

Serial CRP (C-reactive protein) Monitoring in COVID-19 Pneumonia for the Assessment of Severity, Ventilatory Support Requirement and Predicting Early Lung Fibrosis

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Abstract:

Introduction: Robust data of CRP is available in bacterial infection, and now it can be utilized in Covid-19 pneumonia pandemic initial assessment of severity and planning of treatment.

Materials and methods: Multicentric, prospective, observational and interventional study conducted during July 2020 to May 2021 included 1000 Covid-19 cases confirmed with RT PCR. All cases were assessed with lung involvement documented and categorized on HRCT thorax, oxygen saturation, inflammatory marker as CRP at entry point and follow up. Age, gender, Comorbidity and use BIPAP/NIV and outcome as with or without lung fibrosis as per CT severity were key observations. Statistical analysis is done by using Chi square test.

Observations and analysis: Age (<50 and >50 years) and gender (male versus female) has significant association with CRP in predicting severity [$p < 0.00001$] & [$p < 0.010$] respectively. CT severity score at entry point with CRP level has significant correlation [$p < 0.00001$] CRP level has significant association with duration of illness (Doi) [$p < 0.00001$] Comorbidities has significant association with CRP level. [$p < 0.00001$] CRP level has significant association with oxygen saturation [$p < 0.00001$] BIPAP/NIV requirement during hospitalization has significant association with CRP level. [$p < 0.00001$] Timing of BIPAP/NIV requirement has significant association with CRP level. [$p < 0.00001$] Follow-up CRP titer during hospitalization as compared to entry point normal and abnormal CRP has significant association in post-covid lung fibrosis [$p < 0.00001$]

Conclusion: CRP is easily available and universally acceptable inflammatory marker in Covid-19 pandemic and 'serial titer' documented very crucial role in predicting severity of illness, need of ventilatory support and help in predicting post-covid lung fibrosis.

Key words: COVID-19 pneumonia, CRP, Oxygen saturation, Inflammatory marker



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Introduction:

The current pandemic of coronavirus disease 2019 (covid-19) caused by SARS-CoV-2, originally emerged from China, has documented 274,628,461 confirmed cases and 5,358,978 deaths globally, and 34,752,164 confirmed cases 478,007 deaths in India.¹ The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on COVID-19 has been established to synthesize up-to-date

information on the epidemiology, pathogenesis, and laboratory diagnosis and monitoring of Covid-19, as well as to develop practical recommendations on the use of molecular, serological, and biochemical tests in disease diagnosis and management.^{2,3}

The laboratory of Oswald Avery, who first demonstrated unequivocally that DNA is the genetic material, also characterized CRP as a protein with calcium-dependent binding to pneumococcal somatic C-polysaccharide. In addition, he introduced the term 'acute phase' for serum containing CRP from patients acutely ill with infectious disease. Robust data is available regarding its role in infections, inflammatory, ischemic, and traumatic tissue injuries, and malignancy, whilst the advent of sensitive quantitative immunoassays in the 1970s greatly enhanced its clinical utility. In 1974, Kaplan and Volanakis⁴ and Siegel et al.⁵ independently reported that CRP bound to C-polysaccharide and other ligands, and activated the classical complement pathway, and showed that CRP was thereby capable of mediating inflammation.

Covid-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Although Lung is the primary target organ involvement in corona virus disease-19 (Covid-19), many patients were shown pulmonary and extrapulmonary manifestations of diseases variably during first and second wave, which occurred as resultant 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}

The systemic inflammatory response to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a hallmark of the 2019 coronavirus disease (Covid-19), and most hospitalized patients with Covid-19 have abnormal inflammatory biomarkers.⁸ C-reactive protein (CRP), an acute-phase protein first described by Tillet and Francis,⁹ is synthesized by the liver in response to interleukin-6 (IL-6) and is a widely available biomarker of inflammation.^[10] Elevated CRP concentrations are associated with cardiovascular disease and acute kidney injury (AKI) in surgical patients,¹¹ with inflammatory rheumatic diseases such as rheumatoid arthritis and gout, and with incident venous thromboembolism (VTE) in community cohorts.¹² C-reactive protein has also been associated with severe disease in patients with H1N1 influenza pneumonia,¹³ and a

number of recent series have reported an association between CRP and Covid-19 disease severity.^{8,14-19}

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

Materials and methods:

Multicentric, prospective, observational and interventional study, conducted during July 2020 to May 2021, in MIMSR Medical College, Latur and Venkatesh Hospital Latur, India, included 1000 COVID-19 cases confirmed with RT PCR, to find out role of CRP in predicting severity of illness, assessing response to therapy and outcome as post-covid fibrosis in diagnosed covid-19 pneumonia cases admitted in critical care unit. Total 1000 cases were enrolled in study after IRB approval and written informed consent of patient.

Inclusion criteria: Covid-19 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 were undergone following assessment before enrolling in study:

1. Covid-19 RT PCR test performed in all cases, if first test results were negative and radiological features clearly documenting pneumonia, we have repeated RT PCR test and enrolled all cases with positive Covid-19 RT-PCR test.
2. HRCT Thorax to assess severity of lung involvement, and categorized as Mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25.
3. Clinical assessment as- vital parameters like heart rate, respiratory rate, blood pressure and documentation of respiratory adventitious sounds
4. Laboratory parameters- hemoglobin, renal functions, blood sugar level, liver functions, ECG
5. Viral inflammatory markers like CRP, LDH, IL-6 assessed at entry point and repeated whenever required during

course of illness. Normal and abnormal parameter readings were considered as per pathological laboratory standard.

6. Entry point CRP titer was utilized as assessment tool of severity of illness with clinical parameters.
7. If CRP analysis was normal at entry point, then CRP titer was repeated on day of discharge from hospital or done during hospitalization if clinical course deteriorates.
8. If CRP analysis was abnormal at entry point, we repeated on every 72 hours as follow up to assess severity, progression of illness and also titer level utilized to assess response to medical treatment.
9. Follow-up HRCT thorax was done after twelve 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 of CRP titer assessment: Immunoturbidimetry

Normal values: Normal values 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: four-fold raised CRP vale i.e., >24 mg/L
4. Highly significant: sixteen-fold raised values i.e., 96mg/L

5. Follow up significance: values raised or decreased in two-to-four-fold change

The statistical analysis was done using chi-squared test. Significant values of $\div 2$ 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.

Observations and analysis: In present study, 1000 covid-19 pneumonia cases confirmed by Covid-19 RT PCR, males were 650/1000 and females were 350/1000, age >50 were 600 cases and age <50 were 400 cases. CT severity score at entry point with CRP level has significant correlation [$p < 0.00001$] (Table 1) CRP level has significant association with duration of illness [$p < 0.00001$] (Table 2) Significant association in CRP and Covid-19 pneumonia has been documented with variables like age, gender, diabetes mellitus, IHD, Hypertension, COPD, Obesity [$p < 0.00001$] (Table 3) CRP level has significant association with oxygen saturation [$p < 0.00001$] (Table 4) BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with CRP level [$p < 0.00001$] (Table 5) Timing of BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with CRP level [$p < 0.00001$] (Table 6) Follow-up CRP titer during hospitalization as compared to entry point abnormal CRP has significant association in post-covid lung fibrosis [$p < 0.00001$] (Table 7) Follow-up CRP titer during hospitalization as compared to entry point normal CRP has significant association in post-covid lung fibrosis [$p < 0.00001$] (Table 8).

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	$\chi^2=224.87$
9-15 (n=300)	90	210	$p < 0.00001$
>15 (n=400)	40	360	

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	$\chi^2=185.65$
8-15 days (n=460)	160	300	$p < 0.00001$
>15 days (n=200)	130	70	

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)	Chi test value and P value
Age >50 years (n=600)	140	460	$\chi^2=51.77$
Age <50 years (n=400)	180	220	$p<0.00001$
Male gender (n=650)	190	460	$\chi^2=6.5$
Female gender (n=350)	130	220	$p<0.010$
Diabetes mellitus (n=600)	150	450	$\chi^2=33.77$
Without diabetes (n=400)	170	230	$p<0.00001$
Hypertension (n=210)	160	50	$\chi^2=238.55$
Without Hypertension (n=790)	160	630	$p<0.00001$
COPD (n=150)	100	50	$\chi^2=97.46$
Without COPD (n=850)	220	630	$p<0.00001$
IHD (n=200)	110	90	$\chi^2=60.77$
Without IHD (n=800)	210	590	$p<0.00001$
Obesity (n=160)	20	140	$\chi^2=33.28$
Without obesity (n=840)	300	540	$p<0.00001$

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	$\chi^2=60.37$
75-90% (n=490)	150	340	$p<0.00001$
<75% (n=300)	60	240	

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	$\chi^2=26.21$
BIPAP/NIV not required (n=400)	165	235	$p<0.00001$

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)	Four-fold raised CRP level (n=310)	Analysis
Entry point <1 days (n=180)	110	70	Chi test value 31.30
3- 7 days (n=310)	150	160	$p<0.00001$
After 7 days (n=110)	30	80	

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

Post-covid 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 test value 198.45
Pulmonary fibrosis absent (n=470)	360	110	p<0.00001

Table 8. Normal CRP level (n=320) at entry point and follow up and its correlation with post-covid lung fibrosis

Post-covid 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 test value 12.19
Pulmonary fibrosis absent (n=280)	115	165	p<0.00048

Discussion:**Correlation of CT severity (at entry point) and CRP in covid-19 cases**

In present study, CT severity score at entry point with CRP level has significant correlation in COVID-19 pneumonia cases, score <8, 8-15 and >15 documented normal and abnormal CRP level as in 190/110, 90/210 and 40/360 respectively of total 1000 study cases [p<0.00001] We have documented CT severity as best visual marker of covid-19 Pneumonia severity, which can be correlated with inflammatory marker CRP. Various authors have documented similar observation in their study.²⁰⁻²⁷ Our study showed correlation of CRP levels and the diameter of the largest lung lesion i.e., as CT severity increases, disease is progressed and documented with increased inflammatory marker. Numerous authors have documented similar observation. [28,29,30] 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 C et al [30] observed similar role in their study.

Duration of illness (Doi) at entry point during hospitalization and CRP level in COVID-19 pneumonia cases (n=1000)

In present study, CRP level has significant association with duration of illness (Doi) in covid-19 pneumonia cases, Doi <7 days, 8-15 days and >15 days of onset of symptoms documented normal and abnormal CRP levels in 30/310, 160/300 and 130/70 cases respectively. [p<0.00001] We have also documented that proportionate number of cases with duration of illness < 1 week or 7 days and many cases with duration of illness > two weeks or 15 days were having normal CRP level, while pneumonia cases between 7-14 days of

illness were having abnormal or raised CRP level. Rational for this observation is not known, may be inflammatory response pattern is different, and we have correlated CRP pattern with other inflammatory markers like IL-6 and D-dimer and documented that these two markers raised parallel to CRP. Our findings are collaborating with studies by various authors.^{31,32,37} 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 indirectly guiding in management of these cases by assessing follow-up titers.

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

In present study, BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with CRP level; cases received BIPAP/NIV during hospitalization were documented normal and abnormal CRP level in 155/445, 165/235 cases respectively [p<0.00001] We have documented higher CRP levels in severe cases requiring ventilatory support than in nonsevere patients, and suggesting that the CRP level may be a biomarker of disease severity and progression in patients with COVID-19.^{33,34,35,36} have documented similar observation in their studies and mentioned that CRP levels as a potential biomarker of the Covid-19 prognosis, and their results indicated that CRP concentrations remain high in expired patients and could be a promising biomarker for assessing mortality.

Correlation of Oxygen saturation at entry point and CRP level in Covid-19 pneumonia cases (n=1000)

In present study, CRP level has significant association with oxygen saturation in covid-19 pneumonia cases; cases with

oxygen saturation >90%, 75-90%, and <75% observed as normal and abnormal CRP level in 110/100, 150/340 and 60/240 cases respectively [p<0.00001] We have observed that patients with low oxygen saturation (SpO₂ ≤ 90%) had significantly higher levels of CRP compared with patients with high oxygen saturation (SpO₂ >90%), indicating that more severe patients with lung damage have elevated levels of CRP. So, higher levels of CRP indicate more severe disease course which indicates underlying severe lung inflammation and worse prognosis. Various authors³⁸⁻⁴¹ have documented similar observation in their studies.

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

In present study, Timing of BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with CRP level; cases received BIPAP/NIV at entry point <1 day, 3-7 days and after 7 days of hospitalization were documented significance in four-fold raised CRP level in 110/70, 150/160 and 30/80 cases respectively [p<0.00001] we have identified associations between CRP concentrations and respiratory failure requiring mechanical ventilation, with increased risk of acute respiratory distress syndrome (ARDS) reported in patients with higher CRP values as compared with those with lower CRP values, which is collaborating with studies⁴²⁻⁴⁷ by various authors.

Other important observation in this study:

Correlation of Abnormal CRP level at entry point (n=680) and follow up and its correlation with post-covid lung fibrosis

In present study, Follow-up CRP titer during hospitalization as compared to entry point abnormal CRP has significant association in post-covid lung fibrosis [p<0.00001] i.e., CRP at entry point to four-fold raised cases in presence or absence of pulmonary fibrosis were 40/170 and 360/110 cases respectively. Rational for similar observation is exaggerated inflammatory response due 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 fight against the microbes and helping in controlling infection but when the immune system becomes hyperactive, it can damage lung tissue. Thus, CRP production is induced by inflammatory cytokines and by tissue destruction in patients with Covid 19 finally resulting in lung fibrosis. Author Liu et al [48] observed similar finding 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, Follow-up CRP titer during hospitalization as compared to entry point normal CRP has significant

association in post-covid lung fibrosis [p<0.00001] i.e., CRP at entry point to four-fold raised cases in presence or absence of pulmonary fibrosis were 5/35 and 115/165 cases respectively. We have observed that, small proportion of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, we recommend that all health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality. Author Yan LA et al [49] 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 i.e., <50 years and >50 years has significant association in covid-19 cases with normal and abnormal CRP level [p<0.00001]. We have also documented gender of included cases has significant association in covid-19 cases with normal and abnormal CRP level [p<0.010] Authors,⁵⁰⁻⁵² have documented similar findings in their study.

In present study, comorbidity as Diabetes mellitus, COPD, Hypertension, IHD and obesity has significant association in covid-19 cases with normal and abnormal CRP level [p<0.00001] Numerous authors,⁵³⁻⁶² have documented similar observations in their studies.

Conclusions:

CRP is easily available and universally acceptable inflammatory marker in Covid-19 pandemic and documented crucial role in predicting severity of illness, especially follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating CRP with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome.

CRP titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial CRP has progressed to critical course and we have documented 'Serial' titers has played crucial role with other inflammatory markers, and many times in second week of illness rising titers indicates nosocomial bacterial infection and target therapy accordingly. Lastly, 'Serial' CRP titer can help in predicting progression of Covid-19 pneumonia, and assessing risk of post covid lung fibrosis.

Research quality and ethics statement-

This study was approved by the Institutional Review Board / Ethics Committee at Venkatesh Hospital and Critical Care Center Latur India and MIMSR Medical college Latur India,

(Approval #VCC/30-2020-2021; Approval date 10/07/2020). The authors followed the applicable EQUATOR Network (<http://www.equator-network.org/>) guidelines, specifically the Observational studies, STROBE Guidelines, during the conduct of this research project.

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