

Biochemical parameters of mild, moderate & severe COVID-19 patients

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Abstract

Background and objectives: Coronavirus disease 2019 (COVID-19) is affecting millions of people world-wide. It is caused by the severe acute respiratory syndrome corona virus 2(SARS-CoV-2). The laboratory findings are very important to assess the progress of the disease. The present study is aimed to discuss the biochemical parameters among mild, moderate and severe COVID-19 patients.

Materials and methods: A cross sectional study were conducted in the Department of Physiology, Dhaka Medical College, Dhaka from January 2020 to December 2020. After obtaining ethical clearance, a total of 100 real time-polymerase chain reaction (RT-PCR) COVID-19 positive patients were selected from Dhaka Medical College Hospital. With all aseptic precautions, 10 ml of venous blood was collected from ante-cubital vein. D-dimer, prothrombin time, C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, random blood glucose (RBG), serum creatinine, serum glutamic-pyruvic-transaminase (SGPT) and serum albumin measured in the Department of Laboratory Medicine, Dhaka Medical College Hospital, Dhaka. CRP was measured by Immunoturbidimetric method, serum ferritin was estimated by Chemiluminescent microparticle immunoassay. STA-neoplastine CI plus used with STA-R analyzer was used for determination of prothrombin time. D-dimer was estimated by Immunofluorescence Assay method. Serum LDH is measured by Dimention clinical chemistry system, serum albumin is measured by bromocresol purple dye binding method, serum creatinine is measured by Jaffe alkaline picrate method and serum SGPT is measured by colourmetric (IFCC 1980) method and RBG is measured by enzymatic colorimetric method (GOD-PAP). Data were recorded in a pre-designed structured data collection form. For statistical analysis, ANOVA followed by Bonferroni test, Chi square test, Spearman's rho correlation coefficient test was performed as applicable using SPSS for windows version 25.0.

Results: By analyzing biochemical parameters of mild, moderate and severe RT-PCR positive 100 COVID-19 patients revealed evaluation of biochemical parameters shows severity of the disease was significantly associated with CRP, SGPT, S. Creatinine, LDH, Ferritin, D-dimer & Prothrombin time. No significant association was found with RBG & S. Albumin. Bonferroni correction following ANOVA was performed to compare between each group. Spearman's correlation reveals statistically significant strong positive correlation with CRP, Ferritin & D-dimer, moderate positive correlation with S. Creatinine, LDH and mild positive correlation with SGPT & Prothrombin time.

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Conclusion: This study showed D-dimer, prothrombin time, CRP, LDH, ferritin, serum creatinine and SGPT are significantly associated with the severity of the illness that is higher in severe group in comparison to mild and moderate groups. So, comprehensive analysis of the biochemical parameters will be very helpful for early identification & better management of severe disease.

Keywords: C-reactive protein; lactate dehydrogenase; Random blood glucose; Serum glutamic-pyruvic-transaminase; STA

1. Introduction

Corona virus was first isolated and named in the 1960s which belongs to the family Coronaviridae. It is a zoonotic positive strand RNA envelope virus that can spread between animals and humans. This virus has a spherical or pleomorphic shape with glycoprotein in the viral envelope structure. On February 12, 2020, the World Health Organization (WHO) officially named novel corona virus-2(SARS-Cov-2) and the pneumonia caused by novel coronavirus was named COVID-19. The third fatal corona virus identified is the novel corona virus (SARS-CoV2) that causes novel corona pneumonia (COVID-19) which first broke in Wuhan, China in December 2019 [1]. Currently the COVID-19 pandemic is leading to millions of infections and thousands of deaths worldwide [2,3]. Recently, novel coronavirus infection has affected more than 200 countries and regions around the world. Up to mid May 2020, more than 4 million people have been infected and about 300,000 have died [4]. First case of COVID-19 was detected in Bangladesh on 8th March, 2020 [5].

Coronavirus enters the pulmonary alveolar epithelial cells through angiotensin converting enzyme 2 (ACE2) [2,6]. The main mechanism for inflammation and organ damage is cytokines storm, especially in pulmonary vascular endothelial cells with increased inflammatory cytokines such as interleukins (IL1B, IL-6, IL-12, IL-10), tumour necrosis factor (INF) & monocyte chemoattractant protein (MCP-1) [7]. This virus initially undergoes viral replication in the respiratory tract and then spread to other organs and tissues [8, 9, 10].

The presence of circulating viral particles induces the activations of neutrophils and macrophages and leads to synthesis of pro-inflammatory substances such as cytokines. [9]. These inflammation causes changes in the function of several organs, leads to various changes in haematological and biochemical parameters among mild, moderate and severe COVID-19 patients [11, 12]. At the pulmonary level, viral replication causes hypoxia, cell death and lesions in the capillaries. Thus, it triggers the inflammatory process that causes activation of platelets and induces the formation of microcoagulation, this can become widespread, causing damage to other organs such as the heart, liver and kidneys [8, 11, 12]. These inflammatory and pathological process causes changes in the function of several organs, thus leads to biochemical changes in COVID-19 patients. Most common being hypoalbuminemia, increase in CRP, D-dimer, prothrombin time, LDH, ferritin, SGPT and serum creatinine [13].

2. Material and methods

2.1. Study population and case definition

The study was conducted on total number of 100 real time- polymerase chain reaction (RT-PCR) positive COVID-19 patients. Subjects were selected from COVID-19 wards of Dhaka Medical College and Hospital. 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, 25 mild COVID-19 study subjects were included in group A, 38 moderate COVID19 study subjects were included in group B and 37 severe COVID-19 study subjects were included in group C.

2.2. Clinical case definition

2.2.1. 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.

2.2.2. 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.

2.2.3. Severe cases

Cases meeting any of the following criteria: Respiratory distress (respiratory rate \geq 30 breaths / min), oxygen saturation \leq 93% at rest, arterial partial pressure of oxygen (PaO₂) / fraction of inspired oxygen (FiO₂) < 300 mmHg.(1 mm Hg= 0.133kPa) [14].

2.3. 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 Laboratory, Dhaka Medical College Hospital, Dhaka.

3. 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 (\pm SD) age of the study subjects in mild, moderate and severe COVID cases were 41.52 \pm 13.48 years, 47.32 \pm 12.10 years and 45.24 \pm 13.97 years respectively. The *p* value (0.451) was not statistically significant (Table-1). In study subjects, there were 67 (67%) males and 33 (33%) females. No significant difference was found between mild, moderate & severe group and gender distribution (*p* value 0.702).

The mean (\pm SD) D-dimer of the study subjects in mild, moderate and severe COVID-19 cases were 0.98 \pm 2.60, 1.16 \pm 1.06 and 4.78 \pm 3.42 μ g/ml respectively. The mean (\pm SD) Prothrombin time of the study subjects in mild, moderate and severe COVID-19 cases were 13.28 \pm 1.10, 13.89 \pm 1.84 and 14.86 \pm 2.68 seconds respectively. Both D-dimer & prothrombin time were statistically significant (*p* value < 0.001).

The mean (\pm SD) serum creatinine of the study subjects in mild, moderate and severe COVID-19 cases were 0.95 \pm 0.20, 1.04 \pm 0.30 and 1.45 \pm 1.25 mg/dl respectively & statistically significant (*p* value < 0.001).

The mean (\pm SD) RBG of the study subjects in mild, moderate and severe COVID-19 cases were 8.88 \pm 4.50, 10.82 \pm 4.66 and 11.42 \pm 5.75 mg /L respectively and but statistically not significant.

Table 1 Demographic profile of mild, moderate & severe COVID19 patients (N=100)

	Mild (Group A) (n=25)	Moderate (Group B) (n=38)	Severe (Group C) (n=37)	<i>p</i> value
Age (years)				
≤ 30	7 (28.0)	3 (7.9)	7 (18.9)	
31 – 40	7 (28.0)	11 (28.9)	8 (21.6)	
41 – 50	3 (12.0)	9 (23.7)	6 (16.2)	
51 – 60	7 (28.0)	9 (23.7)	12 (32.4)	
>60	1 (4.0)	6 (15.8)	4 (10.8)	
Mean \pm SD (Range)	41.52 \pm 13.48 (18-61)	47.32 \pm 12.10 (23-65)	45.24 \pm 13.97 (18-65)	0.236 ^a
Gender				
Male	18 (72.0)	26 (68.4)	23 (62.2)	0.702 ^b
Female	7 (28.0)	12 (31.6)	14 (37.8)	

N= Total number of subjects., ^a: *p* value reached from ANOVA test, ^b:*p* value reached from chi squared test.

The mean (\pm SD) CRP of the study subjects in mild, moderate and severe COVID-19 cases were 7.40 ± 3.58 , 12.92 ± 7.96 and 23.24 ± 20.81 mg /L respectively. The mean (\pm SD) serum LDH of the study subjects in mild, moderate and severe COVID-19 cases were 281.46 ± 150.13 , 462.95 ± 236.19 and 655.70 ± 223.25 U/ L respectively.

The mean (\pm SD) serum ferritin of the study subjects in mild, moderate and severe COVID-19 cases were 173.62 ± 98.93 , 386.33 ± 238.04 and 1003.36 ± 555.50 ng/ml respectively. These findings are statistically significant (p value < 0.001).

The mean (\pm SD) SGPT of in mild, moderate and severe COVID-19 cases were 32.04 ± 19.74 , 33.74 ± 15.31 and 45.32 ± 20.21 U/L respectively. This finding is statistically significant (p value 0.007). The mean (\pm SD) serum albumin of the study subjects in mild, moderate and severe COVID-19 cases were 3.42 ± 0.47 , 3.26 ± 0.31 and 3.18 ± 0.40 g/dl respectively. This finding of is not statistically significant (p value 0.774).

Correlation study of this study shows statistically significant positive correlation of D-dimer, prothrombin time, serum creatinine, CRP, LDH, Ferritin & SGPT RBG showed positive correlation with the severity of disease. But Serum albumin showed negative correlation with severity of disease.

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)

Bio-chemical findings	Mild (Group A) (n=25)	Moderate (Group B) (n=38)	Severe (Group C) (n=37)	p-value
RBG (mmol/L)	8.88 ± 4.50 (4.8-20)	10.82 ± 4.66 (5.2-22.5)	11.42 ± 5.75 (4.8-23)	0.146
CRP (mg/L)	7.40 ± 3.58 (<6 -18)	12.92 ± 7.96 (<6 -40)	23.24 ± 20.81 (8-48)	<0.001
SGPT (U/L)	32.04 ± 19.74 (12-101)	33.74 ± 15.31 (15-89)	45.32 ± 20.21 (25-112)	0.007
Serum Creatinine (mg/dl)	0.95 ± 0.20 (0.46-1.2)	1.04 ± 0.30 (0.52-2.09)	1.45 ± 1.25 (0.55-2.35)	0.024
S. LDH (U/L)	281.46 ± 150.13 (129-640)	462.95 ± 236.19 (52-1116)	655.70 ± 223.25 (200-1306)	<0.001
S ferritin (ng/ml)	173.62 ± 98.93 (60-425)	386.33 ± 238.04 (25-1012)	1003.36 ± 555.50 (135-3344)	<0.001
D dimer (μ g/ml)	0.98 ± 2.60 (0.11-4.35)	1.16 ± 1.06 (0.10-5.3)	4.78 ± 3.42 (0.87-8.68)	<0.001
S albumin (g/dl)	3.42 ± 0.47 (2.2-4.5)	3.26 ± 0.31 (2.0-4.2)	3.18 ± 0.40 (1.9-4.1)	0.774
Prothrombin time (sec)	13.28 ± 1.10 (12-16)	13.89 ± 1.84 (12-20)	14.86 ± 2.68 (12-27)	0.011

Table 2 shows severity of the disease was significantly associated with CRP, SGPT, S. Creatinine, LDH, Ferritin, D-dimer & Prothrombin time. No significant association was found with RBG & S. Albumin. ANOVA test was done to measure the level of significance. RBG: Random blood Glucose, CRP: C-reactive protein, LDH: Lactate Dehydrogenase

Table 3 Bonferroni correction for biochemical parameters

Biochemical parameters	<i>p</i> -value		
	Mild vs moderate	Moderate vs severe	Mild vs severe
RBG	0.418	1.000	0.166
C reactive protein	0.023	<0.001	<0.001
SGPT	1.000	0.022	0.019
Serum creatinine	0.700	0.002	<0.001
S. LDH	0.008	<0.001	<0.001
S. ferritin	0.086	<0.001	<0.001
D dimer	1.000	<0.001	<0.001
S. albumin	1.000	1.000	1.000
Prothrombin time	0.750	0.133	0.011

Bonferroni correction following ANOVA was performed to compare between groups. The test of significance (p value<0.05) was calculated for all the comparisons.

Table 4 Correlation of diseases severity with biochemical parameters

	r_s	<i>p</i> -value
RBG	+0.157	0.119
C reactive protein	+0.704	<0.001
SGPT	+0.390	<0.001
Serum creatinine	+0.466	<0.001
S. LDH	+0.593	<0.001
S. ferritin	+0.767	<0.001
D dimer	+0.743	<0.001
S. albumin	-0.158	0.117
Prothrombin time	+0.307	0.002

Spearman's correlation coefficient (r) test was performed to compare relationship between haematological parameters and severity of disease. Finding shows statistically significant (p -value<0.05) positive correlation with CRP, SGPT, S. Creatinine, LDH, Ferritin, D-dimer & Prothrombin time.

4. 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 25, 38 and 37 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 COVID-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 [15,16,17,1819].

The mean (\pm 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 [5, 20, 21, 22]. 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) [23].

Patients with viral infection as well as COVID-19 are at higher risk of developing these complications [24,25].

Regarding coagulopathies, increased D-dimer and increased prothrombin time 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 [26,27]. High D-dimer concentration may result from the inflammation associated with COVID-19 and subsequent activation of coagulation system [28]. Elevated D-dimer level suggests a hypercoagulable state and may be contributing to severity of illness and mortality [11].

The mean (\pm SD) Prothrombin time of the study subjects in mild, moderate and severe COVID-19 cases were significant (p value < 0.011). Similar finding was found by [22].

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 is one of the parameters for the analysis of kidney injuries induced by COVID-19 [29]. 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 [30, 31, 32]. The mean (\pm SD) serum creatinine of the study subjects in mild, moderate and severe COVID-19 cases were statistically significant (p value 0.024). This finding was in agreement with the study done by [31] whereas [33] found no association of S. Creatinine with the severity of COVID-19.

In the present study, RBG was also done to see the glycemic status of the study subjects. RBG of the study subject ranges from 4.8 to 23 mmol/L. Frequency of Diabetes Mellitus (DM) was found to be 40%. The mean (\pm SD) RBG of the study subjects in mild, moderate and severe COVID-19 cases were not statistically significant. On the contrary, some studies shows that DM is a risk factor and contributes to the severity and mortality of patients with COVID-19 [34, 35, 36].

CRP, a routinely measured inflammatory marker, is increased in most patients with COVID-19 and associated with disease severity [17,37,38]. [38] 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 [7, 39].

Ferritin, the major intracellular iron storage protein, is an acute phase reactant. Ferritin is elevated in many inflammatory conditions, including acute infections [40]. Elevated ferritin levels due to secondary haemophagocytic lymphocytosis and cytokine storm syndrome have been reported in patients with severe COVID-19 [41].

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 [42].

The mean (\pm 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 [5, 43, 44].

Viral activity induces several inflammatory changes that can lead to liver tissue damage, increased levels of liver enzymes specially SGPT [45]. 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 [45]. In a Chinese study very high SGPT (more than 7500 U/L) has been reported [46]. 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 [47]. COVID-19 induced cytokine storm can causes hepatotoxicity and subsequently critical hypoalbuminemia [48].

The mean (\pm SD) SGPT of in mild, moderate and severe COVID-19 cases were statistically significant (p value 0.007). The mean (\pm SD) serum albumin of the study subjects in mild, moderate and severe COVID-19 cases were not statistically

significant. [45] identified that patients with severe manifestation of COVID-19 exhibited higher level of SGPT but lower serum albumin.

Furthermore, in the present study, CRP, SGPT, serum creatinine, LDH, serum ferritin, D-dimer showed positive correlations. But serum albumin 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, Troponin I, Interleukin-6, Immunoglobulins could not be done due to financial constraints, time and lack of availability.

5. Conclusion

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 the complications and to reduce the overall mortality and morbidity.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The author declares no conflict of interest.

Statement of ethical approval

Ethical clearance of this study was obtained from concerned Departments, Research review committee and Ethical review committee of Dhaka Medical College, Dhaka.

Statement of informed consent

Informed consent was obtained from all individual participants included in this study.

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