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EVALUATION OF C-REACTIVE PROTEIN LEVEL AMONG COVID-19 PATIENTS

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ABSTRACT
Background: Corona Virus Disease-19 (COVID-19) pandemic is a public health crisis that has emerged due to the spread of 2019 novel Corona Virus (2019-nCoV), also called as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). Detection of C-Reactive Protein (CRP) levels serve as a predictive biomarker of infection and inflammation. **Objective:** The aim of the study was to evaluate the CRP levels of all the clinically and diagnostically confirmed COVID-19 patients. **Materials and Methods:** The present prospective study was conducted for a period of 60 days from 28th March to 26th May'2020 in the Serology section of the department of Microbiology of a teaching tertiary care hospital. Three to five ml. of venous blood was collected from 556 clinically and diagnostically confirmed admitted cases of COVID-19 and subjected to semi-quantitative, latex agglutination based CRP test (Rhelax-CRP, Tulip Diagnostics, Goa, India). CRP values equal to or greater than 0.6 mg/dl were considered as abnormal. **Results:** Out of 556 serum samples tested for CRP, 233 (41.9%) samples showed abnormal values. Out of 357 male patients 48.7% and out of 199 female patients 29.6% showed elevated CRP values respectively. A total of 65.6% patients had increased CRP values that belonged to the age group 71~80 years followed by 57.1% patients that belonged to the age group of 81~90 years. **Conclusion:** Our study concluded that large number of COVID-19 patients had elevated serum CRP levels. However, some patients maintained the normal values throughout the course of disease. Male preponderance was detected and elderly patients revealed abnormal values of CRP as compared to young and middle-aged patients.

KEYWORDS: COVID-19, novel Corona Virus-2, C-reactive protein, Latex agglutination test.

INTRODUCTION

Corona Virus Disease-19 (COVID-19) is a new public health emergency that is recently threatening and challenging the entire world. The etiological agent is a 2019 novel Coronavirus (2019-nCoV) also called as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) originated for the first time in Wuhan city of Hubei province of China.[1,2,3,4]

Till 28th May'2020; 1,58,323 laboratory-confirmed cases have been documented in India among which 7,261 are in the state of Madhya Pradesh (MP) with a total of 4,706 and 313 mortalities reported respectively. A total of 3,103 laboratory confirmed COVID-19 cases have been reported in the Indore district of MP with 117 fatalities till date.

Although the disease causes mild symptoms with a good prognosis, severe cases may present with Acute Respiratory Distress Syndrome (ARDS) and systemic inflammation. It has a high case fatality among critically ill patients.[1,4]

Therefore, it is an urgent requirement to evaluate the severity of disease by investigating biomarkers in diagnostic laboratories. Several studies in the past have reported variations in biomarkers like C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Lactate Dehydrogenase (LDH), Ferritin etc. following bacterial and viral infections. Among these, CRP is considered as the representative of the acute phase reactants.[1,3,5,6,7] CRP is a kind of protein marker produced by liver in response to inflammation. Generally, its level is much higher during bacterial infection than in viral infection. Recent studies are revealing a hike in CRP levels during Corona virus infections.[8]

The present prospective study was conducted to explore and evaluate the elevated levels of an infection and inflammation biomarker CRP among the clinically and diagnostically confirmed cases of COVID-19 disease. This would enable to trace the progress of disease and monitor the effect of treatment.

MATERIALS AND METHODS

The present prospective study was conducted for a period of 60 days from 28th March to 26th May'2020 in the Serology section of the department of Microbiology of a teaching tertiary care hospital that has been designated under red zone as a COVID-19 hospital during the present outbreak. Three to five ml.of venous blood was collected from clinically and diagnostically confirmed admitted cases of COVID-19. The serum was separated from the above collected blood samples through centrifugation at 1000 rpm for 5 minutes. Hemolysed and lipemic samples were rejected and hence not included in the study. A semi-quantitative CRP test, based on the principle of Latex Agglutination was performed on serum samples by using Rhelax-CRP kit (Tulip Diagnostics pvt. Ltd, Goa, India). The results were obtained in less than 20 minutes. CRP values equal to or greater than 0.6 mg/dl were considered as abnormal. The procedure and interpretation of results was done according to manufacturer's instructions. The frequency of CRP testing of every patient was done based on the available guidelines.

Statistical Analysis

The collected data was transferred to the computer and Microsoft Excel 2000 (version 9) Analysis Tool Pack was used for analysis of data. Chi-square test was performed and $p \leq 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

A total of 556 serum samples were tested for CRP among which 357 were males and 199 were females. Out of 556 samples, 233 (41.9%) samples revealed abnormal CRP values during the course of disease. Among them, 174 (48.7%) were males and 59 (29.6%) were females. The difference was found to be clinically non significant (p=1.0011) (Table 1). Abnormal CRP levels were also associated with increased leukocyte counts and elevated values of biomarkers like ferritin, LDH and D-Dimer. Out of 323 (58%) patients having normal CRP levels, 59 (18.1%) patients showed elevated leukocyte counts along with the elevated values of biomarkers like ferritin, LDH and D-Dimer. The age wise relation with CRP values has also been demonstrated. (Table 2) The differences were found to be clinically significant (p=0.024386).

CRP is considered as one of the key marker required to diagnose and follow up the treatment of the novel Coronavirus (2019-nCoV) disease. Every single patient who complains of fever and suspected symptoms is required to undergo CRP and Complete Blood Count (CBC) testing. This routine testing would help to identify common cold due to novel virus. Further, confirmation is to be done by chest imaging and nucleic acid testing to confirm Coronavirus infection. During the course of treatment and throughout recovery process, CRP is the important parameter that is monitored along with other biochemical markers. Although, biomarker identification is not recommended during primary examination, CRP is a non specific biomarker of inflammation that is known to trace the progress of infection or monitor the treatment effects.[9,10]

The studies carried out in the past suggest that CRP level typically rises during systemic bacterial infection but latest publications reveal that CRP levels are also elevated in COVID-19 patients.[3,5,11,12] Even, high serum CRP levels were detected in patients affected by Corona Virus during 2002-SARS outbreak and 2009-pandemic influenza A (H1N1), where it was also identified as the predictor of respiratory failure and death.[13] In order to confirm these findings, the present prospective study was conducted on 556 COVID-19 patients.

In the present study, CRP was found to be elevated among 233 (41.9%) patients. Our results were in concordance with those reported by Jeon et al, Zhou et al, Ji et al., Wang L et al, Wang G et al, Zhu et al. and Young et al.[1,2,3,4,8,14,15] Their reports reveal that CRP levels does rise during the Coronavirus infection in large number of patients. However, it does not significantly change in all the patients, while some of the COVID-19 patients maintained a normal CRP level throughout the course of disease. High levels of CRP can also be correlated to secondary bacterial infections and severity of disease. CRP levels are known to activate the complement and enhance phagocytosis, there by clearing the pathogens invading the body.[1,4] CRP levels are used to clinically correlate the cases of pneumonia and other severe pulmonary infectious diseases.[16, 17]

In the present study, comparatively larger number of male patients tested positive for COVID-19 (64.2%) and at the same time large number of males (48.7%) had abnormal CRP value as compared to Coronavirus positive females (29.6%). However, the difference was not found to be statistically significant. Our results were similar to those reported by Guan et al.[18] Men are more vulnerable to COVID-19 infection and are found to have abnormal CRP concentration as compared to women probably because they have a higher concentration of key enzyme Angiotensin-Converting Enzyme-2 (ACE-2) that enables Coronavirus to infect healthy cells. Such male preponderance was also observed during SARS-CoV epidemic of 2003.[19]

Our results reported abnormal value of CRP among the patients in the age group of 71~80 years (65.6%) followed by 81~90 years (57.15%). Large number of patients among age group 51~70 years also had abnormal values of CRP. Our results were similar to those reported by Jeon et al., Wang L et al. and Guo et al.[4,5,20] Although, all age groups are at risk of contracting Coronavirus infection, as seen in our data, geriatric population face significant risk of developing severe illness due to physiological changes that occur with ageing and potential underlying health conditions. CRP in elderly patients was significantly higher than the young and middle-aged population during our study. The

results were similar to those reported by Liu et al.[21] The increased susceptibility of older people with cardiovascular disease and co morbid conditions could also be related to increased concentration of ACE-2 enzyme and ACE-2 is known to be increased in heart failure. Elderly people often have the spectrum of comorbities that include diabetes, hypertension, renal disease and Chronic Obstructive Pulmonary Disease (COPD) responsible for multiple organ failure during COVID-19 disease. COVID-19 patients and patients with severe underlying diseases are known to be in hyper inflammatory state and hence show elevated CRP levels.[19]

CRP was monitored among all the COVID-19 patients throughout the course of study. The elderly population

and patients with underlying illnesses maintained the higher values of CRP over a very long period of their hospital stay, indicating that CRP may be a serum marker of disease aggravation in COVID-19 patients.[8]

About 26.6% of the total younger and middle-aged population (under 40 years of age) that suffered from Coronavirus infection during our study was known to suffer from underlying illnesses like Diabetes and Hypertension. It was also detected in our study that out of 323 (58%) patients having normal CRP levels during the course of disease, a total of 59 (18.2%) patients showed high leukocyte count along with raised values of one or multiple markers such as Ferritin, Lactate Dehydrogenase and D-Dimer.

Table 1: Serum CRP values detected in male and female COVID-19 patients.

Gender	Total Samples tested (556)	Samples with abnormal CRP values		p-value
		N	%	
Male	357	174	48.7	1.0011*
Female	199	59	29.6	
*Statistically non-significant				

Table 2: Patients showing abnormal CRP values in different age groups.

Age group (Year)	Total no. of COVID-19 patients tested for CRP	COVID-19 Patients with abnormal CRP values		p-value
		N	%	
0 month – 1 year	08	01	12.5	0.024386*
1-10	16	03	18.7	
11-20	33	02	6.0	
21-30	69	18	26.0	
31-40	91	38	41.7	
41-50	108	43	39.8	
51-60	110	59	53.6	
61-70	81	45	55.5	
71-80	32	21	65.6	
81-90	07	04	57.1	
>91	02	00	0.0	
*Statistically Significant				

CONCLUSION
In conclusion, our study suggests that CRP levels could be considered as useful markers for prediction of Coronavirus infection. Detection of CRP levels among COVID-19 patients could be predictive and can reflect the severity of disease. These could also be correlated with the secondary bacterial infection and can be of vital importance in reducing the mortality rate of COVID-19 patients. The data can help in decision making on issues related to patient management. Therefore, CRP testing should be carried out during the entire course of disease and should be concurrently done with virus identification tests.

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