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D-DIMER – as a biomarker for severity of COVID-19

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Abstract

Objective: To see the association of D-dimers with the prognosis of covid-19.
Material & Methods: This Retrospective Cross-sectional study was done at Benazir Bhutto hospital Rawalpindi during May –June 2020 obtaining a sample of 200 patients. All those patients being admitted in COVID ward were assessed on the basis of D-dimers and their 28-day outcome. Ethical approval was solicited from the Institutional Research Forum of Rawalpindi Medical University.
Results: The study yielded 200 participants in which the patients with moderate severity of the disease had a mean age of 40.33±6.65, that with severe disease had a mean age of 53.18±12.1 and critical patients had a mean age of 56.67±14.79. The disease severity is significantly related to increased mean age of the patient ($p = 0.050$). Mean serum ferritin levels in patients with moderate disease was 235.67±22.27 micrograms per liter, the patients with severe disease had mean value of 760.75±574.63 micrograms per liter and critical patients had a mean ferritin level of 974.10±773.85 micrograms per liter. This revealed that the ferritin levels increased significantly in patients with severe disease. Our findings establish a consistent increase in the levels of D-dimers with increasing severity of the disease, from mild to severe to critical patients.
Conclusion: D –Dimers are important predictors of prognosis and disease severity which can be utilized to evaluate the treatment outcomes in COVID-19 infection. Further studies are recommended to find out the cut-off value of D-dimers as a biomarker of disease severity.
Keywords: Coronavirus, D-dimers, biomarkers, prognosis.

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Introduction

Covid-19 disease is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It was initially identified in city of Wuhan in December 2019.[2] World Health Organization declared corona virus as a pandemic on 11 March 2020.[3] It is a virus of zoonotic origin thought to be transmitted by air borne route. Symptoms of COVID-19 can be relatively non-specific; most common symptoms are fever, dry cough, sore throat, shortness of breath, myalgias, abdominal pain, diarrhea, loss of sense of smell and taste.[4] Approximately one in five patients who become symptomatic become critical and suffer breathing difficulties, persistent chest pain, sudden confusion, difficulty waking, and bluish face or lips. Complications include pneumonia, acute respiratory distress syndrome, sepsis, septic shock, and kidney failure.[5] Covid-19 related complications are associated with high mortality rate.

Researchers all over the world are trying their best to identify its causative factors, patho- physiology and treatment modalities. Retrospective cohort studies carried out in China showed significant mortality and morbidity associated with high D-dimers value in admitted patients.[6] COVID related acute respiratory distress syndrome (ARDS) showed a pro coagulant pattern and this state depicted significant mortality with pulmonary embolism. Covid-19 infection triggered a inflammatory cytokine response which initiated a thrombotic state. It was observed in many studies mortality was reduced by anticoagulation with Low Molecular Weight Heparin (LMWH). The coagulation abnormalities seen in COVID are

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different from that seen in DIC (sepsis). In DIC, thrombocytopenia is a key finding along with elevated clotting time. However, in cohorts non-surviving patients had an average platelet count and a pro thrombin time which falls within the normal range. It thus may be more likely that local rather than disseminated thrombin generation is at play in COVID-19 patients.[7-9]

The main aim of our study was to see the association of D-dimers with the prognosis of covid-19. Our study investigated COVID patients and role of D-dimers in their mortality and morbidity. There is lack of international & local studies, therefore our study will have a huge impact on researchers and the national data base.

Materials and Methods

This Retrospective Cross-sectional study was done at Benazir Bhutto hospital Rawalpindi, which was nominated by Punjab government as COVID Dedicated Unit. Sampling technique used was consecutive sampling. Total sample size obtained was 200 patients. All those patients being admitted in COVID wards during 2 months May- June 2020 were assessed on the basis of D dimers and their 28 day outcome. As d dimers is an easy and inexpensive test was used a screening tool for risk stratification of Covid-19 patients.

Cases of coronavirus infection were confirmed by RT-PCR. A patient diagnosed as COVID-19 on the basis of ABI 7500 Real Time RT-PCR detection system after RNA extraction (Qiagen Viral RNA Mini Kit) with internal and external positive controls, using the SARS-CoV-2 protocol.

Inclusion and exclusion criteria*:* Confirmed COVID-19 cases were included in our study whereas pregnant women, patients having any hematologic malignancy, chronic liver disease, acute coronary syndrome, surgery or trauma within 30 days and patients without D-dimer testing upon admission were excluded from our study.

Demographic, clinical lab data and outcome (survival or death) was collected form patient records and recorded on self-designed performa. Disease Severity was be defined as per WHO criteria into moderate, severe, critical with ARDS and Critical with Sepsis/Septic shock. Patients were grouped into two: group A (D-dimer < 500ng/ml) and Group B (D-dimer ≥ 500ng/ml)

Data was analyzed via SPSSv25.0. Numerical data was represented as mean and standard deviation. Independent sample t test was used to compare difference of means of numerical variables across severity of the disease according to WHO criteria. Categorical variables were represented as frequencies (%). Distribution of frequencies across severity was compared by Chi-Square test. ROC curve was plotted to determine the cut-off point for D-Dimer to predict mortality.

Ethical approval was solicited from the Institutional Research Forum of Rawalpindi Medical University before securing access to patient data.

Results

The study yielded 200 participants with a mean age of 53.82±12.94 years. On the basis of stratification of severity, the patients with moderate severity of the disease had a mean age of 40.33±6.65, that with severe disease had a mean age of 53.18±12.1 and critical patients had a mean age of 56.67±14.79. The disease severity is significantly related to increased mean age of the patient ($p = 0.050$). At the time of admission, the patients with moderate disease had a mean SpO_2 of 94.67±1.15%, patients with severe disease had a mean SpO_2 of 80.79±6.39%, and critical patients had a mean SpO_2 of 70.43±15.46%. The mean oxygen saturation at the time of admission decreased with increasing severity ($p = 0.000$). The patients with moderate disease had a mean arterial partial pressure of oxygen (pO_2) of 66.67±6.61 mmHg, patients with severe disease had a mean pO_2 of 58.19±9.45 mmHg, and critical patients had a mean pO_2 of 44.54±10.21 mmHg. The mean partial pressure of oxygen showed a decline with increasing severity ($p = 0.000$). Regarding mean arterial partial pressure of carbon dioxide in the patients, the patients with moderate disease had pCO_2 of 34.67±6.61 mmHg, patients with severe disease had a mean pCO_2 of 27.35±5.92 mmHg, and critical patients had a mean pCO_2 of 25.06±3.99 mmHg. The mean partial pressure of carbon dioxide showed a decline with increasing severity ($p = 0.002$). Mean serum ferritin levels in patients with moderate disease was 235.67±22.27 micrograms per liter, the patients with severe disease had mean value of 760.75±574.63 micrograms per liter and critical patients had a mean ferritin level of 974.10±773.85 micrograms per liter. This revealed that the ferritin levels increased significantly in patients with severe disease. Upon investigating the levels of C-Reactive protein, mean serum CRP levels in patients with moderate disease was 235.67±22.27 mg/L, the patients with severe disease had mean value of 760.75±574.63 mg/L and critical patients had a mean ferritin level of 974.10±773.85 mg/L (Table I, II).

Table I: Study variables and their severity along with p-value

Study variables		(n)	(%)	Severity				*p-value*
Gender								
	Male	126	63	1	96	29	126	0.496
	Female	74	37	2	53	19	74	
Shortness of Breath								
	Yes	179	89.5	2	134	43	179	0.429
	No	21	10.5	1	15	5	21	

Fever								
	Yes	100	50.0	1	77	22	100	0.659
	No	100	50.0	2	72	26	100	
Cough								
	Yes	46	23.0	1	77	22	100	0.494
	No	154	77.0	2	72	26	100	
Sore Throat								
	Yes	19	9.5	0	17	2	19	0.282
	No	181	90.5	3	132	46	181	
Diarrhea								
	Yes	11	5.5	1	6	4	11	0.057
	No	187	93.5	2	141	44	187	
Diabetes Mellitus								
	Yes	94	47.0	2	62	30	94	0.033
	No	106	53.0	1	87	18	106	
Hypertension								
	Yes	94	47.0	0	73	21	94	0.212
	No	106	53.0	3	76	27	106	
Ischemic Heart Disease								
	Yes	37	18.5	0	27	10	37	0.648
	No	163	81.5	3	122	38	163	
Chronic Obstructive Pulmonary Disease								
	Yes	9	4.5	0	6	3	9	0.755
	No	191	95.5	3	143	45	191	
Asthma								
	Yes	11	5.5	0	9	2	11	0.810
	No	189	94.5	3	140	46	189	
Rheumatoid Arthritis								
	Yes	3	1.5	0	3	0	3	0.594
	No	197	98.5	3	146	48	197	
Chronic Kidney Disease								
	Yes	7	3.5	0	5	2	7	0.914
	No	193	96.5	3	144	46	193	
Hepatitis B/C Infection								
	Yes	7	3.5	0	6	1	7	0.773
	No	193	96.5	3	143	47	193	
Hypothyroidism								
	Yes	7	3.5	0	5	2	7	0.913
	No	193	96.5	3	144	46	193	
PCR								
	Positive	152	76.0	3	108	41	152	0.117
	Negative	48	24.0	0	41	7	48	
Arterial Blood Gases (ABG) Interpretation								
Normal		68	34.0					
Acute respiratory Failure 1		126	63.0					
Acute respiratory Failure 2		2	1.0					
Compensated/Chronic Respiratory Failure		4	2.0					
Oxygen Flow								
	Normal	110	55.0					
	High Flow	60	30.0					
	Low Flow	30	15.0					
Oxygen Support Device								
	NRBM	108	54.0					
	Nasal canula	3	1.5					
	BIPAP	8	4.0					
	Face Mask	42	21.0					
	Ventilator	30	15.0					
	None	8	4.0					
Methylprednisolone Therapy								
	Yes	101	50.5	2	73	26	101	0.702
	No	99	49.5	1	76	22	99	
Dexamethasone Therapy								
	Yes	156	78.0	2	73	26	101	0.151
	No	44	22.0	1	76	22	99	
Ivermectin Therapy								
	Yes	117	58.5	3	98	16	117	0.000
	No	83	41.5	0	51	32	83	
Tocilizumab Therapy								
	Yes	25	12.5	0	20	5	25	0.692
	No	175	87.5	3	129	43	175	
Heparin Therapy								
	Yes	177	88.5	3	134	40	177	0.377
			11.5	0	15	8	23	
Outcome								
	Expired	36	18.0	0	0	36	36	0.000
	Improved	160	80.0	3	148	9	160	
	Critical	4	2.0	0	1	3	4	
Severity								
	Moderate	3	1.5					
	Severe	149	74.5					
	Critical	48	24.0					

Discussion

Laboratory Hemostasis is believed to provide a very strong evidence in screening, definitive diagnosis and prognosis of many human pathologies.[10] Measuring the levels of D-dimers is one of them. D-dimers are the products of fibrin degradation, which serve as a biomarker in a lot of diseases associated with coagulopathies e.g. in coronary artery atherosclerosis, disseminated intravascular disease and Venous Thromboembolism.[11] D-dimer levels have played a significant role in the evaluation of patients suffering from Community Acquired Pneumonia[12], 2009 novel influenza A (H1N1)[13] and various other members of Coronaviridae family. Covid-19 has also been associated with an increased risk of Venous Thromboembolism.[14-15-16] Hence, the coagulopathy involved in Covid-19 infections can serve as a major determinant of disease prognosis.[17] The levels of D-dimers are consistently elevated in patients suffering from Covid-19.[18-19-20] In this study, we aimed to explore the association of D-dimer levels with disease severity of Covid-19.

Our findings establish a consistent increase in the levels of D-dimers with increasing severity of the disease, from mild to severe to critical patients (Table I). The severity of these patients depended on the duration for which these patients remained in the hospital under care. A strong association was established between these two (Eta sq. 0.128). Many studies concluded the increasing levels of D-dimers to be associated with severity of Covid patients. Huang et al. studies the data of 41 patients and reported a five-fold increase in critical patients (median: 2.4 mg/L; IQR: 0.6–14.4 mg/L) as compared to the non-critical ones (median:

Table II: Biological plausibility and pathogenesis behind increased D-dimers in Covid-19											
	Age	SP O_2 at Admission	pH	pO_2	pCO_2	HCO^{-3}	Ferritin	CRP	LDH	D-Dimers	O_2 Requirement
Mean	53.82	78.65	7.62	55.06	26.91	22.75	804.08	161.84	630.38	778.94	10.98
SD	12.94	10.53	4.36	11.30	5.63	5.06	632.66	183.56	449.21	615.02	8.30

0.5 mg/L; IQR: 0.3–0.8 mg/L; p = 0.004).[21] Another study was performed by Zhou et al. (16). He reported a nine-fold increase in patients who died of Covid (median: 5.2 mg/L; IQR: 1.5–21.1 mg/L) than in those who survived (median: 0.6 mg/L; IQR: 0.3–1.0 mg/L; p < 0.001). Tand et al. [22] and Wang et al.[23] also had consistent findings as ours. Moreover, irrespective of age, BMI, sex, Hypertension or Diabetes, increased coagulation biomarkers in Covid patients invariably required an increased Oxygen supply, which again can be linked as increased severity in patients having adverse coagulopathies.[24]

The underlying biological plausibility and pathogenesis behind increased D-dimers in Covid-19 can be understood by the disease triggering an inflammatory response. Covid-19 is associated with increased acute phase reactant proteins e.g. CRP, as shown in Table II of our findings. Other studies also show a consistent increase in CRP levels with an associated mortality rate of 30 days in coronavirus patients.[25] In the consequence of inflammation, proinflammatory cytokines such as Interleukin 1 (IL-1), Interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) are elevated [[20]]. This results in a cytokine storm that triggers monocytes and macrophages to express tissue factor which leads to thrombin generation.[26] There is also an endothelial damage which results in increased plasma concentrations of tissue-type plasminogen activator (t-PA), up to six-fold increase.[27] This explains the increased levels of D-dimers in Covid-19 patients. Moreover, an accompanied increase in metalloproteinases explains the extracellular matrix modification, resulting in capillary damage and pulmonary edema. The remarkable fibrinolytic profile of Covid patients has also been explained by the studies performed in mice.[28] However, it is noteworthy that increased fibrinolytic profile can still not be translated as DIC or hyper fibrinolytic state. Although coagulopathy may reflect some similar findings, but Covid coagulopathy has a very complex etiology, resulting from intricate interactions between the immune system and coagulation system in the host.[29]

Limitations: There are a few limitations in our study that need to be known. Firstly, the burden of the pandemic itself and an emergency situation in Pakistan has hindered the practicality of Cohort, Case-control or Randomized Control Trial- which could have provided a greater pool of Clinical and Lab findings; making even better associations possible. Secondly, we cannot exclude the strong association of confounding factors with coagulopathies- hence a stratified analysis of these confounders can give us a better picture of using D-dimers as a prognostic marker in Covid-19 patients. Moreover, limitations in the measurement of plasma D-dimer concentration may also exist at the level of Laboratory methods and skills involved at human level.[30]

Conclusion

COVID-19 infection is characterized by hypercoagulability, inflammation, and multi-organ damage mediated by cytokines. These pathologies are manifested by appearance of several acute phase proteins and inflammatory markers in the serum. The levels of these biomarkers are variable in various stages of COVID-19 infection in relation to severity. The prognosis can be predicted by these serum biomarkers. In this study, D-dimers are measured in patients at various stages of disease severity. D-dimers are important predictors of prognosis and disease severity. These biomarkers can be utilized to evaluate the treatment outcomes in COVID-19 infection. Further studies are recommended to find out the cut-off value of D-dimers as a biomarker of disease severity.

References

1. Zu ZY, Jiang MD, Xu PP, et al. Coronavirus Disease 2019 (COVID-19): A Perspective from China. Radiology. 2020 Aug;296(2):E15-E25. doi: 10.1148/radiol.2020200490.
2. Sahin AR, Erdogan A, Agaoglu PM, Et al. 2019 novel coronavirus (COVID-19) outbreak: a re-view of the current literature. EJMO 2020;4(1):1_7
3. https://www.who.int/news/item/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)
4. *Hopkins C. "Loss of sense of smell as marker of COVID-19 infection". Ear, Nose and Throat surgery body of United Kingdom. Retrieved 28 March 2020. https://www.entuk.org/sites/default/files/files/Loss%20of%20sense%20of%20smell%20as%20marker%20of%20COVID.pdf*
5. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)". *U.S.* Centers for Disease Control and Prevention *(CDC). 4 April 2020*. Retrieved 11 April 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
6. Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. Thromb Haemost. 2020 May;120(5):876-878. doi: 10.1055/s-0040-1709650..
7. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844-847. doi: 10.1111/jth.14768..

8. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020 Jul;18(7):1747-1751. doi: 10.1111/jth.14854.
9. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol. 2020 May;7(5):e362-e363. doi: 10.1016/S2352-3026(20)30109-5.
10. Lippi G, Favaloro EJ. Laboratory hemostasis: from biology to the bench. Clin Chem Lab Med. 2018 Jun 27;56(7):1035-1045. doi: 10.1515/cclm-2017-1205. PMID: 29455188.
11. Soomro AY, Guerchicoff A, Nichols DJ, et al. The current role and future prospects of D-dimer biomarker. Eur Heart J Cardiovasc Pharmacother. 2016 Jul;2(3):175-84. doi: 10.1093/ehjcvp/pvv039. Epub 2015 Sep 27. PMID: 27533759.
12. Chalmers J.D., Singanayagam A., Scally C., et al. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. *Ann. Emerg. Med.* 2009;53:633–638. doi: 10.1016/j.annemergmed.2008.12.022.
13. Wang Z.F., Su F., Lin X.J., et al. Serum D-dimer changes and prognostic implication in 2009 novel influenza A(H1N1) *Thromb. Res.* 2011;127:198–201
14. Helms J., Tacquard C., Severac F., et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. *Intensive Care Med.* 2020;46:1089–1098. doi: 10.1007/s00134-020-06062-x. [
15. Leonard-Lorant I., Delabranche X., Severac F, et al. Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. *Radiology.* 2020:201561. doi: 10.1148/radiol.2020201561.
16. Fauvel C., Weizman O., Trimaille A., et al. Pulmonary embolism in COVID-19 patients: A French multicentre cohort study. *Eur. Heart J.* 2020;41:3058–3068. doi: 10.1093/eurheartj/ehaa500. [
17. Tang N., Li D., Wang X., et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.* 2020;18:844–847. doi: 10.1111/jth.14768.
18. Thachil J. All those D-dimers in COVID-19. *J. Thromb. Haemost.* 2020 doi: 10.1111/jth.14939.
19. Lippi G., Favaloro E.J. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. *Thromb. Haemost.* 2020;120:876–878.
20. Huang C, Wang Y, Li Xet al.Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China *Lancet* 2020395(10223):497–506.
21. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020:S0140-6736(20)30566-3.
22. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumoniaJ Thromb Haemost2020. Doi: 10.1111/jth.14768
23. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, ChinaJAMA2020.
24. https://onlinelibrary.wiley.com/doi/10.1111/jth.15067
25. Huang I, Pranata R, Lim MA, et al. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020 Jan-Dec;14:1753466620937175.
26. Levi M, Thachil J. Coronavirus disease 2019 coagulopathy: disseminated intravascular coagulation and thrombotic microangiopathy-either, neither, or both. *Semin Thromb Hemost.* 2020;46:781–784. doi: 10.1055/s-0040-1712156. [
27. Liu ZH, Wei R, Wu YP, et al. Elevated plasma tissue-type plasminogen activator (t-PA) and soluble thrombomodulin in patients suffering from severe acute respiratory syndrome (SARS) as a possible index for prognosis and treatment strategy. *Biomed Environ Sci BES.* 2005;18:260–264.
28. Gralinski LE, Bankhead A, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. *mBio.* 2013;4:e00271–e313. doi: 10.1128/mBio.00271-13.
29. Iba T, Levy JH, Levi M, et al. Coagulopathy of Coronavirus Disease 2019. Crit Care Med. 2020 Sep;48(9):1358-1364.
30. Hardy M., Lecompte T., Douxfils J, et al. Management of the thrombotic risk associated with COVID-19: Guidance for the hemostasis laboratory. *Thromb. J.* 2020;18:17. doi: 10.1186/s12959-020-00230-1.