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## The Impact of COVID-19 on White Blood Cell Subpopulations and Inflammatory Markers

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### Abstract

**Background:** COVID-19 is a disease of the zoonosis class and much has come to light since the onset of the pandemic in December 2019. Understanding COVID-19 pathophysiology is crucial for its effective treatment. The present study is conducted to observe the haematological changes associated with COVID-19 infection among a cohort of Iraqi patients.

**Methods and Design:** A retrospective cohort study involving confirmed (60) COVID-19 patients and (20) individuals in the control group admitted to Al Karama Teaching Hospital in Al-Kut Wasit Province, Iraq. Data captured included complete blood counts (CBC), C-reactive protein (CRP), and D-dimer levels. The statistical analysis covered t-tests for between-group comparison and multiple linear regression to ascertain the associations between the haematological parameters.

**Results:** The COVID-19 patients had a significantly higher total white blood cell count, with a mean of 17.1575 than the control groups of 8.7005 ( $p > 0.001$ ). COVID-19 patients also had significantly greater

mean lymphocyte counts (mean 55.365) compared to controls (mean 29.79;  $p > 0.001$ ), suggesting the presence of lymphocytosis. The COVID-19 patients also showed significantly higher mean neutrophil count (mean 82.9205) than the control group (mean 60.369;  $p > 0$ ). The mean levels of CRP were 75.74667 in COVID-19 patients, which is significantly higher compared to 3.11 as observed in the control group ( $p > 0.001$ ). Similarly, the mean D-dimer levels were higher in COVID-19 patients at 2319.7 compared to 336.65 in the control group ( $p > 0.001$ ). The correlation analysis shows a high negative correlation between WBCs and neutrophils and a moderate positive correlation between CRP and D-dimer, which reflects the complex interplay between inflammatory and coagulation processes.

**Conclusion:** This study highlights striking haematological changes in COVID-19, characterized by lymphocytosis, neutrophilia, and activation of inflammatory and coagulation markers. It underlines the

importance of monitoring these parameters for better patient management. More research is needed to explore therapeutic interventions targeting these specific immune and coagulation responses in COVID-19.

## **Introduction**

The novel zoonotic illness known as COVID-19 that originated from the deadly SARS-CoV-2 virus has tremendously influenced world health [1, 2]. This virus, considered to have stemmed from bats and shifted to humans through a middle animal host [3], has precipitated the following comprehensive and diverse disease. Although the effects of COVID-19 on the respiratory system have been articulated, the virus affects the system holistically with myriad systemic manifestations [4]. As mentioned earlier, this is one of the several ways the given disease influences the systemic level: changes in haematological indicators, WBC, and inflammatory response biomarkers. These changes speak of the interaction of the virus with the host immunity and the emergence of inflammatory and thrombotic events [5].

Leucocytes, or white blood cells, are the functional elements of the immune system, the mandate to fight off pathogens and invaders. Depending on functionality, WBCs are grouped into discrete subcategories [6, 7]. Two major types of lymphocytes are involved in adaptive immunity: T-cells and B-cells. T-cells identify pathogens and launch specific immune responses. Neutrophils are the predominant type of WBCs engaged in innate immunity; they are the first line of defence and are mainly involved in the phagocytosis of pathogenic organisms. D-dimer is a fibrin degradation product demonstrating an increased level, suggesting a hypercoagulable state [8, 9]. Higher D-dimer concentration may indicate the risk of thromboembolic events, such as DVT, PE, and DIC. Respectively, C-reactive protein (CRP), an acute phase protein, increases rapidly with inflammatory response [10, 11]. Higher CRP levels indicate tissue inflammation and cytokines liberation, which depicts the body is inflamed [8]. Thus, this retrospective cohort study seeks to analyze the relationship between these laboratory markers in confirmed COVID-19 patients and a control group in Iraq to determine haematological changes specific to COVID-19 infection. Therefore, understanding these changes can help advance knowledge regarding immune response and related challenges with this zoonotic disease, which can contribute to additional attempts at controlling the COVID-19 currently ravaging the world.

The current study is highly sensitive because there is scarce literature on the effect of COVID-19 on hematological values in Iraqi people. Previous studies have highlighted the heterogeneity of COVID-19 disease severity and its diverse clinical presentations [12, 13]. Understanding the specific hematological alterations associated with COVID-19 in Iraq, a region with unique demographic and epidemiological characteristics, is crucial for tailoring effective treatment strategies and improving patient outcomes. By examining the relationship between WBC subpopulations, inflammatory markers, and COVID-19 severity in a local cohort, this study contributes to the growing body of knowledge about the global impact of this pandemic and informs local clinical management practices.

## **Materials and Methods**

### **Study Design**

The present study was a retrospective hospital-based cohort study investigating 60 patients with COVID-19 and compared their laboratory test results to 20 individuals in a control group. Samples from COVID-19 patients were collected from the 1st of January to the 25th of May 2024 diagnosis by rapid test of COVID-19 from nasal swab specimens. The research occurred at AL Karama Teaching Hospital in Al Kut Wasit Province, Iraq.

## **Diagnostic Criteria**

All individuals involved were verified to have tested positive for COVID-19 through real-time reverse transcription polymerase chain reaction (RT PCR) tests conducted on samples taken from nasal swabs, whereas patients with negative results were considered the control group.

### **Laboratory Tests:**

A complete Blood Count (CBC) was performed using automated hematology analyzers to assess the total white blood cell count. D-dimer levels, a marker of coagulation activation, were measured quantitatively using a commercially available automated immunoassay, the Ichroma II system. C-reactive protein (CRP), a sensitive inflammatory marker, was determined using a Roche Cobas c111 automated analyzer.

## **Statistical Analysis**

Statistical analysis was conducted using GraphPad Prism software. Comparison between groups was as follows: Independent sample t-tests were applied to compare the means of the total WBC count, all specific WBC subpopulations, and levels of CRP and D-dimer from confirmed COVID-19 patients to those of a control group. P-values < 0.05 were considered significant in all tests. Multiple linear regression analysis was used to evaluate the relationship among laboratory parameters: WBC count, all specific WBC subpopulations, CRP, and D-dimer in patients with COVID-19.

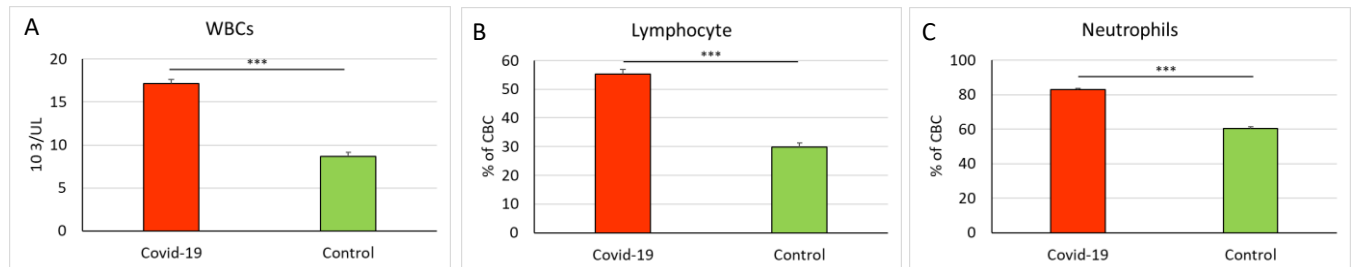
## **Results**

Table (1) compares WBC, Lymphocyte and Neutrophil count in healthy control and COVID patients. Out of them, the mean WBC count was high in COVID-19 patients, which was 17.1575 against 8.7005 in control group; p-value < 0.001 (figure 1A). The current study implies that COVID-19 might impact the overall WBC count. Also, the overall mean lymphocyte count of COVID-19 patients is 55.365, p > 0.001 compared to the mean count 29.79 of the control group, thus establishing lymphocytosis. On the other hand, COVID-19 patients have a significantly higher mean neutrophil count [p > 0.001], as stated in Figure 1C, by obtaining a mean of 82.9205 as against 60.369 were recorded for the controls, implying neutrophilia. These data suggest that COVID-19 infection relates to changes in the different subtypes of WBC, which may express an immune response to the virus.

The observed significant elevation in total white blood cell count, along with lymphocytosis and neutrophilia in COVID-19 patients, highlights the profound impact of the virus on the immune system. These findings suggest that COVID-19 infection triggers a robust immune response characterized by an increase in both lymphocytes, responsible for adaptive immunity, and neutrophils, crucial for innate immunity. This alteration in WBC subpopulations likely reflects the body's attempt to combat the viral infection, but it also raises concerns about potential complications associated with an exaggerated inflammatory response. Further research is needed to understand the specific mechanisms underlying these changes and explore the potential for therapeutic interventions to modulate the immune response and improve outcomes for COVID-19 patients.

**Table (1): Differential white blood cell and subpopulation profiles in control individuals and covid-19 patients**

	WBCs	Lymphocyte	Neutrophils
Control	8.7005	29.79	60.369
Covid-19	17.1575	55.365	82.9205
P-value	> 0.001	> 0.001	> 0.001



**Figure (1): Profiles of WBCs subpopulation in control individuals and covid-19 patients. (A) WBCs, (B) Lymphocyte, and (C) Neutrophils.**

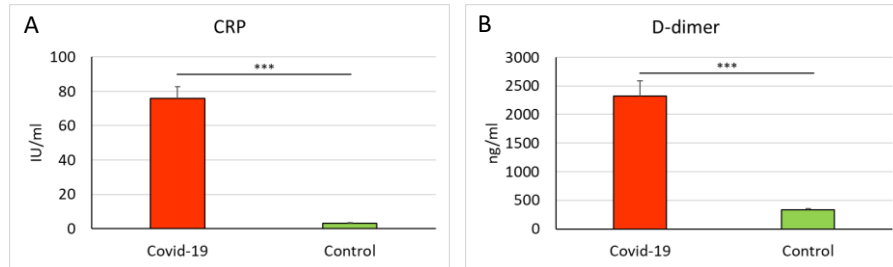
(\*\*\*) = high significant

Table (2) highlights the result of comparing the mean values of the C-reactive protein (CRP) and D-dimer level between the control group and the COVID-19 patients. The analysis of the study indicated that patients with COVID-19 have higher levels of both the CRP ( $p > 0.001$ ) and D-dimer ( $p > 0.001$ ) compared to the group of healthy individuals. The breakdown of mean CRP levels is as follows: 75.15,775 were reported in COVID-19 patients, although the latter figure is still higher than the usual average of 3.11 were examined in the control group (figure 2A). Mean values of D-dimer were also significantly higher in COVID-19 patients, recording an average of 2319.7 compared to 336.35 in the experimental group and 65 in the control group, as presented in (figure 2B). From these results, one can infer more marked tendencies toward inflammation and the possibility of coagulation disorders in persons with COVID-19.

Compared to healthy controls, the significant elevation of both C-reactive protein (CRP) and D-dimer in COVID-19 patients provides strong evidence for a systemic inflammatory response and a heightened risk of coagulation disorders in individuals infected with SARS-CoV-2. The markedly increased CRP levels indicate widespread tissue damage and the release of inflammatory mediators, suggesting a robust but potentially harmful inflammatory response; the elevated D-dimer levels, a marker of fibrinolysis, point towards an increased risk of thrombosis, potentially leading to complications such as pulmonary embolism or deep vein thrombosis. These findings underscore the importance of monitoring these markers in COVID-19 patients to identify those at higher risk for complications and to guide appropriate clinical management.

**Table (2): C-Reactive Protein and D-dimer Levels in COVID-19 Patients**

	CRP	D-dimer
Control	3.11	336.65
Covid-19	75.74667	2319.7
P-value	> 0.001	> 0.001



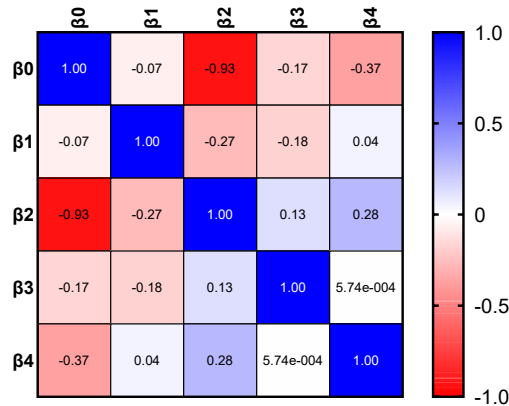
**Figure (2): Diagnostic markers for Covid-19 in diseased and control groups. (A) C-Reactive Protein and (B) D-dimer Levels.**

**(\*\*\*) = high significant**

The correlation matrix in Figure 3 provides insights into the relationships between several key blood markers associated with inflammation and coagulation. The matrix, represented by a color scale where blue indicates a positive correlation, red indicates a negative correlation, and the color's intensity reflects the correlation's strength, reveals several notable relationships.

Firstly, a strong negative correlation between WBCs ( $\beta_0$ ) and neutrophils ( $\beta_2$ ) is observed; this implies an inverse relationship, meaning that as WBCs increase, neutrophils tend to decrease, and vice versa. However, we found that the overall neutrophil concentration increased compared to the control group. This observation aligns with the understanding that neutrophils are a specific type of white blood cell, and their levels may fluctuate in response to various inflammatory stimuli.

Secondly, a moderately positive correlation exists between CRP ( $\beta_3$ ) and D-dimer ( $\beta_4$ ); this suggests that individuals with higher levels of CRP, a marker of inflammation, tend to have higher levels of D-dimer, a coagulation marker. This finding hints at a potential link between inflammatory processes and the activation of the coagulation cascade. While this correlation is not conclusive evidence of causation, it does raise the possibility of a crosstalk between inflammation and coagulation, possibly influencing the severity of certain conditions.



**Figure (3): Correlation Matrix of Regression Coefficients for Blood Cell Counts, CRP, and D-dimer Levels**  
 \* $\beta_0$ : WBCs,  $\beta_1$ : Lymphocyte,  $\beta_2$ : Neutrophils,  $\beta_3$ : CRP,  $\beta_4$ : D-dimer

## Discussion

This cross-sectional study identifies COVID-19 infection's effect on hematological test results, demonstrating substantial modifications to WBC subgroups and increased levels of inflammation and clotting biomolecules. Thus, these observations contribute to a better understanding of the processes occurring in COVID-19 and its consequences for management patients.

### Altered WBC Subpopulations: Lymphocytosis and Neutrophilia

The use of lymphocytosis as a measure in COVID patients indicates the enhancement of the immune response towards the viral infection as opposed to lymphopenia in the case of severe disease. Lymphocytes, especially T cells, are essential in identifying and destroying viral infections. From the analysis of the study, it is evident that the levels of lymphocytes in COVID-19 patients may be rising to fight the viral attack. However, here, the higher level of lymphocytes might not reflect a healthy systemic immune response. Still, it is abnormal and, therefore, can cause immunopathology and tissue injury [14].

The said changes, including the higher neutrophil count known as neutrophilia, contribute to the activation of the innate immune response. These short-lived cells help identify pathogens in the body to be eliminated, as they are the first responders to infection since they are phagocytic cells that enclose pathogens. In COVID-19 patients, their levels are increased to regulate the viral infection, but the uncontrolled activation of neutrophils contributes to tissue damage and inflammation [15].

The observed lymphocytosis in this study among COVID-19 patients indicates the novelty of the response to the viral infection. Thus, the fact that high levels of lymphocyte count may indicate increasing immune system activity is also to be discussed. Sometimes, it may suggest that the immune system becomes dysregulated, resulting in immunopathology and tissue injury.

Likewise, neutrophilia, another indicator of the innate immune response, is significant because it shows the body's initial forces to eliminate the virus. On the other hand, global activation of neutrophil granulocytes results in destructive and inflammation processes within the tissues that worsen the course of the disease.

Thus, these changes in WBC subpopulations signify the body's efforts to fight the virus; nonetheless, the relationship between them and COVID-19 is complex. Although many of these changes have been described in other disease states, the exact nature, specific effect on the disease severity and even contribution to long-term complications needs more research. It could pave the way to therapies on

immune regulation, thereby helping to achieve the correct immune stopgap against the virus that does not harm the body.

### **Elevated Inflammatory and Coagulation Markers**

The C-reactive protein (CRP) and D-dimer levels are significantly up-regulated, indicating a strong inflammatory response and coagulation dysregulation. This protein belongs to the acute-phase proteins [8], meaning that it rises swiftly under injurious factors such as inflammation. Elevated CRP levels in COVID-19 patients would, therefore, have implications in bearing the causation of cytokine storms, an inflammation process that leads to organ failure [9].

D-dimer is a measure of FDP that indicates clotted fibrin in the body since the degradation of fibrin clots generates the FDP. COVID-19 patients support the concept of the elevated risk of thrombosis, a potentially deadly condition that may cause pulmonary embolism, stroke, or deep vein thrombosis [6]. Therefore, raising the serum D-dimer is most probably due to the activation of the coagulation cascade, inflammatory response, and direct viral effect on endothelial cells [7].

The C-reactive protein and D-dimer levels increase significantly in COVID-19 patients, and inflammation merges with coagulation. Hence, the sharp increase in acute inflammation, as the CRP reflects, indicates significant tissue injury and liberation of pro-inflammatory cytokines, which could catalyze cytokine storms – associated with a fatal inflammatory response leading to organ dysfunction.

On the other hand, the D-dimer, a direct indicator of fibrin, indicates that coagulability is high and there is a high risk of thrombosis. These complications can be life-threatening and include pulmonary embolism, stroke, deep vein thrombosis, and many others. The activation of the coagulation cascade, probably due to the inflammatory process and direct viral effects on endothelial cells, is the reason for this high thrombotic risk.

These outcomes stress the importance of comprehending the relationship between inflammation and coagulation in COVID-19. Therefore, it is necessary to recognize patients who may experience such outcomes, watch them for signs of severe COVID-19, and create strategies to change the mentioned processes to manage the risks and raise patient prognosis.

### **Correlation Analysis and Implications**

The findings in the study align with what was discovered in research, where COVID-19 patients showed elevated levels of inflammatory markers like CRP and D dimer, indicating pro-inflammatory and hypercoagulable factors [10, 16]. While earlier studies have noted lymphopenia in COVID-19 cases, our results hint at a rise in lymphocyte count, suggesting an immune response within this specific group of patients. This discovery calls for research as it deviates from the pattern of lymphopenia seen in other studies. Furthermore, the increase in neutrophils we observed reflects the reaction to COVID-19 [17]. The correlation analysis underlines the relationship between these elements, underscoring the importance of delving into their mechanisms and impact on disease severity [11].

The results of this work, in addition to supporting earlier studies discussing the inflammation and hypercoagulation observed in COVID-19 patients, raise the question about the nature of the immune response present in this subpopulation. The findings of lymphocytosis, in contrast to the previously documented lymphocytopenia in COVID-19, require more research into the body's response to this illness. This deviation requires further study to determine the processes that contributed to it and how they influenced the course of the disease.

Moreover, the established enhancement of neutrophils, which reflects a high level of the innate immunity response, also proves the multifactorial nature of the interimmune/coagulation connection in COVID-19. The relevant research direction is to continue investigating the mutual strong interaction of these markers and their relation to the disease's progression severity. The findings from this study could inform the concept of precision medicine and designing intervention approaches to alter the immune system to reduce the severity of the COVID- 19 in patients.

## Conclusions

The present study emphasizes several hematological manifestations discussed in the COVID-19 patients, such as lymphocytosis, neutrophilia, and raised CRP and D-dimer. These outcomes are significant in extending the insight into pathophysiological characteristics of COVID-19 and, importantly, focusing on hematological markers in patients' treatment. It is also an insightful piece of research regarding the immune response in this category of patients, which could open the door to more tailored treatment strategies. More work must be done to investigate the multiple-pronged clinical implications of the current findings, especially concerning the possible treatments designed to target the inflammatory and coagulatory pathways in COVID-19 patients. The above points explain how the processes that trigger SARS-CoV-2 infection can be best decoded to enhance the potential of therapeutic interventions that would decrease the impact of COVID-19 on patients.

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