Exploring Lipoprotein-Associated Phospholipase A2 Levels in Iraqi Patients with Stable Angina: Insights from Coronary Angiography Diagnosis

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Abstract:

Stable angina is a prevalent heart disease which can be defined as a clinical syndrome of stable coronary artery disease (CAD) that refers to the presence of myocardial ischemia. Lipoprotein-associated Phospholipase A2 (Lp-PLA2) is an important biomarker of atherosclerosis progression through pro-inflammatory and anti-inflammatory effects.

Objective: The aim was to detect the role of Lp-PLA2 in the diagnosis of patients with stable angina and normal left ventricular ejection fraction (LVEF).

Patients and methods: The study design was a case-control study. 90 males and females (age 40-76 years) who were presented with chest pain were enrolled in the study, all were subjected to echocardiography, ECG and coronary angiography by the cardiologist. Besides, patient's questionnaire and biochemical analysis were also used. According to the angiography, they were divided into two groups: 60 patients and 30 as a control group. Levels of Lp-PLA2, total cholesterol, triglycerides (TG), high density lipoprotein-Cholesterol (HDL-C), very low density lipoprotein-Cholesterol (VLDL-C) and low density lipoprotein-Cholesterol (LDL-C) in serum were assessed. The biplane M mode method was used to measure left ventricular ejection fraction (LVEF).

Result: It was detected that Lp-PLA2 serum levels were significantly higher in the patients than in the control, ($P \leq 0.01$). ROC analysis showed that Lp-PLA2 had specificity of 100% and sensitivity 100%.

Conclusion: Measurement of Lp-PLA2 can be applied as an excellent biomarker in the diagnosis of patients with stable angina and normal LV ejection fraction.

Keywords: Coronary artery disease, diagnosis, left ventricular ejection fraction, lipoprotein-associated phospholipase A2, stable angina.

استكشاف مستويات الفسفوليباز A2 المرتبطة بالبروتين الدهني لدى المرضى العراقيين المصابين بالذبحة الصدرية المستقرة: رؤى من تشخيص تصوير الأوعية التاجية

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الخلاصة:

ان الذبحة الصدرية المستقرة هي مرض قلبي منتشر يمكن تعريفه على أنه متلازمة سريرية لمرض الشريان التاجي المستقر الذي يشير إلى وجود نقص تروية عضلة القلب. يعد البروتين الدهني المرتبط بالفوسفوليباز A2 علامة حيوية مهمة لتطورمرض تصلب الشرايين من خلال تأثيراته الالتهابية والمضادة للالتهابات.

الهدف: كان الهدف هو اكتشاف دورالفوسفوليباز2Aالمرتبط بالبروتين الدهني في تشخيص المرضى الذين يعانون من الذبحة الصدرية المستقرة والكسر القذفي الطبيعي للبطين الأيسر.

المرضى وطرق العمل: كان تصميم الدراسة دراسة الحالات والشواهد. شملت الدراسة 90 مشاركًا من الذكور والإناث (تتراوح أعمارهم بين 40 و76 عامًا) والذين تعرضوا لألم في الصدر، وخضعوا جميعًا لتخطيط صدى القلب وتخطيط القلب الكهربائي وتصوير الأوعية التاجية من قبل طبيب القلب. الى جانب ذلك، تم عمل استبيان للمرضى والتحاليل الحيوية المختبرية أيضا. اعتمادا على تصوير الاوعية التاجية، تم تقسيمهم إلى مجموعتين: 60 مريضا و30 كمجموعة ضابطة. تم تقييم مستويات فوسفوليباز2Aالمرتبط بالبروتين الدهني والكوليسترول الكلي والدهون الثلاثية وكوليسترول البروتين الدهني عالي الكثافة وكوليسترول البروتين الدهني منخفض الكثافة وكوليسترول البروتين الدهني منخفض الكثافة جدا في المصل. تم ايضا قياس الكسر القذفي الطبيعي للبطين الأيسر باستخدام طريقة ذات السطحين (biplane).

النتائج: لقد تم الكشف عن ان مستويات فوسفوليباز2Aالمرتبط بالبروتين الدهني في المصل كانت اعلى عند المرضى بشكل ملحوظ مقارنة بالاصحاء ($P \leq 0.01$). ان استخدام تحليل منحنى خاصية تشغيل المتلقي (ROC) بين ان البروتين الدهني المرتبط بالفوسفوليباز A2 كانت له خصوصية بنسبة 100% وحساسية بنسبة 100% في تشخيص المرض.

الاستنتاج: ان فوسفوليباز2Aالمرتبط بالبروتين الدهني هو مؤشر حيوي ممتاز لتشخيص المرضى الذين يعانون من الذبحة الصدرية المستقرة والكسر القذفي الطبيعي للبطين الايسر.

الكلمات المفتاحية: مرض الشريان التاجي، تشخيص، الكسر القذفي للبطين الايسر، فوسفوليباز2Aالمرتبط بالبروتين الدهني، الذبحة الصدرية المستقرة.

Introduction:

Stable angina is a prevalent heart disease which can be defined as a symptom or a clinical syndrome of stable coronary artery disease (CAD) that refers to the presence of myocardial ischemia characterized by chest pain on exertion or emotional stress which may radiate to the neck, jaw, back and the upper shoulders, and can be described as crushing with squeezing pressure on the chest and may eventually be relieved by rest or nitroglycerine (1–3). Stable angina occurs because of myocardial need and oxygen supply imbalance. It may occur as a result of multiple factors that lead to the stenosis or obstruction of the coronary arteries like: atherosclerotic plaque, coronary microvascular dysfunction and coronary vasospasm. During stress or exertion, stable angina occurs due to myocardial ischemia as a result of insufficient blood supply to the heart muscle (4). CAD is considered the most prevalent leading cause of myocardial ischemia and mortality worldwide (5). It is usually caused either by vasospasm in the coronary arteries or by the presence of atherosclerotic plaques or blood clot within these arteries that may lead to coronary stenosis or occlusion which in turn limits the blood supply to a specific region of the myocardium leading to ischemia (6,7). The major pathophysiological cause of CAD and ischemic heart disease is atherosclerosis which progresses from endothelial dysfunction, inflammation, intimal plaque formation, plaque erosion and rupture leading to superimposed atherothrombosis and eventually coronary occlusion that restrict the blood flow to a specific area of the heart leading to ischemia (8). The physical examination of the patients and their history regarding the severity, type and duration of the pain represent the first step in the diagnosis of stable angina. The medical history of the patient, assessing the blood pressure, measuring the body weight, cigarette smoking, alcohol consumption and exercise tolerability are very important points

in the diagnosis. There are multiple techniques that can be used in the assessment of the patients such as Pre-Test Probability (PTP) (9), Coronary Computed Tomography Angiography (CCTA), stress echocardiography, stress electrocardiogram (ECG) and Invasive coronary angiography (ICA) which is the gold standard (10). From the new biomarkers that may be of value in the diagnosis is Lipoprotein Associated Phospholipase A2, which is an enzyme that is also referred to as PAF-AH (platelet-activating factor acetylhydrolase) due to its PAF hydrolytic activity in plasma. It is considered a member of PLA2 superfamily group VII and it is produced by macrophages and released into circulation where it circulates by combining with HDL and LDL. Due to its lysophosphatidylcholine part, it shows pro-inflammatory activity (11). Accordingly, it plays a crucial role in CAD, MI and ischemic stroke (12). Lp-PLA2 is an important biomarker of atherosclerosis and atherogenesis progression through its pro-inflammatory effect and chemotactic activity for inflammatory mediators like adhesion molecules and cytokines, by its lysophophatidylcholine (lysoPC) and oxidized non-esterified fatty acids (OxNEFA) products respectively, leading to instability and expansion of the atherosclerotic plaque (13). On the other hand, Lp-PLA2 also shows anti-inflammatory and protective effects against atheroma development and progression through its PAF hydrolytic activity (14).

Patients and methods:

This case-control study was ethically approved by the local ethical committee of the College of Pharmacy/Mustansiriyah University. It was performed on 90 participants who were presented to the outpatient clinic as having chest pain. All participants were asked to fill signed informed consents. Sample collection was done from the Iraqi center for heart diseases at Al-Shaheed Ghazi Al-Hareery/ Medical City teaching hospital. Fasting venous blood samples were taken from all participants. The subjects were examined by echocardiogram to detect any regional wall motion abnormality and by coronary angiography by the cardiologist to look for coronary arteries that causing ischemia. The severity of ischemia and the degree of coronary arteries occlusion was assessed based on American Heart Association (15), as well as the number of the diseased vessels: single vessel, two vessels or three vessels. So depending on the results of the angiography, those subjects were classified into two study groups: angina (atherosclerosis) patients (n=60) and control (n=30). The subjects who showed no evidence of CAD and ischemia on coronary angiography were enrolled in the control group.

Patient selection:

Inclusion criteria:

The patients who enrolled in the study included: Male and female patients who were presented with chest pain, age of 40-76 years old, LVEF > 57%, no or controlled hypertension and diabetes mellitus.

Exclusion criteria:

Patients with acute MI, renal failure or chronic kidney disease, valvular heart disease, congenital heart disease, stroke, chronic heart failure, atrial fibrillation, malignancy and immune diseases.

Methods:

Patient's questionnaire:

Patients' information was collected regarding demographic data (age, gender, weight, height, BMI, region), medical history, medication history, family history and smoking status.

Sample collection: Before the coronary angiography session had been performed, about 6 ml of fasting venous blood samples were collected from each participant. Then, the obtained blood samples were centrifuged at 3000 rpm for 10 minutes to isolate serum, which was divided into 84ppendorf tubes and stored at – 40 c⁰ till the time of the assessment.

Echocardiography and electrocardiography: All patients were subjected to echocardiography and ECG with LV ejection fraction was calculated using the biplane M mode method (it is the most widely used method and it is an operator-dependent and performed by a sub-specialty doctor by taking the ratio between end diastolic dimension to end systolic dimension, results of > 57 were considered as normal,).

Coronary angiography: The X-ray conventional coronary angiography was performed for all participants by the cardiologist himself and his team at the Iraqi center for heart diseases by inserting a catheter with a contrast dye into the femoral or radial artery from both left and right side to take different views for proper assessment of the coronary arteries. The procedure was done under local anesthesia. The number of the diseased vessels and the Degree of stenosis were determined. The participants were asked to be fasting for at least 8 hours before the procedure. The antiplatelet medications, aspirin 300 mg and clopidogrel 600 mg tablets were given as loading doses prior the procedure, while, the unfractionated heparin as an anticoagulant was injected during the procedure.

Assay procedures:
The serum levels of Lp-PLA2 were measured using Human Lp-PLA2 Sandwich ELISA Kit / USA with ELISA reader following the instructions supplied. On the other hand, serum levels of total cholesterol, triglycerides and HDL-C were measured using Cholesterol SL, Triglycerides SL and HDL cholesterol kits, respectively, using Selectra Pro M Automatic Biochemistry Analyzer following the instructions supplied. The serum levels of LDL-cholesterol and VLDL-cholesterol were calculated using the "Friedewald equation": [VLDL-C = TG/5], [LDL-C = Total cholesterol- HDL-C – (TG/5)].

The Statistical Analysis:

The effect of different factors on studied parameters was detected by using IBM SPSS Statistics 26 program. T-test and One-way ANOVA were used to significantly compare between means. GraphPad Prism 9 program was used to draw the figures in this study and Chi-square test was used to significantly compare between percentage (0.05 and 0.01 probability) (16,17).

Results:

Demographic distribution data and the clinical characteristics of the study groups: As illustrated in Table 1, no significant statistical difference was detected between the age distribution in both of the study groups where (P>0.05). Similarly, there was no significant statistical difference had been detected between both groups regarding the BMI (P>0.05). With respect to gender distribution, there was a high significant difference between the study groups (P≤0.01). Regarding the family history for having heart diseases and smoking status of both groups, no significant differences had been found between both groups (P>0.05). It was found that 52% of patients had dyslipidemia while 48% of them did not with a high significant difference between them (P≤0.01). Additionally, there was a high significant difference between the patients who had hypertension (65%) and those who did not have hypertension (35%) (P≤0.01).

There was no significant statistical difference found in LVEF between the patients and the control groups (P>0.05). In addition, the present study detected no significant difference between patients who were on statins (50%) and those who were not on statins (50%) (P>0.05). On the other hand, there was a high significant difference between patients who were on beta blockers (33%) and those who were not (67%) where (P≤0.01) as in Table 1.

Table 1. Demographic distribution and the clinical characteristics of the study groups:

Characteristics	Patients (n=60)	Control (n=30)	*P*- value
Age (years) Mean ± SD	59.35 ± 9.32	58.53 ± 9.40	0.6
BMI (kg/m^2) Mean ± SD	28.35 ± 4.11	28.67 ± 3.97	0.7
Gender			
Male n (%)	47 (78%)	12 (40%)	0.001**
Female n (%)	13 (22%)	18 (60%)	
Total	60 (100%)	30 (100%)	
Family history			0.8
yes	25 (42%)	12 (40%)	
No	35 (58%)	18 (60%)	
Total	60 (100%)	30 (100%)	
Smoking			0.5
Yes	9 (15%)	6 (20%)	
No	51 (85%)	24 (80%)	
Total	60 (100%)	30 (100%)	
Dyslipidemia			
Yes	31 (52%)	–	–
No	29 (48%)		
***P*-value**	0.001**		
Hypertension			
Yes	39 (65%)	–	–
No	21 (35%)		
***P*-value**	0.001**		
LVEF (%) Mean ± SD	63.42 ± 7.24	64.07 ± 6.51	0.6
Statins			
Yes	30 (50%)	–	–
No	30 (50%)		
***P*-value**	1 NS		
Beta blockers			
Yes	20 (33%)	–	–
No	40 (67%)		
***P*-value**	0.001**		

The data were expressed as Mean ± SD, One-way ANOVA and T-test was used to significantly compare between means, Chi-square test was used to significantly compare between percentages * Significant difference (P≤0.05), ** Highly Significant difference (P≤0.01), non-significant difference (P>0.05), BMI: Body Mass Index, n: number, % percentage, SD: standard deviation, LVEF: left ventricular ejection fraction.

Comparing serum levels of the studied biomarkers between the patients and the control groups:

The current study detected high significant increase in serum levels of Lp-PLA2 in the patients compared with the control group where ($P \leq 0.01$) as shown in Table 2 and Figure 1. Besides that, the study found that serum TG and VLDL-C levels were significantly higher in patients compared to that of the control with ($P \leq 0.05$) as in Table 2**.** On the other hand, there were no significant differences between the patients and the control groups in the serum levels of total cholesterol, HDL-C and LDL-C, where (P>0.05) as shown in Table 2.

Table 2. Comparison in the serum levels of lipoprotein-associated phospholipase A2, lipid profile, serum creatinine and blood urea between the patients and the control groups:

Biomarker (mg/dl)	Mean±SD		*P*-value
	Patients (n=60)	Control (n=30)	
Lp-PLA2 (ng/ml)	16.65 ± 2.47	7.36 ± 2.32	0.001**
Total cholesterol	148.73±48.06	143.96±32.27	0.6
TG (mg/dl)	185.50±100.88	143.46±76.73	0.04*
HDL-C (mg/dl)	36.70±13.15	40.47±11.18	0.1
LDL-C (mg/dl)	75.01±40.85	74.83±33.40	0.9
VLDL-C(mg/dl)	37.10±20.18	28.87±15.14	0.05*

The data were expressed as Mean ± SD, One-way ANOVA and T-test was used to significantly compare between means, * Significant difference ($P \leq 0.05$), ** Highly Significant difference ($P \leq 0.01$), non-significant difference ($P > 0.05$).

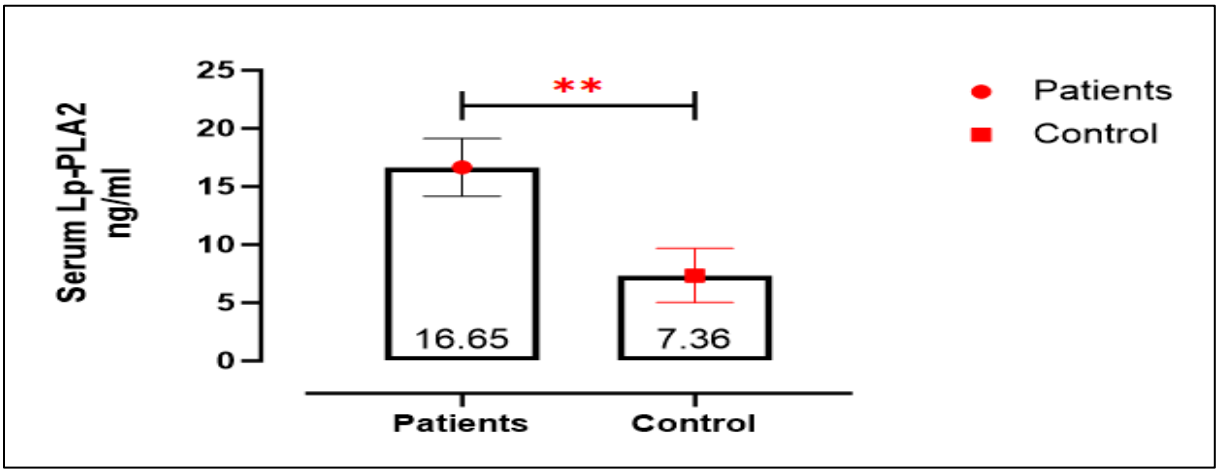

Figure 1. The difference in the serum level of Lp-PLA2 between the patients and the control groups.

The effect of the number of diseased coronary vessels on the serum levels of the studied biomarkers:

The current study detected no significant effect of the number of the diseased coronary arteries (single vessel disease, two-vessel disease and three-vessel disease) on the

serum levels Lp-PLA2, total cholesterol, HDL-C, triglycerides, LDL-C and VLDL-C, where (P>0.05) as in Table 3.

Table 3. The effect of the number of diseased coronary arteries on serum levels of the studied biomarkers:

Biomarker	Mean±SD			*P*-value
	Patients SVD (n=12)	Patients 2VD (n=23)	Patients 3VD (n=25)	
Lp-PLA2 (ng/ml)	17.32±3.31	16.17±2.13	16.77±2.32	0.4
T.Cholesterol (mg/dl)	155.08±49.16	144.00±52.35	150.04±44.89	0.8
HDL-C (mg/dl)	40.75±12.33	34.65±11.78	36.64±14.70	0.4
TG (mg/dl)	190.42±78.94	188.96±104.01	179.96±110.40	0.9
LDL-C (mg/dl)	76.51±44.70	71.63±48.76	77.40±31.46	0.8
VLDL-C (mg/dl)	38.09±15.82	37.80±20.79	35.98±22.08	0.9

The data were expressed as Mean ± SD; One-way ANOVA and T-test was used to significantly compare between means; * Significant difference (P≤0.05), ** Highly Significant difference (P≤0.01), non-significant difference (P>0.05); SVD: single vessel disease; 2VD: two-vessels disease; 3VD: three-vessels disease.

Receiver Operating Characteristic (ROC): By using Receiver Operating Characteristic (ROC) analysis, the current study also detected that the new biomarker (LP-PLA2) is an outstanding and excellent biomarker for the diagnosis of chronic angina patients where (AUC=1.00), the best cut off value was (11.88) with 100% sensitivity and 100% specificity as shown in Table 4 and Figure 2.

Table 4. Receiver Operating Characteristic curve data of Lipoprotein-associated phospholipase A2:

Biomarker	AUC	Explanation	*P*-value	The best cut off	Sensitivity %	Specificity %
Lp-PLA2	1.00	Excellent	0.001	11.88	100	100

AUC: area under curve.

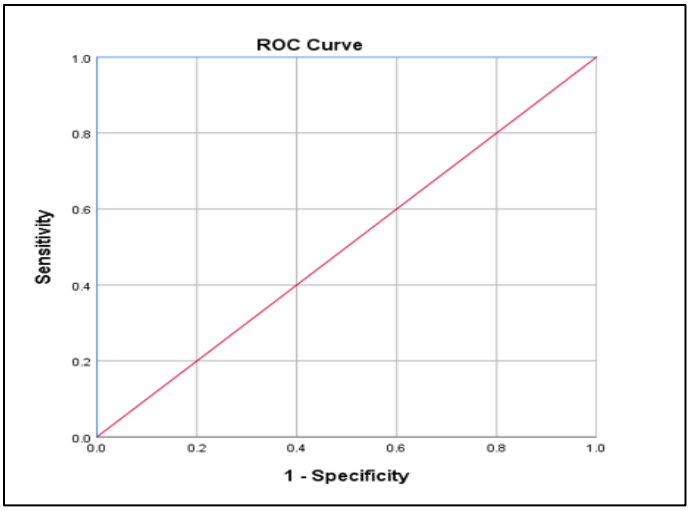

Figure 2. Receiver operating characteristic curve of Lp-PLA2.

Pearson's correlation analysis:

By using the Pearson's correlation coefficient analysis among the studied biomarkers, the current study detected a significant positive correlation between serum levels of Lp-PLA2 and triglycerides (r= 0.208) as illustrated in Table 5. Besides, Serum triglycerides had a high significant positive correlation with each of total cholesterol (r= 0.494) and VLDL-C (r= 1.000), respectively, and a significant negative correlation with LVEF (r= -0.229). In addition, Table 5 also showed a high significant positive correlation between serum total cholesterol and each of LDL-C (r= 0.863) and VLDL-C (r= 0.500), respectively. VLDL-C showed a significant negative correlation with LVEF (r= -0.227).

Table 5. Pearson's correlation coefficient analysis among the studied biomarkers:

		Lp-PLA2	TG	T.Cholesterol	LDL-C	VLDL-C	HDLC	LVEF%
Lp-PLA2	**R=**		0.208*	0.077	0.017	0.205	-0.130	-0.004
	P=		0.049	0.472	0.874	0.052	0.224	0.971
TG	**R=**			0.494**	0.099	1.000**	-0.124	-0.229*
	P=			0.000	0.353	0.000	0.245	0.030
T.Cholesterol	**R=**				0.863**	0.500**	0.062	-0.195
	P=				0.000	0.000	0.561	0.065

LDL-C	**R=**		0.107	-0.190	-0.088
	P=		0.316	0.072	0.407
VLDL-C	**R=**			-0.122	-0.227*
	P=			0.251	0.032
HDL-C	**R=**				-0.031
	P=				0.773
LVEF%	**R=**				
	P=				

**: Correlation is highly significant at the 0.01 level (2-tailed); *: Correlation is significant at the 0.05 level (2-tailed); R: Pearson's correlation coefficient.

Discussion:

Poor quality of life is usually accompanied stable angina pectoris due to the attacks of chest pain and discomfort upon exertion with the unfavorable outcomes like acute MI and heart failure whether it is caused by obstructive or non-obstructive CAD (18). Therefore, chronic angina needs a diagnosis which is sensitive, specific, accurate and non-invasive by using a new biomarker. There was no significant effect of the age on the incidence of stable angina and CAD had been detected in this study, as illustrated in Table 1. This result did not agree with the most common studies which demonstrated that the risk for having atherosclerosis, CAD and angina is usually increased with age which may be attributed to many factors regarding the change in the microvasculature and epicardial coronary arteries like loss of endothelial integrity, loss of vessels elasticity and other changes (19–21). Also, no significant statistical difference was detected in BMI between the patients and the control group, both groups were within overweight range which indicated that stable angina does not correlated with BMI , this is agreed with a study that also found no significant relation between BMI and the incidence of stable angina (22). According to the current study, males were more prone to have stable angina than females and this was in agreement with many studies (23). Regarding the smoking status and the family history and its role as risk factors for heart diseases including stable angina, the present study demonstrated no significant direct effect of smoking and family history on having CAD and stable angina, this result agreed with another study (24), while it did not agree with the most common studies which suggested that smoking is an important risk factor for having CAD, stable angina and other CVDs (25–27). Besides, the current study demonstrated that dyslipidemia and hypertension were important risk factors for having stable angina and CAD, this was agreed with the most studies which also clarified that fact (24,28–31). In this study, it was found that serum levels of Lp-PLA2 were high significantly increased in those patients compared to the control as illustrated in Table 2. The current study also detected no significant change in the serum levels of LDL-C between the patients and the control. There were studies which suggested that 80% of Lp-PLA2 is carried through the circulation via LDL-C and about 20% is carried by HDL-

C (32), however this does not necessarily mean that LDL-C should be in high level to carry Lp-PLA2 since the binding of Lp-PLA 2 on LDL is between the N terminus of Lp-PLA2 and the C terminus of apolipoprotein B (ApoB) which represents the major protein in LDL and since ApoB is also the primary protein in Chylomicrons, VLDL, intermediate density lipoprotein (IDL) and lipoprotein a (33), besides, there was a study which stated that elevations in serum Lp-PLA2 were independent on serum LDL levels in CAD patients (34) and Lp-PLA2 could be transferred in the circulation by binding to ApoB-containing lipoproteins like VLDL (35) which in the current study showed significantly higher levels in patients than in control group. There was a study which suggested that Lp-PLA2 could be used together with ischaemia-modified albumin (IMA) as predictors for myocardial ischemia in CAD patients who were presented with acute MI, stable and unstable angina, as Lp-PLA2 alone did not have sufficient sensitivity and specificity for the diagnosis (36). Another study also suggested that Lp-PLA2 could be of value in predicting severity of CAD but not in the diagnosis of stable angina (37). By studying the role of Lp-PLA2 in distinguishing between the degrees of CAD severity in the stable angina patients, the current study detected no significant difference in the serum level of Lp-PLA2 among those patients with single-vessel, two-vessel and three-vessel disease so, it cannot be used to assess CAD severity, this is not agreed with another study which stated that Lp-PLA2 could be used as a predictor for CAD severity (37). CAD risk and severity can be estimated using Framingham risk score (FRS) (38). A positive correlation was detected for Lp-PLA2 with triglycerides, this was in an agreement with other study which also found a positive correlation of Lp-PLA2 with triglycerides (39). This study was the first of its kind to determine the diagnostic value of Lp-PLA2, for patients who were presented with stable ischemic chest pain and normal LV ejection fraction without chronic heart failure with ≥ 70% stenosis in the coronary vessels with 100% specificity and 100% sensitivity using ROC curve analysis, as shown in Table 4 and Figure 2.

Conclusion:

It was concluded that Lp-PLA2 serum level can be used as a biomarker for the diagnosis of stable angina pectoris with obstructive CAD and normal left ventricular ejection fraction. However, Lp-PLA2 cannot be used to assess the severity of CAD in chronic stable angina patients.

Study limitation:

The current study failed to find any relationship between the serum level of Lp-PLA2 and the number of the occluded coronary arteries.

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