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A Study on Serum D-Dimer Levels among Hospitalized Patients with COVID 19

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ABSTRACT

COVID 19 Pandemic has devastated the world in 2020 with more than 86 million cases and the 18 lakh deaths worldwide. Initially considered as a respiratory infection, more and more studies point towards coagulopathy as a primary mechanism of organ damage and death caused by this virus. The purpose of this study is to look for raised D-dimer level in COVID -19 patients and assess whether they correlated with severity and outcome of the disease. Study was carried out in 100 patients with COVID -19. The mean D-dimer level on admission was 1.064 mg/L. The study finds significantly higher mean D-dimer levels (p=0.0) and significantly higher number of patients with raised (≥ 0.5 mg/L) D-dimer levels (p=0.00) in Critical and Severe Groups as compared to Moderate and Mild groups of patients. There were 48 patients with normal D-dimer (<0.5 mg/L) levels out of which 3 patients died and 52 patients with raised (≥ 0.5 mg/L) D-dimer levels, out of which 18 patients died (p=0.01).There was significantly higher number of patients requiring supplemental oxygen among patients with raised D-dimer levels (p=0.00) in Moderate group.

Key words: D-dimer, COVID-19, coagulopathy, pandemic

Introduction

The world has been shaken to its core by a pandemic of a newly emerged highly infections Novel Coronavirus 2019 infection since January 2020.[1] The first cases started emerging in Wuhan of Hubei province in China since December 2019.[2] Initial patients were found to have got exposed to Huanan Sea Food wholesale Market,[2] a clue that led to tracing bats as the primary source of infection, with evidence of cross species transmission.[3]With availability of full genome sequence data from Global Initiative on Sharing Nevertheless, as a consequence of high covertness and high transmissibility of the outbreak, due to presymptomatic infections and population movements,[4] during Chunyun Holiday Karel Season[5] by leaps and bounds. On the 11th March 2020, WHO declared that the COVID-19 situation can be characterised as a Pandemic.[6]

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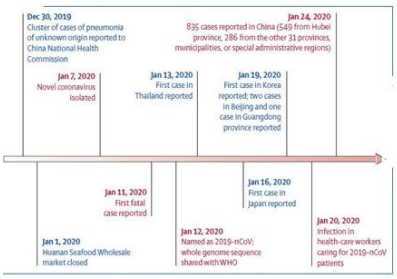

Fig 1: COVID-19 pandemic chronological progression

The whole world a never seen before state of extensive sealing borders and lock down (strict stay at home policy)[7] which kept on extending[8],[9] with centralized isolation and quarantine of affected and at- risk people and yet, till date more than 86 million cases and 18 lakh death have occurred worldwide.[10] There has been a profound negative impact on The World Economy as well ,generating unprecedented stress in capital markets, labour participation and production growth , ultimately leading to large scale real economy freeze.[11]

Fig 2: Geographical distribution of COVID-19 cases

The last 2 decades have witnessed emerging and re-emerging viral infections, mostly originating from China, namely Avian Influenza (1997),[12] Severe Acute Respiratory Syndrome or SARS (2003),[13] and Severe Fever with Thrombocytopenia or SFTS (2010). The twenty first century has seen two previous outbreaks of Coronavirus namely Severe Acute Respiratory Syndrome Coronavirus (SARS-COV)[14] and Middle East Respiratory Syndrome Coronavirus (MERS-COV).[15]

The Prodromal symptoms of 2019 nCOV and other Coronaviruses are nonspecific, like fever, malaise and dry cough.[2] However unlike other human Coronaviruses, upper respiratory symptoms are infrequent.[2] Gastrointestinal symptoms have been commonly reported. SARS-

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COV2 is more infectious and has higher case fatality rate.[17]It is still not clear why some people get more severe disease, but some researchers have reported few risks for disease severity, including elevated D-dimer levels among others.[20]

D-dimer is the degradation product of cross linked (Factor XIII)fibrin, and indicates ongoing activation of haemostatic system. Its reference concentration is <0.4 mg/L.[21] It is useful in the diagnosis and monitoring of disseminated intravascular coagulation,[22] an entity presumed to expedite multi organ dysfunction among Covid-19 patients.[23]

D-dimer levels are believed to correlate with disease severity [24] and is regarded as a reliable prognostic marker of in-hospital mortality of COVID- 19 patients.[25] Very few studies on elevated D-dimer levels have been done in India owing to the high cost of the investigation and presence of resource limited settings.Keeping in mind the above findings, this study was designed to find the relationship between raised D-dimer levels and disease severity and outcome in COVID- 19 patients.

Aim and Objectives

To study D-dimer levels among hospitalized adult COVID-19 patients and to assess whether they correlate with severity and outcome of the disease.

MATERIALS AND METHODS

Study Design – Hospital-based Cross-sectional Observational Study

Sample size- In a study titled "D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study" by Yumeng Yao et al, the prevalence of COVID 19 patients with D-dimer ≥ 0.50 mg/L was 74.6%.[63] Using formula for sample size (n) calculation,

$$n = \frac{4 \times p \times q}{e^2}$$

where, p = 74.6% = 0.746

q = 1 - p = 0.254

Taking e, absolute error of 10%, e = 0.1

So, $n = \frac{4 \times 0.746 \times 0.254}{0.1 \times 0.1}$

$n = 75.79 \approx 76$

The study included 100 patients.

Study Setting – Department of Medicine, Krishna Hospital, Karad, Maharashtra. The written and informed consents from the patients and their relatives were obtained according to ICMR Consent Proforma, before enrolling the patients in the study.

Study duration – 4 months (1st September 2020 to 31st December 2020)

Inclusion Criteria -

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SARS-CoV-2 infected hospitalized patients which included all adults (age >18 years) with documented COVID 19 RTPCR positive status, and who gave consent for the study.
Exclusion Criteria -
1. Patients who had other documented concomitant infections like Dengue, Malaria, Chikungunya, Leptospirosis, H1N1 or Tuberculosis.

2. Trauma patients, postoperative patients, patients with malignancy, alcoholic patients and patients with known chronic liver disease.

3. Patients less than 18 years of age, and who did not give consent for the study.
Sampling technique –Simple random sampling

Study population - Patients, both male and female who were COVID 19 RTPCR positive, and were admitted in Krishna Hospital were included in this study.
SARS-CoV-2 infected patients were admitted in Krishna Hospital under Medicine Department in COVID General Wards and ICUs as per a preliminary clinical assessment in OPD or Emergency Department based on their presenting symptoms and vital signs. Detailed history was taken. During the hospital stay, their vital signs were monitored at regular intervals.The patients were classified into various categories of disease severity suggested by WHO.

D-dimer level was estimated on admission for every patient with AQT90 FLEX immunoassay analyser available in Medicine ICU of KIMS Karad.

Fig 8: D-dimer Analyser

OBSERVATION AND RESULTSAGE AND D-DIMER
In the present study involving 100 patients, 63 (63%) were aged less than 60 years, out of which 31 (49.2%) had raised D-dimer, and 37 (37%) were aged more than 60 years, out of which 21 (56.7%) had raised D-dimer.

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GENDER AND D-DIMER

In the present study involving 100 patients, 33 (33%) were female, out of which 13 (39.3%) had raised D-dimer, and 67 (67%) were male, out of which 39 (58.2%) had raised D-dimer. M;F ratio was 2:1.

SEVERITY DISTRIBUTION

There were 7 cases (7%) of Mild disease without comorbidities, 17 cases (17%) of Mild disease with comorbidities, 38 cases (38%) of Moderate disease, 24 cases (24%) of Severe disease and Critical disease with ARDS, and 14 cases (14%) of Critical disease with sepsis and septic shock.

SEVERITY AND D-DIMER

There was significant difference in means of D-dimer ('p'=0.00) among patients of different categories of severity.Out of 7 patients with Mild disease without comorbidities, no patient (0%) had raised D-dimer, and the mean D-dimer was 0.17 mg/L.Out of 17 patients with Mild disease with comorbidities, 5 patients (29.4%) had raised D-dimer, and the mean D-dimer was 0.35 mg/L.Out of 38 patients with Moderate disease, 17 patients (44.7%) had raised D-dimer, and the mean D-dimer was 0.96 mg/L.Out of 24 patients with Severe disease and Critical disease without ARDS, 18 patients (75%) had raised D-dimer, and the mean D-dimer was 1.26 mg/L.Out of 14 patients with Critical disease with sepsis and septic shock, 12 patients (85.7%) had raised D-dimer, and the mean D-dimer was 2.29 mg/L..

Correlation of Disease severity with D-dimer

There was a significant positive correlation between the disease severity and the D-dimer levels(r=0.477,'p'=0.00).

Table 6: Correlation of Disease severity with D-dimer

Correlation of Disease severity with D-dimer		D-Dimer
Disease severity Mild Disease without comorbidity=1 Mild Disease with comorbidity=2 Moderate Disease=3 Severe Disease and Critical Disease with ARDS=4 Critical Disease with sepsis and septic shock=5	Pearson Correlation	0.477**
	Sig. (2-tailed)	0.000
	N	100
**. Correlation is significant at the 0.01 level (2-tailed).		

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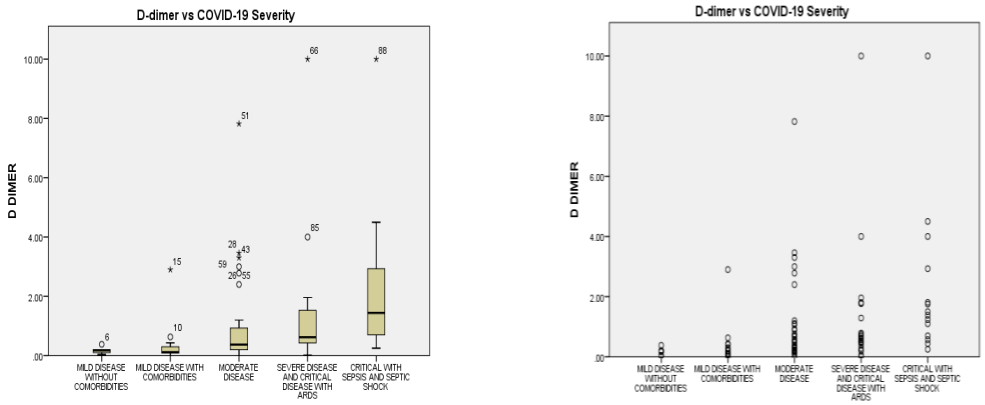

Fig 15: Correlation of D-dimer with disease severity

Oxygen and ventilator requirements and D-dimer levels

1) Moderate disease

There was significant association (‘p’=0.00) between oxygen requirement and D-dimer levels in Moderate Disease.Out of the 17 patients with raised D-dimer, 14(82.35%) required oxygen support, while only 1(4.76%) of the 21 patients with normal D-dimer required oxygen.

2) Severe and critical disease with ARDS

There was no significant association (‘p’=0.346) between ventilator requirement and D-dimer levels in Severe Disease and Critical Disease with ARDS.Out of the 18 patients with raised D-dimer, 10(55.55%) required ventilator support, while only 2(33.33%) of the 6 patients with normal D-dimer required ventilator support.

3) **Critical Disease with Sepsis and Septic Shock**

There was no significant association (‘p’=0.64) between type ventilator requirement and D-dimer levels in Critical Disease withSepsis and Septic Shock.Out of the 12 patients with raised D-dimer, 8(66.66%) required invasive ventilatory support, while only 1(50%) of the 2 patients with normal D-dimer required invasive ventilatory support.

OUTCOME AND D-DIMER

There was significant association between D-dimer levels and outcome of the patients (‘p’=0.01).There were 18 (34.6%) deaths out of the 52 cases with raised D-dimer, and 3 (6.25%) deaths out of the 48 patients with normal D-dimer.

DISCUSSION

In the present study, the prevalence of raised D-dimer was 52% overall, 44.7% in Moderate Disease, 75% in Severe Disease and Critical Disease with ARDS, 85.7% in Critical Disease with Sepsis and Septic shock patients, 85.7% among non-survivors and 43.03% among survivors. The

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mean D-dimer was 1.064 mg/L. D-dimer levels are found to positively correlate with disease severity and poorer outcome. These findings corroborate the following similar studies conducted on COVID 19 patients.

Table 11: Comparison of various studies with the present study

Author	Type of study	Observations
Mishra Y et al[93] Pune, India July-August 2020	Cross-sectional Study N=98	Mean D-dimer was 0.97 mg/L (SD 1.7) overall, 1.5(SD 2.4) among Diabetics(n=45) and 0.51(SD 0.62) among non-Diabetics(n=53); 'p'=0.002. Mean D-dimer was 1.7(SD2.9) among Moderate Disease with Diabetes, 0.41(SD 0.39) among Moderate Disease without Diabetes('p'=0.041), 1.36(SD 2.02) among Severe Disease with Diabetes and 0.68(SD 0.67) among Severe Disease without Diabetes('p'=0.066)
Bhandari S et al[62] Jaipur, India (March 2020)	Prospective study N=21	Prevalence of raised D-dimer was 19.04% overall and 100% among ICU patients requiring oxygen.
Tang N et al[60] Wuhan, China (February 2020)	Prospective study N=183	Mean D-dimer was 0.66 (0.38-1.50) overall, 0.61(0.35-1.39) among survivors(n=162) and 2.12(0.77-5.27) among non-survivors(n=21); 'p'<0.001
Zhou F et al[61] Wuhan, China (January 2020)	Retrospective study N=191	Mean D-dimer was 0.8 (0.4-3.2) overall, 0.6(0.3-1.0) among survivors(n=137) and 5.2(1.5-21.1) among non-survivors(n=54); 'p'<0.0001. Prevalence of raised D-dimer was 68% overall, 92% among non-survivors and 57% among survivors('p'<0.0001)
Yao Y et al[63] Wuhan, China (January-March 2020)	Retrospective study N=248	Mean D-dimer was 1.34 overall, 1.02(0.47-2.66) among survivors(n=231) and 6.21(3.79-16.01) among non-survivors(n=17); 'p'=0.0047. Prevalence of raised D-dimer was 74.6% overall, 100% among non-survivors and 72.72% among survivors.
Zhang L et al[64] Wuhan, China	Retrospective study N=343	Mean D-dimer was0.54 (0.20-1.41) overall, 0.41 mg/L (0.15–0.69) in non-severe cases and 4.76 mg/L (2.99–11.9) in severe cases (P < 0.001). Prevalence of raised D-dimer was 52.18% overall, 92.93% among non-survivors and 49.69% among

(January-March 2020)		survivors. 'p'<0.001
Huang C et al[68] Wuhan, China (December 2019 – January 2020)	Prospective study N=41	Mean D-dimer was 0.5 (0.3-1.3) overall. D-dimer level on admission was higher in ICU patients (median D-dimer level 2·4 mg/L[0·6–14·4]) than non-ICU patients (median D-dimer level 0·5 mg/L [0·3–0·8], p=0·0042).
Wang L et al[70] Wuhan, China (January-February 2020)	Retrospective study N=138	Mean D-dimer was 0.2 (0.12-0.4) overall. D-dimer level on admission was higher in ICU patients (median D-dimer level 0·41 mg/L[0·19–1·32]) than non-ICU patients (median D-dimer level 0·16 mg/L [0·1–0·28], p<0·001). Longitudinal increase was noted in non-survivors.
Wu C et al[71] Wuhan, China (December 2019-February 2020)	Retrospective study N=201	Higher D-dimer level was associated with ARDS development (HR = 1.03, 95%CI: 1.01-1.04, P < .001) and poor survival (HR = 1.02, 95%CI: 1.01-1.04, P = .002) in the incremental models.
Guan W et al[94] China (December 2019 – January 2020)	Prospective study N=1099	Prevalence of raised D-dimer was 46.4% overall, 43.2% among non-severe disease patients and 59.6% among severe disease patients('p'= .002)
Demelo-Rodriguez P et al[76] Madrid, Spain April 2020	Prospective study N=156	Patients with DVT had higher median D-dimer levels: 4527 (IQR 1925-9144) ng/ml vs 2050 (IQR 1428-3235) ng/ml; *p* < 0.001. D-dimer levels > 1570 ng/ml were associated with asymptomatic DVT (OR 9.1; CI 95% 1.1–70.1). D-dimer showed an acceptable discriminative capacity (area under the ROC curve 0.72, 95% CI 0.61–0.84).
Wichmann D et al[19] Hamburg, Germany (April-May 2020)	Prospective study N=12	The most striking features of the initial laboratory test were elevated levels of D-dimer (available for 5 patients; median, 495.24 nmol/L [range, 20.38 to >1904.76 nmol/L])
Nahum J et	Prospective	Mean D-dimer was 5.1 mg/L (SD 5.4) overall, 3.3 mg/L (SD

al[78] Paris, France (April-May 2020)	Case Series N=34	2.6) in non-DVT cases and 5.4 mg/L (SD 5.8) in DVT cases.
Bompard F et al[79] Paris, France (March-April 2020)	Retrospective study N=135	Mean D-dimer was 1.6 (1.01-3.64) overall, 9.8(2.9-10.0) among PE patients(n=32) and 1.2(0.89-2.7) among non-PE patients(n=103); 'p'<0.001
Leonard-Lorant I L et al[80] Strasbourg, France March 2020	Retrospective Study N=106	Prevalence of raised D-dimer was 73.58% overall, 88% among PE patients and 68% among non-PE patients. Mean D-dimer was 15.38mg/L (IQR 14.41) among PE patients(n=32) and 1.94mg/L (IQR 3.06) among non-PE patients(n=74); 'p'=0.001
Garcia et al[95] Europe January-April 2020	Prospective Study N=639	Mean D-dimer was 1.32 (0.8-2.8) overall, 1.14(0.72-2.03) among ICU survivors(n=301) and 1.9(0.83-4.62) among ICU non-survivors(n=97); 'p'=0.016
Richardson S et al[96] New York, USA March-April 2020	Prospective Study N=5700	The median level was 438 ng/ml (IQR: 262–872 ng/ ml) (Reference normal range [0–229 ng/ml]).
Goshua G et al[97] Yale, USA April 2020	Cross-sectional Study N=68	Mean D-dimer was 4.2(2.6-6.9) among ICU patients(n=48) and 0.7(0.4-1.2) among non-ICU patients(n=20); 'p'<0.0001
Lippi G et al[65] (January-March 2020)	Pooled Analysis N=553 (4 published studies)	D-dimer values are considerably higher in COVID-19 patients with severe disease than in those without (WMD: 2.97mg/L; 95% CI: 2.47–3.46mg/L). The heterogeneity across the studies was found to be relatively high (i.e., I2, 94%; p< 0.001).
Bikdeli B et al[66]	Pooled Analysis	Mean D-dimers in Severe vs Non-severe patients in studies by Han et al(n=94), Huang et al(n=41), Gao et al(n=43) and

(January-April 2020)		Wang et al(n=138) were 19.1 vs 2.1, 2.4(0.6-14.4) vs 0.5(0.3-0.8), 0.5(0.3-0.9) vs 0.2(0.2-0.3), and 0.4(0.2-13.2) vs 0.2(0.1-0.3), respectively. Mean D-dimers in Survivors vs Non-survivors in studies by Zhou et al(n=191), Wu et al(n=201) and Tang et al(n=183) were 0.6(0.3-1.0) vs 5.2(1.5-21.1), 0.5(0.3-1.2) vs 4.0(1.0-11.0) and 0.6(0.4-1.3) vs 2.1(0.8-5.3), respectively.
Present study Karad, India (September-December 2020)	Cross-sectional study N=75	The prevalence of raised D-dimer was 52% overall, 44.7% in Moderate Disease, 75% in Severe Disease and Critical Disease with ARDS, 85.7% in Critical Disease with Sepsis and Septic shock patients, 85.7% among non-survivors and 43.03% among survivors. The mean D-dimer was 1.064 mg/L.

CONCLUSION

D-dimer is a parameter found to be high in a considerable number of COVID 19 patients. The number of patients with raised D-dimer levels on admission is significantly higher in patients with Severe and Critical Disease as compared to Moderate and Mild Disease. In patients with Moderate Disease, the number of patients requiring oxygen is significantly more in patients with raised D-dimer, than in those with normal D-dimer. D-dimer levels are found to correlate positively with increased 2019-nCoV Disease severity and poorer outcome. Thus, D=dimer is a prognostic indicator useful in triaging COVID 19 patients on admission.

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