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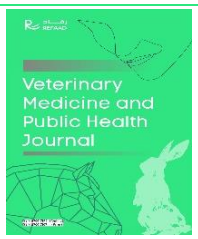

The Biomarkers Associated with Unstable Angina Pectoris (UAP)

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Abstract:

Objectives: Coronary artery disease (CAD) is the most common form of CVD that begins as stable angina pectoris (SAP) followed by unstable angina pectoris (UAP) and finally critical stage myocardial infarction (MI), which results from rupture of atherosclerotic plaque and a thrombus that blocks the coronary artery supplying the heart, resulted from the death of part of the heart muscle. The underlying cause of coronary artery disease (CAD) is atherosclerosis, which results from the formation of layers of fatty deposits on the inner walls of the arteries. Early diagnosis of MI has an important role in assisting clinicians in prompt planning for its treatment and thus reducing the number of its deaths.

Methods: The present study included 20 UAP patients and 20 healthy individuals (controls). In all the cases and controls, levels of cardiac and inflammatory biomarkers were measured by special kits from Hotgen Company via phosphorous technology using UPT-3A converting phosphor immunological analyzer.

Results: The levels of both cardiac and inflammatory biomarkers were significantly increased in UAP cases as compared to controls. Also, there was significant positive correlation between cardiac and inflammatory biomarkers in UAP cases.

Conclusions: The positive correlation between most cardiac and inflammatory biomarkers in UAP indicates that inflammation occurs in UAP. Hence it is concluded that inflammatory biomarkers (CRP, Hs-CRP and PCT) and cardiac biomarker (cTnI, H-FABP, CK-MB, NT-proBNP and D-dimer) can be markers of UAP and can be used for diagnostic purposes in patients.

Keywords: *UAP; CAD; myocardial infarction.*

1 Introduction

Cardiovascular disease is the leading cause of death worldwide. The number of cardiovascular deaths is higher than cancer deaths and more than any other cause of death (AHA, 2019). The deaths reach up to 17.9 million annually, which is equal to 31% of all deaths (Wierer *et al*., 2020). In Iraq, the mortality rate due to cardiovascular diseases is about 33% of all deaths (Turk-Adawi, *et al*., 2020). Myocardial infarction is a type of coronary heart disease (CHD), that results from rupture of an arterial sclerosis plaque and a thrombus that works to block the coronary artery, which supply the heart, causing necrosis and death of part of the heart muscle (Shi *et al*., 2016; Rathore *et al*., 2017). Internationally, it was reported that at least one American develops myocardial infarction approximately every 40 minutes (AHA, 2019). Unstable angina pectoris is an unexpected pain in the chest, and it is one of the important stages of coronary artery disease, which precedes the occurrence of a myocardial infarction. It usually occurs during rest or sleep, due to the decrease in sufficient blood flow to the heart muscle due to atherosclerosis (). In the past, it was based solely on the theory of lipids role in the etiology of atherosclerosis. Currently, inflammation has been stated to play an essential role in developing atherosclerosis. Monocytes, macrophages, lymphocytes and smooth muscle cells accumulates release many cytokines or inflammatory biomarkers (Beverly *et al*., 2020). The underlying cause of a heart attack (MI) is atherosclerotic, which is caused by the development of layers of fatty deposits on the inner walls of the arteries (Amirfakhryan *et al*., 2020). The development of these deposits leads to narrowing and gradual blockage of blood flow in the artery. It is a long-term disease that progresses slowly (Lacy *et al*., 2020).

Atherosclerosis is a chronic pathology of multiple modifiable risk factors (diabetes, hypertension, obesity, sedentary life, emotional stress, unhealthy food habit, smoking, and alcohol consumption) and non-modifiable factors (age, gender, race, and family history). It has been stated that chronic inflammation has a role in increasing the risk of cardiovascular disease, especially psoriatic arthritis and rheumatoid arthritis (Groh *et al*., 2020). Moreover, the statement of bacterial and viral infections participation in the process of atherosclerosis development, justifies mentioning that targeting infections with antibiotics can be promising as being a part of a protocol option to reduce atherosclerosis (Moriya *et al*., 2019; Ridker *et al*., 2020). Measuring biomarkers levels in the patient's serum is a method for decision-making and can predict the severity of atherosclerosis (Martinez *et al*., 2020).

Cardiac troponin I (cTnI) is an extremely sensitive biomarker in diagnosing and determining the severity of coronary heart disease, and highly specific in excluding the disease. It gives more predictive values than the stress ECG (Anwar *et al*., 2016; Aydin *et al*., 2019). Creatine kinase – Myocardial Band (CK-MB) is an enzyme found in the heart muscle, which is an important biomarker for the diagnosis of myocardial infarction. It is more specific than other heart enzymes and considered the golden standard for diagnosing myocardial infarction. (Lacy *et al*., 2016; Aydin *et al*., 2019; Mythili *et al*., 2015). D-dime is a promising and important vital indicator for identifying blood clots, which molecules result from the breakdown of fibrin in the blood vessels (Zhang *et al*., 2020). N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a diagnostic marker for detecting heart failure (Pan *et al*., 2020; Eriksson *et al*., 2019). C-reactive protein (CRP) is a biomarker secreted by the liver after being stimulated by cytokines in cases of infections, and can be used to assess the risk of cardiovascular disease; however, it has a low specificity (Zhu *et al*., 2018).

High sensitivity-CRP (Hs-CRP) is a technique developed to detect very low levels of CRP to more accurately determine the existence of the inflammation process compared to CRP (Peluso *et al*., 2019) [20]. Procalcitonin (PCT) hormone is a peptide consists of 116 amino acids with low molecular weight, approximately 13 kDa (Jiao *et al*., 2015). The proportion of the hormone is 0.033 ng/ml and rises to 5000 ng/ml in cases of bacterial infection only, but it does not rise in viral infections (Bradford *et al*., 2019).

Interlukine-6 (IL-6) is a type of cytokines, which has hormone-like properties. It has pro-inflammatory properties, has a role in innate and adaptive immunity, causes fever during infection, and is secreted by monocytes, macrophage devoured in response to other cytokines such as IL-11, TNF. Its function is to regulate acute phase proteins and chronic infections, and its levels increase in patients with vascular diseases compared to healthy people (Naseem *et al*., 2016).

2 Materials and Methods

Out of a total of 20 patients, 5 (25%) were females and 15 (75%) males participated in this study. All

patients were diagnosed as having UAP. A total of 20 healthy individuals enrolled in this study as a control group; their age and gender were matched with the patients group. Cancer and hepatitis patients were excluded from this study. Data were collected from the cardiac center in Al-Sadr Teaching Hospital via specially structured questionnaire. This included sociodemographic and health data. The study took place during the period from 13 October 2019 to 27 October 2020.

Venous blood was collected from patients and controls in EDTA, sodium citrate and gel tube. Centrifugation processes were being done to obtain serum and plasma by Rotofix 32 A at a speed of 3000 cycles per minute for 10 minutes. Then cardiac and inflammatory biomarker tests were done by special kits from Hotgen Company via phosphorous technology using UPT-3A converting phosphor immunological analyzer.

All statistical analyzes were performed using Statistical Package of Social Sciences (SPSS) version 24. Categorical variables are expressed as percentages, was made between patients and the control groups using chi-square test or Fisher's exact test qualitative variables, and Mann-Whitney test for quantitative nonparametric variables. Spearman's test was used to find the correlation between the nonparametric quantitative variables. The level of significance was set at ($P < 0.05$).

3 Results

A total of 40 individuals were included in this study. Of those, 20 were cases of UAP and 20 were controls. (Table 1) shows the levels of cardiac and inflammatory markers in cases and controls. The levels of these markers were statistically significantly ($p<0.05$) increased in UAP cases as compared to controls.

(Table 2) and (Figure 1) show the correlation between cardiac and inflammatory markers in UAP cases. Positive correlations were found between cardiac and inflammatory markers in UAP cases.

Serum CRP levels were found to be strongly positively correlated with (CK-MB, D-dimer, NT-proBNP and H-FABP, (r=0.646, 0.604, 0.561 and 0.527, respectively, in a significance level of $p<0.01$). A strong positive correlation was found between serum Hs-CRP levels with (CK-MB, D-dimer and H-FABP, (r= 0.703, 0.613 and 0.531 respectively, in a significance level of $p<0.01$) in UAP patients. A strong positive significant correlation was found between serum PCT levels with (H-FABP, MYO, NT-proBNP and CK-MB, (r= 0.621, 0.581, 0.564 and 0.549 respectively, in a significance level of $p<0.01$). On the other hand, we found medium positive significant correlations of Serum IL-6 levels with H-FABP and cTnI (r= 0.356, 0.316 respectively, both $p<0.01$); CRP with MYO and cTnI (r=0.418, 0.364) respectively, both $p<0.01$); Hs-CRP with NT-proBNP, MYO and cTnI (r= 0.495, 0.416 and 0.346 respectively, in a significance level of $p<0.01$); PCT with D-dimer (r=427).

Finally, a small positive correlation of IL-6 with NT-proBNP, CK-MB, MYO, LP-PLA2 and D-dimer) (r=0.297, 0.258, 236. 0.218 and 0.181 respectively, in a significance level of $p<0.01$); A small positive correlation of PCT with cTnI and LP-PLA2 (r=0.291, 0.218) respectively, in a significance level of $p<0.01$). A small negative correlation of CRP with LP-PLA2 (r=-0.085); Hs-CRP with LP-PLA2 (r=-0.182).

Table 1: The differences in the levels of cardiac and inflammatory biomarkers in UAP cases and controls.

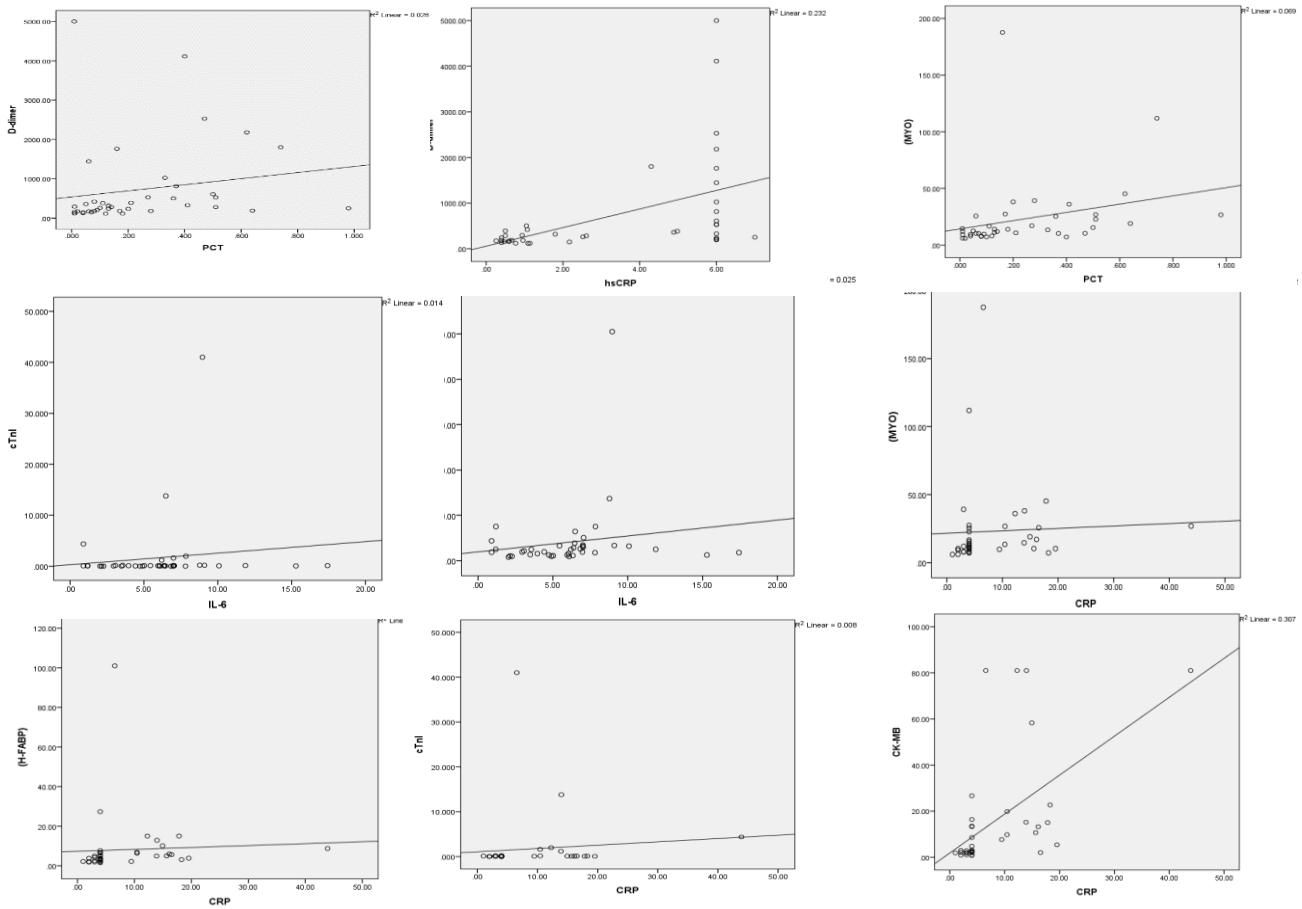
Biomarker	UAP No. (%)	Control No. (%)	P-Value
IL-6 (pg/ml)			0.091
<7	11(55%)	16 (80%)	
≥7	9(45%)	4 (20%)	
CRP (mg/L)			0.0001
<8	6(30%)	19 (95%)	
≥8	14(70%)	1 (5%)	
Hs-CRP (mg/L)			0.001
<1	2(10%)	12 (60%)	
≥1	18(90%)	8 (40%)	
PCT(ng/ml)			0.0001
<0.5	7(35%)	20 (100%)	
≥0.5	13(65%)	0 (0%)	
PCR			0.008
Negative	13(65%)	20 (100%)	
Positives	7(35%)	0 (0%)	
LP-PLA2 (ng/ml)			0.462

< 175	14(70%)	16(80%)	
≥ 175	6(30%)	4(20%)	
H-FABP (ng/ml)			0.003
<7	12(60%)	20 (100%)	
≥ 7	8(40%)	0 (0%)	
MYO (ng/ml)			0.487
<48	18(90%)	20 (100%)	
≥ 48	2(10%)	0 (0%)	
cTnI (ng/ml)			0.020
<0.5	14(70%)	20 (100%)	
≥ 0.5	6(30%)	0 (0%)	
CK-MB (ng/ml)			0.0001
<4.99	1(5%)	20 (100%)	
≥4.99	19(95%)	0 (0%)	
NT-proBNP (pg/ml)			0.0001
<450 (age≤750) <900 (age≥75)	10(50%)	20 (100%)	
≥ 450 (age≤75) ≥900 (age≥75)	10(50%)	0 (0%)	
D-dimer (ng/ml)			0.0001
<500	8(40%)	19 (95%)	
≥500	12(60%)	1 (5%)	

Table 2: The correlation coefficient, r-values, between cardiac and inflammatory biomarkers in patients of UAP

Inflammatory Biomarkers	Cardiac biomarkers						
	LP-PLA2	**H-FABP**	**MYO**	**cTnI**	**CK-MB**	**NT-ProBNP**	**D-dimer**
IL-6	0.218	0.356*	0.236	0.316*	0.258	0.297	0.181
CRP	-0.058	0.527**	0.418**	0.364*	0.646**	0.561**	0.604**
Hs-CRP	-0.182	0.531**	0.416**	0.364*	0.703**	0.495**	0.613**
PCT	0.215	0.621**	0.581**	0.291	0.549**	0.564**	0.427**

* Significant (p<0.05), ** highly significant (p<0.01)



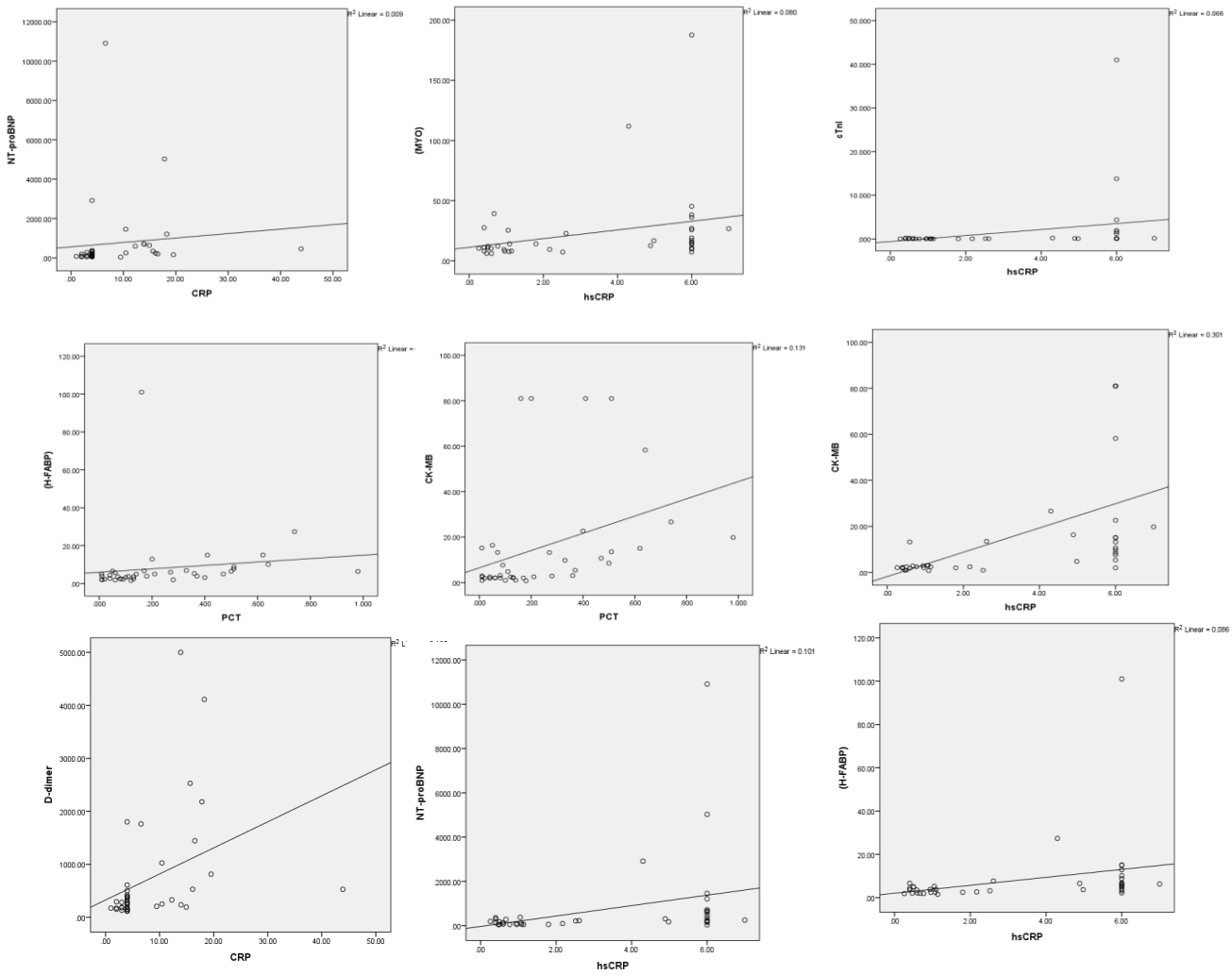


Figure 1: The correlation between cardiac and inflammatory markers in UAP cases and control groups

4 Discussion

In the present study, the association of cardiac markers (cTnI, H-FABP, MYO, CK-MB, NT-proBNP and D-dimer) and inflammatory markers (CRP, Hs-CRP, IL-6 and PCT) with SAP was assessed and the correlation between the two types of markers was tested.

We found significantly increased levels of most cardiac and inflammatory biomarkers in UAP cases compared to controls ($p<0.05$), which is mostly consistent with the results of several previous studies that documented a role for inflammation in the development of atherosclerosis. Moreover, we found significant correlations between most markers from the two groups.

Cardiac Markers:

H-FABP is mainly found in the heart muscle; and in case of heart muscle cells, it is released early to the blood. An elevated level of H-FABP can be tested in 30 minutes after the injury, reaches its peak in up to 8 hours and decreases to its original level after 24 hours (Mythili *et al*., 2015). This goes with the finding of the current study, which found that it is extremely significantly statistically associated with MI when compared to control individuals.

Rathore *et al*., (2017) in their study observed significant higher mean levels of cardiac markers MYO activity in AMI cases when compared to that of controls, which agrees the results of this study. Again it is one of the early elevated markers in the blood after the onset of injury to the heart muscle, reaches its peak in up to 12 hours and declines to its original level very shortly (Rathore *et al*., 2017). However, it lacks specificity to the heart tissue. That is why its level is recommended to be tested in conjunction with the cTnI or CK-MB (Mythili *et al*., 2015). Concluded that a combination of cTnI activity was sufficient for the early diagnosis of acute myocardial infarction (AMI). It is specific for the myocardium, which has made it an excellent cardiac marker of injury.

It starts to increase in up to 8 hours post heart muscle injury (Mythili *et al*., 2015). It is a highly sensitive test for diagnosing and predicting coronary artery disease and plays a considerable role in the process of risk stratification (Tibaut *et al*., 2019). These facts can explain the results of our study, when it was found to be extremely associated to MI.

Rathore *et al*., (2017) Documented higher levels of CK-MB in AMI patients when compared to controls, which agrees the results of this study (Rathore *et al*., 2017). It is not measured as a single diagnostic indicator, but in conjunction with the troponins or MYO (Mythili *et al*., 2015). Although, previously, the total CK was used to assess myocardial infarction, Mythili *et al*., (2015) and Singh *et al*., (2002) concluded that a CK-MB activity can be sufficient for the early diagnosis of acute myocardial infarction (AMI) (Mythili *et al*., 2015; Singh *et al*., 2002).

Eriksson *et al*., (2019) stated that NT-proBNP has a prognostic value in patients with heart failure (Eriksson *et al*., 2019). Although, NT-proBNP was found to be significantly associated with MI, and previous research has shown that its elevation can be a predictive marker of death and heart failure, it was stated that it cannot be used for the diagnosis of AMI (Mythili *et al*., 2015). D-dimer was shown to be associated with the extent of coronary heart disease, which agrees the results of this study, but it has a low specificity; therefore, all other fibrinolysis conditions should be excluded when used as a risk marker for atherosclerosis (Tibaut *et al*., 2015).

Inflammatory Markers:

IL-6 has a major role in the recruitment and activation of inflammatory cells in response to ischemia (Mythili *et al*., 2015).

Wennberg *et al*., (2012) documented an association between IL-6 and MI risks; and Filardo *et al*., (2015) reported that seropositivity of IL-6 may be predictive of atherosclerotic cardiovascular risk (Wennberg *et al*., 2012; Filardo *et al*., 2015). Furthermore, it is considered as one of the important tools for assessing the risk of coronary atherosclerosis, which supports the results of this study (Ridker *et al*., 2015).

Sesani *et al*., (2016) and Rathore *et al*., (2017) who mention that CRP is the most frequent marker of inflammation, which its relation to MI has been studied extensively in recent years (Sesani *et al*., 2016; Rathore *et al*., 2017). In agreement with the present study findings, Wennberg *et al*., (2012) documented an association of inflammatory markers, such as CRP, with MI risks. Moreover, it was stated that these markers are of considerable importance in the pathophysiology of the disease (Ahmed *et al*., 2017). Mentioned in their study that it is of benefit to measure serum levels of PCT and CRP in diagnosing cardiovascular complications in type 2 diabetic patients. Our study results agree the results of (Baruah *et al*., 2012). In their study showed that the role and importance of the CRP, contributes to provide a predictive value in the diagnosis of AMI. Also, it sensitivity and specificity (Mythili *et al*., 2015).

When Hs-CRP is considered, it has been documented that screening techniques have been developed, to detect it, are used to assess heart disease risk associated with infections (Baruah *et al*., 2012). Recent studies have also demonstrated the ability of HS-CRP to predict the presence of atherosclerotic plaques and it is an important tool that can help physicians in putting immediate treatment plans (Ammirati *et al*., 2015; Ridker *et al*., 2017). As it was found that it has a major role in improving the risk stratification of CAD (Koenig *et al*., 2013; Fonseca *et al*., 2016; Chong *et al*., 2020). The mechanism has been stated to link high serum Hs-CRP levels to the process of inflammation of the myocardium and higher levels of Hs-CRP are correlated with the severity of the inflammation of the injured myocardium (Yao *et al*., 2013). In addition, Filardo *et al*., (2015) reported that seropositivity of HS-CRP may be predictive of atherosclerotic cardiovascular risk (Filardo *et al*., 2015). All the above support the results of our study, when we found that Hs-CRP is associated with MI and is positively correlated to the cardiac biomarkers. This study results agreed the results of Kafkas *et al*., (2008) who documented that PCT was significantly associated with MI (Kafkas *et al*., 2008). Moreover, ENTürk *et al*., (2007) and Özbay *et al*., (2020) who recommended its use in assessing the prognosis and severity of coronary artery disease (Kafkas *et al*., 2007; ENTürk *et al*., 2020).

Limitations:

Researchers find it is crucial to point out the following limitations of the study, without which, the results would be better conclusive:

- The time for blood samples to be taken for examination was variable among patients after admission to the hospital's coronary care unit. This was a rather wide range for the levels of the marks tested. This means that levels among patients do not represent a close/similar time period after UAP. However, despite this, the differences between most marker levels were highly statistically

significant, and the wide variance in the post-UAP period cannot mask the significance.
- The results based on a single center only, which could lead to selection bias.
- The sample size was too small to produce conclusive results. That was because of the restriction imposed due to the outbreak of COVID-19. However, the result was not different from other studies worldwide.

5 Conclusions

The current results found increased levels of inflammatory markers (CRP, Hs-CRP, and PCT) along with cardiac markers (cTnI, H-FABP, CK-MB, NT-proBNP and D-dimer) and significant positive correlations among the markers of the two groups in UAP patients. It indicates that there was significant inflammatory process associated with UAP.

Recommendations:

More in depth research is needed to justify and recommend adding testing inflammatory markers for diagnostic purposes in patients of UAP.

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