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A Prospective Study Investigating the Relationship Between Infection-Associated Biomarkers, Inflammatory Cytokines, and the Severity of COVID-19

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Abstract: ***Background: Sepsis-linked biomarkers and inflammatory cytokines are markedly associated with potential risks of progression to severity in coronavirus disease 2019 (COVID-19). Clinical studies that find a plausible association between sepsis biomarkers and the inflammatory cytokine response in the Indian community need to be studied with clarity. Objectives: To study the relationship between sepsis-linked biomarkers and inflammatory cytokines interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, and D-dimer linked to clinical severity resulting from COVID-19 infection. Materials and methods: The present observational study was conducted between March and December 2023 in the Department of Medicine at a tertiary care, Uttar Pradesh, India, on COVID-19 patients. Upon patient admission, inflammatory biomarkers such as IL-6, CRP, ferritin, and D-dimer were recorded. Oxygen requirements during hospitalization, invasive mechanical ventilation (IMV), high-flow nasal cannula (HFNC), noninvasive mechanical ventilation (NIV), duration of ventilator use, intensive care unit (ICU) stay, and mortality were documented. Results: The average levels of IL-6, CRP, D-dimer, and serum ferritin protein recorded at the time of patient arrival were notably higher in the severe (S) group compared to the nonsevere (NS) group. The average duration of ventilator use, ICU stay, and hospital stay was significantly longer in the S group than in the NS group. The percentage of patients who required HFNC, NIV, IMV, and mortality was significantly higher in the S group compared to the NS group. Conclusion: Sepsis-linked biomarkers and inflammatory cytokines such as IL-6, CRP, D-dimer, and serum ferritin levels at the time of admission were markedly associated with severity outcomes in COVID-19 infection.***

Keywords: COVID-19, D-dimer, Ferritin, Sepsis, IL-6.

1. Introduction

The pandemic coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARSCoV-2), with the first reported outbreak case in Wuhan, China, in December 2019. COVID-19 has affected a total of 219 countries, resulting in >765,222,932 confirmed positive cases and 6,921,614 recorded deaths as of 3rd May 2023. In India, the prominent number of cases were seen in states of Delhi, Tamil Nadu, Kerela Maharashtra, Karnataka, and Andhra Pradesh.1-3

The coronavirus enters the human cell through the functional receptor angiotensinconverting enzyme 2 (ACE2) with its spike protein structures. Pathogenesis involves indirect mechanisms such as an inflammatory response and excessive production of cytokines, which is known as a cytokine storm. SARS-CoV-2 triggers a cascade cycle that leads to the generation of proinflammatory cytokines, such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor α, contributing to the cytokine storm, which in turn causes lung tissue damage and cell death.4–6

Patients with COVID-19 may suffer from complications such as SARS, acute respiratory distress syndrome (ARDS), cardiac dysfunction, liver dysfunction, and kidney failure, leading to multi-organ failure and loss of life.7 The elevated risks of progression to severe COVID-19 may be caused by the presence of inflammatory markers such as serum ferritin, procalcitonin, C-reactive protein (CRP), IL-6, and erythrocyte sedimentation rate (ESR).8–10

Clinical manifestations of COVID-19 include fever, cough, breathing difficulty, myalgia, sore throat, dyspnea, muscle fatigue, and gastroenterological disturbances such as nausea and indigestion. Complications may include thrombocytopenia, impaired coagulation functions, thrombi formation, and the development of microthrombi in the lungs.

Due to the limited study size of COVID-19 progression in the Indian population and their varied responses related to the interplay of sepsis-linked biomarkers and inflammatory cytokine responses, associated with the severity and outcome of COVID-19 inflammation. The primary aim of the present research was to establish a correlation between sepsis-related biomarkers and inflammatory cytokines such as CRP, ferritin, IL-6, and D-dimer with the severity and outcome of COVID-19 infection.

2. Materials and Methods

This observational study was conducted between March and December 2023. The study included data of subjects of both sexes, aged 18 years and above, with a confirmed positive reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19, who were admitted to a tertiary care hospital in Uttar Pradesh, India. Demographic details, medical history, signs and symptoms, and laboratory examinations were recorded. Laboratory examinations

included complete blood count, blood biochemical parameters such as total serum bilirubin, serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT), serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), total blood urea, total serum creatinine, serum electrolytes, coagulation functions including international normalized ratio (INR) and D-dimer, infection related biomarkers (CRP, serum ferritin), and inflammatory cytokines (IL-6). Inflammatory markers were recorded at the time of admission. COVID-19-positive cases were categorized according to WHO classification into mild, moderate, severe, and critical based on the severity of the disease. These groups were further divided into two groups—group severe (S), consisting of severe and critical COVID-19 patients, and group nonsevere (NS), consisting of NS COVID-19 patients, including those in the mild/moderate disease category. The oxygen requirement during hospitalization (O2 mask/nasal cannula, O2 nonrebreather mask), noninvasive mechanical ventilation (NIV), high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), number of days on a ventilator, intensive care unit (ICU) stay, and hospital stay were noted. C-reactive protein (quantitative) test was conducted . Serum ferritin was tested by enzyme-linked immunofiltration assay (ELIFA), with a normal reference value of 15.00–300.00 ng/mL. Total IL-6 levels were estimated using enzyme-linked immunosorbent assay (ELISA), with a normal reference value of 0.00–6.50 pg/mL. D-dimer was measured by immunoturbidimetric assay, with a normal reference value of <500 ng/mL.

The aforementioned test data were tabulated in Microsoft Excel Worksheet, and statistical analysis was performed using Statistical Package for the Social Sciences for Windows, version 25.0. Categorical variables are presented as n (% of cases), while continuous variables are reported as mean and standard deviation (SD). Associations among categorical variables were assessed using the Chi-squared test or Fisher's exact test. Unpaired t-tests were used to compare continuous variables between groups. The significance level was set at 95% with a p-value < 0.05.

3. Results

A total of 94 patients were included in this observational research. Mild and moderate COVID-19 patients accounted for 29 (30.9%) subjects each, while severe and critical patients were observed in 32 (34.0%) and 4 (4.2%) subjects, respectively. The mild and moderate subjects were categorized into the NS group, and severe and critical cases were categorized into the S group. The age-groups, gender distribution, prevalence of ischemic heart disease, and history of smoking were comparable between the NS and S groups. However, the prevalence of diabetes mellitus, hypertension, and chronic kidney disease was significantly higher in group S compared to the NS group. The average levels of mean hemoglobin, total white blood count, platelet count, serum sodium, serum creatinine, serum alkaline phosphatase (ALP), and INR were comparable between the NS and S groups. However, serum potassium, blood urea, SGOT, SGPT, CRP, serum ferritin, IL-6, D-dimer, and NEWS score at the time of admission were significantly elevated in the S group compared to the NS group.

Parameters in mean	*NS group*	*S group*	*p-value*
Hematological parameters			
Hemoglobin%	12.8	12.1	0.08
Total leukocyte count	7916.5	9753.2	0.11
Platelets count	2.2	2.0	0.19
Serum electrolytes			
Sodium	134.3	135.0	0.28
Potassium	4.2	4.5	0.02
Biochemical parameters			
Blood urea	31.3	55.9	0.01
Serum creatinine	1.1	1.6	0.06
Serum bilirubin	0.7	1.1	0.02
SGOT	36.3	81.5	0.02
SGPT	31.6	55.7	0.02
ALP	66.5	71.3	0.25
INR	1.1	1.1	0.13
CRP at admission	54.0	105.8	0.01
D-dimer at admission	820.8	1618.4	0.01
Serum ferritin at admission	276.8	858.9	0.01
IL-6 at admission	72.74	259.28	0.01
NEWS score at admission	3.8	4.4	0.01

The mean duration of ventilator requirement, mean duration of ICU stay, and mean duration of hospital stay were significantly higher in group S compared to group NS. Additionally, the average number of COVID-19 patient subjects who required HFNC, NIV, and IMV was significantly higher in group S compared to group NS. The mortality rate was notably higher in group S compared to group NS.

4. Discussion

The present observational study was conducted to investigate the association of sepsis-linked biomarkers and levels of

inflammatory cytokines with the severity and outcome of COVID-19 infection. The ongoing study establishes a significant correlation between CRP, serum ferritin, and IL-6 levels at the time of patient admission and the severity and outcome of COVID-19. The ongoing study categorically proposes that severe COVID-19 patients demonstrate significantly higher levels of infection/ sepsis-linked biomarkers compared to NS COVID-19 patients.

Specifically, procalcitonin levels (0.1 vs 0.05 ng/mL with p-values < 0.001), total serum ferritin protein levels (800.4 vs 523.7 ng/mL with p-value < 0.001 and total CRP levels (57.9 vs 33.2 mg/L with p-value < 0.001) were markedly elevated in severe cases. Inflammatory cytokines were also found to be higher in severe cases compared to NS cases, including IL-2R (757.0 vs 663.5 U/mL with p-value = 0.001), IL-6 levels (25.2 vs 13.3 pg/mL with p-values < 0.001), IL-8 levels (18.4 vs 13.7 pg/mL with p-values < 0.001), and IL-10 levels (6.6 vs 5.0 pg/mL with p-value < 0.001).

5. Conclusion

The serum potassium, blood urea, SGOT, SGPT, CRP, D-dimer, serum ferritin, IL-6, and NEWS scores at admission were significantly elevated in the S group compared to the NS group. The mean duration of ventilator required, ICU stay, and hospital stay was significantly longer in the S group compared to the NS group. The percentage of patients who required HFNC, NIV, and IMV was significantly higher in the S group compared to the NS group. The mortality rate was also significantly higher in the S group compared to the NS group. There was a significant association between infection-related biomarkers and inflammatory cytokines such as CRP, D-dimer, serum ferritin, and IL-6 at admission and the severity and outcome of COVID-19 infection.

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