Studying C-reactive protein and D-dimer levels in blood may prevent severe complications in Bangladeshi COVID-19 patients

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Abstract

The ongoing COVID-19 pandemic has been a scientific, medical and social challenge. Since clinical course of this disease is largely unpredictable and can develop rapidly causing severe complications, it is important to identify laboratory biomarkers which may help to classify patient's severity during initial stage. Previous studies have suggested C - reactive protein (inflammatory) and D-dimer (biochemical) as an effective biomarker. The differential severity in patients across the world and our limited understanding in the progression of the disease calls for a multi-country analysis for biomarkers. Therefore, we have analyzed these biomarkers among 228 Bangladeshi COVID-19 patients. We show significant association of COVID-19 severity with these two biomarkers. Thus, we suggest using these biomarkers for Bangladeshi COVID-19 patients for disease monitoring. Such validated preventive measures may decrease the case fatality ratio substantially.

Introduction

COVID-19 patients are categorized into mild, moderate, severe, and critical based on disease severity. In order to stratify high risk patients there is an urgent need for reliable biomarkers related to coronavirus disease 2019 (COVID-19) progression. Novel biomarkers are also needed to understand viral pathogenetic mechanisms and to categorize patients into those who suffer rapid disease progression to severe complications like death. Association of severity with some hematological parameters like white blood cell (WBC), lymphopenia, and some biochemical parameters, such as LDH, creatine kinase (CK), IL-6 and troponin have already been reported to be associated with COVID-19 severity[1].

C-reactive protein (CRP) is a pentameric protein, synthesized primarily in liver under the action of cytokine interleukin 6 (IL-6)[2]. Levels of CRP > 50 mg/dL are reported to be associated with bacterial infections while more elevated levels are also seen in injuries, cardiovascular processes and other inflammatory states[2]. D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis[3] Higher D-dimer levels are indicative of the activation of coagulation and following fibrinolytic process[3] and, are reported in influenza like infections by respiratory viruses even before the outbreak of coronavirus pandemic[4].

Although number of studies have already shown the association of COVID-19 severity with CRP and D-dimer levels in blood, there are limited studies done on Bangladeshi populations [5, 6, 7, 8, 9]. In a recent study done by Ullah, Waqas et al [2] both high D-Dimer (> 501 ng/ml) and high CRP (> 101 mg/dl) were associated with increased need for upgrade to the ICU and higher requirement for (intermittent mandatory ventilation) IMV on day-7 of hospitalization(2,25). Therefore, for the first time in Bangladeshi individuals, plasma CRP and D dimer levels is demonstrated to assist for discerning patients with low to severe (live and dead) COVID-19 pneumonia belonging to different age groups. This suggest that these testing may be useful as an earlier indicator for severe illness and help physicians to stratify patients for intense care unit transfer[10]. Our aim is to focus on CRP and D-dimer levels, which are potentially predictive of patients with severe complications and death in COVID-19 infection. In order to screen out biochemical

indicators that are meaningful for the diagnosis of disease progression, we consulted the laboratory test results of all the dead and recovered patients from cabin/Ward and ICU.

Methods

Data Collection

In this retrospective study, we include hematological data of all confirmed cases of COVID-19 from Anwar Khan Modern Medical College Hospital, Lab Aid Medical College Hospital, and in some cases communication with patient's family from June 2020 to November 2020. Ethical permission was taken from the Biological Science Faculty, Dhaka University, Bangladesh. The medical treatment consent was obtained by the physicians of the two Hospitals. We have called few patients (or their family) and explained this study to them to obtain their consent.

COVID-19 test were done using reverse transcriptase polymerase chain reaction (RT-PCR) technique. We have accessed to patients' data at the end of November 2020, only with serial number (fully anonymous). We include those patients with criteria having CRP and D-dimer results and admitted to ICU and non-ICU. We considered 144 cases from ICU, 84 cases from non-ICU and through telephone communication. The patients' lab test data also include age, gender, patients' status and hospital status.

All medical laboratory data including the concentrations of D-dimer, and high-sensitivity C-reactive protein (CRP), were generated by the Biochemistry laboratory of two Hospitals recorded electronically in their database. The samples for laboratory tests were collected on admission and during the hospital stay or visit. Peripheral venous blood was collected and D-dimer was measured with a latex particle-enhanced immune turbidimetric assay Sysmex 1000 (Siemens Healthcare, NY, USA)). It is worth mentioning that CRP tests were detected using Dimensional RxL Max integrated chemistry system (Siemens Healthcare, NY, USA) in both hospitals.

Statistical Analysis

CRP and D-Dimer levels were collected from the patients admitted in Cabin/Ward and ICU. The Pearson Correlation test was applied to test the correlation among patient's age, hospital status, D-dimer and CRP value and patient's status (Survived or Died) using SPSS v 26.0.0.0. We recoded patient recovered and dead status as 0 and 1 respectively. Similarly, male and female sexes were coded as 1 and 0 respectively. Hospital Cabin/Ward patients and ICU patients were coded into 0 and 1. We ran Logistic Regression Test for the combined dataset keeping Severity as dependent variable and CRP and D-dimer levels as independent. A *P* value below 0.05 was considered statistically significant.

Results And Discussion

Inflammatory responses play a crucial role in progression of COVID-19 [11, 12, 13]. Rapid viral replication of the SARS-CoV-2 virus involves recruitment of macrophages and monocytes, release of cytokines and

chemokines, thus triggering inflammatory responses[14]. CRP (C-Reactive protein) has been reported in dengue patients[15]. Dengue virus and SARS-CoV-2 are RNA virus, share similarity in the course of infection[15]. CRP is rapidly synthesized in response to a variety of eukaryotic and prokaryotic pathogens, by hepatocytes when stimulated by inflammation, facilitating complement activation through classical pathway[16], indicating immune activation, lymphocyte infiltration, immune molecules consumption and inflammation outbreak. It is also inferred that increased CRP levels could be early indicators of nosocomial infections in COVID-19 patients who were slow to recover [10]. Higher levels of CRP, a potential inflammatory biomarker has been reported to be significantly associated with disease severity in COVID-19 infections[10, 17, 18]. CRP levels have also been reported to be increased in elderly or old age individuals [17, 18].

A total of 228 patients with a confirmed diagnosis of COVID-19 were included in our study. [Supplementary Tables 1 and 2].Based on disease severity, patients were divided into two comparison groups (Cabin/Ward and ICU patients).We found significantly strong correlation between D-dimer and CRP levels with age and severity in the combined dataset of ICU and non-ICU COVID-19 patients [Fig. 1 and Table 1].Increased age and D-dimer values were found to be significantly associated with the patients admitted to ICU. Significant correlation of CRP levels with Age (Correlation coefficient = 0.250, P-value < 0.05), and Severity (Correlation Coefficient = 0.445, P-value < 0.001) was found in non-ICU patients [Supplementary Table 3]. In patients admitted to ICU, we found strong correlation of D-dimer with age (Correlation Coefficient = 0.304, P-value < 0.01) and Severity (Correlation Coefficient = 0.465, P-value < 0.001);correlation of CRP levels with severity (Correlation Coefficient = 0.292 P-value < 0.01) and D-dimer (Correlation coefficient = 0.193, P-value < 0.05) [Supplementary Table 4].Both Higher D-dimer (odds ratio = 1.723, 95% confidence interval: 1.420–2.089, $p < 0.001$) and CRP-values (odds ratio = 1.011, 95% confidence interval: 1.004–1.019, $p = 0.001$) were associated with increased severity in patients (Table 2).

Table 1

Correlations between Age, Gender, D-dimer value, CRP value, Hospital ward and Severity for the combined dataset of ICU and non-ICU COVID-19 patients

		Age	D-dimer Value (mg/L)	CRP value (mg/L)	Hospital ward	Severity	Gender
Age	Pearson Correlation	1	.382**	.148*	.391**	.210**	0.109
	Sig. (2-tailed)		< 0.001	0.029	< 0.001	0.002	0.103
	N	223	223	220	223	222	223
D-dimer Value (mg/L)	Pearson Correlation	.382**	1	0.147*	.658**	.504**	-0.016
	Sig. (2-tailed)	< 0.001		0.027	< 0.001	< 0.001	0.809
	N	223	228	225	228	227	228
CRP value (mg/L)	Pearson Correlation	.148*	.147*	1	0.012	.313**	-0.016
	Sig. (2-tailed)	0.029	0.027		0.853	< 0.001	0.816
	N	220	225	252	225	224	225
Hospital ward	Pearson Correlation	.391**	.658**	0.012	1	.269**	-0.018
	Sig. (2-tailed)	< 0.001	< 0.001	0.853		< 0.001	0.788
	N	223	228	225	228	227	228
Severity	Pearson Correlation	.210**	.504**	.313**	0.269**	1	0.028
	Sig. (2-tailed)	0.002	0	0	0		0.679
	N	222	227	224	227	227	227
Gender	Pearson Correlation	0.109	-0.016	-0.016	-0.018	0.028	1
	Sig. (2-tailed)	0.103	0.809	0.816	0.788	0.679	
	N	223	228	225	228	227	228
**. Correlation is significant at the 0.01 level (2-tailed).							

Age	D-dimer Value (mg/L)	CRP value (mg/L)	Hospital ward	Severity	Gender
*. Correlation is significant at the 0.05 level (2-tailed).					

Table 2
Logistic regression analysis predictive of severity in COVID-19 patients.

Variable	OR (95%CI)	P-value
CRP (mg/l)	1.011 (1.004– 1.019)	0.001
D-dimer (µg/ml)	1.723 (1.420– 2.089)	< 0.001
Supplementary Table 1. Values of D-dimer and CRP in ICU patients admitted to Hospital.		
Supplementary Table 2. Values of D-dimer and CRP in non-ICU patients admitted to Hospital.		
Supplementary Table 3. Correlations between Age, Gender, D-dimer value, CRP value, Hospital ward and Severity for non-ICU COVID-19 patients.		
Supplementary Table 4. Correlations between Age, Gender, D-dimer value, CRP value, Hospital ward and Severity for ICU COVID-19 patients.		

It is interesting to note that D-dimer is commonly high in patients with COVID-19. D-dimer levels indicate disease severity and are reliable prognostic test to rule out the presence of a serious blood clot in patients who were admitted for COVID-19 treatment. While higher levels of C reactive protein (CRP) may be a predictive marker in determining systemic inflammation and can predict which patients with mild COVID-19 will progress to a severe case.

Processes that involve production and breakdown of fibrin cause an elevation in D-dimer levels [2, 19]. Increased D dimer levels are reported to develop acute respiratory distress in COVID-19, with the more chances of micro pulmonary embolism especially in severe forms of COVID-19 [22]. D-dimer levels have been reported to vary among patients with confirmed venous thromboembolism (VTE) depending on clot burden, timing of measurement, and initiation of treatment [23]. D-dimer has also been shown to increase with age, which can cause more false positive tests in older patients [24]. Also, several potential risk factors during hospitalization like, disseminated intra vascular coagulation, infection, dehydration, prolonged immobilization, mechanical ventilation, and central venous catheter use may further increase D-dimer concentrations [23, 24].

In conclusion, we confirm the association of two main, inflammatory and biochemical covariates with COVID-19 severity for the first time in Bangladeshi patients. The study can help in detail understanding of the complications caused and predict the progression of the disease with much more confidence.

Declarations

Acknowledgements

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Ethical approval: This study was approved by the ethics committee of Biological Science Faculty, University of Dhaka, Bangladesh.

Author Contribution

GNNS, GC conceived and designed the study. GNNS, KA, PPS, MAI, MFR collected the data. AS and GNNS performed statistical analysis. AS, GNNS and GC wrote the paper with inputs from other authors.

Competing interests: The authors declare no competing interests.

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Tables

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D-dimer (µg/ml)	1.723 (1.420–2.089)	< 0.001

Figures

Figure 1

Box-and-whisker plot showing distribution of D-dimer (left) and CRP (right) values among various categories of COVID-19 patients.

Supplementary Files

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- [4.SupplementaryTables.pdf](#)