Original Article

Impact of Various Hematological and Biochemical Parameters in Severe and Nonsevere COVID-19 Patients: A Retrospective Single-Center Study

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Abstract

Background: COVID-19 infection has been declared a pandemic in 2020 and since then it has been affecting the vast population of the world till today. Alteration of various hematological and biochemical parameters has been documented in various literatures. **Aim:** The aim of our study is to find out the prognostic role of hematological and biochemical parameters in severe and nonsevere COVID-19 patients. **Materials and Methods:** It was a retrospective record-based study conducted in a district-level COVID hospital of West Bengal, India. The COVID-confirmed patients admitted to the hospital during the second wave of COVID were included and data from records, including laboratory investigations were collected from the hospital registry. The severity of COVID was categorized based on the national guidelines. Independent samples *t*-test was applied to find out any relation of hematological and biochemical parameters abnormality in relation to disease severity. $P < 0.05$ was considered statistically significant. **Results:** A total of 94 COVID-confirmed cases were included in our study. Males constitute the majority of cases (51 males vs. 43 females). Seventeen cases were categorized as severe COVID (18.09%), whereas others were nonsevere COVID. Among hematological parameters, total leukocyte count (TLC), neutrophil and lymphocyte percentage, and neutrophil-to-lymphocyte ratio (NLR) were significantly altered among the severe compared to the nonsevere group ($P < 0.05$). While C-reactive protein (CRP), D-dimer, and serum ferritin levels also showed significant alteration among severe COVID patients ($P < 0.05$). **Conclusion:** Our study showed that severe COVID patients were significantly associated with neutrophilia, raised NLR, CRP, D-dimer, and serum ferritin levels.

Keywords: Biochemical parameters, COVID-19, hematological parameters, nonsevere COVID, severe COVID

Introduction

The novel coronavirus disease or COVID-19 was first described in December 2019 from Wuhan, the People's Republic of China, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] SARS-CoV-2 is a single-stranded RNA virus with a large genome (30 kb).[2] It is the third type of coronavirus after SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV, identified in 2003 and 2012, respectively.[3,4] While SARS-CoV-1 infection killed 774 people in 2002–2003 and MERS-CoV caused a localized epidemic in the Middle East in 2012, SARS-CoV-2 is very much contagious and has affected 212 countries/regions worldwide till 2021.[5,6] The WHO has declared COVID-19 disease a pandemic on March 12, 2020.[7]

The COVID-19 virus is highly contagious and transmitted through respiratory droplets and aerosols from person to person. After the entry inside the human body, the viral S protein binds to angiotensin-converting enzyme-2 (ACE-2) receptors which are highly expressed on pulmonary epithelial cells.[8] The virus then goes through local replication and propagation. At this stage, the viral burden is low, but these persons are infectious.

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Then, in the next few days, the virus migrates from the nasal epithelium to the upper respiratory tract through the conducting airways. There is a greater immune response at this phase of the disease with release of C-X-C motif chemokine ligand 10 (CXCL10) and interferons. Patients at this phase develop symptoms of fever, malaise, and dry cough. About 20% of all COVID-19 patient progress to acute respiratory distress syndrome (ARDS) with involvement of the lower respiratory tract. The virus invades and enters the type 2 alveolar epithelial cells through ACE-2 receptor and undergoes replication to produce more nucleocapsids. Then, the virus-laden alveolar epithelial cells produce and release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, and IL-12), tumor necrosis factor-α, IFN-γ and IFN-β, CXCL10, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein 1-α.[8] This "cytokine storm" acts as chemoattractant for neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells, and these cells are sequestered in the lung. This phenomenon along with persistent viral replication leads to the loss of both type 1 and type 2 pneumocytes, causing diffuse alveolar damage and eventually leading to ARDS.

Although all age and sex are vulnerable, there are various risk factors of COVID-19 disease. Risk factors include close contact of cases, health-care providers, older age, male gender, dementia, renal disease, cerebrovascular disease, obesity, etc.

Patients of COVID-19 show wide spectrum of clinical symptoms ranging from asymptomatic infection, mild fever, cough, myalgia-to-severe cases with ARDS leading to respiratory failure, and cytokine storm leading to death.[9,10]

There is a need for the identification of clinical as well as laboratory parameters which can predict disease progression and severity to fight COVID-19 disease.[11] In the natural history of COVID-19 disease, various inflammatory biochemical markers such as C-reactive protein (CRP), serum ferritin, coagulation indices like D-Dimer, and hematological parameters such as total leukocyte count (TLC) and neutrophil-to-lymphocyte ratio (NLR) have been evaluated and found to have prognostic value.[12-14] These biochemical and hematological parameters have found to be elevated in severe cases of COVID-19 infection.[15]

In this regard, we have undertaken this study with the following aims and objectives:

i. To estimate various hematological and biochemical parameters among hospital-admitted confirmed COVID-19 patients
ii. To compare these laboratory parameters between severe and nonsevere COVID-19 patients and to find out any correlation of these parameters between the two groups.

Materials and Methods

Study design

This was a retrospective, record-based study conducted at a district-level COVID care hospital of West Bengal, India. The hospital caters to patients from the Western part of West Bengal and the nearby state of Jharkhand, India.

The study was conducted for 2 months duration from April 2021 to May 2021. The study population includes all admitted patients of COVID-19 confirmed by reverse transcriptase–polymerase chain reaction (RTPCR) in nasopharyngeal swabs.

Inclusion criteria

All admitted RTPCR-confirmed COVID-19 patients whose case record data including demographic variables, clinical data, and laboratory reports were available for the collection were included in the study irrespective of age and sex.

Exclusion criteria

Unconfirmed cases of COVID-19, patients whose sociodemographic variables, clinical data, and laboratory reports were unavailable or partly available were excluded from the study.

Determination of the severity of COVID-19

The severity of COVID-19 was determined as per guidelines issued by the Ministry of Health and Family Welfare, Government of India.[16]

Mild cases: COVID-19 patients who had uncomplicated upper respiratory tract infection with no evidence of breathlessness or hypoxia.

Moderate cases: Patients with radiological and clinical features of pneumonia with SpO2 range from 90% to ≤93% on room air or respiratory rate ≥24/min.

Severe cases: Patients with clinical signs of pneumonia with one of the following: respiratory rate >30/min, severe respiratory distress, SpO2 <90% on room air; along with features of ARDS, sepsis, and septic shock.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and the subject information were reviewed and approved by a local ethics committee according to the document number 24, dated September 7, 2021. However, individual patient consent was not obtained as it was a record-based retrospective study.

Laboratory method

Complete blood count (CBC) was done using automated hematology analyzer SYSMEX XT-4000i. The blood films were stained using Leishman stain and examined under microscope. Biochemical tests of D-dimer and serum ferritin were done by automated quantitative enzyme-linked fluorescent assay using VIDAS (Vitek Immunodiagnostic Assay System). Estimation of CRP was done by nephelometry using Mispa i2 biochemistry analyzer.

Data collection

Demographic variables, clinical findings, and laboratory results of biochemical and hematological parameters were collected

from the hospital registry for each patient. Information regarding age and sex and laboratory investigation reports of CBC, NLR, CRP, serum ferritin, and D-dimer level were collected for each patient. Every patient having all these reports was then categorized as non severe (mild and moderate) and severe disease according to the above mentioned criteria. Data were then analyzed to see any association between the nonsevere and severe groups.

Statistical analysis

All data were entered into EPI info version 7 (Atlanta, Georgia, USA) and then exported to Statistical Package for the Social Sciences (SPSS) for Windows (version 25) (IBM Corporation, Armonk, NY) for analysis. For analysis, mild and moderate cases of COVID-19 cases were grouped into one group, namely, the "nonsevere COVID-19 group" and the rest patients were grouped as the "severe COVID-19 group." Independent sample *t*-test or unpaired *t*-test was applied to find out any relation of these hematological and biochemical parameters between the nonsevere and severe groups of COVID-19 patients. $P \leq 0.05$ was considered statistically significant.

Results

A total of 94 RT-PCR-confirmed COVID-19 patients were included in our study. Most of our patients to be male than females (54.26% vs. 45.76%) [Table 1]. The majority of our COVID patients having nonsevere (mild and moderate) disease compared to severe disease (81.91% vs. 18.09%) [Table 1].

When compared to the age groups of the nonsevere and severe COVID-19 patients, the severe disease occurred in slightly older patients; however, this age difference was not statistically significant [Table 2].

Table 3 shows the various hematological parameters among nonsevere and severe COVID patients. Among various hematological parameters, severe COVID patients showed leukocytosis, neutrophilia, and lymphopenia, and all these findings were statistically significant. The NLR is also high in the severe group of patients and this finding was also statistically significant ($P = 0.01$).

The various biochemical parameters, namely, CRP, serum ferritin, and D-dimer levels were documented in Table 4. It shows that all of these parameters, namely, CRP, serum ferritin, and D-dimer levels were elevated significantly in severe COVID patients compared to nonsevere COVID ($P = 0.01$, 0.00 and 0.00, respectively) [Table 4].

Discussion

Clinical symptoms of COVID-19 vary from person to person. In fact, about 50%–75% of throat swab RT-PCR-positive COVID-19 patients remain asymptomatic.[16] Clinical symptoms of COVID-19 are varied and include fever, cough, weakness, myalgia, diarrhea, shortness of breath, pneumonia, ARDS either with or without sepsis coagulation dysfunction, and multi-organ failure.[17,18]

Table 1: Demographic variables of COVID-19 patients

Variable	*n*=94, *n* (%)
Gender	
Male	51 (54.26)
Female	43 (45.74)
Age (years)	
18-60	46 (48.94)
>60	48 (51.06)
Category	
Nonsevere COVID	77 (81.91)
Severe COVID	17 (18.09)

Table 2: Age distribution of cases in relation to nonsevere and severe COVID-19

Age (years)	Mean±SD	*P*
Nonsevere group	58.97±12.95	0.01
Severe group	64.82±14.07	

SD: Standard deviation

Table 3: Various hematological parameters in nonsevere and severe COVID-19 patients

Parameters	Mean±SD		*P*
	Nonsevere group	Severe group	
Hemoglobin (g/dL)	10.82±2.02	11.24±1.85	0.43
TLC (/cmm)	8597.66±5075.89	12079.41±4555.19	0.01
Neutrophil (%)	74.92±12.36	87.71±6.77	0.00
Lymphocyte (%)	23.61±13.94	16.29±12.46	0.05
Monocyte (%)	2.01±1.42	1.53±0.85	0.18
Eosinophil (%)	2.82±1.45	1.88±1.11	0.01
Basophil (%)	0	0	-
NLR	4.88±3.66	8.09±6.72	0.01

SD: Standard deviation, NLR: Neutrophil-to-lymphocyte ratio, TLC: Total leukocyte count

Table 4: Difference in levels of serum C-reactive protein, ferritin, and D-dimer in COVID-19 patients according to the severity of disease

Parameter	Mean±SD		*P*
	Nonsevere group	Severe group	
CRP (mg/L)	75.17±70.31	129.67±92.06	0.01
Ferritin (ng/mL)	567.95±370.95	890.62±365.03	0.00
D-dimer (ng/mL)	578.59±440.36	1010.79±733.61	0.00

CRP: C-reactive protein, SD: Standard deviation

Hematological tests including CBC are a routinely performed tests in all admitted patients. Biochemical tests such as CRP, D-dimer, and serum ferritin are also usually performed in COVID-19 patients which are inflammatory markers. Several hematological and inflammatory parameters including these are thought to be associated with the severity of COVID-19 disease.[19] We described the clinical profile of COVID-19 patients according to the disease severity and change in laboratory parameters with disease severity.

We studied a total of 94 COVID-19-positive hospital-admitted patients during our 2-month study period. Most of our patients were males (51 males vs. 43 females) than females. This finding is like various previous studies done within India and abroad.[2,4,5,13] However, the opposite result was found in a study done by Dawood *et al*. in Iraq and they found females were affected more than males by COVID-19.[20] Females and males have a variable response to viral infection and this may lead to variations in disease severity and incidence of disease between males and females.[11] Multiple factors such as sex-specific hormones and the activity of X-linked genes, both of which probably modulate the innate and adaptive immune response to viral infection including SARS-CoV-2. Another important factor may be the difference in the expression of ACE 2 receptor and the cellular proteases TMPRSS2, which is essential for binding and priming of SARS-CoV-2.[20] There is a positive correlation between ACE-2 expression and coronavirus, and studies indicate that Asian males had higher expression of ACE-2 than females.[21] We found slightly more COVID-19 patients aged >60 years than 18–60 years of age. In our study, we found 17 (18.09%) cases were in a severe disease group, whereas the rest of the patients were in nonsevere (mild and moderate). Previous studies have also found similar findings with the majority of cases are mild and moderate COVID-19.[4,22,23]

In our study, the mean age of severe COVID-19 patients was 64.82 years compared to 58.97 years in nonsevere patients. Age is an important independent factor regarding the severity of COVID-19 disease. Wu *et al*. in their study comprising 194 COVID-19 patients found that patients with age 50 and above were strongly associated with the development of ARDS and mortality was higher in patients aged 65 years and above.[24] They concluded that older age is associated with ARDS and high mortality in COVID-19 disease due to the less rigorous immune response. Various age-related comorbid conditions such as hypertension and diabetes mellitus were also found to be associated with disease severity in elderly patients of COVID-19.[24]

Despite that age is an independent factor for severe disease, it is also seen that many younger individuals develop severe COVID, and many died of it. This is since the immune responses to SARS-CoV-2 are variable, and in some cases, the excessive inflammatory response contributed to disease severity and greater mortality. Recent advances in this field have identified potential genes in certain populations that may modify the host immune responses that can lead to dysregulated host immunity, including genetic defects of type I interferon pathway and dysregulation of the adaptive immune system.[25]

Among the various hematological parameters, we have found that there is leukocytosis and neutrophilia in COVID-19 patients and both two parameters have been significantly elevated among severe COVID-19 patients. Neutrophils are leading cells in innate immunity and the primary function of neutrophils is the clearance of pathogens and debris through phagocytosis. They also have a distinct array of other immune roles such as the liberation of neutrophil extracellular traps (NETs) that causes viral inactivation and the production of cytokine that try to restrict viral replication.[26] NETS are sophisticated network of DNA which is produced through a process called NETosis; in where, there is liberation of web-like structure of nucleic acid wrapped with histones and oxidative enzymes that are released by neutrophils that detain viral particles.[27] Researchers have found SARS-CoV-2 virus causes activation of NETosis and this process is associated with increased levels of intracellular reactive oxygen species (ROS) in neutrophils and plays a role in thrombus formation.[28]

Leukocytosis is significantly associated with severe COVID-19 and it is one of the parameters that can be used to assess the severity of the disease.[5,6,22,29] NLR is also an independent risk factor for severe disease.[30] NLR is significantly increased in severe COVID-19 patients in our study which collaborates well with various previous studies.[15,16,29] Dawood *et al*. also concluded that NLR is increased significantly in COVID-19 patients with more length of hospitalization.[20] NLR in peripheral blood is regarded as an inflammatory marker and it is found to be elevated in various solid tumors, and many chronic diseases such as cardiovascular, kidney, and lung diseases.[20,31] COVID-19 infection is associated with a decreased count of lymphocytes and this lymphocyte depletion is associated with the severity of disease. Henry concluded that the survival of patients with severe and critical COVID-19 may be associated with the ability of T-lymphocytes which are essential for the killing of infected viral particles.[32]

CRP is an inflammatory marker. The increased level of CRP reflects a systemic inflammatory syndrome which is seen in the severe form of COVID-19, which is usually accompanied by a massive release of inflammatory cytokines creating a "cytokine storm" responsible for acute tissue damage with the onset of severe ARDS followed by multiorgan failure.[18] Our study showed a significant increase in CRP levels in severe COVID-19 patients. Similar findings were also recorded by previous studies.[5,11,19,29]

The serum ferritin level in COVID-19 patients was high and increased significantly in the severe group ($P = 0.00$). Various previous studies done around different parts of the world found similar results.[5,11,29] Researchers also found that elevated ferritin levels are usually associated with worse outcomes, along with several other pro-inflammatory makers including CRP and IL-6.[33] Elevation of ferritin occurs in COVID-19 may be due to secondary hemophagocytic lymphohistiocytosis which is a hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinemia with multiorgan failure.[34] Severity and mortality in COVID-19 could be due to virally induced hyperinflammation which is substantially associated with increased levels of ferritin.

In addition to CRP and ferritin, the study reported a significant rise of D-dimer in COVID-19 patients. The increase of D-dimer level was significantly correlated with disease

severity ($P = 0.00$). D-dimer is fibrin degradation product that indicates the presence of a demolished fibrin in bloodstream and represents the activation of coagulation and fibrinolytic systems. D-dimer is used as a predictive biomarker for disseminated intravascular coagulation (DIC) and coagulation disorders associated with COVID-19 infection.[35] COVID-19 predisposes patients to thrombosis and hence patients with COVID-19 are also at risk of developing deep-vein thrombosis, venous thromboembolism (VTE), and pulmonary embolism.[36] Pathological episodes such as excessive inflammation characterized by cytokine storm, endothelial and macrophage activation, DIC, and hypoxia secondary to severe lung injury in COVID-19 can result in VTE events which lead to excessive generation of D-dimer.[37] A four-fold increase of D-dimer is found to be associated with poor prognosis in hospitalized COVID-19 patients.[30] Our findings were similar to various previous studies.[5,38] Kadhim and Abdullah found that although D-dimer level increases more in severe COVID, that was not significant compared to nonsevere COVID.[11]

Limitations of our study

There are several limitations of our study. The first and most important one is the small sample size. Therefore, the results of our study may not be applicable for the large-scale population. Second, our study is a retrospective record-based study and only the laboratory data are collected. Clinical findings and radiological findings are not collected. Third, we have not followed up with the patients regarding their outcomes. Finally, few other laboratory parameters such as IL-6, lactate dehydrogenase, and procalcitonin were not assessed as the facility was not available.

Conclusion

COVID-19 is an emerging disease. Although many patients remain asymptomatic, the disease can be severe leading to mortality. The significant rise of leukocytes, neutrophilia, and increased NLR in addition to CRP, serum ferritin, and D-dimer can provide useful prognostic information among COVID-19-affected patients and these parameters help in assessing disease severity and can guide clinicians regarding the condition of the patients.

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Conflicts of interest

There are no conflicts of interest.

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