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RESEARCH ARTICLE

A CLINICAL AUDIT DONE ON ASSOCIATION BETWEEN D-dimer AND OTHER MARKERS OF PROGNOSIS IN COVID-19 PATIENTS

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ABSTRACT:

COVID-19 disease is known to cause coagulopathic complications by inducing inflammatory mechanisms. D-dimer is an effective marker of active fibrinolysis that has been considered relevant in the assessment of such complications and in the treatment course of the disease. Focus of this cross-sectional study conducted among COVID 19 in-patients was to assess

whether any significant statistical association exists between their D-dimer values and eight other markers of prognosis.

OBJECTIVE: To assess the association between D-dimer and other markers of prognosis in COVID-19 patients admitted and treated in a tertiary Care Centre in Central Kerala.

METHODS: A cross-sectional study was conducted among 129 COVID-19 patients admitted in the COVID Care Unit of the study Centre, selected through Simple Random Sampling. A predesigned, pretested, validated checklist was used to collect the required data from medical records of patients during the period of October-December 2021.Association between variables were estimated with Pearson Chi-square test.

RESULTS: Out of the markers, Age(p=0.000), Diabetic status (p=0.042), Hypertensive status (p=0.007), Need for Critical Care(p=0.001) and Treatment Outcome(p=0.039) showed significant association with D-dimer values while Sex (p=0.331), Duration of Hospital Stay(p=0.768) and Vaccination Status (0.755) did not.

CONCLUSION; As the results of the study suggest, significant association exist in COVID-19 patients between their elevated D-dimer values and pre-existing co-morbidities like Age, Diabetes and Hypertension. Such patients were also more in need of Critical Care and had worse Treatment Outcome. In such patients, assessment of laboratory D-dimer values can be an early indicator of thromboembolic complications. Thus, D-dimer can be a valuable tool in prompting suspicion and early detection of coagulopathy in COVID-19 which shall reduce mortality to an extent by ensuring timely intervention.

KEYWORDS: D-dimer, COVID-19, Coagulopathy, Covishield, Diabetes, Hypertension.

INTRODUCTION

Many patients with severe COVID-19 present with coagulation abnormalities such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy. One of the most typical findings in patients with COVID-19 and coagulopathy is an increased D-dimer concentration.[1] D-dimer, which indicates the presence of demolished fibrin in the bloodstream. D-dimer represents the activation of coagulation and fibrinolysis systems.[2] Results of a multi-center clinical study showed that D-dimer is related to the clinical classification of COVID-19 patients and can be used to evaluate the prognosis of patients. Advanced age, male gender and

underlying diseases became the influencing factors of D-dimer value, impacting the prognosis of patients.[3]The ICMR COVID-19 treatment guidelines during the study periodadvised D-dimer evaluation for susceptible patients falling under moderate and severe disease categories which was followed in the study Centre. This study is intended to assess association between D-dimer value in COVID-19 and other markers of prognosis namely Age, Sex, Diabetes, Hypertension, Vaccination Status, Duration of Hospital Stay, Need for Critical Care andOutcome of Treatment among patients admitted and treated in a tertiary Care Centre in Central Kerala.

METHODS

A cross sectional study was conducted among COVID-19 positive patients admitted in the COVID Care Unit of a tertiary Care Centre in central Kerala. All patients tested positive for novel Corona Virus Disease and admitted in COVID Care Unit of the study Centre who had laboratory assessment of D-dimer values done were included whilethose who were not willing to give consent were excluded.Sample size was calculated using Cochran's formula based on the study 'Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19' conducted in New Yorkwhere prevalence of elevated D-dimer was 76%.[4]Simple Random Sampling was done to identify the participants from a total of 639 patients. Informed written consent was taken from the study participants. A predesigned, pretested, validated checklist was used to collect the required data from both electronic and manual records of patients admitted and treated inthe Centre during the period of 61 days starting from 26/10/2021 and ending on 25/12/2022. Cross verification of the data done from the participants through phone and email done whenever deemed necessary.

Evaluation of D-dimer was done in the study Centre among warranted patients as per ICMR COVID-19 treatment guidelines at the time of study. It was measured in the laboratory of Study Centre using automated quantitative test which combines a two-step enzyme immunoassay sandwich method with a final fluorescent detection. A value more than or equal to 500 ng/ml was considered to be Significantly elevated. In cases with more than estimated values, the most elevated levels were taken into account. Details of the patient including Age, Sex, Vaccination Status (number of COVID-19 vaccine doses received) and Duration of Hospital Stay were easily obtainable from medical records. Age was classified into below 50 and 50 or above. The subjects were classified as 'Diabetic' and 'Hypertensive',if they were diagnosed so on the basis of standard guidelines prior to testing positive for COVID-19.'Need for Critical Care'is classified as any subject admitted into Intensive Care Unit at any time of treatment course on falling under Severe Disease category under ICMR guidelines. 'Outcome of Treatment' is classified into two categories - one among which include the patients who were discharged out of the facility on testing negative for COVID-19 and the other include those who were deceased within the hospital during the course of treatment.

ETHICS

The Institutional Ethical Committee has reviewed and approved this study at each stage.

STATISTICS

All the data was entered into, coded and decoded in MS EXCEL.It was analyzed using SPSS version 20.0 in which statistical significance was determined with Pearson Chi-Square test. A p value less than 0.05 was taken as statistically significant.

RESULTS

In total, details of 129 patients were collected.Among these 91 patients (70.54%) had a significant rise in D-dimer values. The mean age of patients taken for this study is 63.05. The mean duration of hospital stay of the patients were 10.19 days.

Table 1. D-dimer association with Age & Gender

D-dimer (ng/ml)	**Age(years)**		**Gender**	
	<50	_>50	Female	Male
<500	22 (68.8%)	16 (16.5%)	24 (32.9%)	14 (25.0%)
_>500	10 (31.2%)	81 (83.5%)	49 (67.1%)	42 (75.0%)
Total	32 (100.0%)	97 (100.0%)	73 (100.0%)	56 (100.0%)

Age *p value <0.05* Sex *p value = 0.331*

Among the 129, 28 patients were not vaccinated against covid, 30 received single dose and 71 received two doses. Chi-square test revealed no association between Number of Vaccine Doses (0,1,2) and Significant D-dimer elevation (p=0.755). No association was found when the data was stratified as ‘Vaccinated’ or ‘Not’ also (p=0.725). Duration of Hospital Stay showed nil

association

Table 4. D-dimer association with Vaccination & Length of Hospital Stay

either on classifying the data as '<7days, 7-14 days and >14days' or as '<14 and _>14' (p values 0.768 and 0.969 respectively).

Table 2. D-dimer association with Need for Critical Care & Treatment Outcome

D-dimer (ng/ml)	Need for Critical care		Treatment Outcome	
	No	Yes	Discharged	Deceased
<500	36 (37.5%)	02 (06.0%)	37 (32.5%)	01 (06.7%)
_>500	60 (62.5%)	31 (94.0%)	77 (67.5%)	14 (93.3%)
Total	96 (100.0%)	33 (100.0%)	114 (100.0%)	15 (100.0%)

Need for Critical Care *p-value 0.001*

Treatment Outcome *p-value 0.039*

Table 3. D-dimer association with Hypertension and Diabetes

D-dimer (ng/ml)	**Hypertension**		**Diabetes**	
	No	Yes	No	Yes
<500	25 (41.0%)	13 (19.1%)	27 (36.5%)	11 (20.0%)
_>500	36 (59.0%)	55 (80.9%)	47 (63.5%)	44 (80.0%)
Total	61 (100.0%)	68 (100.0%)	74 (100.0%)	55| (100.0%)

Hypertension *p-value 0.007* Diabetes *p-value 0.042*

D-dimer (ng/ml)	Vaccination status		Length of Stay	
	No	Yes	≤14 days	>14 days
<500	09 (32.1%)	29 (28.7%)	35 (29.4%)	03 (30.0%)
_>500	19 (67.9%)	72 (71.3%)	84 (70.6%)	07 (70.0%)
Total	28 (100.0%)	101 (100.0%)	119 (100.0%)	10 (100.0%)
Vaccination status *p-value 0.725*				
Length of Hospital Stay *p-value 0.331*				

DISCUSSION

Coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus was declared a pandemic in March of 2020. While most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment, some will become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, Diabetes etc. are more likely to develop serious illness.[5] It is of prime importance in the treatment of any disease and especially in case of such a pandemic to predict the risk of complications in various populations.

Fibrinolytic system breaks down the fibrin mesh after the formation of clot. The D-dimer, which comprises two D fragments of the fibrin, is formed by the activation of the plasmin enzyme. This indicates the presence of a demolished fibrin in the bloodstream. D-dimer represents the activation of coagulation and fibrinolysis systems. The D-dimer test is usually used in clinical practice to exclude a diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE)

and confirm the diagnosis of disseminated intravascular coagulation (DIC). Furthermore, several studies have shown that COVID-19 predisposes patients to thrombosis, both in arteries and veins. Pathological episodes such as excessive inflammation (cytokine storm, endothelial, and macrophage activation), diffuse intravascular coagulation (DIC), immobilization, hypoxia secondary to excessive lung injury in COVID-19 can result to VTE events.[2] Consequently, D-dimer has been extensively investigated and is used routinely for these indications.[6] Patients with severe COVID-19 have a higher level of D-dimer than those with non-severe disease, and D-dimer greater than 0.5 µg/ml is associated with severe infection in patients with COVID-19.[7] Results of our study is congruous with the known association between severity of COVID-19 infection and higher levels of D-dimer.[8,9]

Our study intending to assess whether D-dimer can stand as a predictive marker in patients with comorbidities like Hypertension, Diabetes, Old Age etc. for bad prognosis during hospital stay has resulted in positive association. Various other studies have also shown that patients with hypertension were more likely to have severe pneumonia, excessive inflammatory reactions, organ and tissue damage, whereas those with diabetes also had significantly higher D-dimer levels and more likelihood to cause hypercoagulable state with a worse prognosis. [10-11] Similarly, Age in association with an increased D-dimer level at admission is an important covariate or independent prognostic marker for the outcomes of COVID-19. The cut-off value of D-dimer (0.5 µg/mL) is age-dependent for healthy cohorts. Subgroup analysis is consistent with the concept that adults older than 50 approach the threshold of the D-dimer levels seen in normalcy. The difference in D-dimer between men and women is minor in a healthy population. D-dimer's positive association with the percentage of male patients in COVID studies suggests more severe cases in men than women when admitted.[12]

D-dimer elevation post COVID-19 vaccination mirrors an increased risk of developing vaccine-induced thrombocytopenia and thrombosis (VITT).[13]Two vaccines were granted emergency use authorization by the Central Drugs Standard Control Organization (CDSCO) in India, Covishield® (AstraZeneca's vaccine manufactured by Serum Institute of India) and Covaxin® (manufactured by Bharat Biotech Limited). Almost all the subjects of this study received Covishield provided by the Government.

Diagnosis and treatment of COVID-19 in the Centre of this study were based on most recently updated guidelines published by Government of Kerala, Government of India, AIIMS, ICMR and WHO.

The studied hypercoagulable and thrombotic state in patients itself shows the importance of early investigation of D-dimer in COVID-19 treatment. It is also clear that correlations exist between COVID-19 infection, severe elevation of D-dimer levels, and increase in the rate of complications and composite end-point. The appropriateness of early and continuous D-dimer monitoring and labelled anticoagulation as management tools for COVID-19 disease deserves accurate investigation, to prevent complications and reduce interventions. [14]

CONCLUSION

As the results of the study suggest, significant association exist in COVID-19 patients between their elevated D-dimer values and pre-existing co-morbidities like Age, Diabetes and Hypertension. Such patients were also more in need of Critical Care and had worse Treatment Outcome. In such patients, assessment of laboratory D-dimer values can be an early indicator of thromboembolic complications. Thus, D-dimer can be a valuable tool in prompting suspicion and

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REFERENCES

1. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 May 11; 7(6): E438-40. https://doi.org/10.1016/S2352-3026(20)30145-9
2. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev. Hematol. 2020; 13(11): 1265-75. Doi:https://doi.org/10.1080/17474086.2020.1831383
3. He X, Yao F, Chen J. et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Sci Rep. [Internet]. 2021 Jan 19 [cited 2022 Sep 10]; 1830 (2021). Available from: https://www.nature.com/articles/s41598-021-81300-w#citeas . doi: https://doi.org/10.1038/s41598-021-81300-w

4. Berger JS, Kunichoff D, Adhikari S. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. ArteriosclerThrombVasc Biol. 2020 Aug 25; 40(10): 2539-47. Doi: https://doi.org/10.1161/ATVBAHA.120.314872
5. World Health Organisation. Coronavirus disease (COVID-19) [Internet]. [place unknown: publisher unknown]; [date unknown] [cited 2022 Sep 18]. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1
6. Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. J. Am. Coll. Cardiol. 2017; 70 (19): 2411-2420.
7. Yu HH, Qin C, Chen M, et al. D-dimer level is associated with the severity of COVID-19. Thromb. Res. 2020; 195: 219-225.
8. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS ONE. 2021;16(8): e0256744. doi:10.1371/journal.pone.0256744
9. Paliogiannis P, Mangoni A A, Dettori P, et.al. D-dimer concentrations and COVID-19 severity: a systematic review and meta-analysis. Public Health Front. 2020; 8: 432.
10. Huang S, Wang J, Liu F, et al. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. Hypertens. Res. 2020; 43: 824–831.
11. Mishra Y, Pathak BK, Mohakuda SS, et al. Relation of D-dimer levels of COVID-19 patients with diabetes mellitus. Diabetes Metab. Syndr.: Clin. Res. Rev. 2020; 14(6): 1927-1930.

12. Zhao R, Su Z, Komissarov AA, et.al. Associations of D-Dimer on admission and clinical features of COVID-19 patients: a systematic review, meta-analysis, and meta-regression. Front. Immunol. 2021 May 7;12:691249.
13. Lippi G, Mullier F, Favaloro EJ. D-dimer: old dogmas, new (COVID-19) tricks. ClinChem Lab Med. 2022, Jul, 14. 0633.
14. Vidali S, Morosetti D, Cossu E, et.al. Dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review. ERJ Open Res. 2020; 6: 00260.