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# Original article

# Interplay of Viral RNAemia, Interleukin-6 and Interleukin-6 Gene Polymorphism with COVID-19 Patients

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**Abstract**

***Background:*** Coronavirus Disease 2019 (COVID-19) represents a formidable global pandemic attributed to the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2). Elevated IL-6 levels, detectable serum SARS-CoV-2 viral load (RNAaemia) in critically ill patients, IL-6 gene polymorphismcontribute to excessive yet ineffective host immune responses, culminating in impaired lung function and expedited mortality among COVID-19 patients. ***Objectives:*** The primary objective of this study is to scrutinize the associations between IL-6, SARS-CoV-2 viral load (RNAaemia), IL-6 gene polymorphismconcerning disease severity in COVID-19 patients. ***Methodology:*** Conducted within the Department of Microbiology and Immunology at Bangabandhu Sheikh Mujib Medical University (BSMMU), this cross-sectional study spanned from March 2021 to January 2022. A cohort comprising 84 confirmed COVID-19 patients via positive RT-PCR and 28 healthy subjects was enrolled. Peripheral venous blood samples were procured for the detection of SARS-CoV-2 viral RNA (RNAemia) through Real-time reverse transcription polymerase chain reaction assay (RT-PCR), serum IL-6 levels via the chemiluminescence method, single nucleotide polymorphisms (SNPs) of IL-6 through sequence-specific primer polymerase chain reaction (SSP-PCR). ***Result:*** Serum IL-6 levels (pg/ml) were markedly elevated in critical patients (102.02±149.7) compared to severe (67.20±129.5) and moderate (47.04±106.5) patients. The prevalence of serum SARS-CoV-2 nucleic acid-positive cases was predominantly observed in critical patients (39.28%), and a strong correlation between extremely high IL-6 levels, RNAaemia, and high mortality was established (R=.912, P<0.001). Genotype distribution for IL-6 174G/C (rs 1800795) gene indicated.CC and GC genotypes exhibited a robust association with the severity of COVID-19 when compared to the GG genotype. A significant statistical difference in genotypes was discerned between critical and moderate groups (p<0.001, OR-10.316, CI-3.22-23.86), with the CC genotype being linked to COVID-19 severity and mortality. ***Conclusion:*** Serum IL-6, IL-6 174 G/C gene, and SARS-CoV-2 RNAaemia may prove valuable in clinical practice for risk assessment, disease progression and mitigate morbidity and mortality.

***Keywords:*** RNAemia, Interleukin-6, gene polymorphism, COVID-19 patients

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**Introduction**

The COVID-19 pandemic, initially detected in December 2019 in Wuhan, Hubei Province, China, has become a worldwide public health issue.On December 31, 2019, Chinese authorities notified the World Health Organization (WHO) about multiple instances of pneumonia of unknown origin.[1] By January 7, 2020, it was established that the cause of these reported cases was the novel coronavirus known as 2019-nCoV, later renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to the designation of the outbreak as COVID-19.[1-2] Cytokine release syndrome (CRS) emerged as the primary cause of morbidity in patients with SARS-CoV and it is also responsible for inducing acute respiratory distress syndrome (ARDS) in those infected with SARS-CoV-2.[3] The presence of ARDS is associated with elevated serum IL-6 levels and unfavorable clinical outcomes. IL-6, a versatile cytokine, plays a crucial role in regulating a wide array of cellular activities and serves as a major immune-modulatory agent. It actively participates in the control of acute phase reactions, the activation of T helper cells, the inhibition of T regulatory (Tregs) cells, and the differentiation of B cells, thereby coordinating both innate and adaptive immune responses. [3-4]During the early stages of infectious inflammation, monocytes and macrophages, stimulated by TLRs, produce IL-6. In the acute stage of SARS-CoV-1 infection, high levels of both interleukin 6 (IL-6) and interleukin 8 (IL-8) were detected, particularly in association with lung lesions.4Notably, IL-6 can induce a hyper-innate inflammatory response as a result of SARS-CoV-1 invading the respiratory tract.[4-5] Immune dysregulation, particularly, is induced by Interleukin-6 (IL-6) rather than Interleukin-1β (IL-1β). Elevated IL-6 levels have been observed in hospitalized patients, particularly those in critical condition, and are linked to ICU admission, respiratory failure, and a bleak prognosis. The real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for detecting SARS-CoV-2 in throat swab samples has been widely employed for diagnosing COVID-19 patients. Nucleic acids have been identified in serum or plasma samples for all novel coronaviruses, although the duration of viremia remains unclear. SARS-CoV-2 RNA exhibits relative stability in plasma, even though its presence may not necessarily indicate an active. Viral RNA in blood has been detected in COVID-19 patients within the first 2 to 3 days after the onset of symptoms; however, there is no evidence regarding the viral load in plasma and serum during the incubation period. [5-6] The presence of a substantial IL-6 level, coupled with a meaningful Ct (cycle threshold) value of viral RNA in serum samples, can be regarded as a reliable and precise biomarker revealing adverse outcomes. Detectable serum SARS-CoV-2 viral load (RNAemia) was identified exclusively in the critically ill group, and IL-6 levels in critically ill patients showed a significant increase, nearly tenfold compared to other patients. The notably elevated IL-6 level was closely associated with the detection of RNAemia.[7-8] The combination of IL-6 levels and serum viral RNA Ct-value may be considered an effective indicator for standard clinical assessments, offering a high level of accuracy in predicting impending adverse outcomes.[9] Several studies have reported the association of IL-6 with SARS-COV-2 RNAemia in critically ill COVID-19 patients, linked IL6 gene polymorphism to susceptibility and the severity of pneumonia, and established a connection between lymphocytes, inflammatory monocytes, and elevated IL-6 expression, leading to an excessively ineffective host immune response, resulting in lung functional impairment and swift mortality.[9-10] The objective of this study is to investigate the relationships between Interleukin-6, SARS-COV-2 viral RNA (RNAemia), Interleukin-6 gene polymorphism with the severity of the disease in COVID-19 patients.[11]SARS CoV-2 exist in blood or rectal swabs, may not to be detected in the throat swab and is important to examine samples from different sources to validate the infection.[12]

**Materials and methods:**

This was a cross-sectional study which was conducted in the Dept. of Microbiology & Immunology, Dept. of Anaesthesia, Analgesia and Intensive Care Medicine and COVID Unit, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka andsubjects were selected from the persons who attended Fever clinic, BSMMU. This study was conducted from March 2021 to January 2022. Informed written consent was obtained from patients and control and ethical clearance was sanctioned by the Institutional Review Board (IRB) at BSMMU.Purposive sampling procedure was followed.According to MORGAN'S table for sample size was calculated and sample size was = 28 x 4 = 112 where 28 was severe COVID-19 category admitted into BSMMU ICU. Data were collected by the pre-designed data collection sheet. All statistical analysis was performed using the statistical package for social science (SPSS) program, 26 versions.Theconfidentiality of data and the privacy of the respondentswere maintained strictly.A total of 84 COVID-19 patients confirmed by positive RT-PCR for SARS-CoV2 from nasopharyngeal or oropharyngeal swab were enrolled in this study. The moderate, severe and critically ill COVID-19 patients were recruited from Intensive Care Unit (ICU) and COVID unit of BSMMU, Shahbag, Dhaka and categorized according to National Guideline on Clinical Management of COVID-19, version 9.0, published on 6th May, 2021, Bangladesh. SARS-COV-2 viral RNA (RNAemia) detection by Real-time reverse transcription polymerase chain reaction assay (RT-PCR) and detection of IL-6 gene polymorphism by single plex SSP- PCR, Detection of serum level of IL-6 by chemilumi-

nescence Assay. Inclusion criteria were following accordingto National Guideline on Clinical Management of COVID 19, version 10.0 published on 9th February, 2022, Bangladesh.[13]

**Result:**

The overall median age was 55 years (interquartile range 40–69) and Individuals with detectable RNAemia were significantly older than those without RNAemia (63 vs 50 years; P = .04).

Table 1: Demographic, Laboratory Characteristics of 84 Patients with SARS-CoV-2 RNAemia

| Variables | | Total patient n=84 | Detectable SARS-CoV-2 RNAemia (n = 11) | Nondetectable SARS-CoV-2 RNAemia (n = 73) | P value |
|---|---|---|---|---|---|
| **Age, median (IQR)** | | 55 (40–69) | 63 (47.5–71) | 50 (37–67) | **.04** |
| **Sexno. (%)** | Male | 28 (33.33) | 3 (10.71) | 25 (89.28) | .703 |
| | Female | 56 (66.67) | 8 (14.28) | 48 (85.71) | |
| **Lymphopenia at presentation no. (%)** | No | 35 (41.67) | 3 (27.27) | 32 (43.83) | .721 |
| | Yes | 49 (58.33) | 8 (72.71) | 41 (56.16) | .961 |
| **Median Ct (IQR)** | | 36.4 (34.0-38.5 ) | | | |

Table 1 shows, Fisher's exact test, p value<.05 is significant.

Table 2: Association of serum level of IL-6 with severity of COVID-19 infection and healthy controls

| Category of patient | IL-6(pg/ml) Mean ± SD | Mean rank | P value |
|---|---|---|---|
| **Control groupn=28** | 3.5±1.8 | 17.9 | <0.001 |
| **Moderate groupn=28** | 47.04±106.5 | 32.5 | |
| **Severe groupn=28** | 67.2±129.5 | 63.7 | |
| **Critical groupn=28** | 102.02±149.7 | 76.4 | |

Table 2 shows, Kruskal Wallis test, P<.05 indicated statistical significance.

In control, the mean IL-6 was 3.5 ±1.81, in moderate group of patients it was 47.04±106.5, in severe group of patients, it was 67.2±129.5and in critical group of patients it was 102.02±149.7. Kruskal Wallis test showed that there was significant statistical difference among the groups regarding IL 6 as p<0.001.

Table 3: The correlation analysis of RNAaemia and vital signs withserum IL-6 level

| Variables | | All patients n=84 | IL-6 (<100 pg/ml) | IL-6 (100> pg/ml) | R | P-value |
|---|---|---|---|---|---|---|
| **RN Aaemia** | **Negative** | 73 | 68 | 5 | 0.912 | <0.001 |
| | **Positive** | 11 | 1 | 10 | | |
| **Vital Signs** | **Death** | 5 | 0 | 5 | 0.983 | 0.102 |
| | **Alive** | 79 | 69 | 10 | | |

Pearson correlation, P<.05 indicated statistical significance.

Table 3 shown that, the incidence of RNAemia was closely correlated with IL-6 high in critically ill patients (R=0.912).

Table 4: Allele and genotypic frequencies of IL-6 174G/C genes in COVID-19 patients and healthy controls

| Gene and SNP | Genotype /Allele | Patient (n=84) (%) | Healthy controls (n=28) (%) | P value | OR (95% CI) |
|---|---|---|---|---|---|
| IL-6 174G/C (rs 1800795) | **GG** | 59 (70.24) | 23 (82.14) | .927 | 1.027 (0.45-4.65) |
| | **GC** | 23 (27.38) | 5(17. 85) | .896 | 2.043 (0.3-3.45) |
| | **CC** | 2 (2.38) | 0 | - | - |
| | **G allele** | 141 (83.92) | 52(91.07) | .706 | 0.847 (0.32-3.24) |
| | **C allele** | 27 (16.07) | 5(8.92) | | |

Note: OR = Odds ratio, 95 % CI= 95% Confidence interval. P value and Odds ratio were calculated using Chi-square test for (3 x 2 and 2 * 2 ) contingency table. P value< 0.05 was considered as statistically significant. IL-6 174 G/C polymorphism in different categories of patients and controls. Table 4.5 shows frequency of GG, GC and CC genotype in patients were 70.24%, 27.38% and 2.38% respectively which were not significantly different from healthy control .Frequency of G and C allele was 83.92% and 16.07% respectively in patients; 91.07% and 8.92% in healthy control Any of these associations were not statistically significant.

Table 5: Allele and genotypic frequencies of IL-6 174G/C gene with different category of study population

| Study population | IL-6 174G/C gene | | | | |
|---|---|---|---|---|---|
| | GGn (%) | GC&CCn (%) | OR | CI | p value |
| Moderate<br>Control | 25 (89.20)<br>23 (82.14) | 3 (10.71)<br>5 (17.85) | 3.47 | .851-5.290 | .821 |
| Severe<br>Control | 19 (67.85)<br>23 (82.14) | 9 (32.14)<br>5 (17.85) | 3.106 | 0.89-8.24 | .092 |
| Critical<br>Control | 15 (53.57)<br>23 (82.14) | 13 (46.42)<br>5 (17.85) | .015 | 0.09-3.23 | .023 |
| Moderate<br>Severe | 25 (89.20)<br>19 (67.85) | 3 (10.71)<br>9 (32.14) | 4.983 | 1.25-4.36 | .018 |
| Moderate<br>Critical | 25 (89.20)<br>15 (53.57) | 3 (10.71)<br>13 (46.42) | 8.316 | 3.22-9.86 | .019 |
| Severe<br>Critical | 19 (67.85)<br>15 (53.57) | 9 (32.14)<br>13 (46.42) | 3.327 | 0.823-12.01 | .854 |

Note: OR = Odds ratio, 95 % CI= 95% Confidence interval. P value and Odds ratio were calculated using Chi-square test for (3 x 2 and 2 * 2 ) contingency table. P value< 0.05 was considered as statistically significant.In the control, 23 (82.14%) had GG genotype while in moderate group, 25 (89.20%)patients had GG genotype (p=0.821). severe group, 19 (67.85%)patients had GG genotype. critical group, 15 (53.57%)had GG genotype. In the moderate group, 25 (89.20%) patients had GG genotype while in severe group, 19 (67.85%) patients had GG genotype (p=.018). Odds ratio expressed that in the severe group, the odds of having GC and CC was 4.983times compared to moderate group. In the moderate group, 25 (89.20%) patients had GG genotype while in critical group, 15 (53.57%) GGgenotype (p=.019). Odds ratio expressed that in the critical group, the odds of having GC and CC was 8.316times compared to moderate group. In the severe group, 19 (67.85%) patients had GG genotype while in critical group, 15 (53.57%)GGgenotype. There was no significant statistical difference between the groups regarding IL-6 174G/C SNP gene as p=0.854.

Table 6: Correlation between IL-6 and IL-6 174G/C genotype according to disease severity

| **Category of patients** | | **IL-6 174G/C genotype** | |
|---|---|---|---|
| **IL-6** | **Moderate group** | Pearson Correlation | .067 |
| | | p-value | 1.01 |
| | **Severe group** | Pearson Correlation | **.481*** |
| | | p-value | **.05** |
| | **Critical group** | Pearson Correlation | **.651**** |
| | | p-value | **<.001** |

Here, Correlation is significant at the 0.05 level (2-tailed).Correlation is significant at the 0.01 level (2-tailed). Correlation is significant at the 0.001 level (2-tailed).Serum IL-6 level significantly correlated with IL-6 174G/Cgenotype in critical group (p<.001).

Figure 1: Mean level of IL-6 according to genotype distributions

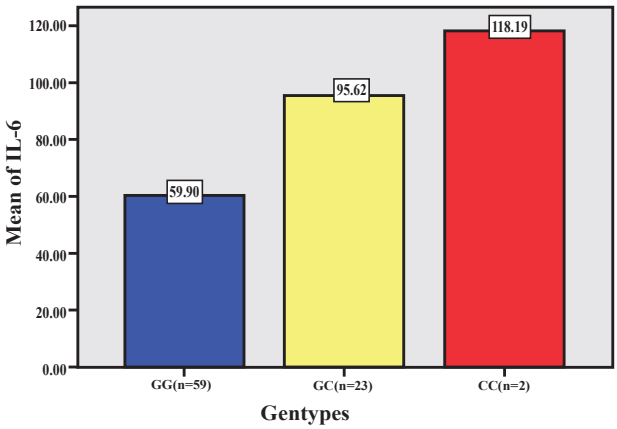


Figure 1 shows bar diagram showing the mean level of IL-6 according to genotype distributions of IL-6 174G/C. Statastical association found between the mean level of IL-6 and GC and CC genotypes (P-0.03).

## Discussion:

In this study, the distribution of serum SARS-CoV-2 nucleic acid positive cases in various patients groups, and the result showed that those cases were confirmed mostly in critically ill patients group (39.28%), the extremely high IL-6 level was closely correlated with the incidence of RNAaemia and the mortality. (R=.912, P<0.001) Chen et al., (2020) showed that serum SARS-CoV-2 viral load and IL-6 level could serve as an indicator of poor prognosis.[14] The association between RNAemia, ICU admission (p=.04) and invasive mechanical ventilation (p=.02) suggests the potential utility of plasma SARS-CoV-2 RNA testing as a prognostic indicator .[15] Preliminary data from a limited number of patients have shown an association between RNAemia and severe COVID-19 and support the presence of RNA in extrapulmonary sites .[14] A similar association between detection of SARS-CoV-1 RNA in serum and clinical

complications including oxygen desaturation, mechanical ventilation, and mortality was noted in various types of studies.[16] Thus, in the absence of a robust COVID-19 clinical scoring system, plasma may be considered as a complementary modality for the early identification of individuals likely to develop severe COVID-19.[17] In this study serum level of IL-6 was found statistically significant ($p<0.001$) among different COVID-19 patient groups. But another studies show found that IL-6 level increased in critically ill group than moderate and has statistically significant association ($p<0.001$) with disease severity.14 Different types of studies showed that serum level of IL-6 in severe and critical patients compared with moderate and mild patients has significant statistical difference ($p=0.004$).[18] In this study, patients with critical Covid-19 had mean IL-6 level76.4 pg/mL compared to 32.5 pg/mL in moderate and 63.7 pg/mL in severe Covid-19 group. A metanalysis of 9 studies concluded that increased IL-6 is highly associated with severe disease and patients with severe Covid-19 had mean IL-6 higher (58pg/mL) compared to mild disease (17 pg/mL).[19] A study by Herold et al. found that IL-6 > 80 pg/mL predicts respiratory failure and need for mechanical ventilation in Covid-19. Among hospitalized patients with COVID-19, patients with high IL-6 ($R = -0.535$, $P < 0.001$)levels at admission are at increased risk of developing a severe form of the disease, requiring mechanical ventilation and ICU, and progressing to respiratory distress syndrome and multiorgan failure.[20] In this study, IL-6 174 genotype and allele frequency in total patients were not significantly different from healthy control.Comparison of genotype and allele frequency among moderate and severe and critical groups showed similar pattern: significantly reduced GG genotype and G allele, along with increased GC genotype and C allele in severe and critical group. This denotes that genotype GG and G allele were protective while genotype GC and C allele increased the odds of severe disease and mortality. It is likely that IL-6 174 C allele is a risk factor for critical illness and mortality and IL-6 GG genotype and G allele seems to be protective. [21] Findings of this study support the pilot analysis by Rajkumar (2020) and Ulhaq and Soraya (2020) across several nations where IL-6 174 G allele was negatively correlated with COVID-19 prevalence and mortality and IL-6 174 C allele was significantly associated with the severity of COVID-19 associated pneumonia.[21-22] Similar results were found in several studies on community acquired pneumonia (CAP) and ARDS. [23]

## Conclusion:

IL-6 increased in critically ill COVID-19 patients compared to moderate group and healthy groups and statistically significant among different category of COVID-19 patients.Extremely high IL-6 level correlated with the incidence of RNAemia and the mortality.IL-6 174 GC genotype may be one of the most important risk factors for severe COVID-19 disease and mortality.

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## Conflict of interest:

The authors declare that no conflict of interest exists.

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