RESEARCH

STUDY OF BIOCHEMICAL MARKERS OF COVID-19 IN WESTERN PUNJAB

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Abstract

Background: To determine the association between various demographic indicators and biochemical markers in COVID-19 patients in Western-Punjab. **Materials and Methods:** An observational cross-sectional study was done on one hundred and fifty cases of all ages admitted in Isolation ward, reporting to Adesh Institute of Medical Sciences and Research, Bathinda, India with COVID-19(RT-PCR/ or RAT) from January 2022 to March 2022 were included. Clinical features like fever, cough and shortness of breath were recorded. Blood sample was collected in plain tube for biochemical markers like serum albumin, creatinine, ferritin, LDH, CRP and urea, SGOT, SGPT, procalcitonin, D-dimer, ESR, IL-6, ALP, bilirubin were analysed. Association of the clinical features and these biochemical markers were determined. **Result:** Patients were divided into 3 groups according to different ages (<40 years, 40-60 years, >60 years). Out of 150 patients 26 (17.3%) belonged to age group < 40, 60 (40.0%) belonged to age group 40-60 years and 64 (42.7%) belonged to age group >60 years. Mean age was 55.93 + / - 14.91. Out of 150, 39 (26.0%) were females and 111(74.0%) were males. 44 (29.3%) cases had hypertension and 59(39.3%) cases had diabetes mellitus. Urea levels in 118 (78.7%) patients were above normal reference values **e** and was statistically significant (p<0.015). 73 (48.7%) had SGOT levels above normal range [statistically significant (p<0.025)] while as 63 (42%) had SGOT above normal range [statistically significant (p<0.001)]. 98 (65.3 %) had IL-6 above normal range [statistically significant (p<0.003)]. While as albumin levels in 38 (25.3%) patients were within normal range and 112 (74.7%) patients had albumin below normal range [statistically significant (p<0.014)]. ESR (100%), D-dimer (100%), procalcitonin (100%), LDH (94%) were uniformly raised in almost all patients. Rest of the markers like ferritin (74%), bilirubin (6%), CRP (90%), creatinine (15.3%), ALP (14.7%) was also raised but was not statistically significant. Conclusion: Indian patients with COVID-19 disease showed variable pattern of clinical features.

INTRODUCTION

COVID-19 was first detected in 2019 in Wuhan, China, allegedly linked to the wet animal market and was found to target the respiratory system of humans.[1,2] Almost all countries were affected including United States, Canada, Thailand, Sri Lanka, Japan, Germany, India, France, Cambodia, Singapore, Malaysia, Vietnam, Nepal etc.[3] The fatality rate was estimated to be 170 out of 7,824. This disease, COVID-19, spread to different continents of this Globe, which compelled WHO to recognize this outbreak as a pandemic, SARS-CoV-2 on 11th March.[4] This has been observed to be the third serious worldwide outbreak in last 20 years.[5] The common symptoms of this ailment are headache, lymphopenia, diarrhea, dyspnoea and haemoptysis: and is transmitted from person to person through direct contact or via droplets in sneezing or coughing from the diseased person.[6] SARS-CoV-2 belongs to enveloped viral family with large diversity, single stranded RNA and positive sense which infects both animals and human leading to gastrointestinal, hepatic and respiratory diseases.[7] COVID-19 belongs to seventh member of the family of coronaviruses with subfamily orthocoronavirinae.[8] SARS-Cov-2 has 96% similar genetically with Bat CoV RaTG13. A

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bat corona virus leading to the believe that this virus originated from bat but transmitted directly or by a vector, still to be determined.[9]Strict preventive measures such as refraining from public transport, avoiding contact with sick people, avoiding crowds, unnecessary travel and most importantly maintain good personal as well as social hygiene help in preventing spread of this disease.[10] In India, 3,01,34,445 suspected individuals were reported till 25th June 2021 with mortality of 3,93,310. This study basically plans to observe clinical features and biochemical markers, which were associated with COVID-19 positive patients.

Several diagnostic and therapeutic challenges have come up due to this severe acute respiratory syndrome caused by CORONAVIRUS-2. First case of this infection was reported from Wuhan in China in December 2019, this infection was officially named by the World Health Organization on February 11, 2020 as coronavirus disease 2019 (COVID-19) and the virus has been labelled as SARS-CoV-211. On March 11, 2020 it was declared as a pandemic.[11] As on December 9, 2020, there had been more than 67 million cases worldwide leading to more than 1.5 Million deaths.[12]

In adults, though SARS-CoV-2 mainly it causes acute respiratory distress syndrome and pneumonia but now it is being recognized as a multisystem disease. Children on the other hand are asymptomatic or show mild symptoms. Critical illness has rarely been observed in children.[13,14] A polymerase chain reaction (PCR) test is used for confirmation of diagnosis which detects of SARS-CoV-2 nucleic acids in respiratory tract specimens.[15] A rapid and accurate diagnosis has a greater role for the patient, healthcare institution, and the public health and administration. In the current pandemic, as number of infected cases are rising healthcare systems are struggling to meet their increasing demands. Effective utilization of available resources is very essential to save maximum lives. Clinical assessment of course is indispensable, but laboratory markers, or biomarkers, have shown to provide additional, objective information which has an impact on patient care. Zoonotic origin of outbreak has been suggested, and just like other respiratory pathogens, the spread is via human-to-human transmission for example coughing and sneezing.[16] Transmission of this disease even occurs among the asymptomatic.[17]Fever, high temperature (>37.3 °C), cough, myalgia, production of sputum, headache, haemoptysis, dyspnoea, diarrhoea and sometimes acute respiratory distress syndrome, acute cardiac injury or secondary infection are the main manifestations' of this disease.[18,19,20,21]The use of biological markers (biomarkers) make the interpretation of these clinical manifestations' more confident. The progression of the disease can easily be assessed by the use of these biomarkers.[19] These biomarkers are used in categorizing patients into mild, severe or critical, allowing for earlier interventions.[20]

The role of different biomarkers in the disease pathogenesis of COVID-19 and assess how their levels vary depending on the severity of the disease is the main aim of this study. Biomarkers also serve as a tool for clinicians to group patients and predict prognosis and mortality. The biomarkers we are reviewing in this study include, C-reactive protein (CRP), IL-6, white cell count (WCC), lactate dehydrogenase (LDH), D-dimers, platelet count, cardiac troponin and renal markers.

MATERIALS AND METHODS

A sample size of 150 was used. Study participants comprised of cases of both genders of all ages, having PCR positive for COVID-19 (continuously detectable COVID RNA on qualitative polymerase chain reaction), having different co morbidities and willing to be part of this research. Patients having negative PCR for COVID-19 were excluded.

After taking relevant history, like cough, fever and history of contact and physical examination, like temperature and respiratory rate, venous blood sample of each patient was taken and sent in plain tube and ABGs sample in heparinised syringe to institutional laboratory for analysis of serum ferritin, LDH, albumin, bilirubin, creatinine, AST, ALT,D-dimer, alkaline phosphatase, procalcitonin, urea, IL-6 and CRP. **A** specialised proforma was designed to record all the study information.

SPSS version 21.0 was used for data analysis. Mean and standard deviation was estimated regarding age, while median (IQR) for ferritin, LDH, albumin, bilirubin, creatinine, AST, ALT, D-dimer, alkaline phosphatase, procalcitonin, urea, IL-6 and CRP levels. One-sample Chi-square test was applied to compare qualitative variables considering p-value less than 0.05 as statistically significant. Spearman's correlation was also applied and p-value <0.05 considered as statistically significant.

RESULTS

One fifty patients, who met the inclusion criteria of different ages, were included in this study. Patients were divided into 3 groups according to different ages (<40 years, 40-60 years, >60 years).Out of 150 patients 26 (17.3%) belonged to age group <40, 60 (40.0%) belonged to age group 40-60 years and 64 (42.7%) belonged to age group >60 years. Mean age was 55.93 + / - 14.91. Out of 150, 39 (26.0%) were females and 111 (74.0%) were males. 44 (29.3%) cases had hypertension and 106 cases did not have hypertension. 59 (39.3%) cases had diabetes mellitus and 91 cases did not have diabetes mellitus.

Urea: 118 (78.7%) patients had urea levels above normal reference values while 32 (21.3%) had urea levels within range and was statistically significant (p<0.015).Urea was above reference values for 15

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(57.7%) patients of age group <40 years, 49 (81.79 %) for 40-60 years, 54 (84.4%) for > 60 years age group. 92 (82.9%) males and 26 (66.7 %) females had urea above normal reference values.

Creatinine: 127 (84.7%) patients had creatinine within normal range and 23 (15.3%) had creatinine above normal range. Creatinine was above reference value for 1 (3.8%) patients of age group <40, 12 (20%) for age group 40-60 years, 10 (15.6%) for age group > 60 years. 4 (10.3%) females and 19 (17.1%) males had creatinine above normal range.

Bilirubin: 141 (94%) patients had bilirubin levels within normal range and 9 (6%) had bilirubin above normal range. Bilirubin was above reference value for 11.5 % patients of age group <40 years, 6.7% for age group 40-60 years and 3.1% for age group >60 years. 2.6% females and 7.2 % males had bilirubin above normal range.

SGOT: 77 (51.3%) patients had SGOT levels within normal range and 73 (48.7%) had SGOT levels above normal range [statistically significant (p<0.025)]. SGOT was above reference value for 16 (61.5%) patients of age group <40, 34 (56.7%) for age group 40-60 years, 23 (35.9%) for age group > 60 years. 14 (35.9%) females and 59 (53.2%) males had SGOT above normal range.

SGPT: 87 (58.0%) patients had SGPT within normal range and 63 (42%) had SGOT above normal range [statistically significant (p<0.001)]. SGPT was above reference value for 18 (69.2%) patients of age group <40, 28 (46.7%) for age group 40-60 years and 17 (26.6%) for age group >60 years. 10 (25.6%) females and 53 (47.7%) males had SGPT above normal range.

ALP: 128 (85.3 %) patients had ALP within normal range and 22 (14.7%) patients had ALP above normal range. ALP was above reference value for 2 (7.7%) patients of age group <40, 9 (15%) for age group 40-60 years, 11 (17.2%) for age >60 years. 11 (28.2%) females and 11 (9.9%) males had ALP above normal range.

S.Albumin:38 (25.3%) patients had albumin within normal range and 112 (74.7%) patients had albumin below normal range [statistically significant (p<0.014)]. Albumin was below reference value for 24 (92.3%) patients of age group <40, 47 (78.3%) for age group 40-60 years, 41 (64.1%) for age group >60 years. 25 (64.1%) females and 87 (78.4%) males had abnormal values.

CRP: 15 (10%) patients had CRP within normal range and 135 (90%) had CRP above normal range. CRP was above reference value for 24 (92.3 %) patients of age group <40, 55 (91.7%) for age group 40-60 years, 56 (87.5%) for age groups > 60 years. 33 (84.6%) females and 102 (91.9%) males had CRP above normal range.

LDH: 9 (6%) patients had LDH within normal range and 141 (94%) had LDH above normal range. LDH was above reference value for 25 (96.2%) patients of age group <40, 53 (88.3%) for age group 40-60 years, 63 (98.4%) for age group >60 years. 37 (94.9%) Females and 104 (93.7%) males had LDH above normal range.

D-dimer: Almost all had D-dimer above normal range. D-dimer was above reference value for 26 (100%) patients of age group <40, 60 (100%) for patients 40-60 years, 64 (100%) for patients >60 years.

Procalcitonin: 1 (0.7%) patients had procalcitonin within normal range and 149 (99.3 %) patients had procalcitonin above normal range. Procalcitonin was above reference value for 26 (100%) patients of age group <40, 60 (100%) patients of age group 40-60 years, 63 (98.4%) patients for age group >60 years. 39 (100%) females and 110 (99.1%) males had abnormal values.

ESR: Almost all patients had ESR above normal range. ESR was above reference value for 26 (100 %) patients of age group <40 years, 60 (100 %) for patients of age group 40-60 years, 64 (100 %) for patients of age group > 60 years.

Ferritin: 39 (26%) patients had ferritin within normal range and 111 (74%) had ferritin above normal range. Ferritin was above reference value for 23 (88.5 %) patients of age group <40 years, 43 (71.7 %) for patients of age group 40-60 years, 45 (70.3%) for age group >60 years. 21 (53.8%) females and 90 (81.1%) males had abnormal values.

IL-6: 52 (34.75 %) patients had IL-6 within normal range and 98 (65.3 %) had IL-6 above normal range [statistically significant (p<0.003)]. IL-6 was above normal range for 20 (76.9 %) patients of age group <40 years, 46 (76.7%) for age group 40-60 years and 32 (50%) for age group > 60 years. 25 (64.1%) females and 73 (65.8%) males had IL-6 above normal range.

Table 1: Distribution of parameters according to age

		Age group						Total	Chi-square value	p-value
		< 40 (n=26)		40-60 (n=60)		> 60 (n=64)				
Urea	6-24.0	11	42.3%	11	18.3%	10	15.6%	32	8.380	0.015
	> 24	15	57.7%	49	81.7%	54	84.4%	118		
Creat	< 0.7	3	11.5%	4	6.7%	6	9.4%	13	3.973	0.410
	0.7-1.4	22	84.6%	44	73.3%	48	75.0%	114		
	> 1.4	1	3.8%	12	20.0%	10	15.6%	23		
Bilirubin	< 0.6	4	15.4%	18	30.0%	23	35.9%	45	5.291	0.259
	0.6-1.4	19	73.1%	38	63.3%	39	60.9%	96		
	> 1.4	3	11.5%	4	6.7%	2	3.1%	9		
SGOT	8-45.0	10	38.5%	26	43.3%	41	64.1%	77	7.412	0.025

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	> 45	16	61.5%	34	56.7%	23	35.9%	73		
SGPT	7-56.0	8	30.8%	32	53.3%	47	73.4%	87	14.712	0.001
	> 56	18	69.2%	28	46.7%	17	26.6%	63		
ALP	< 45	2	7.7%	4	6.7%	9	14.1%	15	3.743	0.442
	45-110	22	84.6%	47	78.3%	44	68.8%	113		
	> 110	2	7.7%	9	15.0%	11	17.2%	22		
S.Albumin	< 3.5	2	7.7%	13	21.7%	23	35.9%	38	8.509	0.014
	3.5-5.0	24	92.3%	47	78.3%	41	64.1%	112		
CRP	< 10	2	7.7%	5	8.3%	8	12.5%	15	0.783	0.676
	> 10	24	92.3%	55	91.7%	56	87.5%	135		
LDH	< 105	1	3.8%	2	3.3%	0	0.0%	3	7.416	0.115
	105-330	0	0.0%	5	8.3%	1	1.6%	6		
	> 330	25	96.2%	53	88.3%	63	98.4%	141		
D-DIMER	> 0.5	26	100.0%	60	100.0%	64	100.0%	150		
S.Procalcitonin	< 0.1	0	0.0%	0	0.0%	1	1.6%	1	1.353	0.508
	> 0.1	26	100.0%	60	100.0%	63	98.4%	149		
ESR	> 22	26	100.0%	60	100.0%	64	100.0%	150		
FERRITIN	< 24	0	0.0%	5	8.3%	1	1.6%	6	8.198	0.085
	24-300	3	11.5%	12	20.0%	18	28.1%	33		
	> 300	23	88.5%	43	71.7%	45	70.3%	111		
IL-6	< 40	6	23.1%	14	23.3%	32	50.0%	52	11.585	0.003
	> 40	20	76.9%	46	76.7%	32	50.0%	98		

Table 2: Distribution of parameters according to gender

		Age group				Total	Chi-square value	p-value
		F (n=39)		M (n=111)				
Urea	6-24.0	13	33.3%	19	17.1%	32	4.522	0.033
	> 24	26	66.7%	92	82.9%	118		
Creat	< 0.7	9	23.1%	4	3.6%	13	14.118	0.001
	0.7-1.4	26	66.7%	88	79.3%	114		
	> 1.4	4	10.3%	19	17.1%	23		
Bilirubin	< 0.6	18	46.2%	27	24.3%	45	6.953	0.031
	0.6-1.4	20	51.3%	76	68.5%	96		
	> 1.4	1	2.6%	8	7.2%	9		
SGOT	8-45.0	25	64.1%	52	46.8%	77	3.44	0.093
	> 45	14	35.9%	59	53.2%	73		
SGPT	7-56.0	29	74.4%	58	52.3%	87	5.79	0.016
	> 56	10	25.6%	53	47.7%	63		
ALP	< 45	3	7.7%	12	10.8%	15	7.749	0.021
	45-110	25	64.1%	88	79.3%	113		
	> 110	11	28.2%	11	9.9%	22		
S.Albumin	< 3.5	14	35.9%	24	21.6%	38	3.109	0.089
	3.5-5.0	25	64.1%	87	78.4%	112		
CRP	< 10	6	15.4%	9	8.1%	15	1.698	0.219
	> 10	33	84.6%	102	91.9%	135		
LDH	< 105	0	0.0%	3	2.7%	3	1.226	0.542
	105-330	2	5.1%	4	3.6%	6		
	> 330	37	94.9%	104	93.7%	141		
D-DIMER	> 0.5	39	100.0%	111	100.0%	150		
S.Procalcitonin	< 0.1	0	0.0%	1	0.9%	1	3.54	0.552
	> 0.1	39	100.0%	110	99.1%	149		
ESR	> 22	39	100.0%	111	100.0%	150		
FERRITIN	< 24	3	7.7%	3	2.7%	6	11.181	0.004
	24-300	15	38.5%	18	16.2%	33		
	> 300	21	53.8%	90	81.1%	111		
IL-6	< 40	14	35.9%	38	34.2%	52	0.035	0.851
	> 40	25	64.1%	73	65.8%	98		
Total		39	100.0%	111	100.0%	150		

DISCUSSION

COVID-19 has a broad spectrum of systemic manifestations. Some of the complications included are coagulopathy, pneumonia, myositis, kidney and liver dysfunctioning and lymphopenia[22] .The level of C-reactive protein (CRP) can be used for diagnosis of pneumonia in early stages,[23]and increased CRP level can be noted with the increase of severity of SARS Corona virus disease. According to a retrospective study from Wuhan, China during the early pandemic it was shown that WBC and neutrophil counts were normal in the first week of disease and increased subsequently.[24] Lymphocytes play a key role in maintaining immune homeostasis and inflammatory response that protects the body against viral infections.[25]

In a study it has been seen that that there is a positive correlation between CRP levels and lung lesion diameter.[26]Besides abnormal blood coagulation functioning, the elevation of C-reactive protein is crucial inflammatory index.[27] Increased

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CRP level in patients suffering from corona virus disease has been observed in many other studies.[28]IL-6 in the liver induces production of this non-specific biomarker CRP. Clinically, CRP is has been in use as a biomarker for different inflammatory and infectious conditions. There is a direct correlation of elevated CRP with levels of inflammation and severity of disease. Therefore, CRP is an important biomarker in diagnosis and assessing the severity of diseases of infectious etiology.[29]

Increase in levels of LDH and aspartate transferase, which are associated with myocardial injury, has also been observed in previous studies.[30] Increased aspartate transferase is also associated with liver dysfunctioning; and its elevated level has been noticed in patients with non-severe COVID-19 disease.[31] Increased ferritin levels have also been observed in covid patients in some previous studies.[32] According to study in China on 191 patients suffering from COVID- 19, non-survivors were observed more often with elevated level of LDH and ferritin levels as compared to survivors.[33] LDH is found in tissues throughout the body and function of LDH is in the interconversion between pyruvate and lactate through an nicotinamide adenine dinucleotide (NADH)-dependent reaction. Decreased oxygenation results in abnormal LDH levels, leading to an upregulation of the glycolytic pathway and thus leading to multiple organ injury. The mechanism through which lactate leads to injury is through the action of metalloproteinases enzymes and enhanced macrophage-mediated angiogenesis.[34] LDH levels in early part of the disease can be a good predictor of lung injury in severe COVID-19 cases.[35] High LDH levels have also been to be associated with worse outcomes in many studies.[36,37,38] Elevated LDH levels were also associated with a more than sixteen-fold increase in chances of mortality and a six fold increase in chances of severe disease.[39] Our overall results also demonstrate the odds of having higher LDH in patients with poor outcomes compared with better outcomes.

Similarly, in another study conducted in China, the ferritin levels were elevated in COVID-19 patients (in non-survivors verses survivors were found 1297.6 ng/ml and 614·0 ng/ml, respectively). Increased level of serum ferritin is found to be associated with ARDS development.[40]

Decreased in level of albumin which is also associated with liver injury, has also been noticed in corona virus patients in previous studies.[41] In nutritional status, albumin is most instinctive index of our body. Decreased level of albumin is associated with less resistance of body against virus, which leads to progression of disease.[42] Elevated level of serum creatinine and blood urea nitrogen, which are associated with damage of kidney, have also been observed in some previous studies also. Creatinine as we know is a marker for kidney function. In a prospective cohort study done on COVID-19 patients, it was found that during hospitalisation, the incidence of acute kidney injury and death was significantly higher in patients with elevated serum creatinine levels than in patients with normal values.[43] Haematogenous spread of virus and accumulation of virus in kidney leading to renal cell necrosis is the mechanism behind this . It was also found by our study that elevated levels of creatinine increase the chance of poor outcomes by nearly twofold.

COVID-19 patients with elevated D-dimer had higher rates of poor outcomes. The increase in inflammatory response in COVID-19 and hypoxia caused by severe pneumonia, eventually leads to the activation of coagulation and fibrinolysis, followed by a hypercoagulable state leading to DIC, thus multi organ dysfunction.[44,45] Additionally, previous studies show that D-dimer levels greater than 2.0 μg/mL on admission could effectively predict in-hospital mortality rates of patients with COVID-19.[46] Patients having higher D-dimer levels requiring intubation were also associated with a greater probability of developing pulmonary embolism after hospital admission. A study by Yu et al found that D-dimer levels were significantly higher in COVID-19 patients than patients of community acquired pneumonia.[47] The study also found the relation of elevated D-dimer with markers of inflammation, especially with CRP. In this study, treatment with anticoagulants led to a decrease in D-dimer as well as CRP levels in patients with good clinical prognosis.[48] We have also found that patients having elevated D-dimer values have higher risk of poor outcomes. This clearly signifies that use of anticoagulants and anti-inflammatory drugs could lead to a decrease in poor outcomes in COVID-19 patients.[49]

SGOT and SGPT are released if hepatocytes are damaged thus leading to increased serum levels (abnormal LFTs e.g. raised liver enzymes). According to studies COVID-19 has shown to only transiently increases levels of SGOT and SGPT and have explained that secondary liver damage is responsible for liver dysfunction instead of direct insult. The cause of this secondary liver damage in COVID-19 is inflammatory response to disease as well as hepatotoxic drugs given for managing the disease. Inflammatory response is responsible to multi-organ failure that leads to activation of both natural as well as cellular immunity in critically ill COVID-19 patients.[50] Additionally, hepatocellular necrosis is caused by hypoxia which is present in COVID-19 patients through the marked increase in reactive oxygen species which lead to activation of redox-specific transcription factors that amplify the release of proinflammatory factors which are hepatotoxic.[51,52] RITONAVIR and LOPINAVIR used for managing the disease further contribute to liver injury.[53] According to some studies conducted initially, more than one-third of patients had elevated SGOT and SGPT which was directly associated with longer hospital stay.[54,55,56] In a

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study done by Cai et al,[57] of the 417 patients with COVID-19, in 76.3% liver tests were abnormal while 21.5% developed liver injury during hospitalisation, which was defined by SGOT, SGPT, total bilirubin and GGT levels elevated to more than three times the upper limit of normal reference values. The study showed that patients who had abnormal liver tests had significantly higher chances of developing severe pneumonia.[58] This is also consistent with our study that shows a significant increase in SGOT and SGPT among COVID-19 patients and the potential for these biomarkers to signify poor prognosis among these patients.

In another study conducted on 249 patients with median age 51 years, the most common symptoms at the start of corona virus disease were fever (87.1%), fatigue (15.7%) and cough (36.5%). Similarly, in another study conducted on corona virus patients, 73.1% people got treatment for fever. In 39.7% patients, 37.3 - 38.0°C was the maximum body temperature that was observed. At admission the body temperature remains significantly higher in older people than younger one (38.2° vs. 37.5°C).

CONCLUSION

COVID-19 positive patients showed particular pattern of clinical features and biochemical markers, which may facilitate diagnosis of COVID-19 infection.

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