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A Study of correlation between Viral load, Clinical and Biochemical Parameters of COVID-19 Patients In a Tertiary Care Centre in North India.

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Abstract:

Introduction: Corona virus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS CoV-2). It emerged in Wuhan and then it had a global spread.

Objective: 1. To study the viral load (cycle threshold value) of COVID 19 patients with the clinical severity of the disease.

2. To assess various clinical and biochemical parameters in COVID 19 patients according to their clinical severity.

3. To correlate the association of Ct value of COVID 19 patients with their clinical and biochemical parameters in accordance to their clinical severity.

Aim: To study the correlation of viral load with clinical and biochemical parameters of COVID-19 patients.

Material and Methods: Our study was a cross-sectional, retrospective single center study, where 200 COVID-19 admitted patients were divided into three groups in accordance to their cycle threshold (Ct)values collected from reverse transcription polymerase chain reaction (RT-PCR). Those groups were 1 (9-20), group 2 (21-30) and group 3 (31-36). The correlation of COVID-19 Ct value with biochemical parameters and clinical presentation (taken as mild, moderate and severe) was done and analyzed. The chi-square test was used for the correlation and calculated by using SPSS V-26.0 (IBM Corp, Armonk, NY). P value<0.05 was considered significant statistically. One way analysis of variance (Anova) was used as statistical test of significance to compare each biochemical parameter with different Ct value based groups.

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Results: Clinical groups (mild, moderate and severe) correlated with different Ct values in all the three groups (p value<0.05). All the biochemical parameters like albumin, bilirubin, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, procalcitonin (PCT), total leucocyte count (TLC) were analyzed and showed a significant p value (<0.05) in all the three groups. However, alanine transaminase (ALT) and aspartate transaminase (AST) did not show any statistically significant association in the groups studied.

Conclusion: The severity of the disease was statistically significant (p<0.05) in the Ct value groups. Biochemical parameters like albumin, bilirubin, CRP, D-dimer, PCT and TLC were also statistically significant. All these parameters can be used as a prognostic indicator to monitor disease progression in COVID-19 patients.

Key words: COVID-19, cycle threshold, viral load, RT-PCR.

Introduction:

A novel corona virus, designated as the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) was first identified in Wuhan, China in December 2019 [1] which is an enveloped positive-sense single-stranded RNA virus belonging to genus *Betacoronavirus* from *Coronaviridae* family [2]. Since then cases are rapidly spreading globally and it was declared a global pandemic by WHO in 2020 [3]. COVID-19 has a diverse clinical spectrum and most of infected individuals have only a mild or subclinical disease especially in early stage of the disease [4]. Co morbidities such as advanced age, diabetes, hypertension and cardiovascular diseases [5] are also associated with severeness of the disease.

Real-time reverse transcription-polymerase chain reaction (RT-PCR) is the mainstay of molecular diagnosis of COVID-19 which detects the viral RNA from the clinical sample. Here we encompass the utility of Ct values of RT-PCR which is the number of amplification cycles that are needed by the target gene to exceed a certain threshold level. These values are inversely proportional to viral load and can be indirectly used for quantifying the virus [6].

According to ICMR guidelines, COVID-19 disease has been clinically divided into Mild (upper respiratory tract symptoms with or without fever), Moderate (breathlessness but oxygen saturation >90% on room air), Severe (oxygen saturation <90% on room air) [7].

COVID-19 patients have deranged biochemical parameters like increase in CRP levels, raised aminotransferases and LDH, raised D-dimer among others[7]

Our study aims to assess the correlation of viral load of COVID-19 with clinical and biochemical parameters among mild, moderate and severe cases which may help in performing early appropriate clinical intervention.

Material and Methods:

Place of the study: Department of Microbiology, Rajshree Medical Research Institute and Hospital, Bareilly.

Study design: Cross-sectional retrospective study.

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Study period: 12 months from January 01, 2021 to December 30, 2021.
Sample size: 200.
Study population
Inclusion criteria: Confirmed RT-PCR positive patients (Ct value $\leq$ 36 for COVID-19) along with available biochemical and clinical data were included in the study.
Exclusion criteria: Suspected COVID-19 patients with negative RT-PCR report were excluded from the study.
The information of patients such as demographic, clinical and laboratory details were collected retrospectively from hospital records system and analyzed. Institutional Ethical committee permission was obtained to conduct the study.
RT-PCR for COVID-19:
SARS-CoV-2 was detected by RT-PCR at the molecular laboratory of Microbiology Department which is a Bio-Safety Level- II laboratory.
NP/OP samples were subjected to manual nucleic acid extraction. The amplification and detection of viral RNA were performed on Quant Studio 5 molecular system (Applied Biosystems, Waltham, Massachusetts). The molecular detection is based on the principle of RT-PCR, which simultaneously amplifies and detects two genes – Envelope (E) gene and RNA dependent RNA Polymerase (RdRp) gene. The fluorescent channels FAM and CY5 were used to detect E and RdRp gene respectively whereas VIC channel was used to detect the fluorescent signal of internal control (IC).
The thermocycler protocol for RT-PCR assay was as followed: Reverse transcription at 50 ^{0}C for 15 minutes, initial denaturation at 95 ^{0}C for 3 minute, denaturation at 95 ^{0}C for 10 seconds, annealing, extension and fluorescent signal collection at 60 ^{0}C for 30 seconds.
On the basis of Ct values, the patients were divided into three groups (Table 1).

Group	Ct value
1	9-20
2	21-30
3	31-36

Table 1: Ct values groups
Ct: cycle threshold
Clinical categories
Mild disease: Patients with upper respiratory tract symptoms with or without fever.
Moderate disease: Patients who had fast breathing, breathlessness but oxygen saturation $\geq$90% on room air.
Severe disease: Patients with oxygen saturation <90% on room air.
Laboratory parameters:
The patients were tested for the following biochemical parameters:
1. Biochemistry parameters: Total bilirubin, CRP, LDH, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), pro-calcitonin tests were performed on serum samples

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taken from COVID-19 RT-PCR positive patients. All biochemical tests were carried out on the automated clinical chemistry analyzer (Transasia Diagnostics, Mumbai, India).

2. Hematological parameters: Total leucocyte count (TLC) was obtained from whole blood sample by semiautomated cell counter and D-dimer were tested on plasma samples by semi automated biochemistry analyzer (BeneSphera, Avantor materials, Gurgaon, India) from COVID-19 RT-PCR positive patients

Statistical analysis:

Data on clinical and biochemical parameters, including total bilirubin, CRP, LDH, albumin, ALT, AST, pro-calcitonin, TLC, D-dimer were demonstrated as mean $\pm$ standard deviation. Chi-square test was used for the correlation and calculated by using SPSS V-26.0 (IBM Corp, Armonk, NY). P value<0.05 was considered significant statistically. One way analysis of variance (Anova) was used as statistical test of significance to compare each biochemical parameter with different Ct value based groups.

Results:

In this study, a total of 200 patients were included and divided into three groups.

Group 1 (Ct value 9-20) (n=50)

In this group, we observed 52% (n=26) male patients were infected with COVID-19 as compared to 48% female patients (n=24) (Fig1). All patients in this group have been classified clinically into mild (n=13, 26%), moderate (n=20, 40%) and severe (n=17, 34%) (Table 2). Whereas blood biochemistry parameters were ALT (68.90 ± 35.59), AST (56.28 ± 11.707), albumin (39.96 ± 4.76), CRP (39.67 ± 20.40), total bilirubin (1.03 ± 0.7), LDH (441.38 ± 174.31), D-dimer (1.55 ± 0.80), PCT (0.25 ± 0.22) and TLC (9.64 ± 2.34) (Table 3).

Group 2 (Ct value 21-30) (n=100)

This group's male patients were 60% (n=60) as compared to female patients 40% (n=40) (Fig1). Clinically both mild and moderate category accounted for 43% (n=43) and severe was 14% (n=14) (Table 2).. Whereas blood biochemistry parameters were ALT (62.37 ± 29.418), AST (56.02 ± 14.19), albumin (38.99 ± 4.36), CRP (32.12 ± 25.16), total bilirubin (0.83 ± 0.58), LDH (393.82 ± 158.7), D-dimer (0.99 ± 0.58), PCT (0.13 ± 0.2) and TLC (5.89 ± 1.44) (Table 3).

Group 3 (Ct value 31-36) (n=50)

In this group, the male patients were 54% (n=27) as compared to female patients 46% (n=23) (Fig1). Clinically they were classified into mild (52%, n=26), moderate (46%, n=23) and severe (2%, n=1) (Table 2). Whereas blood biochemistry parameters were ALT (55.48 ± 21.27), AST (53.92 ± 12.4), albumin (37.24 ± 6.11), CRP (24.05 ± 17.11), total bilirubin (0.66 ± 0.31), LDH (339.78 ± 102.75), D-dimer (0.68 ± 0.49), PCT (0.08 ± 0.13) and TLC (6.32 ± 1.5) (Table 3).

In our study, co morbidities like diabetes, hypertension and chronic obstructive pulmonary disease were observed among patients of three Ct value groups but no significant association was found between various co morbidities and disease severity.

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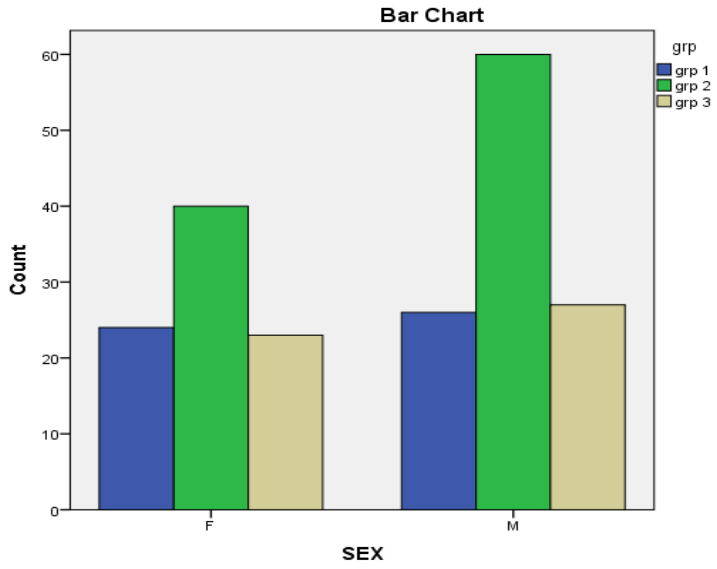

Fig1: Showing sex distribution among three groups

Table 2: Showing correlation between Ct value groups and Clinical groups

		Group 1(n=50)	Group 2(n=100)	Group 3(n=50)
Ct Value		9 to 20	21 to 30	31 to 36
Mean Ct value	E gene	17.78± 2.06	25.76± 2.52	32.72± 1.32
	RdRp gene	18.93± 0.96	27.26± 2.21	33.84± 1.66
Clinical groups	Mild	13 (26%)	43 (43%)	26 (52%)
	Moderate	20 (40%)	43(43%)	23 (46%)
	Severe	17 (34%)	14 (14 %)	1 (2%)
	p-value	0.001	0.021	0.001

Table 3: Showing various biochemical parameters among three Ct value groups (n=200)

Group		WBC X 10 ^3/µL	TBIL(mg/dL)	ALBUMIN(g/L)	AST(U/L)	ALT(U/L)	LDH(U/L)	D-dimer(ug/ml)	CRP(mg/L)	PCT(ng/ml)
Gr 1	Mean	9.64	1.034000	39.96	56.28	68.90	441.38	1.552000	39.674000	.259400
	N	50	50	50	50	50	50	50	50	50

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	Std. Deviation	2.345	.7072828	4.768	11.707	35.595	174.310	.8051467	20.4031891	.2262598
	Mean	5.89	.830000	38.99	56.02	62.37	393.82	.990000	32.120000	.131600
Gr 2	N	100	100	100	100	100	100	100	100	100
	Std. Deviation	1.442	.5868078	4.364	14.191	29.418	158.786	.5824886	25.1640396	.2084416
	Mean	6.32	.662000	37.24	53.92	55.48	339.78	.686000	24.052000	.083000
Gr 3	N	50	50	50	50	50	50	50	50	50
	Std. Deviation	1.518	.3116055	6.113	12.403	21.272	102.755	.4985735	17.1148729	.1352285
	Mean	6.93	.839000	38.79	55.56	62.28	392.20	1.054500	31.991500	.151400
Total	N	200	200	200	200	200	200	200	200	200
	Std. Deviation	2.332	.5795328	5.024	13.142	29.607	154.674	.6985842	22.8107106	.2074275

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Table 4: ANOVA Table showing correlation of biochemical parameters with Ct values in the three groups (n=200)

Biochemical parameters			Sum of Squares	df	Mean Square	F	Sig.
WBC X 10 ^3/µL	Between Groups	(Combined)	493.965	2	246.982	82.721	.000
	Within Groups		588.190	197	2.986		
	Total		1082.155	199			
TBIL(mg/dL)	Between Groups	(Combined)	3.476	2	1.738	5.404	.005
	Within Groups		63.360	197	.322		
	Total		66.836	199			
ALBUMIN(g/L)	Between Groups	(Combined)	192.565	2	96.282	3.927	.021
	Within Groups		4830.030	197	24.518		
	Total		5022.595	199			
AST(U/L)	Between Groups	(Combined)	181.560	2	90.780	.523	.594
	Within Groups		34189.720	197	173.552		
	Total		34371.280	199			
ALT(U/L)	Between Groups	(Combined)	4504.030	2	2252.015	2.611	.076
	Within Groups		169932.290	197	862.600		
	Total		174436.320	199			
LDH(U/L)	Between Groups	(Combined)	258588.880	2	129294.440	5.657	.004
	Within Groups		4502287.120	197	22854.249		
	Total		4760876.000	199			
D-dimer(ug/ml)	Between Groups	(Combined)	19.581	2	9.790	24.876	.000
	Within Groups		77.535	197	.394		
	Total		97.116	199			
CRP(mg/L)	Between Groups	(Combined)	6104.475	2	3052.237	6.171	.003
	Within Groups		97440.901	197	494.624		
	Total		103545.376	199			
PCT(ng/ml)	Between Groups	(Combined)	.856	2	.428	10.946	.000
	Within Groups		7.706	197	.039		
	Total		8.562	199			

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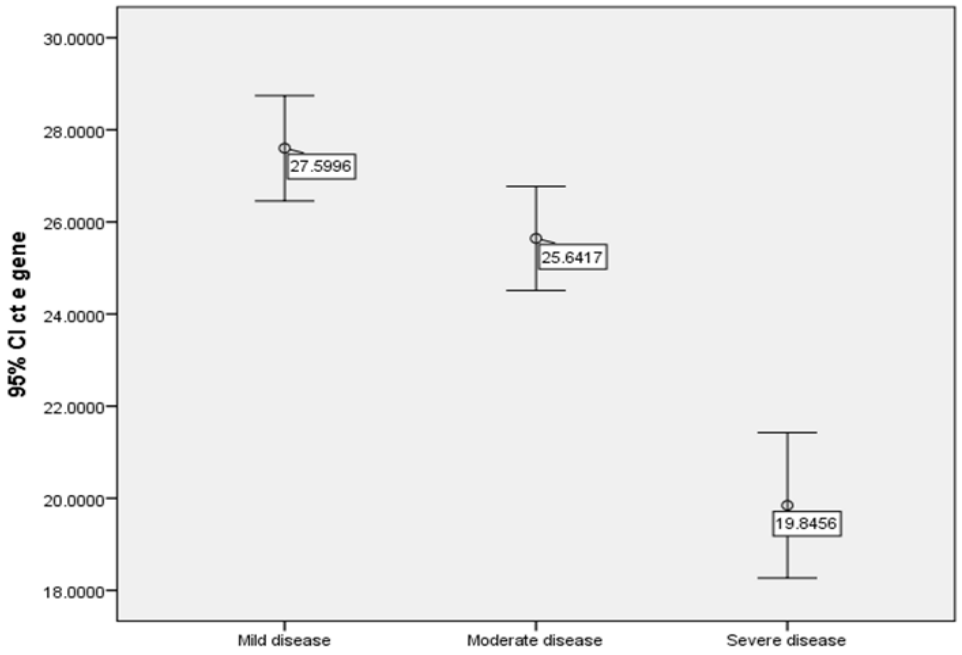

Figure 2: Whisker plot showing distribution of Ct (E gene) values among clinical groups

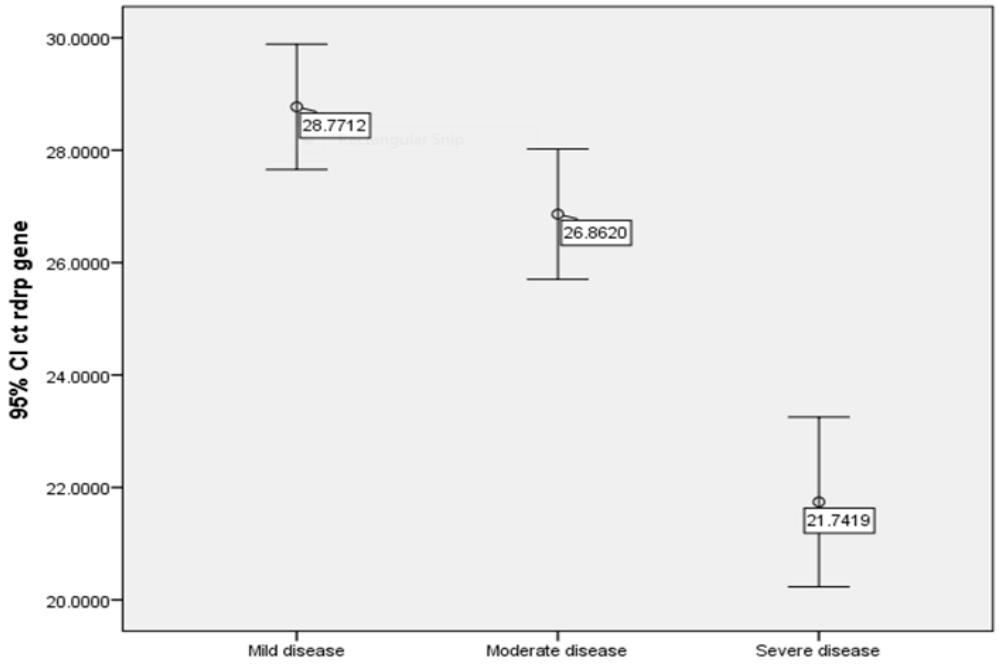

Figure 3: Whisker plot showing distribution of Ct (RdRp gene) values among clinical groups

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Discussion

Despite the fact that, qualitative reporting of SARS-CoV-2 RT-PCR is done by most of the laboratories but the reporting of Ct values will help the clinicians for better management of patients. Inversely proportional relationship between Ct values and viral load has been reported in various literatures. In this study, we aimed at finding out the correlation between Ct values of COVID-19 RT-PCR with disease severity and biochemical parameters.

Clinical presentation

It was noticed that all the three groups with different Ct values had significant p-value in terms of clinical presentation as shown in table 2, figure 2 and figure 3. This suggested that the disease advancement in these patients has a direct correlation with the viral load. This is in accordance with studies like Huang et al[8] and Filho et al[9] who reported lower Ct values in patients with severe disease.

Describing the Ct value of SARS-CoV-2 RT-PCR depends upon multiple factors like the type of sample collected, timing of sample collection and sample transportation[10]. Limited data are available for the relationship between viral load and factors attributing to severe disease.

Co morbidity

In our study, no significant association was found between various co-morbidities and disease severity. This is not in accordance with studies like Wang et al[4] and Dan Wang et al[11] which reported that co morbidities are observed in severe category of COVID-19 patients than mild to moderate category. This is attributed to paucity of clinical data from patients.

Biochemical and hematological parameters

Our study exhibited that both hematological and biochemical markers had correlation with Ct values.

Pattern of ALT, AST and albumin in three Ct value-based groups

Biochemical parameters like ALT, AST, bilirubin and albumin can predict the severity of COVID-19 patients as reported by Mardani et al.[12] ALT and AST are marker of liver damage which gets elevated in COVID-19 patients. In the present study, ALT and AST both showed a downward trend from low Ct value based groups to high Ct value-based groups (Fig 4). This is in concordance with study of Zhang et al [13] which reported elevated AST and ALT levels in COVID-19 patients. However, the correlation of these two enzymes with Ct values were found to be statistically insignificant ($p>0.05$) in this study (Table 4).

Most of the critically ill COVID-19 patients are having a systemic inflammation including liver damages and also are exposed to adverse drug reactions. As a result, serum albumin level is decreased in them.

Present study showed that albumin in all three Ct value-based groups presented as mean ± standard deviation in its normal range from 35-50 g/L and it was statistically significant association (p value<0.05) (Table 4).. This is in accordance with studies like Atique et al[10] and Li J et al[14].

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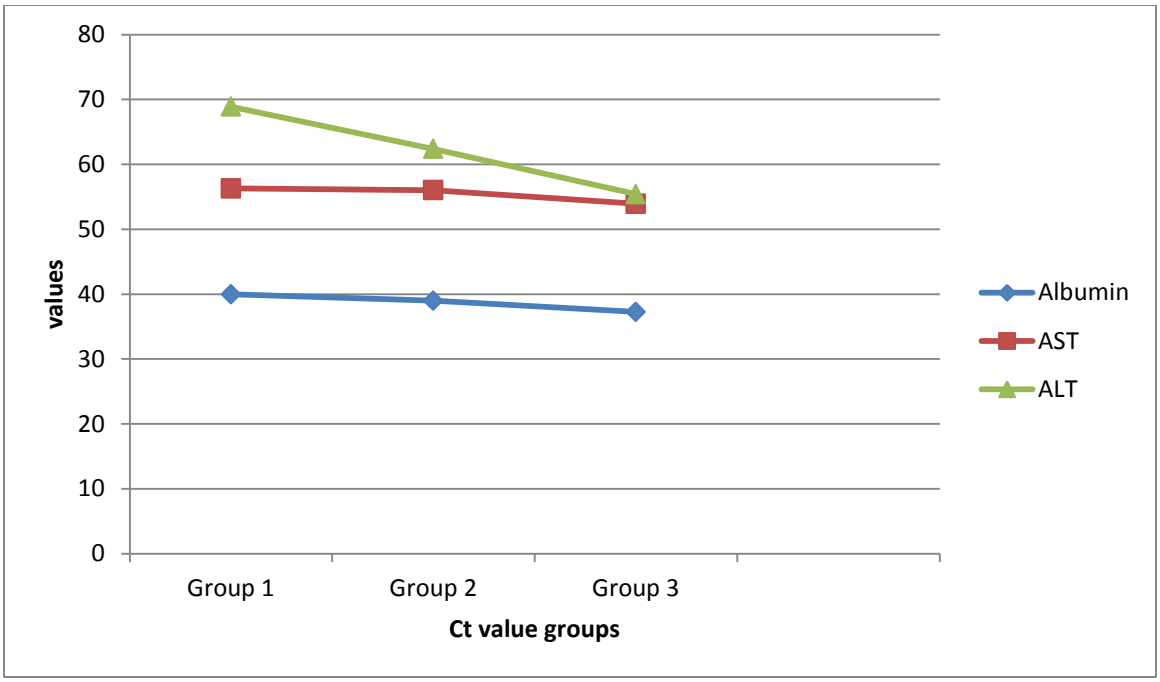

Fig 4: Correlation of AST, ALT and albumin with viral load in three groups

Pattern of TLC and bilirubin

In accordance with study of Selim S[15], our study also found that TLC was normal at the initial phase of the disease and TLC were significant in all the three groups studied ($p<0.05$) (Table 4). However, there was no significant trend change seen among different groups (Fig 5). This is not correlating with the findings of Liu J et al[16] and Anurag A[17] et al who concluded that lymphopenia was observed in severe COVID-19 pateints.

Bilirubin gets elevated in liver injury and hemolysis. Hence, it is an abnormal diagnostic biochemical parameter in COVID-19 patients [18].

In this study, bilirubin showed a decreasing trend among different groups and was significantly associated with disease severity (p value <0.05) (Table 4) (Fig 5).This finding is correlating with studies like Liu Z et al[19].

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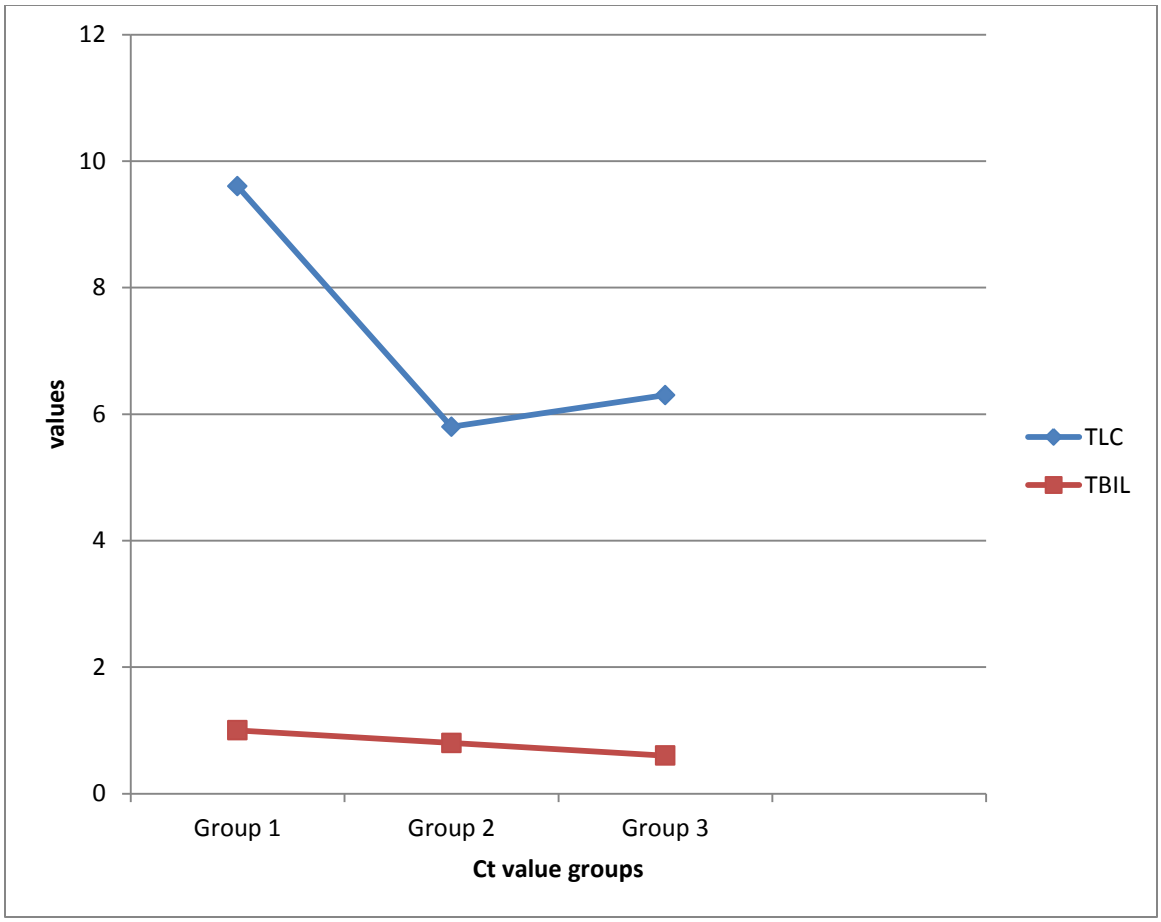

Fig 5: Correlation of total leucocyte and bilirubin with viral load in three groups

Pattern of LDH and D-dimer

LDH (isoenzyme 3) is the major biochemical marker present in lungs which is responsible for lung damage. LDH level is usually increased in COVID-19 patients[20]. In our study, significant association was found between LDH and disease severity in all groups (p value<0.05) (Table 4). LDH also showed a decreasing trend among different groups (Fig 6).

D-dimer being a fibrin breakdown product has a correlation with pro-inflammatory cytokines[21] in critically ill patients of COVID-19. In the present study, D-dimer values showed downward trend from group 1 to 3 (Fig 6). We observed a significant association (p value<0.05) as well (Table 4).

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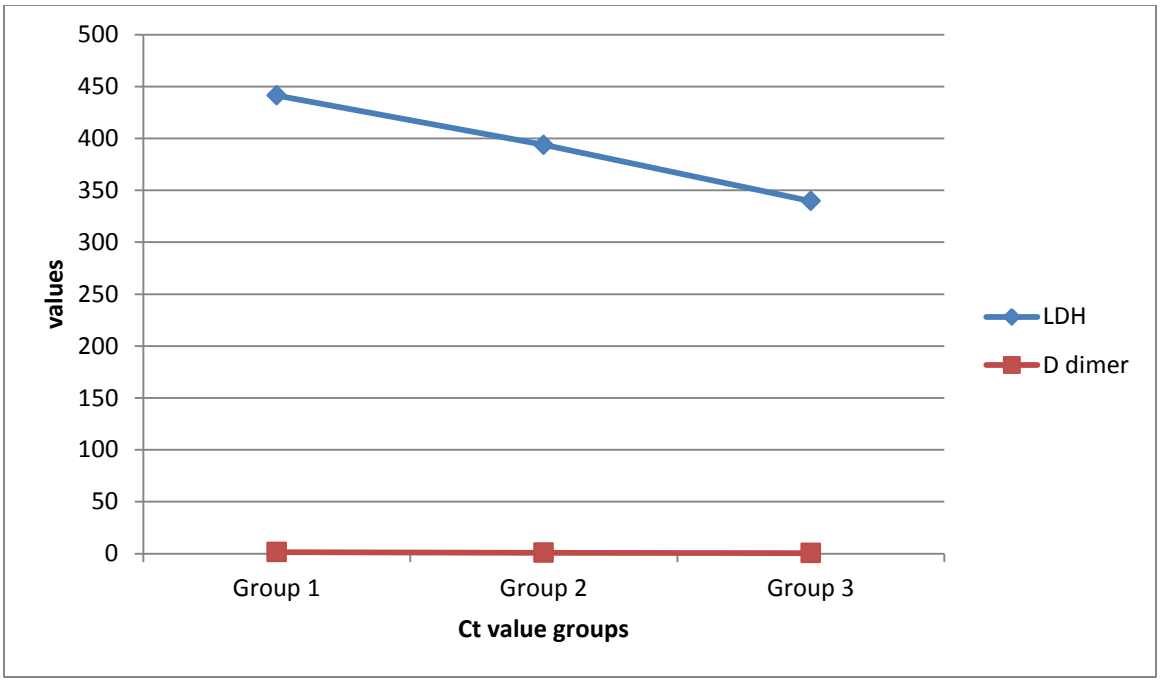

Fig 6: Correlation of biochemical parameters like LDH and D-dimer with viral load in three groups

Pattern of PCT and CRP

Procalcitonin (PCT) level in serum is elevated in systemic inflammatory response, Bacterial infection, and fungal infections. Whereas viral infections do not contribute to rise in PCT [22]. In this study, mean values of serum PCT were found to be higher in all the three groups and were significant (p value <0.05) (Table 4) which is similar with the findings of studies like Atique et al[10] and Wang et al[11]. A high level of PCT value suggests the possibility of multiple infections in COVID-19 patients. PCT values also showed a downward trend from group 1 to 3 (Fig 7).

In COVID-19 patients CRP is considered a specific marker of inflammation. In studies like Yang et al[23] and Warusevitane et al[24] they have a strong correlation of CRP with disease severity and lung damage in COVID-19 patients. In current study, mean values of CRP were found high in all three groups and showed significant values (p value <0.05) (Table 4).

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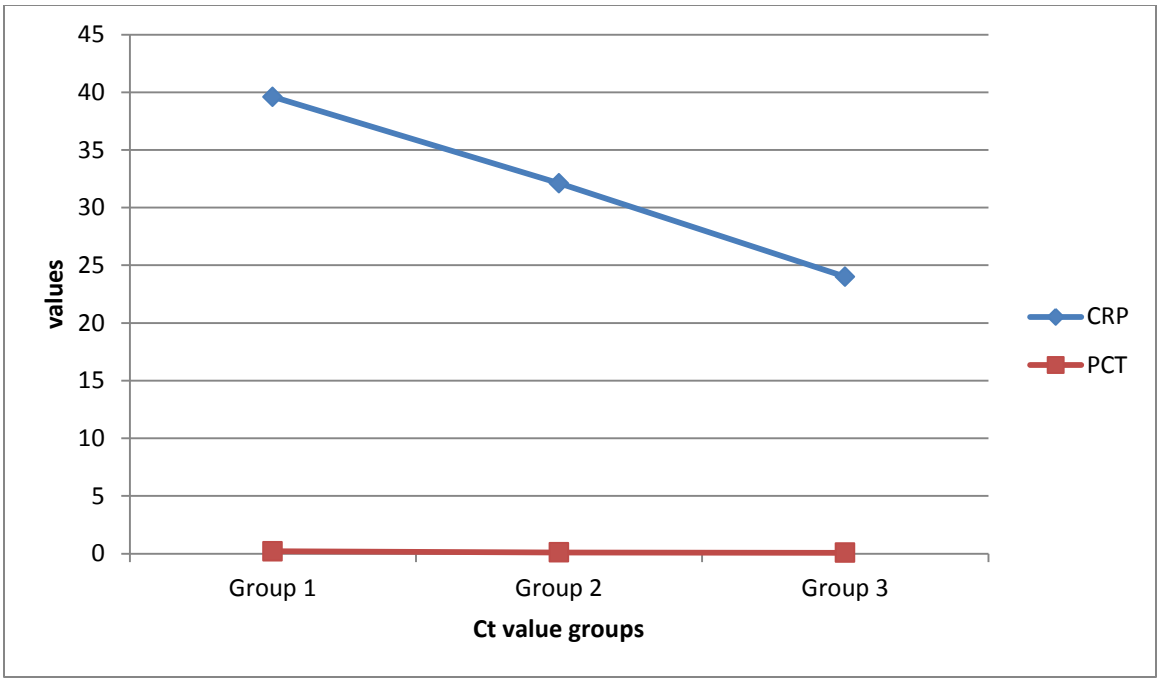

Fig 7: Correlation of biochemical parameters like CRP and PCT with viral load in three groups

Conclusion: Our study showed that the severity of the disease was statistically significant ($p<0.05$) in the Ct value groups. Biochemical parameters like albumin, bilirubin, CRP, D-dimer, PCT and TLC were also found to be statistically significant. Hence all these parameters can be used as a prognostic indicator to monitor disease progression in COVID-19 patients.

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