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Inflammatory Profile in Omicron Variant-Associated Covid-19: Evaluating Biomarkers for Severity Prediction

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Abstract

Background: The COVID-19 pandemic demands effective biomarkers for assessing disease severity. C-reactive protein (CRP), D-Dimer, and White Blood Cell counts (WBCs) have emerged as potential indicators of COVID-19 severity and prognosis.

Materials and Methods: This study, conducted at Qalla Hospital, enrolled 112 confirmed COVID-19 patients and 35 healthy controls. Comprehensive clinical and laboratory evaluations included CRP, D-Dimer, and WBC measurements. Diagnosis of COVID-19 followed established clinical criteria and confirmed through SARS-CoV-2 testing. Rigorous assessments were conducted to ensure precise participant classification.

Results: Significantly elevated CRP (p-value=0.0001), D-Dimer (p-value=0.0001), and WBCs were observed in COVID-19 patients compared to healthy controls. Elevated CRP levels indicating inflammation, increased D-Dimer levels associated with coagulation abnormalities, and raised WBCs within CRP level (0.943) indicative of an immune response were prevalent in COVID-19 patients. Gender distribution was balanced, while comorbidities such as diabetes mellitus (25%), hypertension (34.8%), kidney disease (6.2%), and multiple concurrent diseases (34%) were prevalent in the COVID-19 cohort.

Discussion: The substantial differences in CRP, D-Dimer, and WBCs underscore their potential as valuable biomarkers for diagnosing and monitoring COVID-19 severity. These biomarkers could serve as critical tools in evaluating disease progression, predicting complications, and guiding tailored therapeutic interventions. **Conclusion**: CRP, D-Dimer, and WBCs exhibited marked disparities between healthy individuals and COVID-19 patients,

indicating their potential as diagnostic and prognostic indicators. Continued investigation into these biomarkers' utility may refine risk stratification and treatment strategies, ultimately improving patient outcomes in COVID-19 management. Understanding the clinical implications of CRP, D-Dimer, and WBC levels could profoundly impact disease management and patient care strategies.

Keywords: COVID-19, CRP, D-Dimer, WBCs, biomarkers, severity

Introduction

Since the initial emergence of coronavirus disease 2019 (COVID-19) in China[1,2], the virus has swiftly disseminated worldwide, resulting in a global pandemic[3]. The fatality rate associated with COVID-19 stands at approximately 2%, while 5–10% of afflicted individuals progress to severe and potentially life-threatening illness[3]. COVID-19 primarily manifests as heightened inflammation and an immune system imbalance, leading to extensive damage across multiple organs. The chief contributor to mortality from COVID-19 is severe acute respiratory distress, stemming from the infection of lung epithelial cells and activation of alveolar macrophages[4].

Certain individuals affected by COVID-19 may experience severe illness or succumb to the disease[5], while a larger proportion generally encounter mild or moderate symptoms[6]. Risk factors linked to severe illness in COVID-19 include a range of elements, comprising advanced age (≥65 years), fertility, chronic obstructive pulmonary disease, chronic kidney conditions, diabetes mellitus, hypertension, hyperlipidemia, obesity, smoking, and immunodeficiency following transplantation[7–12]. Several biomarkers, including white blood cell (WBC) count, lymphocyte count, platelet count, albumin, ALT, lactate dehydrogenase (LDH), D-dimer, ferritin, interleukin-6, procalcitonin (PCT) levels, and prothrombin time (PT), have been identified as specific indicators of disease severity[13,14].

During the ongoing COVID-19 pandemic, instances of reinfection with SARS-CoV-2 have emerged, shedding light on the potential for individuals to contract the virus multiple times, often involving different viral clades or strains. This phenomenon suggests a certain level of vulnerability to reinfection, potentially from distinct genetic variants or lineages of the virus[14,15]. The evolution of SARS-CoV-2 has been marked by the emergence of various genetic mutations, leading to the development of diverse strains or variants. These alterations in the virus's genetic makeup contribute to its ability to adapt and survive in different environments. Consequently, individuals who have previously been infected with one variant may remain susceptible to infection from another variant due to differences in the viral structure or key components that the immune system recognizes[16].

Studies have indicated that immunity acquired from prior infection might wane over time. The duration and strength of immunity following natural infection vary among individuals, and some individuals may experience a decline in protective immunity, potentially rendering them susceptible to reinfection. Furthermore, while natural infection can induce an immune response,

it may not provide comprehensive protection against all variants. Certain variants could possess mutations that allow them to partially evade the immune response generated by previous infections, increasing the risk of reinfection in individuals previously infected with a different strain[17,18].

Behavioral factors, such as adherence to preventive measures and exposure to high viral loads, also play a role in susceptibility to reinfection. Instances of reinfection underscore the ongoing challenges in controlling the spread of SARS-CoV-2 and emphasize the need for continued vigilance, widespread vaccination, and adherence to public health guidelines to mitigate the risk of reinfection and curb the transmission of the virus. Scientific research continues to investigate the frequency, implications, and mechanisms behind reinfections to better understand and address this aspect of the pandemic[19].

This study examined specific biomarkers associated with severity and abnormalities in blood clotting in 152 patients across Omicron variants of COVID-19 in Iraq.

Materials and Method

Study design and patients:

The present study was conducted at Qalla Hospital, focusing on patients diagnosed with COVID-19 and a control group of healthy individuals. A total of 147 cases were enrolled, comprising 112 confirmed COVID-19 patients and 35 control cases. Among the COVID-19 patients, there were 53 males (47.3%) and 59 females (52.7%), whereas the control group consisted of 16 males (45.7%) and 19 females (54.3%). The enrollment of participants aimed to achieve representation across genders in both COVID-19 and control cohorts. The demographic characteristics of the COVID-19 patient cohort revealed comorbidities prevalent among the enrolled individuals. The distribution of comorbidities in COVID-19 patients was as follows: diabetes mellitus was observed in 28 cases (25%), hypertension in 39 cases (34.8%), kidney disease in 7 cases (6.2%), and multiple concurrent diseases in 38 cases (34%).

All COVID-19 cases were diagnosed based on established clinical criteria and confirmed through laboratory testing for SARS-CoV-2 infection. The control group, comprising healthy individuals, underwent assessments to ensure the absence of COVID-19 symptoms and a negative SARS-CoV-2 test result. Data collection involved detailed medical history reviews, physical examinations, laboratory investigations, and analysis of various biomarkers and clinical parameters to assess disease severity, prognosis, and associated comorbidities among COVID-19 patients.

Table(1)Clinical and Demographic characteristics of Covid-19 patients and control cases

Parameters		Control Cases % (N=35)	Patients % (N=112)
Age		35 (24-48)	44(33-57)
Gender:	Male	16 (45.7%)	53 (47.3%)
	Female	19 (54.3%)	59 (52.7%)
Comorbidities	Diabetes	0	28 (25%)
	Hypertension	0	39 (34.8)
	Kidney	0	7 (6.2%)
	Multiple	0	38 (34%)

Biological Biomarkers:

Biological marker tests conducted in this study aimed to evaluate specific indicators associated with COVID-19 severity and prognosis. The investigation included comprehensive analyses utilizing various laboratory analyzers for the assessment of key biomarkers.

The study utilized a range of analyzers for the quantification of specific biological markers. The Cobas C111 analyzer (Roche Diagnostics) was employed for the investigation of C-reactive protein (CRP) levels in serum. CRP quantification aids in assessing the degree of inflammation, with normal values for adults considered to be <5.0 mg/L. This quantitative immunological determination of CRP provided essential insights into the inflammatory status among study participants[20].

Furthermore, the Cobas E411 analyzer (Roche Diagnostics) was utilized for the measurement of ferritin, a marker often associated with inflammation and iron storage regulation. The ferritin investigation aimed to provide additional information regarding inflammatory processes and potential iron metabolism abnormalities related to COVID-19 infection.

The study also assessed D-dimer levels, a fibrin degradation product indicative of blood clot formation, using the fluorescence immunoassay iChroma™ II (Boditech Med Inc.). The D-dimer Rapid Quantitative Test identified elevated levels of D-dimer (>500 ng/ml) that might be associated with increased coagulation activity, aiding in the assessment of thrombotic risk among COVID-19 patients.

Additionally, cardiac troponin I, a marker for myocardial injury, was analyzed using the Cobas E411 analyzer. Troponin I tests were conducted through a fully automated immunoassay analysis using ElectroChemiLuminescence technology. The normal range for troponin I levels in the study was defined between 0 and 0.4 ng/ml, providing crucial insights into potential cardiac complications among the participants.

The Medonic M-Series haematology analyzer (Medonic M32; Boule Medical AB) was primarily employed for conducting complete blood count (CBC) tests, offering comprehensive insights into various blood cell parameters.

The selection of these biological markers and the utilization of specialized analyzers aimed to provide a comprehensive understanding of the inflammatory, coagulation, and cardiac profiles among the study participants.

Statistical Analysis:

Statistical analysis involved the utilization of Analysis of Variance (ANOVA) to examine variations in CRP levels and D-Dimer. Additionally, simple linear regression was utilized to assess the relationship between CRP and WBCs.

Ethical Approval:

The research conducted in this study adhered to ethical guidelines and received approval from the General Directorate of Health (Approval Code: 0011-22). Prior to commencing the study, all protocols and procedures were reviewed and approved to ensure compliance with ethical standards and participant welfare.

Results:

Figure 1A and Figure 1B in the study present essential comparisons between healthy control individuals and patients in terms of CRP (C-reactive protein) and D-Dimer levels, respectively. The significance of these comparisons is emphasized by the remarkably low p-values of 0.0001, indicating highly significant differences between the groups.

In Figure 1A, the focus is on CRP levels. CRP is an indicator of inflammation, and its elevation in the body can signal various conditions. The comparison reveals a substantial discrepancy between the healthy control group and the patient cohort regarding CRP levels. This substantial difference, indicated by the very low p-value, suggests that CRP levels significantly vary between these two groups. Typically, higher CRP levels are associated with inflammation or infection, and the stark difference observed here between the healthy control and patient groups could imply a potential health disparity or disease-related marker within the patient population studied.

Moving to Figure 1B, the analysis centers on D-Dimer levels, which are often associated with blood clotting and can be elevated in certain medical conditions such as thrombosis or pulmonary embolism. The noteworthy contrast in D-Dimer levels between the healthy control group and the patient population, highlighted by the p-value of 0.0001, indicates a substantial difference. Elevated D-Dimer levels in patients compared to the healthy controls could suggest a potential thrombotic or clotting issue prevalent in the patient group. This finding might be indicative of a specific health condition or risk factor within this patient population.

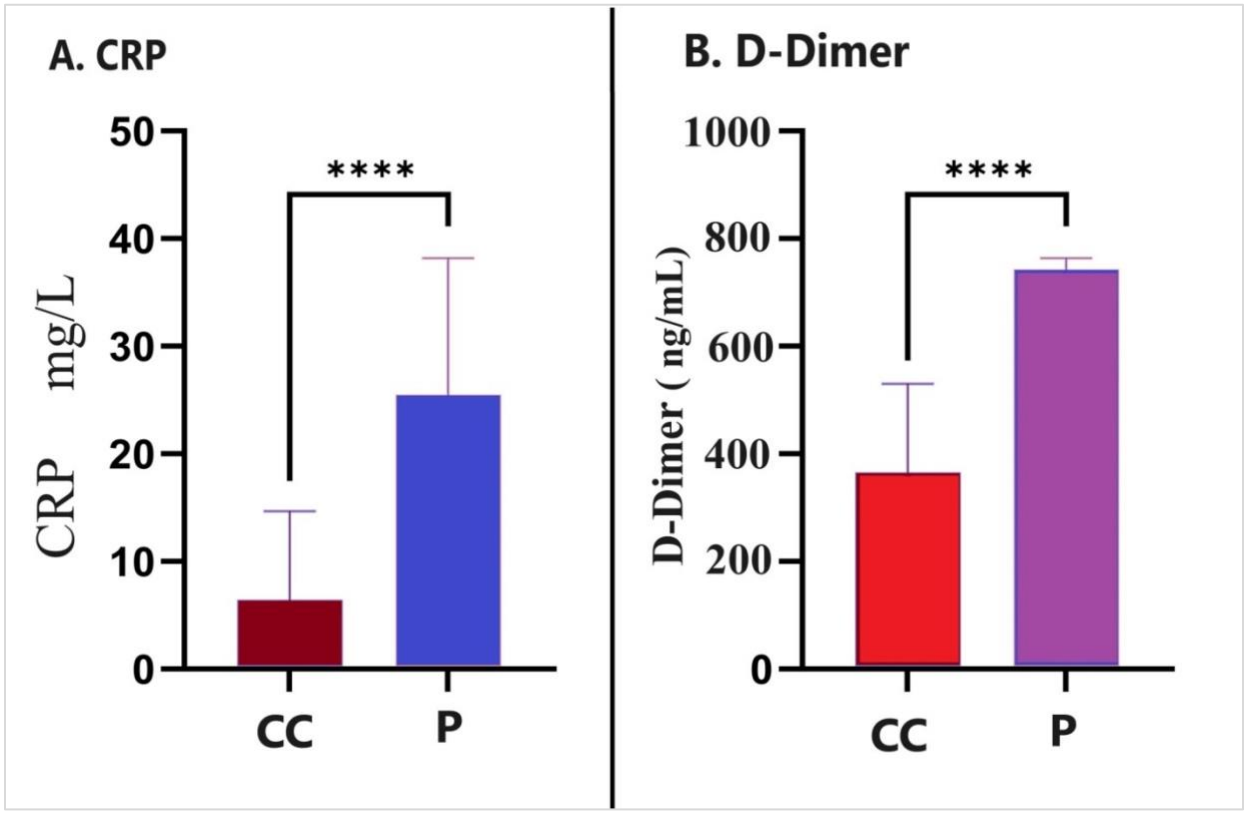

Figure (1)_ A: displays significant CRP level differences (p=0.0001) between healthy controls and patients, indicating potential health disparities in inflammation. Meanwhile, Figure 1B reveals noteworthy D-Dimer level contrasts (p=0.0001) between these groups, suggesting possible thrombotic issues in the patient population.

The study, employing simple linear regression, identified a strong link between CRP and WBC levels, illustrated by an R-squared value of 0.943. This finding indicates that a significant proportion of the changes in CRP levels can be explained by fluctuations in WBC levels. Essentially, it implies that alterations in CRP levels hold considerable sway over the variations observed in WBC levels within the study group.

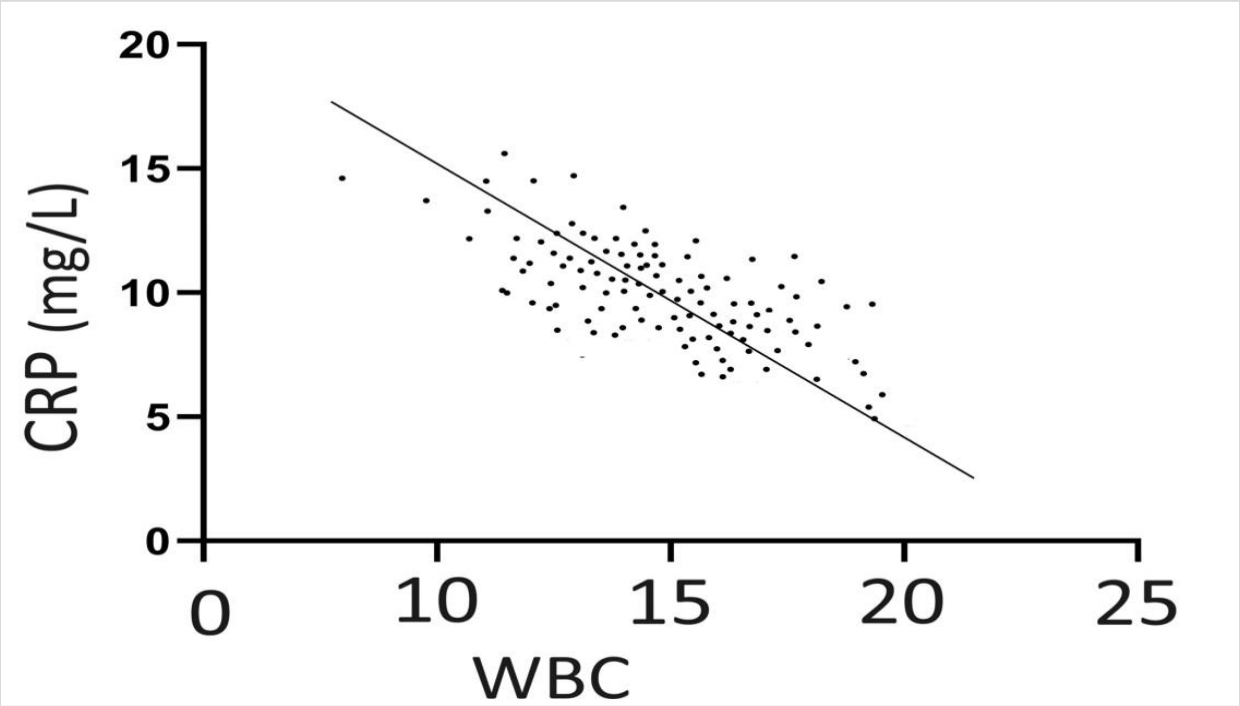

Figure (2) The meaningful correlation between CRP (mg/dL) and WBC levels when the correlation coefficient surpasses 0.5. Using simple linear regression, the study uncovered a robust connection between CRP and WBC levels, evident from an R-squared value of 0.943. This suggests that a significant portion of the changes seen in CRP levels can be accounted for by variations in WBC levels. Essentially, within the study group, fluctuations in WBC levels are substantially influenced by CRP levels.

Discussion

In the present study, the comparison of CRP, WBCs and D-Dimer levels between healthy controls and COVID-19 patients provides valuable insights into the disease's pathophysiology, severity, and potential clinical implications. The enrollment aimed for gender-balanced representation in both groups. The COVID-19 patient demographic indicated prevalent comorbidities: diabetes mellitus in 25%, hypertension in 34.8%, kidney disease in 6.2%, and multiple concurrent diseases in 34%. Diagnosis of COVID-19 adhered to clinical criteria and confirmed via SARS-CoV-2 testing. Healthy controls underwent assessments to ensure absence of COVID-19 symptoms and negative SARS-CoV-2 results.

In contrast, elevated CRP levels are often indicative of inflammation and infection. In COVID-19, increased CRP levels have been extensively reported and associated with disease severity[21,22]. The substantial difference between healthy controls and COVID-19 patients' CRP levels, supported by a significant p-value of 0.0001, underscores the pronounced inflammatory response typically seen in COVID-19 patients. This finding aligns with previous

studies highlighting CRP as a valuable biomarker for monitoring disease progression and severity in COVID-19 cases. The observed disparity emphasizes the potential of CRP as a diagnostic and prognostic indicator in assessing the severity and monitoring the course of COVID-19[23,24].

Additionally, elevated D-Dimer levels are commonly linked to coagulation abnormalities and thrombotic events[22]. In COVID-19, coagulopathy and increased risk of thrombosis have been reported as significant complications. The noteworthy difference in D-Dimer levels between healthy controls and COVID-19 patients, supported by a p-value of 0.0001, suggests a heightened risk of thrombotic complications in the patient group. This finding corroborates the existing literature highlighting the association between elevated D-Dimer levels and increased thrombotic events in severe COVID-19 cases. Monitoring D-Dimer levels could aid in assessing the thrombotic risk and guiding therapeutic interventions in COVID-19 patients[5,25].

In addition, the strong correlation between CRP and WBC levels, reflected by the high R-squared value of 0.943, emphasizes the interconnectedness between inflammatory markers and the immune response in COVID-19. This finding suggests that changes in CRP levels significantly influence fluctuations in WBC counts within COVID-19 patients. The intricate relationship between CRP and WBC levels highlights the dynamic immune-inflammatory response characterizing COVID-19 pathology. Understanding this relationship could offer insights into disease progression and guide therapeutic strategies targeting the immune-inflammatory pathways in COVID-19[26–28].

Hence, The significant disparities observed in CRP and D-Dimer levels between healthy individuals and those diagnosed with COVID-19 highlight the promising role of these biomarkers in the diagnosis and monitoring of disease severity in COVID-19 cases. These findings suggest the potential clinical utility of CRP and D-Dimer as valuable indicators for identifying and tracking the progression of COVID-19-related complications. Further research efforts should focus on delving deeper into the utility of these biomarkers in risk stratification, prognosis determination, and their potential role in guiding therapeutic interventions for COVID-19 patients. Understanding the dynamics of these biomarkers in relation to disease severity and progression could aid in developing more effective strategies for patient management, potentially enabling earlier identification of severe cases and facilitating tailored treatment approaches. Therefore, continued investigations are warranted to elucidate the full extent of these biomarkers' clinical significance in the context of COVID-19[21,29].

Moreover, elucidating the mechanistic insights into the relationship between CRP, WBC levels, and COVID-19 pathology could pave the way for targeted therapies and interventions aimed at modulating the immune-inflammatory response to improve patient outcomes.

In conclusion, the distinct biomarker profiles observed between healthy controls and COVID-19 patients, along with the strong association between CRP, D-Dimer, and WBC levels, highlight the potential clinical relevance of these biomarkers in COVID-19 management. Further research

into these biomarkers' roles in disease progression and their implications for therapeutic interventions is crucial for enhancing our understanding and management of COVID-19.

Author Contributions All authors equally participated in writing, reviewing, and editing the manuscript.

Conflict Of Interest Statement The authors declare no conflict of interest.

The data that support the findings of this study are available from the corresponding author upon reasonable request

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