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Spectrum of Biochemical Derangements in Patients with Covid-19 Infection

Sajjad Ali Haider, Zujaja Hina Haroon, Athar Iqbal Paracha, Muhammad Aamir, Saima Bashir, Syed Raza Jaffar

ABSTRACT

Objectives: To evaluate the biochemical derangements in COVID-19 patients according to disease severity.

Place and Duration of Study: This Cross-Sectional Study was conducted at Chemical Pathology Department of Armed Forces Institute of Pathology, Rawalpindi from March to August 2021.

Methodology: A total of 996 patients of age between 20 to 75 years admitted at Pak Emirates Military Hospital Rawalpindi with COVID-19 were selected and further categorized into mild, moderate, and severe groups. Serum samples were collected and analyzed for various biochemical parameters. A mean comparison of the results of these biochemical markers amongst three groups was carried out by applying a one-way analysis of variance (ANOVA), p value = 0.05 was statistically significant.

Results: The values of total bilirubin, ALT, AST, CK, CK MB, troponin I, LDH, urea, creatinine, CRP, PCT, and ferritin increased with the severity of the disease. Whereas the values of albumin and total protein decreased with the severity of the disease. The difference in these parameters amongst all three groups was found to be statistically significant with p value <0.05. However, the values of GGT, total cholesterol, and TG were found non-significant amongst all three groups (p value>0.05).

Conclusion: Derangement of biochemical parameters increased proportionately with the severity of the disease. Hence these markers can provide significant assistance to categorize patients into different severity groups as well as monitoring and prognosis of the disease. In this way, earlier and more accurate medical interventions can be provided to patients for a better outcome from this pandemic.

Keywords: COVID-19, Biochemical markers, Severity groups

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INTRODUCTION:

Emerging pathogens have always been a threat to the whole world. In December 2019, an outbreak of pneumonia of unknown origin was reported in Wuhan, China. On further workup of pneumonia, it was found that the disease is caused by a new respiratory virus whose genome analysis revealed it to be a novel coronavirus related to SARS-CoV and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The outbreak then spreaded to many countries causing thousands of deaths worldwide. World Health Organization (WHO) declared coronavirus disease (COVID-19) a pandemic on 12 March 2020.[2] WHO statistical data reveals that 570 Million cases of COVID-19 along with 6.3 Million deaths have been reported worldwide till July 2022. Pakistan is also severely affected by this disease. According to the number of COVID-19 cases worldwide, Pakistan ranks in the 51st position with 1.5 Million confirmed cases and 30 thousand deaths.[3] Various treatment modalities and vaccines have been developed to curtail the spread of disease and to minimize the mortality rate from this outbreak.[4] So far 12.2 billion doses of vaccines have been administered globally.

The virus spreads from one individual to another through respiratory droplets which are produced during sneezing and coughing. The incubation period varies from 2 to 14 days with an average of 5 days. The laboratory plays a significant role in the clinical management of COVID-19, starting from screening to diagnosis, prognosis, and

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monitoring of the disease. The standard investigation to diagnose COVID-19 is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal or throat swab. However, a combination of the history of disease exposure, clinical symptoms, and a chest CT scan showing features of pneumonia are also used to augment the diagnosis.[5]

COVID-19 patients can be identified and prognosticated by changes in their biochemical and haematological parameters. The liver, lungs, heart, kidneys, brain, striated muscles, and RBCs produce more lactic dehydrogenase (LDH). A variety of pathophysiological processes can be triggered by cytokine-mediated tissue damage. LDH is often used in COVID-19 as a non-specific indicator of cellular death. Inflammatory cytokines produce CRP, which increases in response to tissue destruction and the overproduction of inflammatory cytokines. The level of inflammation influences and correlates with CRP levels. An early marker of pneumonia can be used to diagnose the disease and predict its progression.[6]

COVID-19 has a broad spectrum of clinical manifestations, with various degrees of disease severity ranging from asymptomatic patients to acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and death.[7] The disease affects multiple organs of the body including the liver, kidneys, heart, and CNS, hence leading to various biochemical derangements. These biochemical findings may help the clinician to ensure adequate clinical monitoring, administration of supportive interventions, and assessment of disease severity, progression, and outcome.[8]

Despite abundant research regarding the number of patients and the death rates, there is a scarcity of data regarding biochemical derangements in COVID-19 patients. There has been limited data regarding the pattern of the outcome of disease in relation to biochemical derangements. Our study aims on quantifying the levels of biochemical parameter derangements in relation to the severity of disease which will help in distinguishing the survival and mortality rate of individuals.

METHODOLOGY:

A cross-sectional study was conducted at the Chemical Pathology Department of the Armed Forces Institute of Pathology, Rawalpindi over a period of six months from March to August 2021 after getting approval from the Institute Ethical Committee (FC-CHP19/17/READ-IRB/570). WHO sample size calculator was used to estimate the sample size with a 95% confidence interval and 5% margin of error taking 17.5% as the prevalence of COVID-19 in the Pakistani population.[9] A total of 996 patients who were admitted to the COVID ward of the Pak Emirates Military Hospital Rawalpindi (PEMH) were included in the study. Sampling was done using a nonprobability convenient sampling technique. Inclusion criteria for this research were patients of either gender aged between 20-75 years, diagnosed cases of COVID-19 by using rRT-PCR from a nasopharyngeal swab, and hospitalized in the COVID ward of PEMH Rawalpindi. Whereas, patients without proper medical history and incomplete investigations were excluded from the study. According to the severity of symptoms, patients were categorized into three groups i.e. mild (598), moderate (197), and severe (201). Those who had uncomplicated disease with mild clinical symptoms and without radiological evidence of pneumonia were categorized into a mild group, whereas those who had a fever, respiratory distress, and evident pneumonia on chest imaging were categorized into a moderate group. While, patients who had respiratory complications having a respiratory rate of more than 30 breaths per min, a saturation of oxygen less than 93% at rest, and an oxygenation index (PaO2/FiO2) less than 300 mm Hg were categorized into the severe group.[10]

The blood sample of the patients was collected in a gel tube. After separation of serum samples were analyzed for serum total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), albumin, creatinine kinase (CK), CK-MB, troponin I, lactate dehydrogenase (LDH), urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), ferritin, total protein, total cholesterol and triglycerides (TG). Analysis of all these biochemical markers was performed on an automated chemistry analyzer ADVIA 1800 (Siemens). Controls were run on the instrument and plotted on the LJ chart before analysis and were within normal limits.

Statistical analyses were performed using IBM SPSS 26. On applying the Shapiro-Wilk test of normality the data was found to be normally distributed. Percentage and frequencies were used for qualitative variables whereas quantitative variables were expressed as mean ± SD. One-way analysis of variance (ANOVA) was applied to compare means of biochemical markers amongst all three patient groups. p-value = 0.05 was considered to be statistically significant.

RESULTS:

A total of 996 patients were included in our study. Amongst those, 598(60%) had mild, 197(19.7%) had moderate and 201(20.3%) had severe disease. Out of total 996 patients, 739(74.2%) were male and 257(25.8%) were female. Amongst 739 male patients, 470(63.6%) had mild, 166(22.4%) had moderate and 103(14%) had severe disease. Whereas out of 257 females 128(49.9%) had mild, 31(12%) had moderate and 98(38.1%) had severe disease. The mean age of patients was 52.6±9.4 years. The patients with mild, moderate, and severe disease had a mean age of 38.79±9.79, 51.84±13.3, and 67.17±5.27 years respectively.

There have been asymptomatic patients who did not experience any symptoms during the whole duration of the disease but were Covid-19 positive. Table I shows the frequency and percentage of patients who suffered from the major clinical features of COVID-19 which included fever, cough, shortness of breath, and myalgia/ fatigue according

to their disease severity. The recovery and mortality data of the patients were also followed up. Out of 996 patients, 872(87.5%) recovered and were discharged, 93(9.3%) were under treatment and 31(3.2%) patients who were in the severe group died during our study. The patients who recovered and discharged were the highest in the mild group. All the patients who died were in the severe group. On comparing various biochemical markers amongst different severity groups it was found that the values of total bilirubin, ALT, AST, CK, CK MB, troponin I, LDH, urea, creatinine, CRP, PCT, and ferritin increased with the severity of the disease. Whereas, the values of albumin and total protein decreased with the severity of the disease. The difference in these parameters amongst all three groups was statistically significant with a p-value <0.05. However, the values of GGT, total cholesterol, and TG were found insignificant amongst all three groups (p value>0.05) as shown in Table II.

Table 1: Frequency Table of clinical symptoms according to disease severity

	Fever		Cough		Shortness of Breath		Myalgia / Fatigue	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Mild (n=598)	430 (72%)	168 (28%)	280 (46.8%)	318 (53.2%)	25 (4.1%)	573 (95.9%)	450 (75.2%)	148 (24.8%)
Moderate (n=197)	175 (89%)	22 (11%)	154 (78%)	43 (22%)	124 (63%)	73 (37%)	160 (81%)	37 (19%)
Severe (n=201)	189 (94%)	12 (6%)	193 (96%)	8 (4%)	201 (100%)	0 (0%)	197 (98%)	4 (2%)

Table 2: Comparison of biochemical markers amongst various severity groups

Parameters	**Mild** (Mean ± SD)	**Moderate** (Mean ± SD)	**Severe** (Mean ± SD)	**p-value***
Total Bilirubin (umol/L)	8.04 ±1.45	9.40 ±2.20	11.60 ±2.56	.001
ALT (U/L)	38.80 ±11.5	42 ±26.02	52.21 ±11.0	.004
AST (U/L)	26.21 ±5.50	30.25 ±7.67	49 ±13.60	<.001
GGT (U/L)	45.2±5.50	41.5±3.93	48.62±4.65	.584
Albumin (g/L)	45.46 ±3.93	36.82 ±9.89	29 ±4.24	<.001
CK (U/L)	71.57 ±17.19	101.08 ±23.28	149 ±15.1	<.001
CK.MB (U/L)	15.18 ±3.03	22.6 ±8.5	35 ±9.8	.001
Troponin I (ng/mL)	0.02±0.01	0.69±0.52	1.29±0.22	<.001
LDH (U/L)	233.2 ±28.27	289.38 ±43.83	338.8 ±34.6	.001
Urea (mmol/L)	5.33 ±1.37	6.14 ±2.29	8.5 ±2.19	.001
Creatinine (umol/L)	80.01 ±11.74	109.51 ±19.26	131.6 ±23.3	<.001
CRP (mg/L)	6.66 ±4.75	63.74 ±3.12	97.2 ±26.39	<.001
PCT (ug/L)	0.14±0.24	2.65±1.25	3.58±1.89	<.001
Ferritin (ng/mL)	128.2 ±54.96	384.88 ±26.36	529.5 ±201.4	<.001
Total Protein (g/L)	68.1 ±4.2	66.3 ±5.3	61.3 ±3.9	<.001
Total cholesterol (mmol/L)	4.19±1.27	4.26±2.96	4.24±1.90	.432
TG (mmol/L)	1.77±0.65	1.36±1.1	1.74±0.97	.587

*One-way ANOVA

DISCUSSION:

Coronaviruses comprises of four structural proteins; Spike (S), membrane (M), envelop (E), and (N). The surface of the virus contains Spike which is a major determinant factor for the diversity of coronaviruses. These proteins bind with Angiotensin-converting enzyme 2 (ACE2).[11] ACE2 receptors are found on lung epithelial cells, heart, ileum, kidney, and urinary. The presence of ACE2 expression on multiple organs, tissues, and cell types could allow virus entry, multiplication, spread, and pathogenesis which may lead to clinical symptoms like breathing difficulties, diarrhea, myocardial injury, and renal failure.[12] Effect of COVID-19 on multiple organs leads to the release of a wide spectrum of biochemical markers which can be used as an important predictor of disease progression and outcome.[13]

In our study, we found that levels of total bilirubin, ALT, AST, CK, CK MB, troponin I, LDH, urea, creatinine, CRP, PCT, and ferritin increased with the severity of the disease.

The values of all these biochemical parameters progressively increased with the severity of the disease. However, serum albumin and total protein were found to be lower in patients with severe disease. Whereas, GGT, total cholesterol, and TG had no role as a prognostic markers of disease severity. Similar results were seen in various studies.

Pourbagheri-Sigaroodi., et al[14] in a study concluded that increased levels of LDH, ALT, AST, CK, creatinine, total bilirubin, and hypoalbuminemia are the most common biochemical findings in COVID-19. Chen., et al[15] revealed that LDH, ALT, AST, bilirubin, and CK were found elevated in 76%, 28%, 35%, 18%, and 13% of patients respectively, whereas albumin level was found to decrease in 98% patients. Guan., et al[16] showed that ALT and AST levels were raised by 21.3% and 22.2% respectively in COVID-19 patients representing virus-induced liver injury. Another study carried out on 149 COVID-19 patients revealed that the serum creatinine levels were raised in 28.8% of patients indicating the ability of SARS-CoV-2 to induce kidney injury.[17] Li., et al[18] found that raised ferritin levels in 90.7% of COVID-19 patients. As an acute phase reactant, raised serum ferritin during inflammation, also its release from dying cells may indicate the extent of organ damage and can be used as a diagnostic tool in COVID-19.[19] Another study revealed that increased levels of PCT and CRP levels could be an important tool for the physician to differentiate between severe and non-severe COVID-19 cases.[20] Major limitation of this study was that it was conducted in a single hospital setting on admitted patients only and biochemical findings of patients were not followed up after they were discharged, secondly the data regarding the effect of treatment given during the course of illness on these markers was not obtained which could be added in subsequent studies. Therefore, a multicentric study with a large sample size involving more hospitals may give a good representation of the desired comparison of various biochemical markers amongst different COVID-19 severity groups.

CONCLUSION:

Diverse variation in the clinical symptoms which range from asymptomatic to severe disease necessitates the use of biochemical markers such as total bilirubin, ALT, AST, CK, CK MB, troponin I, LDH, urea, creatinine, CRP, PCT and ferritin for early and economical prediction of prognosis of COVID-19. Although the gold standard diagnostic test for COVID-19 is rRT-PCR however these biochemical parameters can also provide significant assistance to categorize patients into different severity groups. In this way, earlier and more accurate medical intervention can be provided to patients for a better outcome from this pandemic.

Authors Contribution:
Sajjad Ali Haider: Data collection, data analysis, results, discussion, and literature review
Zujaja Hina Haroon: Data Analysis, results, discussion, and literature review
Athar Iqbal Paracha: Results, discussion, and literature review
Muhammad Aamir: Discussion and literature review
Saima Bashir: Data Analysis and Results
Syed Raza Jaffar: Data collection, Discussion, and literature review

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