Original Article

Dynamic profile and clinical implications of hematological and immunological parameters in COVID-19 patients. A retrospective study

Shekhar Yashwant Suryawanshi[1], Shrishtee Priya[2], Sandarbh Saumya Sinha[3], Srinath Soni[4], Naqoosh Haidry[5], Shilpi Verma[6], Supriya Singh[7]

[1]Department of Oral and Maxillofacial Surgery, ACPM Dental College, Dhule, Maharashtra, [2]Department of Conservative Dentistry and Endodontics, Hazaribag College of Dental Sciences, Hazaribagh, Demotand, Jharkhand, [3]Department of Oral and Maxillofacial Surgery, Sarjug Dental College and Hospital, Darbhanga, Bihar, [4]Department of Prosthodontics,Crown and Bridge and Implantology, [5]Department of Oral and Maxillofacial Surgery, Patna Dental College and Hospital, [6]MDS Prosthodontics Crown and Bridge, Private Practitioner, Dental Clinic FF13 Luv Kush Tower, Patna, [7]Senior Resident Department of Community Medicine, Private Practitioner New Delhi, India

Abstract

Background: Ever since the World Health Organization (WHO) announced the SARS-CoV-2 or nCOVID-19 infection (a pandemic), continuous spread of the virus has been observed which has continuously seen to affect and kill multitudes of individuals all over the world. An understanding of the pathophysiology of this disease is necessary for an effective treatment. Laboratory investigations play an important role in the diagnosis as well as treatment of this infectious disease. Hematological parameters demonstrate alterations during the progression of nCOVID-19 infection. Of these, many are indicative of extremely poor clinical outcome. Hematological findings like leukopenia, lymphopenia, thrombocytopenia and coagulation-related abnormalities are the most common manifestations. The aim of this study was to assess the dynamic profile and clinical implications of hematological and immunological parameters among nCOVID-19 infections. **Materials and Methods:** This retrospective study was designed after categorizing patients suffering from COVID-19 into three groups: (a) Group I; (b) Group II and (c) Group III or severe critical patients. Hematological and immunological parameters of neutrophilic and white blood cell counts, d-dimer levels, hemoglobin levels, immunoglobulin G (IgG) and M (IgM) levels and interleukin-6 (IL-6) levels were assessed. Statistical analysis using Kruskal–Wallis test was used. **Results:** Normal white blood cell and neutrophil count among COVID-19 patients was seen. However, median values in Group II ($P < 0.01$) and Group III ($P < 0.0001$) were found to show significantly higher values when compared to Group I. A significant ($P < 0.01$) decrease in lymphocytic counts was found among severe and critical patients. Hemoglobin level was found to demonstrate higher decrease ($P < 0.01$) among severe and critical patients. Platelet count was found in normal range in all COVID-19 patients. Routine coagulation tests revealed increased fibrinogen ($P < 0.01$) and d-dimer levels ($P < 0.0001$) in severe and critical patients. Normal proportions of total CD3+ and CD4 + T lymphocytes were observed in COVID-19. However, CD8 + T lymphocytes proportion was found to be decreased (P-value < 0.05). Immunoglobulin G levels among Groups II and III patients were found to be lower when compared with Group I ($P < 0.001$). No statistical significance was observed between the groups in IgM levels. Plasma IL-6 levels were found to show progressive rise among Groups II and III patients ($P < 0.05$). **Conclusion:** Analysis of hematological and immunological parameters profiles in COVID-19 patients may help in deciphering the clinical progression of patients suffering from COVID-19 disease. Thus, regular monitoring of the hospitalized patients may help in planning the management of these cases.

Keywords: CD lymphocytes, COVID-19, hematological, interleukin-6, subsets, thrombocytopenia

Address for correspondence: Dr. Supriya Singh, Department of Community Medicine, Private Practitioner, New Delhi, India.
E-mail: ssssingh13459@gmail.com

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Introduction

The COVID-19 outbreak has resulted in an unexpected health crisis all around the world. It was on March 11, 2020, when the WHO declared it as a pandemic. Ever since, an exponential increase in the disease has been seen.[1] The coronavirus disease 2019 or COVID-19 is a beta-coronavirus that has been closely related to the SARS-CoV-2 by means of genetic sequencing methods. This disease is associated with alterations in the complete blood picture and coagulopathies.[2] The beta-coronavirus is a member of the extreme acute respiratory syndrome-related coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV). It has 79 and 51.8% genetic homology to the SARS-CoV and MERS-CoV, respectively. Among the biochemical parameters, a significant increase in lactate dehydrogenase (LDH), creatinine phosphokinase (CPK) and C-reactive protein (CRP) ($P < 0.05$) was observed.[3] Ferritin has been associated with dysregulation of the immune system. At high serum levels, the immune system undergoes suppression. Its proinflammatory activity plays a vital role in cytokine storm crisis. Thus, it is indirectly related to causation of acute respiratory distress syndrome (ARDS) and severe SARS-CoV-2 infectiousness. All of this results in secondary hemophagocytic lymphohistiocytosis in COVID-19 or SARS-CoV-2 infection.[4]

It has been estimated that the median period for incubation is between 2 and 14 days. Symptoms of COVID-19 infection include fever, dry cough, headache, fatigue, hemoptysis, dyspnea, diarrhea and lymphopenia.[5,6]

Patients infected with COVID-19 exhibit mild to severe acute respiratory infection syndromes. Patients with mild disease show symptoms like fever, fatigue, dry cough, malaise and may be an abnormal chest radiograph or computed tomography scan. In a few patients, there is a rapid progression of the disease that develops into ARDS or multi-organ failure in a short period of time. This rapid progression may be attributed to various immunological factors. Thus, it is important to study these immune factors for timely and early identification of a severe disease.[1]

The study of biochemical parameters may be used to evaluate prognosis of patients during the entire period of patient hospitalization. Thus, an increase in the levels of the inflammation causing cytokines results in a condition known as "cytokine storm". This phenomenon is considered to be the reason behind acute pulmonary injury leading to tissue damage.[7] Virus-induced infection of the endothelial cells causes activation of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF- α). IL-6 plays an important role on the janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway and increases vascular endothelial factor secretion along with an increase in IL-8 synthesis. These proinflammatory cytokines along with the immunologically active molecules cause an increase in the production of chemokines, colony stimulating factors and interferons which cause cytokine storm. The cytokine storm along with a hyper-inflammatory physiological condition results in a pro-thrombotic situation along with activation of endothelial cells and platelets.[8,9]

There is a pressing and urgent requirement for an early identification of effective diagnostic as well as prognostic biomarker of disease progression towards clinical decline, and resultant patient mortality. Lymphocytopenia is a prominently consistent feature in the affected subjects. This virus shows affinity towards the ACE-2 receptors localized on lymphocytes and is attributable for its cytopathic effects.[7]

It has been observed that individuals with blood group A demonstrate a higher risk of SARS-CoV-2 infection while the group O subjects demonstrate a lower risk.[10] Blood tests play an important role in the early diagnosis as they can provide useful information regarding the process of inflammation within the body which may include lymphocyte count, CRP levels and collateral damage such as acute renal failure, hepatic and renal disease severity.[10]

Xu *et al.*[11] (2020) have reported three mechanisms of thrombocytopenia: (a) According to the first mechanism, there is a viral infection of hematopoietic tissues of bone marrow leading to depleted synthesis of platelets; (b) According to the second hypothesis, it is because of impaired immunological system and (c) According to the third hypothesis, platelets undergo aggregation within lungs which may lead to their consumption and formation of microthrombi.

The pulmonary as well as systematic inflammation-based response due to SARS-CoV-2 infection is triggered by innate immunological system following viral replication.[12,13]

Patients with mild to moderate COVID-19 disease show recovery following medical therapy. However, patients with severe disease have a fatality rate ranging from 1 to 15%.[14-16]

Radiological features of chest radiography show features such as consolidation, ground-glass opacifications and paving pattern. The frequency of ground-glass opacifications and consolidation reduce as there is progression of the disease while there is an increase in consolidation with the paving pattern concomitantly. It has been hypothesized that lymphopenia is the result of direct viral infection of lymphocytes, destruction of lymphocytic organs and apoptosis of lymphocytes. Worsening of lymphopenia is seen in severely infected patients.[17,18] Tian *et al.*[19], in 2020, reported radiological changes in chest findings which include injury to the alveolar epithelial cells, formation of hyaline membrane and type II pneumocytic hyperplasia. There is an extensive proliferation of fibroblasts which radiographically appear as consolidation.

The commonest complications observed in patients suffering from COVID-19 include acute renal injury, alkalosis, cardiac failure, sepsis, acute respiratory failure and hypoxia-induced

encephalopathy. Biochemical alterations seen associated with COVID-19 infection include hypokalemia, hyponatremia and hypocalcemia in severe infection. Hypokalemia causes exacerbation of ARDS and acute cardiac stress. The reduction in ACE-2 receptors causes an increase in angiotensin II levels which may result in an increased excretion of potassium from the kidneys which results in hypokalemia.[20]

The aim of the study was to retrospectively analyze the dynamic profile and clinical implications of various hematological and immunological parameters in patients diagnosed with COVID-19.

Material and Methods

The approval for conducting this study was obtained from the Institutional Ethical Committee (IEC12/21-2020). Additionally, permission was provided for exemption of obtaining informed consent from the patients. The patients diagnosed with COVID-19 were selected from dedicated COVID-19 medical units during the period extending from January to December, 2020.

Inclusion criteria for selected patients were based upon the clinical state of the infected patients at the time of hospital admission and were classified into

(a) Regular COVID-19 group: This group consisted of patients suffering from pyrexia, respiratory symptoms and radiographic features of pneumonia
(b) Severe COVID-19 group: This group of patients presented with clinical symptoms such as (i) shortness of breath; (ii) greater than 30 breaths per minute of respiratory rate; (iii) peripheral blood oxygen saturation lesser than 93% at rest; (iv) PaO2/FiO2 measuring 300 mmHg or may be lesser; (v) pulmonary radiographic imaging indicative of disease progression greater than 50% within 24-48 hours and (c) Critically ill patients: These patients suffered from respiratory failure; shock and failure of vital organs. Each group consisted of 100 patients; hence, the total number of study participants was 300.

Data collection

Patient case records were coded to avoid any duplication of cases. For this study, details such as patient's age, gender, systemic complications, clinical symptoms, routine blood, biochemical analysis of blood, immunoglobulin and cytokine assays, T-cell subsets and inflammatory biomarkers were obtained.

Statistical analysis

The GraphPad Prism 6 software was used for statistical analysis of the collected data. The obtained measurement data were found to have a non-normal distribution and had a uniform representation by median or quartile spacing. Non-parametric statistical tool Kruskal–Wallis was employed. Obtained data was represented as percentage and $P < 0.05$ was considered to be of statistical significance.

Results

Of the 300 patients studied, the median age was found to be 67 years (an inter-quartile range of 58-75; range of 30-92 years); 49.1% of the study subjects were males. No significant difference in the median age and sex ratios in any of the groups was found ($P > 0.05$). The chief clinical manifestations among the patients were found to be cough, fever and fatigue while shortness of breath was more commonly observed in severe and critically ill subjects.

Investigations of hematological and immunological profile:

I. Routine blood investigations: The laboratory results demonstrated normal white blood cell (WBC) and neutrophil counts among COVID-19 patients. Although, median values in severe (group II) and critically sick groups (group III) was found to have significantly greater values compared to the first group ($P < 0.01$ and $P < 0.0001$, respectively). Most of the patients suffering from COVID-19 were found to demonstrate decreased lymphocyte counts and were found to be much lesser among the severe and critically morbid patients ($P < 0.01$). The hemoglobin levels were found to show a decrease which was found to be more so among the severe and critically sick patients ($P < 0.01$). The platelet count was found to be normal among the COVID-19=infected patients. Routine tests for coagulation showed increased fibrinogen and D-dimer levels in patients suffering from COVID-19. This was more pronounced in the severe and critically ill patients ($P < 0.01$ and $P < 0.0001$, in respective manner).
II. Lymphocytic investigations: The laboratory test results demonstrated the normal reference range proportion of total CD3 + and CD4 + T lymphocytes in COVID-19 patients. But, the proportion of CD8 + T lymphocytes was found to be reduced. This reduction was more in group I. A statistically significant difference was noted among all groups ($P < 0.05$) [Table 1].
III. Immunological and complement assays: Immunoglobulin G (IgG) levels among the severe and critical COVID-19 patients were found to be lesser when compared to group I. A statistical difference of $P < 0.001$ was obtained. On comparing the immunoglobulin M (IgM) levels, no statistical significance was observed between the groups [Table 2].
IV. Cytokine assays: Plasma levels of IL-6 in most COVID-19 patients were found to have a slight increase whereas they were found to show a progressive increase among the severe and critical patients. The plasma IL-6

Table 1: Table demonstrating comparisons between median T-cell subsets's

T-cell subsets	Group I	Group II	Group III	*P*
CD 3 +	76.57	74.84	71.65	0.63
CD 4 +	47.23	45.12	43.27	0.76
CD 8 +	22.34	23.67	27.76	0.04
CD4/CD8	2.12	1.67	1.23	0.13

levels among severe and critical patients were found to be significantly greater than the group I patients. A statistical significance of *P* less than 0.05 was obtained [Table 2]. Graph 1 indicates P values for various hematological and immunological parameters.

Discussion

There are variations in the clinical symptoms and hematological and immunological profile of patients diagnosed with COVID-19. Acute illness related to COVID-19 may be defined as 'clinical features (for example, dyspnea or hypoxia) which result in hospital admission.'[21]

In our study, the white blood cell and neutrophilic counts were found to demonstrate statistically higher significance in patients with severe clinical presentations. The CD8 + T-lymphocyte counts were found to be statistically lower in subjects with severe disease than the mild symptomatic patients. An extremely significant statistical difference in IgG levels was observed. Also, a significant level of increase in IL-6 was seen in patients who had severe disease. Our findings have been widely corroborated by multiple study findings as discussed.

Seddigh-Shamsi *et al.*[22] (2021) reported that among the hematological parameters were the WBC count, mean corpuscular hemoglobin and red cell distribution width.

Margekar *et al.*[23], in 2021, reported that the neutrophil to lymphocyte ratio may act as a biomarker for the assessment of the disease severity as an early risk of COVID-19 infection, especially among the pediatric population; 27.3% subjects suffering from COVID-19 demonstrate neutrophil to lymphocyte ratio of 3.13. The platelet to lymphocyte ratio is used as a parameter for predicting the extent of cytokine storm.

Usul E *et al.* (2021) found a significant increase in WBC count ($P = 0.004$), neutrophil to lymphocyte ratio ($P = 0.001$), D-dimer levels ($P = 0.001$), ferritin levels ($P = 0.0001$) and LDH levels ($P = 0.0001$).[24]

Zhang *et al.*[1], in 2020, in their study evaluated various lymphocytic subsets along with clinical features of COVID-19. The total CD4 + AND CD8 + lymphocyte counts were found to show significant reduction in COVID-19 patients. The lower T lymphocyte subsets were shown to be significantly associated with higher incidences of end-point events which included intensive care unit hospitalizations, use of mechanical ventilation and/or death. The over-activation and exhaustion of T lymphocytes exist simultaneously. There is a reduction in absolute CD4 + T lymphocytic cell counts and interferon-ϒ (IFN-ϒ) secretion.

Dawood *et al.*[2], in 2020 in their study demonstrated that 9.82% of the subjects were diagnosed with leukocytosis, 5.4% had leucopenia, 5.36% had lymphopenia while 14.28% patients had neutrophilia. Among the coagulation disorders, 6.25% suffered from thrombocytosis whereas 5.36% had thrombocytopenia.

Henry *et al.*[7], in 2020, reported significant alterations in hematological, biochemical, coagulation and immune biomarkers which were associated with severe morbidity and mortality in COVID-19. These included an increase in neutrophilic and WBC count; reduction in platelets and eosinophil counts; reduction in hemoglobin and albumin levels; increases in alanine aminotransferases, aspartate aminotransferases, bilirubin, blood urea nitrogen, creatinine kinase, lactate dehydrogenase, creatinine kinase-MB, cardiac troponin-1 levels, and also, increased levels of C-reactive protein (CRP), IL-2R, IL-6, IL-8 and IL-10 levels. Thus, the analysis of these biochemical patterns may be useful in the identification of risks.

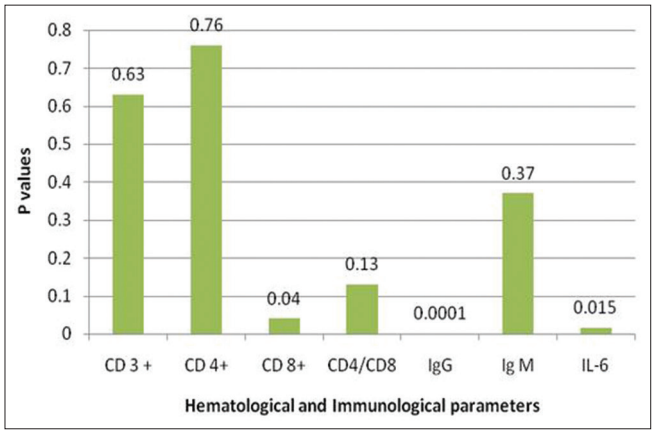
Taj S *et al.*, in 2020, found statistical significance ($P < 0.05$) among neutrophils, lymphocytes and eosinophil counts.[25]

Abdulla in 2020 showed a decrease in the lymphocytic count and elevated levels of serum ferritin, blood urea, serum creatinine and D-dimer.[26] Also, Xu *et al.*[27] (2020) reported that the ACE-2 receptors get expressed within the lymphocytes present in oral mucosa, lungs and the digestive system.

Yuan *et al.*[28], in 2020, in their assessment of hematological and immunological parameters among COVID-19 positive patients demonstrated statistically significant lower counts of lymphocytes, decreased red blood cells, hemoglobin levels, levels of immunoglobulins ($P < 0.01$), fibrinogen WBC count, neutrophil counts, C-reactive protein, procalcitonin, erythrocyte

Table 2: Comparisons between median immunoglobulin and cytokine levels

Immunoglobulin/ Cytokine levels	Group I	Group II	Group III	*P*
IgG	12.34	9.87	8.56	0.0001
IgM	0.98	1.23	1.24	0.37
IL-6	7.56	14.24	17.27	0.015



Graph 1: Graph showing *P* values in various hematological and immunological parameters studied

sedimentation rate, IL-6, ferritin and LDH. IgG antibodies against SARS-CoV-2 among severely critical patients was found to be significantly lesser than the normal subjects. Thus, it has higher transmissibility from person to person.

Liao *et al.*[29] in 2020 reported significantly a high thrombocytopenic disease when compared to those with moderate disease ($P < 0.0001$). Lymphocytic and eosinophilic counts were found to be significantly lesser among individuals with critical disease than compared to severe or moderate COVID-19 infection.

The novel scope of this research included investigation of various laboratory parameters that were associated with the severity and mortality of COVID-19 infection. These parameters included WBC count; lymphocytes, platelet count, D-dimer and ferritin were screened and evaluated in patients during the progression of this pandemic.

Careful evaluation of laboratory parameters at baseline and during the course of this disease can assist physicians in formulating an effective treatment approach and promptly provide intensive care to critically ill patients. Preventive measures for thromboprophylaxis and early identification of potentially lethal complications including Disseminated intravascular coagulation (DIC) in order to effectively intervene will improve patient outcomes, and will probably reduce the death rate overall among infected patients without significant comorbidities.[30]

Conclusion

Study of different laboratory parameters has been associated with severity and mortality in COVID-19 infection, specially, the anti-inflammatory biomarkers such as IL-6 and IL-10. Our study has distinctly studied various hematological and immunological parameters in mild to severe cases of COVID-19 infection. Thus, emphasizing the usefulness of these parameters in predicting disease progression.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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