ROLE OF CRP TO STRATIFY SEVERITY OF COVID-19 INFECTION: A COMPARISON WITH CHEST COMPUTED TOMOGRAPHY

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Abstract:

Background: *COVID-19 is the pandemic disease causes severe acute respiratory infection. T-cell mediated responses are activated and responses are initiated by antigen presentation via DCs and macrophages. Immunologically SARS-CoV showed that virus infected lung epithelial cells produced IL-8 in addition to IL-6. A hyperinflammatory environment has been a hallmark of COVID 19 infection and is thought to be a key mediator of morbidity and mortality. C-reactive protein (CRP), an inflammatory marker, can be used in the diagnosis of COVID pneumonia.*

Purpose*: To find out the role of CRP in COVID-19 Infection and comparison with Chest Computed Tomography.*

Materials and method: *This cross sectional prospective study was conducted in Department of Medicine, Dhaka Medical College Hospital, among the 100 patients with symptomatic and positive RT-PCR for SARS-CoV-2. C-reactive protein (CRP) level was compared with HRCT findings. All the information collected in data collection sheet and analyzed using SPSS version-22.*

Result*: Mean age of the patient was 45.2 ± 8.5 years. Fever and cough was commonest presentation, 79.0% and 36.0% of patients respectively. It showed, 27.0% cases were found to have raised CRP where 73.0% had normal level with mean value 14.1 mg/L. Chest HRCT imaging finding revealed, 44% patients had 26–50% lung involvement and 16 patients had 51–75% involvement. In maximum patients (57.0%), chest CT showed single or multiple GGO. HRCT score was significantly higher in patients with raised CRP, and a significant positive significant correlation (r=0.941; p=0.001) between the HRCT scores and CRP level.*

Conclusion: *The rising CRP can aid in predicting COVID-19 pneumonia and significantly correlates with percentage of lung involvement on HRCT in COVID-19 pneumonia.*

Key words: *COVID-19, HRCT, CRP.*

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Introduction:

The novel Coronavirus Disease 2019 (COVID-19) is the major public health burden in the world. The morbidity and mortality of the global community due to this disease is dramatically increasing from time to time. The majority (95%) of currently infected patients at active cases were mild to moderate and the remaining (5%) were serious or critical condition related to COVID-19.[1] According to the World Health Statistics published in 2020, the COVID-19 pandemic is causing significant loss of life, disrupting livelihoods, and threatening the recent advances in health and progress towards global sustainable development goals. In Bangladesh, COVID-19 infections are being reported from Directorate General of Health Service on daily basis. So far, we have around 38292 cases with 544 deaths (28th May, 2020).[2] Early recognition and rapid diagnosis are essential to prevent transmission and provide appropriate care in time frame.

Epidemiology and virologic studies suggest that transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by direct contact with

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infected persons, or by contact with contaminated objects and surfaces. Clinical and virologic studies that have collected repeated biological samples from confirmed patients demonstrate that shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease,[3-5] within the first 3 days from onset of symptoms. The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5–6 days, but can be up to 14 days. During this period, also known as the "presymptomatic" period, some infected persons can be contagious, from 1–3 days before symptom onset.[6]

More than 80% of infected patients manifest only with mild clinical symptoms[7], early identifying the risks of an adverse outcome remains the key to optimize management and improve survival. Previous studies found that advanced age and presence of comorbidity (e.g., cardiovascular disease or hypertension) were risk factors associated with an adverse outcome such as admission to intensive care unit (ICU), need for mechanical ventilation, or death.[8,9] In addition, some laboratory indicators e.g., elevated CRP, leukocytosis, neutrophilia, lymphopenia, and elevated D-dimer were found to be linked with unfavorable clinical outcomes. Presence of consolidation on computed tomography (CT) was also considered to be predictive of poor outcome in COVID-19.[10] Despite the above, the identification of early prognostic signs of COVID-19 remains of urgent importance due to the diversity in clinical and imaging findings as well as the severity and rapid progression of disease.

Chest computed tomography (CT) has been widely used to assess COVID-19 pneumonia and is a key tool for the detection of lung abnormalities. Patients with COVID-19 usually exhibit radiological patterns classified as ground-glass opacity (GGO), crazy paving (CP), linear opacities (LO), and consolidation.[11] Although HRCT is more specific, it is expensive and not available in all level of health care canter. Recently, several studies have reported that C-reactive protein (CRP) is positively associated with the severity of COVID-19.[12]

CRP is an acute phase reactant elevated in many inflammatory conditions. Clinically, increased CRP levels might be early indicators of nosocomial infections in COVID-19 patients. Wang et al (2020) noted that CRP could be a valuable marker to anticipate the possibility of aggravation of nonsevere adult COVID-19 patients, with an optimal threshold value of 26.9 mg/L.[13] Therefore aim of this study was to find out the role of CRP inCOVID-19 Infection and comparison with Chest Computed Tomography.

Methodology:

This cross sectional prospective study was conducted in DMCH. Study subjects were patients with SARS-CoV-2 interstitial pneumonia, positive RT-PCR for SARS-CoV-2. Patients with a history of malignancy, immunosuppressive condition, abnormal liver or renal function (serum aminotransferase activity >40 IU/L, glomerular filtration rate [GFR] < 60 mL/min/1.72 m2), thyroid or parathyroid disease, sarcoidosis, tuberculosis, rickets type I, II, III, hypophosphatemic rickets, nephrotic syndrome, autoimmune disease and presence of bacterial infection (Secondary/ super infection) were excluded. Routine blood tests were performed for all patients and the following parameters evaluated: CBC, RBS, serum creatinine, electrolyte, liver enzyme, D-dimer, etc. Serum C-reactive protein (CRP) was assessed and labeled as normal when found <6gm/L in blood and when >6mg/L, CRP labeled as rising value.

HRCT analysis: CT images reconstructed with a 1-mm slice thickness in all cases using the classic filtered back-projection method. Coronal and sagittal multiplanar reconstructions were evaluated in all cases. Definitions of radiological terms like ground glass opacity (GGO), crazy-paving pattern, and pulmonary consolidation based on the standard glossary for radiological impression. All HRCT chest images were rechecked by radiologist of Dhaka Medical College Hospital to increase accuracy of chest finding. Visual quantitative or semi quantitative evaluation for each of the five lung lobes assessed for degree of involvement and scored as follows: 0, no involvement; 1, <5% involvement; 2, 5–25% involvement; 3, 26–50%

involvement; 4, 51–75% involvement; and 5, > 75% involvement. The resulting global CT score is the sum of each individual lobar score and (0 to 25). Finally HRCT score (percentage) was correlate with CRP values. All the information collected in data sheet. Data as collected by using a preformed data sheet. Statistical analysis of the data was done using statistical processing software (SPSS) and Microsoft. Quantitative data expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparison was done by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagrams, histogram and charts etc.

Result and Observation:

Total of 100 patients fulfilling inclusion/ exclusion criteria were studied. Results and observations are given below:

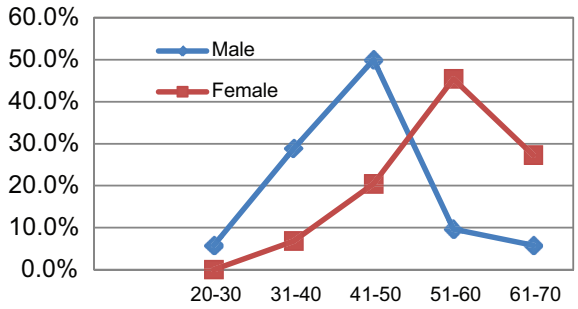

Fig.-1: *Demographic characteristics of study subject (n=100)*

Figure 1 demonstrates that maximum number of patients (43.0%) were between 41-50 years age group, next (24.0%) were between the age group of 31-40 years. Mean age of the patient was 45.2 ± 8.5 years. Out of 100 cases 78% were male and 22% were female. Male and female ratio was 3.54:1

Table I

Clinical manifestation of respondents (n=100)

Clinical manifestation	Frequency	Percentage
Fever	100	100.0
Cough	47	47.0
Dyspnoea	25	25.0
Generalized weakness	361	36.0
Diarrhoea	20	20.0
Tachycardia	29	29.0

*Multiple respondents

Table I shows the distribution of cases according to clinical manifestation. Fever and cough was commonest presentation.

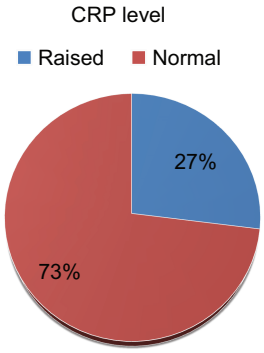

Fig.-2: *Evaluation of CRP level (n=100)*

Figure 2 shows the CRP level in the study population. In this study amongst patients, 27.0% were found to have raised CRP where 73.0% were normal level.

Table II

HRCT findings of lung (n=100)

Variables	Frequency	Percentage
Number of affected lobe		
0	8	8.0
1	29	29.0
2	45	45.0
3	18	18.0
4	0	0
5	0	0
Percentage of involvement		
0 or no involvement	8	8.0
<5% involvement	7	7.0
5–25% involvement	25	25.0
26–50% involvement	44	44.0
51–75% involvement	16	16.0
>75% involvement	0	0
Pattern of HRCT findings		
Ground-glass opacities	57	57.0
Consolidation	35	35.0
No pattern	8	8.0

In HRCT, 29% of 100 patients had opacities in 1 lobe, 45 patients had 2 lobes and 18% had 3 lobes affected. Most of the patients (e.g., 78%) had lesions located in the lower lobes. The left lower lobe was the most vulnerable lobe, whereas the right middle lobe was the least affected lobe in this study dataset. In terms of percentage of involvement, 44% patients had 26–50% involvement and 16 patients had 51–75% involvement. In maximum patients (e.g., 57.0%), chest CT showed single or multiple GGO. In some cases (e.g., 35.0%) consolidation seen.

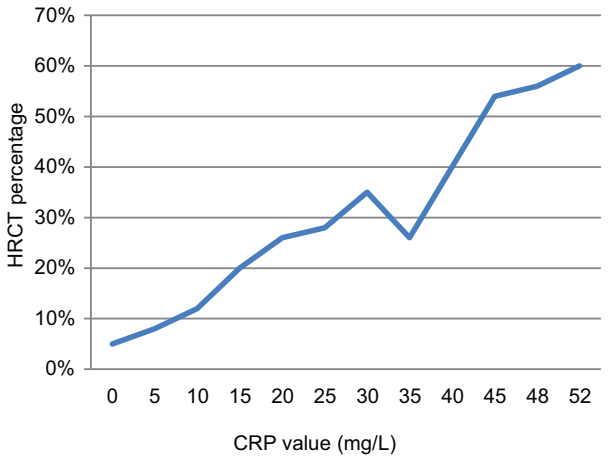

Fig.-3: *Correlation between the HRCT findings and CRP level (n=100)*

Figure 3 shows significant positive significant correlation (r=0.941; p=0.001) between the HRCT scores and CRP level. It means that increasing the score of opacifications associated with increases of CRP level.

Discussion:

In this study mean age of the patient was 45.2 ± 8.5 years. Out of 100 cases 78% were male and 22% were female. Male and female ratio was 3.54:1. Result of present study was consistent with the results of a study. Xiong et al (2020) reported that maximum number of cases (e.g., 66.0%) were 40 to 68 years and male predominance (e.g., 60.0%). The average age of the 25 male and 17 female patients was 49.5 ± 14.1 years (range, 26–75 years old) .[11] In another study mean age was 41.9±13.3 years with male predominance (52.1%).[12] A correlate of CT-based semi-quantitative score of pulmonary involvement in COVID-19 pneumonia with clinical staging of disease and laboratory findings revealed, mean age 63.2±15.8, range 27–90 years with 84 males, 46 females.[14]

In this study fever and cough was commonest presentation. On evaluation of CRP, 27.0% were found to have raised CRP where 73.0% were normal level. HRCT imaging revealed, 29% patients had opacities in 1 lobe, 45 patients had 2 lobes and 18% had 3 lobes affected. Most of the patients (e.g., 78%) had lesions located in the lower lobes. The left lower lobe was the most vulnerable lobe, whereas the right middle lobe was the least affected lobe in this study dataset. In terms of percentage of involvement, 44% patients had 26–50% involvement and 16 patients had 51–75% involvement. In maximum patients (e.g., 57.0%), chest CT showed single or multiple GGO. In some cases (e.g., 35.0%) consolidation seen.

Similar study demonstrated that in terms of HRCT lesion distribution, the lower lobes are preferentially affected, especially the left lower lobe. In initial CT, 10 (24%) of 42 patients had opacities in 1 lobe, and 32 patients (76%) had 2 or more lobes affected. Most of the patients (38/42, 90%) had lesions located in the lower lobes. The left lower lobe was the most vulnerable lobe (34/42, 81%), whereas the right middle lobe was the least affected lobe (26/42, 62%). Pulmonary lesions were most commonly in the subpleural, peribronchovascular area, or distributed diffusively. In the early stages, single or multiple small ground glass infiltration, consolidation, and interstitial thickening could be seen. As the disease progressed, severe cases had more consolidation and air bronchograms in the relevant lobes.[11] In another study most common patterns of disease included GGO, observed in 125 patients (96.2%), followed by crazy-paving pattern (n=68; 52.3%) and parenchymal consolidations (n =75; 57.7%). Pathological involvement was most common in the inferior lobes, right lower lobe (RLL) in 122 patients (93.8%), and left lower lobe (LLL) in 123 patients (94.6%).[14]

In this study, a semi-quantitative CT severity score was calculated per each of the 5 lobes. Relationship of HRCT scores and clinical category of COVID-19 shows that a significant difference ($p < 0.05$). Similarly, a significant positive significant correlation ($r=0.941$; $p=0.001$) between the HRCT percentage/scores and CRP level. It means that increasing the score of opacifications associated with increases of CRP level.

Xionag et al (2020) noted that significant positive correlations were found between CRP, ESR, and LDH levels and several CT features, of which the sum score, area of the max lesion, consolidation, and air bronchograms showed weak to moderate correlations (range, 0.36–0.75) .[11] Francone et al (2020) was compared CT score with clinical categories in their study and significant difference was observed when all categories were compared together ($p < 0.0001$). When multiple comparisons were made, CT score was significantly higher in the critical category (mean value ± SD: 20.3 ± 3; range 15–24) than in the mild category (8.7 ± 4; range 0–19) ($p<0.0001$). CT score was also significantly higher in the severe category (17.4 ±3.1; range 11–24) versus the mild category (8.7 ± 4; range 0–19) ($p < 0.0001$). CT score was significantly correlated with CRP ($p< 0.0001$, $r = 0.6204$) and D-dimer ($p<0.0001$, $r = 0.6625$) levels.[14]

In another study, several laboratory parameters, including specifically the ESR, CRP, and LDH, showed significant positive correlation with the severity of pneumonia quantified on initial CT.[11,12] Elevation of ESR, CRP, and LDH levels might indicate the extent of inflammation or extensive tissue damage and are frequently observed in pneumonia.[13, 15] In a previous study of convalescent patients after SARS, thin-section CT scores for GGO or interstitial opacities were found to be correlated with neutrophil count, CRP, and LDH level.[11,14] It was evident that severe cases of COVID-19 prominently had elevated levels of CRP as compared with nonsevere cases.[12,13]

All studied[11, 12, 14] found that, the HRCT opacification was positively correlated with the level of CRP. Chen et al demonstrated that level of plasma CRP was positively correlated to the severity of COVID-19 pneumonia. Findings could assist to discern patients of moderate to severe COVID-19 pneumonia from the mild ones[12]. Therefore, cautious attention to symptoms and application of CT examination and CRP, as soon as possible, are helpful for early detection of COVID-19 infection and standardized treatment and isolation. Especially for those who were unaware of the concealed discomfort, HRCT can assist clinicians and antiepidemic workers with finding potentially infectious patients. Because of the individualized treatments and individual heterogeneity, the same correlation was not significant after admission to the hospital. However, the total opacification severity score was still increasing with an increasing of CRP.

Conclusions:

In this study correlation between C Reactive Protein with lung involvement on CT scan in COVID-19 Pneumonia has proven. HRCT is important in the diagnosis and management of the COVID-19 infection. CT score is highly correlated with laboratory findings and disease severity and might be beneficial to speed-up diagnostic workflow in symptomatic cases. The clinical and imaging manifestations in the early stage of COVID-19 are particularly important. They can be used to confirm the diagnosis, judge the changes in severity, adjust the treatment plan, and infer the prognosis. Our clinical and radiologic study findings show that CRP level positively correlate with the severity of lung abnormalities quantified on CT; moreover, high CRP is associated with high score of CT. In the context of the COVID-19 pandemic, CRP could be a relevant alternative to chest HRCT.

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