Coagulation profile of covid patients : In a single tertiary teaching hospital in Rajasthan

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Abstract

Background: The COVID-19 has taken the world by storm. It primarily affects the lungs causing respiratory distress and leading to ARDS.

Aim: The aim of this study is to evaluate the coagulation dysfunction in patients which predisposes the patients to venous and arterial thromboembolism due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation (DIC).

Material & Methods: We assessed 2281 COVID RT PCR positive patients who were admitted with moderate to severe disease in wards and ICU respectively. The coagulation profile was done for each of these patients and the tests included Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT) and D-Dimer. The PT and APTT were estimated on ACL elite pro (Fully automated coagulation analyser) which is based on nephelometry. D- Dimer was measured using ACL elite pro and latex agglutination (semi quantitative method).

Results: Out of 2281 COVID RT PCR positive patients 1655 (72.5%) were males and 626 (27.5%) were females. It was observed that percentage of patients admitted in ICU had increased D dimer values and it was statistically significant. Our study showed that larger number of patients admitted in ICU had PT value more than 12.5 seconds and APTT more than 35.5 seconds, however it was not statistically significant. Our study also demonstrated that patients having higher D dimer required longer hospitalization with significant *p* value.

Conclusion: We concluded that assessment of coagulation profile is necessary for patients infected with this virus so as to prevent any thrombotic complications and therefore preventing morbidity and mortality.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of respiratory transmitted virus which belongs to family Corona viridae with 80% genetic similarities to SARS-CoV-2. By mid-March 2020, it had sickened more than 80,000 people and killed more than 3000 in China, triggering a global pandemic[1,2].

A number of studies have shown that coagulation dysfunction exists in patients with severe novel coronavirus pneumonia (NCP) which is clearly correlated with poor prognosis. The normal coagulation parameters of intensive care unit (ICU) patients were remarkably higher than those of non-ICU patients[2]. COVID-19 may make patients vulnerable to both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation (DIC). Accurate knowledge of the incidence of thrombotic complications in COVID-19 patients is important for decision making concerning the intensity of thromboprophylaxis, especially in patients admitted to the intensive care unit (ICU) who are at highest thrombotic risk[3]. Based on the currently available literature, there is recommendation for measuring D-dimers, prothrombin time, and platelet count (in decreasing order of importance) in all patients who present with COVID-19 infection. This may help in distinguishing patients who may need admission and close monitoring or not. Any underlying condition (e.g., liver disease) or medication (e.g., anticoagulants) which may change the parameters should be accounted for while using the algorithm[4].

Available data suggests that the coagulopathy

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associated with COVID-19 is an amalgamation of low-grade DIC and localised pulmonary thrombotic microangiopathy, which could have a considerable impact on organ dysfunction in the most severely affected patients. Severe COVID-19 is also linked with raised concentrations of proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukins (IL), including IL-1 and IL-6. IL-6 can induce tissue factor expression on mononuclear cells, which subsequently commences coagulation activation and thrombin generation. TNF-α and IL-1 are the main mediators driving an abolishment of endogenous anticoagulant pathways. In a group of patients most severely affected by COVID-19, a cytokine storm profile can be found, identified by high concentrations of proinflammatory cytokines and chemokines. Coronavirus infections are also associated with a considerable activation of the fibrinolytic system. Observations in urokinase-type plasminogen activator knock-out mice intimated to a urokinase-driven pathway stimulating fibrinolysis and being an important factor in lethality. Also, plasma levels of tissue type plasminogen activator (t-PA) were 6-times higher in patients infected with human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-II) than in patients who did not have the infection. Inflammation-induced endothelial cell injury could result in enormous release of plasminogen activators, which could explain the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19. Thrombotic microangiopathy is classically caused by pathologically intensified platelet-vessel wall interaction due to ultra-large von Willebrand factor multimers. These multimers are released from disturbed endothelial cells and are under normal circumstances cleaved by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). In many severe inflammatory states, upon systemic infection a secondary deficiency of ADAMTS13 has been accepted. The coagulation changes related to COVID-19 suggest the presence of a hypercoagulable state that might increase the risk of thromboembolic complications. Other factors that can increase the risk of thrombosis are immobilisation and vascular damage. Patients with COVID-19 have circumstantially been reported to have had pulmonary embolism, indicating that there could be a disproportionately high incidence of venous thromboembolism and possibly arterial thrombosis in patients with COVID-19[5].

Based on the study and the experience from published literature on septic coagulopathy, monitoring PT, D-dimer, platelet count, and fibrinogen can be helpful in determining prognosis in COVID-19 patients requiring hospital admission. If these parameters worsen, more vigrous critical care support is warranted and consideration should be given for more "experimental" therapies and blood product support as appropriate. If these markers are stable or improving, it gives the added confidence for de-escalation of treatment if corroborating with the clinical condition. Hence, we present to you the study of 2281 patients admitted in our hospital which were COVID RTPCR positive and their PT, APTT and D- Dimer levels were performed.

Material and Methods

We assessed 2281 COVID RT PCR positive patients who were admitted with moderate to severe disease in wards and ICU respectively. The coagulation profile was done for each of these patients and the tests included PT, APTT and D-Dimer. The PT and APTT were estimated on ACL elite pro which is based on nephelometry. D- Dimer was measured using ACL elite pro and latex agglutination (semi quantitative method).

Results

In our study we included 2281 COVID-19 RT PCR positive patients and studied the coagulation profile of these patients. The tests included D-Dimer, (PT) Prothrombin time and APTT (Activated partial thromboplastin time). Out of 2281 patients D-dimer was done in 2142 patients, while PT and APTT were done in all the patients.

Table 1 : Gender profile of Covid RT-PCR positive patients

Gender	Number	Percentage (%)
Males	1655	72.5
Females	626	27.5
Total	2281	100

We observed that in our study out of 2281 Covid RT-PCR positive patients, 1655 (72.5%) were males and 626 (27.5%) were females.

Table 2 : Correlation of D dimer Values (ng/ml) with distribution of patients in ICU and Wards

D-Dimer Levels	ICU	Ward	Total no. of patients	P Value*
Less than 251	293 (25.8%)	842 (74.2%)	1135	<0.001
251-999	89 (12.6%)	615 (87.4%)	704	
> 999	126 (41.6%)	177 (58.4%)	303	
Grand Total			2142	

The D-dimer value cut off was taken as <251 ng/mL, between 251-999ng/mL and > 999 ng/mL. The patients having D-Dimer <251ng/mL were 1135 and 74.2% of them were admitted in ward and 25.8% in ICU. The patients having D-Dimer levels between 251-999ng/mL were 704 and 87.4% were admitted in ward and 12.6% in ICU. Lastly the patients having D-Dimer level >999 ng/mL were 303 and out of them 58.4% were admitted in ward and 41.6% were admitted in ICU. Out of 2281 patients admitted in the hospital D-Dimer test was not done in 6.09% of the patients.

Table 3 : Correlation of PT values of Covid RT-PCR Positive patients

PT in Sec.	ICU	Ward	P-Value*
Greater than 12.5	392 (73.82%)	1175 (67.14%)	0.500
Less than 12.5	139 (26.17%)	575 (32.8%)	0.496
Grand Total	531	1750	

We divided the patients into two groups according to PT values, the one having PT more than 12.5 sec and another having PT less than 12.5 sec. Among the patients admitted in ICU, >12.5 sec PT value was found in 73.82% patients and 26.17% had <12.5sec value of PT. Patients admitted in ward, 67.14% had >12.5 sec and 32.85% had <12.5sec.

Table 4 : Correlation of APTT Values of Covid RT - PCR Positive Patients

APTT in sec	ICU	P Value*	Ward	P Value*
Greater Than 35.5	193 (36.34%)	0.767	562 (32.11%)	0.042
Less Than 35.5	338 (63.65%)		1188 (67.88%)	
Grand Total	**531**		**1750**	

We divided the patients into 2 groups, the one with more than 35.5 sec and another with less than 35.5 sec. In patients admitted in ICUw, 36.34% had more than 35.5 sec and 63.65% had less than 35.5 sec. Patients admitted in ward 32.11% had more than 35.5 sec APTT values and 67.88% had less than 35.5 sec of APTT value. However, the APTT values were not found to be statistically significant.

In our study, the length of stay (LOS) was divided into <3 days, 4-10 days, 11-30 days and >30 days. The patients having D-Dimer <251ng/mL and their length of stay in the hospital is as follows, patients with LOS less than 3 days were 11.36%, between 4-10 days were 44.46% between 11-30 days were 44.17%. The patients having D-Dimer levels between 251-999ng/mL and correlation with the length of stay showed < 3days were 9.42%, 4-10 days were 36.38%, 11-30 days were 51.71% and > 30 days were 2.46%. Lastly, the patients having D-Dimer level >999ng/mL, the length of stay of these patients were < 3days was 9.90%, between 4-10 days was 30.36%, between 11 -30 days was 51.48% and > 30 days was 8.25%. Out of 2281 patients admitted in the hospital D-dimer test was not done in 6.09% of the patients.

Table 6: Correlation of age of patients with their D dimer levels

D-Dimer level (ng/mL)	Greater Than 60	60 years and below	P Value*
Less Than 251	149 (27.74%)	555 (34.57%)	0.004
More Than 251	388 (72.25%)	1050 (65.42%)	
Total	**537**	**1605**	
Percentage (%)	25.07	74.93	

We divided the patients into two groups, one group constituted patients more than 60 years of age and the other group constituted patients of 60 years and below. We further divided according to D-Dimer cut off values i.e. < 251ng/mL and > 251 ng/mL. We found that patients in age greater than 60 years 72.25% had D dimer more than 251 and 27.74% had D dimer less than 251. While in the age group of 60 years and below, 65.42% of patients had D dimer more than 251 and 34.57% had D dimer less than 251 so there was not much difference in both the age groups.

Discussion: Out of 2281 COVID RT PCR positive patients 1655 (72.5%) were males and 626 (27.5%) were females. Luo HC et al[6] studied 85 patients out of which 56.47% were males which were similar to our finding indicating male predominance. We observed that the percentage of patients admitted in ICU increased as the D-Dimer value increased more than 999ng/ml indicating that D-Dimer played an important

Table 5: Correlation of length of stay of Covid Positive Patients with their D Dimer levels

D-dimer levels (ng/ml)	< 3 days	4-10 days	11-30 days	>30 days	P-Value*	Total no of patients
<251	80 (11.36%)	313 (44.46%)	311 (44.17%)	0	<0.001	704
251-999	107 (9.42%)	413 (36.38%)	587 (51.71%)	28 (2.46%)		1135
>999	30 (9.90%)	92 (30.36%)	156 (51.48%)	25 (8.25%)		303

role in assessing the severity of COVID-19. Ozen M et al[7] retrospectively studied 120 patients whose COVID-19 diagnosis was based on RT-PCR and found the D-Dimer elevation(>243ng/ml) was detected in 63.3% of the patients. Also Lippi G et al[8] in their study found D-Dimer values to be frequently raised in 36-43% of COVID-19 patients. Our study showed that more number of patients admitted in ICUs had PT values > 12.5 sec as compared to patients admitted in ward, however they were not statistically significant. Hui long et al[9] studied 115 patients and found significant correlation of PT levels with disease progression. In our study the APTT values were not found to be statistically significant but Hui long et al[9] in their study found significant correlation of APTT value with disease progression which did not corroborate with our findings. Our study demonstrated that the patients with high D-dimer value required longer hospitalization with significant *p* value. Zhou F et al[10] retrospectively studied 191 patients and found that patients with high D-dimer levels had longer hospitalizations in ICUs and length of stay. Ozen M et al[7] retrospectively studied 120 patients and also demonstrated positive correlation of D-Dimer values with duration of stay in the hospital. Our study on the other hand depicted more involvement of patients with less than 60 years of age i.e 74.93% as Indian population has more number of people in the age group of 15-64 years. However He X et al [11] studied 1,114 COVID-19 patients and found that most of the patients (49.7%) with abnormal D-Dimer values were above 60 years of age and patients below or equal to 60 years of age, 23.65% patients had abnormal D-Dimer values.

Conclusion

Our study indicates that hypercoagulation was found in COVID-19 patients and it is related closely to disease progression and clinical outcome and therefore it necessitates the monitoring of coagulation profile of patients especially D-Dimer for early detection of any possible thrombotic complications and thus preventing morbidity and mortality of COVID-19 infected patients.

References

1. *Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020 Jun; 18(6):1421-1424.doi: 10.1111/jth.14830. Epub 2020 May 6.*
2. *Cheung CKM, Law MF, Lui GCY, Wong SH, Wong RSM. Coronavirus Disease 2019 (COVID-19): A Haematologist's Perspective. Acta Haematol. 2021; 144(1):10-23.*
3. *Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020; 191:145-147. doi:10.1016/j.thromres.2020.04.013.*
4. *Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18:1094-1099.*
5. *Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 Jun; 7(6):438-440.*
6. *Luo HC, You CY, Lu SW, Fu YQ. Characteristics of coagulation alteration in patients with COVID-19. Annals of hematology. 2021 Jan; 100(1):45-52.*
7. *Ozen M, Yilmaz A, Cakmak V, Beyoglu R, Oskay A, Seyit M, Senol H. D-Dimer as a potential biomarker for disease severity in COVID-19. Am J Emerg Med. 2021 Feb; 40:55-59. doi: 10.1016/j.ajem.2020.12.023. Epub 2020 Dec 14.*
8. *Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020 Jun 25; 58(7):1131-1134. doi: 10.1515/cclm-2020-0198.*
9. *Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, Ren H, Liu W, Wang Q, Wu Q. D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. Biomed Res Int. 2020 Jun 16; 2020:6159720. doi: 10.1155/2020/6159720. PMID: 32596339; PMCID: PMC7301188.*
10. *Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020 March 28; 395(10229):1054-62.*
11. *He X, Yao F, Chen J, Wang Y, Fang X, Lin X, Long H, Wang Q, Wu Q. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Scientific reports. 2021 Jan 19; 11(1):1-7.*

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