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Evaluating 13-HODE and 15-LOX as novel lipid-derived biomarkers in acute coronary syndrome: Insights from Iraqi patients

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ABSTRACT

Background and objective: 13-HODE, a bioactive lipid derivative of linoleic acid, has emerged as a significant mediator in acute coronary syndrome (ACS), influencing inflammation and vascular function. Arachidonate 15-lipoxygenase (15-LOX) plays a crucial role in ACS by modulating inflammatory processes and influencing lipid metabolism within cardiovascular tissues. This study aims to assess the concentrations of 13-HODE and 15-LOX and their potential role as predictive biomarkers in ACS patients.

Methods and materials: The study enrolled 90 ACS patients and 90 controls aged 30–70. Blood samples were analyzed for biomarkers (troponin [Tp], creatine kinase MB [CK-MB], high-sensitivity C-reactive protein [hs-CRP], lipid profile, 13-HODE, and 15-LOX) via ELISA and Ichroma device in addition to measurement of HbA1c%. Data were statistically analyzed using SPSS, ANOVA, and ROC tests and correlation coefficient.

Results: This study examined 13-HODE and 15-LOX levels in 90 ACS patients and 90 controls, finding significantly higher levels in ACS patients ($p < 0.0001$ and $p = 0.015$, respectively). 13-HODE demonstrated strong diagnostic potential (area under the curve [AUC] 0.735, sensitivity 70%, specificity 71.9%), while 15-LOX showed a moderate value (AUC 0.622). CK-MB, hs-CRP, and Tp exhibited superior diagnostic accuracy (e.g., CK-MB AUC 0.963). 13-HODE correlated negatively with HbA1c, and 15-LOX linked negatively with LDL and cholesterol, highlighting their roles in lipid metabolism and atherosclerosis, and supporting their utility as complementary ACS biomarkers.

Conclusions: The study found that 13-HODE and 15-LOX differ significantly between ACS patients and controls, with 13-HODE showing stronger diagnostic potential. CK-MB, hs-CRP, and Tp exhibited high diagnostic utility, while 15-LOX correlates with lipid oxidation and atherosclerosis.

Keywords: acute coronary syndrome, 13-hydroxyoctadecadienoic acid, 15-lipoxygenase, inflammation biomarker, lipid peroxidation

INTRODUCTION

Acute coronary syndrome (ACS) includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). It results from atherosclerotic plaque rupture (PR), thrombosis, and coronary blood flow obstruction, posing a major global health risk, especially for individuals over 35 [1]. Clinical presentation, electrocardiogram (ECG) abnormalities, and cardiac biomarkers like troponins (Tp) are the main criteria used to diagnose ACS. Tp levels help confirm myocardial necrosis, while ECG is essential for differentiating between STEMI and NSTEMI [2].

13-hydroxy octadecadienoic acid (13-HODE) is a significant metabolite derived from linoleic acid, primarily produced through the action of the enzyme 15-lipoxygenase-1 (ALOX15) and cyclooxygenases (COX-1 and COX-2) [3]. 13-HODE plays a crucial role in the regulation of inflammatory processes, which are particularly relevant in the context of ACS and myocardial infarction (MI) [4]. 13-HODE is synthesized through the lipoxygenase pathway, which is essential for generating several eicosanoids that influence cardiovascular health [5]. This compound stimulates prostacyclin production in endothelial cells, which is crucial for maintaining vascular health and preventing thrombosis. Prostacyclin acts as a vasodilator and inhibits platelet aggregation, thereby counteracting thrombus formation, which is a critical factor in the development of ACS [6]. Moreover, 13-HODE plays a role in modulating inflammatory responses, which are pivotal in the pathophysiology of ACS. It alters cell adhesion molecules and influences transcription factors involved in inflammation, thereby impacting metabolic processes associated with atherogenesis and cancer [4].

15-lipoxygenase (15-LOX) is involved in inflammation and atherogenesis, which contributes to the pathophysiology of ACS. High-density lipoprotein (HDL), and more especially HDL (3), is altered by this enzyme, which is essential for its anti-inflammatory qualities. The inflammatory response linked to atherosclerosis depends on the inhibition of adhesion

molecule production and monocyte recruitment, both of which are rendered ineffective by HDL (3) when it is altered by 15-LOX [7]. The pro-inflammatory effects of 15-LOX contribute to the oxidation of low-density lipoprotein (LDL) and the recruitment of monocytes to the vessel wall, exacerbating coronary artery disease (CAD) [8]. Furthermore, the enzyme's activity is linked to the formation of atherosclerotic plaques, which can rupture and lead to acute coronary events [9]. This study aims to investigate the roles of 13-HODE and 15-LOX in the pathogenesis of ACS, with a focus on their involvement in inflammation, endothelial function, and atherogenesis.

METHODS AND MATERIALS

Study Design

Ninety patients with ACS were enrolled in this study, in addition to 90 samples as controls, their ages ranged from 30 to 70 years. The study period of study sample collection was from 23December 2023 to 13 June 2024. Patients presented with chest pain or typical symptoms suggestive of ischemic heart disease (IHD) presented to the coronary care unit (CCU) and emergency department (ED) in Al-Ramadi Teaching Hospital, Ramadi and Madinat al-Amamin al-Kadhimin Al-Tbbia Hospital, Baghdad.

Criteria

Inclusion

1. All the patients had no complaints of other chronic or systemic diseases. The patients were divided into two groups:
    a. MI patients were sixty patients classified clinically into STEMI (n = 30) and NSTEMI (n = 30), depending on the diagnosis of the cardiologist and confirmed by ECG and cardiac enzyme Tp level.
    b. UA patients were thirty patients presented to the ED with acute chest pain and ECG changes suggestive of ischemia (inverted T or Q wave), and then referred to CCU and thus, diagnosed as cases of UA.
2. Controls: The control group consists of 90 non-ischemic individuals, i.e., those without symptomatic CAD or any significant luminal narrowing on coronary angiography. All individuals in the control group adapted to the history questionnaire and confirmed by laboratory diagnostic of (Tp, creatine kinase MB [CK-MB], and hs-CRP).

Exclusion criteria

Patients aged less than 30 years and above 70 years with severe renal failure and renal dysfunction, known moderate or severe liver disease, diabetes mellitus, neurological disease, cancer, endocrine diseases, patients who take statins and NSAID, patients who had normal levels of cardiac biomarkers, patients with cardiac surgery and post-percutaneous coronary intervention (PCI) and pregnant women.

Specimen Collection and Procedures

Ten milliliters of venous blood samples were drawn from each patient that presented to CCU or ED after diagnosis with ACS. The same quantity of blood was drawn from the control group. The whole blood is divided into two parts:

1. Eight milliliters of blood samples were left for 20 minutes in the gel tube at room temperature. After coagulation, sera were separated by centrifugation in 2000 xg for 10 min. Sera were divided into small aliquots and put in a multi-eppendorf tube (1.5ml) for:
    a. Immediate measurements of cardiac troponin (cTnI) by (nipigon device "ECLIA"), CK-MB, hs-CRP by ichroma™ II device (uses a semiconductor diode laser as the excitation light source for illuminating the test cartridge membrane). In addition, lipid profile parameters are achieved by (smart-150 fully automatic chemistry analyzer) and the principle of this device is by colorimetric and turbidimetry methods.
    b. The rest was stored at -26 °C (super freeze) until assayed for (13-HODE and 15-LOX) assay were measured using enzyme-linked immune sorbent assay (ELISA) kits provided by (elyue) company with the lot number (FY-EH60050) for 13-HODE and by (SUNLONG) company with lot number (SL0012Hu) for 15-LOX.
2. Two milliliters of the fresh blood sample left in the EDTA tube for HbA1c measurement.

Data Analysis

Data were statistically analyzed by utilizing SPSS version 24, GraphPad prism9, and Microsoft Excel. A comparison of data between the two groups was performed by applying for an unpaired student's t-test. Analysis of variance (ANOVA) with post hoc Tukey test which was used for comparison of the means of more than two groups. P-value < 0.05 values were considered significant. The association between 2 categorical variables was assessed by the Chi-square test. Pearson correlation to find the association between 13-HODE and 15-LOX with the other parameters of study groups. Sensitivity, specificity, cut-off value, and predictive utility were explored with receiver operating characteristic (ROC) curve analysis. ROC analysis was carried out on the levels of 13-HODE, 15-LOX Tp, CK-MB, and hs-CRP, HbA1c% for ACS and other study groups.

RESULTS

The general characteristics of all study groups (UA, STEMI, NSTEMI, and control) are presented in **Table 1**, including sex, age, and body mass index (BMI) distribution. The UA group comprised 17 males and 13 females, whereas the NSTEMI group included 23 males and 7 females. The STEMI group included 21 males and 9 females, bringing the total number of males and females across patient groups to 61 and 29, respectively. The control group included 60 males and 30 females. The study targeted individuals aged 30-70 years. The mean (M) ± standard deviation (SD) age for the UA group was 49.8 ± 2.33 years, with a skewness of 0.060 and a non-significant p-value (0.284) compared to the control group, which had an M ± SD of 52.3 ± 0.95 years. The NSTEMI group had an M ± SD of 54.8 ± 2.13 years, skewness of -0.485, and a highly significant p-value (< 0.01). The STEMI group had an M ± SD of 59.8 ± 1.58 years, a skewness of -0.673, and a highly significant p-value (< 0.01). The overall patient group had an M ± SD of 54.8 ± 1.24 years, a skewness of -0.476, and a non-significant p-value (> 0.01) compared to controls. In terms of BMI, the ACS group had

Table 1. Distribution of sex, M ± SD, and differences for age and BMI in the sample study

Variables	Controls (n = 90)	Total patients (n = 90)	UA (n = 30)	NSTEMI (n = 30)	STEMI (n = 30)
Sex					
Male: N (%)	60 (66.7)	61 (67.8)	17 (56.7)	23 (76.7)	21 (70.0)
Female: N (%)	30 (33.4)	29 (32.3)	13 (43.3)	7 (23.4)	9 (30.0)
Total: N (%)	90 (100)	90 (100)	30 (100)	30 (100)	30 (100)
Chi-square	-	0.102	0.679	0.037	0.286
p-value	-	0.750	0.410	0.847	0.593
Age (years)					
M ± SD	52.3 ± 0.95	54.8 ± 1.24[aa]	49.8 ± 2.33[aa]	54.8 ± 2.13[ad]	59.8 ± 1.58[ae]
Minimum	35	30	30	30	38
Maximum	70	70	70	70	70
Skewness value	0.996	-0.476	0.060	-0.485	-0.673
p-value	-	0.213	0.313	0.008**	0.0001**
BMI (kg/m^2)					
M ± SD	27.2 ± 0.33	28.09 ± 0.44[aa]	27.5 ± 0.77[aa]	28.7 ± 0.71[aa]	27.9 ± 0.83[aa]
Minimum	18.1	17.3	17.3	22.2	20.0
Maximum	35.2	37.8	34.7	37.8	36.4
p-value	-	0.122	0.973	0.190	0.793

Note. Data were expressed as M ± SD; Statistical analyses were performed by ANOVA followed by a post-hoc test (Tukey's test) for multiple comparisons; ‡ ANOVA significance test (2-tailed); Significant values are bolded; [aa]No significant differences; [a]Control; [b]ACS patients; [c]UA; [d]NSTEMI; & [e]STEMI

an M ± SD of 28.09±0.44, while the control group had 27.2 ± 0.33, with no significant difference (p > 0.05). The UA, NSTEMI, and STEMI groups had M ± SD BMI values of 27.2 ± 0.33, 28.7 ± 0.71, and 27.9 ± 0.83, respectively, with no significant differences between groups or in comparison to the control group. All study groups were classified as overweight.

ANOVA and paired t-tests were used to analyze the differences between the study groups. **Table 2** presents the results for patients with UA, NSTEMI, and STEMI compared to the control group. Tp is a key biomarker for MI. The M ± SD Tp level for patients was 6.05 ± 1.48, which was significantly higher than that of the control group (0.007 ± 0.0007, p = 0.0001). The UA group had an M ± SD 0.01 ± 0.001, which was similar to that of the control (p > 0.05), as UA typically does not cause significant myocardial damage. The M ± SD Tp levels were 9.59 ± 3.67 in the NSTEMI group and 8.55 ± 2.21 in the STEMI group, both significantly elevated (p = 0.0001). CK-MB, a heart-specific enzyme, was significantly elevated in ACS patients' M ± SD (22.03 ± 3.67) vs. controls (1.04 ± 0.051) and the p-value was 0.0001. The UA group M ± SD was 3.17 ± 0.66, with no significant difference from controls, unlike NSTEMI (24.19 ± 6.16) and STEMI (38.75 ± 8.01), which showed significant elevations (p < 0.05). The interpretation of the study results because CK-MB is high in NSTEMI/STEMI due to heart muscle necrosis but low in UA since ischemia doesn't cause cell death. CK-MB remains normal in most UA cases as it is less sensitive than Tp to minimal injury and is only released with actual muscle damage [10].

hs-CRP is an indicator of acute-phase inflammation. The study found significantly higher hs-CRP levels in ACS patients (M ± SD 7.38 ± 0.56) compared to the control group (M ± SD 0.69 ± 0.035). Subgroup analysis showed M ± SD hs-CRP levels of 5.10 ± 0.87 in the UA group, 8.57 ± 0.98 in the NSTEMI group, and 8.47 ± 0.96 in the STEMI group, with significant differences compared to the control group (p < 0.05).

Glycated hemoglobin (HbA1c%) was measured to assess glycemic control and exclude diabetes. The ACS group had M ± SD 5.5 ± 0.063 vs. 4.77 ± 0.037 in controls with highly significant differences (p = 0.0001). UA M ± SD was 4.96 ± 0.080 showing no significant difference, while NSTEMI M ± SD was 5.89 ± 0.077 and STEMI M ± SD was 5.81 ± 0.082 was significantly higher (p = 0.0001). The overall between-group p-value was 0.0001.

Lipid accumulation in blood vessels is a major risk factor for UA and MI. Cholesterol levels were higher in patients than controls, with an M ± SD of 184.5 ± 5.27 for patients and 171 ± 3.58 for controls (p = 0.041). For UA, the M ± SD was 177.4 ± 8.82, for NSTEMI it was 190.5 ± 8.69, and for STEMI M ± SD was 185.6 ± 9.98, showing no significant differences with controls. Triglyceride (Tg) levels showed no significant differences between groups (p = 0.723), with ACS patients having an M ± SD of 148.2 ± 9.73 and controls 151.9 ± 4.43. The M ± SD Tg levels were 130 ± 13.55 in the UA group, 170.7 ± 19.45 in the NSTEMI group, and 143.8 ± 16.75 in the STEMI group, with no significant differences (p > 0.05). HDL M ± SD was lower in patients 51.84 ± 1.67 compared to controls 57.63 ± 1.35, with a p-value of 0.041. The M ± SD for UA was 58.1 ± 2.93, for NSTEMI 47.06 ± 2.59 with high differences (p = 0.003), and M ± SD for STEMI was 50.3 ± 2.87, with no significant differences compared to controls. LDL M ± SD levels were higher in patients 99.8 ± 3.60 compared to controls 83.1 ± 3.08 with significant differences (p = 0.001). The M ± SD for UA was 91.43 ± 5.42 with non-differences compared to the control (p = 0.598), while the M ± SD for NSTEMI was 101.76 ± 6.10 and p-value was 0.029 and M ± SD for STEMI was 106.36 ± 6.97 and p-value was 0.003. The M ± SD concentration of VLDL for ACS patients was 30.63 ± 2.05, similar to controls (30.28 ± 0.88, p = 0.871). In subgroups, UA had M ± SD 29.33 ± 3.89, NSTEMI 34.13 ± 3.69, and STEMI 28.44 ± 3.06. No significant differences were found between groups (p = 0.472), with all p-values > 0.05 when compared to controls.

The concentration of 15-LOX differed significantly between patients with M ± SD 357.4 ± 4.71 and controls 338.5 ± 5.93 and p was 0.015. But no significant differences were observed among UA (351.82 ± 8.7), NSTEMI (360 ± 7.3), and STEMI (360.5 ± 8.5) groups, with p > 0.05. M ± SD concentration of 13-HODE was significantly higher in patients (166.4 ± 7.48) compared to control (112.9 ± 6.25, p = 0.0001). UA patients had M ± SD 175.02 ± 12.98 with high differences compared to control. NSTEMI patients had an M ± SD of 166.54 ± 12.87 (p = 0.001), while STEMI patients had an M ± SD of 157.63 ± 13.26, showing significant differences compared to controls (p = 0.008).

Table 2. Comparison of Tp, CK-MB, hs-CRP, and PPAR-alpha parameters among the studied groups

Parameters	C (n = 90)	Patients (n = 90)	UA (n = 30)	NSTEMI (n = 30)	STEMI (n = 30)	p-value
Tp (ng/ml): M ± SD	0.007 ± 0.0007[a]	6.05 ± 1.48[ab]	0.01 ± 0.001[ac, cd, ce]	9.59 ± 3.67[ad]	8.55 ± 2.21[ae]	0.0001
Minimum-maximum	0.001-0.020	0.01-100.00	0.001-0.02	0.032-100	0.083-45.200	
p-value	-	0.0001**	1.0	0.0001**	0.0001**	
CK-MB (ng/ml): M ± SD	1.04 ± 0.051[a]	22.03 ± 3.67[ab]	3.17 ± 0.66[ac, cd, ce]	24.19 ± 6.16[ad]	38.75 ± 8.01[ae]	0.0001
Minimum-maximum	0.43-2.43	1.02-122.60	1.02-21.14	1.43-122.10	1.28-122.60	
p-value	-	0.0001**	0.970	0.0001**	0.0001**	
hs-CRP (mg/L): M ± SD	0.69 ± 0.035	7.38 ± 0.56[ab]	5.10 ± 0.87[ac, cd, ce]	8.57 ± 0.98[ad]	8.47 ± 0.96[ae]	0.0001
Minimum-maximum	0.12-2.04	0.08-15.59	0.08-14.65	0.43-15.59	1.02-15.40	
p-value	-	0.0001**	0.0001**	0.0001**	0.0001**	
HbA1c %: M ± SD	4.77 ± 0.037	5.5 ± 0.063[ab]	4.96 ± 0.080[aa, cd, ce]	5.89 ± 0.077[ad]	5.81 ± 0.082[ae]	0.0001
Minimum-maximum	4.20-5.40	4.20-6.70	4.2-5.8	4.9-6.5	4.8-6.7	
p-value	-	0.0001***	0.130	0.0001**	0.0001**	
Cholesterol (mg/dl): M ± SD	171 ± 3.58	184.5 ± 5.27[ab]	177.4 ± 8.82[aa]	190.5 ± 8.69[aa]	185.6 ± 9.98[aa]	0.1200
Minimum-maximum	118-237	81-302	81-282	110-302	109-298	
p-value	-	0.041*	0.892	0.138	0.372	
Tg (mg/dl): M ± SD	151.9 ± 4.43	148.2 ± 9.73[aa]	130 ± 13.55[aa]	170.7 ± 19.45[aa]	143.8 ± 16.75[aa]	0.1610
Minimum-maximum	97-299	48-463	53-406	52-433	48-463	
p-value	-	0.723	0.462	0.594	0.948	
HDL (mg/dl): M ± SD	57.63 ± 1.35	51.84 ± 1.67[ab]	58.1 ± 2.93[aa, cd]	47.06 ± 2.59[ad]	50.3 ± 2.87[aa]	0.0010
Minimum-maximum	30-90	13-87	19-87	13-73	25-87	
p-value	-	0.004**	0.998	0.003	0.072	
LDL (mg/dl): M ± SD	83.1 ± 3.08	99.8 ± 3.60[ab]	91.43 ± 5.42[aa]	101.76 ± 6.10[ad]	106.36 ± 6.97[ae]	0.0010
Minimum-maximum	42.8-147.0	19-192	37-153	19-181	56.0-192.4	
p-value	-	0.001**	0.598	0.029*	0.003*	
VLDL (mg/dl): M ± SD	30.28 ± 0.88	30.63 ± 2.05[aa]	29.33 ± 3.89[aa]	34.13 ± 3.69[aa]	28.44 ± 3.06[aa]	0.4720
Minimum-maximum	19-60	10-112	11-112	10-86	10-93	
p-value	-	0.871	0.990	0.617	0.937	
13-HODE (pg/ml): M ± SD	112.9 ± 6.25	166.4 ± 7.48[ab]	175.02 ± 12.98[ac]	166.54 ± 12.87[ad]	157.63 ± 13.26[ae]	0.0001
Minimum-maximum	50.2-257.9	41.2-261.5	41.2-251.3	55.3-261.5	79.2-243.4	
p-value	-	0.0001***	0.0001**	0.001**	0.008*	
15-LOX (pg/ml): M ± SD	338.5 ± 5.93	357.4 ± 4.71[ab]	351.82 ± 8.7[aa]	360 ± 7.3[aa]	360.5 ± 8.5[aa]	0.0850
Minimum-maximum	237.2-542.0	218.6-469.9	246.0-437.5	218.6-427.5	273.6-469.9	
p-value	-	0.015*	0.606	0.193	0.177	

Note. Data were expressed as M ± SD; Statistical analyses were performed by ANOVA followed by a post-hoc test (Tukey's test) for multiple comparisons; ‡ ANOVA significance test (2-tailed); Significant values are bolded; [aa]No significant differences; [a]Control; [b]ACS patients; [c]UA; [d]NSTEMI; & [e]STEMI

Table 3. Correlation coefficient for 13-HODE and 15-LOX with study parameters among patient groups

Variables	13-HODE		15-LOX	
	r	p-value	r	p-value
BMI	0.065	0.273	0.045	0.336
HbA1c %	**-0.187***	**0.039**	**0.177***	**0.05**
Tp	-0.078	0.233	0.077	0.236
CK-MB	0.044	0.340	**0.187***	**0.038**
hs-CRP	0.062	0.279	0.018	0.431
Cholesterol	-0.074	0.244	**-0.229***	**0.015**
Tg	0.148	0.085	0.006	0.476
HDL	-0.072	0.249	-0.034	0.376
LDL	-0.134	0.104	**-0.211***	**0.023**
VLDL	0.104	0.165	0.020	0.426
13-HODE	1.000	-	0.039	0.358

The Pearson correlation coefficient (often denoted as r) was used to assess the linear relationship between the study variables. The results are presented in **Table 3**.

The results of the current study showed a significant negative correlation between 13-HODE concentration and HbA1c%, with a correlation coefficient of -0.187 and a p-value of 0.039. This indicates that as 13-HODE concentration increases, the level of glycated. Additionally, 15-LOX concentration was correlated with several study variables. The concentration of 15-LOX showed a positive correlation with HbA1c percent and CK-MB with coefficient values 0.177 and 0.187, and p-value 0.05 and 0.038, respectively. It also showed a negative correlation with cholesterol concentration and LDL with coefficient values -0.299, -0.211, and p-value 0.015 and 0.023, respectively.

Table 4. Sensitivity and specificity of Tp, CK-MB, hs-CRP, 15-LOX, 13-HODE, and PPAR-alpha in sera of patients compared with controls

Parameter	AUC	Specificity	Sensitivity	Cut-off value	Sig.
Tp	0.888	100%	67.8%	0.0235	0.0001
CK-MB	0.963	92.1%	90.0%	1.6950	0.0001
hs-CRP	0.928	95.5%	92.2%	1.0150	0.0001
13-HODE	0.735	71.9%	70.0%	107.0500	0.0001
15-LOX	0.622	50.6%	72.2%	336.9500	0.0050

The accuracy, specificity, and sensitivity of the primary study parameters were determined using the ROC analysis and area under the curve (AUC) test. The results are presented in **Table 4**.

The results of the ROC test for ACS patients showed that the most predictive parameter was CK-MB, with a predictive cut-off value of 1.695 ng/ml, an AUC of 0.963, a specificity of 92.1%, and a sensitivity of 90%, hs-CRP coming after CK-MB and a predictive cut off value 1.015 mg/L, AUC 0.928, specificity 95.6%, sensitivity 92.2%. Tp had a predictive cut-off value of 0.0235 ng/ml, an AUC of 0.888, a specificity of 100%, and a sensitivity of 67.8%. Acceptable predictive parameters in the

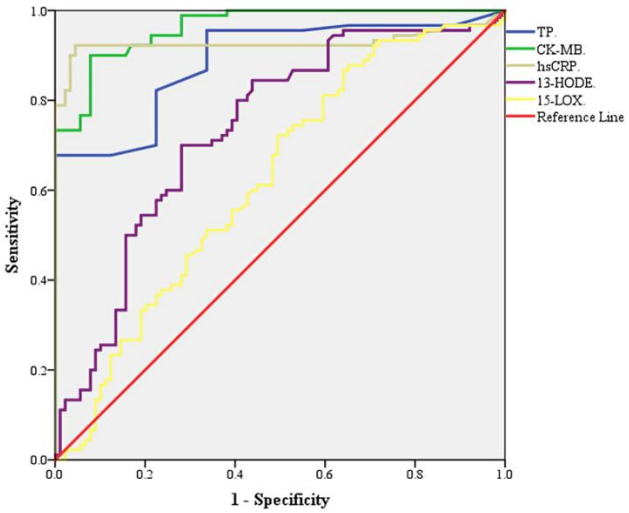

Figure 1. ROC representing discrimination of patients from control groups for the Tp, CK-MB, hs-CRP, 13-HODE, and 15-LOX (Source: Authors' own elaboration)

study were 13-HODE having a predictive cut-off value 107.05 pg/ml, AUC 0.735, specificity 71.9%, and sensitivity 70%. At last, acceptable predictive parameters in the study 15-LOX with AUC 0.622 with specificity 50.6% and sensitivity 72.2% and cut off value was 336.95 for 15-LOX.

DISCUSSION

PR is the most common cause of ACS across all sexes and ages. However, plaque erosion (PE) shows a distinct pattern, being more prevalent in younger males, while older females exhibit higher PE incidence. Calcified nodules are less common but increase with age, particularly in those over 80 years old [11]. Women with ACS have a higher adjusted risk for cardiovascular death and heart failure hospitalization post-PCI compared to men. This aligns with historical data showing higher short-term mortality but better long-term survival for women [12]. Age significantly impacts the clinical presentation, treatment, and outcomes of patients with ACS. Elderly patients are typically defined as those aged 75 years and older [13]. Younger patients, particularly those under 55, are more likely to have modifiable risk factors like smoking and dyslipidemia, whereas older patients are often present with multi-vessel CAD [14].

The relationship between the BMI and the risk of developing ACS in patients with pre-existing cardiovascular disease is complex and multifaceted. Research indicates that both low and high BMI can influence cardiovascular outcomes, with varying implications for patients with CAD or ACS. The "obesity paradox" suggests that higher BMI may sometimes be associated with better outcomes in these patients, although this is not universally accepted [15]. A study found no significant difference in in-hospital mortality between obese and normal-weight patients undergoing PCI [16]. This study agrees with the current results study.

The study in [17] showed that cTnI, a decision limit of 3.1 µg/L is used for acute MI, while 0.2 µg/L is the threshold for minimal myocardial damage. While our current study showed a critical limit of diagnosis ACS for TP was 0.0235. A study showed that the critical cutoff value for cTnT in diagnosing ACS is 0.10 ng/mL, with a sensitivity of 90.9% and specificity of 87.9% [18]. Our results study showed that the cutoff value for TP was 0.0235 with a specificity 100% and sensitivity 67.8% and the previous study partially agreed with our study results. The results of Tp between study groups (UA, NSTEMI, and STEMI) showed a gradual increase in levels and this increase may be considered as a differential variable for ACS groups. These results come following other study results confirming the efficacy of hscTnT in the diagnosis of ACS [19, 20]. The use of cardiac-specific TpT helped estimate the amount and severity of the infarcted area, and it may be one of the parameters used to distinguish STEMI from NSTEMI [21].

The UA group's level of CK-MB isoenzyme (CK-MB) was higher than that of healthy individuals, which is consistent with earlier research. CK-MB levels can identify mild ischemia myocardial damage that might not be noticeable by clinical signs or ECG abnormalities. Due to its correlation with an increased risk of progression to MI or cardiac mortality, this diagnosis is critical [22]. Also, the results showed increasing in CK-MB levels for the NSTEMI and STEMI groups that agreement with the study result that conducted CK-MB levels are particularly useful in cases where Tp levels are elevated without ST-segment elevation, helping to identify myocardial necrosis in a broader patient population [23]. CK-MB levels, when compared to Tp levels, have shown slightly better discrimination in predicting mortality in both STEMI and NSTEMI patients, suggesting their utility in risk stratification and guiding treatment decisions [24]. A study results showed that serial CK-MB measurements in patients with chest pain and non-diagnostic ECGs have shown high sensitivity for detecting MI, with sensitivity increasing significantly over time from the onset of symptoms [25].

Studies demonstrated a positive correlation between hs-CRP levels and the severity of CAD. Higher hs-CRP levels are associated with a greater burden of CAD, indicating a more severe disease [26, 27]. These Studies correspond with current results study that showed increasing in concentration of hs-CRP for all ACS groups compared to healthy persons. In comparing STEMI and NSTEMI patients, STEMI patients tend to have higher peak hs-CRP levels, suggesting a more pronounced inflammatory response in this subgroup [28]. This study's results correspond with current findings according to the increase in CK-MB and hs-CRP concentrations in three groups of ACS (UA, NSTEMI, and STEMI). Tp levels, particularly when combined with CRP measurements, can stratify mortality risk in NSTEMI patients. High Tp levels, even in the presence of normal CRP levels, are associated with increased short-term mortality, highlighting the prognostic value of Tp in assessing patient outcomes [29]. The cutoff value of hs-CRP for the current study between Healthy persons and ACS patients was 1.015 mg/L indicating that the person changes from a normal state to an ACS state at this value. Sargowo's research highlighted the diagnostic value of hs-CRP, with a M concentration of 4.04 ± 1.94 mg/L in ACS cases, significantly higher than in controls. This study used ROC analysis to determine the cutoff, emphasizing hs-CRP's utility in diagnosing ACS [30].

ACS patients often exhibit elevated LDL cholesterol levels. For instance, one study reported M LDL levels of 122.64 ± 42.01 mg/dl in ACS patients, significantly higher than in controls [31]. Also, this study reported that the M of HDL levels of 34.78 mg/dL in ACS patients, was significantly lower than in controls. Another study found that patients with LDL levels greater than

208 mg/dL at admission had higher LDL and Tg levels, which were associated with increased mortality risk [32]. These two studies correspond with the current study that showed an increase in LDL-cholesterol levels. HDL levels are typically lower in ACS patients. A study highlighted that HDL cholesterol and apolipoprotein A1 levels were significantly lower in ACS patients compared to those with stable CAD [33]. High lipid content in the proximal external erosion zone of plaques is associated with increased plaque vulnerability and poor prognosis in STEMI patients [34]. During the acute phase of MI, there is a notable decrease in total cholesterol and LDL-C, while Tgs tend to increase. These changes are part of the body's inflammatory response to the infarction [35]. This study's results conflict with the current study that found increasing in levels of cholesterol and LDL and agrees with an increase in Tg levels. Tgs rise and HDL-C levels fall dramatically over time; these effects may last for weeks following the infarction. These alterations imply that to accurately estimate and manage risk, cholesterol levels should be measured as soon as possible following the infarction [36].

There are no studies evaluating the level of 13-HODE in people with ACS, but there are studies that prove the involvement of 13-HODE is associated with ACS. In the early stages of atherosclerosis, 13-HODE is produced enzymatically in macrophages by 15-lipoxygenase-1. It activates peroxisome proliferator-activated receptor (PPAR)-γ, which enhances the clearance of lipids and lipid-laden cells from the arterial wall, thus exerting a protective effect against atherosclerosis progression [37]. 13-HODE increases the expression of cholesterol transporters such as ABCA1, ABCG1, and SR-BI in macrophages, promoting cholesterol efflux and reducing cellular cholesterol levels. This process is mediated through the PPAR-LXRα-ABCA1/SR-BI pathway, which is crucial for maintaining lipid homeostasis and preventing foam cell formation, a key event in atherogenesis [38]. 13-HODE has been shown to inhibit the secretion of triacylglycerol-rich lipoproteins in CaCo-2 cells, suggesting a role in lipid metabolism [39]. 13-HODE is a major component of oxidized LDL (Ox-LDL) and is implicated in atherogenesis, with its presence detected in atherosclerotic plaques [40]. 13-HODE may be important in the pathogenesis of ACS because of its role in inflammation and endothelial function. The results of ACS may be indirectly impacted by 13-HODE's control of endothelial cell activity and lipid metabolism [41].

The levels of 15-lipoxygenase (15-LO) in ACS are not directly addressed in the papers provided. 15-LO is an enzyme involved in the metabolism of arachidonic acid to produce bioactive lipids, which play roles in inflammation and vascular biology. In IHD, a condition closely related to ACS, increased expression of 15-LO and its product 15-HETE has been observed in ischemic heart tissue, suggesting a potential role in thrombosis and vascular inflammation which may contribute to clot formation and thrombosis. Also, this study showed that the enzyme's expression is also noted in hypoxic conditions, which are common in IHD, further linking it to ACS-related processes [42]. ALOX15B, a 15-LO variation, is more prevalent in symptomatic plaques in carotid atherosclerotic lesions, indicating a connection to cerebrovascular episodes and possibly ACS [43]. A study showed that 15-LO is present in atherosclerotic lesions, particularly in macrophage-rich areas, and is associated with oxidative modification of LDL, a key event in atherogenesis [44].

Glycated hemoglobin levels have been shown to correlate with oxidative stress markers in type 2 diabetes mellitus. As HbA1c increases, markers of oxidative stress such as malondialdehyde also increase, while antioxidant levels decrease [45]. Oxidative stress like 13-HODE is a known factor in the pathogenesis of diabetic complications, and enzymes like 15-LOX are involved in the oxidative modification of lipids, which could suggest a potential indirect relationship with HbA1c levels.

15-LOX preferentially oxidizes LDL cholesterol esters, a process implicated in early atherogenesis. The enzyme is highly expressed in foamy macrophages within atherosclerotic lesions, suggesting its involvement in the progression of atherosclerosis by oxidizing LDL into an atherogenic form [46]. In macrophages, 15-LOX influences cholesterol homeostasis by modulating sterol regulatory element binding protein (SREBP)-2 signaling, which is crucial for cholesterol metabolism. Inhibition of 15-LOX reduces cholesterol and its intermediates, impacting immune functions such as CCL17 production [47]. The results of this study explain the negative correlation of the current study between 15-LOX and cholesterol levels. 15-LOX-mediated modification of HDL impairs their ability to mediate cholesterol efflux, reducing their atheroprotective effects. This is due to structural alterations in HDL particles that affect their interaction with cholesterol transporters [46]. Hypercholesterolemia induces systemic activation of 15-LOX, particularly in cardiovascular tissues, which is associated with increased lipoprotein oxidation and atherogenesis [49].

CONCLUSIONS

The study found that 13-HODE and 15-LOX concentrations differed significantly between ACS patients and healthy controls, indicating their roles in inflammation and atherosclerosis in the Iraqi population. While 15-LOX showed slight elevation, its diagnostic value was less robust than 13-HODE. CK-MB, hs-CRP, and Tp demonstrated strong diagnostic utility, while 13-HODE and 15-LOX had acceptable and moderate predictive value. 13-HODE negatively correlated with HbA1c suggesting an interplay between lipid metabolism and glucose regulation. While 15-LOX correlated with cholesterol and LDL, supporting their roles in lipid metabolism.

The study is limited to Iraqi patients, which may restrict the generalizability of findings to other ethnicities and populations. Also, the study needs more participants. Although efforts were made to exclude patients with diabetes, liver disease, and other chronic conditions, residual confounding variables could still influence the results. Although the effect of the concentration of the 15-LOX enzyme has been studied, the study of the enzyme's activity may be clearer and more influential on ACS. 13-HODE and 15-LOX have effects on other metabolic diseases such as diabetes and cancer, but in our study, we were unable to study these diseases due to the limitations of the study.

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Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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