Original Research Article

C-Reactive Protein As An Effective Biologic Factor In Covid-19 Patients: An Evidence Based Study

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Abstract

Introduction: Coronavirus diseas-2019 (COVID-19) has been an emerging global health threat since its outbreak. The hospitalized COVID-19 patients are monitored regularly, but anytime they could develop mild and moderate symptoms into a severe disease course is challenging. However, early identification and diagnosis of the patients progressing to severity is essential to start a more relevant treatment that profoundly would help to improve the percentage outcomes of COVID-19 recovery. The present aims to investigate the serum C-reactive protein (CRP) levels in COVID-19 patients and its prognostic value. The C- reactive protein could prove to be an effective biologic factor in COVID-19 Patients.

Methods: After clinical examination of patients, routine blood investigation, for example CBC, KFT, LFT, serum electrolytes, D-dimer and CRP was done. The 5ml of peripheral blood was collected from each study subject, which was aliquoted in clot activator (Red top tube) vials until furhter processing. The separted serum was used for the crictical diagnostic estimation of CRP, using CS400 fully Automatic Biochemical Analyzer.

Results: The preliminary results have shown a significant difference in CRP levels in COVID-19 patients. Significantly, the severe patients had higher CRP levels than the moderate ones p-value < 0.05, also the COVID-19 infected patients who have under lying medical conditions had higher levels of CRP as compared to the patients who were having normal conditions prior to COVID-19 infection, p-value < 0.05.

Conclusion: The out come of the results indicate that the C- reactive protein could be an interesting molecule to determine early symptoms of COVID-19 Patients**.**

Keywords: COVID-19, CRP, shortness of breath, sore throat, fever, lung inflammation, biomarker.

Introduction

A novel Coronavirus (nCoV) or COVID-19, classified by the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses, a highly pathogenic virus, declared by the World Health organisation (WHO) as a pandemic largely responsible for the sudden outbreak of pneumonia initially originated in Wuhan City, Hubei Province of China, in December 2019[1]. Generally, the Coronaviruses are very minute (65-125 nm in diameter) containg a single positive stranded RNA as a genetic material, size ranging from 26-32kbs in length. The subgroups include alpha (α), beta (β), gama (γ)**,** delta (δ)[2,3] and a surge in coronavirus cases due to strain that is a sub-variant of the highly infectious Omicron variant: BF.7 or BA.5.2.1.7 and XBB.1.5 are currently in different countries. Earlier these viruses were known to be infecting animals only until the human population in Guangdong, China (2002)[4] contracted the infection causing Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS-CoV) causing endemic in the Middle Eastern countries[5]. SARS-CoV-2 affects the respiratory system of the infected individuals most of the infected individuals develop pneumonia and acute respiratory distress syndrome. Infected individuals experience a number of symptoms like headache, fever, cough, sore throat, fatigue, myalgia, loss of smell and taste etc.[6] The SARS-CoV-2 initiates its pathogenic process through the renin angiotensin system (RAS). Sars-CoV-2 binds to angiotensin converting enzyme II (ACE2) receptor which is distributed through -out the body. Next to binding of SARS-CoV-2 by means of spike protein (S protein) to ACE2 receptor a series of proinflammatory events are initiated[7], that induce the release of cytokines (also known as cytokine storm), which is the hallmark clinical feature in COVID-19 infections[8]. The cytokines, for example IL-6, inturn act affecting liver and resulting production of acute-phase reactant substance, C-reactive protein (CRP) and significantly, it could provide clinically relevant information about the status of infection at the earliest stage[9]. The present study aims to examine the presence of CRP levels in the COVID-19 patients at earliest stages of the infection progression and to correlate it with the severity of the disease.

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Materials and Methods

The present study was carried out in the Department of Biochemistry in larger collaboration with the Department of Medicine, Government Medical College Baramulla (GMC). Those patients with clear symptoms of COVID-19 were advised to go for Rapid Antigen Testing (RAT) and to further confirm it with RT-PCR COVID-19 testing. However, RT-PCR was done to even patient who were RAT negative. The RT-PCR positive COVID-19 patients fulfilling the criteria for hospitalization, were slectively admitted in the Covid Care Centre (CCC-1) associated adjacent with the hospital. A total of 108 RT-PCR confirmed COVID-19 patients were taken for study and all the patients were fully informed about the nature of this research study and accordingly a written consent form was formally filled after the patient aproval.

The main aim of this study was to critically examine the CRP levels during COVID-19 disease progression of the patients and to corelate its clinical outcome.

A Comprehensive Study Design

This cross-sectional study was conducted in which a comprehesive collected data of patients, including a detailed patient history, general physical examination, CRP levels, vitals and the systemic examination and a detailed questionnaire for each patient. However, all the recommended proper standard operating procedures (SOPS) were strickly followed while collected the reseach data.

The inclusion criteria:

1. Age > 18 years.
2. Only admitted patients.
3. RT-PCR confirmed cases.
4. Pneumonia confirmed by HRCT

The exclusion criteria:

1. RT-PCR negative patients.
2. Patients without pneumonia.
3. Patients already taking anti-inflammatory drugs.

After clinical examination of patients, routine blood investigation, for example CBC, KFT, LFT, serum electrolytes, D-dimer and CRP was done. The patients were regularly monitored during their stay in the hospital. Finally, the patients were discharged as per the Ministry of Health and Family Welfare (MOHFW) guidelines.

Preparation of patient blood samples

The 5ml of peripheral blood was collected from each study subject, which was aliquoted in clot activator (Red top tube) vials until furhter processing. The separted serum was used for the crictical diagnostic estimation of CRP, using CS400 fully Automatic Biochemical Analyzer.

Preparation of Data Analysis

The statistical data analysis was performed by using SPSS 22.0 (IBM, New York, U.S.A.). The exclusive demographic data was shown in number (n) and percentages (%), whereas, the clinical data was normally distributed and is presented as mean (SD) and the percentages for continuous and categorical variables, respectively. An independent samples t-test was used to compare the means of different groups. Continuous variables were compared among the patients applying Pearson's Correlation and Binary Logistic Regression Model was applied to study the association between severity of the disease and various underlying clinical conditions, if any? The ROC curve was generated to evaluate specificity and sensitivity of C-reactive protein.

Results

The demographic profile of the COVID-19 patients

The demographic data is presented in number (N), percent (%) and their clinical parameter CRP as means, standard deviation (SD), as shown in **Table 1**. The study comprises of 108 COVID-19 patients who were admitted in CCC-1 associated with GMC Baramulla. The 67 (62%) were males, with CRP 50.61 mg/L (25.48) and 41 (38%) females, with CRP 53.64 mg/L (20.62). The mean age of the patients was 51.76 years. The majority of these patients were falling in the age group of 51 and above 59 (54.6%), with CRP levels 52.66 mg/L (22.09) followed by age group of 31-50, 47 (43.5%), CRP 50.4 mg/L (25.66) and least under age group of 18-30 were 2 (1.9%), CRP 57.25 mg/L (36.41). The distribution of the study subjects is shown in **Figure 1.**

Table 1: Shows the number of COVID-19 patients and their mean CRP levels

	Patients	N	Percentage %	Mean CRP (SD)
Gender	Females	41	38	53.64 (20.62)
	Males	67	62	50.61 (25.48)
Age group	18-30 years	2	1.9	57.25 (36.41)
	31-50 years	47	43.5	50.4 (25.66)
	51 and above	59	54.6	52.66 (22.09)

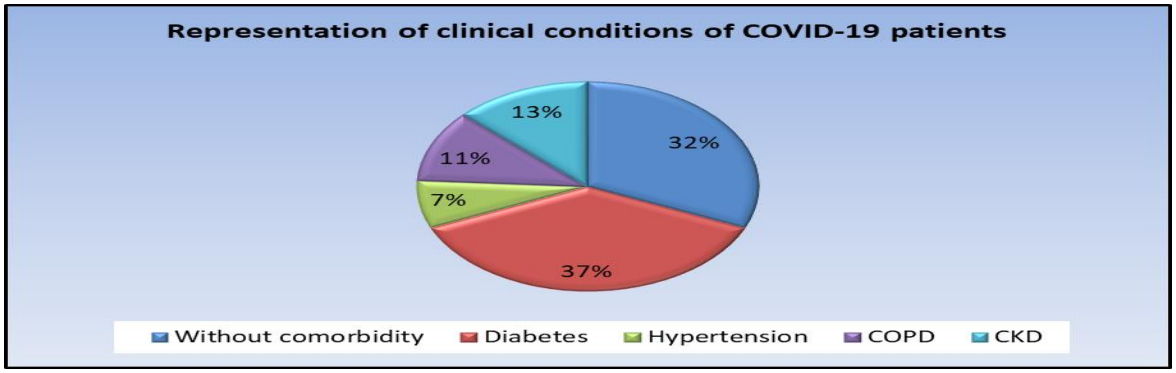

Figure 1: Representation of the percent of COVID-19 patients without comorbidity, diabetes, hypertension, COPD (chronic obstructive pulmonary disease) CKD (chronic kidney disease).

The clinical manifestations of the patients

The Figure 2 shows that the most common symptom was Headache 102 (94.4%), followed by fever 98 (90.8%), cough 98 (90.8%), breathlessness 91 (84.25), sore throat 80 (74.9%), Myalgia 69 (6.8%), anosmia 65 (60.1%), dysphagia 40 (37%) and diarrhoea in 30 (27.8%) of the patients. However, we didn't find conjunctivitis and rashes in any patient.

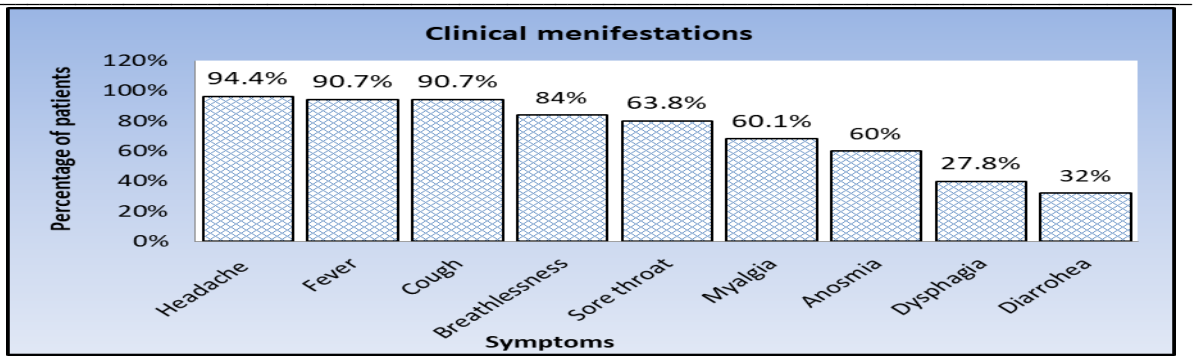

Figure 2: Symptoms of COVID-19 study subjects.

The clinical profile of the patients

The clinical data of the patient is represented as mean (SD). Of 108 COVID-19 patients the CRP levels were found to be higher in CKD patients 66.3 mg/L (20.6) followed by hypertension patients 64.47 mg/L (20) then patients having diabetes 51.49 mg/L (24.6) and COPD 46.13 mg/L (24) and least in patients having no underlying comorbidity 45.09 mg/L (22.04) as shown in Figure 3 a,b,c &d.

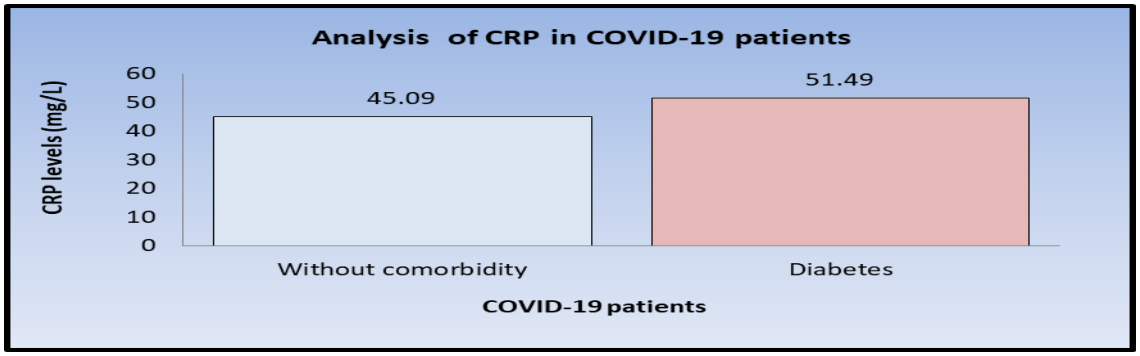

Figure 3 (a) shows COVID-19 patients with Diabetes had higher levels of CRP 51.49mg/L as compared to patients with-out any comorbidity 45.09mg/L.

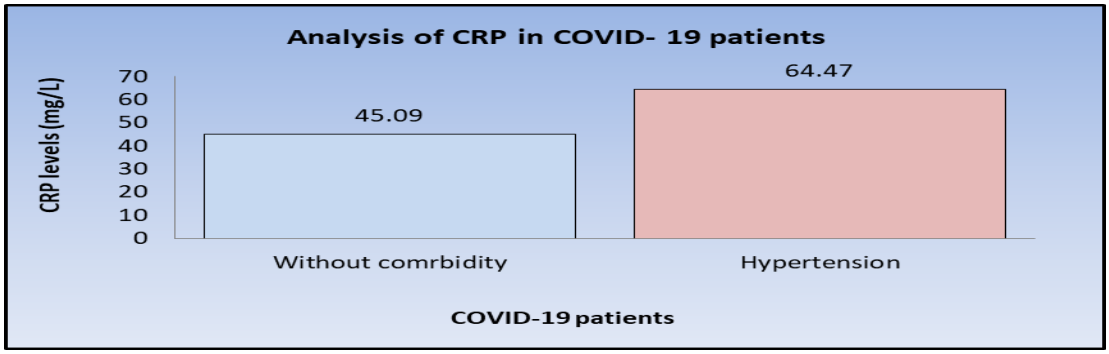

Figure 3 (b) shows COVID-19 patients with Hypertension had higher levels of CRP 64.47mg/L as compared to COVID-19 patients with-out any comorbidity 45.09mg/L.

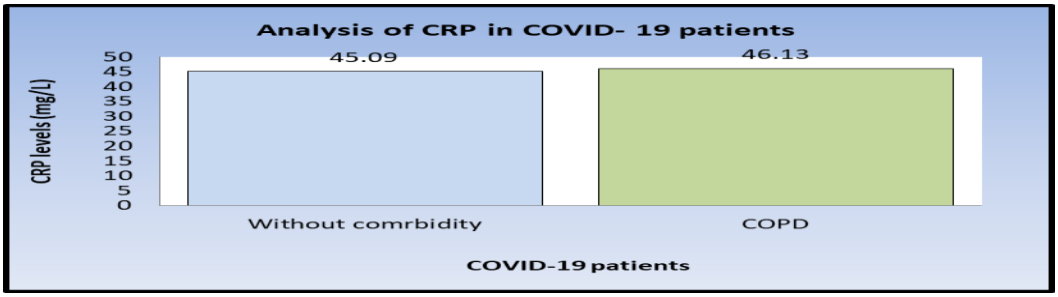

Figure 3 (c) shows patients COVID-19 patients with COPD had slightly higher levels of CRP 46.13 mg/L as compared to COVID-19 patients with-out any comorbidity 45.09mg/L.

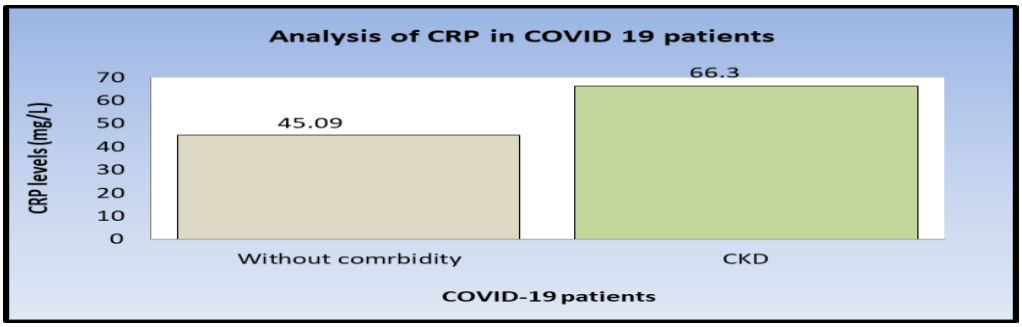

Figure 3 (d) shows COVID-19 patients with CKD had higher levels of CRP 66.3 mg/L as compared to COVID-19 patients with-out any comorbidity 45.09 mg/L.

Importantly, an independent sample t-test was conducted to compare the CRP levels of patients with comorbidity and the patients with-out comorbidity. **Table 2** shows that there was a significant difference **(*f* (106), t = 2.00, p = 0.04**) in the CRP levels with mean CRP for patients with underlying comorbidities **54.83 mg/L (23.95)** was higher than the patients who had no comorbidities **(45.09 mg/L (22.04)**. The magnitude of the difference in means **9.73, (95% CI: 0.12 – 10.33)** was significant.

Table 2: Shows CRP levels in the COVID-19 patients.

Patients	Mean	St. Dev.	f	p- value	Mean Dif.	95% CI of the differences
With comorbidity	54.83	23.95	106	0.04	9.73	0.12 - 10.33
With-out comorbidity	45.09	22.04				

Based on the criteria of severe and moderate patients, 75 (69.4%) were severe and 33 (30.6%) were moderate. Table 3 shows higher levels of CRP observed in severe COVID-19 patients as compared to moderate COVID-19 patients. There was a statistically significant difference in CRP levels of the two groups, mean 55.86 mg/L (24.1) vs. 42.44 mg/L (20.15), p value; < 0.05.

Table 3: Shows the mean CRP levels in moderate and severe COVID-19 patients

Patients	N	Mean	St. dev.	p-value	95% confidence Interval
Moderate	33	42.44	20.15	< 0.05	3.90 – 22.94
Severe	75	55.86	24.1		

Bivariate analysis

The bivariate analysis revealed a negative correlation between CRP and SpO2 as shown in Table.4, and the correlation was statistically highly significant (r= -0.20, p<0.05). This complete analysis shows that with the increasing CRP levels there was a decrease in SpO2 of the COVID-19 patients.

Table 4: Shows correlation between CRP levels and SpO2

Parameters	Mean	*r*	p-value
CRP	51.76	-0.207	0.031
SpO2	85.44		

The COVID-19 patients with other clinical conditions

The analysis of severity of COVID-19 patients on the basis of underlying medical conditions is shown in Table 5. There was a significant difference p < 0.05. The reference category was patients without underlying comorbidities, the odds ratio for covid-19 patients who had underlying comorbidity OR= 2.456, and the odds ratio for patients who had no underlying comorbidity OR =0.40 (95% CI 1.03 - 5.80). This indicates that the COVID-19 patients who had underlying comorbidities have higher risk of developing severity as compared to patients who had no underlying comorbidities. Gender of the patients revealed no statistical significance p= 0.84 (95% CI 0.38 – 2.16). However, the females had higher odds as compared to males.

Table 5: Shows COVID-19 patients and Odds ratio

Patients	N	OR	95% Confidence interval
Patients without comorbidity	34	0.4	1.03 - 5.80
Patients with comorbidity	74	2.45	
Males	67	0.916	0.38-2.16
Females	41	1.09	

The prognostic value of CRP

Furthermore, Table 6 of ROC curve analysis illustrated an area 0.659 under the curve (AUC) for CRP levels as a predictor of severity of disease (95% CI: 0.552-0.766) P<0.05. The AUC of CRP indicated a high diagnostic value for severity of the disease, with an optimal threshold of ≥ 45.6 mg/L with a sensitivity of 62.7% and a specificity of 39.4%, as shown in Figure 4.

AUC	Optimal cut off value mg/L	Sensitivity %	Specificity %	p value	95% confidence interval
0.659	45.6	62.7	39.4	0.009	0.552 – 0.766

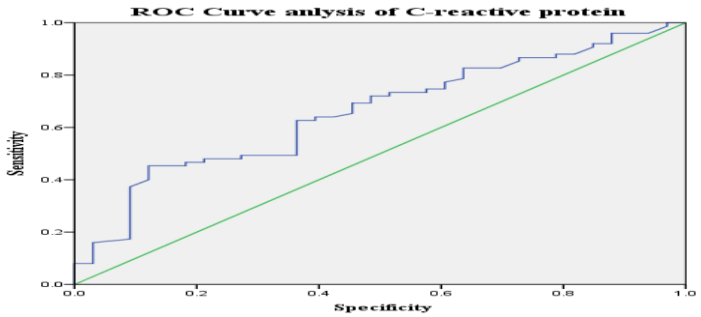

Figure 4: ROC curve of C-reactive protein to predict COVID-19 disease severity

Discussion

The Coronavirus diseas-2019 (COVID-19) has been an emerging global health threat since its outbreak. The healthcare workers are facing immense challenges in reducing the aggravation and mortality of COVID-19 across the world. The hospitalized COVID-19 patients are monitored regularly, using the highest standard operating procedures, but there are the emerging clinical consequences that maximally the mild and moderate COVID-19 patients could further develop into a severe disease course.

Early identification of the patients progressing to severity is utmost important to start an early treatment and that is clinically anticipated to improve the outcomes of COVID-19 disease symptoms. In this analysis of COVID-10 patients hospitalized in GMC Baramulla associated CCC1, we examined the association between key inflammatory biomarker and a realm of clinical characteristics as well as outcome of the patients. Of 108 RTPCR confirmed COVID-19 positive patients fulfilling all inclusion criteria were taken for the study. We critically analyzed CRP levels of the COVID-19 positive patients. The study found that nearly all the COVID-19 patient hospitalized had far elevated CRP levels 51.76 mg/L, a value nearly 5-fold higher than the upper limit of normal 10 mg/L, as earlier documented by *Young et al., 2020*[10]. Their study had also found mean CRP levels in hospitalized patients to be 51.4 mg/L that is almost parallel to this finding. It was found that most of the patients were belonging to age group of 51 and above followed by age group 30-50 years then 18-30 years.

The CRP levels were found to be elevated in patients irrespective of their age and gender**,** but represented with all those COVID-19 symptoms, suggesting of its clinical significance for identifying the disease. However, conjunctivitis and skin rashes were not found in any patient, as discussed. Mostly the patients who had developed moderate illness experienced the loss of smell and taste. In addition, the patients were divided into groups viz, patients without underlying comorbidities and patients with underlying comorbidities like diabetes, hypertension, COPD, CKD. The highest number of patients were diabetic followed by hypertension, COPD, CKD. Significantly, the CRP levels were higher in patients who had underlying comorbidities as compared to patients who had no underlying clinical condition, inline with the recent studies, but the actual research data have not been reported by any study yet. The CRP levels were also observed to be higher in severe patients as compared to moderate patients. Importantly, we found that the patients with low oxygen saturation (SpO2 ≤ 90%) had CRP levels significantly higher than patients with higher oxygen saturation (Spo2 90-93%). It clearly indicates that higher CRP levels are linked to lung injury and severe disease course. Additionally we have found the there is a higher risk of developing severe disease course in patients who have underlying comorbidities. Furthermore the prognostic value of the CRP in the disease progression has been revealed. The current study examined the association between CRP and Covid-19 severity and the findings indicated that a patient with a CRP level ≥ 45.6mg/L were more likely to develop the severe form of the disease. It clearly indicates that CRP can be very useful to assess the progression of COVID-19 disease, as described by *Mahmoud et al., 2021*[11], they have found that the CRP levels > 64.75 mg/L threshold of CRP. In this contrast our reseach has shown CRP levels lesser than their findings to be the threshold for progression of disease to develop into its severe advanced form. Multiple studies imply that the altered levels of some of the blood markers might be linked with the extent of severity of patients with COVID-19. Of these clinical parameters, serum CRP has been found to be a pivotal marker in COVID-19 patients, levels of which change significantly raised in the inflammatory conditions[12]. The CRP is an acute phase protein that is produced by the liver when there is an inflammation in the body[13]. However CRP is a non-specific protein and is elevated in many inflammatory conditions. Also, CRP is a well-established marker of systemic inflammation and severe infection[14]. As an acute phase reactant, CRP binds to phosphocholine in pathogens and host cells and acts as an opsin to enhance phagocytosis and facilitate clearance[15]. In serum, the normal CRP concentrations were less than 10 mg/L. However, its levels were elevated within 4 to 8 hours and went on increasing to its peak in 48 hours from the disease onset. It is illustrious that inflammation is hallmark of COVID-19. Prior to the COVID-19 global pandemic, up to 90% of all marked elevations in CRP concentration were attributed to an infectious aetiology, most often from bacterial pathogens[16,17], but elevated CRP concentrations have also been reported in severe viral infections, including H1N1 influenza pneumonia, and in SARS-CoV-2 infection. In previous study of 298 patients with COVID-19, patients who died had an initial CRP that was 10-fold higher than that of survivors (100.0 vs. 9.7mg/L, $P < 0.001$), and CRP concentrations were associated with mortality, with an area under the receiver operating characteristic curve (AUC) of 0.896[18]. Recent reports also identified associations between CRP concentrations and respiratory failure requiring mechanical ventilation, with a nearly five-fold greater risk of acute respiratory distress syndrome (ARDS) reported in patients with high-sensitivity CRP >5 mg/L compared with those with lower CRP values[19,20]. CRP is associated with extra-pulmonary disease in COVID-19, and correlations between CRP concentrations and myocardial injury have been reported in multiple series. Our results were supported by multile recent studies about CRP level with disease severity elsewhere. In dengue's infection, CRP has been suggested to be used as a prognostic marker, and higher levels of CRP indicating increased risk of disease progression[21,22]. It's noticeable that dengue virus and SARS-CoV-2 are RNA virus, sharing similarity in the course of infection. The CRP is rapidly synthesized by hepatocytes when stimulated by inflammation. It binds to a variety number of eukaryotic and prokaryotic pathogens, facilitating complement activation through classical pathway[23], indicating immune activation, lymphocyte infiltration, immune molecules consumption and inflammation outbreak. Clinically, increased CRP levels might be early indicators of nosocomial infections in COVID-19 patients who were slow to recover, and might aid physicians to administer empirical antibiotics treatment early to prevent worsened outcome[24,25]. The CRP levels are correlated with the level of inflammation, and its concentration level is not affected by factors such as age, sex, and physical condition. CRP levels can activate the complement and enhance phagocytosis, thus clearing the pathogenic microorganisms invading the body, indicating that the CRP levels

could be used for early diagnosis of pneumonia , and patients with severe pneumonia had high CRP levels. It is an important index for the diagnosis and assessment of severe pulmonary infectious diseases. Matsumoto's study also showed the value of CRP levels in severe pneumonia[26]. The present study showed that CRP levels and the diameter of the largest lung lesion increased as the disease progressed. The CRP levels correlated well with the severity of the disease. This suggests that in the early stage of COVID-19, CRP levels could an important factor reflecting lung lesions and disease severity[27].

The main limitations of the present study were small sample size, time duration and the less number of clinical parameters examined. The study also did not measure viral load of the patients. However, further extensive multidynamic studies with a large sample size would be needed to yield better meaningful results, maximally reduce the bias and increase reproducibility of the outcomes. Significantly, that would help to research whether CRP could act as determining factor of COVID-19 infections.

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