ORIGINAL RESEARCH

Inflammatory biomarkers and other biochemical and haematological parameters in Covid-19 patients

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ABSTRACT
Background: The Covid-19 spread and outburst since December, 2019 and has lead to many serious complication. Old age people and the patients with co-morbid conditions like hypertension, Diabetes and COPD, are more susceptible to severe Covid-19 disease. **Aims:** The aim of the present study was to find the association between inflammatory biomarker and other parameters with severity of the covid-19 disease. **Material and Method:** This study was carried out in the Department of Biochemistry, Muzaffarnagar Medical College and Associated Hospital from April 2021 to June 2021. Biochemical parameters IL-6, Ferritin, D-dimer, CRP, and LDH were estimated by fully auto analyzer (AU-480 & Acces-2 chemistry analyzer). Hematological parameters were measured by cell counter (NIHON KOHDEN)**. Results:** In this study, the biochemical biomarkers like IL-6, Ferritin, CRP, D-dimer and LDH were elevated in Covid-19 patients and the increase in these parameters were more in severe patients as compared to non-severe patients. **Conclusion:** In conclusion, the inflammatory parameters can be used as laboratory biomarkers and could help to the clinician/physician to rapidly identify the severity of Covid-19 disease.
Keywords: CRP, LDH, Ferritin, IL-6, NLR

INTRODUCTION

In December 2019, the primary case of Covid-19 was detected in Wuhan town of China. The unfold and outburst of coronavirus disease 2019 (COVID- 19) since December, 2019, has lead serious challenges to world public health (1). On 30 January 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 to be a "public health emergency of international concern". Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be transmitted from person to person through close contact, respiratory droplets and aerosol (2).

The incubation period of COVID-19 may vary from 1 to 14 days and causes respiratory tract infection characterized by a broad spectrum of clinical presentation with a different degree of severity, from symptomless patients to respiratory disease which may lead to acute respiratory distress syndrome and multiple organ failure, resulting to death (3). Old people (>65 years) and the patients with comorbidities like, diabetes, hypertension, and chronic obstructive pulmonary disease, are more prone to severe disease. The clinical laboratory may provide critical support for the appropriate clinical management of COVID-19 patients, from screening to diagnosis, prognosis, and monitoring (4).

Because proinflammatory cytokines and cytokine storm strongly correspond with the severity and COVID-19 mortality, it has been hypothesised that a notable increase are important contributions to the development of the disease (5). In addition, growing lymphopenia and immune cell infiltration, particularly the neutrophil-to-lymphocyte ratio (NLR), are considered as prognostic indicators (6). The most common technique for diagnosing COVID-19 is rRT-

PCR, while high-risk diagnoses may benefit from CT scanning (7).

The term "biomarker" refers to a trait that may be objectively measured and assessed as a predictor of typical biological and pathological processes, or pharmacological reactions to a therapeutic intervention (8). Hospital laboratories are crucial for both the early detection of viruses and patient monitoring (9). The management of COVID-19 requires the use of laboratory measures validated for SARS-CoV-2 because they assist clinical decision-making for controlling infections, which may lead to rapid isolation, adequate treatment, and subsequently lower contagion rates (10).

Numerous laboratory indicators may be used to evaluate the disease's severity and forecast risks including multiple organ failure, disseminated intravascular coagulation, and acute respiratory distress syndrome (ARDS) (11). Absolute neutrophilia, thrombocytopenia, hypoalbuminemia, elevation of liver enzymes, creatinine, and non-specific inflammatory markers such C-reactive protein (CRP) and Interleukin 6 (IL-6) are the following criteria, which have been linked to a poor course of the disease (12). In addition, lymphopenia, high D-dimer, and raised ferritin are significant biomarkers. LDH, CPK, and troponin are further potential biomarkers (13).

Vasoconstriction may result from COVID-19 infection of endothelial cells, which may lead to edoema and hypercoagulability as well as vasoconstriction in various organs. The management of chronic conditions such liver disease, renal disease, and diabetes mellitus may become worse as a result of COVID-19 infection. (14) In order to provide the best care at the bedside, the treating physician must be properly updated due to the abundance of research that have been published on the dynamics of biochemical markers in Covid-19. The evaluation of laboratory markers can offer extra objective data that can have a big impact on many aspects of patient management. Determining the relationship between biochemical and immunological indicators and the severity and mortality of Covid-19 patients was the study's primary objective.

MATERIAL AND METHOD

This study was carried in the Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar from April 2021 to June 2021. Level-2 and Level-3 patients of Muzaffarnagar region were admitted in this Hospital. Blood sample was collected and investigated in central laboratory under complete precaution as per guidelines of ICMR.

PARAMETERS MEASURED

Total WBCs were estimated Serum Ferritin, quantitative CRP, D-dimer and IL-6 were measures by fully automatic chemistry analyzer (Access-2) and other biochemical parameters were measured by AU 480 analyzer. Platelet, Neutrophil, Eosinophil and cell counter were estimated by cell counter (NIHON KOHDEN CELL COUNTER).

STATISTICAL ANALYSIS

Data analysis was performed by using SPSS version-20. Sample size and the need for reliable markers for disease severity, the continuous variables were transformed into categorical variables.

ETHICAL APPROVAL

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee (MMC/PO/2022/67).

RESULTS

This study conducted on 253 covid patients admitted in Muzaffarnagar Medical College and associated hospital, Muzaffarnagar. The mean age of severe patients was 62.4 years and non-severe patients were 49.5 years. The percentage of male patients was higher (60.07%) than female (39.93%). In this study, 38 patients were COPD patients, 69 Diabetics, 93 Hypertensive, 43 CKD and 51 were cardiac patients. This study shows that 11 COPD patients (28.94%), 43 (25.58%) CKD, 51 (35.29%) Cardiac Patients, 69 (36.23%) Diabetics and 93 (48.39%) Hypertensive patients were severe and were on intubation. (Table:-1)

In Hematological study, the platelet count changes in severe and non-sever patients but it was in-significant. The mean value of WBC, Neutrophil, Lymphocyte count and neutrophil to lymphocyte ratio were found to be increase significantly in covid patients and the increase in these parameters were more in patients who were on intubation/in severe condition. (Table:-2)

The biochemical parameters IL-6, Ferritin, CRP, D-Dimer, LDH and ALT were found to be increased in covid patients. On comparison sever and non-sever patients; the increase in these parameters was more in patients who were severe and it was statistically significant. In case of AST and total bilirubin it was in-significant. (Table:-2)

Table:-1 Co -morbidities and demographic parameters in studied subjects

Variables	No. of Covid Patients (253)	Severe Patients (134)	Non-Severe patients (119)
Age	-	62.4 +12.4	49.5 +13.4
Male (60.08%)	152	76	76
Female (39.92%)	101	58	43
COPD (15.01%)	38	11	27

Diabetes (27.27%)	69	25	44
Hypertension (36.76%)	93	45	48
Cardiac Disease (20.16%)	51	18	33
Chronic Kidney Disease (16.99%)	43	11	32

Table:-2 Blood Parameters in studied subjects

Parameters	No. of Covid-19 Patients			Mean	S.D	p-Value
Platelet (X 10^9/L)	186	Severe	97	169.23	88.24	**=0.7 NS**
		Non Severe	89	174.21	85.23	
WBCs (X 10^9/L)	186	Severe	97	6.5	2.8	**=0.005 S**
		Non Severe	89	5.3	2.9	
Neutrophils (X 10^9/L)	186	Severe	97	5.4	4.89	**=0.006 S**
		Non Severe	89	3.7	3.2	
Lymphocyte (X 10^9/L)	186	Severe	97	0.9	0.5	**= 0.014 S**
		Non Severe	89	1.1	0.6	
NLR	186	Severe	97	10.04	9.12	**= <0.0001S**
		Non Severe	89	5.35	4.66	
IL-6 (</1.8 pg/ml)	214	Severe	119	14.76	12.18	**=0.0016 S**
		Non Severe	95	10.23	7.22	
LDH (140-270 IU/L)	172	Severe	89	1025.86	212.23	**= 0.0006 S**
		Non Severe	83	924.23	162.63	
D-Dimer (<0.5 µg/mL)	114	Severe	68	7.12	4.46	**= 0.008 S**
		Non Severe	46	5.07	3.12	
Ferritin (10-250 ng/ml)	120	Severe	72	875.45	214.23	**<0.0001 S**
		Non Severe	48	630.23	186.24	
CRP (<5.0 mg/ml)	115	Severe	70	219.75	58.67	**= 0.043 S**
		Non Severe	45	196.56	60.45	
ALT (5-35 IU/L)	86	Severe	36	112.34	45.34	**=0.02 S**
		Non Severe	50	86.24	55.23	
AST (5-40 IU/L)	89	Severe	38	124.12	39.86	**=0.5 NS**
		Non Severe	51	118.23	42.44	
Total Bilirubin (0.2-1.0 mg/dl)	78	Severe	33	2.11	0.25	**= 0.14 NS**
		Non Severe	45	1.98	0.45	

DISCUSSION

This study demonstrates the alterations in Covid-19's biochemical and inflammatory characteristics. In this, both severe and non-severe COVID patients had higher levels of CRP, D-Dimer, ferritin, IL-6, LDH, and NLR. However, the rise in these parameters was greater in severe patients compared to non-severe patients.

In this study, patients with COVID have elevated levels of AST, ALT, and total bilirubin beyond the normal range, however when we compared patients with severe and non-severe COVID, the changes in ALT were significant while the changes in AST and bilirubin were insignificant. According to some research, liver injury may be the cause of elevated levels of AST, ALT, GGT, and bilirubin and decreased levels of albumin. Drug toxicity, a cytokine storm, and/or hypoxia brought on by pneumonia may cause an elevation in the levels of the liver enzymes (AST & ALT). SARs validated by pathological inspection demonstrate virus in liver tissue, and ACE2 is expressed in both liver cells and bile duct cells. As bile duct cells produce this enzyme more, the liver damage in Covid-19 is more closely tied to its destruction. (15)

Numerous investigations revealed that alterations in hepatic markers were not clinically meaningful and had no bearing on Covid 19 results. Most studies have found that liver dysfunction is minor, temporary, not clinically significant, and has no effect on COVID-19 outcomes (16), but these patients were at higher risk of developing severe disease while they were in the hospital. (17)

According to a study by Saini et al., 58.5 % of patients were with raised liver enzymes, 43.31 % of patients had more severe liver injuries and were admitted to the intensive care unit. Only 41.5 % of patients had normal liver enzymes. The patient has raised levels of bilirubin, albumin, and total blood protein as well as elevated serum liver enzymes. They discovered a favourable correlation between liver measures and inflammatory markers. (18)

C-reactive protein is a liver-produced acute-phase inflammatory protein that is transcriptionally controlled by the cytokines IL-6 and IL-1. (19) It is a crucial marker for identifying and assessing severe infectious lung illnesses. (20).

According to Mahat et al meta-analysis's, severe COVID-19 patients had higher serum concentrations of CRP, ESR, PCT, IL-6, IL-10, IL-2R, ferritin, SAA, and NLR than non-severe COVID-19 patients did. Non-survivors also had higher increases in CRP, PCT, IL-6, ferritin, and NLR indices than survivors did. They came to the conclusion that the clinicians could quickly diagnose the severity of COVID-19 patients using these inflammatory indicators. (21)

Serum levels of CRP, LDH, IL-6, and ferritin were shown to be higher in COVID-19 patients in a study by Iqbal et al. They also came to the conclusion that these parameters could be employed as laboratory biomarkers for a bad outcome in COVID-19. Additionally, CRP may be utilised to track COVID-19 disease improvement in addition to serving as a prognostic marker. (22) Age, sex, and physical condition have little bearing on the severity of the inflammation linked with CRP levels and concentration. (23) According to a study (24), CRP levels are higher in Covid-19 patients and are directly correlated with illness severity. According to a prior study, either bacterial or viral infections can cause a rise in CRP, however bacterial infections considerably raised CRP levels compared to viral infections (25).

Inflammatory biomarkers such as IL-6, CRP, and D-dimer aid in the diagnosis of disease severity. It has been discovered that IL-6 is a reliable indicator of hypoxemia necessitating oxygen therapy. Numerous studies have linked IL-6 to the severity of the Covid -19 condition. IL-6 is the strongest predictor of severe Covid-19, according to research by Han et al. that looked at the predictive efficacy of other cytokines. (26) In the lungs, nearly all immune system cells produce IL-6, and proinflammatory cytokines, particularly interleukin 1 (IL-1) and tumour necrosis factor (TNF), boost its secretion. Elevated IL-6 levels in Covid -19 may accelerate the onset of acute lung damage. IL-6 increases lung capillary permeability, which leads to the development of ARDS. It also activates the coagulation pathway, which results in microthrombi in the circulation of the lungs and raises the risk of thrombotic events. (27)

In this study, we found that co-morbidities, including diabetes, hypertension, heart failure, and coronary artery disease, may play important roles in disease severity. Additionally, in patients with severe instances, dyspnea was the most noticeable symptom. According to a study, compared to the moderate group, the majority of severe COVID-19 patients (85.4%) had diabetes or cardiovascular problems. (28) A study found that among COVID-19 patients, hypertension accounts for 17 percent of all comorbidities. (29) In severe COVID-19, ferritin has been well-defined as an acute phase stimulant and a regulator of immune system dysregulation. Ferritin may therefore contribute to both the inflammatory biomarker and the cytokine storm that define severe COVID-19.

Ferritin plays a crucial role in the dysregulation of immunological response, especially in supereme hyperferritinemia, where it directly suppresses the immune system and promotes inflammation, which in turn fuels the cytokine storm. (31) Of 99 covid patients studied, 63 had serum ferritin levels that were above the normal limit. The serum ferritin levels were higher in covid-19 patients, according to study (32) and the increase was greater in the more severely ill individuals.

Isoenzyme 3 of LDH is present in lung tissue. Severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation leading to severe form of interstitial pneumonia. However, the contribution of the different LDH isoenzymes to the LDH elevation observed in COVID-19 has not been determined. LDH levels may also elevate in thrombotic microangiopathy, which is associated with renal failure and myocardial injury. (34)

Death and illness severity are both directly connected with lymphocytopenia. According to a study, patients with ARDS, seriously ill patients admitted to the ICU, and non-survivors had decreased lymphocyte counts (35). According to this study, increased NLR was a distinct predictive biomarker that influenced the development of pneumonia in COVID-19 patients. Additionally, predictive nomograms may be improved by adding higher neutrophil-to-lymphocyte ratios (NLR) to them. Our results were in line with those of earlier research on the connection between NLR and the prognosis of numerous other infectious disorders. (36) The main white blood cell, the neutrophil, can activate and move from the venous system to an immunological organ or system. As reactive oxygen species are released and the host cell becomes virus-free, it might cause DNA cell damage. As a result, the antibody dependent cell mediated cell (ADCC) has the potential to directly kill viruses, expose virus antigen, and create humoral and cell-specific immunity. (37)

The correlation between cardiac biomarkers and other biomarkers has been observed; individuals with myocardial damage had greater leukocyte, lower lymphocyte, and lower platelet counts. However, because regular tests on all individuals could be inaccurate, cardiac biomarkers must be utilised carefully. A meta-analysis of 4189 verified cases of COVID 19 found that cardiac biomarker levels had risen above average by the halfway point of hospitalisation and had peaked just before death. In more severe situations, the levels rose (38).

CONCLUSION

In this study, we have observed significantly increased levels of CRP, D-dimer, LDH, ferritin, IL-6, levels and NLR in Covid-19 patients and the increase in these parameters were more in severe patients as compared to non-severe patients suggesting that the levels of these parameters are associated with the severity of covid-19 disease. Hence these inflammatory parameters can be used as laboratory

biomarkers and could help to the clinician to rapidly identify the severity of Covid-19 disease.

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