C-REACTIVE PROTEIN LEVELS AND THE SEVERITY OF COVID-19

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ABSTRACT

Objective: To compare the C-reactive protein levels in different groups of COVID-19 patients to assess disease severity.
Study Design: Cross sectional study.
Place and Duration of Study: Combined Military Hospital Kohat, from Apr 2020 to Jun 2020.
Methodology: Forty five Confirmed cases of COVID-19 patients were included by non-probability consecutive sampling. Patients were divided into five groups (Asymptomatic, Mild, Moderate, Severe and Critical). Serum sample for C - reactive protein levels were collected at presentation and compared in different clinical groups by Paired sample "t" test and one way Anova (Post Hoc LSD).
Result: Out of 45 cases in our study 28 (62.2%) were male and 17 (37.8%) were female. Mean age of patients was 51.96 ± 16 and mean C-reactive protein levels were 76.61 ± 75 mg/L. When compared by paired sample t-test C-reactive protein levels were: higher in the mild patient group than asymptomatic group, higher in the moderate group than mild group, higher in severe group than moderate group and those in the critical group were higher than those in the severe group. The difference was statistically significant with *p*-value <0.05 in each group.
Conclusion: C-reactive protein levels were lowest in asymptomatic and highest in critical patients in early COVID-19. This may help guide management.

Keywords: COVID-19, C-reactive protein, Disease severity classification.

INTRODUCTION

Coronavirus pneumonia (COVID-19) is a respiratory and systemic viral disease which originated from the town of Wuhan, China[1-2]. It is still spreading around the world, and has been declared a pandemic emergency[3]. COVID-19 is highly infectious[4]. Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is the causative agent of this type of pneumonia. Older adults and persons who have co-morbidities like diabetes mellitus, chronic lung disease, and heart disease are at high risk for critical disease and increased mortality[5].

Clinically the disease can be divided into five groups. (1) Asymptomatic: Molecular evidence of presence of COVID-19 (SARS-CoV-2 PCR positive) but with no symptoms or signs. (2) Mild disease: Molecular evidence of presence of COVID-19 infection and with symptoms i.e, fever, sore throat, cough, new loss of taste or smell and muscle pain, but no dyspnea, no lung infiltrates on Chest x-ray (CXR) and no hypoxemia. (3) Moderate disease: Molecular evidence of presence of COVID-19 infection with symptoms, dyspnea plus lung infiltrates on CXR. (4) Severe disease: Molecular evidence of presence of COVID-19 infection with symptoms plus lung infiltrates on CXR plus hypoxemia. (5) Critical disease: Molecular evidence of presence of COVID-19 infection and evidence of respiratory failure PaO2 <60 mmHg or multi organ failure or septic shock[6].

Diagnostic methods of COVID-19 are still evolving. The disease can be confirmed by Polymerase Chain Reaction (RT-PCR) test from respiratory samples[7]. Antibody test for SARS-CoV-2 from serum samples can also be used but it appears late in the disease and cannot differentiate between active disease or immunity. Other modalities being investigated are viral

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cultures and Computed Tomography (CT) scan chest.

C-reactive protein (CRP) is one of the acute phase reactants that is used to identify the presence and degree of inflammation during infective diseases. CRP production occurs due to tissue destruction and cytokines[8]. A recent study from Wuhan China reported that CRP levels were higher in severe patient group (54.15 ± 1.06) than the moderate group (16.76 ± 18.38)[9]. CRP levels may be used for early diagnosis of pneumonia and assess its severity. It can be used as a prognostic marker in patients with severe pneumonia; higher the CRP levels worst is the prognosis. Repeat testing is primarily useful to follow the course of illness[10]. CRP levels with other clinical parameters are used for initial workup and follow up of COVID-19 patients. The purpose of our study was to compare CRP levels in different clinical groups of COVID-19 patients at early stages of the disease. It will help the clinician to classify the patients correctly and tailor management accordingly.

METHODOLOGY

This cross sectional study was carried out in department of Medicine, Combined Military Hospital Kohat from April 2020 to June 2020. Sample size was calculated using WHO sample size calculator using two sided hypothesis testing for two population means formula with population standard deviation of 18.76, test population mean 16.76 and anticipated population mean 54.15 for CRP[9]. 45 confirmed cases of COVID-19 patients of both genders coming to Combined Military hospital Kohat were included by non-probability consecutive sampling after informed consent of patient. This project was reviewed and approved by IRB of CMH Kohat certificate no E-2004 dated 08 July 2020. Patients with bacterial infection, presentation after 7 days of onset and incomplete data were excluded from this study. These patients were assigned into one of five groups (Asymptomatic, Mild, Moderate, Severe and Critical) as per clinical criteria defined in government of Pakistan Guidelines for COVID-19. Serum sample for CRP levels were collected at presentation. CRP levels were measured by Roche Cobas c501 automated chemistry analyzer by quantitative immmunoturbiditimetry method.

SPSS version 23 was used for data entry and analysis. Mean and SD were calculated for quantitative variables like age and CRP levels and for qualitative variables like gender percentages were calculated. CRP levels between different clinical groups of COVID-19 patients were compared by paired sample t-test and within groups by one way analysis of variance (Post Hoc LSD). The *p*-value <0.05 was taken as statistically significant.

RESULTS

Out of 45 selected cases 28 (62.2%) were male and 17 (37.8%) were female. Mean age of patients was 51.96 ± 16 and mean CRP levels were 76.61 ± 75 mg/L (reference value in healthy adults <6.0). Descriptive statistics for quantitative variable like age and CRP levels in all patients and different patient groups is shown in table-I. When compared CRP levels were: higher in the mild group than asymptomatic group (*p*-value <0.05), higher in the moderate group than mild group (*p*-value <0.05), and higher in severe group than moderate group (*p*-value <0.05) and those in the critical group were higher than those in the severe group (*p*-value <0.05). Results of paired sample t-test are shown in table-II. One way analysis of variance (ANOVA) showed that between groups and within groups difference was statistically significant with *p*-value <0.01 as shown in table-III. Multiple comparison by Post Hoc LSD (homogeneity of variance) test also showed that difference was significant between all groups ($p<0.05$) except between Asymptomatic and mild group ($p=0.196$) as shown in table-IV.

DISCUSSION

The number of COVID-19 patients is increasing rapidly worldwide as the disease can also be spread by asymptomatic cases[11]. Early detection of disease severity is important for management of patients and improves final outcome[12]. COVID-19 damages lung and immune system.

CRP levels correlate with degree of inflammation. Age, gender, and physical health have no effect on CRP levels[13]. CRP works by activating the complement and increasing phagocytosis, thus removing microorganism. Bacterial diseases show higher CRP levels as compared to viral diseases[14-16]. It is an important marker for diagnosing and assessing severe lung infection[17]. COVID-19 patients inour study had raised CRP levels, which is same as other studies[18].

CRP levels may be used in diagnosing pneumonia early as shown by Warusevitane study on patients having post stroke pneumonia. They recruited 60 stroke patients, of these 44 patients developed pneumonia and CRP was raised in 38 (86%) patients. His results suggested that patients with a CRP >25 mg/L need pneumonia workup. The study suggested that CRP value more than 65 mg/L may be used as diagnostic marker for post stroke pneumonia[10].

Table-I: Descriptive statistics for CRP levels and age in different groups.

Patient groups	n	CRP levels (mg/L) Mean ± SD	AGE (Years) Mean ± SD
All Patients	45	76.6 ± 75.6	51.9 ± 16.3
Asymptomatic group	12	10.7 ± 10.7	46.8 ± 18.8
Mild group	10	33.3 ± 25.0	45.9 ± 15.6
Moderate group	8	80.0 ± 39.1	54.0 ± 14.9
Severe group	8	120.6 ± 34.2	56.7 ± 16.5
Critical group	7	196.8 ± 79.9	61.5 ± 10.0

Table-II: Paired sample "t" test results of CRP levels between different groups of patients.

Groups		CRP (mg/L) Mean ± SD	n	*p*-value
Pair 1	Asymptomatic	11.7 ± 11.0	10	<0.05
	Mild	33.3 ± 25.0		
Pair 2	Mild	36.0 ± 26.6	8	<0.05
	Moderate	80.1 ± 39.1		
Pair 3	Moderate	80.1 ± 39.1	8	<0.05
	Severe	120.6 ± 34.2		
Pair 4	Severe	114.2 ± 31.5	7	<0.05
	Critical	196.8 ± 79.9		

Table-III: Results of One way ANOVA of CRP levels in different disease severity patient groups.

	Sum of Squares	Mean Square	F	*p*-value
Between Groups	187466.31	46866.57	29.190	<0.01
Within Groups	64223.06	1605.57		

Table-IV: Multiple Comparisons results of Post Hoc LSD Anova for CRP in different disease severity patient groups.

		Mean Difference	Standard. Error	*p*-value
Asymptomatic Group	Mild	-22.59	17.15	0.19
	Moderate	-69.32	18.28	<0.01
	Severe	-109.85	18.28	<0.01
	Critical	-186.05	19.05	<0.01
Mild Group	Moderate	-46.73	19.00	<0.01
	Severe	-87.25	19.00	<0.01
	Critical	-163.45	19.74	<0.01
Moderate Group	Severe	-40.52	20.034	<0.05
	Critical	-116.72	20.73	<0.01
Severe Group	Critical	-76.20	20.73	<0.01

The mean difference was significant at the 0.05 level.

Guyi Wang study reported that patients with non-severe COVID-19 and raised CRP levels developed aggravation of disease than those non-severe patients who had normal CRP levels. Around 7.7% of non-severe adult COVID-19 patients aggravated post admission. In non-severe patients, those patients whose disease aggravated CRP levels were much higher than those who remained stable (43.8 mg/Lvs. 12.1 mg/L, *p*-value <0.001)[19].

Wang study on 27 patients also showed positive correlation between disease severity and CRP levels. He compared diameter of lung lesion on CT scan chest and CRP levels in different clinical groups of COVID-19 patients. The size of the largest lung lesion on CT scan and CRP levels in the moderate group was higher as compared to mild group ($p<0.05$), that in the severe group was higher than moderate group ($p<0.05$), and critical group values were more than those in severe group ($p<0.05$). CRP levels and diameter of lung lesion increased from mild to critical group with significant *p*-value <0.05[9].

Result in our cases also show that higher the levels of CRP at presentation; worst is the severity of the disease. These findings were similar to studies mentioned above. Mean CRP levels increased from asymptomatic patients (10.7 ± 10.7 mg/L) to critical patients (196.8 ± 79.9 mg/L). When Mean CRP levels in different clinical groups were compared the result showed that CRP levels were: higher in the mild group as compared to asymptomatic group (33.3 ± 25.0 mg/L vs. 11.7 ± 11.0 mg/L), higher in the moderate group than mild group (80.3 ± 39.5 mg/L vs. 36.0 ± 26.6 mg/L), higher in severe group than moderate group (120.6 ± 34.2 mg/L vs. 80.3 ± 39.5 mg/L) and higher in critical group than the severe group (196.8 ± 79.9 mg/L vs. 114.2 ± 31.5 mg/L). *p*-value was <0.05 within each group which is statistically important.

To our knowledge this is the first study on COVID-19 patients in Pakistan comparing CRP levels and disease severity. The results suggest that in initial stages of COVID-19, CRP levels show disease severity. This may guide the clinician regarding the management plan. Patients with severe and critical disease are managed in Intensive Therapy Centre (ITC) or High Nursing Care (HNC), where as other patients may be monitored in isolation wards. Patients with very high CRP levels are more likely to have severe disease so they should be actively monitored and treated to reduce mortality.

Our study is limited by small sample size and it is a single center study and large multicenter studies are required to further evaluate the CRP levels in COVID-19 patients.

CONCLUSION

In initial stages of COVID-19, CRP levels increased with disease severity, with lowest levels in asymptomatic patients and highest in critical patients. CRP levels may be used for assessment of disease severity which can help guide management and improve prognosis.

CONFLICT OF INTEREST

This study has no conflict of interest to declare on any author.

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