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Evaluation of Interleukin-23 and Creatine Kinase –MB (CK-MB) Levels in Acute Coronary Syndrome Patients with COVID-19 in Baghdad City

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Abstract

Acute coronary syndrome (ACS) is considered a common cardiovascular disease, in which there is a blood supply reduction to the myocardium, mostly due to atherosclerosis in the coronary arteries. the present study was designed to detect serum markers in Acute coronary syndrome patients infected with COVID-19 in Baghdad Governorate, by evaluating the level of Interleukin-23(IL-23) and level of creatine kinase isoenzyme (CK-MB). Methods: A total of one hundred fifty participants were enrolled in the current study divided into three groups 50 patients with ACS and 50 ACS with COVID-19 patients, while 50 participants as apparently healthy controls. age and sex-matched as healthy controls were involved in the present study. The serum IL-23 and CK-MB levels were measured using an ELISA technique.
Serum concentrations of IL-23 and CK-MB were significantly higher in ACS patients and ACS with COVID-19 patients compared to healthy controls ($P \leq 0.01$) also there was a highly significant difference at ($P \geq 0.01$) between ACS patients and ACS with COVID-19 patients.
IL- 23 can be considered a biomarker for ACS patients and ACS with COVID-19 patients.

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Keywords: Acute coronary syndrome (ACS); COVID-19; Interleukin-23 (IL-23); Creatine kinase isoenzyme (CK-MB).

1. Introduction

Acute coronary syndrome (ACS) is an expression used to characterize the continuum of myocardial ischemia. ACS is considered a common cardiovascular disease, in which there is a blood supply reduction to the myocardium, mostly due to atherosclerosis in the coronary arteries [1], which includes narrowing or blockage of the coronary artery [2] leading to the death of the heart muscle because of decreased oxygen supply, and forming (unstable angina pectoris) or infarction with ST elevation myocardial infarctions (STEMIs) or myocardial Infarction without ST elevation (NSTEMI) have the exact pathophysiology and clinical signs, but there is increase heart muscle necrosis in NSTEMI [3, 4].Symptoms of acute coronary syndrome: Chest pain or discomfort, which may involve pressure, pain or discomfort in one or both arms, the jaw, neck, pain in the back, stomach, shortness of breath, feeling dizzy, nausea, and sweating [4]. Severe acute respiratory syndrome coronavirus 2 (SARS-CO-V2) caused the outbreak of the novel coronavirus disease (COVID -19), the most serious health problem in the current century. COVID-19 is correlated with remarkable elevation in the global mortality and morbidity. The present conditions, such as cardiovascular diseases (CVDs) are associated with higher severity and a notable rise in the mortality rates of infection with COVID-19 [5].
COVID-19 became increasingly identified as a cause of the inflammatory responses and cytokine storms and as a result, leading to damage of multiple organs and systems [6]. The final cardiac damage appeared as the most serious complication of COVID-19 which remarkably increased the overall death rate [7]. Patients who have pre-existing heart problems were shown to have increased cytokine storms which result in more serious heart injuries and overall worsening [8, 9]. Heart failures, acute myocardial injuries (AMI), left ventricular systolic dysfunctions, arrhythmia and acute coronary event are among different cardiac features of COVID-19 [10]. In regard to the death rate, if a patient with acute coronary syndrome is infected with COVID-19, the mortality rate will be shown to be greater than that of non-COVID infected [11]. Multiple studies have demonstrated that levels of disease-related biomarkers may be elevated in the onset of symptomatic Acute coronary syndrome (ACS) patients and ACS patients infected with covid-19. These biomarkers include CK-MB: creatine kinase myocardial band as well as cytokine/chemokine [12, 13]. Accumulated evidence revealed that cytokines are playing important roles in the presence and development of cardiovascular diseases. Interleukin-23 is a cytokine of IL-12 family members that regulates a variety of biological impacts; and are closely associated with the progression of different cardiovascular disease such as acute coronary syndromes [14]. The Interleukin-23 (IL-23) biomarker is a cytokine, regarded as a pro inflammatory factor which amplifies downstreams inflammatory signal, and is principally derived from macrophages, effector T-lymphocytes and dendritic cell [14]. In 2000, Oppmann and his colleagues discovered the IL-23. The IL-23 shares IL-12p40 subunits with IL-12 and combines with IL-23p19 subunits forming the biologically-active IL-23 [15]. This cytokine is generally known to act as a proinflammatory and is engaged in Th17 cell stabilization and differentiation via acting on memory T-lymphocytes (16). Moreover, it contributes to activation of memory T lymphocytes and recruiting IL-17 mediated neutrophils [17]. The enzyme creatine kinase (CK) is expressed by different tissues and catalyzes the reversible transfer of high-energy phosphate bond from adenosine triphosphate (ATP) to creatine, and it is a dimer composed of two subunits that are either B (Brain) or M (Muscle).

Nomenclature			
ACS	Acute Coronary Syndrome	CNS	Centrel Nervus System
COVID-19	Coronavirus Disease-19	SD	Standard Deviation
IL-23	Interleukin-23	SPSS	Statistical Package For Social Science
CK-MB	Creatine Kinase –Myocardial Band	NS	Non–Significant
CVD	Cardiovascular Disease	S	Significant
CHD	Coronary Heart Disease	HS	Highly Significant
AMI	Acute Myocardial Injury	Ng/dL	Nanogram Per Deciliter
ELISA	Enzyme-Linked Immunosorbent Assay	Pg/dL	Picogram Per Deciliter
Rpm	Revolutions Per Minute		

The creatine kinase isoenzyme CKMB is cardio-specific and is considered as the most specific and sensitive indicator for the necrosis of myocardial cells [18]. Creatinine kinase (CK)-MB is a CK isozyme which is mainly found in the myocardium, however, 5–7% of this isozyme is present in the skeletal muscles [19]. The object of this study is to evaluate the roles of certain disease markers such as CK-MB: creatine kinase myocardial band as well as cytokine/chemokine, interleukin-23 (IL-23) in the pathogenesis of ACS and ACS with COVID-19 as panel useful in assessing disease.

2. Materials and Methods

2.1. Study design

This study was done on 150 serum samples collected from (92 males and 58 females), the age ranging between (20-80) years. patients divided into (50 ACS and 50 ACS with COVID-19), while 50 samples as apparently healthy controls. The patients who had a sign and symptoms were primarily diagnosed with ACS and ACS with COVID-19 by the physician at Iraqi Center for Heart Disease (Cardiac Care Unit), Baghdad Teaching Hospital, Al- Kadhimiya Teaching Hospital, Dar Al-Salam Hospital, and Ebn Al-Khatib Hospital –Baghdad/IRAQ during the period from November 2021 to March 2022. The study used 100 samples to measure IL-23 and CK-MB levels and compare them to 50 healthy people, each ACS patient was chosen after excluding any of the following states as "COVID-19 vaccination, malignancy, pregnancy, CNS" depressants, hormonal therapy. The Medical City of Iraqi Center for Heart Disease (cardiac care unit) laboratories were used for this study.

2.2. Collection of samples

Five milliliters of blood were drawn from each subject via vein puncture with disposable syringes. The serum was separated by centrifugation of blood at 3000 rpm at 10 min to determine (IL-23 and CK-MB). IL-23 and CK-MB level was detected by using the Elisa kit (My BioSource-USA).

2.3. Statistical analysis

The (SPSS) version-26 was used to revise, code and analyze the data. The mathematical presentation method (Means & Standard Deviations) was used for data presentation. Chi-Square test (X2) and independent sample t-test were used for data analysis. The P-value of ($P \leq 0.05$) was considered as statistically significant (S). The P-value of ($P \leq 0.01$) was considered as highly significant (HS), while P-value of ($P > 0.05$) was considered as non-significant (NS).

3. Results

3.1. Demographic characteristics of the studied groups

The distribution of studied "Risk Factors", such that (Age and Sex) are shown in Tables 1 & 2 with a comparison of statistical significance in studied groups.
The patient's age was categorized into three groups and presented in Table 1 which show that most patients were adults with age between (40-≥50) years. The percentages of participants aged (20-29) years was 28.0%, 24.0%16.0%, and (30-39) years was 22.0%, 22.0%, 24.0% while the age range (40-≥50) years was 50.0%, 54.0%, 60.0% respectively in the control group and the patients group.

Table 1 Distribution of studied groups according to age groups

Age groups (years)		Groups ACS	ACS+COVID-19	Healthy control
(20-29)	No.	14	12	8
	%	28.0%	24.0%	16.0%
(30-39)	No.	11	11	12
	%	22.0%	22.0%	24.0%
(40-≥50)	No.	25	27	30
	%	50.0%	54.0%	60.0%
Total	No.	50	50	50
	%	100.0%	100.0%	100.0%

The result in Table 2 shows the observed frequencies in the male group were more than in the female group. The number of females in the group ACS was 19 (38.0%) and a male was 31(62.0%). The number of females in the group ACS with COVID-19 was 18 (36.0%) and a male was 32 (64.0%). The number of females in the control group was 20 (40.0%) and a male was 30 (60.0%).

Table 2 Distribution of studied groups according to gender

Gender		Groups		
		ACS	ACS+Covid-19	Healthy control
Male	No.	31	32	30
	%	62.0%	64.0%	60.0%
Female	No.	19	18	20
	%	38.0%	36.0%	40.0%
Total	No.	50	50	50
	%	100.0%	100.0%	100.0%

3.2. serum levels of IL-23 among studied groups

Descriptive statistics of serum levels 0f IL-23 were listed in Tables 3 & 4. The mean ±Std was (310.26±5.27 Pg/mL) in patients suffering from acute coronary syndrome and the mean ±Std was (355.29±7.15 Pg/mL) in patients have acute coronary syndrome with COVID -19 infection, while in the control groups the mean ±Std was (276.54±7.45 Pg/mL). The mean IL-23 level in (ACS & ACS with COVID-19 infected persons) was significantly higher than the controls groups at ($P \leq 0.01$) with highly significant differences between ACS patients & ACS with COVID-19 patients at ($P \leq 0.01$) as illustrated in a Table 4.

Table 3 The mean ± standard deviation value of IL-23 for the studied groups

Immunological marker	Groups	No.	Mean ±Std.
IL-23 (Pg/mL)	ACS	50	355.29±7.15
	ACS+ COVID-19	50	310.26±5.27
	Healthy control	50	276.54±7.45

Table 4 Comparison of IL-23 between the ACS and ACS+COVID-19 with healthy control groups and comparison between the ACS and ACS+ COVID-19 groups

Immunological marker	ACS with healthy control		ACS and COVID-19 with healthy control		ACS with ACS and COVID-19	
	t-test	P-Value	t-test	P-Value	t-test	P-Value
IL-23 (Pg/mL)	53.919	.000 (HS)	26.126	.000 (HS)	35.867	.000 (HS)

3.3. serum levels of CK-MB among studied groups:

Data in a Table 5 & 6 demonstrate that the mean value of CK-MB in sera of patients suffering (ACS and ACS with COVID-19) was significantly higher($P \leq 0.01$), (289.53±8.22 ng/mL), (311.43±9.67 ng/mL) when compared with the mean value in sera of a control group (112.20±9.10 ng/mL) and there were highly significant differences ($P \leq 0.01$) between ACS patients & ACS with COVID-19 patients as shown in Table 6.

Table 5 The mean ± standard deviation value CK-MB for the studied groups

Cardiac enzyme	Groups	No.	Mean ±Std.
CK-MB (ng/mL)	ACS	50	289.53±8.22
	ACS+ COVID-19	50	311.43±9.67
	Healthy control	50	112.20±9.10

Table 6 comparison in CK-MB level among studied groups

Immunological marker	ACS with healthy control		ACS andCOVID-19with healthy control		ACS with ACS and COVID-19	
	t-test	P-Value	t-test	P-Value	t-test	P-Value
CK-MB (ng/mL)	102.793	.000 (HS)	106.607	.000 (HS)	12.202	.000 (HS)

4. Discussion

The acute coronary diseases result from events of vulnerable atherosclerotic plaques. The plaque events appear if the intimal thrombus of walls of coronary arteries become subject to ruptures or erosions [20]. Inflammation plays a main role in the pathogenesis of atherothrombosis and CHD, including acute coronary syndrome [21]. Atherosclerosis has a long-term incubation, and the major complication is that myocardial infarction occurs suddenly and sometimes without time warning [22].

The results of this study found that the majority of patients were (40- ≥50) years of age, these findings were consistent with [23, 24], who stated that the incidence of ACS is more common in elderly people. The acute coronary syndromes remains commonly high and remains the major mortality cause among individuals of more than 35 yrs old. Older age is associated with ACS presenting with vague symptoms [25]. Age plays an essential role in MI anticipation. With the age progression, there is also an increase in the danger of artery damage and narrowing. It will thicken or weaken heart muscles which participate in ischemic heart diseases resulting in MI occurrence [26].

Old adults infected with COVID-19 possess a more atypical features, more complications with more mortalities [27]. The age impact on COVID-19 outcome has been further attributed to immune- and inflammatory-mediated mechanisms [28]. Pre-existing cardiovascular diseases, as well as older ages and other comorbidities, is an established risk for adverse consequences among patients infected with COVID-19 [29]. The outcomes and severity of COVID-19 depend greatly on patients' ages, with older adults more than 60 years forming the majority of hospitalized

patients with higher risk of mortality than young adults (30). This could be associated with two immune phenomena related to aging, immune and cellular senescences, that may lead to impaired immunological response to SARS COV-2 and increase systemic inflammations because of irreversible cell-cycle arrests [31].

Although male patient group frequency is greater than female frequency in our study, the data showed no significant difference between them indicating that the ACS may influence both males and female but with the tendency to male patients.

The current results were in agreement with the results performed by [32] who stated that a male predominance with major modifiable risk factors for females. A previous study by [34] revealed that females had less coronary atherosclerosis than males with comparable ages. This may be because of a direct effect of estrogen hormone in females that inhibit atherosclerosis formation [33]. The high death and disability rates in women occur following menopause [26], suggesting that aging affects sex-specific differences in cardiovascular disease [34].

The male COVID-19-infected patients are obviously symptomatic and show highly severity of the disease, high rate of complications and finally highly mortalities. Potential sexual dimorphisms in ACE2 expression, like the docking site utilized by SARS COV-2 to enter the cell, indicate that sexual dimorphisms in immune and inflammatory responses can immediately affect the association between a risk of cardiovascular disease and Covid-19 thereby, contribute to the highly mortality rates among male patients [35].

CK-MB, the isoenzyme specific to cardiac muscles, has been the main biomarker for heart injuries until its supplementation by troponin. In case of myocardial infarctions, serum CK-MB levels typically increase about 4-6 hrs following the chest pain onsets. This level peaks within 12-24 hrs and returns to the baseline level within 24-48 hrs. Serial measurements taken every 6-8 hrs (three times at least) are warranted until determination of peak levels [36]. The purpose of CK-MB level measuring in the present study is to set up ACS diagnosis in the suspected people. In the current study, the CK-MB levels in patients were highly significantly different ($P \leq 0.01$) compared with control and it agrees with [37] that also found high CK-MB levels in ACS patients.

CK-MB levels showed significantly high results in patients of ACS with COVID-19, these results agree with other results done by [38] who stated that there is a significant relation between increased CK-MB levels cardiac biomarker and COVID-19 severity, that underlines the highly acute heart injury risks with a more serious viral infections. Mechanistically, the interaction between S protein of the COVID-19 structure which bind to angiotensin-converting enzymes-2 (ACE-2) on the host cell surfaces may play a significant role in the disease pathogenicity, particularly in cardiovascular diseases [39].

The heterodimeric IL-23, mainly produced by macrophages and activated dendritic cells, acts as a link between adaptive and innate immunities through promotion of immune cell proliferation and cytokine secretion [40]. The novel IL-23 pro inflammatory cytokine, is important in autoimmune disease, infection, tumor and inflammatory disease such as myocardial ischemia and reperfusion (I/R) injuries by promotion of inflammatory cytokine expression and inflammatory response [41]. The biological influence of IL-23 is obtained through binding with specific high-affinity IL-23 receptors (IL-23R) on the surfaces of target cells [42]. Moreover, IL-23 can produce IL-1, TNF-α, and IL-23 itself by activating inflammatory macrophages [43].

In recent time, certain studies showed that IL-23 has distinctive impacts on immunologic responses, that can act as a pro inflammatory via Th1 and Th17 cell regulations. During antigen presentation to naïve T-cells, the IL-23 signal through JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway. The STAT pathway activation via STAT protein phosphorylation results in gene transcription induction and thus forming a cytokine-induced gene transcription bridge [44] as well as IL-23 & IL-23R play an important role in initiating, accelerating, maintaining IL-23/Th17 inflammatory signal transductions pathways to produce inflammatory factors IL-17, IL-6, IL-22, TNF-α with GM-CSF [43]. The results demonstrated that the axis of IL-23/ IL-17 may be engaged in CHD pathogenesis. Also, the study of [41] hypothesized that IL-23 enhanced myocardial injury I/R through elevating myocardial apoptosis and inflammatory response, that can be related to higher IL-17A expression levels with upregulations of JAK2-STAT3 signaling pathways. Our results are in line with these findings demonstrating higher levels of IL-23 in ACS patients, compared with the normal control group and even more serum IL-23 levels increased in the ACS with COVID-19 infection group compared with the ACS without COVID-19 group, which suggested that IL-23 may affect the development of COVID-19 in ACS patients.

Previous studies by [44–47] demonstrated that IL-23 may contribute to atherosclerosis development. For example, patients with peripheral arterial diseases have high serum IL-23 which has been associated with increased mortality during follow up underscoring the association between IL-23 and carotid atherosclerosis. Many researchers stated that levels of mRNA of IL-23 with IL-23R have been remarkably elevated in carotid plaque, and that IL-23 caused increased release of IL-17 in monocytes, especially in peripheral mononuclear cells which caused aggravation of carotid atherosclerosis, indicating the probable roles of IL-23/Th17 Axis. Moreover, the axis of IL-23/Th17 was shown to play basic roles in autoimmune and chronic inflammatory disorders.

Other results were done by [48] who stated that in addition to atherosclerosis, recent studies have also implicated IL-23 to have a major role in injuries of cardiac ischemia-reperfusion and in remodeling of (LV) in a mice models of myocardial infarctions (MIs). A functional link was determined between IL-23 signaling axis and late-stage left ventricle (LV) remodeling following (MI). These findings demonstrate higher levels of IL-23 in CHF patient, and support the direct roles of IL-23 in remodeling processes of LV which can contribute to the development and progression of CHF, Therefore, it suggested that the expression of IL-23 in Peripheral blood mononuclear cells (PBMCs) can play important mediating role in activation of systemic inflammations which could eventually result in the progression of cardiac failures. On the other [49] shows that IL-23 may function as a negative regulator for IL-12 induced IFN-γ production and Th1 immunity withour dependence on of other Th17 cytokines. This may suggest the involvement of IL-23 in the CAD pathogenesis by other means rather than regulation and expansion of Th17 cells, which should be more studied.

The result of IL-23 level is higher in the serum patients with COVID-19 than in the normal control group these findings were in agreement with [50] which detected an elevation in serum IL-23 levels among patients with COVID-19 in comparison to the control group. It is well understood that IL-23 plays an essential role in Th cell polarization versus the Th17 subset, that secretes the pro inflammatory cytokine IL-17 and promotes inflammations. IL-23 is also able to activate IL-10 formation in naïve T-lymphocytes [51]. This also clarifies the relationship between IL-10 and IL-23 among COVID-19 patients. Patients with higher levels of serum IL-23 and IL-10 have remarkable higher risk to die. Thus, evaluation of serum IL-23 and IL-10 levels can help in early indication of disease progress and help in making decision associated with treatments for preventing complications of the disease and death. The study of [52] disagreed with the result of the present study that IL-23 can be a potential serum biomarker for the detection of patients with COVID-19, this hypothesized that IL-23/IL-17A axis plays no important role in COVID-19 pathogenesis in the Iranian patients. found that increased IL-23 in the men did not affect Th17 functions and it may induce some pro-inflammatory responses independent of IL-17A.

5. Conclusion

In this research, there was an elevation in both serum levels IL-23 and CK-MB in the patients' group compared to the control group. According to this study, COVID-19 has the main role in affecting ACS because the result of IL-23 was significantly higher, and would act as a pro-inflammatory cytokine and an important regulatory marker which connects the adaptive and innate arms of immune system in a complicated mechanism correlated with ACS development as well as CK-MB was significantly higher during the disease course of ACS with COVID-19. therefore IL-23 could be used as a biomarker for ACS and ACS with COVID-19.

Ethical Clearance

Ethical approval to conduct this study was obtained from the Iraqi of Ministry of Health (no A9226).

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