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ORIGINAL ARTICLE

Change of CRP and D-dimer Level of COVID-19 Patients: An Observational Prospective Study

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Abstract:

Background: *COVID-19 is a global pandemic causing million of death during last two years, so it became a global health and economic burden right now. COVID-19 is a Novel infectious disease, for which there is no definite curable treatment till now. It is therefore necessary to explore biomarkers to determine the extent of lung lesions and disease severity. CRP levels are elevated in patients with COVID-19 and may be different with severity of the disease. Elevated plasma D-dimer is a hallmark to determine cardiovascular complications related to patients.*

Objective: *The primary objective of the present study was to evaluate the changes of CRP and D-dimer level of COVID-19 patients in respect to severity of the disease.*

Methods: *This prospective observational study was conducted in Private set up and OPD, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka, between January 2020 to July 2020. A total of 49 patients with COVID-19 were included in the study. Diagnosed case of RT-PCR positive patients with or without respiratory symptoms were assessed by CRP and D-dimer level on the first visit. After 7 days CRP and D-dimer levels were collected to compare with baseline levels. All other clinical, laboratory, and outcome data were documented using a standardized data collection form.*

Results: *In this study 49 patients with COVID-19, majority 22(44.9%) patients belonged to age 41 to 60 years. The mean age was 53.3±14.7 years. Male patients were predominant 41(83.7%) with male female ratio was 5.1:1. More than one third 17(34.7%) patients had hypertension followed by 15(30.6%) had diabetes mellitus, 4(8.2%) had COPD, 3(6.1%) had asthma and 2(4.1%) had CKD. Co-morbidity was significantly higher in respiratory symptoms than without respiratory symptoms. CRP level was significantly reduced after 7 days compared with baseline (10.1±13.0 mg/L vs39.6±54.6 mg/L). Twenty three (46.9%) patients were found D-dimer >3.0 gm/dl in baseline and 14(28.6%) in after 7 days, that was not significant (p=0.066).*

Conclusion: *At the early stage of COVID-19, CRP levels were positively correlated with lung lesions. Co- morbidity was significantly associated with respiratory symptoms. This study found significant reduced CRP levels after 7 days compared with baseline. D-dimer levels also reduced but not significant. CRP levels and D-dimer could reflect disease severity and should be used as a key indicator for disease monitoring.*

Key words: *COVID-19, CRP and D-dimer*

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Introducton:

Coronavirus disease 2019 (COVID-19), caused by the Severe acute respiratory syndrome coronavirus 2, was first recorded in Wuhan, the capital of Hubei province of China in December 2019.1 While COVID-19 is primarily a respiratory illness, it can affect multiple organ systems including gastrointestinal, hepatic, cardiac, neurological, and renal systems.[2] COVID-19 is usually characterized by lower respiratory tract symptoms with fever, dry cough, and dyspnea, a manifestation similar to those of two other diseases caused by coronaviruses, severe acute respirato ry syndrome (SARS) and Middle East respiratory syndrome, MERS.[3] The reported overall case-fatality rate (CFR) for COVID-19 by now was 2.3%, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR.4 In some patients, severe pulmonary and extra-pulmonary complications may lead to respiratory failure and life-threatening events.

CRP is an acute-phase, nonspecific marker of inflammation or infection and has been found to broadly correlate with disease severity and treatment response across a variety of infectious and noninfectious conditions.[5] Elevated CRP levels have been previously reported in severe acute respiratory syndrome, Middle East respiratory syndrome, H1N1 influenza.[6-8] Recent studies have reported that CRP levels are elevated in patients with COVID-19 and may correlate with severity of disease and disease progression.[9] As such, CRP holds promise as a potential prognostic biomarker.

Coagulopathy was reported, and D-dimer elevations were seen in 3.75–68.0% of the COVID-19 patients.[10-12]

Previous studies in community-acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) patients have shown that D-dimer level is higher in severe cases and may be used as a prognostic biomarker[13-15], and D-dimer > 1 ìg/ml is one of the risk factors for mortality in adult inpatients with COVID-1912. However, the role of D-dimer in COVID-19 patients has not been fully investigated. A comprehensive description of trajectories of change in D-dimer levels in COVID-19 patients is lacking, and whether early levels and/or the early rate of change in D-dimer levels are predictive of risk of VTE or death remain unknown.[16] In our experience, biomarkers, which can identify thrombus formation at earlier stages, might be used to evaluate the formation of thrombus and response to treatment. D-dimers are fibrin degradation products which have been shown to be useful in a clinical decision rule for ruling out pulmonary embolism[17], highlighting its role as a potentially helpful biomarker. However, the relationship between CRP and D-dimer of COVID-19 and the level changes during disease development were not fully reported. In this study, we evaluate the changes of CRP and D-dimer level of COVID-19 patients and explored its association with markers of inflammation.

Methods:

This prospective observational study was conducted in Private set up and OPD, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka, between January 2020 and July 2020. The diagnosis of COVID-19 was according to World Health Organization interim guidance and confirmed by RNA detection of the SARS -CoV-2 in onsite clinical laboratory. A total of 49 participants who had a CRP and D-dimer levels on first visit and had a definite outcome were enrolled. All clinical, laboratory and outcome data were extracted using a standardized data collection form. Blood samples were collected on first visit to perform routine laboratory tests, such as blood count, coagulation profile, serum biochemical tests (including renal and liver function) et al in onsite laboratory. Baseline CRP levels were collected. D-dimer was determined on CS5100 automatic coagulation analyzer (Sysmex, Kobe, Japan) by utilizing a latex-enhanced photometric immunoassay (Siemens, Marburg, Germany, The laboratory reference range was 0-0.5 ìg/ml. The D-dimer result was expressed in ìg/ml FEU (Fibrinogen Equivalent Unit). All measurements were done within 2 hours after blood sampling. After 7 days CRP level s and D-dimer levels were collected for compared with baseline

levels.Collected data were compiled and appropriate analyses were done. Qualitative variables were expressed as percentage. Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. Paired t-test was used for continuous variables. P values <0.05 was considered as statistically significant.

Results:

Out of 49 COVID-19 patients, majority 22(44.9%) patients belonged to age 41 to 60 years. The mean age was 53.3±14.7 years. Forty one (83.7%) patients were male with male: female ratio was 5.1:1 (Table-1). Seventeen (34.7%) patients had hypertension followed by 15(30.6%) had diabetes mellitus, 4(8.2%) had COPD, 3(6.1%) had asthma and 2(4.1%) had CKD (Table-2). Twenty five (51.0%) patients had respiratory symptoms (Table-3). Co- morbidity was significantly higher in respiratory symptoms than without respiratory symptoms (Table-4). Mean CRP was found 39.6±54.6 mg/L in baseline and 10.1±13.0 mg/L in after 7 days. The difference was statistically significant (p<0.05) between baseline and after 7 days groups (Table-5). Twenty three (46.9%) patients were found D-dimer >3.0 gm/dl in baseline and 14(28.6%) in after 7 days. The difference was not statistically significant (p>0.05) between baseline and after 7 days (Table-6). CRP and D-dimer were not statistically significant (p>0.05) between age groups (Table-7).

Table-I

Demographic characteristics of the study patients (n=49)

	Frequency	Percentage
Age (years)21-40	9	18.4
41-60	22	44.9
61-80	18	36.7
Mean±SD	53.3+14.7	
Range (min-max)	21.0-75.0	
Sex		
Male	41	83.7
Female	8	16.3

Table-II

Co-morbidity of the study patients (n=49)

Co-morbidity	Frequency	Percentage
No	27	55.1
Yes	22	44.9
Hypertension	17	34.7
Diabetes mellitus	15	30.6
COPD	4	8.2
Asthma	3	6.1
CKD	2	4.1

Table-III

Respiratory symptoms of the study patients (n=49)

Respiratory symptoms	Frequency	Percentage
Present	25	51.0
Absent	24	49.0

Table-IV

Association between respiratory symptoms with co-morbidity (n=49)

Co-morbidity	Respiratory symptoms				P value
	Present		Absent		0.030s
	n	**%**	**n**	**%**	
Yes	15	60.0	7	29.2	
No	10	40.0	17	70.8	

s= significant
P value reached from chi square test

Table-V

CRP in different follow up (n=49)

CRP (mg/L)	Baseline		After 7 days		P value
	n	%	n	%	
<6.0	12	24.5	36	73.5	
>6.0	37	75.5	13	26.5	
Mean±SD	39.6±54.6		10.1±13.0		0.001s
Range (min-max)	5.0-302.4		3.0-69.7		

s= significant
P value reached from paired t-test

Table-VI

D-dimer in different follow up (n=49)

D-dimer (gm/dl)	Baseline		After 7 days		P value
	n	%	n	%	
<0.5	8	16.3	17	34.7	
0.5-3.0	18	36.7	18	36.7	0.066ns
>3.0	23	46.9	14	28.6	

ns= not significant
P value reached from chi square test

Table-VII

Association between baseline CRP and D-dimer with age (n=49)

	Age (years)						P value
	21-40		41-60		61-80		
	n	%	n	%	n	%	
CRP (mg/L)<6.0	3	33.3	5	22.7	4	22.2	0.792ns
>6.0	6	66.7	17	77.3	14	77.8	
D-dimer (gm/dl)							
<0.5	0	0.0	3	13.6	5	27.8	
0.5-3.0	6	66.7	9	40.9	3	16.7	0.094ns
>3.0	3	33.3	10	45.5	10	55.6	

ns= not significant
P value reached from chi square test

Discussion:

Coagulation dysfunction in COVID-19 patients insidiously drives progression to severe illness and fatal outcome, and is characterized by elevated D-dimer and thrombi in the veins and arteries.18 The high level of D-dimer in COVID-19 is triggered by excessive clots and hypoxemia. In addition, D-dimer elevation is frequently observed in COVID-19 patients with severe disease, and correlates significantly with mortality.12,19 CRP levels were positively correlated with lung lesion and disease severity. This suggests that in the early stage of COVID-19, CRP levels could reflect lung lesions and disease severity.[20]

In this study 49 patients with COVID-19 majority 22(44.9%) patients belonged to age 41 to 60 years. The mean age was 53.3±14.7 years with age range 21 to 75 years. In a study done by Yuet al.[21] observed that for COVID-19 patients, the median age was 65 years (IQR 54–72). Zhang et al.22 reported that the median age was 62 years (IQR,

48-69 years), ranging from 18 years to 92 years. 37.6% (129/343) patients were older than 65 years. Sharifpour et al.[23] described that the mean age of the cohort was 63±15 years. Another study done by Poudel et al.[24] demonstrated that the mean age of enrolled participants was 58.16±15.65 years.Present study observed that 41(83.7%) patients were male with male: female ratio was 5.1:1. In a study conducted by Poudel et al.24 reported that 113 (62.1%) were males and 69 (37.9%) were females. Sharifpour et al.[23] had observed that 63.6 patients were men and 44.4% were women. Another study done by Creel-Bulos et al.16 described that 61.0% were males and 41.0% females.

Regarding co-morbidity, observed that 17(34.7%) patients had hypertension followed by 15(30.6%) had diabetes mellitus, 4(8.2%) had COPD, 3(6.1%) had asthma and 2(4.1%) had CKD. Yu et al.21 demonstrated that 20(35%) patients had hypertension, 9(16%) had diabetes mellitus, 4(7%) had cardiovascular diseases, 1(2%) had CKD and

1(2%) had pulmonary disease. Sharifpour et al.[23] found hypertension (197 [73.5%]), obesity (141 [52.6%]), diabetes mellitus (118 [44.0%]), and a history of tobacco use (72 [26.8%]) were the most common comorbidities. Yao et al.[25] showed nearly one third of the patients had comorbidities, with

hypertension being the most common (31.5%), followed by diabetes mellitus (17.7%). Creel-Bulos et al.16 also found hypertension was present in 83(72%) and diabetes in 60 (52%).

This study found that 25(51.0%) patients had respiratory symptoms. Co-morbidity was significantly higher in respiratory symptoms than without respiratory symptoms. Bangladeshi study, Rahman et al.26 observed that majority of COVID-19 patients 300(60.0%) were symptoms free during follow-up and 40.0% had persistent respiratory symptoms.

This study observed that mean CRP was found 39.6±54.6 mg/L in baseline and 10.1±13.0 mg/L in after 7 days. The difference was statistically significant ($p<0.05$) between baseline and after 7 days groups. In a study done by Yu et al.21 reported that the specific relationship between D-dimer levels and CRP levels in COVID-19 patients, and found that both CRP levels and D-dimer levels decreased after treatment. They analyzed their relationship before and after treatment stratified by untreated CRP quartiles, as expected, after therapy, CRP levels were significantly decreased in the 2nd, 3rd and 4th quartiles of untreated CRP. Wang20 showed that CRP levels and the diameter of the largest lung lesion increased as the disease progressed. CRP levels were positively correlated with lung lesion and disease severity. Sharifpour et al.23 had described that the median CRP during hospitalization for the entire cohort was 130 mg/L (IQR 82–191 mg/L), and the median CRP on ICU admission was 169 (IQR 111–234). The hospitalization- wide median CRP was significantly higher amongst the patients who died, compared to those who survived [206 mg/L (157–288 mg/L) vs 114 mg/L (72–160 mg/L), $p<0.001$]. CRP levels increased in a linear fashion during the first week of hospitalization and peaked on day 5. Within the first 7 days, the maximum CRP was significantly higher in patients who died [median 309 mg/L (246–387 mg/L)] compared to those who survived [median 234 mg/L (148–312 mg/L), $p = 0.01$]. The slope of change in daily CRP levels within the first 7 days was also greater in patients who died [22.6, (5.12–41.7)] compared to those who survived [-0.84, (-18.4–13.4), $p<0.001$].

This study found that 23(46.9%) patients were found D-dimer >3.0 gm/dl in baseline and 14(28.6%) in after 7 days. The difference was not statistically significant ($p>0.05$) between baseline and after 7 days. Huang et al.2 showed D- dimer levels on admission were higher in patients needing critical care support than those who did not require it (median: 0.5 ìg/ml). Therefore, a recent guidance on recognition and management of coagulopathy in Covid-19 from International Society of Thrombosis and Haemostasis (ISTH) "arbitrarily defined markedly raised D-dimers on admission as three-four folds increase".[27] Yao et al.[25] also reported that D-dimer elevation (e" 0.50 mg/L) was seen in 74.6% (185/248) of the patients.

Limitation of the present study was the small sample size. Further clinical studies with larger sample size are required. Multiple-parameter prediction model including CRP, D-dimer and other variables might provide better predictive ability for COVID-19 patients.Conclusion:

At the early stage of COVID-19, CRP levels were positively correlated with lung lesions. Co-morbidity was significantly associated with respiratory symptoms. This study found significant reduced CRP levels after 7 days compared with baseline. D-dimer levels also reduced but not significant. There was no significant association between CRP and D-dimer with different age group. CRP and D-dimer levels could reflect disease severity and should be used as a key indicator for disease monitoring.

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