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# Role of CRP in COVID-19 pneumonia: A single-center experience of 1000 cases in a tertiary care setting in India

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## Abstract

### Introduction

Robust data are available for C-reactive protein (CRP) in bacterial infection, and it can be used in this coronavirus disease 2019 (COVID-19) pneumonia pandemic for initial assessment before planning of treatment in indoor settings in comparison with other inflammatory markers and computed tomography (CT) severity.

### Materials and methods

A prospective, observational, follow up study was conducted that included 1000 COVID 19 cases confirmed with RT PCR. All cases were assessed with lung involvement documented and categorized based on high resolution computed tomography (HRCT) thorax, oxygen saturation, and inflammatory markers such as CRP at the entry point and follow up. Age, sex, comorbidities, use of BIPAP/NIV (Bi-level positive airway pressure/Non-invasive ventilation), and outcomes such as with or without lung fibrosis as per HRCT severity were key observations. Statistical analysis was done using  $\chi^2$  test.

### Results

Age (<50 and >50 years) and sex (male versus female) had a significant association with CRP in predicting severity ( $P < 0.00001$  and  $P < 0.010$ , respectively). CT severity score at the entry point with CRP level had a significant correlation ( $P < 0.00001$ ). CRP level had a significant association with duration of illness ( $P < 0.00001$ ). Comorbidities had a significant association with CRP level ( $P < 0.00001$ ). CRP level had a significant association with oxygen saturation ( $P < 0.00001$ ). BIPAP/NIV requirement during hospitalization had a significant association with CRP level ( $P < 0.00001$ ). Timing of BIPAP/NIV requirement had a significant association with CRP level. ( $P < 0.00001$ ). Follow-up CRP titer during hospitalization as compared with the entry point normal and abnormal CRP levels showed a significant association in post-COVID lung fibrosis ( $P < 0.00001$ ).

### Conclusion

CRP is an easily available and universally acceptable inflammatory marker and documented to play a very crucial role in predicting timings of interventions and post-COVID lung fibrosis.

**Keywords:** COVID-19 pneumonia, CRP, inflammatory marker, oxygen saturation

## INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, originally emerged from China, has documented (as on 24 december 2021) 274628461 confirmed cases and 5358978 deaths globally, and 34752 164 confirmed cases 478007 deaths in India [1]. The current practical guidelines stating recommendations on the use of molecular,

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serological, and biochemical tests in disease diagnosis and management in COVID-19 disease have been developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Task Force [2,3]

The laboratory of Oswald Avery first documented C-reactive protein ('CRP') as an inflammatory protein released in serum of patients with acute infections and later on labeled it as 'acute-phase reactant.' Robust data are available regarding its role in infections, inflammatory, ischemic and traumatic tissue injuries, and malignancy, and the advent of sensitive quantitative immunoassays in the 1970s greatly enhanced its clinical utility. In 1974, Kaplan and Volanakis[4] and Siegel *et al.*[5] reported the 'pro-inflammatory' role of CRP.

COVID-19 pneumonia is a heterogeneous disease with variable effects on lung parenchyma, airways, and vasculature, leading to long-term effects on lung functions. Although lung is the primary target organ involvement in COVID-19, many patients had shown pulmonary and extrapulmonary manifestations of diseases variably during the first and second waves, which occurred as a result of pathophysiological effects of immune activation pathway and direct virus-induced lung damage. In COVID-19, pneumonia pathophysiology constitutes different pathways like immune activation, inflammatory, thrombogenic, and direct viral affection to lungs and extrapulmonary tissues [6,7]. CRP can be used as a marker of inflammation in COVID-19 pneumonia [8]. CRP can be used as an inflammatory marker and can help in analyzing infective and noninfectious causes, surgical, postoperative, and inflammatory conditions such as rheumatoid, gout, and venous thromboembolism [9–12]. Data on CRP in severe H1N1 viral pneumonia are available [13], and a number of recent series have reported an association between CRP and COVID-19 disease severity [8,14–19].

In the present study, we have used CRP as a basic marker in laboratory panel workup in all COVID-infected patients and analyzed it as a core marker during follow-up in all admitted patients to assess response to therapy and predictor of post-COVID fibrosis as a dismal outcome of this pandemic of pneumonia in a tertiary care setting.

## MATERIALS AND METHODS

A prospective, observational, follow-up study was conducted during July 2020 to May 2021 in MIMS Medical College, Latur, and Venkatesh Hospital, Latur, India, and included 1000 COVID-19 cases confirmed with RT-PCR to find out the role of CRP in predicting severity of illness and assessing response to therapy and outcomes such as post-COVID fibrosis in diagnosed COVID-19 pneumonia cases admitted in the critical care unit. A total of 1000 cases were enrolled in study after IRB approval, and written informed consent of all included cases was taken at the respective center of study in Venkatesh Hospital and MIMS Medical College, Latur. This study was approved by the Institutional Review Board/Ethics Committee at Venkatesh Hospital and Critical Care Center, Latur, India,

and MIMS Medical College, Latur, India. Approval number: VCC/10-2020-2021, and approval date: 01/07/2020

**Inclusion criteria:** COVID-19-infected patients, confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, including those with comorbidities and irrespective of severity and oxygen saturation were included in the study.

**Exclusion criteria:** those not willing to give consent, not able to perform D-dimer, and not willing to remain in follow-up were excluded.

All study cases underwent following assessment before enrolling in the study:

- (1) COVID-19 RT-PCR test was performed in all cases; if first test results were negative and radiological features clearly documented pneumonia, we repeated the RT-PCR test and enrolled all cases with positive COVID-19 RT-PCR test results. RT-PCR test was performed on nasopharyngeal samples collected with all standard institutional infection control policies.
- (2) High-resolution computed tomography (HRCT) thorax was done to assess severity of lung involvement and categorized as mild if score less than 7, moderated if score 8–15, and severe if score greater than 15 or 15–25.
- (3) Clinical parameters with oxygen saturation and respiratory system examination were assessed.
- (4) Laboratory parameters such as hemoglobin, renal functions, blood sugar level, liver functions, and ECG were recorded.
- (5) Viral inflammatory markers like CRP, lactate dehydrogenase, and interleukin-6 were assessed at entry point and repeated whenever required during the course of illness. Normal and abnormal parameter readings were considered as per the pathological laboratory standard.
- (6) Entry point CRP titer was utilized as the assessment tool of severity of illness with clinical parameters.
- (7) If CRP analysis was normal at the entry point, then CRP titer was repeated on the day of discharge from hospital or done during hospitalization if clinical course deteriorated.
- (8) If CRP analysis was abnormal at the entry point, we repeated it every 72 h as follow-up to assess severity and progression of illness, and also, the titer level was used to assess response to medical treatment.
- (9) Follow-up HRCT thorax was done after 12 weeks or 3 months of discharge from hospital for analysis of post-COVID lung fibrosis in selected cases with abnormal D-dimer level at discharge and required BIPAP/NIV during hospitalization and cases required oxygen supplementation at home.

## Methodology

A total of 1190 COVID-19 RT-PCR cases admitted in Venkatesh Hospital (390 cases) and MIMS Medical College (800 cases) were enrolled.

However, 190 cases were excluded (168 cases excluded owing to not willing to follow-up till 12 weeks of study and death of 22 cases).

Triaging of 1000 cases with complete analysis with HRCT thorax, inflammatory marker CRP, oxygenation saturation was done and hospitalization was done in indoor units and intensive care units accordingly.

CRP follow-up titers were used to analyze severity assessment. Oxygen saturation, ventilator support requirement, and timings of ventilator application were recorded.

CRP follow-up titers were used to analyze clinical outcome. Clinical parameters and improvement or deterioration in association with CRP follow-up titers were monitored.

CRP follow-up titers were correlated with follow-up HRCT thorax to analyze its association with the final radiological outcomes as post-COVID lung fibrosis at 12 weeks of discharge from hospital.

#### Methodology of CRP titer assessment: immunoturbidimetry

Normal values: normal values were up to 6 mg/l.

#### Interpretation of results

- (1) Negative: value up to 6 mg/l.
- (2) Positive: value above 6 mg/l.
- (3) Significant: fourfold raised CRP value, that is, greater than 24 mg/l.
- (4) Highly significant: sixteen-fold raised values, that is, 96 mg/l.
- (5) Follow-up significance: values raised or decreased in two-to-fourfold change.

#### Statistical analysis

The statistical analysis was performed using Chi-square test in R-3.4 is available as a Free Software under the terms of the (Free Software Foundation's GNU General Public License in source code form, Vienna, Austria). Significant values of  $\chi^2$  were seen from probability table for different degree of freedom required. P value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

## RESULTS

In present study, 1000 COVID-19 pneumonia cases confirmed by COVID-19RT-PCR were included. Males were 650 and females were 350 cases. Age greater than 50 years represented 600 cases and age below 50 represented 400 cases. CT severity score at the entry point showed a significant correlation with CRP level ( $P < 0.00001$ ) (Table 1). CRP level showed a significant association with duration of illness (DoI) ( $P < 0.00001$ ) (Table 2). A significant association was documented between CRP and variables in COVID-19 pneumonia cases such as age, sex, diabetes mellitus, ischemic heart disease (IHD), hypertension, chronic obstructive pulmonary disease, and obesity ( $P < 0.00001$ ) (Table 3). CRP level had a significant association with oxygen saturation ( $P < 0.00001$ ) (Table 4). BIPAP/NIV requirement during the course of COVID-19 pneumonia in the critical care setting had a significant association with CRP level ( $P < 0.00001$ ) (Table 5). Timing of BIPAP/NIV requirement during the course of COVID-19

**Table 1: Correlation of CT severity (at entry point) and CRP in COVID-19 cases (n=1000)**

CT severity	Normal CRP (n=320)	Abnormal CRP level (n=680)	Analysis
<8 score (n=300)	190	110	$\chi^2=224.87$ $P<0.00001$
9-15 (n=300)	90	210	
>15 (n=400)	40	360	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography.

**Table 2: Duration of illness (DoI) at entry point during hospitalization and CRP level in COVID-19 pneumonia cases (n=1000)**

Duration of illness	Normal CRP (n=320)	Abnormal CRP (n=680)	Analysis
<7 days (n=340)	30	310	$\chi^2=185.65$ $P<0.00001$
8-15 days (n=460)	160	300	
>15 days (n=200)	130	70	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

**Table 3: Other variables and CRP level in COVID-19 pneumonia cases (n=1000)**

COVID-19 RT-PCR positive (n=1000)	CRP level normal (n=320)	CRP level abnormal (n=680)	Analysis
Age>50 years (n=600)	140	460	$\chi^2=51.77$ $P<0.00001$
Age<50 years (n=400)	180	220	
Male sex (n=650)	190	460	$\chi^2=6.5$ $P<0.010$
Female sex (n=350)	130	220	
Diabetes mellitus (n=600)	150	450	$\chi^2=33.77$ $P<0.00001$
Without diabetes (n=400)	170	230	
Hypertension (n=210)	160	50	$\chi^2=238.55$ $P<0.00001$
Without hypertension (n=790)	160	630	
COPD (n=150)	100	50	$\chi^2=97.46$ $P<0.00001$
Without COPD (n=850)	220	630	
IHD (n=200)	110	90	$\chi^2=60.77$ $P<0.00001$
Without IHD (n=800)	210	590	
Obesity (n=160)	20	140	$\chi^2=33.28$ $P<0.00001$
Without obesity (n=840)	300	540	

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IHD, ischemic heart disease.

pneumonia in the critical care setting had a significant association with CRP level ( $P < 0.00001$ ) (Table 6). Follow-up CRP titer during hospitalization as compared with the entry point abnormal CRP had a significant association in post-COVID lung fibrosis ( $P < 0.00001$ ) (Table 7). There was

**Table 4: Oxygen saturation at entry point and CRP level in COVID-19 pneumonia cases (n=1000)**

Oxygen saturation	Normal CRP level (n=320)	Abnormal CRP level (n=680)	Analysis
>90% (n=210)	110	100	$\chi^2=60.37$ $P<0.00001$
75-90% (n=490)	150	340	
<75% (n=300)	60	240	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

**Table 5: Correlation of BIPAP use with CRP level in COVID-19 pneumonia cases (n=1000)**

BIPAP/NIV	Normal CRP (n=320)	Abnormal CRP level (n=680)	Analysis
BIPAP/NIV required (n=600)	155	445	$\chi^2=26.21$ $P<0.00001$
BIPAP/NIV not required (n=400)	165	235	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

**Table 6: BIPAP/NIV initiation time at entry point and CRP level COVID-19 pneumonia cases (n=600)**

BIPAP used (n=600) with duration of illness	Abnormal CRP level (n=290)	Fourfold raised CRP level (n=310)	Analysis
Entry point <1 day (n=180)	110	70	$\chi^2=31.30$ $P<0.00001$
3-7 days (n=310)	150	160	
After 7 days (n=110)	30	80	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

**Table 7: Abnormal CRP level at entry point (n=680) and follow-up and its correlation with post-COVID lung fibrosis**

Post-COVID pneumonia fibrosis	CRP titer increased/ abnormal at entry point (n=400)	CRP titer fourfold increased during follow-up (n=280)	Analysis
Pulmonary fibrosis present (n=210)	40	170	$\chi^2=198.45$ $P<0.00001$
Pulmonary fibrosis absent (n=470)	360	110	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

a significant association between follow-up CRP titer during hospitalization and the entry point normal CRP in post-COVID lung fibrosis ( $P < 0.00001$ ) (Table 8).

## DISCUSSION

### Correlation of CT severity (at the entry point) and CRP in COVID-19 cases

In the present study, there was a significant correlation between CT severity score at the entry point and CRP level in COVID-19

pneumonia cases; with scores less than 8, 8–15, and greater than 15, the documented normal and abnormal CRP levels were 190 and 110, 90 and 210, and 40 and 360, respectively, of the total 1000 study cases ( $P < 0.00001$ ). We have documented CT severity as the best visual marker of COVID-19 pneumonia severity, which can be correlated with inflammatory marker CRP. Various authors have documented similar observations in their study [20–27]. Best ‘visual marker’ of severity of illness is CT thorax, and we have documented CRP as a stronger inflammatory marker associated with it. Numerous authors have documented similar observation [28–30]. We have documented usefulness of CRP and CT severity in triaging the cases and proper use of interventions in indoor setting according to ‘clinical, radiological, and inflammatory marker panel’ in our institute. Huang *et al.*[30] observed a similar role in their study.

### DoI at entry point during hospitalization and CRP level in COVID-19 pneumonia cases (n = 1000)

In present study, CRP level had a significant association with DoI in COVID-19 pneumonia cases; at DoI less than 7 days, 8–15 days, and more than 15 days of onset of symptoms, the documented normal and abnormal CRP levels were 30 and 310, 160 and 300, and 130 and 70, cases, respectively ( $P < 0.00001$ ). We have also documented that a proportionate number of cases with DoI less than 1 week or 7 days and many cases with DoI more than 2 weeks or 15 days had normal CRP level, whereas pneumonia cases between 7 and 14 days of illness had abnormal or raised CRP level. The rationale for this observation is not known. May be the inflammatory response pattern was different. Moreover, we have correlated CRP pattern with other inflammatory markers like interleukin-6 and D-dimer and documented that these two markers were increased in parallel to CRP. Our findings corroborate the results of various studies [31–33]. Raised CRP after second week of illness may indicate worsening of COVID-19 pneumonia or secondary bacterial infection, which will help clinician to formulate antibiotics policy accordingly and may indirectly guide in the management of these cases by assessing follow-up titers.

### Correlation of BIPAP use with CRP level in COVID-19 pneumonia cases (n = 1000)

In the present study, BIPAP/NIV requirement during the course of COVID-19 pneumonia in the critical care setting had a significant association with CRP level. Cases that received BIPAP/NIV were documented to have normal and abnormal CRP levels in 155 and 445 cases, and cases that did not receive BIPAP/NIV during hospitalization were documented to have normal and abnormal CRP levels 165 and 235 cases, respectively ( $P < 0.00001$ ). We have documented higher CRP levels in severe cases requiring ventilatory support than in nonsevere patients; thus, it will help in predicting severity timely and help in analyzing disease severity. Several authors [17,34–36] have documented similar observations in their studies and mentioned the role of CRP as a ‘biomarker of severity’ of COVID-19 pneumonia.

**Table 8: Normal CRP level ( $n=320$ ) at the entry point and follow-up and its correlation with post-COVID lung fibrosis**

Post-COVID pneumonia fibrosis	CRP normal at entry point and remained less than fourfold ( $n=120$ )	CRP titer fourfold increased during follow-up ( $n=200$ )	Analysis
Pulmonary fibrosis present ( $n=40$ )	5	35	$\chi^2=12.19$ $P<0.00048$
Pulmonary fibrosis absent ( $n=280$ )	115	165	

COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

### Correlation of oxygen saturation at the entry point and CRP level in COVID-19 pneumonia cases ( $n = 1000$ )

In present study, CRP level had a significant association with oxygen saturation in COVID-19 pneumonia cases. Cases with oxygen saturation greater than 90% were observed to have normal and abnormal CRP levels in 110 and 100, respectively; cases with oxygen saturation 75–90% were observed to have normal and abnormal CRP levels in 150 and 340 cases, respectively; and cases with oxygen saturation less than 75% were observed to have normal and abnormal CRP levels in 60 and 240 cases, respectively ( $P < 0.00001$ ). Various authors in their studies [18,37–39] have documented similar findings to our observation, mentioning that hypoxia is the best trigger of inflammation apart from infection and leads to significant rise in CRP level, that is, higher CRP indicates advanced disease with hypoxia.

### Correlation of BIPAP/NIV initiation time at entry point and CRP level in COVID-19 pneumonia cases ( $n = 600$ )

In present study, timing of BIPAP/NIV requirement during the course of COVID-19 pneumonia in critical care setting showed a significant association with CRP level. Cases that received BIPAP/NIV at entry point less than 1 day had abnormal and fourfold raised CRP levels in 110 and 70 cases, respectively; cases that received BIPAP/NIV after 3–7 days of hospitalization had abnormal and fourfold raised CRP levels in 150 and 160 cases, respectively; and cases that received BIPAP/NIV after 7 days of hospitalization abnormal and fourfold raised CRP levels in 30 and 80, cases, respectively ( $P < 0.00001$ ). Similar observations have been documented in various studies, that is, there was a positive correlation of CRP with ventilatory requirement and ARDS in these cases, and thus it will help in predicting ‘timing of ventilatory support’ requirement [19,40–44].

### Other important observations in this study

#### Correlation of abnormal CRP level at the entry point ( $n = 680$ ) and follow-up and its correlation with post-COVID lung fibrosis

In present study, there was a significant association between follow-up CRP titer during hospitalization and the entry point

abnormal CRP in post-COVID lung fibrosis ( $P < 0.00001$ ), that is, CRP titer increased or abnormal at the entry point in the presence or absence of pulmonary fibrosis represented 40 and 170 cases, respectively, and CRP titer fourfold increased during follow-up in the presence or absence of pulmonary fibrosis represented 360 and 110, cases, respectively. The rationale for similar observation is exaggerated inflammatory response owing to advanced lung inflammation and necrosis resulting in overproduction of inflammatory cytokines linked to elevated levels of CRP in severe patients with COVID-19. Cytokines had a ‘double-edge sword effect’, that is, cytokines have a protective role in controlling infection, whereas in the hyperactive state, cytokines caused exaggerated lung inflammation and lung parenchymal damage and resultant lung fibrosis. Liu *et al.*[45] observed similar findings in their study.

#### Correlation of normal CRP level ( $n = 320$ ) at entry point and follow-up and its correlation with post-COVID lung fibrosis

In present study, there was a significant association between follow-up CRP titer during hospitalization and the entry point normal CRP in post-COVID lung fibrosis ( $P < 0.00001$ ), that is, CRP at the entry point without a fourfold increase and CRP titer with fourfold increase during follow-up in the presence of pulmonary fibrosis were 5 and 35 cases, respectively, whereas CRP at the entry point without a fourfold increase and CRP titer with fourfold increase during follow-up in the absence of pulmonary fibrosis were 115 and 165 cases, respectively. We have documented progression in few cases with nonsevere illness, and we recommend follow-up titer has a crucial role in analyzing progression and preventing worsening in these cases. Yan *et al.*[46] in their retrospective analysis in Wuhan, China, documented similar findings.

#### Correlation of other variables and CRP level in COVID-19 Pneumonia cases

In present study, age of patient, that is, less than 50 years and above 50 years had a significant association in COVID-19 cases with normal and abnormal CRP level ( $P < 0.00001$ ). We have also documented sex of the included cases had a significant association in COVID-19 cases with normal and abnormal CRP level ( $P < 0.010$ ). Several authors [47–53] have documented similar findings in their study.

In the present study, comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, hypertension, IHD, and obesity had a significant association in COVID-19 cases with normal and abnormal CRP level ( $P < 0.00001$ ). Numerous authors [18,54–62] have documented similar observations in their studies.

## CONCLUSION

CRP is an easily available, sensitive, reliable, cost-effective, and universally acceptable inflammatory marker in COVID-19 pandemic. Correlating CRP with variables like DoI, oxygenation status, and timing of BIPAP/NIV at the entry

point is important to have satisfactory treatment outcome. CRP titer has significant associations with predicting progression of pneumonia, as a proportionate number of pneumonia cases with mild variety on CT thorax and normal initial CRP have progressed to critical course, which were documented with the help of rising titers, and we have documented follow-up rising titers to play a crucial role with other inflammatory markers. Rising CRP titers in the second week of illness indicate nosocomial bacterial infections and need targeted therapy accordingly. Moreover, decreasing CRP titers have very well been assessed and analyzed with improved oxygenation status and excellent response to treatment and decreased underlying inflammation.

CRP titer can help in predicting progression of COVID-19 pneumonia and assessing risk of post-COVID lung fibrosis if CRP titer is persistently high in these cases, and a proportionate number of cases with normal or abnormal CRP at entry point were predicted with underlying fibrosis or ongoing inflammation and necrosis of lung parenchyma if CRP was persistently high. CRP titer can guide antifibrotic treatment response in follow-up post-COVID care setting.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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