Inflammatory markers in patients who presented with acute coronary syndrome and history of COVID-19 infection: a cross-sectional study [version 1; peer review: awaiting peer review]

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Abstract

Background: During the COVID-19 outbreak, the number of patients who have developed acute coronary syndromes (ACS) has soared rapidly, cardiovascular disease and mortality are influenced by the elevated inflammatory biomarkers. The aim of this study is to compare inflammatory markers between patients with ACS who hadn't previously had COVID-19 and those who'd be infected within the preceding three months; as well as, evaluating the effect of statins on inflammatory biomarkers.

Methods: This is a comparative cross-sectional study of 42 patients who presented with ACS and had previously had COVID-19 and 48 patient who had never had COVID-19, who were admitted to the coronary care unit at the Iraqi Center for Heart Disease and Baghdad Teaching Hospital, Iraq. Inflammatory biomarkers (TNF-α, IL-6, and HS-CRP) levels were determined in serum samples of all patients at admission to these centers then one month later, after administration of statins daily using the Sandwich-ELISA Principle, and Immunofluorescence technique for these markers.

Result: The baseline for patients who had ACS and COVID-19 three months previously, were IL6 (85.87 ±45.80), HS-CRP (23.19 ± 14.49), and TNF-α (161.94± 240.96) were higher than patients that had ACS but not COVID-19; IL6 (50.77±22.48), HS-CRP (13.64± 12.09), and TNF-α (117.73 ±71.23),(p<0.0001), (p=0.003) and (p=0.201) for IL6, HS-CRP, and TNF-α respectively. Rosuvastatin showed a significant reduction in HS-CRP and IL6 (P<0.001), while Atorvastatin a significant reduction in HS-CRP (P<0.001) after one month of therapy. Yet there was no significant difference in the level of TNF α in these two groups at the end of this study. Conclusions: The patients with previous COVID-19 still had higher inflammatory markers than those who didn't. Rosuvastatin 40mg had a more reduction in IL6 than Atorvastatin 40mg after one month and both of them could reduce HS-CRP, but
neither could reduce TNF-α in this short period.

**Keywords**
inflammatory markers, Acute Coronary Syndrome, COVID-19, statins.
Introduction
Coronavirus (COVID-19) has caused considerable death and morbidity worldwide. Acute coronary syndromes (ACS) have highlighted various clinical concerns throughout the outbreak, owing to the hazards of COVID-19-induced cardiac damage and the ambiguities surrounding the therapy of these cardiologic crises. ACS is a term that is used to describe the acute stage of coronary artery disease (CAD) by reducing blood supply to heart and worsening the heart attack; however, many risk factors triggered the ACS such as age, gender, smoking, obesity, hypertension, and diabetic Mellitus. The earlier symptoms are identified, the more probable pathology exists. The three types of ACS related to cardiac ischemia include ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina. High-sensitivity cardiac troponin (hs-cTn) has emerged as a key diagnostic and prognostic biomarker in cardiovascular disease, in addition to clinical criteria and ECG (electrocardiogram)\textsuperscript{3,4}; however, it is clear that viral infection, as well as hypoxia and systemic inflammation, are all independent risk factors that may contribute to the instability of pre-existing cardiovascular disorders (CVD).\textsuperscript{5} In individuals previously infected with COVID-19, classic acute myocardial damage includes several routes like direct angiotensin-converting enzyme (ACE) destruction, which is damaging the angiotensin-converting enzyme receptors in myocytes signaling pathways are affected by the converting enzyme 2 (ACE2). Another possible mechanism is systemic hypoxia-induced cardiac ischemia. Multiple microthromboses, coronary spasm, cytokine storm-induced systemic inflammatory response, and vasculitis-like vascular injury are all probable causes of severe COVID-19 with acute respiratory distress syndrome (ARDS), which may lead to atherosclerotic plaque rupture in extreme cases. COVID-19 is characterized by an inflammatory state manifested by elevated inflammatory biomarkers due to multiple cytokines and chemokines, including Interleukin 6 (IL6), Tumor necrosis factor-alpha (TNF-\alpha), and chemotactic protein of monocytes, which are released into the blood after SARS-CoV-2 internalization and duplication in epithelial cells. These pro-inflammatory cytokines are also thought to play a role in the development and mortality of cardiovascular illnesses. On the other hand, circulating monocytes, neutrophils, and platelets are major predictors of unfavorable cardiovascular (CV) events.\textsuperscript{6} Interleukin-6 (IL-6) and Tumor necrosis factor-alpha (TNF-\alpha) are pleiotropic cytokines that depend on the target cell type and can be either pro- or anti-inflammatory. The presence of IL-6 in the blood has been related to an increased risk of cardiovascular disease.\textsuperscript{9,10} To identify low but persistent levels of inflammation, the High-sensitivity C-reactive Protein (HS-CRP) test monitors low levels of CRP effectively and so helps to forecast a person’s risk of developing cardiovascular disease.\textsuperscript{9,11} TNF production in the atherosclerotic plaque and TNF levels in the blood are always closely correlated with the advancement of atherosclerosis.\textsuperscript{12} Statins are the most widely used and successful treatment for hyperlipidemia in cardiovascular disease. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting enzyme in cholesterol production, which these drugs suppress. Statins have anti-inflammatory, anti-oxidant, anti-apoptotic, and tissue-protective properties in specific clinical situations. This study has been conducted to compare the inflammatory makers between two groups of patients with ACS; those who have not been infected by COVID-19 and those who contracted COVID-19 in the last three months. This study also aims to evaluate the effect different types of statins on inflammatory biomarkers among the two groups.

Methods
Ethics
The study was conducted based on the declaration of Baghdad University's Ethical Committee, College of Medicine, and according to the Ministry of Health Ethical Policy (ethical permission letter No. 1386). Written informed consent was obtained from all participants before inclusion in the study.

Study design
This is comparative cross-sectional research of two groups pretest-posttest design to the patients diagnosed with ACS and was to determine the inflammatory markers IL6, HS-CRP, and TNF-\alpha in this serum.

Study setting and participants
There were 90 individuals in this study who were admitted at Baghdad Teaching Hospital's the Cardiac Care Unit (CCU) and the Iraqi Center of Cardiology/Medical City in Baghdad, Iraq. Participants were patients admitted in the period from November 2021 to April 2022. All individuals diagnosed with ACS were asked if had a previous history of COVID-19 infection in the last 3 months from admission to CCU; confirmed by qualitative Reverse Transcription Polymerase Chain Reaction (RT-RNA) tests on a nose/throat swab positive for COVID-19 and/or CT scan.\textsuperscript{12} The participants were divided into two groups:

Group 1: 42 patients who had ACS and had previously been infected with COVID-19.

Group 2: 48 patients who had ACS but had not had COVID-19.
Both of these groups determent the inflammatory markers IL6, HS-CRP, and TNF-α in the serum of all patients at the admitted day and after one month of taking different types of statins. The patients included in this study had an age range between 35-70 years with a mean (53.63). According to INTERHEART, the youngest median age experienced acute myocardial infarction which is around ten years younger than in North America (59 years) and Western Europe (63 years). Risk factors were also recorded, such as ischemic heart disease, diabetes mellitus, smoking, hypertension, family history, and dyslipidemia; furthermore, COVID-19 infection in the last three months of admission and types of statins were used as one of the management methods for ACS. The exclusion criteria for participants in this study was all patients with congestive heart failure, Coronary Artery Bypass Graft (CABG), urgent Percutaneous Coronary Intervention (PCI), patients have cancer, patients with renal impairment, liver disorder, and acute and chronic inflammatory diseases such as arthritis and pancreatitis. This is because all these criteria effect the level estimation of biomarkers.

**Data collection**

A cardiologist diagnosed the patient with ACS based on their symptoms and ischemic heart disease history, which were both supported by qualitative cardiac troponin and an ECG. So, AS interviewed every patient to collect the data by using a questionnaire designed for this study, consisting of demographic information (age, sex), past medical history focused on (diabetes mellitus, smoking, hypertension, family history, dyslipidemia), measurement height and weight of the patients to calculate the body mass index (BMI) to determine the obesity which was calculated by the following equation (Weir and Jan 2020):

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\text{BMI} = \frac{\text{weight in kilograms}}{\text{square of height in meters}}
\]

BMI<18.5 underweight.

BMI=18.5-24.9 normal weight.

BMI=25-29.9 overweight.

BMI≥30 obese.16

The other section of the questionnaire recorded the types of ACS: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina, COVID-19 infection in the last three months of admission confirm by Transcription Polymerase Chain Reaction (PCR) tests & review the chest CT scan, and the statin type & dose used.

Five milliliters of venous random blood were collected for laboratory investigations using one disposable needle and plastic syringes taken one day after CCU admission. The same procedure was done one month later for each patient. The blood samples were left for about 1 hour for clotting at room temperature and centrifuged 1000 \( \times \) g for 20 minutes. Then the serum was transferred into several parts with 500 \( \mu \)l in Eppendorf tubes in each part was kept frozen in the Hospital laboratory at a temperature of -80°C to analyze it later. This procedure was done according to the leaflet instructions of interleukin 6 & tumor necrosis factor-alpha.16,17

The laboratory investigations were for Hypersensitivity C reactive protein (HS-CRP), Tumor Necrosis Factor-Alfa (TNF-α), and Interleukin 6 (IL6). HS-CRP was estimated at the beginning and after 1 month of the therapy, by using the STANDARD F CRP kit SD BIOSENSOR Korea (for protein analyzer by SD STANDARD) and the Immunofluorescence technique. IL-6 and TNF-α were estimated at the beginning and end of the therapy by using the Elabscience Human IL-6 ELISA KIT, Elabscience Human TNF-αELISA KIT ELABSCIENCE BIOTECHNOLOGY USA (using the Sandwich-ELISA Principle) by HumaReader HS Human.16,17

**Statistical analysis**

The data was analyzed by using the IBM SPSS Statistics for Windows, Version 21 (the free access alternative software is PSPP) to measure the demographic information (age, sex), risk factors & type of ACS by using frequency, percentage, mean and standard deviation. The significance of the difference between the two groups with ACS was tested by using independent means T-Test or chi-square (X² test). Lab results, which include serum of hypersensitivity C reactive protein (HS-CRP), Tumor Necrosis Factor Alfa (TNFα), and Interleukin 6 (IL6), used the dependent-T test to compare the values within the groups (baseline vs one month). When a p-value is less than 0.05, it means there is a difference between the two values, and the null hypothesis is not valid.
Results
One hundred patients were involved in the study; 90 of them completed the research; 42 of them had ACS and had had COVID-19 during the last three months before admission, 48 of them had ACS but had not had COVID-19. Ten patients were lost to follow-up, so they have not been included in the final analysis.

We found that age, sex, smoking, obesity, the presence of hypertension, diabetes mellitus, and the type of ACS NSTMI statistically do not have significant differences between the two groups. Other factors like STEMI, unstable angina, and dyslipidemia have significant differences between the two groups p<0.000. While STEMI had a significantly increased number and mean proportion of ACS patients who had COVID-19 where it was 32 patients and the mean proportion was 76.2%, dyslipidemia had a significantly increased number and mean proportion of ACS patients who had not had COVID-19; 26 patients and a mean proportion of 54.2%. Unstable angina was observed only in the group of ACS patients who had not COVID-19 where their number was 17 and the mean proportion was 35.4% (see Table 1).

At the baseline, the biochemical characteristics of the ACS for the group who had COVID-19 during the last three months before admission, showed IL6 (85.87±45.80), HS-CRP (23.19±14.49), and TNF-α (161.94±240.96). However, the other group who had ACS without COVID-19 showed IL6 (50.77±22.48), HS-CRP (13.64±12.09) and TNF-α (117.73±71.23), p-value<0.000 for IL6, p-value=0.003 for HS-CRP, and p-value=0.201 for TNF-α. This means the first group had a detected inflammatory marker more than the second group (see Table 2).

When statin therapy was used for one month, the inflammatory marker showed a significant difference in the two groups in reducing levels of HS-CRP, and IL6 (p<0.001). Yet there was no significant difference in the level of TNF-α in these two groups at the end of this study (p=0.813) and (p=0.553) (see Table 3).

Among the patients with ACS and COVID-19, who have huge inflammatory markers at baseline, used Atorvastatin 40 mg 21 (50%) or Rosuvastatin 40 mg 21 (50%). After one month of receiving the drug, the inflammatory markers showed statistically significant lowering HS-CRP (p<0.001) for patients who were receiving both of them, but those receiving Rosuvastatin 40 mg showed statistically significant lowering IL6 (p<0.001) while those receiving Atorvastatin

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Table 1. Assessment of basic data in each treatment group.

| Group | Parameter | ACS + COVID 19 previously (N=42) | ACS non-COVID 19 (N=48) | p-value |
|-------|-----------|---------------------------------|-------------------------|---------|
|       | Age       | Mean±SD Proportion n(%)         | Mean±SD Proportion n(%) |         |
|       |           | 52.0±9.0 34 (80.9) %            | 55.0±10.0 40 (83.3) %   | 0.137   |
|       | Sex       | M 34 (80.9) %                   | F 8 (19.1) %            |         |
|       | Hypertension | 22 (52.4) %                      | 29 (61.7) %             | 0.44    |
|       | Diabetes mellitus | 21 (50.0) %                       | 24 (50.0) %             | 0.373   |
|       | Smoking   | 12 (28.5) %                      | 23 (47.9) %             | 0.498   |
|       | Obesity (BMI) | 29.94±3.87                        | 27.81±4.43             | 0.471   |
|       | Dyslipidemia | 3 (7.1) %                          | 26 (54.2) %             | 0.000   |
|       | STEMI     | 32 (76.2) %                       | 23 (47.9) %             | 0.000   |
|       | NSTEMI    | 10 (23.8) %                       | 8 (16.7) %              | 0.160   |
|       | Unstable Angina | ------------                 | 17 (35.4) %             |         |

Table 2. Assessment of inflammatory biomarkers in each group.

| Inflammatory markers | ACS+ COVID19 Previously at baseline N=42 | ACS without COVID19 at baseline N=48 | p-value |
|----------------------|-----------------------------------------|--------------------------------------|---------|
| IL6                  | 85.87±45.80                             | 50.77±22.48                         | 0.000   |
| HS-CRP               | 23.19±14.49                             | 13.64±12.09                         | 0.003   |
| TNF-α                | 161.94±240.96                           | 117.73±71.23                       | 0.201   |
Table 3. Comparison of patients who have ACS with COVID-19 in the last three months & without COVID-19, reducing inflammatory markers after using a statin.

| Inflammatory marker     | Group                              | At baseline | After one month | Mean change | p-value* |
|-------------------------|------------------------------------|-------------|-----------------|-------------|----------|
| IL6                     | ACS with COVID19 N=42              | 80.95±52.97 | 47.87±44.01     | 33.08±8.96  | .000     |
|                         | ACS without COVID19 N=48           | 50.77±22.48 | 28.05±10.49     | 22.72±11.49 | .000     |
| HS-CRP                  | ACS with COVID19 N=42              | 23.19±14.49 | 4.81±6.83       | 18.38±7.66  | .000     |
|                         | ACS without COVID19 N=48           | 13.64±12.09 | 4.19±6.18       | 9.44±5.91   | .000     |
| TNF-α                   | ACS with COVID19 N=42              | 161.94±240.96 | 191.22±86.45  | 29.28±154.51 | .813     |
|                         | ACS without COVID19 N=48           | 117.73±71.23 | 130.22±62.37  | 12.49±8.86  | .553     |

*In each group compared at one month from baseline.

Table 4. Comparison of Atorvastatin and Rosuvastatin in reducing inflammatory markers in patients who have ACS with COVID-19 in the last three months.

| ACS and COVID-19 Previously N=42 | Types of statin | IL6               | HS-CRP             | TNF-α               |
|----------------------------------|-----------------|-------------------|-------------------|-------------------|
|                                  | Rosuvastatin 40 mg N=21 | 79.06±26.88     | 28.78±17.59      | 17.66±98.87      | 0.629 |
|                                  | Atorvastatin 40 mg N=21 | 95.11±71.13       | 70.59±54.67      | 24.52±16.46      | 0.083 |

Table 5. Comparison of Atorvastatin and Rosuvastatin in reducing inflammatory markers in patients who have ACS without COVID-19.

| ACS without COVID-19 N=48 | Types of statin | IL6               | HS-CRP             | TNF-α               |
|--------------------------|-----------------|-------------------|-------------------|-------------------|
|                          | Rosuvastatin 40 mg N=25 | 65.86±29.24     | 33.69±23.95      | 16.01±10.54      | 0.000 |
|                          | Atorvastatin 40 mg N=23 | 56.69±25.28     | 47.68±35.69      | 9.01±10.41       | 0.243 |

40 mg statistically not significant in the decreasing IL6 (p=0.083). Another inflammatory marker, TNF-α was not a statistically significant change from baseline (p=0.629) in the patients who were using Rosuvastatin 40 mg and (p=0.870) in those who were using Atorvastatin 40 mg (see Table 4).
The patients with ACS and COVID-19, were divided into subgroups: the first group used Atorvastatin 40 mg was made up of 21 patients and the mean proportion was (50%), and the second group used Rosuvastatin 40mg was also made up of 21 patients and the mean proportion was (50%). The ACS group without COVID-19 was also divided into subgroups: one group used Atorvastatin 40 mg was 25 patients and mean proportion was (52%) and the other group used Rosuvastatin 40 mg was 23 patients and the mean proportion was (48%). For the both main groups, Rosuvastatin 40 mg was statistically significant in decreasing HS-CRP, and IL 6 (P<0.001) while Atorvastatin 40 mg was statistically significant in decreasing HS-CRP (p<0.001); however, both of these drugs in the two groups did not statistically significant change TNF-α from baseline to the end of this study period (see Table 4 and Table 5).

Discussion
This study found that there were not any differences in these traditional CAD risk factors between the two groups, those who had COVID-19 and those who hadn’t, yet COVID-19 aggravates ACS syndromes. The risk variable results of this study are comparable with many studies that found the traditional CAD risk factors aggravate COVID-19.19–21

In this study, dyslipidemia doesn’t aggravate COVID-19, but it is one of the risk factors that trigger ACS because atherogenicity has been linked to lifting the low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) cholesterol, yet it lowers HDL cholesterol levels. These changes increase the risk of cardiovascular disease, and when accumulated with the atherosclerotic plaque and rupture, ulceration, or erosion, cause intraluminal thrombus development and restrict myocardial blood flow; resulting in myocardial necrosis.22,23 This mechanism isn’t a trigger for COVID-19 infection, but when patients have a history of dyslipidemia and COVID-19, this may cause ACS and increase the severity of COVID-19.24

The acute phase induces the production of adhesion molecules and chemokines such as monocyte, macrophage, and neutrophile by endothelial cells leading to the formation of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL-6).25 The key determination of acute-phase protein such as CRP is synthesis and released from the liver, rise as a result of IL-6, which are characteristics that promote the progression of cardiovascular disease.26

This research found the inflammatory markers HS-CRP, IL6, and TNF-α at baseline of the group who had COVID-19 previously with ACS, is greater than another group with ACS. Therefore COVID-19 triggers ACS directly by causing systemic inflammation associated with hypercoagulation status and might cause increased thrombosis in the coronary, and the result can be STEMI.27

So, in this study, the patients who had COVID-19 virus were more susceptible to STEMI or its complication than non-COVID-19 patients. While NSTEMI can happen when there is partial or temporary artery occlusion, Platelet emboli may cause small regions of myocardial necrosis.28 When comparing NSTEMI between the two groups there weren’t differences between them, but unstable angina occurred only in the non-COVID-19 group and did not occur in the other group. The result of this study about STEMI, NSTEMI, and unstable angina were compatible with thrombus viral load and thrombus size are examined in observational cohort research occurred with a similar study.27,29

Statin are one of the drugs used in the management of ACS and is known as an anti-inflammatory, and anticoagulant, therefore is used to measure how to reduce the inflammatory effect, especially in individuals who previously had COVID-19, because these patients, according to this study, had higher inflammatory markers than others who did not have COVID-19, because SARS-CoV-2 is targeting the endothelium which is one of the biggest organs in the human body so, most of these patients had risk factors such as hypertension, diabetic mellites, smoking which are increasing the disturbance of the endothelium function and make clotting cascade and inflammation.30

In this study, statins reduced HS-CRP and IL-6 in both groups after one month when compared to the baseline, but the change mean was higher in ACS with the COVID-19 group than in the other group. This reduction in inflammatory markers agrees with the prospective study when using the statin in hospitalized patients with COVID-19 and coronary heart disease.31

In this study, when comparing the types of statins, the reduction of Rosuvastatin on HS-CRP, and IL6, it was observed that the magnitude of the reduction was double that of Atorvastatin during this period of study. So Rosuvastatin 40 mg can lower the risk of recurrent coronary events in both groups, within a short time while Atorvastatin decreases the level but takes more time to be a significant reduction of IL6 which is directly responsible for atherosclerosis formation and progression processes.29,32
Although the statin decreases the inflammatory biomarkers of both HS-CRP and IL-6, it was not shown on the Tumor necrosis factor (TNF-\(\alpha\)), instead, it was increased in the two groups and markedly increased in those with ACS and previous COVID-19 infection. The suggested cause is a proinflammatory cytokine and COVID-19, which have a mortality relationship.\(^{33}\) So, in the case of ACS, the level of TNF-\(\alpha\) increased within two weeks after the onset and increased the serum level expression around one year after onset.\(^{34}\) This is because of the duration of a statins prescription required to decrease TNF-\(\alpha\) is from 12 weeks up to 6 months or more, depending on the types of statins and level of lipid profile,\(^{35,36}\) however, our follow up in this study was only after 1 month.

**Conclusion**

Although the patients who were infected previously with COVID-19 still had higher inflammatory markers than didn’t, both showed a significant reduction of inflammatory markers after statin therapy. ACS patients who previously had COVID-19 are more liable to STEMI. Rosuvastatin was more powerful in a reduction in IL6 and HS-CRP than Atorvastatin but neither could reduce TNF-\(\alpha\) in this short period.

**Data availability**

**Underlying data**

Zenodo: ACS WITH AND WITHOUT COVID19, https://doi.org/10.5281/zenodo.6907978.\(^{37}\)

This project contains the following underlying data:

- ACS WITHOUT COVID19.xlsx
- ACS+COVID 19.xlsx

Zenodo: Result of ACS patients in the CCU who have and haven't Covid-19 for the last three months before the CCU admission, https://doi.org/10.5281/zenodo.6908166.\(^{38}\)

This project contains the following underlying data:

- Basic data.xlsx
- Inflammatory biomarkers at baseline.xlsx
- comparison between two group after using statins.xlsx
- atorvastatin used in ACS with COVID19.xlsx
- atorvastatin used in ACS without COVID19.xlsx
- Rosuvastatin used in ACS with COVID19. Xlsx
- Rosuvastatin used in ACS without COVID19. Xlsx

**Extended data**

Zenodo: questionnaire

https://doi.org/10.5281/zenodo.6908205\(^{14}\)

This project contains the following extended data:

- questionnaire.docx

Data are available under the terms of the Creative Commons Attribution 1.0 Generic license (CC-BY 1.0).
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