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Study of Potential Biochemical Parameters in Patients Of Covid-19

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Abstract

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is a respiratory disease, which can evolve into multiorgan failure (MOF), leading to death. Therefore, it makes sense to search for potential biomarkers that could rapidly and effectively identify severe cases early. Clinical samples from 100 cases of COVID-19 (25 severe cases, 37 mild cases and 38 moderate cases) was collected, enrolled from August 2020 in American International Institute of Medical sciences (AIIMS) & Hospital, Udaipur. We have evaluated the role of routine laboratory biomarkers and observed statistically significant abnormal values of biochemical and immunoassay parameters: C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-Dimer, Interleukin 6 (IL-6), Ferritin, Aspartate aminotransferase (AST) Alanine aminotransferase (ALT), Serum Albumin, Total Bilirubin (T Bil), and Creatinine in COVID 19 patients. Lymphopenia represents the hallmark of the disease, and it can be detected since the early stage of infection. Increased levels of several inflammatory biomarkers, including c- reactive protein, have been found in COVID-19 patients and associated with an increased risk of severe disease, which is characterized by “cytokine storm”. Also, the increase of cardiac and liver dysfunction biomarkers has been associated with poor outcome. Based on the findings of this study we may conclude that early detection of these parameters helps to reduce the severity of this disease.

Keywords
COVID-19, diagnosis, SARS-CoV-2, biomarkers, cytokine storm.

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INTRODUCTION:

A novel coronavirus, designated as the severe acute respiratory syndrome, was first identified in Wuhan, China in December 2019 [1]. This is highly infectious and asymptomatic, patients may also become the source of infection [2]. Then, it has been seen that the number of cases has spread rapidly all over the world. World Health Organization (WHO) announced that the disease caused by SARS-CoV-2 was coronavirus disease 2019 (COVID19) on February 11, 2020. Patients with COVID-19 have a series of clinical manifestations, such as pharyngalgia, fever, cough, fatigue, anorexia, headache, diarrhoea, nausea or vomiting, dyspnoea, even acute respiratory distress syndrome (ARDS) [3]. Most of them were mild in the early days, some patients progressed rapidly to acute respiratory failure, metabolic acidosis, septic shock, ARDS (acute respiratory distress syndrome) or death. Pneumonia mostly occurs in the second or third week of a symptomatic infection [4]. Ferritin is a key

mediator of immune dysregulation, especially under extreme hyperserotonaemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm [5]. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome [1].

Many patients with Covid-19 had liver function abnormalities with elevated ALT, AST, and LDH levels [6]. They also showed elevated CRP and creatine kinase levels, lymphopenia and leukopenia [7]. Early identification of risk factors for critical patients could facilitate appropriate supportive care and thus reduce the mortality [8]. Chen et al. observed in a cohort of 799 patients (113 non-survivors and 161 recovered) markedly higher concentrations of ALT, AST, creatinine, CK, LDH, cardiac troponin I, N-terminal pro-brain natriuretic peptide (proBNP) and D-dimer in non-survivors compared to recovered patients [9]. Increased inflammation related indicators were also found in patients with Covid19, including erythrocyte sedimentation rate (ESR), interleukin-6 and C-reactive protein (CRP) [10].

Recently, there have been limited studies on relationship between disease severity and biochemical parameters of patients with Covid-19 in Indian population; however, the sample sizes of each article were different; and the reported clinical characteristics, especially blood biochemical indices, were quite different.

Aim and Objective:

As blood biochemical changes play an essential role in estimating the patient's condition and prognosis, directing treatment, and even evaluating the curative effect. This study retrospectively analyses biochemical parameters between mild, moderate, and severe patients, which may help to identify severity in the cases to perform appropriate clinical intervention early.

Material and Methods:

Study design

In this retrospective, single-centre study, all data was collected from a total of 100 patients enrolled from August 2020 in American International Institute of Medical sciences (AIIMS) & Hospital, Udaipur. The study was conducted on total number of 100 COVID-19 patients who were admitted with rRT-PCR (real time- polymerase chain reaction) positive test results of SARS-CoV-2 in nasopharyngeal or oropharyngeal samples in the hospital.

Data collection

The demographic and laboratory findings will be extracted from the electronic medical records of the patients. All data was reviewed by internal medicine specialists. Information recorded included demographic data, medical history, exposure history, underlying comorbidities, signs and symptoms, laboratory findings, chest computed tomographic (CT) scans and treatment measures (antiviral therapy, Anti-retroviral therapy, anti-malarial therapy, respiratory support).

Based on radiological features, respiratory rate and oxygen saturation, study subjects were categorized into mild, moderate and severe COVID-19 cases. Blood samples were collected from total 100 subjects during different course (mostly in 2nd week) of their illness. Out of them, 38 mild COVID-19 study subjects were included in group A, 37 moderate COVID19 study subjects were included in group B and 25 severe COVID-19 study subjects were included in group C.

Clinical case definition:

1. Mild cases

The clinical symptoms are mild and there is no signs of pneumonia on imaging. Symptoms may be fever, cough, sore throat, malaise, headache, muscle pain without shortness of breath or abnormal chest imaging.

2. Moderate cases

Fever and respiratory symptoms with radiological findings of pneumonia with respiratory rate with < 30 breaths/min and oxygen saturation> 93% at ambient air.

3. Severe cases

Cases meeting any of the following criteria: Respiratory distress (respiratory rate > 30 breaths / min), oxygen saturation <93% at rest, arterial partial pressure of oxygen (PaO2) / fraction of inspired oxygen (FiO2)<300 mmHg.(1 mm Hg= 0.133kPa) [11] .

Sample collection:

With all aseptic precautions, 10 ml of venous blood was collected from ante-cubital vein by 10cc disposable plastic syringe, from each subject. Then blood samples were sent for biochemical analysis in the Department of Central Laboratory, AIIMS Hospital, Udaipur.

Data Processing

All biochemical parameters were processed by **Roche Cobas c 111** chemistry analyser and special parameters **by Cobas e 411 immunoanalyzer** according to the manufacturing protocols. We have evaluated the role of routine laboratory biomarkers and observed statistically significant abnormal values of biochemical and immunoassay parameters: C Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-Dimer, Interleukin 6 (IL6), Ferritin, Aspartate aminotransferase (AST), Alanine

aminotransferase (ALT), Serum Albumin, Total Bilirubin (T Bil), and Creatinine in COVID 19 patients.

RESULTS:

A total of 100 RT-PCR positive COVID-19 patients were included in this study. The age range of the study subjects was from 18 to 65 years. The mean (±SD) age of the study subjects in mild, moderate and severe COVID cases were 41.52± 13.48 years, 47.32 ± 12.10 years and 45.24 ± 13.97 years respectively. The *p* value (0.451) for age group was not statistically significant (Table-1). In study subjects, there were 82 (82%) males and 18 (18%) females. No significant difference was found between mild, moderate & severe group and gender distribution (*p* value 0.539).

Finding shows statistically significant (p-value<0.05) positive correlation with Hb, TLC, PLT, RBC, Urea, Creatinine, SGOT, SGPT, Trop I, Albumin, Glucose, Total Bil., ALP, Uric acid, Na^+ , K^+ , D-dimer, CRP, Ferritin, IL-6, Calcium & LDH.(Table-2)

Spearman's correlation coefficient (r) test was performed to compare relationship between biochemical parameters and severity of disease. Bonferroni correction for biochemical parameters following ANOVA was performed to compare between groups. The test of significance (p value<0.05) was calculated for all the comparisons as Mild versus Moderate, Moderate versus severe and Mild versus severe, which was significant for all the groups.(Table-3)

Table no.1 Demographic profile of mild, moderate & severe COVID 19 patients (N=100)

	Mild (Group A) (n=38)	Moderate (Group B) (n=37)	Severe (Group C) (n=25)	*p* value
Age(years)≤ 30	4(10.5)	6(16.2)	3(12)	
31- 40	12(31.5)	7(18.9)	5(20)	
41- 50	9(23.6)	5(13.5)	6(30)	
51- 60	8(21)	13(35.1)	3(12)	
>60	5(13.2)	6(16.2)	8(32)	*0.231[a]
Gender				
Male	33 (86.8)	30 (81)	19 (76)	
Female	5 (13.2)	7 (18.9)	6 (24)	*0.539[b]

N= Total number of subjects, [a] : *p* value reached from ANOVA test, [b] : *p* value reached from chi squared test.
Table 1 shows no significant difference of severity of COVID-19 in respect of age and gender.

Table 2: Biochemical findings of the study subjects (N=100)

Biochemical Findings	Mild (Group A) n=38	Moderate (Group B) n=37	Severe (Group C) n=25	*p* value
Hb(g/dl)	14.83 ± 1.17	11.85 ± 1.18	8.82 ± 1	.001
TLC(10^9/L)	11.08 ± 1.80	9.60 ± 0.85	7.91 ± 1.50	.001
PLT(10^9/L)	312.05 ± 58.00	229.08 ± 51.43	113.56 ± 52.52	.001
RBC(10^12/L)	5.46 ± 0.57	4.48 ± 0.67	2.67 ± 0.86	.001
Urea(mg/dL)	26.32 ± 11.07	60.34 ± 11.79	109.16 ± 27.70	.001
Cre (mg/dl)	0.93 ± 0.25	1.35 ± 0.49	2.52 ± 1.25	.001
SGOT(U/L)	28.69 ± 11.47	71.73 ± 15.74	129.30 ± 39.54	.001
SGPT (U/L)	26.22 ± 10.37	46.97 ± 19.76	127.53 ± 60.28	.001
TROP I(ng/mL)	5.18 ± 1.41	12.24 ± 2.99	34.26 ± 10.88	.001
Alb(g/dl)	6.26 ± 0.92	4.20 ± 0.77	2.87 ± 0.65	.001
Glu(mg/dl)	153.18 ± 8.92	198.92 ± 7.17	231.92 ± 14.22	.001
T Bili(mg/dl)	0.54 ± 0.27	1.87 ± 0.95	4.70 ± 1.54	.001
ALP(U/L)	61.55 ± 12.77	113.70 ± 22.90	300.80 ± 120.49	.001
Uric acid(mg/dl)	4.55 ± 1.25	7.90 ± 0.94	11.18 ± 1.33	.001
Na(mmol/L)	134.55 ± 6.77	112.30 ± 14.62	91.04 ± 24.03	.001
K(mmol/L)	4.47 ± 0.75	3.31 ± 0.31	2.46 ± 0.57	.001
D Dimer(µg/ml)	2.04 ± 1.43	3.85 ± 1.50	6.31 ± 1.62	.001
CRP (mg/L)	10.52 ± 4.86	31.06 ± 7.99	115.02 ± 54.23	.001
Ferritin(ng/ml)	158.28 ± 74.37	369.48 ± 155.77	928.28 ± 359.23	.001
IL 6 (pg/mL)	18.38 ± 6.26	35.38 ± 11.07	75.94 ± 19.75	.001
Cal(mg/dl)	10.06 ± 0.87	7.98 ± 0.58	6.92 ± 0.96	.001
LDH (U/L)	280.08 ± 97.60	406.01 ± 141.63	598.49 ± 162.89	.001

Table 2 shows severity of the disease was significantly associated with Hb, TLC, PLT, RBC, Urea, Creatinine, SGOT, SGPT, Trop I, Albumin, Glucose, Total Bil., ALP, Uric acid, Na^+, K^+, D-dimer, CRP, Ferritin, IL-6, Calcium & LDH. ANOVA test was done to measure the level of significance.

Table 3. Correlation of diseases severity with biochemical parameters:

Biochemical Parameter	r_s	*p* value
Hb	-0.913	<0.001
TLC	-0.653	<0.001
PLT	-0.817	<0.001
RBC	-0.828	<0.001
Urea	+0.909	<0.001
Creatinine	+0.663	<0.001
SGOT	+0.932	<0.001
SGPT	+0.813	<0.001
Trop I	+0.936	<0.001
Albumin	-0.877	<0.001
Glucose	+0.928	<0.001
Total Bilirubin	+0.896	<0.001
ALP	+0.916	<0.001
Uric acid	+0.917	<0.001
Sodium	-0.766	<0.001
Potassium	-0.898	<0.001
D dimer	+0.735	<0.001
CRP	+0.932	<0.001
Ferritin	+0.819	<0.001
Interleukin-6	+0.871	<0.001
Calcium	-0.867	<0.001
LDH	+0.665	<0.001

Table 3 shows Bonferroni correction for biochemical parameters.

DISCUSSION:

The present study was undertaken to assess the findings of biochemical parameters of mild, moderate and severe COVID-19 patients. For this purpose, a total number of 100 RT-PCR positive COVID-19 patients with age ranging from 18 to 65 years were included in this study on the basis of inclusion and exclusion criteria. In this study, the number of mild, moderate and severe COVID-19 cases were 38, 37 and 25 respectively.

In the study, pulse, blood pressure and temperature were measured to assess the general condition of the patients. Based on radiological features, respiratory rate and oxygen saturation, study subjects were categorized into mild, moderate and severe COVID-19 cases.

Pathogenesis of COVD-19 may be associated with a high cytokine level. Severe COVID-19 infection is typically characterised by a massive pro-inflammatory response or cytokine storm, triggered by the immune system that results in acute respiratory distress syndrome (ARDS) and multi organ dysfunctions [12-16].

The mean (±SD) D-dimer of the study subjects in mild, moderate and severe COVID-19 cases were statistically significant (p value < 0.001). Similar types of observations were found by some researchers [17-19]. D-dimer is a specific and sensitive marker of coagulation and fibrinolysis activation, as well as being crucial to the diagnosis of disseminated intravascular coagulation (DIC) [20].

Patients with viral infection as well as COVID-19 are at higher risk of developing these complications [21-22].

Regarding coagulopathies, increased D-dimer can be observed, which can be seen in 40 % patients with COVID-19. These would be associated with influence of the virus and cytokines in the bone marrow [23-24]. High D-dimer concentration may result from the inflammation associated with COVID-19 and subsequent activation of coagulation system [25]. Elevated D-dimer level suggests a hypercoagulable state and may be contributing to severity of illness and mortality.

The inflammatory and pathological process causes changes in the function of several organs. When these inflammations involved kidney, it causes injury to kidney. So serum creatinine, urea, uric acid are the parameters for the analysis of kidney injuries induced by COVID-19 [26]. Due to higher accumulation of ACE-2 receptors in renal tubules , kidney is able to express this enzyme more than 100

times as much as the lungs [27-29]. The mean (±SD) serum creatinine of the study subjects in mild, moderate and severe COVID-19 cases were statistically significant (p value <0.001). This finding was in agreement with the study done by Abdi et al. whereas Li Q et al. found no association of creatinine with the severity of COVID-19.

In the present study, RBG was also done to see the glycemic status of the study subjects. The mean (±SD) RBG of the study subjects in mild, moderate and severe COVID-19 cases were statistically significant. Many studies showed that DM is a risk factor and contributes to the severity and mortality of patients with COVID-19 [31-33]. CRP, a routinely measured inflammatory marker, is increased in most patients with COVID-19 and associated with disease severity [34-35]. Yang et al. evaluated 85 patients diagnosed with COVID-19, of which 96.47 % showed an increase in CRP, being influenced by the severity level of the pathology. As one of most distinctive acute phase reactants, CRP can increase rapidly after onset of inflammation, cell damage or tissue injury. Pulmonary diseases with inflammatory features usually raise serum CRP level in response to several inflammatory cytokine such as IL-6, IL-1 or TNF. Hence, markedly elevated serum CRP level in severe illness indicates excessive inflammatory response, which is consistent with raised serum pro-inflammatory cytokines observed in COVID-19 patients [36].

Ferritin, the major intracellular iron storage protein, is an acute phase reactant. Ferritin is elevated in many inflammatory conditions, including acute infections [37]. Elevated ferritin levels due to secondary haemophagocytic lymphocytosis and cytokine storm syndrome have been reported in patients with severe COVID-19 [38].

LDH is found in all cells, especially in myocardial and liver cells. Raised LDH is an indicator of multi-organ injury (Huang C. et al, 2020), study showed that increase in LDH level was associated with poor outcome [39].

The mean (±SD) CRP, LDH & serum ferritin of the study subjects in mild, moderate and severe COVID-19 cases were statistically significant (p value < 0.001). Similar significant finding was found by some researchers of different countries [40-41].

Viral activity induces several inflammatory changes that can lead to liver tissue damage, increased levels of liver enzymes specially SGPT, SGOT and ALP [42]. In most cases, the liver injury was transient and in mild form. However, severe liver dysfunction has been reported in patients with severe COVID-19 [42]. In a Chinese study very high SGPT (more than 7500 U/L) has been reported [43]. It is not clear whether the observed SARS- CoV-2 associated liver injury is caused by direct viral injury or related to hepatotoxic drugs, coexisting systemic inflammatory changes, sepsis, respiratory distress syndrome induced hypoxia or a part of multiple organ failure [44]. COVID-19 induced cytokine storm can causes hepatotoxicity and subsequently critical hypoalbuminemia [45].

The mean (±SD) of SGPT in mild, moderate and severe COVID-19 cases were statistically significant (p value< 0.001). The mean (±SD) of serum albumin of the study subjects in mild, moderate, and severe COVID-19 cases were also statistically significant. Youssef *et al*. identified that patients with severe manifestation of COID-19 exhibited higher level of SGPT but lower serum albumin [42].

Furthermore, in the present study, CRP, SGPT, SGOT, ALP, total bilirubin, creatinine, LDH, ferritin, D-dimer showed positive correlations. But serum albumin, Hb, RBC, WBC and platelets showed negative correlation with severity of disease. These correlations further strengthen the findings of the present study.

This present study had some limitations. Samples were taken purposively so that there may be chance of bias which can influence the results. Blood samples were not taken in specific time of course of illness of study subjects. More investigations like serum procalcitonin, serum lipase, Immunoglobulins could not be done due to financial constraints, time and lack of availability.

CONCLUSION:

Covid 19 outbreak is spreading rapidly worldwide. Based on the findings of this study we may conclude that early detection of these parameters helps to reduce the severity of this disease.

Several biochemical parameters have significant association with the severity of COVID19 infection as shown in this study. So, routine screening of these biochemical parameters will be very much helpful for better management and identification of the complications and to reduce the overall mortality and morbidity.

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