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Research Article

Evaluation of IL-8, C3, and C4 as Immune Activation Markers in COVID-19 Patients: A Cross-Sectional Study from Iraq

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I N F O

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A B S T R A C T

Background: The COVID-19 pandemic, caused by SARS-CoV-2, has led to diverse clinical outcomes and global health challenges. Identifying reliable immunological biomarkers is essential for disease monitoring, severity prediction, and therapeutic decisions.

Objective: This study aimed to evaluate the serum levels of Interleukin-8 (IL-8), complement component 3 (C3), and complement component 4 (C4) in COVID-19 patients compared to healthy individuals, and to assess their correlation with disease severity.

Methods: A cross-sectional study was conducted on 100 RT-PCR–confirmed COVID-19 patients and 50 age- and sex-matched healthy controls in Ramadi, Iraq. Serum IL-8 levels were measured using ELISA, while C3 and C4 were quantified via radial immunodiffusion. Statistical analysis was performed using ANOVA and Bonferroni tests, with $p < 0.05$ considered significant.

Results: COVID-19 patients showed significantly elevated levels of IL-8 (246.6 ± 11.5 pg/mL), C3 (2.52 ± 0.12 g/L), and C4 (0.49 ± 0.01 g/L) compared to controls ($p < 0.001$). Biomarker levels correlated positively with disease severity: IL-8, C3, and C4 progressively increased from mild to severe cases. No significant gender-based differences were observed.

Conclusion: IL-8, C3, and C4 levels were markedly elevated in COVID-19 patients and significantly associated with disease severity. These biomarkers may serve as indicators of immune activation and potential prognostic tools in COVID-19. Larger, multicenter, and longitudinal studies are needed to validate their clinical utility for early risk stratification and management in SARS-CoV-2 infections.

Keywords: COVID-19, Interleukin-8, Complement C3, Complement C4, Biomarkers, Immune response

Introduction

Coronavirus disease (COVID-19), caused by SARS-CoV-2, was first reported in Wuhan, China, in December 2019 and rapidly spread worldwide.[1] Clinical presentations range from asymptomatic or mild flu-like symptoms to severe pneumonia, respiratory failure, and multi-organ dysfunction. About 80% of patients develop mild to moderate illness, 15% progress to severe disease, and 5% experience critical outcomes requiring hospitalization.[2] Elderly individuals and those with comorbidities such as cardiovascular disease, diabetes, and chronic lung disorders are at higher risk of poor prognosis.[3]

Immune dysregulation is central to disease severity. The neutrophil-to-lymphocyte ratio is an accessible marker of systemic inflammation.[4] Interleukin-8 (IL-8), a neutrophil chemoattractant produced by epithelial and endothelial cells, is elevated in viral infections and linked to severe lung injury.[5,6] Complement activation further amplifies inflammation through cleavage of C3 and C5, generating fragments that promote opsonization, cytokine release, and membrane attack complex formation.[7] High C5a levels and C5aR1 expression in severe COVID-19 underline the role of complement in hyperinflammation and coagulation.[8,9] SARS-CoV-2 infection also triggers uncontrolled cytokine release ("cytokine storm"), which contributes to multi-organ damage.[10,11] Identifying biomarkers reflecting immune activation is therefore crucial in predicting severity and guiding treatment.

This study aimed to evaluate serum IL-8, C3, and C4 levels in COVID-19 patients and compare them with healthy controls, to assess their potential role as markers of disease severity and prognosis.

Material and Methods

Patients

This was a cross-sectional study among patients suffering from COVID-19 infection. Clinical samples (blood) were collected from two groups coronavirus patients and healthy groups. 100 male and female patients with an average age of 30-50 years old, samples were collected from the Al-Ramadi Teaching Hospital, Respiratory unit, and private clinical lab between November 2021 and April 2022. Written informed consent was obtained from every patient giving blood samples for the study.

Sample distribution

100 COVID-19 patients and 50 healthy controls

Selection Criteria

- **Cases:** RT-PCR–confirmed COVID-19, admitted to hospital. Categorized as mild, moderate, or severe based on WHO clinical criteria.
- **Controls:** Age- and sex-matched healthy individuals without history of COVID-19 or chronic illness.

Sample Collection

Whole blood is one of the samples used for analysis most frequently. The gel tube was filled with blood to prepare the serum. Before being processed for serum preparation, the blood sample tube (gel tube) was kept at room temperature (20 to 25 degrees Celsius) and was not treated with any anticoagulant agents. Specimens that are clotted or hemolyzed ought to be rejected.

Sample Size Calculation

Sample size was calculated using the formula for comparing two means, considering an expected 20% difference in biomarker levels between cases and controls, power of 80%, and confidence interval of 95%. The minimum required sample was 80; we included 100 patients and 50 controls to improve reliability.

Ethical Clearance

The study was approved by the Institutional Ethics Committee of Al-Ramadi Teaching Hospital. Written informed consent was obtained from all participants.

Measured parameters

Assay principle of human interleukin- 8 ELISA kits

The interleukin 8 was using a human interleukin ELISA kit, equipped with (SUNLONG Biotech Co., LTD, www.sunlongbiotech.com, China), and the assay was carried out according to the company's instructions. Serum IL-8 levels were measured using a Human IL-8 Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions."

"Serum C3 and C4 concentrations were determined by radial immunodiffusion (RID) using NOR Partigen plates (Siemens Healthcare Diagnostics, Germany), following the manufacturer's protocol."

Determination of the C3 and C4 protein

Test summary

When a protein is analyzed, it diffuses in an agarose gel that has been exposed to a particular antibody, creating an immuno-complex that surrounds the well and can be seen as a ring. The diameter of this ring corresponds exactly to the protein concentration under study. After 72 hours (steps 1-3), the square of the diameter will be in linear proportion to the concentration; this proportionality relates to the diffusion duration. On the other hand, process 2 will result in the square of the diameter being in logarithmic proportion to the concentration after a shorter diffusion period. Creating a calibration curve with a minimum of three calibration points is crucial in both situations. There

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is a reference table that shows the connection between the procedure's finish and any concentration.

Reagents

- **Plate:** Agarose gel containing the goat antiserum C3 and C4

Procedure

To allow any condensed water in the wells to evaporate, take the plate out of its envelope and leave it at room temperature for a few minutes. Before handling the plate, make sure the sample and/or controls have been completely absorbed by adding 5 µl to each well. Put the plate in a wet chamber after closing it. Give yourself the required amount of time to incubate (72 hours for procedures 1 or 3 and 18 hours for procedures 2). It is possible to place the plates in a thermostat to speed up the analysis process.

Results interpretation of C3 and C4 protein

Following the prescribed incubation time-72 of 18 hours, depending on the protocol—measure the precipitating ring to the closest 0.1 mm.

Expected values of C3 and C4 protein

C3 (0.8 – 1.85) mg/dl

C4 (0.1 – 0.4) mg/dl

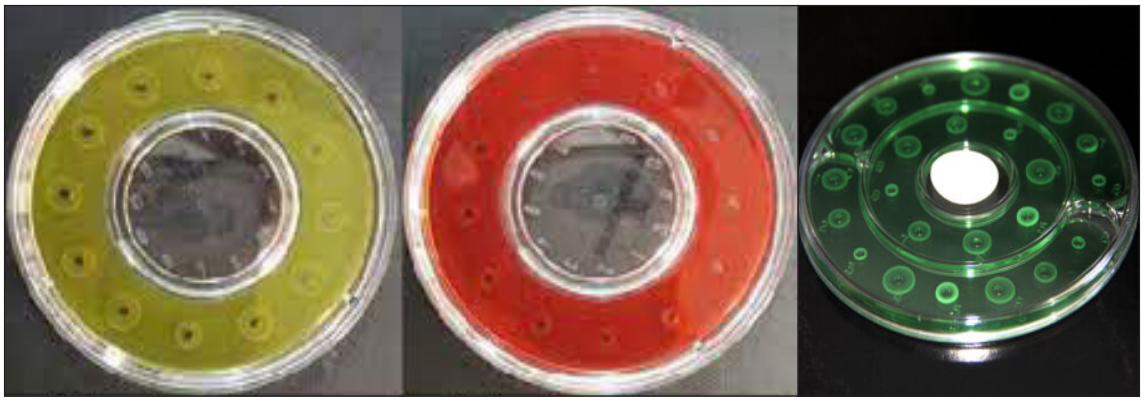

Table 1.Baseline characteristics of study participants

Parameter	COVID-19 Patients (n=100)	Controls (n=50)	p-value
Age (years), Mean ± SD	42.3 ± 8.5	41.8 ± 7.9	0.72
Sex, n (%)			
Male	58 (58%)	27 (54%)	0.65
Female	42 (42%)	23 (46%)	
Severity, n (%)			
Mild	50 (50%)	—	
Moderate	30 (30%)	—	
Severe	20 (20%)	—	

Table 2.Comparison of IL-8, C3, and C4 between COVID-19 patients and controls

Biomarker	Controls (n=50) Mean ± SD	COVID-19 Patients (n=100) Mean ± SD	p-value
IL-8 (pg/mL)	37.7 ± 12.5	246.6 ± 11.5	<0.001
C3 (g/L)	1.22 ± 0.32	2.52 ± 0.12	<0.001
C4 (g/L)	0.23 ± 0.09	0.49 ± 0.01	<0.001

Table 3.Biomarker levels stratified by COVID-19 severity

Biomarker	Mild (n=50) Mean ± SD	Moderate (n=30) Mean ± SD	Severe (n=20) Mean ± SD	p-value (ANOVA)
IL-8 (pg/mL)	180.4 ± 15.2	250.8 ± 20.5	320.6 ± 25.3	<0.001
C3 (g/L)	2.10 ± 0.20	2.50 ± 0.18	2.90 ± 0.22	<0.001
C4 (g/L)	0.40 ± 0.06	0.49 ± 0.05	0.60 ± 0.07	<0.001

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Statistical analysis

A one-way analysis of variance (ANOVA) using GraphPad Prism® Version 5.0 software or the Bonferronis Multiple Comparison tests was used to examine the statistical significance of differences between mean values from the control and treated groups; $p < 0.05$ was considered significant.

Results

Characteristics of the study groups

Baseline characteristics of study participants

The baseline characteristics of the study population are shown in Table 1. The mean age of COVID-19 patients was 42.3 ± 8.5 years, which was comparable to that of the control group (41.8 ± 7.9 years), with no statistically significant difference ($p = 0.72$). The sex distribution was also similar between the groups, with males comprising 58% of patients and 54% of controls, and females accounting for 42% and 46%, respectively ($p = 0.65$). Among the COVID-19 cohort, 50% presented with mild disease, 30% had moderate disease, and 20% were categorized as severe cases, indicating a representative distribution across the clinical spectrum.

Comparison of IL-8, C3, and C4 between COVID-19 patients and controls

Table 2 compares the mean levels of IL-8, C3, and C4 between COVID-19 patients and healthy controls. Serum IL-8 levels were markedly elevated in COVID-19 patients (246.6 ± 11.5 pg/mL) compared with controls (37.7 ± 12.5 pg/mL), with the difference being highly significant ($p < 0.001$). Similarly, mean C3 concentrations were significantly higher in patients (2.52 ± 0.12 g/L) than in controls (1.22 ± 0.32 g/L, $p < 0.001$). C4 levels also showed a comparable pattern, being raised in patients (0.49 ± 0.01 g/L) compared with controls (0.23 ± 0.09 g/L, $p < 0.001$). These findings confirm that immune activation markers were significantly altered in COVID-19 patients compared with healthy individuals.

Biomarker levels stratified by COVID-19 severity

Table 3 demonstrates the relationship of IL-8, C3, and C4 with disease severity among COVID-19 patients. IL-8 levels showed a progressive increase across severity groups, with mean values of 180.4 ± 15.2 pg/mL in mild cases, 250.8 ± 20.5 pg/mL in moderate cases, and 320.6 ± 25.3 pg/mL in severe cases ($p < 0.001$). A similar trend was observed for complement proteins. C3 concentrations rose from 2.10 ± 0.20 g/L in mild cases to 2.50 ± 0.18 g/L in moderate cases, and further to 2.90 ± 0.22 g/L in severe cases ($p < 0.001$). Likewise, C4 levels increased significantly with disease severity, ranging from 0.40 ± 0.06 g/L in mild cases to 0.49 ± 0.05 g/L in moderate cases and 0.60 ± 0.07 g/L in severe cases ($p < 0.001$). These results indicate that IL-8, C3, and C4 are strongly associated with disease progression, with higher levels reflecting increasing severity.

Comparison of serum Interleukin 8 production in healthy and COVID-19 patients

To assess the potential role of interleukin 8 in patients with coronavirus, healthy and patient samples were utilized. However, serum of healthy control was suggestively within the normal value. While, the serum of patients for interleukin 8 in the COVID-19 group was significantly high as compared to healthy controls (mean ± SEM 37.66 ± 12.45 versus 246.616 ± 11.483, $p = 0.0002$)

Characterization of serum C3 levels in both healthy individuals and those with COVID-19 to understand the distinctions.

The C3 concentration in patients in comparison to the healthy group is shown in Figure 2. The Figure shows that healthy control (HC) represents a substantial normal value of C3 concentration as expected (mean ± SE, 1.216 0.32) and these values were significantly increased in the patients with COVID-19 group (mean ± SE 2.519±0.124) respectively. However, healthy was with normal values while significantly high in COVID-19 patients.

C4 concentration in healthy group (mean ± SE 0.233± 0.088) and patients group (mean ± SEM 0.488± 0.006). This difference was also significant.

The Characterization of interleukin 8 induction between male and female patients

The impact of COVID-19 on interleukin-8 (IL-8) production was also analyzed based on gender. The results showed that there was no significant effect of COVID-19 on IL-8 production in either males or females. There was only a slight difference between the genders, with the male group exhibiting a small increase in IL-8 levels that were not statistically significant compared to the female group. (male = mean ± SEM 248.858±84.918 and female = mean ± SEM 243.869±86.5486).

The Characterization of C3 concentration between male and female patients

Similarly, C3 levels were studied in both males and females using the same method. As shown in Figure 6, there were no significant differences between males and females in terms of C3 estimation (male = mean ± SEM 2.182±0.407 and female = mean ± SEM 2.466±0.516).

The Characterization of C4 concentration between male and female patients

The figure 6 illustrates a marginal rise in C4 concentration within the male group; however, this increase did not attain statistical significance when compared to the female group. (male = mean ± SEM 0.566± 0.093 and female = mean ± SEM 0.443± 0.09).

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Discussion

This study was conducted within Al-Ramadi Teaching Hospital to explore the impact of COVID-19 infection on serum levels of interleukin-8, C3, and C4. The immunological alteration has been observed in another study also.[12] The key findings indicated a notable increase in the concentrations of serum interleukin-8, C3, and C4, respectively. Since the emergence of SARS-CoV-2, the worldwide COVID-19 pandemic has led to approximately a million fatalities from over fifty million confirmed cases globally.[13] Our ongoing investigations provide supporting evidence indicating that IL-8 could serve as a valuable diagnostic tool for identifying severe cases of COVID-19. The same has been observed by others.[14]

The assessment of cytokine levels in blood samples collected from COVID-19 patients at various phases of severe illness or recovery revealed unique cytokine profiles that might be connected to COVID-19 disease state.[15] IL-8 serum levels were significantly higher in individuals with severe COVID-19. Significantly, our findings indicate that IL-8 may work differently as a biomarker, giving information about both the severity and prognosis of COVID-19-associated disorders. In comparison to healthy donors, COVID-19 patients, whether moderate or severe, had significantly greater amounts of IL-8 in their serum.[20]

The study population had a comparable mean age between COVID-19 patients (42.3 ± 8.5 years) and controls (41.8 ± 7.9 years, $p = 0.72$), with a similar sex distribution (males: 58% vs. 54%; females: 42% vs. 46%, $p = 0.65$). Among COVID-19 cases, 50% were mild, 30% moderate, and 20% severe. Immune markers were significantly elevated in patients, with markedly higher IL-8 (246.6 ± 11.5 vs. 37.7 ± 12.5 pg/mL, $p < 0.001$), C3 (2.52 ± 0.12 vs. 1.22 ± 0.32 g/L, $p < 0.001$), and C4 (0.49 ± 0.01 vs. 0.23 ± 0.09 g/L, $p < 0.001$) compared to controls, confirming substantial immune activation in COVID-19, suggesting that it might be a biomarker for disease prognosis.[16] Our findings are congruent with those of recent research reported earlier.[17] Our findings are consistent with a recent study, which found that IL-8 causes a considerable compartmentalized response in the lungs. When addressing the cellular immune response,[18] these findings are consistent with the documented function of IL-8 in attracting neutrophils to the lungs during acute pulmonary inflammation. IL-8 was identified as the particular activator for neutrophils.[19] These findings align with the study conducted by.[20]

The outcomes of our project highlight the significant impact of COVID-19 on the concentrations of C3 and C4.[21] Individuals with COVID-19 exhibited a significant response involving the major components of the complement system, particularly the C3 and C4 proteins.[22] Given the pivotal role of C3 in all complement activation pathways, our project focused on examining the impact of COVID-19 on both C3 and C4.[23] The observed results indicated a noteworthy elevation in the serum concentrations of complement C3 and C4 in COVID-19 patients, which contrasts with the findings reported in a separate study.[24] Contrary to our findings, the mentioned study reported disparate results, indicating a notable decrease in the concentrations of C3 and C4 in patients with coronavirus infection.[25] The evaluation of serum levels of complement components C3 and C4 proves valuable in diagnosing and monitoring blood-related infectious diseases and immune complex disorders.[26]

When an infection occurs, C3 typically decreases as a result of consumption, but immunological complex illnesses typically exhibit a simultaneous drop in both C3 and C4.[27] Because uncontrolled activation of the complement system can have detrimental consequences on the structural and functional integrity of numerous organs and tissues, evaluation of the complement system in the context of SARS-CoV-2 has received a lot of interest.[28] Research highlighting the advantages of corticosteroid therapy for COVID-19 patients lends credence to this idea.[29] These results imply that an excessively aggressive host immune response results in tissue and organ damage, rather than viral infection directly causing harm.[30]

Strengths of this study include being one of the first hospital-based analyses in Iraq assessing IL-8, C3, and C4 in COVID-19 patients. The inclusion of both male and female participants improves generalizability. However, limitations include modest sample size, single-center design, and lack of longitudinal follow-up to assess biomarker changes over time. Furthermore, confounding factors such as comorbidities were not fully controlled.

Conclusion

The levels of IL-8, C3, and C4 in patients with Covid-19 were significantly high suggesting inflammation in them. More the research is required to understand these markers of COVID-19 immunocompetence and their potential utility in advanced settings to monitor treatment for the impact of COVID-19.

The study demonstrated significantly elevated serum IL-8, C3, and C4 levels in COVID-19 patients compared to healthy controls. IL-8 may serve as a potential marker of disease severity, while complement activation indicates heightened immune response. Further multicenter studies with larger sample sizes and severity-based analyses are required to establish these markers as prognostic tools for COVID-19 management.

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