pilot study reported that higher serum LOX-1 in patients with stable coronary artery disease was associated with major adverse cardiovascular events [6]. All these observations with our results ascertain that LOX-1 has a great role in the pathogenesis of acute STEMI disease.

Furthermore, serum level of sLOX-1 was found in other diseases such as type 2 diabetes mellitus [14, 15], coronary artery disease in patients with metabolic syndrome [16], polycystic ovary syndrome [17], and hypertension [18], which all associated with endothelial dysfunction.

Our results also showed that serum sLOX-1 level was positively correlated with cholesterol, LDL, troponin I, CK-MB, CRP, TG, and VLDL. As consistent with our results, Balin et al. [19] suggested that as the level of sLOX-1 was positively correlated with CK, CK-MB, and TnT, it could be a biomarker to predict the risk of periprocedural myocardial damage in stable patients undergoing PCI. Also, serum sLOX-1 levels were

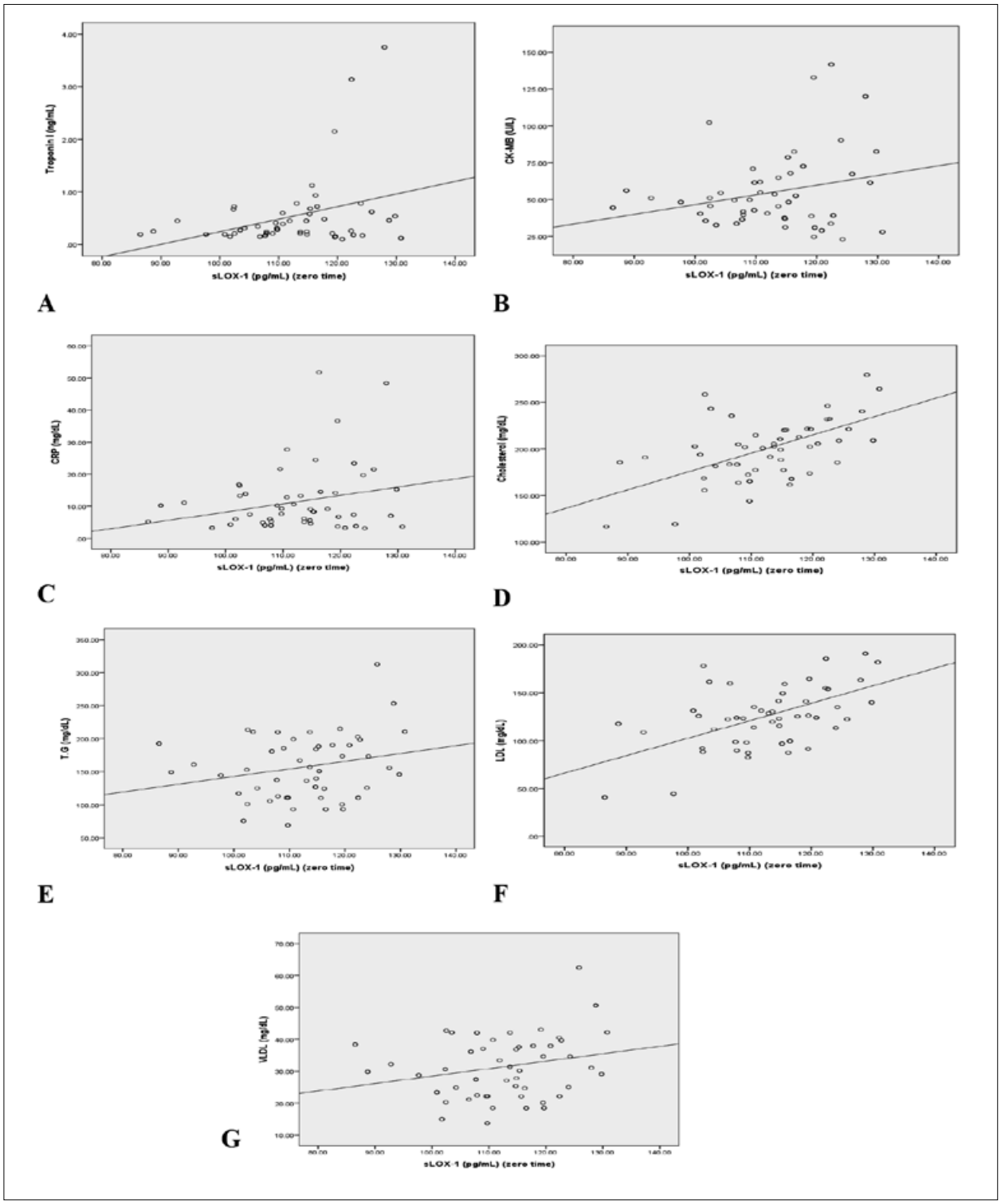

Figure 2. Correlations of serum sLOX-1 with different parameters among acute STEMI patients

measured before and after the procedure to assess whether it could predict in-stent restenosis (ISR) during the follow-up of patients with MI who underwent successful primary PCI [20]. According to our results, after the treatment of acute STEMI patients with the primary PCI, the level of serum sLOX-1 was not sigificantly decreased either after 12 hrs or 48 hrs from PCI management, which may reflect that these patients are at low risk to develop ISR.

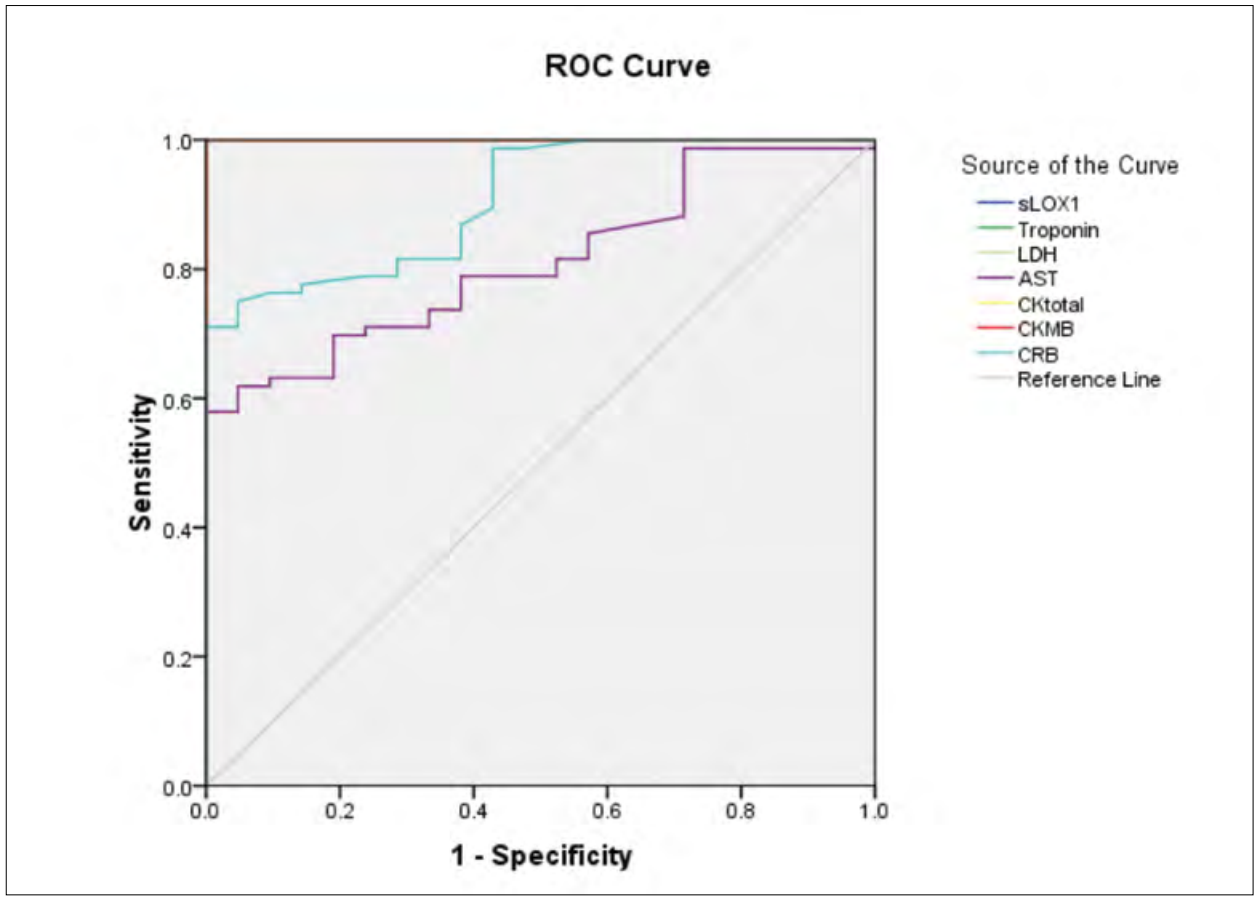

Figure 3. ROC curve of serum sLOX-1 and other parameters for detection of acute STEMI disease

LOX-1 is undetectable in healthy vessels but overexpressed in atherosclerotic lesions [21], and sLOX-1 is generated through proteolytic cleavage of the extracellular domain of LOX-1, released into the bloodstream reflecting the expression of LOX-1, therefore sLOX-1 can be used as a diagnostic biomarker of the acute coronary syndrome [22].

Results obtained from ROC curve analysis showed that serum sLOX-1 is an excellent biomarker for acute STEMI disease, its AUC is one with 100% sensitivity and specificity, such as global cardiac biomarkers like troponin I, LDH, and CK-MB.

It was found that the level of sLOX-1 was elevated at the earliest stages of acute STEMI (about one hour and a half from the symptom onset) and then declined to basal levels after 16 days from the onset of STEMI, while other cardiac biomarkers peaked later (troponin T and CK-MB after 6 hrs from the symptom onset) and declined rapidly [23]. Also, Kume et al. [24] reported that the circulating sLOX-1 is a more sensitive and specific biomarker for ACS than troponin and can detect ACS in subjects with normal troponin levels. Therefore, it was suggested that circulating sLOX-1 may be a useful biomarker for diagnosing STEMI, and the evaluation of sLOX-1 combined with troponin levels could improve the accuracy of ACS diagnosis [25].

Results obtained from this study also revealed that our STEMI patients had significantly increased values of systolic and diastolic blood pressure. Several studies reported that there is a crosstalk between LOX-1 and renin-angiotensin system (RAS) and therefore evolution of blood pressure [26–28], also blockade and deletion of LOX-1 was found to reduce angiotensin II type 1 receptor (AT1R) expression in the cardiovascular system [29]. The authors believed that LOX-1 may contribute to the evolution of hypertension in STEMI patients. It is well known that LOX-1 mainly binds ox-LDL which is more important in the genesis and progression of hypertension leading to endothelial dysfunction, an early and common event in the pathogenesis of hypertension [30]. One of the limitations of this study is the impact of elevated blood pressure values on the increase of sLOX-1 and further investigations are needed to explore this and clarify the link between hypertension and sLOX-1.

Conclusions

Finally, from the above results, we can conclude that LOX-1 has a crucial role in the pathogenesis of acute STEMI; also, serum sLOX-1 could be a good diagnostic clinical biomarker for the detection of acute STEMI disease and to monitor the response to PCI.

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