ASSOCIATION BETWEEN SERUM C-REACTIVE PROTEIN (CRP) AND D-DIMER LEVELS IN COVID-19 PATIENTS IN A TERTIARY LEVEL HOSPITAL, KHULNA

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Abstract

Background: *The novel corona virus disease 2019 (COVID-19) is major public health issue. It is the most significant global health challenge in the world. Biomarkers play a significant role to detect the severity of COVID-19 infection in the perspective of management of the patients.*

Aim and objective: *We aimed to assess the association between the levels of C-Reactive Protein and D-dimer in COVID-19 patients.*

Methods: *This cross-sectional study was conducted in the department of Pathology and department of Microbiology GMCH, Khulna. 152 patients with SARS-CoV-2 (COVID -19) positive patients were enrolled in this study. C-reactive protein and D-dimer levels are measured in the laboratory of Pathology department, GMCH, Khulna. All statistical computations were performed by using window-based computer software devised with Statistical Packages for Social Sciences (IBM SPSS Statistics 21 version).*

Results: *In this study CRP level was found of mean value of 62.84± 44.64 mg/L with a range of 1.40-195.20 mg/L. It was normal in 21 (13.8%) patients and increased in in 131 patients (86.2 %). The mean value of D-dimer was 2.48 ± 02.20 mg/L with a range of 0.10-9.35 mg/L. D-dimer was normal in 26 (17.1%) patients, whereas it was increased in 126 patients (82.9 %). We performed Pearson's correlation-coefficient (r) test to compare the association between the levels of CRP with D-dimer in COVID-19 positive patients. There was moderately positive and significant correlation ($r = +0.647$, $p < 0.05$) between the levels of CRP and D-dimer.*

Conclusion: *There was statistically significant correlation between the levels of serum CRP with D-dimer in COVID-19 positive patients. These two biomarkers can be used to assess the severity in patients with COVID-19 positive with thrombotic disorder for reduction of morbidity and mortality of COVID positive patients.*

Keywords: *COVID-19, CRP, D-dimer.*

DOI: https://doi.org/10.3329/jdmc.v32i1.76448
J Dhaka Med Coll. 2023; 32(1) : 57-62

Introduction:

In recent era, the novel corona virus disease 2019 (COVID-19) has become one of the life-threatening pandemics.[1] It is the most significant global health challenge which has devastated the world.[2] This novel member of human corona virus was first identified in Wuhan, China in December, 2019.

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Received: *09.02.2023* ***Revision:*** *04.12.2023* ***Accepted:*** *09.02.2024*

International Committee on Taxonomy of Viruses (ICTV) designated it as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).[3] According to WHO, 500,186,525 confirmed cases were detected till to date. Among them 6,190,349 were confirmed death.[4] Therefore the COVID-19 pandemic is a principal concern to nations worldwide,[5] The major group of patients with COVID-19 represents with mild influenza-like symptoms or may remain asymptomatic while others develop severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure and even death.[6] Due to this major asymptomatic group it is of utmost importance to identify the risk factors and laboratory parameters to identify patients.[5,7]

High-sensitive cardiac troponin, creatinine, aspartate aminotransferase (AST), procalcitonin, lactate dehydrogenase, CRP, lymphocyte count, interleukin 6 (IL-6) and D-dimer concentrations are increased in COVID-19 patients. Among these parameters, serum CRP concentration is crucial that strongly correlates with the severity of COVID-19 infection.[8] In COVID-19 infected patient excessive inflammation is considered to be the main cause of critical illness and death. Systemic inflammatory response occurs which can be evident by raised C-reactive protein level.[9] C-reactive protein is an acute phase protein, synthesized by the liver in response to cytokine (such as IL-6, TNF-a).[10] A cytokine response storm (CRS) is provoked in COVID associated pneumonia which stimulates hepatocyte to produce CRP. In this context CRP is a sensitive index to evaluate the inflammation associated tissue injury in COVID patients.[11] The average level of CRP in the blood is less than 10.0 mg/L. However, it rises within 6– 8 hours at the initial stage and reaches to its peak within 48 hours as the diseases progress.[2]

D-dimer is considered as the reliable marker to define hemostatic abnormalities in COVID 19 patients.[12] D-dimers are multiple peptide fragments which is produced as a result of degradation of crosslinked fibrin.[13] The level is increased in hypercoagulable state and fibrinolytic disorders. SARS-CoV-2 infection activates the coagulation cascade which is associated with a hypercoagulable state.[14] Any processes that involve production and breakdown of fibrin cause an elevation in D-dimer levels.[4] Moreover macrophages also contribute to elevate D-dimer level in COVID-19 patients. As macrophages produce plasmin in fibrin thrombi, whose ultimate fate is degradation of fibrin into D-dimer. [15] The normal value of D-dimer in blood is less than 0.50 mg/L. However, this value may be increased in complications caused by COVID-19 such as pneumonia. Thus, CRP and D-dimer level may act as potential biomarkers to represent the severity of disease as well as can be used to evaluate the response to treatment. [16]

Bangladesh represents the eighth among the most populated countries in the world with a population of 161 million. [17] The country has faced nearly 3,75, 870 SARS-CoV-2 cases till 9th October 2020 and 5,477 death occurs due to covid (https://iedcr.gov.bd/).[18] Screening of this large population with RT-PCR or ICT based technique is a challenging task.[19] In hospital indistinguishable respiratory symptoms poses a challenge of ensuring the identification and isolation of potential cases of COVID-19.[20] CRP and D-dimer not only help to assess the disease severity of COVID-19 patients they can also help to identify the suspected group of COVID-19 patients in hospital.[7,21] There are limited studies regarding potential association between CRP and D-Dimer concentration in COVID-19 patients in Khulna region, Bangladesh. Therefore, the aim of this study is to explore the association between CRP and D-dimer concentrations in patients with COVID-19 who were hospitalized in a tertiary healthcare system in Khulna, Bangladesh.

Methodology:

This cross-sectional study was conducted at the Department of Pathology, in collaboration with Department of Microbiology, Gazi Medical College Hospital (GMCH), Khulna over a period of six months from April to October, 2021. 152 COVID-19 patients who admitted in the Gazi Medical College Hospital, Khulna were enrolled by random sampling in the study. Within this period samples were assessed for SARS-CoV-2

RNA by real-time reverse transcription polymerase chain reaction (rRT-PCR) assay in the department of Microbiology, GMCH. All laboratory investigations were carried in the department of pathology, GMCH. Demographic and clinical profile of every patient were collected from patient's files.

Inclusion criteria:

i. Patients above the age of 18 years of both genders.

ii. rRT-PCR for SARS-CoV-2 (COVID -19) positive patients and

iii. Patients whose investigations were done from Pathology and Microbiology department, GMCH, Khulna.

Exclusion criteria:

i. Patients below the age of 18 years

ii. Suspected co-infection

iii. Covid-19 with pregnancy, trauma, liver disease, heart disease, sepsis or recent surgery

Statistical Analysis:

All statistical computations were performed by using window-based computer software devised with Statistical Packages for Social Sciences (IBM SPSS Statistics 21 version). In the study continuous data were expressed as means and standard deviations. Categorical data were expressed as numbers and percentages. The relationship among biomarkers was assessed using Pearson correlation coefficient test. For all statistical analysis we considered p value < 0.05 as statistically significant.

Results:

A total of 152 patients with COVID-19 were enrolled in this study. In this study all SARS-CoV-2 patients were confirmed by real-time reverse transcription polymerase chain reaction (rRT-PCR).

Figure 01 showed that 54% was male and 46% was female. The ratio was 1.7:1. Out of which male were 82 and female were 70. Male predominance was observed in the study.

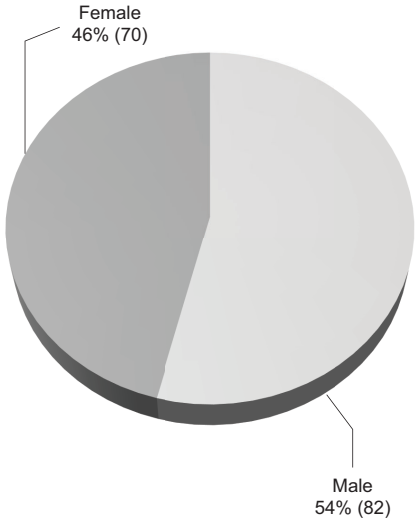

Figure 1: *Gender distribution of COVID-19 patients (n=152)*

Table-I

Mean value, Standard Deviation and range of Age (years), CRP (mg/L) and D-dimer (mg/L) level among patients with COVID-19 patients (n=152)

	Mean	Standard Deviation	Range
Age	55.91	16.34	19-90
CRP	62.84	44.64	1.40-195.20
D-dimer	2.4809	2.20574	0.10-9.35

Table I showed that mean value of age, CRP and D-dimer of COVID- 19 patients were 55.91 ± 16.34 (mean± SD) years with a range of 19-90 years, 62. 84± 44.64 mg/L with a range of 1.40-195.20 mg/L and 2.48 ± 02.20 mg/L with a range of 0.10-9.35 mg/L respectively.

Table-II

Laboratory findings of CRP and D-dimer levels of COVID-19 patients (n=152)

	No of patients	Percentage
CRP<10	21	13.8%
CRP>10	131	86.2%
D-dimer <0.5	26	17.1%
D-dimer >0.5	126	82.9%

In table II CRP level was normal (10.0<mg/L) in 21 (13.8%) patients and increased in (e"10.0 mg/L) in 131 patients (86.2 %). D-dimer level

was normal (<0.5 mg/L) in 26 (17.1%) patients, whereas it was increased in (e"0.5 mg/L) in 126 (82.9%) patients.

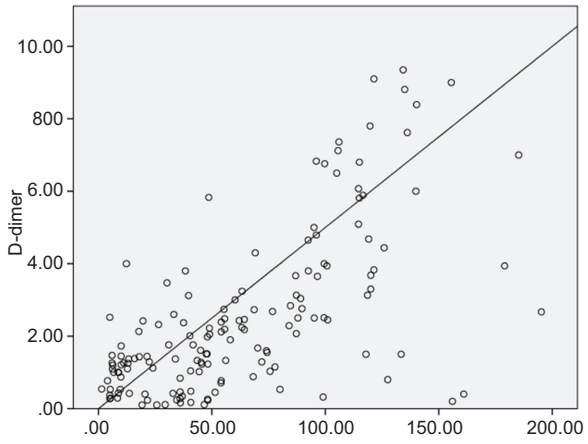

Figure 2: *Correlation between serum CRP and D-dimer level (n=152)*

In figure 02 positive and moderately significant correlation (r = + 0.647, p <0.05) was found between serum CRP and D-dimer level. Serum D-dimer and CRP concentrations were measured in 152 covid patients and expressed as mg/L.

Discussion:

The cross-sectional study was conducted in the department of Pathology in collaboration with department of Microbiology, Gazi Medical College & Hospital, Khulna. In this study, we investigated 152 Covid-19 patients who fulfilled the inclusion criteria of the study.

In this study, out of 152 patients of COVID-19, male patients were 82 and female patients were 70. Gender distribution of overall patients showed 54% male and 46% female. Male and female ratio was 1.7:1. In another study conducted by Barek Md. A. et al. in non-severe cases of COVID patients the males were 53.04% and 46.6 % were female which is similar with our study, however, in severe cases of covid patients, males were 62.83% and females were 37.17% .[22] In our study male predominance was observed in the study population, which was consistent with the study of Noman et al. in which 71% were male and 29% were female patients.[23] The study of Wang G et al. expressed that 62.5% were male in their aggravated patients.[8] In the study of Poudel et al. 113 (62.1%) were male and 69 (37.9%) were female among their 182 enrolled patient.[16]

In our study, the mean (± SD) age of patients was 55.91 ± 16.34 years with a range of 19- 90 years. Wang G et al. also observed that the median age of their study population was 54 years with a range of (35–68) years.[8] Poudel e al. showed that the mean age of their enrolled patients was 58.16 years (±15.65 years) in their studies.[16] The study of Chowdhury SN et al. expressed that mean age of their studied population was 53.5 ± 10.1 years which is consistent with our study.[24]

Regarding CRP level, mean CRP value was found 62.84± 44.64 mg/L with a range of 1.40-195.20 mg/L. In this study the cut off value of CRP was considered as <10.0 mg/L. It was normal (<10.0 mg/L) in 21 (13.8%) patients, whereas increased in (e"10.0 mg/L) in 131 patients (86.2 %) which is consistent with other studies.[9,14,22] Wang G et al. states that many COVID-19 patients in their study had raised CRP levels, which was significantly higher in aggravated cases than nonsevere patients.[8] Moreover in the study of Koozi et al. the standardized mortality ratio (SMR) of their patients was higher in the high CRP group (P = .001).[25] The CRP levels also correlated with ICU and hospital LOS (length of stay) in survivors (P<0.001 and P=0.002).[25]

Analysis of D-dimer study showed that mean value of D-dimer was 2.48 ± 02.20 mg/L with a range of 0.10-9.35 mg/L. The cut off value of D-dimer was considered as <0.5 mg/L. D-dimer was normal (<0.5 mg/L) in 26 (17.1%) patients and increased in (e"0.5 mg/L) in 126 patients (82.9 %). In other studies, D-dimer level has been markedly increased in COVID-19 patients which was in accordance with our studiy.[2,26] Debi et al. expressed that, the concentration of D-dimer level was comparatively higher in diabetic patients suffering from COVID-19 [Standard mean difference was 0.32 mg/L, 95% CI (0.17–0.47) mg/L, p-value < 0.0001.[2] Poudel et al. showed that the mean value of D-dimer among COVID patients who died was 3.208 ìg/ml (±2.613 ìg/ml). This is a highly statistically significant difference (p< 0.001, independent

samples T-test). They concluded that, D-dimer value on admission was an accurate and inexpensive biomarker for predicting COVID-19 prognosis and mortality of the patients.[16]

We performed Pearson's correlation-coefficient (r) test to compare the association between the levels of CRP with D-dimer in covid-19 positive patients. We observed that the level of D-dimer was increased with the level of CRP. There was moderately positive and significant correlation between the levels of CRP and D-dimer. Pearson's correlation coefficient was r = +0.647, p <0.05. A study conducted by Qi X et al. observed that there was significant and positive correlation between CRP and D-dimer levels (r= + 0.535, p< 0.0001).[27] On the contrary, Sukrisman L et al. observed a significant but weakly positive correlation between D-dimer and CRP (r = + 0.327; p < 0.001).[28] Other study conducted by Debi H et al. reported that pearson's correlation analysis was positive between the CRP and D-Dimer and age of COVID-19 diabetic and non-diabetic patients.[2] Poudel A et al. also expressed that CRP levels were increased with high D- dimer values which was statistically significant among diseased cases of COVID-19.[16]Limitations:

The study has some limitations. Other important biomarkers were not assessed in this study. Moreover, this study was conducted in only tertiary level hospital, not primary level. For this it may not reveal the real scenario.

Conclusion:

COVID-19 is a serious health issue with clinical features which may differ with age and presence of co-morbidities. Biomarkers will play a critical role in early diagnosis, prognosis of disease as well as management of the patients. Our study revealed that there was statistically significant correlation between the levels of serum CRP with D-dimer in COVID-19 positive patients. These two biomarkers are good indicator to assess the severity in patients with Covid-19 positive with thrombotic disorder. Moreover, raised levels of CRP can determine the thrombotic disorder of Covid patients at early stage as this level correlates with the level of D-dimer. Thus, increased CRP and D-dimer level suggest early initiation of treatment for reduction of morbidity and mortality of COVID positive patients.

Acknowledgement:

Authors of this study are thankful to the authority of the Department of Pathology and the Department of Microbiology, Gazi Medical College & Hospital, Khulna for their nice cooperation during sample collection and laboratory procedure.

Conflict of interest:

None declared.

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