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Research Article

D-Dimer Trends as a Prognostic Factor of Critical Illness in COVID-19 Patients

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Abstract: Raised levels of D-dimer have been noted in patients with COVID-19. The existing evidence emplies that the highest levels of D-dimer in the critically ill Covid-19 patient shows a linear relationship between the D-dimer measurement and the severity of the disease. However, that should also mean a patient on the road to recovery would have decrease in pro-thrombotic state and hence lower D-dimer readings. This study hypothesized that D-dimer trend would start to return towards normal as patients recovered from this illness. The present study included 43 patients with COVID-19 infection treated in the ICU at Khoula Hospital, Muscat, Oman from 10th May to 5th August 2020. Six readings of D-dimer were taken from the time of admission of Covid-19 npatient to their discharge from the ICU or demise. The data was statistically analyzed using generalized linear model, paired 't' test and Wilcoxon Signet Ranks test. D-dimer demonstrated a statistically significant difference by the value of 4 µg/ml in patients who were eventually extubated compared to those who died while in the ICU, despite that, as a trend over time was insignificant. In conclusion, this study suggests that D-dimer would be noteworthy in assessing severity as a single time-point, however not as a prognostic value in evaluating improvement of critically ill patients of COVID-19.

Keywords: COVID-19, D-dimer trend.

INTRODUCTION

Since the outbreak of Coronavirus in December of 2019 there has been an overwhelming increase in hospital admissions and a tremendous burden on healthcare services globally once it evolved into a pandemic. Many patients with COVID-19 present with typical symptoms of acute respiratory distress syndrome [1]. However, the myriad facets of this disease's pathophysiological profile are not yet fully understood. One of the important observations is the activated coagulation cascade secondary to a cytokine storm, which in turn causes thrombotic complications [2].

D-dimer is a fibrin degradation product [3]. Measurement of circulating plasma D-dimer concentrations is a sensitive test in the diagnoses of thrombotic states, including pulmonary embolism and disseminated intravascular coagulation [4, 5]. Several studies have demonstrated that elevated D-Dimer levels were a prognostic factor for adverse outcomes in respiratory diseases [6]. Hence given COVID-19 is a pro-thrombotic state; this marker might be considered in assessing the severity of the disease [7-9].

In this study we hypothesized that the trend of D-dimer levels would be decreasing as the inflammatory status reduces and the coagulation performance normalizes in patients who were entering a recovery phase of COVID-19 disease and therefore could be a promising predictor of a healthy recovery. To test this hypothesis, we included 43 patients with documented COVID-19 positivity who were critically ill and admitted to the intensive care unit (ICU) for ventilatory management.

METHODOLOGY

This was a retrospective single-center study, which included 43 patients with COVID-19 infection treated in the ICU at Khoula Hospital, Muscat, Oman from 10th May to 5th August 2020. Permission from Departmental Management Board was obtained to retrieve patients' data for analysis and reporting. All 43 patients were shifted to the ICU after meeting the following transfer criteria: confirmation of COVID-19 infection via polymerase chain reaction test of respiratory or blood samples. Along with two or more clinical features such as fever and/or respiratory distress with respiratory rate ≥ 30/min; mean oxygen saturation

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< 92% while receiving >5 L/min O2; hypotension not responding to initial fluid resuscitation or requiring vasopressors; arterial blood oxygen partial pressure/oxygen concentration < 300 mmHg, acidosis with a pH <7.3 or PCO2 >50 mmHg, any evidence of acute end organ involvement and/or rapidly progressive respiratory failure.

All patients were intubated and kept on appropriate mode of mechanical ventilatory support whether from referring hospitals or on admission to the ICU. Given the continuously evolving recommended managements in COVID-19, several modalities of treatment were utilized including use of antiviral, antibiotic and steroids. Anticoagulant therapy was a standard of care for all the ICU patients provided no contra-indications were present. And a prophylactic weight-adjusted dose was given with regular coagulation profile monitoring.

D-dimer test was determined using an automatic coagulation analyzer that utilized a latex-enhanced photometric immunoassay (Siemens, SYSMEX CS2500, Germany). The laboratory's normal reference range was 0-0.5 μg/ml.

The endpoint of this study was successful tracheal extubation, discontinuation of any form of ventilatory support and discharge of the patient to the ward/ referring institution or death of the patient while still on ventilatory support.

Since the duration of patients' ventilatory and ICU management ranged from 5 days to over 2 month, six readings of D-dimer per patient were taken; the first on the day of admission/intubation, the last on the day of discharge or demise while 4 readings were taken in between for each patient. We could not continue to monitor D-dimer beyond discharge as several patients were directly transferred to their parent referring hospitals.

Statistical analysis: Generalized Linear Model, Paired 't' test and Wilcoxon Signet Ranks test were used for statistical analysis of the data. P-Value < 0.05 has been taken as statistically significant finding for this study. Analysis was performed using SPSS 22.0 statistical package (SPSS, Inc., Chicago, IL, USA).

RESULTS

Gender distribution showed greater frequency of male patients however no difference was noted in recovery rate between male and female patients. In addition, mean age of patients who recovered and were discharged to those who died while in the ICU was comparable. The mortality rate in Khoula Hospital's ICU for COVID-19 patients at the time this analysis was done was 27.9%. With patients staying for periods of 17.58 days as a collective mean value in cases who survived compared to 12.67 days in patients who were highly critical and passed away (Table-1).

When comparing the first D-dimer value (on admission) to every consecutive value measured over the course of the ICU stay, the reduction noted in the patients who recovered was not sufficient to produce any statistical significance. The patients who failed to improve clinically and died did not show any significant increase in the D-dimer measurement either despite being of high values compared to normal (Table-2).

In Table-3, we considered each D-dimer measurement as a single time point entry after which we compared the two groups of patients; those who recovered and those who died. Based on a general linear regression analysis we could conclude that there was a statistically significant negative difference by the value of 4 μg/ml in patients who were eventually extubated compared to those who died while in the ICU.

Table-1: Demographic data of analyzed patients in Khoula Hospital and final outcome.

Gender Distribution; M (%) : F (%) No. (%) No. (%)	**Mean age of all 43 patients (Yr) Mean ± SD**	**Mean age of patients who died (Yr) Mean ± SD**	**Mean age of patients who recovered (Yr) Mean ± SD**
34 (79.1) : 9 (20.9)	53.79 ± 15.68	53.25 ± 20.0	54.0 ± 14.02
Patient group; discharged : died No. (%) No. (%)	**Number of female patients discharged: No. (%)**	**Number of male patients discharged: No. (%)**	**Days in ICU; Discharged : Died Mean (±SD) Mean (±SD)**
31 (72.09) : 12 (27.9)	7/9 (77.7)	24/34 (70.6)	17.58 (11.37) 12.67 (5.61)

±□SD = Standard Deviation, Yr= year, No.= Number of patients

Table-2: Wilcoxon Signet Ranks test of paired D-dimer values of patients in Khoula Hospital according to recovery or death

	Recovery			Deaths		
	Mean ± SD	**P-Value**	**N***	**Mean ± SD**	**P-Value**	**N***
D-DIMER 1	4.35 ± 6.64	0.19	31	9.63 ± 11.13	0.95	9
D-DIMER 2	5.77 ± 6.84			12.17 ± 20.57		
D-DIMER 1	4.16 ± 6.66	0.08	26	8.30 ± 10.14	0.74	7
D-DIMER 3	7.54 ± 9.91			7.77 ± 4.77		
D-DIMER 1	4.40 ± 7.17	0.12	22	3.46 ± 5.18	0.07	4
D-DIMER 4	6.40 ± 7.10			10.85 ± 8.28		
D-DIMER 1	4.71 ± 7.85	0.21	12	3.46 ± 5.18	0.14	4
D-DIMER 5	4.32 ± 2.61			9.47 ± 2.79		
D-DIMER 1	6.18± 9.45	0.67	8	0.87 ± 0.24	0.11	3
D-DIMER 6	3.13 ± 1.97			5.66 ± 4.61		

N*: number of measurement taken as a single time point to compare as a pair

Table-3: Generalized Linear Model of the analyzed patients in ICU Khoula Hospital

	Continuous Variable Information					
	N	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**	
Dependent Variable D-DIMER	166	0.23	65.50	6.48	8.52	
Parameters	**B**	**Std. Error**	**95% Wald Confidence Interval**		**Wald Chi-Square**	**P-Value**
			Lower	Upper		
Patient Outcome	-4.09	2.07	-8.15	-0.03	3.90	0.04

B= time point difference in D-dimer of recovered patients against deaths

DISCUSSION

Rostami M *et al*., preformed a systemic review on publications that analyzed D-dimer levels in COVID-19 patients. Majority of the data and research considered D-dimer as a single reading on admission; many implying that a four-fold increase in the level of D-dimer was a reliable predictor of mortality in COVID-19 which might help in medical resource allocation [10-12].

The marked rise of D-dimer levels indicated a hypercoagulable state in patients with COVID-19 supporting the notions that a crucial component of the pathophysiology results from thromboembolic phenomena. When reviewing the medical literature, various points were suggested as an explanation. First, the hypoxia presented in severe COVID-19 patients can stimulate thrombosis through both increasing blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathway [13, 14]. Second, viral infections typically not only demonstrate an aggressive pro-inflammatory response but an insufficient control of an anti-inflammatory response [15]. This might prompt the dysfunction of endothelial cells, consequently leading to excess thrombin generation [16]. Third, patients critical enough to present to the ICU were more likely to have underlying medical conditions and requiring invasive treatment which in turn meant long-term bed rest all of which are risk factors of hypercoagulation or thrombosis [17-19]. As evidence, the lung organ dissection of critical patient with COVID-19 have reported occlusion and microthrombosis formation in pulmonary small vessels [20]. Lastly, some patients might progress to sepsis-induced coagulopathy or even disseminated intravascular coagulation [21, 22].

Some might argue that medically compromised patients as well as geriatric age groups especially more than 80 years old are shown to have a significantly elevated baseline D-dimer requiring a higher cut-off threshold for illness significance. The counter argument would be a mounting evidence of stroke in young patients and high rates of venous thromboembolisms in critically ill COVID-19 patients that were proven in autopsy reports [23-26].

Our hypothesis was that there would be a significant downward trend of D-dimer in COVID-19 patients who were showing improvement, as a sign of good prognosis provided. We noted that D-dimer measurements were in fact lower in the patients who clinically improved as a whole in contrast to patients who failed to recover by a value of 4µg/ml. Nevertheless, as a shift over time, we could not establish a trend that supported the use of this parameter as a prognostic indicator.

Other underlying conditions were reviewed in this study including smoking, diabetes, hypertension and COPD, as factors that may influence the COVID-19 outcome [21]. A total of only ten patients had

associated comorbidities, and therefore a correlation of its contribution could not be assessed.

Possibly an added input to the existing data might be the ethnic correlation with this illness. All of the 43 patients were of Asian or Middle Eastern descends and previous studies have suggested strong evidence that the prevalence of venous thromboembolism in general varies significantly among different ethnic/racial groups [27, 28]. In the United States, immerging data showed African-Americans having higher mortality with COVID-19 incompletely explained by age, multiple comorbidities and sociodemographic disparity [29]. The American CDC's current statistics showed the risk markers of African-Americans and Hispanic persons as 2.8 compared to Caucasians and Asian at 2.6 and 1.1 respectively. Looking at the World Health Organization's most recent statistics from a bird's-eye view the percentage of confirmed cases that lead to death was 2.5% in the region of Africa compared to 2.2% in Europe [30]. Fractionation of this disease's prevalence and its severity amongst Middle Eastern population as well as other regions is lacking. Perhaps a global study might be considered for further risk stratification in this particular illness.

In regards to anticoagulants; one patient had estimated Glomerular Filtration Rate of 10 hence was excluded however the remaining 41 patients were given Low Molecular Weight Heparin (Enoxaparin; Sodium Claxane), one patient received unfractionated Heparin given his compromised renal functions. Anticoagulant regiments had been escalated in 23 patients (i.e. from once daily to twice), which revealed that 74% of those have shown clinical improvement. Thereby, suggesting the benefit of higher dose anticoagulant regiment, perhaps even in conjunction with other complex treatments such as Mesenchymal Stem Cells as one study has addressed, at reducing the severity of the disease and complications of thrombosis in clinical practice yet any plausible correlation requires validation in larger cohorts taking possible confounding factors in consideration [31].

Limitations of the study: there were several limitations in this study. First, the low number of subjects. Secondly, given that patients who progressed beyond their stay in this center's ICU could not be followed as many had to be discharged directly to their referring institutions and hence the study could not include data of the final survival outcome of patients. Lastly, due to a novice disease, there was no gold standard management yet established hence no collective standardization in approach and treatment in all studied cases.

CONCLUSION

In conclusion, the study evinces that the D-dimer measurements of patients who survived were of lower values compared to patients who died while in the ICU. However, as a trend over time, it was insignificant as a biomarker for prognosis neither in the patient who were progressively worsening nor the cases that improved.

REFERENCES

1. Du Toit, A. (2020). Outbreak of a novel coronavirus. *Nat Rev Microbiol*, 18:123.
2. Liu, B., Li, M., Zhou, Z., Guan, X., & Xiang, Y. J. (2020). Can we use interleukin-6 (IL-6) blockade for coronavirus disease. (COVID-19)-induced cytokine release syndrome (CRS). *J Autoimmun*, 111:102452.
3. Adam, S. S., Key, N. S., Greenberg, C. S. (2009). D-dimer antigen: current concepts and future prospects. *Blood*, 113:2878–2887. doi: 10.1182/blood-2008-06-165845..
4. Weitz, J. I., Fredenburgh, J. C., & Eikelboom, J. W. (2017). A test in context: D-dimer. *J Am Coll Cardiol*, 70:2411–2420. doi: 10.1016/j.jacc.2017.09.024.
5. Olson, J. D. (2015). D-dimer: an overview of hemostasis and fibrinolysis, assays, clinical applications. *Adv Clin Chem*, 69:1–46. doi: 10.1016/bs.acc.2014.12.001.
6. Fruchter, O., Yigla, M., & Kramer, M. R. (2015). D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. *Am J Med Sci*, 349(1):29–35.
7. Zhang, L., Yan, X., Fan, Q., Liu, H., Liu, X., Liu, Z., & Zhang, Z. (2020). D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *Journal of Thrombosis and Haemostasis*, *18*(6), 1324-1329.
8. Shah, S., Shah, K., Patel, S. B., Patel, F. S., Osman, M., Velagapudi, P., ... & Garg, J. (2020). Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: a systematic review and meta-analysis. *Cardiology in review*. https://www.medrxiv.org/content/10.1101/2020.04.29.20085407v1. Accessed May 5, 2020.
9. Rodelo, J. R., De la Rosa, G., Valencia, M. L., Ospina, S., Arango, C. M., Gómez, C. I., ... & Jaimes, F. A. (2012). D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. *The American journal of emergency medicine*, *30*(9), 1991-1999.
10. Rostami, M., & Mansouritorghabeh, H. (2020). D-dimer level in COVID-19 infection: a systematic review. *Expert review of hematology*, *13*(11), 1265-1275.
11. Velavan, T. P., & Meyer, C. G. (2020). Mild versus severe COVID-19: laboratory markers. *Int J Infec Dis*, 95:304–307.
12. Zhang, L., Yan, X., Fan, Q., Liu, H., Liu, X., Liu, Z., & Zhang, Z. (2020). D-dimer levels on admission to predict in-hospital mortality in

patients with Covid-19. *Journal of Thrombosis and Haemostasis*, *18*(6), 1324-1329.
13. Gupta, N., Zhao, Y. Y., & Evans, C. E. (2019). The stimulation of thrombosis by hypoxia. *Thromb Res*, 181:77-83.
14. Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*, 18:1094–1099.
15. Wong, J. P., Viswanathan, S., Wang, M., Sun, L. Q., Clark, G. C., & D'Elia, R. V. (2017). Current and future developments in the treatment of virus-induced hypercytokinemia. *Future Med Chem*, 9:169-178.
16. Levi, M., & van der Poll, T. (2017). Coagulation and sepsis. *Thromb Res*, 149:38-44.
17. Harper, P. L., Theakston, E., Ahmed, J., & Ockelford, P. (2007). D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. *Intern Med J*, 37:607-613.
18. Barbar, S., Noventa, F., Rossetto, V., Ferrari, A., Brandolin, B., Perlati, M., ... & Prandoni, P. (2010). A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *Journal of Thrombosis and Haemostasis*, *8*(11), 2450-2457.
19. Hess, K., & Grant, P. J. (2011). Inflammation and thrombosis in diabetes. *Thromb Haemost*, 105(Suppl 1):S43-54.
20. National Health Commission of the People's Republic of China. Chinese management guideline for covid–19 (version 6.0)
21. Leung, J. M., Yang, C. X., Tam, A., Shaipanich, T., Hackett, T. L., Singhera, G. K., ... & Sin, D. D. (2020). ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *European Respiratory Journal*, *55*(5).
22. Kabrhel, C., Mark Courtney, D., Camargo Jr, C. A., Plewa, M. C., Nordenholz, K. E., Moore, C. L., ... & Kline, J. A. (2010). Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Academic emergency medicine*, *17*(6), 589-597.
23. Cui, S., Chen, S., Li, X., Liu, S., & Wang, F. (2020). Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*, *18*(6), 1421-1424.
24. Oxley, T. J., Mocco, J., Majidi, S., Kellner, C. P., Shoirah, H., Singh, I. P., ... & Fifi, J. T. (2020). Large-vessel stroke as a presenting feature of Covid-19 in the young. *New England Journal of Medicine*, *382*(20), e60.
25. Barton, L. M., Duval, E. J., Stroberg, E., Ghosh, S., & Mukhopadhyay, S. (2020). Covid-19 autopsies, oklahoma, usa. *American journal of clinical pathology*, *153*(6), 725-733.
26. Liu, X., Liu, X., Xu, Y., Xu, Z., Huang, Y., Chen, S., ... & Li, Y. (2020). Ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19–associated acute respiratory distress syndrome. *American journal of respiratory and critical care medicine*, *201*(10), 1297-1299.
27. Bick, R. L. (2006). Hereditary and acquired thrombophilic disorders. *Clin Appl Thromb Hemost*, 12: 125-135.
28. White, R. H., & Keenan, C. R. (2009). Effects of race and ethnicity on the incidence of venous thromboembolism. *Thrombosis research*, *123*, S11-S17.
29. Golestaneh, L., Neugarten, J., Fisher, M., Billett, H. H., Gil, M. R., Johns, T., ... & Bellin, E. (2020). The association of race and COVID-19 mortality. *EClinicalMedicine*, *25*, 100455.
30. World Health Organization Coronavirus Dashboard; https://covid19.who.int
31. Debuc, B., & Smadja, D. M. (2020). Is COVID-19 a new hematologic disease? *Stem Cell Rev Rep*, 12: 1–5.

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