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Evaluation of CRP Titre in Cases of Covid-19 at the time of Hospitalization and its Correlation with RT-PCR Curve time (Viral Load), Disease Severity and Outcome

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Abstract

Background: The global pandemic coronavirus disease 2019 due to SARS-CoV2 is a highly contagious and deadly disease; therefore, early identification of severe forms is absolutely essential for timely triaging of patients. The aim of our study was to assess significance of CRP titre with disease severity and outcome at the time of hospitalization.

Methods: This hospital based prospective cross sectional study was done on consecutive cases of COVID-19 confirmed by RT-PCR. The clinical evaluation, laboratory findings and radiological assessment were done to classify the patients into mild, moderate and severe category. Association between CRP titre and various clinical, haematological and biochemical parameters and severity of COVID-19 disease were evaluated.

Results: A total of 188 patients (mean age 54.58±16.6 years and M: F 2.68:1) were evaluated. Sex, comorbidities like Hypertension and Diabetes, Duration of illness, hospital stay, neutrophil, lymphocyte, N-L ratio, RDWcv, SpO2 level and lung lesion (HRCT chest score), oxygen requirement, mechanical ventilator support, inflammatory markers (LDH, D-dimer and IL-6) and outcome were significantly correlated with high CRP titre. Compared with survived patients, the non-survived patients had much higher level of CRP (mean 81.89±61.69 vs43.20 ± 39.66, p-value <0.0001). Regression analysis showed that CRP was significantly associated with high morbidity and mortality in COVID-19 patients, with an area under curve of 0.705 (p-value - 0.031, 85% sensitivity and 34% specificity) and an optimal threshold value of 16.15mg/L.

Conclusions: Our study shows that CRP titre is simple, rapid and effective serological inflammatory marker to predict morbidity and mortality in COVID-19 cases.

Keywords: CRP titre; COVID-19; SARS-CoV2; RT-PCR; SpO_2; HRCT.

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Introduction

During this COVID-19 pandemic worldwide, more than 240 millionpeople got infected and more than 50 lakh deaths have happened. According to the WHO interim guidance[1], the clinical manifestations of COVID-19 disease are heterogeneous, including severe and non-severe forms. The management of patients is therefore adapted to the severity of the clinical situation. The majority of infected persons are not severely affected and can recover without medical intervention, whereas a small number of cases need to be carefully treated and hospitalized in an intensive unit.[2,3]

The biological analysis, especially the inflammatory and hematologic one, represents a major tool in the diagnosis[4], and in the detection of severe forms.[5] Many prognosis factors including lymphocyte count, lactate dehydrogenase, IL-6, procalcitonin, and CRP were evaluated[6], but the predictive power of each of these indicators in disease classification and prognosis remains largely unclear. Previous studies have indicated that the aberrant host immune response and cytokine storm may play an important role in the severity of COVID-197.

CRP is an acute-phase protein that serves as an early marker of inflammation or infection. The CRP serum level is routinely measured in early diagnosis of pneumonia[8], and some Chinese publications have reported the prognosis value of CRP.[9] The pathological and physiological processes and diagnostic methods of COVID-19 are still in the exploratory stage. Clinical monitoring and appropriate treatment strategies were essential to improve case fatality. Therefore this prospective study is planned to assess significance of CRP level with diseases severity and outcome and its correlation with viral load (CT value) at the time of hospitalization.

Material and Methods

This prospective cross sectional study was conducted in the Department of Medicine, S.P. Medical College & Associated Group of P.B.M. Hospitals, Bikaner on cases of COVID-19 confirmed by RT-PCR admitted in dedicated COVID-19 Hospital. The study was approved by institutional ethical committee. Written informed consent was taken from all subjects or their legal guardians before enrolling for the study.

Inclusion Criteria

- All the consequent cases of COVID-19 confirmed by RT-PCR and admitted in dedicated COVID hospital.
- Patient giving consent to participate in the study.

Exclusion Criteria

- Patients not giving informed consent.

Clinical Protocol

All patients were evaluated as per Proforma. A detailed clinical history, physical examination, and Laboratory investigations including complete blood count, renal function test, liver function test, blood sugar, chest X-ray, CRP titre was done in all cases. Other investigations like D-Dimer, LDH, IL-6, HRCT Thorax, ABG analysis was done as when required. SpO_2 was taken in all the cases using pulse oxymeterand cases were classified depending on severity (Mild: >94; Moderate: 90–93; Severe: <90).[10] Cases were also classified according to HRCT Chest score (Mild: 1–7; Moderate8–17; Severe: 18–25).[11] CRP was done using Turbidimatric method.[12] We also classified cases according to CRP titer (Mild: >6–20 mg/L; Moderate: >20–40 mg/L; Severe :> 40 mg/L).[13]

Data Analysis

Data analysis was done in terms considering objectives of the study using descriptive and inferential statistics frequency and percentage distribution was done to analyse demographic variables. P value of <0.05 was considered significant. Values were represented in terms of mean and standard deviation and linear regression. Appropriate statistical analysis was applied as when required using SPSS software for statistics version 16.0 or above.

Results

We studied 188 cases suffering from COVID-19 confirmed by RT-PCR admitted in dedicated COVID hospital during the period from 1st July 2020 to 31st Dec 2020. Out of them 137 (72.87%) were male and 51 (27.13%) were female (M: F 2.68:1). The mean age of the patients was 54.58±16.6 and majority of patients (37.77%) were in the age group of 41-60 years followed by 61–80 years (36.17%). We found that CRP titre was raised (>6mg/L) in 161 (85.63%) cases at the time of hospitalization. There was statistically significant difference in mean age of patients having CRP greater than 40.0 mg/l. We also found significantly large number of males having highly elevated CRP (76.71%-56 cases) in comparison to

females (23.28% -16 cases). We found positive correlation of CRP titer in relation to age, sex, day of admission after symptom onset (duration of illness before hospitalization), and hospital stay (p<0.0001) as shown in table 1.

Majority of patients had symptoms of fever (89.36%) followed by breathlessness 76.06%, other symptoms were loss of appetite (55.85%), cough with Sputum (39.36%), fatigue/malaise and altered taste (32.44%), sore throat (27.13%), body ache (25.53%), dry cough (23.4%), anosmia (19.68%) and headache (18.62%) etc. The mean BMI was 27.05 Kg/m^2 with majority (48.40%) were overweight followed by 28.19% had normal BMI and 21.81% were obese. 3.72% were smoker, 3.19% alcoholics and 1.06% were tobacco chewer. Majority (90.96%) of the cases were vegetarian.

Table 1: Distribution of cases according to CRP titer in relation to various demographic and Clinical parameters.

CRP titre	Age (Mean± SD)		Gender	DOA after symptoms	Duration of illness	Hospital stay (days)	Oxygen reqirement	Outcome
	Male	Female	M/F	Mean±SD	Mean± SD	Mean±SD	Yes(%)	Death(%
Normal (0-6) (N=27)	43.33±16.72	51.16±10.81	21/6	7.30±3.06	10.81±4.75	5.33±3.55	7(25.9%)	1 (3.70%)
Mild (>6-20) (N=51)	53.36±16.83	48.83±16.68	33/18	5.78±3.87	13.71±4.73	7.94±3.85	17(33.3%)	3(5.88%)
Moderate(>20-40) (N=37)	56.11±15.08	52.8±16.9	27/10	5.11±3.17	15.97±3.55	11.40±3.27	20(54.0%)	3(8.11%)
Severe (>40) (N=73)	61.53±15.73	55.82±14.73	56/17	4.62±3.36	17.19±4.12	14.56±7.63	44(60.2%)	13(17.8%)
P-value	0.0112*	0.0345*	0.03*	0.005*	<0.0001*	0.0034*	<0.0001*	<0.0001*

Our study shows severity of hypoxemia (as measured by SpO_2) at the time of hospitalization was having linear correlation with CRP titre as shown in figure 1 and oxygen requirement was also higher in patients with higher CRP titre. 60.27% cases who were having CRP titre>40 mg/L required oxygen support. We also found that as HRCT score (lung lesion) increases mean CRP titre was also increased although mean CRP titre was highest in moderate category. While evaluating CRP titre with severity of COVID-19 according to HRCT score we found that mean CRP titre was 33.50±80.72 in mild category, 55.49±46.82 in moderate category and 45.62±35.17 in severe category (p<0.0001) as shown in figure 1.

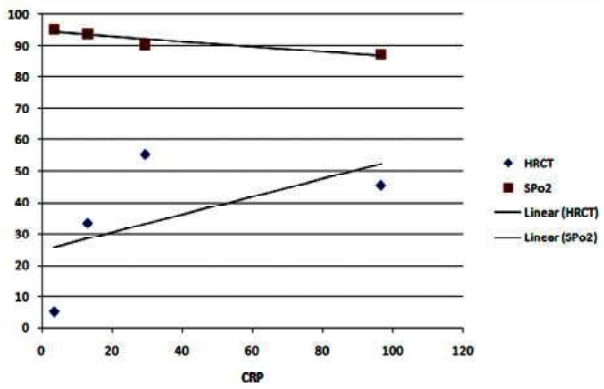

Fig. 1: Association of CRP with SpO2 and HRCT.

Analysis of various Hematological parameters showed that neutrophil count, lymphocyte count and neutrophil lymphocyte ratio (NLR) were significantly correlated with CRP titre (p<0.05). Analysis of various Biochemical parameters showed that Blood Urea, Serum Creatinine, SGOT, SGPT and ALP Level weresignificantly correlated with CRP titre (p<0.001) as shown in table 2.

Table 2: Association of CRP with various hematological and biochemical parameters.

	Normal (0-6) (N=27)		Mild (>6-20) (N=51)		Moderate (>20-40) (N=37)		Severe (>40) (N=73)		P-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
HB	13.10	2.38	12.29	2.15	12.86	2.32	12.47	1.99	0.3462
TLC	7487.41	3418.28	10346.47	13379.45	7967.86	4434.50	10269.68	6582.80	0.2378
MON	438.47	337.56	503.29	639.57	396.39	310.91	417.64	418.99	0.6920
NEU	5009.11	3172.61	6779.47	4687.14	5887.62	4206.18	7770.60	5115.44	0.035*
LYM	2088.04	971.26	3844.35	355.02	1473.30	806.41	1799.30	705.35	<0.0001*
HCT	37.32	4.66	37.58	4.61	37.78	7.47	38.08	6.77	0.6886
RDWcv	16.28	5.74	17.75	8.83	17.04	9.01	16.83	6.69	0.3421

Table to be cont....

PLT	2.55	0.84	2.35	1.00	2.05	0.81	2.39	0.92	0.3019
NLR	2.87	2.24	3.96	2.06	5.53	3.92	7.40	6.37	<0.0001*
NMR	21.56	22.90	46.69	182.92	72.13	215.31	30.09	28.41	0.3882
RBS	146.15	59.00	146.13	64.49	155.78	57.22	153.48	71.81	0.1231
Urea	35.70	20.97	46.24	21.38	69.10	41.62	53.14	25.27	0.0059*
Creatinine	1.11	0.65	1.3	1.29	1.98	2.55	234	0.75	0.002*
SGOT	47.05	23.82	59.44	34.84	53.34	34.54	100.37	95.81	0.0091*
SGPT	49.34	19.97	51.01	31.09	54.23	62.10	85.04	97.86	0.0050*
Total Protein	6.21	0.67	6.30	1.13	6.36	0.70	6.34	0.80	0.3288
Albumin	3.82	0.35	3.60	0.79	3.71	0.48	3.61	0.56	0.6712
Total Bilirubin	0.89	0.20	0.93	0.26	0.99	0.50	1.01	0.36	0.4011
Direct Bilirubin	0.36	0.19	0.40	0.25	0.45	0.24	0.45	0.23	0.3433
ALP	148.26	83.8	170.73	84.6	178.36	90.01	205.73	92.76	0.0105*

We also found that higher CRP titre was correlated with higher RDWcv in non survived patients (p<0.05) as shown in Table 3.

Table 3: Association of RDWcv with CRPat the time of Hospitalization.

	RDWcv				
	Survived		Non-survived		P-value
	Mean	SD	Mean	SD	
<6 (Normal)	16.40	5.82	13.2	-	0.015*
6-20 (Mild)	17.49	8.58	21.83	14.01	0.049*
21-40 (Moderate)	16.78	9.12	20	8.66	0.049*
>40 (severe)	16.01	5.07	20.64	11.12	0.0013*

Hypertension and Diabetes Mellitus were the commonest comorbidities present in our cases (57 cases each, 30.22%). Mean CRP titre of patients with Hypertension was significantly high (71.57±45.01, p< 0.013) and similarly it was also significantly highin patients with Diabetes Mellitus (69.55±48.08, p<0.021) in comparison to patients with no comorbidities (47.59±63.19).

Patients who were having other comorbidities like IHD, COPD, Tuberculosis and Thyroid disorder were not having statistically significant difference in CRP titre. CRP titre was significantly related with requirement of Oxygen, mechanical ventilator support and poor outcome. The cut off value of CRPtitre was 63.62 for patients who required oxygen and 174.65 for the patients who required mechanical ventilation.

The mean CRP titre was significantly high in patients who died as compared to survived patients. (81.89±61.69 vs43.20±39.66, p<0.0001) as shown in Table 4.

Table 4: Association of CRP with comorbidities, oxygen requirement, mechanical support andoutcome.

	Mean±SD	p value
Co-morbidity		
Diabetes–N=57 (30.32%)	69.55±48.08	0.0211*
Hypertension–N=57 (30.32%)	71.57±45.01	0.0135*
Ischemic Heart Disease–N=13 (6.91%)	53.36±48.84	0.3411
Chronic Obstructive Pulmonary		
Disease – N=10 (5.32%)	62.63±46.71	0.1229
Tuberculosis – N=8 (4.26%)	62.23±47.52	0.1892
Thyroid disorder – N=8 (4.26%)	39.56±46.39	0.1892
No co-morbidity	47.59±63.19	–
Ventilation		
(NC/FM)	55.14±5.16	
NRBM	55.77±65.58	
Non-Invasive (BiPAP)	57.11±55.71	0.0001*
Invasive	70.81±63.13	
Outcome		
Non-Survived (N=20)	81.89±61.69	0.0001*

A total of 20 cases (10.63%) died out of them 13 (65%) were having CRP >40 mg/L as compare to 1(5%) death in normal range CRP, 3 (15%) deaths each in mild and moderate CRP range. 73 cases (38.82%) were having CRP greater than 40 mg/L and all of them required oxygen support, 46.67 required oxygen via NC/FM, 19.22% via NRBM, 34.11% required non-invasive ventilation (BiPAP) and during the course 82.35% of them required invasive mode of ventilation (mechanical ventilation).

Regression analysis of CRP with LDH, D-dimer and IL6 were also significantly correlated as shown in

figure 2 with p-value of <0.013, <0.0003 and <0.0001 respectively.

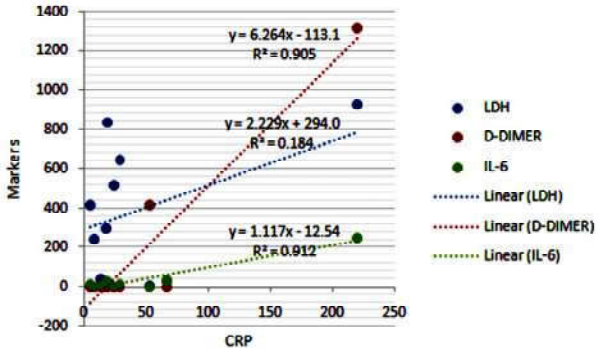

Fig. 2: Association of CRP with other inflammatory markers (LDH, D-dimer and IL-6).

We found that as per RT-PCR report low CT value which is suggestive ofhigh viral load was associated with higher CRP titre as shown in Table 5.

Table 5: Association of CRP level with CT value at the time of hospitalization.

CT-Value	CRP Mean±SD	0-6 (27)	>6-20 (51)	>20-40 (37)	>40 (73)
17 (7)	106.01±169.84	1(14.28%)	1(14.28%)	—	5(71.42%)
18 (2)	71.80±98.41	—	1(50%)	1(50%)	—
19 (8)	64.89±35.82	—	1(12.5%)	1(12.5%)	6(75%)
20 (6)	56.38±65.36	1(16.6%)	1(16.6%)	1(16.6%)	3(37.5%)
21 (12)	54.14±51.62	1(8.33%)	4(33.33%)	3(25%)	3(25%)
22 (18)	41.22±47.58	4(22.22%)	5(27.78%)	1(5.55%)	8(44.44%)
23 (39)	40.27±61.70	5(12.82%)	11(28.20%)	7(17.94%)	16(41.02%)
24 (31)	40.26±40.50	5(16.12%)	10(32.25%)	5(16.12%)	11(35.48%)
25 (15)	38.79±34.33	2(13.33%)	5(33.33%)	2(13.33%)	6(40%)
26 (20)	33.99±47.01	5(25%)	4(20%)	7(35%)	4(20%)
27 (11)	32.98±22.85	—	6(54.54%)	3(27.27%)	2(18.18%)
≥28 (19)	19.75±1.06	3(15.78%)	2(10.52%)	5(26.31%)	9(47.36%)

The AUC of CRP for adverse outcome prediction were 0.705 (p=0.031). We found a cut off value of 16.15 of CRP at 85% sensitivity and 34% specificity to predict adverse outcome like longer hospital stay, increase morbidity and mortality as shown in table 6; figure 3.

Area	0.705
P-value	0.031*
cut-off	16.15
Sensitivity	85%
Specificity	34%

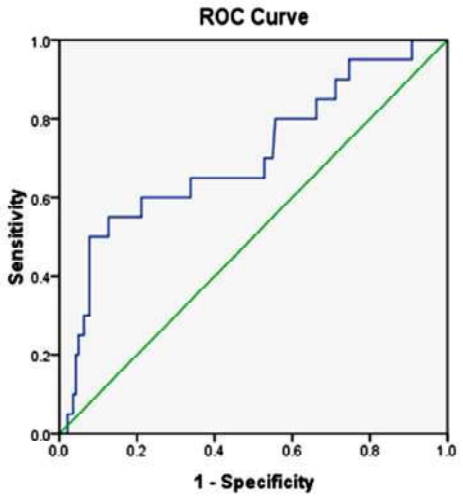

Fig. 3: ROC analysis of CRP with outcome.

Diagonal Segments are produced by ties.

Discussion

The present global pandemic of COVID-19 has brought serious burden to the medical health system. It is essential to identify COVID-19 patients who might become severely ill atearly stage, which would greatly facilitate to manageaccordingly for improvement in the prognosis of patient.

As in SARS–CoV and MERS–CoV infection, several pro inflammatory cytokines and interferon are increased and CRP is a known non-specific acute phase reactant protein induced by IL-6 in the liver and sensitive biomarker of inflammation, infection and tissue damage,so, this study was planned to evaluate any correlation between the CRP titre and COVID-19 disease severity and its outcome.

The mean age of our patients was 54.58+16.6 years, more than 74% patients were above the age of 40 years with male preponderance. Similar observation has been made by previous workers Huang et al[14] studied 415 laboratory-confirmed COVID-19 patients, the mean age was 54.1 years with half (217, 52.3%) of all patients were male. Cheng et al[15] reported mean age of 50.4 years with 27.3% females and 72.7% males. Zhu et al[16] reported mean age of patients was 50.9 years with 64.6% females and 35.4% males. Liu et al[17] reported mean age of 56 years with 57.15% females and 42.9% males.

The clinical character of these patients indicated that the age, sex and underlying diseases were the most important risk factor for disease severity. We found that CRP titre was higher in males in comparison to females and the mean age of male patients in severe CRP titre was 61.53+15.73 and of female was 55.82+14.73. Among the underlying

diseases, the most common were hypertension and diabetes (30.22% each). Huang et al[14] concentrated on that patients showed comorbidities, including hypertension (48.28%), diabetes (20.69%), constant obstructive pneumonic infection (51.72%). Wang et al[18] reported that 39.7% had hypertension followed by 21.4% had diabetes, 10.7% had cardiovascular illness. Yang et al[19], Zhou et al[20] and Guan et al[21] revealed that Diabetes is the third most common fundamental comorbidity in COVID-19 patients.

The main pathological changes of COVID-19 are lung and immune system damage shown by hypoxemia (measured by SpO2 level) and lung lesion by HRCT score.[22] In our study we found linear correlation of CRP with SpO2 level and HRCT score ($p<0.0001$). Chen et al[23] also reported that when the CT evaluating expanded from gentle to direct, the CRP fixation expanded 11.47 mg/L ($p=0.029$); while when CT reviewing expanded from gentle to serious, CRP focus expanded 23.40 mg/L ($p=0.025$). Ali N[24] saw that patients with low oxygen immersion ($SpO2 \leq 90\%$) had essentially more significant levels of CRP (middle 76.5mg/L) contrasted and patients with high oxygen immersion ($SpO2 \geq 90\%$) (middle 12.7mg/L), demonstrating that more extreme patients with lung harm have raised degrees of CRP.

The exact pathogenesis of COVID-19 is although poorly understood but its seems to be a result of systemic inflammatory response syndrome demonstrated by rise in the proinflammatory cytokines like LDH, IL6, D-dimer, procalcitonin.[25] In our study we found linear correlation of CRP with IL6 ($p<0.0001$), D-dimer ($p<0.0003$) and LDH ($p<0.013$). Luo et al[26] concentrated on that as perhaps the most particular intense stage reactant, CRP can increment quickly after the beginning of aggravation, cell harm or tissue injury. Pneumonic illnesses with provocative components for the most part raise serum CRP level in light of fiery cytokines, for example, IL-6, IL-1. Huang et al[14] found that D-dimer level on affirmation were higher in ICU patients. In another study Guan et al[27]described that C-responsive protein (CRP) was raised in 60.7% of patients, raised lactate dehydrogenase (LDH) in 41% of patients. More serious cases showed a more stamped increment contrasted and the non extreme ones (81.5% versus 56.4% for CRP, and 58.1% versus 37.2% for LDH).

In our study very high CRP titre was associated with high mortality ($p<0.0001$). Similarly Gao et al[28] revealed that patients with more serious indications had on normal CRP grouping of 39.4mg/L and patients with gentle manifestations CRP centralization of 18.8mg/L. CRP was found at expanded levels in the extreme gathering at the underlying stage than those in the gentle gathering. In another study, by Mo et al[29] the mean centralization of CRP was essentially higher in extreme patients (46mg/L) than non severe patients (23mg/L) (BN-21). The patients who died from COVID-19 had around 10 overlay more significant levels of CRP than the recuperated patients (middle 100 versus 9.6mg/L).[30] Tan et al[31] also showed that around 7.7% of non severe COVID-19 patients were advanced to extreme sickness courses after hospitalization and contrasted with non severe cases, the irritated patients had altogether higher centralizations of CRP (middle 43.8 versus 12.1mg/L). Regression analysis showed that CRP was significantly associated with aggravation of non severe COVID-19 patients, with an area under curve of 0.705

(p-0.031, 85% sensitivity and 34% specificity) and an optimal threshold value of 16.15mg/l.Luo et al[26] discovered the AUC of CRP for unfavourable result forecast was 0.832 ($p<0.001$) with a remove worth of 56.3, CPR showed affectability 81.3%, particularity 71.4%. Sharifpour et al[32] concentrate on ROC bend investigations exhibited middle CRP esteems during the whole hospitalization had a moderate discriminative ability to anticipate mortality (AUC= 0.83). This probably mirrors a roof for the relationship between CRP levels and mortality.

Conclusion

Thus, our study shows measurement of CRP titre at the time of hospitalization is very important to predict morbidity and mortality in cases of COVID19. Higher CRP titre was associated with longer hospital stay, oxygen requirement, mechanical ventilator support and poor outcome.

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