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Correlation of D-Dimer Level with Severity of Pneumonia, Hospital Stay and Mortality in Case of Covid-19 Infection: A Retrospective Study an a Tertiary Care Hospital.

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Abstract

Introduction: Worldwide there was a pandemic of novel corona virus infection in which one of the major concern was the risk of thrombosis and the mortality associated with it.

Aim: In this study our aim was to observe the changes in D-dimer levels during disease progression and its correlations with severity of Pneumonia, duration of hospital stay and mortality of COVID-19 patients.

Materials & Methods: In this study we reported the clinical, radiological and pathological laboratory results of 432 cases of confirmed COVID-19 infection. In these patients their clinical presentation, concentration of D-dimer, coagulation parameters, CBC, severity of Pneumonia on HRCT, hospital stay and higher mortality were retrospectively analyzed.

Result: All the statistical variables were expressed in % and compared with x^2 test. Out of the 432 cases in 45 cases (10.41%) the D-dimer values were >2.4µg/ml and in 15 cases the value were very high (3.47%). When correlated these patients found to have severe degree of pneumonia, longer hospital stay and higher mortality rate in comparison to patients with D-dimer level of <2.4 µg/ml.

Conclusion: D-dimer level could be used as an early marker for the clinical classification, risk stratification and improved management of COVID-19 patients.

Keywords: COVID-19, D-dimer , pneumonia, hospital mortality.

Introduction

Worldwide there was a pandemic of a novel member of human corona virus which is newly identified in Wuhan, China. It is officially named as severe acute respiratory Syndrome corona virus -2 (SARS-CoV-2) by International Committee on taxonomy of viruses, ICTV.[1-3] SARS-CoV-2 belongs to the beta-corona virus 2 and is a new strain of RNA Virus. Recently the disease caused by SARS-CoV-2 is named as COVID-19 (Corona Virus disease 2019) by World Health Organization(WHO).

It is typically spread via respiratory droplets and during close contact. The main clinical manifestation is lung injury. [4,5] COVID-19 is usually characterized by symptoms of fever, dry cough and dyspnoea similar to the other two diseases caused by Corona viruses, severe acute respiratory syndrome(SARS) and Middle East Respiratory Syndrome, MERS. [6,7]

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Most of the patients have a favourable prognosis but some rapidly progress to severe and critical cases with respiratory distress syndrome, coagulation dysfunction ,multi-organ failure etc. [8,9] The reported overall case fatality rate (CFR) for COVID-19 by now was 2.3% but in cases of aged individuals (70-79 years) had an 8% CFR and in cases of aged 80 years and older had a 14.8% CFR. [10] It has been reported that about 50% of the patients had increased D-dimer levels and abnormal D-dimer levels are associated with poor prognosis.[4,9] It has been reported that markedly elevated D-dimer levels were observed in non-survivors. [11]

One of the key issues in this outbreak of COVID-19 infection is very high number of patients presenting to hospitals and health centres leading to overwhelming of human & mechanistic capacity available specially the need for critical care support. For this reason risk stratification of the COVID-19 patients is absolutely helpful for better management of patients. [9,4] Therefore early and effective predictors of clinical outcomes are urgently needed for risk stratification.

Aim

The aim of our study was to compare the D-dimer level with that of the severity of Pneumonia, with inflammatory and coagulation markers and duration of hospital stay along with mortality in COVID-19 patients.

Materials and Methods

Study design

This is a retrospective study done in a tertiary care hospital (CMSDH, Kolkata) of West Bengal.

Duration

The study was conducted from 30th June 2020 to 30th June 2021.

Participants

Inclusion Criteria - The patients having a positive result of SARS-CoV2 by RT-PCR are included in the study.

Exclusion Criteria - Patients with absent/negative SARs-CoV-2 RT-PCR test are excluded from the study.

The study was approved by the Institutional Ethics committee (IEC) of our institute. In this retrospective study the data collected involves no potential harm to the patients and there was no link between the researcher and the patients.

Clinical Classification of the patients :

All the COVID-19 patients are clinically categorized into four groups, mild, moderate, severe and critical.

1) **Mild cases** - Mild clinical symptoms of fever with no features of Pneumonia in imaging.
2) **Moderate cases** - Fever, respiratory symptoms like cough and there is features of Pneumonia in imaging and Spo2 more than equality 90% in room air.
3) **Severe cases** - They have severe respiratory distress, RR> 30 breaths/min, the oxygen saturation is < 90% at resting state in room air and on imaging >50% lesion in the lung.
4) **Critical cases** - These patients have any of the following.

Respiratory failure with requirement of mechanical ventilation,

or shock or multi-organ failure that require monitoring in the CCU.

The outcome of illness were divided into four categories -

1. Hospital discharge.
2. Improved
3. Exacerbation.
4. Death.

Laboratory investigation

Laboratory interventions were done at the following point of time and the data were analysed.

First - Within 24 hours of admission into the General Covid Ward the following assays were done. Blood samples were collected for - CBC, D-dimer, PT/APTT.

Routine biochemical tests were sent to the Central Laboratory of our hospital.

ECG and HRCT of thorax were simultaneously done.

Second - After initial evaluation then all the Blood tests and HRCT repeated after 5-6 days and again

evaluated for the outcome as follows -

1. Hospital discharge.
2. Improved.
3. Exacerbation.
4. Death.

Out of these only in improved cases the laboratory assay repeated while they continued to stay at the general Covid ward.

The third laboratory assay:

It is done in CCU segment of our hospital. The laboratory assay includes those patients which are very critical at the initial time of assay and immediately shifted to CCU and also those patients which were exacerbated in the general Covid ward and then shifted to CCU.

The following parameters were evaluated.

1. **CBC** (Complete blood count) done from peripheral venous blood by automated cell counter 5 part (Sysmex Xs-800i) and were studied for increased leukocyte counts as a surrogate marker of Pneumonia.
2. **Inflammatory markers** (IL6 &hs-CRP) were analyzed by full auto biochemistry analyzer ERBAXL 640, Germany.

   hs-CRP (N-range) 0.5 to 10 mg/L.
3. **D-dimer levels & coagulation parameters (PT-INR, APTT**) were estimated by fully automated coagulation analyzer STA satellite Max, stago, France by utilizing CL89050422.
4. **HRCT** Routinely in all COVID-19 patients HRCT of thorax were done to assess the severity of involvement of lungs by organizing Pneumonia and fibrosis. Reporting were done basing on the CT severity score. (CT-SS).

Left lobe and right lobe of lungs were divided into 10 segments each. Basing on the severity of Pneumonia in each segment scoring were done, as follows

Score 0 (No involvement of the parenchyma), Score 1(< 50% of parenchymal involvement) and Score 2 (> 50% of parenchymal involvement).

Lowest Score - 0

Highest Score - 40

-> All the data were retrospectively analyzed from the records in the Radio-diagnosis department of our hospital.

-> Categorization of covid Pneumonia basing on CTSS were as follows Mild(Score < 7 or = 7}, Moderate (Score 8- 17) and Severe (> 18 or = 18).

Results

All the categorical variables were expressed as number(%) and compared by x2 test.

We used IBM SPSS software version 20.0 for statistical analysis.

P values <0.0001 were considered statistically significant Association of D-dimer level with severity of Covid Pneumonia on HRCT of thorax were studied.

D-dimer levels were correlated with hospital stay and mortality.

D-dimer levels also correlated with the levels of inflammatory markers and coagulation parameters.

Table 1: Basic clinical parameters of Covid-19 patients at the time of admission

n= 432

(A) AGE & SEX		
Age(In years)	**Male**	**Female**
>80	06 (2.4%)	02 (1.1%)
60-80	136 (53.9%)	100 (55.5%)
40 -59	90 (35.7%)	74 (41.1%)
20-39	18 (7.1%)	06 (3.3%)
(B) Clinical Presentation	Number Of Cases	%
Fever	402	93
Cough	380	87
Shortness Of Breath	350	81
Myalgia	180	41
Diarrhea	54	12
Joint Pain	38	8.7

Table-2 : D -dimer level, CT- severity Score and Categories of patients (WHO guidelines) at the time of Admission.

n=432

D-dimer level	Number of cases	%
0.4-1 µg/ml	234	54.1%
1-2.4 µg/ml	138	31.9%
>2.4 µg/ml	45	10.41%
Very high level	15	3.47%
CT Severity Score		
CT severity score	No of cases	%
< or =7 (Mild	238	55.09%
8-17(Moderate)	136	31.48%
> or = 18 (Severe)	58	13.42%
Categories of Patients (WHO guidelines) according to severity		
Mild	240	55.55%
Moderate	132	30.55%
Severe	42	9.72 %
Critical	18	4.16 %

Table-3: Comparison of D-dimer level with severity of Pneumonia by HRCT.

n=432

D-dimer level	CT severity score	P. value
(Cut off value 2.4µg/ml.)	<7, 8-17, > or= 18	
< 2.4 µg/ml.(n-373)	238, 132, 2 < 0.0001	
> 2.4 µg/ml.(n=59)	1 3 56 < 0.0001	

Table 4: Comparision of D-dimer value with Inflammatory markers, coagulation parameters , hospital stay and mortality

	D dimer value		
	< 2.4 ug / ml	**>2.4 ug/ ml**	**P value**
A. Inflammatory Marker			
i. hs-CRP			
<20.44 ug / ml	368	02	<0.0001
>or = 20.44 ug/ml	4	58	<0.0001
ii. IL-6			
>37.65pg/ml	372	60	<0.0001
B. Coagulation Parameter			
PT-INR(>20secs)/ (>1.2)	362	72	<0.0001
Hospital Stay			
>4 weeks	10	59	<0.0001
<4 weeks	362	1	<0.0001
Non survivor (Mortality)	1	24	<0.0001

Discussion

Covid-19 is an acute infections disease caused by a novel member of human Corona Virus (SARS-Cov-2).

Clinically the patient presents with fever mild or severe in few cases. [8,2,3]

In contrary in severe cases the disease progress very rapidly and patient develops septic shock, multi organ failure and die. [12,13,14,15]

An important observation is that in many of the severe, critical and deceased patients have significant coagulation abnormalities. [4,5,8,9]

In our study the primary observation was associated of higher D-dimer value with that of severity of Pneumonia and with mortality rate.

D-dimer elevation is one of the commonest laboratory findings noted in Covid-19 patients requiring hepatization.

Guan and colleagues found the non-survivors had a significantly higher D-dimer (Median : 2.12 µg/ml) than that of survivors (Median : 0.61 µg/ml) (9). Ming T et al observed markedly elevated D-dimer in deaths with Covid-19(16). Huang and colleagues showed D-dimer levels on admission were higher in patients needing critical care support.

Now coming to the mechanism of elevation of D-dimer level in Covid-19 patients.

First- Virus (SARS- CoV-19) infection leads to aggressive pro-inflammatory response and insignificant anti-inflammatory response [17] which might induce endothelial dysfunction resulting in excess thrombin generation. [18]

Second-Hypoxia induced by severe Covid-19 infection stimulate thrombosis through hypoxia-inducible transcription factor dependent signaling pathway and increasing blood viscosity. [19,20]

Third-Hospitalized patients having elder age, underlying co-morbidity conditions, long term bed rest and invasive treatment etc.All are associated with increased rick for thrombosis or hyper-coagulation. [21,22,23]

Fourth-Some patients develop sepsis-induced coagulopathy like DIC . [11,24]

In our study it was found that patient who had higher D-dimer levels at the time of admission (cut off value > 2.4 µg/ml) had severe Pneumonia as correlated with CT severity score. In addition the result of this study also showed that patients with higher D-dimer levels had a significant higher value of other inflammatory markers and markers forincreased risk of thrombosis.

Out of 432 cases in total 60 cases D-dimer level were elevated. (45 cases with D-dimer >2.4 µg/ml and 15 cases with very high level of D-dimer >20 µg/ml). A total of 25 deaths occurred all of which had a higher D-dimer level at the time of admission.

Another interesting observation was that patients with moderate clinical presentation but having higher D-dimer level had higher duration of hospital stay in comparison to the patients having low D-dimer level with same clinical presentation.

Conclusion

The results of this study showed that elevated D-dimer level at the time of admission could effectively predict the severity of Pneumonia and mortality in patients with Covid-19 infection.

To conclude D-dimer level could be used as an early marker for the clinical classification and improved management of Covid-19 patients.

Conflict of interest

None.

Contribution from the author:

All authors have equal contribution for the paper.

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