Measurement level of stem cell factor and lipid profile in the sera of Iraqi patients who have acute coronary syndrome with COVID-19

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Abstract

Acute coronary syndrome (ACS) is the umbrella of ischemic myocardial diseases and involves unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). UA and NSTEMI, share similar pathophysiology, but at increasing severity. The study aimed to assess the levels of stem cell factor (SCF)in acute coronary syndrome patients infected with Covid-19 in Baghdad Governorate, and healthy subjects and to analyze the levels of lipid profile including total cholesterol (TC), triglyceride (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL) as well as very low density lipoproteins (VLDL). one hundred patients with acute coronary syndrome were divided into two groups 50 ACS with COVID-19 infected patients and 50 ACS without COVID-19 infected, and 50 healthy controls. Levels of serum stem cell factor (SCF) were analyzed by ELISA technique and serum levels of lipid profile were measured manually by Spectrophotometer. The (ACS COVID-19 infected and ACS without COVID-19 infected) patients had lower levels of stem cell factor (SCF) as compared to healthy controls ($P \leq 0.01$). TC, LDL, TG, and VLDL concentrations in the sera were higher in (ACS without COVID-19 & ACS with COVID-19) patients, while lower levels of HDL in the same patients when compared with healthy control. The present study exhibited lower serum SCF levels in both groups ACS with COVID-19 infected and ACS without COVID-19 infected patients compared to healthy controls. Therefore, SCF can be considered a biomarker for ACS with COVID-19 infected and ACS without COVID-19 infected

Keywords: *Acute coronary syndrome (ACS); covid-19; SCF; lipid profile.*

قياس مستوى عامل الخلايا الجذعية والدهون في مصل المرضى العراقيين الذين يعانون من متلازمة الشريان التاجي الحادة مع COVID-19

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تمثل متلازمة الشريان التاجي الحادة (ACS) مجموعه من مرض عضلة القلب وتشخيصات تشمل الذبحة الصدرية غير المستقرة (UA) ، واحتشاء عضلة القلب غير المرتفع ST (NSTEMI) ، واحتشاء عضلة القلب بارتفاع ST (STEMI). UA و NSTEMI ، يشتركان في فسيولوجيا مرضية متشابهة ، ولكن في شدة متزايدة. هدفت الدراسة إلى تقييم مستويات عامل الخلايا

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الجذعية (SCF) في مرضى متلازمة الشريان التاجي الحادة المصابين بـ Covid-19 في محافظة بغداد ، والأشخاص الأصحاء وتحليل مستويات ملف الدهون: الكوليسترول الكلي (TC) ، والدهون الثلاثية (TG). والبروتين الدهني عالي الكثافة (HDL) والبروتين الدهني منخفض الكثافة (LDL) والبروتين الدهني منخفض الكثافة جدًا (VLDL). تم تقسيم مائة مريض مصاب بـ (ACS و ACS مع عدوى COVID-19) إلى مجموعتين (50 مريض ACS و 50 ACS مع مرضى مصابين بـ -COVID 19) ، و 50 مجموعة من الأصحاء. تم تحليل مستويات عامل الخلايا الجذعية في الدم (SCF) بتقنية ELISA وتم قياس مستويات الدهون في المصل يدويًا بواسطة مقياس الطيف الضوئي كان لدى مرضى (ACS و ACS مع عدوى COVID-19) مستويات أقل من عامل الخلايا الجذعية (SCF) مقارنة بالضوابط الصحية (متوسط ± Std للمرضى) ، (متوسط ± Std السيطرة). P≤0.01) TC كانت تركيزات LDL و TG و VLDL في المصل أعلى في مرضى (ACS & ACS مع COVID-19) بينما كانت المستويات المنخفضة من HDL في نفس المرضى عند مقارنتها بالتحكم الصحي أظهرت الدراسة الحالية انخفاض مستويات SCF في الدم في ACS و ACS مع مرضى مصابين بـ covid-19 مقارنة بالضوابط الصحية. لذلك ، يمكن اعتبار SCF علامة بيولوجية لـ ACS و ACS المصابة بـ COVID-19.

الكلمات المفتاحية: *متلازمة الشريان التاجي الحادة (ACS) ، كوفيد -19 ,SCF، بروفيل الدهون.*

Introduction

One of the most serious types of coronary heart diseases is the acute coronary syndrome, which participates in huge numbers of global morbidities and mortalities. ACS involves a set of conditions including ST-elevation myocardial infarctions (STEMI), non-ST elevation myocardial infarctions (NSTEMI) as well as unstable anginas, which is the main cause of one-third of deaths among individuals of more than 35 years of age. Some coronary heart disease forms may be symptomless, however, ACS is usually symptomatic [1]. ACS is a feature of CHD and the American often results from disruption of plaque in the coronary arteries i.e. (atherosclerosis). Among the well-known risk factors of ACD are diabetes, hypertension, smoking, hyperlipidaemia, male sex, physical inactivities, obesity in addition to poor nutritional habits. Cocaine abuse may also cause vasospasms [2]. The fundamental ACS pathophysiology is low blood flow to the cardiac musculature, which is often secondary to plaque ruptures and thrombus formations. Occasionally, ACS may become secondary to vasospasms with or without fundamental atherosclerosis, which leads to low blood flow to some cardiac musculature leading first to ischemias followed by cardiac infarctions [3]. ECG is the initial step for assessment, as it aids in differentiation between STEMI & NSTEMI unstable anginas. The instructions of American Heart Association stated that ECG must be performed within ten minutes of arrival to all patients with complaints suspected to be ACS. After STEMI is confirmed, the Cath lab must be activated in a center of percutaneous coronary intervention (PCI). To assess NSTEMI versus myocardial ischemia without tissue damage, it is necessary to measure the cardiac enzymes particularly troponins, and the CK-MB/CK ratio. The chest X-ray is important to diagnose

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causes other than MI suffering from chest pains such as pneumothorax and pneumonia. In addition to X-ray, blood tests like complete blood count (CBC), liver function tests, and lipase may be useful in the differentiation of intra-abdominal pathology suffering from chest pains. Aortic dissections and pulmonary embolus must be kept in preference and carried out if the situation warrants [4،5]. There is a significant effect of (COVID-19) pandemic on the managing of cardiovascular emergency worldwide. In the early time of the pandemic distribution, an unexpected decrease in hospital admission of acute cardiovascular emergency patients was observed [6]. The survey done by the Society of Cardiovascular Angiography and Intervention (SCAI) revealed that persons considered visiting hospitals have high risk behaviors to contract COVID-19, and those older than 60 yrs. showed more fear to contract the disease than developing cardiac attacks [7]. Furthermore, COVID-19 gave rise to a great demand for resources, leading to deferral and alteration of necessary elective and preventive health services for patients with stable heart disorders [8]. In the USA, during the pandemic, there was a statistically significant elevation in death records because of ACS, with a geographical correlation with the numbers of cases in that area. In the beginning of the pandemic, prospective information from 55 international centers were employed for the creation of the "COVID-ACS" register including individuals who had positive COVID-19 or those with high index of clinical suspicion for COVID-19 infection [9].

Stem cell factor (SCF), is a hematopoietic cytokine, and is known as steel factor or kit ligand. It is the growth factor that is found as a membrane-bound or in soluble forms [10], represented by endothelial cells and fibroblasts within the body, and promotes proliferations, survival, migrations, and differentiations of hematopoietic progenitor, melanocyte as well as germ cell [11]. It is the dimeric molecule that practices its biological function via activating and binding with the receptor tyrosine kinase c-Kit [12] together with its receptor, c-Kit, SCF play important roles in the maintenance of hematopoietic stem cells (HSC), and hematopoiesis [13]. SCF is important for tissue repairing and vasculogenesis through stimulation of activation and recruitment of the bone marrow (BM), which is also represented by other tissue cells such as cardiovascular system [14,15]. Collectively, SCF can function as a signal when a cardiovascular cell repair is required and when an inadequate SCF expression compromises the structural and functional integrities of cardiovascular systems [16]. Atherosclerosis is lipid-driven, immune-inflammatory systemic disease. The well known dyslipidemia is risk factor for atherosclerosis development, which is a lipid- driven disorder.

Atherogenic dyslipidemia is referred to as the common combined occurrence of high fasting serum triglycerides (TG) and low high- density lipoprotein cholesterol (HDL-c) levels [17]. Lipid

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peroxidation and production of reactive oxygen species (ROS) damage the cardiac cell membrane[18]. Younger age, female, lower knowledge score, and smoking status are good predictors of lipid attainment among ACS patients [19]. The main cholesterol-carrying lipoprotein is the low-density lipoprotein cholesterol (LDL-C) and is regarded as the major atherogenic lipoprotein. Nevertheless, other lipoproteins like HDL-C or very low-density lipoproteins were shown always to play important roles in atherogenesis. Recently, epidemiological studies suggest that the low HDL-C levels in persons with normal triglyceride and LDL-C levels was equil to increased LDL-C levels as a coronary risk factors. In addition, in the novel CVD risks, low levels of HDL-C and the total serum cholesterol (TC) to HDL-C ratio were introduced [20].The current study aimed to assess the role of some markers such as the lipid profile including total cholesterol, triglyceride , high density lipoproteins (HDL), low density lipoproteins (LDL) and very low density lipoproteins (VLDL) as well as serum stem cell factor (SCF), in the pathogenesis of ACS with and without covid-19 as panel useful in assessing disease.

Materials and methods

In the present study, 150 serum samples (92 males and 58 females) with the age ranging between (20 - 80) years were collected from 100 patients and 50 healthy control, patients who had signs, and symptoms were primarily diagnosed ACS with and without covid-19 by the clinic's cardiologists in 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. Patient groups were classified into two clinical subgroups: 50 ACS with COVID-19 infected, and 50 without COVID-19 infected according to characteristic chest pain, laboratory investigations, electrocardiogram (ECG) findings, and Polymerase Chain Reaction (PCR). Each ACS patient was selected following exclusion of the following conditions: COVID-19 vaccinations, malignancies, pregnancy and CNS depressants. The control group included randomly selected unrelated, 50 healthy samples who were age and gender matched with the patients. From all the study groups, 5 ml of morning venous blood was taken.

After centrifugation of blood samples, serum samples were used for biochemical and serological investigations. The levels of serum SCF in both patients and controls were measured by the use of ELISA technique based on the instructions of the manufacturer in the kit from (MyBioSource, USA). Lipid profile including (Triglyceride, total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and very low density lipoproteins (VLDL) were measured manually by Spectrophotometer using (Randox kit. the UK).

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Statistical Analysis

The SPSS version 26 program was used for statistical analysis of data. The mathematical presentation method (Mean and standard deviation) was used for data presentation. The t-test and Chi-Square test (X2) were used for data analysis. The ($P > 0.05$) was regarded as non significant (NS) ($P \leq 0.05$) significant (S). ($P \leq 0.01$) highly significant (HS).

Result and discussion

Demographic characteristics of the study group

Distribution of study according to (Age and Gender) are shown in tables (1) and table (2). Data in table (1) show three groups of age, 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 (year)		Groups			Total
		ACS without COVID-19	ACS withCOVID-19	Healthy control	
(20-29)	No.	14	12	8	34
	%	28.0%	24.0%	16.0%	22.7%
(30-39)	No.	11	11	12	34
	%	22.0%	22.0%	24.0%	22.7%
(40-≥50)	No.	25	27	30	82
	%	50.0%	54.0%	60.0%	54.7%
Total	No.	50	50	50	150
	%	100.0%	100.0%	100.0%	100.0%

The results of this study found that the majority of patients were (40- ≥ 50) years of age, these findings were consistent with [21، 22], who stated that the incidence of ACS is more common in elderly people. The prevalence of ACS remains increased and is an important death cause among patients older than 35 years, and older age is associated with ACS presenting with vague symptoms [23]. There is an important role of age in IM anticipation. With age progression, danger of narrowed and damaged arteries also increased. Age progression leads to thickening or weakening of hear muscles resulting in ischemic heart diseases and MI [24]. Older adults with COVID-19 have a more atypical presentation, more complications, and higher mortality [25]. The age impact on COVID-19 outcome has been further attributed to immune- and inflammatory-mediated mechanisms [26]. A previously existing cardiovascular disease along with aging and other comorbidities, is a confirmed risk factor

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for adverse consequences in COVID-19 infection [27]. The severity and consequence of COVID-19 are highly dependable on the patient's age, and adults in sixties constitute the major hospitalization rates with a higher death risk than young adult people [28]. This can be explained by 2 immune phenomena related to aging, immune and cellular senescences, that may lead to impaired immunologic response to SARS-CoV-2 with elevated systemic inflammations because of irreversible cell cycle arrests [29]. 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 of ACS patients was 19 (38.0 %) and a male was 31 (62.0 %). The number of females of the ACS group with covid-19 infection patients was 19 (38.0%) and a male was 31 (62.0 %). 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.

		Groups			Total
		ACS without COVID-19	**ACS with COVID-19**	**Healthy control**	
Male	No.	31	31	30	92
	%	62.0 %	62.0%	60.0 %	61.3 %
Female	No.	19	19	20	58
	%	38.0 %	38.0%	40.0 %	38.7 %
Total	No.	50	50	50	150
	%	100.0 %	100.0 %	100.0 %	100.0 %

The study showed a higher male patient frequency than females with no statistical significant difference ($p > 0.05$) indicating that the disease may influence both males and females but with tendency to males. The result agreed with the findings of [30] who stated that a male predominance with major modifiable risk factors for females. However, another study demonstrated that females had significantly less coronary atherosclerosis than males of comparable age [31]. This may be because of a direct effect of estrogen hormone in females that inhibit atherosclerosis formation [32]. The reason is the high women mortality and disability following menopause, indicating that aging influences sex-specific variations in CVD [33].

Male COVID-19 patients show more symptoms and high deverity of the disease, higher complication rates and finally high mortalities. Possible sexual dimorphisms in ACE2 expression, like the docking sites used by SARS- CoV-2 for cell entrance, indicate that sexual dimorphisms in immune- inflammatory responses can immediately affect the association between CVDs and Covid-19 risks, and thus be attributed to the higher death rates in males [34].

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The concentration levels of lipid profile among studied groups

The levels of total Cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and very low-density lipoprotein (VLDL) are among the strongest risk factors for ACS without COVID-19 & ACS with COVID-19, were assessed in the patients included in the study. Our results reveal that the TC, LDL, TG, and VLDL concentrations in the sera are higher among (ACS & ACS with COVID-19) patients (227.58±5.96, 200.82±11.78 mg/dL), (153.16±9.60, 175.19±13.39 mg/dL), (251.26±11.08, 200.82±11.78 mg/dL) (50.27±2.21, 40.44±2.94 mg/dL) than the healthy subjects (152.54±30.14 mg/dL), (79.36±29.96 mg/dL), (129.62±17.18 mg/dL), (26.16±3.67 mg/dL) in ($p \leq 0.01$). The ACS & ACS with COVID-19 patients were also found to have lower levels of HDL (24.14±9.62, 23.02±10.15 mg/dL) when compared with healthy control (47.34±6.55 mg/dL) ($p \leq 0.01$) these result show in a table (3).

Table (3): The levels of lipid profile for the studied groups.

Lipid profile	Groups	Mean ±Std.	P.value
TG (mg/dL)	ACS without COVID-19	251.26±11.08	.000 (HS)
	ACS with COVID-19	200.82±11.78	.000 (HS)
	Healthy control	129.62±17.18	
TC (mg/dL)	ACS without COVID-19	227.58±5.96	.000 (HS)
	ACS with COVID-19	238.82±13.33	.000 (HS)
	Healthy control	152.54±30.14	
HDL (mg/dL)	ACS without COVID-19	24.14±9.62	.000 (HS)
	ACS with COVID-19	23.02±10.15	.000 (HS)
	Healthy control	47.34±6.55	
LDL (mg/dL)	ACS without COVID-19	153.16±9.60	.000 (HS)
	ACS with COVID-19	175.19±13.39	.000 (HS)
	Healthy control	79.36±29.96	
VLDL (mg/dL)	ACS without COVID-19	50.27±2.21	.000 (HS)
	ACS with COVID-19	40.44±2.94	.000 (HS)
	Healthy control	26.16±3.67	

Serum lipid profiles were appearing to significantly increase altogether in the ACS and ACS with COVID-19 groups, there was more clearly a lipid disorder, apart from S. HDL that was decreased significantly in comparison to the controls as seen in the table (3).The cholesterol test usually considers the range (0- 200 mg/dl) for both males and females to be normal, where the results of the test indicated that patient groups illustrated increased cholesterol levels, these are agreed with [35]. High cholesterol level is a predictive risk factor and plays a role in atherosclerosis formation[36].

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The TG test usually considers the (0-150 mg/dl) range for males and females to be normal, where the results of the test indicated that the ACS and ACS with COVID-19 groups illustrated increased TG levels, with a highly significant difference at $P \leq 0.01$ with the control. The increased blood cholesterol levels and TG are the bad risk factor for ACS, so the high cholesterol and TG levels are considered the risk factors for the occurrence of ACS in Iraqi patients.

The main reason for atherosclerosis, is the inflammation amid the accumulation of fat inside the artery wall, as noted from the results of the present study increased levels of lipid profile (TC, TG, VLDL-C, and LDL-C) while decreased (HDL-C), in patients groups according to statistical analysis great differences found between patients and control group as the displayed in the table (3), this agreement with [37] who show that chronic inflammatory disease of vascular related to endothelial dysfunctions. The LDL cholesterol oxidation is one of the main factors in establishing atherosclerosis. The key factor for the development of atherosclerosis is the oxidation of LDL-C, while non-oxidized LDL has a little affinity for macrophages, so non-oxidized LDL has not a risk factor and a common clinical practice to decrease oxidation and the risk of major events in patients with CVD is the reduce LDL-C level. The present study was in agreement with a previous study of [38] who also revealed significant lower levels of HDL in non-diabetic people with AMI. A study by [39] found that the majority of patients had elevated LDL cholesterol levels and a decline in HDL cholesterol levels after 24 hours of the IM onset. In previous studies, it was shown that the increased LDL & VLDL levels, and reduced HDL levels suggest an increased arterial hardness and carotid intima-media densities [40].Our study showed that the lipid profile according to statistical analysis great differences found between ACS with COVID-19 infection patients group and control group as displayed in table (3), this agreement with [41] who show that the physical activity reduction during COVID-19 resulted in increased levels of LDL, and hence, increased risk of IHD in patients with dyslipidemia with higher risk for CHD. other studies [42، 43] show that subjects admitted to the cardiac care unit(CCU) in COVID-19 have an elevated lipid profile.

The concentration level of SCF among studied groups

Descriptive statistics of SCF serum levels were illustrated in table (4). The mean ±Std was (200.35 ± 6.99 Pg /mL) in patients suffering from acute coronary syndrome and the mean ±Std was (152.36 ± 6.63 Pg / mL) in patients have acute coronary syndrome with COVID -19 infection, while in the control groups the mean ±Std was (380.54 ± 7.77 Pg/mL). The mean SCF level in (ACS & ACS with COVID-19 infected persons) was significantly lower than the controls groups at ($P \leq 0.01$) with lower significant differences between ACS patients & ACS with COVID-19 patients at ($P \leq 0.01$).

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Table (4): The mean ± standard deviation value and Comparison of SCF for the studied groups.

Immunological marker	Mean ±Std.		
	ACS without COVID-19	Control	ACS with COVID-19
SCF(Pg/mL)	200.35±6.99	380.54±7.77	152.36±6.63
	P-Value.000 (HS)		P-Value .000 (HS)
	ACS without COVID-19 and ACS with COVID-19		
	P-Value .000 (HS)		

Our study demonstrated lower SCF levels in the acute coronary syndrome patients group compared with the controls group this agreement with [44] who found decreased levels of SCF related to more serious carotid diseases compared with control subjects and who indicated that SCF can be important to maintain heart functions. exploring probable correlations between the contents of plaque SCF and plaque stability, who determined the SCF, elastin and collagen amounts in 201 endarterectomy samples. The complete plaque (except the 1-mm section from the majority of stenotic lesion portions used for histologic analysis) was homogenized and the elastin and collagen contents were standardized. The contents of plaque homogenate of SCF was determined and standardized relative to the wet weight of plaque. The SCF level in the plaque was significantly related to both elastin contents of the plaque, indicating the presence of cells expressing the SCF receptor in certain atherosclerotic plaques of humans, providing an evidence for the relation between increased levels of SCF and less severe atherosclerotic disorders. Moreover, vascular progenitor cells were applied in heart tissue repair and in some clinical studies showed to be inhibiting myocardial function loss among patients.

A study by [45] demonstrates that intramyocardial administration of SCF sustainably directs more lin-/c-kit stem cells to the heart thus favorably influencing cardiac remodeling following myocardial infarction with acute myocardial infarction. Other research [46] uses stem cells as therapy in acute myocardial infarction. Stem cell transplantation via intracoronary infusions following acute myocardial infarctions (AMIs) represented a new treatment method that was claimed for restoring heart functions. Nonetheless, the mechanism behind its potential effectiveness is still unclear. It was proposed that the transplanted cell apoptosis can modulate the local immune reactivity, resulting in macrophage and dendritic cell deactivation and stimulation of regulatory T- cell lymphocytes. Such phenomena caused repressed apoptosis of myocardial cells, therefore causing cardiac outcome improvement. Other repair mechanisms induced by stem cells demonstrated both in experimental models and in humans are associated with self-regeneration characteristics and plasticity of heart tissues which included (1) direct cell differentiations from mononuclear cells to cardiac myocytes and

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(2) cytokine-induced growths of residual viable myocyte (3) resident cardiac stem cell stimulations (4) cell fusion induction between resident myocyte and transplanted stem cell and (5) interactions between a cardiomyocyte and an endothelial cell. Therefore, such mechanisms can result in a significant elevation of perfusion indices and life quality.

A study [47] demonstrated that SCF supports stem cell recruitment and activation, the ligand for c-Kit, was reported to activate multiple signaling pathways including RAS/ERK, PI3- Kinase, Src kinase, and Janus kinase/signal transducer, the activator of JAK/STAT transcription pathways. The JAK/STAT pathway can mobilize mesenchymal stem cells and may help maintain cardiac function after cell therapy in this subset of patients. Overexpression of SCF by cardiomyocytes was shown to promote stem cell migration and improve outcomes after MI, and thus patients with elevated levels of SCF might be more receptive to cell therapy. Our study found that the SCF level was lowest in ACS with COVID-19 than in other groups included in this. A study of [48] agrees with our study, which shows a strong decrease in SCF. SCF (also known as KIT-ligand) is a cytokine that binds to the c-KIT receptor (CD117) and plays an important role in the regulation of hematopoietic stem cells (HSCs) in the stem cell in the bone marrow. Another study by [49] found a positive correlation between SCF and specific COVID-19 neutralizing antibody titers., and that reduced SCF expression might contribute to the observed lymphopenia in severe forms of COVID-19 and lower antibody titers.

Conclusion

In this study, SCF is an essential hematopoietic cytokine that plays an important role in maintaining hematopoietic stem cells and lymphoid progenitor cells in the bone marrow. The main findings of this study are low SCF levels in patients with ACS, especially with ACS who have COVID-19 infection and this is the first study in Iraq to demonstrate that serum SCF levels decreased in ACS with COVID-19 infection patients. These findings suggest that low SCF levels are associated with the extent and severity of COVID-19. Additionally, externally induced SCF secretion might be used in atherosclerosis treatment. Further studies conducted in larger populations are required.

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