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Original Research Article

Correlation between D-dimer and computed tomography severity score in middle aged young adults with COVID-19 pneumonia: a retrospective study

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ABSTRACT

Background: An unknown pneumonia broke out in Wuhan City in December 2019 and it was confirmed as an acute respiratory infectious disease caused by Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, formerly known as 2019-nCoV). Consumption coagulopathy, which should be obviated in order to decrease mortality, arises in disseminated intravascular coagulation with a decrease in fibrinogen and an increase in D-dimer levels. However, studies on the predictive and prognostic values of coagulation parameters in the setting of patients with COVID-19 are still limited. The objective of this retrospective study was to investigate the correlation of D-dimer and computed tomography severity score in patients with COVID-19 pneumonia.
Methods: The present retrospective study was conducted among 108 subjects reported COVID RT-PCR positive admitted during the study period i.e.; January-August 2021 in the department of medicine of Rural Medical College, Loni. Pneumonia was confirmed by Computed tomography (CT) examination and coagulation test completed within 12 hr after admission were enrolled. Coagulation tests, which Fibrinogen (Fib) and D-dimer were performed. CT score was categorized into mild (0-7), moderate (8-16) and advanced grade (17-25 points).
Results: The mean age of male and female was 38.52±5.34 and 35.67±3.22 years respectively, with an overall age of 37.79±4.58 years. Mean D-dimer level was 0.54±0.09, 0.91±0.22 and 1.96±0.47 mcg/ml among subjects having mild, moderate and severe CT score respectively. According to multivariate analysis, higher D-dimer (OR:3.61, $p<0.01$) was significantly associated with CT severity score.
Conclusions: Study concluded that the D-dimer level's time point was matched to the time of CT scan, we have reasons to correlate that the D-dimer level may predict the severity of inflammation prior to coagulopathy/thrombosis.

Keywords: COVID-19, Pneumonia, D-dimer, Computed tomography severity score

INTRODUCTION

An unknown pneumonia broke out in Wuhan City in December 2019, and it was confirmed as an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV). The disease was subsequently named coronavirus disease 2019 (COVID-19) by the WHO on 11 February 2020. SARS-CoV-2 is highly contagious and can cause serious lung injury, resulting in death.[1] Generally, the majority of COVID-19-positive patients are present with general symptoms of respiratory infection with a case fatality rate of 1.4-4%.[2,3] In some cases that develop severe or critical illness, death may be due to massive alveolar damage and progressive respiratory failure, with a higher mortality rate (38-60%).[3,4]

Disseminated intravascular coagulation (DIC) is one of the major underlying causes of death in these patients.

Consumption coagulopathy, which should be obviated in order to decrease mortality, arises in DIC with a decrease in fibrinogen and an increase in D-dimer levels. In fact, fibrinogen and one of its end products, D-dimer, have also been reported to have predictive value regarding the mortality of patients with non-COVID sepsis secondary to complications of DIC. Therefore, anticoagulation, considering its mortality benefits in non-COVID sepsis, may also have an important role in the treatment of COVID-19.[4,5]

The gold-standard technique for diagnosis is Reverse transcription-polymerase chain reaction (RT-PCR), with high specificity. Still, this investigation's downside is the lack of sensitivity and the lengthy time to reach diagnosis. On the other hand, computed tomography (CT) is a readily available fast technique and high sensitivity. Despite having a very high sensitivity, which can be up to 97.2%, unfortunately, CT has a very low specificity, which can reach as little as 25%. Thus, this has made CT one of the cornerstones in diagnosing COVID-19 infection.[6]

The influence of coagulation dysfunction on the prognosis of COVID-19 is attracting increasing attention. However, studies on the predictive and prognostic values of coagulation parameters in the setting of patients with COVID-19 are still limited. The objective of this retrospective study was to investigate the correlation of D-dimer and CT severity score in patients with COVID-19 pneumonia.

METHODS

The present retrospective study was conducted in the department of general medicine of Rural Medical College of Pravara Institute of Medical Sciences, Loni, Ahmednagar, Maharashtra, India. The data was taken from all the entries of COVID register. The study comprised of 108 subjects reported COVID-19 positive during the study period i.e. from January 2021-August 2021. Out of 108, about 40 young adults having age of 30-40 years with no co-morbidities were selected. The subjects were included and excluded according to the following mentioned criteria:

Inclusion criteria

All COVID-19 RT-PCR positive patients in age group of 30-40 years with no known comorbidities

Exclusion criteria

Subjects having following characteristics were excluded from the study- (a) chronic liver disease; (b) patients on anti-coagulant drugs; (c) previous history of pulmonary embolism and DVT; (d) patients with sepsis and myocardial infarction; and (e) patients with known co-morbidities such as hypertension, diabetes, thyroid disorders, cerebrovascular accidents, COPD, PCOS, ischemic heart disease were excluded. COVID-19 was diagnosed on the basis of the WHO interim guidance. The severity of COVID-19 was defined according to WHO clinical management guidance of COVID-19.[7] Severe type was defined as followed: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 < 90% on room air. A questionnaire was prepared to collect the patient's demographic profile. Patients date of admission and discharge was recorded. Patient's diagnosis was identified.

COVID-19 infection was confirmed by real-time RT-PCR assay from nasopharynx swab samples. Pneumonia was confirmed by CT examination and coagulation test completed within 12 hr after admission were enrolled. Patients with specific cardiovascular disease who used anticoagulants before admission were also excluded. Coagulation tests, which Fibrinogen (Fib) and D-dimer were performed using a Sysmex CS5100 automatic coagulation analyzer (Japan) and proprietary reagents.

Image acquisition

CT chest scanning was performed for all patients using a 16-channel CT scanner. The scanning range included the whole chest from the thoracic inlet down to the diaphragm. All the patients were scanned without contrast media injection. The patient was in the supine position and scanned with breath holding at the end of inspiration.

The scanning parameters were as following: tube voltage, 120 kV; tube current, 50 mA; rotation time, 0.5 s; and slice thickness of 5 mm.

CT analysis

Two experienced radiologists evaluated all the CT chest examinations independently, and the discrepancies were resolved by agreement. CT images of each patient were assessed for the presence and distribution of parenchymal abnormalities, including Ground-glass opacities (GGO), consolidation, multifocality, distribution (peripheral or diffuse), septal thickening, crazy paving, pulmonary nodules, pleural effusion, and mediastinal lymph nodes with short-axis >1 cm.

The CT severity score was assigned for each lobe as the following: 0 score- no involvement; 1 score- <5% involvement; 3 score- 25-50% involvement; 4 score- 50-75% involvement; and 5 score- >75% involvement. Score was multiplied by 5 to calculate the overall severity score. A mild grade is of 0-7 points, a moderate grade is of 8-16 points, and an advanced grade is of 17-25 points.

Statistical analysis

The means and standard deviations of the measurements per group were used for statistical analysis (SPSS version -22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test and the level of significance was set at $p<0.05$. Logistics

regression was used to associate factors with severity of COVID-19.

RESULTS

As Table 1 shows that the present study comprised of 40 subjects, out of which 11 were females and 29 were males. The mean age of males and females was 38.52±5.34 and 35.67±3.22 years respectively with an overall age of 37.79±4.58 years.

It was seen from Table 2 that the mild, moderate and severe CT score was reported among 40%, 52.5% and 7.5% of the subjects respectively.

Table 1: Gender distribution according to mean age.

Gender	N	Age (in years)	
		Mean	SD
Female	11	35.67	3.22
Male	29	38.52	5.34
Total	40	37.79	4.58

Table 2: Distribution of cases according to CT severity score.

CT severity score	N	Percentage
Mild (0-7)	16	40
Moderate (8-16)	21	52.5
Severe (17-25)	03	7.5

Table 3: Comparison of D-dimer level with CT severity score.

CT severity score	D-dimer (µg/ml; normal range- 0-0.5)		
	Mean	SD	Median (IQR)
Mild	0.54	0.09	0.5 (0.36-1.09)
Moderate	0.91	0.22	0.78 (0.51-1.42)
Severe	1.96	0.47	1.84 (0.87-4.77)
ANOVA test		6.91	
P value		<0.01 (significant)	

Table 4: Multivariate analysis of D-dimer with CT severity score.

D-dimer (µg/ml)	Multivariate analysis		
	Odds ratio	95% CI	P value
<0.5	1 (Reference)	2.29-6.97	<0.01 (Significant)
≥0.5	3.97		

It was evident from Table 3 that the mean D-dimer level was 0.54±0.09, 0.91±0.22 and 1.96±0.47 µg/ml among subjects having mild, moderate and severe CT score respectively. When mean D-dimer level was compared statistically between mild, moderate and severe CT score, it was found to be statistically significant. As seen in Table 4 that according to multivariate analysis, D-dimer (OR: 3.61, p<0.01) was significantly associated with CT severity score.

DISCUSSION

The aim of the study was to investigate the correlation of D-dimer and CT severity score in patients with COVID-19 pneumonia. The present study comprised of 40 subjects, out of which 11 were females and 29 were males. The mean age of males and females was 38.52±5.34 and 35.67±3.22 years respectively, with an overall age of 37.79±4.58 years. In this study, mean D-dimer level was comparatively and significantly higher among subjects having moderate/severe CT score as compared to mild CT score. According to multivariate analysis, higher D-dimer (OR: 3.61, p<0.01) was significantly associated with CT severity score. Similar results were reported by Yu et al and Luo et al.[1,8]

Another study by Guan et al analyzed 1099 patients with laboratory-confirmed COVID-19 from over 550 hospitals in China and found the non-survivors had a significantly higher D-dimer (median: 2.12 mcg/ml) than that of survivors (median: 0.61 mcg/ml).[9] Similarly, a study by Tang N et al. also observed abnormal coagulation results, especially markedly elevated D-dimer in deaths with COVID-19.[10] Also Zhou et al conducted a retrospective study involved 191 patients with COVID-19 and found that D-dimer greater than 1 mcg/ml on admission was associated with in-hospital death (HR:18.42, 95%CI: 2.64-128.55).[11]

Another study by Huang et al showed that D-dimer levels on admission were higher in patients needing critical care support than those who did not require it (median: 0.5 µg/ml).[4] Therefore, a recent guidance on recognition and management of coagulopathy in COVID-19 from International Society of Thrombosis and Hemostasis (ISTH) 'arbitrarily defined markedly raised D-dimers on admission as three-four folds increase'.[7]

Similarly, Mohamed et al in their study revealed that CT severity score and D-dimer were predictive for death.[6] According to Wang et al the D-dimer levels were significantly different across CT score tertiles [0.37 mg/l (IQR, 0.31-0.87), 0.66 mg/l (IQR, 0.39-1.43), 1.83 mg/l (IQR, 0.85-4.41), p<0.001].[12]

The natural logarithm of the D-dimer level was significantly associated with the CT score (RS=0.586, p<0.001). These findings were similar to our study.

Limitations

First, our study might have selection bias because it was a single-center. Despite our efforts to include all qualified patients, some patients still excluded in enrollment due to absence of D-dimer level on admission. Second, due to difference of patient's size and medical resources, the lengths from illness onset to admission of the included

patients might not be representative, which might influence D-dimer and fibrinogen levels on admission.

CONCLUSION

Based on our findings in which the D-dimer level's time point was matched to the time of CT scan, we have reasons to correlate that the D-dimer level may predict the severity of inflammation prior to coagulopathy/thrombosis. Uncontrolled inflammation response itself could result in severe lung injury and sequentially aggravate coagulopathy/thrombosis and then lead to poor outcomes, even death. This could be an additional explanation for the mechanism of elevated D-dimer level predicting higher mortality. Further researches are needed to investigate the relationship between the dynamics of D-dimer level and severity of inflammation and coagulopathy.

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