Evaluation Role of CXCL-8 levels and SARS-CoV-2 Variants in Progression of Infection
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**ABSTRACT**

**Background:** The SARS-CoV-2 virus underwent genetic alterations during viral genome replication, leading to the development of numerous variations including Alpha, Delta, Delta plus, Omicron, and other variants. The chemokine CXCL8 is known to directly restrict viral proteins by producing interferon as the antiviral efficacy.

**Subjects and methods:** A total of 137 nasal swabs and blood samples were collected from 89 positively corona virus infection disease-19 (COVID-19) patients and 48 healthy individuals. RNA was extracted and real-time reverse transcriptase polymerase chain reaction (rRT-PCR) was performed to variants detection by using special kits. CXCL8 levels were determined in Enzyme linked immune-sorbent assay (ELISA) assay.

**Results:** Significant difference (p < 0.001) in the median levels of CXCL8 in patient higher than healthy control groups. Highest median of CXCL8 levels was shown with severe infection 308.6 (IQR: 66.6 – 783.5). Receiver-operating characteristic (ROC) analysis revealed that CXCL8 level was a good biomarker for immune response (Area under the curve (AUC) was 0.707). CXCL8 showed a significant difference with variants of SARS-CoV-2 (p < 0.001), where Delta/Delta plus variant patients had the highest median of CXCL8 level than other SARS-CoV-2 variant infections.

**Conclusion:** Patients infected with Delta/Delta plus and Omicron had higher level of CXCL-8. CXCL-8 had positive relation with cardiac disease, renal failure, leukemia with COVID-19 infection.

**Keywords:** SARS-COV-2, CXCL8, rRT-PCR, TaqPath, ELISA.

**INTRODUCTION**

Since it started over two years ago, the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic has continued to spread (COVID-19). The virus has harmed millions of people, hampered free travel, disturbed the global economy, and put a pressure on medical staff, leaving them emotionally vulnerable and physically and mentally spent (1). SARS-CoV-2 has developed into a variety of variants, including Alpha, Delta, Delta plus, Omicron, and other variants. With the ongoing evolution of the viral genome, mutations may modify the virus' ability to infect, the severity of the disease, or interactions with the host immune system. To combat the pandemic, the World Health Organization (WHO) has announced the specific variants of interest (VOIs) and variants of concern (VOCs) by working with academics from around the world to analyze the rising risk of SARS-CoV-2 variations (2).

The Alpha variant (B.1.1.7) of the spike protein contains a number of important modifications. Spike protein had the following mutations: N501Y, P681H, D614G, and E484K. In September 2020, the B.1.1.7 strain of SARS-CoV-2 first appeared in England (3).

The Delta variant (B.1.617.2) genome has undergone a number of mutations. In the delta lineage, there are eight spike mutations: T19R, G142D, del157/158, L452R, T478K, D614G, P681R, and D950N. India was the first country to report a delta variation toward the end of 2020, and it has since spread throughout the world (4). In March 2021, the Delta Plus variant (B.1.617.2.1) was found for the first time in India. The prevalence of Spike's hallmark mutations (G142D, A222V, and T95I) was higher in the Delta Plus variety than the Delta variation. All three of Spike's mutations—K417N, V70F, and W258L—were detected only in the Delta Plus form. The Delta Plus variant is the only one to include the new ORF1a mutation A1146T (5).

As for Omicron (B.1.1.529) variant, the WHO classified a recently found, severely mutated viral strain as a VOC on November 26, 2021. The most mutated SARS-CoV-2 variation is Omicron, which has over 50 mutations in its genome. Given that 15 of these modifications are in the receptor-binding domain (RBD), which makes up 26–32 of these mutations in the viral spike (S) protein region, there is particular cause for concern (6). There are roughly 30 mutations in the Omicron spike (S) protein, some of which are shared with the VOCs Alpha (del69/70, P681H), Beta (K417N, N501Y), and Delta (G142D and T478K). One of these mutations known to be suspected to affect immune escape or transmissibility is the del69/70 mutation (7).

The Kappa (B.1.617.1) variant, which has significant mutations (T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H), was initially discovered in India in December 2021 and is classified by the WHO and the Centers for Disease Control and Prevention (CDC) as a variant of interest (8).

Chemokines represent a group of chemotactic cytokines secreted from a variety of cell types, following
viral or bacterial infection. Chemokines play a critical role in fighting viral infections by recruiting innate and adaptive immune cells to sites of infection, and by enhancing their cytotoxic function and their ability to produce antiviral mediators and one of them is CXCL-8 (9).

Alveolar epithelial cells and monocytes/macrophages both release CXCL-8, caused by IL-17A and IL-17F released by IL-6-dependent Th17 cells, which are more prevalent in COVID-19 patients' peripheral blood. CXCL8 is functionally in charge of neutrophil recruitment, activation, and accumulation. Additionally, CXCL8 induces the highly immunogenic and toxic neutrophil extracellular traps (NETs), which result in inflammation and endothelial/epithelial cell death (10). The ability of CXCL8 to trigger neutrophil exocytosis and an oxidative burst of superoxide and hydrogen peroxides helps to explain this (11). Then, additional CXCL8 is produced by lung NETs, which draws in more neutrophils and prevents them from going through apoptosis (12). All of the aforementioned functions of CXCL8 explain how they may interact to affect COVID-19 development and disease severity (9).

Chemokines like CXCL-8 was predicted a powerful biomarkers and future therapeutic targets. Furthermore, it’s roles of CXCL8 also explain how it might influence the etiology and COVID-19 severity. Thus, this study aimed to found association of CXCL-8 levels and severity of Sars-CoV-2 variants infection.

SUBJECTS AND METHODS

137 individuals between the ages of 17 and 68 who were suspected of having the SARS-CoV-2 virus had their nasal swabs and blood samples taken, with the vaccinated patients being excluded. Additionally, 48 health control person, taken their blood and swabs were taken as a control for CXCL-8 levels. The respiratory Nasal swabs were selected randomly during the period from March 2021 to March 2022 for testing SARS-CoV-2 and their variants during these periods. Moreover, the blood samples were collected from 89 COVID-19 patients only and all control group (48) from Baghdad Central Public Health Laboratory (CPHL) and Baghdad teaching hospital to perform the complete blood count and CXCL8 detection.

A specialized lab kit (AddPrep Viral Nucleic Acid Extraction Kit, Add Bio, Korea) was used in accordance with the manufacturer's instructions to extract viral RNA. A specialist SARS-CoV-2 detection kit was used (Accupower® SARS-COV-2 multiplex real time RT-PCR kit, Bioneer, Korea), reverse transcriptase real-time PCR (rRT-PCR) test was used to validate the diagnosis of SARS-CoV-2 infection and calculate cycle number threshold (Ct) value. Alpha, Delta/Delta plus, and Kappa SARS-COV-2 variants were detected by using the Accupower® SARS-COV-2 variations ID 2 kit (Bioneer, Korea) and rRT-PCR test in contrast to the wild type. The TaqPath COVID-19 PCR test (TaqPATH COVID-19 CE-IVD RT-PCR Kit, Thermo Fisher, Germany) was used to diagnose Omicron. When a patient's TaqPath COVID-19 PCR test was positive and the ORF1lab or nucleocapsid gene targets had a cycle threshold of 36 or less, but the S gene wasn't detectable, infections were classed as SGTF (S gene target failure assay) (13). The serum levels of selected patients (16 wild type, 22 Alpha, 8 Delta, Delta plus, 43 Omicron) were measured using a human CXCL-8 ELISA kit from the Al-Shkairate establishment for medical supply in Jordan, along with 48 healthy control cases. CXCL-8 was detected in serum samples using the ELISA method. The CXCL-8 test had a sensitivity of 18.75 pg/m and a detection range of 31.25-2000 pg/ml. Additionally, the Roche Cobas Integra 400 plus (Roche Diagnostics, Netherlands) and the ABX Micros ES 60 Automated Hematology Analyzer (HORIBA ABX SAS, Japan) respectively, were used to examine the CRP and neutrophil count.

Ethics approval

An approval of this study was obtained from the University of Baghdad Academic and Ethical Committee (CSEC/0921/0046). Informed consent of all the patients was taken. This study was carried out in accordance with the World Medical Association Code of Ethics (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Using the statistical package, data were input, handled, and analyzed. Variables were reported as median with interquartile range (IQR), frequencies, and percentages as appropriate. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine the normality of continuous variables, which were not normally distributed and so they were compared by Kruskal-Wallis test and the Mann-Whitney U test. Statistical significance was defined as a probability (p) value <0.05. The Fisher's exact test is employed to determine the relationship between categorical variables. When the variable did not follow a normal statistical distribution, a non-parametric test was used as an alternate test to compare the median values of a variable or parameter across severity categories. To evaluate significant differences between medians and compare nonparametric variables (not normally distributed), the Kruskal-Wallis test and the Mann-Whitney U test probability were used (Asterisk indicates significant differences). In terms of the median and interquartile range, they were presented (IQR). Statistical significance was defined as a probability (p) value 0.001.
Receiver operating characteristics curve (ROC) analysis is used to calculate the area under the curve (AUC), 95% confidence interval (CI), cut-off value, sensitivity, and specificity in order to evaluate the validity of significantly different parameters, such as the SARS-CoV-2 variant across disease severity in the prediction of severe or critical disease. The AUC was calculated and is a measure of a test's validity; an AUC of less than 0.600 denotes a test's failure as a predictor, one between 0.600 and 0.700 is adequate, one between 0.700 and 0.800 is good, one between 0.800 and 0.900 is very good, and one above 0.900 indicates an excellent predictor test. The Youden J statistic, also known as the Youden Index, which measures the efficacy of a dichotomous diagnostic test, was used to determine the ideal cutoff point. The test Youden J statistic is derived as: alternative, $J = \text{Sensitivity} + \text{Specificity} - 1$. The higher index value reflects the better validity of the test.

In order to determine the correlation coefficient between CXCL8 and the biomarkers CRP and neutrophil percentage in COVID-19 patients, Spearman's rank-order correlation was used. The area under the curve (AUC), 95% confidence interval (CI), cut-off value, Youden index, sensitivity, and specificity were evaluated using ROC curve analysis.

The Odds ratio (OR) and 95% confidence interval (CI) for the three models I (unadjusted), II (age-adjusted), and III were calculated using logistic regression analysis (age and gender-adjusted).

According to a median of CXCL8 in this analysis, patients and HC were divided into low and high production groups (and > median, respectively), with the high production group serving as the reference category.

For statistical analysis, GraphPad Prism version 8.0.0 (San Diego, California, USA) and IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp.) were both utilized. The power of the sample size was calculated using the G*Power version 3.1.9.2 software [kind of power analysis: compromise; error probability: 0.05; power (1-error probability): 0.80; effect sized: 0.55; actual power: 0.80].

**RESULT**

**1. Median levels of CXCL-8 in patients and healthy control**

Table 1 shows median levels of CXCL-8, which shows that patients older than 40 had lower median levels, while patients younger than 40 have higher median levels when compared to the healthy control group (≤ 40).

Additionally, as seen in table 1, females had greater median levels of CXCL8 compared to males.

The results show that patients with diabetes mellitus (DM) had lower immunity (a lower level of CXCL8) than individuals without DM. In terms of hypertension and other diseases, no statistically significant differences were found between those with or without the diseases.

In the current study, the mild to moderate group had the higher median CXCL-8 level than the severe groups.

**Table 1: Median levels of CXCL8 stratified according to characteristics of COVID-19 patients and healthy controls**

<table>
<thead>
<tr>
<th>Character</th>
<th>Patient (no.89)</th>
<th>Control (no.48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>≤ 40</td>
<td>315.8 (59.3 - 783.5)</td>
</tr>
<tr>
<td></td>
<td>&gt; 40</td>
<td>74.7 (51.9 -289)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>71.4 (50.6 - 289)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>308.6 (65.1 – 783.5)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.01</td>
<td>p = 0.094</td>
</tr>
<tr>
<td>DM</td>
<td>No</td>
<td>260.7 (57.3 –783.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>140.1 (51.9 –789)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.05</td>
<td>p = 0.056</td>
</tr>
<tr>
<td>Other Disease</td>
<td>A</td>
<td>195.2 (56.7 – 598.8)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>315.7 (315.7)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>21.3 (21.3)</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>21 (21)</td>
</tr>
<tr>
<td>p-value</td>
<td>p = 0.27</td>
<td>p = 0.56</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild-moderate</td>
<td>308.6 (66.6 – 783.5)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>68.1 (51.9 – 269.1)</td>
</tr>
<tr>
<td></td>
<td>Critical</td>
<td>21.4 (21)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.01</td>
<td>p = 0.01</td>
</tr>
</tbody>
</table>

IQR: Interquartile range; NA: Not applicable; DM: Diabetic mellitus; HTN: Hypertension; A: no chronic disease (Included hypertension and diabetic mellitus); B: cardiac disease (3 cases); C: renal failure (3 cases); D: leukemia (2 case).

**2. Analysis of CRP with Age, Gender, Disease, and Severity**

Figure 1 illustrates that the median CRP exhibited higher significant differences with severity, chronic disease and no disease, then with age.

Age (≤ 40) patients had median CRP of [14.90 IQR (4.425-27.40)], but age (> 40) patients had median [29.70 IQR (13.15-67.40)].

As well as, patients with chronic diseases had median CRP values that were greater than those of patients without diseases [53.10 IQR (20.10-72.90) vs. 7.650 IQR 3.800-21.50).

Patients with critical disease had the highest median CRP across severity groups, with a range of 88 IQR (68.95-98.900), followed by severe disease (63.10 IQR 33.10-75.60)) and mild to moderate disease (7.400 IQR (3.800-17.20)).
3. Median of CXCL8 with COVID-19 patients, Healthy control, and SARS-CoV-2 variants

The findings demonstrated that patients' median levels of CXCL-8 were greater than those of the healthy control group (205.2 IQR (57.6–552.3) compared to 94.9 IQR (57.8–199.2)) (Figure 2). The highest median of CXCL-8 among variations was with Delta or Delta plus [987.4 IQR (717.5–1261)]. Additionally, the sample size (8 variants) and CXCL8 level for all Delta variants evaluated were mild-moderate, reporting more information than any other variant under investigation. While the median of CXCL8 with wild type and Alpha variation were lower [233.2 IQR (54.3–287.3)] and [126.8 IQR (74.7–324.5)] respectively, along with severe infection in most instances, they were followed by CXCL-8 with Omicron [249.2 IQR (68.1–594.50) and Omicron in most cases.

4. Correlation between CXCL8 with Neutrophil and CRP

There was a significant difference in the correlation of CXCL8 with neutrophils and CRP. According to Figure 3, an increase in neutrophil percentage causes a drop in CXCL8 levels ($rs=-0.34$), indicating that there are additional components involved in the attraction of neutrophils.

Additionally, increasing the amount of CRP caused a dramatic drop in the level of CXCL8 with ($rs=-0.39$), indicating an antagonistic correlation between CRP and CXCL8.
5. Logistic regression analysis of CXCL8 in COVID-19 patients

Logistic regression shows that the OR for patients without age or gender adjustments was (1.003), followed by those with those adjustments (1.004) and without them (1.004) (Table 2).

Table 2: Logistic regression analysis of CXCL-8 in COVID-19 patients versus control group

<table>
<thead>
<tr>
<th>Model†</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (unadjusted)</td>
<td>1.003</td>
<td>1.001 – 1.005</td>
<td>0.003</td>
<td>0.707</td>
</tr>
<tr>
<td>II (age adjusted)</td>
<td>1.004</td>
<td>1.002 – 1.006</td>
<td>0.001</td>
<td>0.707</td>
</tr>
<tr>
<td>III (age and gender adjusted)</td>
<td>1.004</td>
<td>1.001 – 1.006</td>
<td>0.002</td>
<td>0.707</td>
</tr>
</tbody>
</table>

†: The reference category is > Median; OR: Odds ratio; CI: Confidence interval.

6. ROC curve of CXCL8 with SARS-COV2 variants

According to the receiver operating characteristic (ROC) curve analysis, the level of CXC-L8 was a reliable indicator of the severity of the VID-19. The AUC was 0.707. The cut-off value was 160.2 pg/mL (optimized by the Youden index).
DISCUSSION

Age and Gender with CXCL-8

According to present study and in table 1, patients aged more than 40 years (>40) had less median level of CXCL-8 [74.7 IQR (51.9-289)], while patients aged less than 40 years (≤40) had higher median level of CXCL-8 [315.8 IQR (59.3-783.5)]. This result denoted that older patients had less or fragile immune system due to many factors. While young patients have strong immune system. This is approved by different studies which indicate that aging causes a variety of changes to the innate and adaptive components of immunity. This process, known as immunosenescence, causes a decrease in the immune system's ability to guard against infections that are harmful to older persons. (13).

Moreover, the results revealed that females had higher median level of CXCL-8 [308.6 IQR (65.1-783.5)] when compared to males which had lesser [71.4 IQR (50.6-289)]. This explains the high rate of infection and mortality in male more than females, who had powerful immune system. Evidence suggests that this difference is caused by a number of complicated mechanisms involving behavioral, genetic, hormonal, and immunological factors. Furthermore, sex hormones and certain X-related genes altered innate and adaptive immunity in responses to viral infection. These factors may also contribute to the difference in sex-specific COVID-19 results. Furthermore, androgen-dependent TMPRSS2 expression may provide an explanation for the predominance of COVID-19 in the male population. These findings may help to partially explain the underlying causes of the increased incidence of COVID-19 severity in males compared to females (14).

COVID-19 infection and comorbidity with CXCL8

For DM and HTN patients, the results revealed that level of CXCL-8 is low in both of DM and HTN. On the other hand, 72.5% of severe and critical patients had DM. Further study revealed that, while other pro-inflammatory chemokines increased in many cases of severe and critical disease, CXCL-8 levels decreased. In COVID-19 patients, diabetes was assumed to be associated with disease progression and to increase the number of ICU admissions, ventilation rates, and mortality (15). For innate immunity, many immune cells abnormalities causes COVID-19 exacerbation in DM patients. For instance, dendritic cells maturation and apoptosis are encouraged by hyperglycemia. Moreover, DM may increase ACE2 expression, which facilitates greater neutrophil infiltration, and neutrophils are more susceptible to NETosis (16).

In addition, this study revealed (90%) of severe and critical patients with HTN. Several reports, have demonstrated an association between HTN and the risk of SARS-CoV-2 infection as well as the worsening of COVID-19's prognosis. However, it was common to find hypertension and diabetes together in the medical records of patients with more serious medical histories, who required mechanical breathing or were even close to death. The correlation between COVID-19 and hypertension does not necessarily imply a causative relationship and does not appear surprising given the widespread prevalence of high blood pressure around the world (17).

Moreover, data showed low level of CXCL-8 in leukemia, renal failure, no chronic disease and high level in cardiac disease. Patients with leukemia are frequently immunosuppressed and myelosuppressed and immunoglobulin-deficient, making them potentially very vulnerable to COVID-19. Recent study declared that, because of a multitude of factors including their underlying condition, treatment, and patient-specific factors, people with leukemia may have a disproportionally higher chance of acquiring COVID-19. Each leukemia subtype may also be connected to specific COVID-19-associated risk due to the biology of the disease or an associated treatment. For instance, diminished humoral response brought on by disease- or treatment-related hypogammaglobulinemia in patients with lymphoid malignancies increases the risk of infection. Secondary bacterial or fungal pneumonia may also be more common in COVID-19 patients with immune-compromised leukemia (18).

According to studies, renal failure and acute kidney injury (AKI) are more likely to occur in severe coronavirus illness cases in 2019. The deterioration of the immune system seems to affect how AKI develops (19). Additionally, this imbalance had a strong correlation with a high viral load and was linked to AKI without regard to mortality. This demonstrates that the absence of immunological homeostasis has a significant role in the development of kidney damage in COVID-19. Numerous investigations had shown that SARS-CoV-2 infection resulted in hypercytokinemia, which leads to a situation of hyperinflammation as well as unchecked and persistent activation of T cells and macrophages, especially in people with the severe forms of the disease (20).

Finally, cardiovascular disease and COVID-19 have been linked in numerous clinical investigations. Although COVID-19 alone can potentially result in myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism, it appears that individuals with pre-existing cardiovascular disease have a worse prognosis and a higher probability of dying. According to early research from China, people with COVID-19 typically
had pre-existing conditions like hypertension and diabetes mellitus that were linked to cardiovascular diseases (CVD). As a potential target for COVID-19 prevention and treatment, the interaction between the S protein and ACE2 was also assumed to be crucial to the disease’s etiology in general and the cardiovascular manifestations in particular. (21)

For severity, the highest level of CXCL-8 was recorded in mild to moderate cases. Previous research suggested that during the early stages of infection, CXCL-8 was elevated similarly in mild and severe cases, and it remained at steady levels in mild cases. According to a different study, CXCL-8 was higher in mild/moderate and severe patients than in severely ill ones (22).

**CXCL-8 and SARS-CoV-2 variants**

With regard to variants, the results of current study elucidated that highest median of CXCL-8 was recorded in Delta then Omicron followed by wild type and lastly Alpha variants. This result confirmed the previous study about CXCL-8 being present in mild/moderate cases and severe, because Delta variant tend to cause severe illness and, in some cases, causes mild infection also. Omicron is less severe than Delta variant. Moreover, compared to infections caused by the Delta variation, infections caused by the Omicron variant were less clinically severe. Furthermore, the Omicron variant according to WHO COVID-19 Clinical Progression Scale severity categories were less severe than those for the Delta variation (23).

Wild type and Alpha variants were found in patients suffered from severe disease. This is supported by numerous reports, and more than 15 studies show that the probability of transmission is lower for the wild type than for the Alpha variant. According to a different study, the Alpha variant had a greater risk of hospitalization, ICU admission, and mortality than the wild-type version did (24).

**C-Reactive Protein and COVID-19 infection**

The liver produces the pentameric protein known as C-reactive protein, whose quantity rises in reaction to inflammation. IL-6 acts primarily on the gene that makes CRP during the acute phase of an inflammatory or viral event to produce C-reactive protein (CRP), an acute-phase reactant protein. C-reactive protein, which has both proinflammatory and antinflammatory properties, aids in the detection and elimination of invasive infections and wounded cells by binding to phosphocholine, phospholipids, histone, chromatin, and fibronectin (25).

In the current study C-reactive protein was elevated in older patients more than younger. This explain previous finding that older people have weak immune system and may have chronic disease, which lead to increase CRP. The finding indicated that COVID-19 patients with severe disease were older, had more comorbidities, and had breathing issues than patients with less severe disease (26).

Furthermore, the level of C-reactive protein (CRP) is routinely used to evaluate the degree of inflammation. Hypertension, diabetes mellitus, and heart disease are the three most common comorbidities in COVID-19 patients, and they all increase inflammatory marker levels like CRP. CRP is used to detect inflammation or infection early on. The CRP serum level is typically measured when diagnosing COVID19 for the first time (27). However, this explains why CRP increases more in severe illness than in critical illness in the current study. In patients with COVID-19, CRP is highly connected with critical illness and in-hospital death, according to multiple studies (28). As a result, considerably higher serum C-reactive protein readings in those with COVID-19 point to a vigorous inflammatory response and are consistent with increased serum proinflammatory cytokines (29).

**Correlation of C-reactive protein, Neutrophil and CXCL-8**

Supplemental data of this study shows that levels of CXCL-8 decreased with elevation of C-reactive protein and neutrophil, which indicates that CXCL-8 is elevated in early stage of infection and during mild case and may decline with increased severity. A recent study supposed that serum IL-8 levels were higher in the mild-moderate and severe groups compared to healthy people. The severe patient group also exhibited considerably higher CRP and neutrophil levels. Further investigation showed a positive correlation between CRP and CXCL8 in the early stages of disease (30).

This study revealed negative correlation between CXCL-8 and neutrophil, which indicates that there are other factors contributing in the attraction of neutrophil.

Neutrophils, are highly adaptable granulocytes that comprise 50% to 70% of all leucocytes in peripheral blood in humans and are the first to respond to infection and tissue damage. After being attracted to sites of infection and inflammation by the local action of chemokines (such as CXCL8), neutrophils can phagocytose and kill pathogens, release cytotoxic substances and degradative enzymes, produce reactive oxygen species (ROS), and expel neutrophil extracellular traps (NETs) (31). Additional experimental results demonstrated a favorable correlation between neutrophil counts and disease severity and mortality. (32,33). Excessive inflammation may form as a result of neutrophil infiltration and the insufficient antiviral response in COVID-19. In one study, it was found that SARS-CoV-2 infection affected neutrophil immunometabolism, and that neutrophils contribute to hypersensitivity pneumonitis by the buildup of succinate,
which was connected with the severity of the illness \(^{(22)}\). Neutrophil extracellular traps (NETs), which are web-like chromatin structures generated by neutrophils to destroy virulence factors and kill bacteria, are another phenomenon. Previously uncontrolled in severe COVID-19 or sepsis A NETs-associated cytokine storm damages numerous organs, including the kidneys, the nervous system, and the liver, and results in arterial hypotension, hypoxemia, coagulopathy, and renal failure \(^{(34,35)}\). 

**CONCLUSION**

Patients infected with Delta/Delta plus and Omicron had higher level of CXCL-8. CXCL-8 had positive relation with cardiac disease, renal failure, leukemia with COVID-19 infection.

**Financial support and sponsorship:** Nil.

**Conflict of interest:** Nil.

**REFERENCE**


