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Original Research Article

Covid-19: Consumption coagulopathy with increased severity and mortality - A retrospective study

Kunal Gaur[1,*], **Suresh Natarajan**[1], **Mohini Gupta**[1]

[1] *Dept. of Pathology, Sree Balaji Medical College and Hospital Chennai (Bharath University deemed Chennai), Chennai, Tamil Nadu, India*

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ABSTRACT

Objective: To compare quantitative values of parameters of coagulation pathway like Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR) and D-Dimer (DD) on date of admission versus date of patient's mortality.

Materials and Methods: A total of 50 patients who were tested positive for COVID-19 in our hospital between April 21, 2021 and May 30, 2021, were taken into this study. The changes in PT, APTT, INR and DD were compared at day of admission and day of patient's mortality.

Results: The study involved 50 patients (36 male and 14 female). D-dimer at the day of admission (mean 1540.79 ng/ml; IQR 231-8776) was found with an elevation of 250% at the day of mortality (mean 5379.04ng/ml; IQR 434-10000). PT at the day of admission (mean 13.602; IQR 11.6-14.8) was found elevated (Normal range-10.5-13.5sec) in 19/50 patients which increased to 43/50 patients at the day of mortality, an increase of 126%.

Conclusion: According to the study done, the number of patients with increased levels of PT, APTT, INR and DD were substantially greater at the time of mortality compared to the same patients at their time of admission, suggesting a dynamic coagulation process in COVID-19 patients. This likely suggested that the patients were in progression from a hypercoagulating state that transforms into a fibrinolytic state as a result of the extensive use of coagulation factors.

1. Introduction

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China, in December 2019.[1,2] Following which the infection has spread around the world, resulting in more than 246.5 million confirmed cases of COVID-19 and 5 million deaths as of the time of writing.

It classically spreads via nasal secretions and proximity. The focal clinical manifestation is pulmonary injury.[3] The majority of patients only have minor symptoms and fully recover, while some patients quickly deteriorate into a critical condition with severe respiratory distress syndrome, coagulopathies, failure of various organ systems, etc.[4,5] Therefore, assessing the severity timely is imperative in these patients.

Underlying mechanism of its focal presentation as well as the pathophysiology of COVID-19 still remains ambiguous.[6] However, numerous studies have outlined abnormal coagulation parameters, particularly in patients with acute respiratory distress syndrome (ARDS) and COVID-19 associated pneumonia.[7,8]

Elevated D-dimer is a critical independent biomarker of bad prognosis in COVID-19.[9] Furthermore, these studies indicated that COVID-19 coagulopathy is most likely a form

* *Corresponding author.*
E-mail address: kunalgaur0517@gmail.com (K. Gaur).

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of disseminated intravascular coagulation (DIC).

Patients with severe COVID-19 infection develop pulmonary embolism (PE) and deep vein thrombosis (DVT). It has been generally postulated that coagulopathy may be involved in the pathophysiology of COVID-19 [10,11] specifically, those admitted in intensive care units (ICU). Additionally, autopsy reports revealed pulmonary microthrombi and stasis in capillaries contributing to cause of death. [8,11]

Coagulation parameters like D-dimer (DD), prothrombin time (PT), activated partial thromboplastin time (APTT) and International Normalized Ratio (INR) quantify the clotting state and are tested commonly in labs.

The aim of the study is to retrospectively review the dynamic change in Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR) and D-Dimer (DD) from admission to mortality.

2. Materials and Methods

2.1. Sample size and criteria of diagnosis

A total of 50 mortality patients with confirmed SARS-COV 2 infection who were hospitalized between April 21, 2021 and May 30, 2021 were included in the study. COVID-19 diagnoses were done at our hospital in central laboratory utilizing RT-PCR (real-time reverse transcriptase polymerase chain reaction) to analyze swab taken from nose and pharynx according to World Health Organization (WHO) guidelines.

2.2. Inclusion criteria

All COVID-19-infected hospitalized patients over the age of 18 were included in the study.

2.3. Exclusion criteria

Patients with confirmed COVID-19 with other comorbidities such as carcinoma, hematological disorders, cardiac diseases, systemic diseases, and pulmonary fibrosis were excluded.

Cases with insufficient data or hospitalization of less than 2 days were also excluded.

2.4. Outcome of Illness

All 50 mortality patients data was collected for the following study.

2.5. Data collection

The data were collected at two time points: admission and at mortality.

DD, PT, APTT, and INR were obtained and labeled as DD1-2, PT1-2, APTT1-2 and INR1-2, respectively.

2.6. Study design

All patients laboratory tests were collected and documented at the time of their admission to the hospital (before any intervention).

All laboratory tests, including DD, PT, APTT, and INR, were performed using conventional techniques in the hospital laboratory. DD, PT, APTT, and INR laboratory reference values were <500 ng/ml, 10.5-13.5 sec, 27-38 sec, and 0.9-1.2, respectively.

3. Results

A total of 50 hospitalized patients with positive COVID-19 were studied. Mean age of the sample was 59.68 years and 72% of the patients were male. Average number of days of hospitalization the 10.89 days (IQR 4-25).

3.1. Evaluation of coagulation parameters

1. The evaluation of the coagulation parameters showed that the D-dimer levels were substantially increased at the time of mortality (mean 5379.04ng/ml; IQR 434->10000) when compared with the values at admission (mean 1540.79 ng/ml; IQR 231-8776)
2. 10 out of 50 patients had an elevated DD value of more than 10000ng/ml which was alarming increase considering the fact that none of these patients had a D-Dimer>2000ng/ml at the time of admission. However, 35 out of 50 patients had a higher DD value than standard at the time of admission which indicates a poor prognosis in patients with higher admission time D-Dimer value.
3. PT at the day of admission (mean 13.602; IQR 11.6-14.8) was found elevated in 19/50 patients which increased to 43/50 patients at the day of mortality (mean 15.47; IQR 11.6-12.8-24), while INR at the day of admission (mean 1.25; IQR 1.08-1.49) was found elevated in 22/50 patients which increased to 44/50 patients at the day of mortality (mean 1.442; IQR 1.09-2.19), an increase of 100%.

3.2. Axis determines the total number of patients (n=50)

Series 1 denotes the number of patients with higher value of the respective coagulation parameter against the standard value at the time of admission. Series 2 denotes the number of patients with a higher value of the respective coagulation parameter against the standard value at the time of mortality. (Reference Range - DD: <500 ng/ml, PT: 10-13.5 sec, APTT: 27-38 sec, INR: 0.9-1.2.

4. Discussion

COVID-19 is a novel form of coronavirus that causes an acute viral illness (SARS-CoV-2). COVID-19 presents as

Table 1: Comparison of coagulation parametersin COVID-19 patients at the time of admission versus at the time of mortality:

Parameters	Values of COVID-19 Patients at admission time (n=50)		Values of COVID-19 Patients at the day of mortality (n=50)		Reference Range
	Mean Value	Range (min-max)	Mean Value	Range (min-max)	
D-Dimer (DD)	1540.79	231-8776	5379.074	432 - >10000	<500 ng/ml
Prothrombin time (PT)	13.602	11.4-16.8	15.47	12.8-24	10.5-13.5 sec
Activated partial thromboplastin time (APTT)	33.762	28.9-42.6	37.206	28.9-43.1	27-38 sec
International normalized ratio (INR)	1.2508	1.08-1.49	1.442	1.01-2.19	0.9-1.2

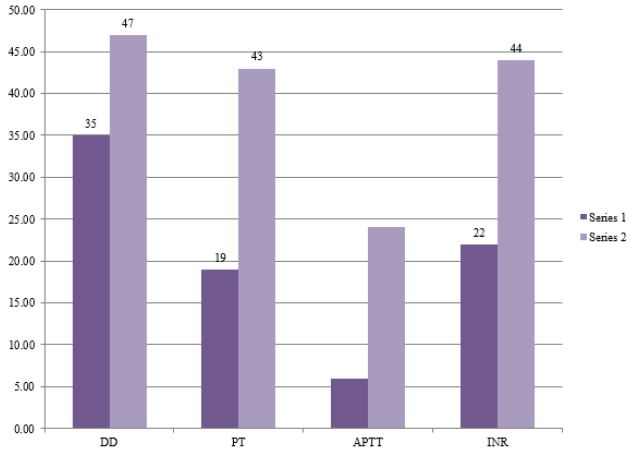

Fig. 1: Comparison of coagulation parameters in COVID-19 patients the time of admission versus at the time of mortality.

mild to severe fever.[12,13] Dyspnea may develop gradually in certain patients. However, in severe situations, the illness progresses rapidly, causing individuals to develop acute septic shock and perhaps eventually die.[14,15] It's worth noting that some critically ill and deceased people have considerable coagulation dysfunction.[8,12]

When SARS-CoV-2 enters the body via the angiotensin-converting enzyme 2 (ACE2) receptor, it attaches on the surface of mucosal epithelial cells,[16,17] The pathogen-associated molecular pattern (PAMP) is recognized by the immune system, which then initiates an immunological response to eradicate the virus. A cytokine storm, on the other hand, might be brought on by an overactive immunological response. Cytokine storm damages endothelial cells lining the blood vessel which in turn promotes clotting, inhibits fibrinolytic and anticoagulant activities. Excessive microvascular thrombosis is the underlying cause of disseminated intravascular coagulation (DIC), microcirculatory illness, and severe multiple organ dysfunction syndrome.[18] As a result, early diagnosis and treatment of coagulation disorder could significantly improve the prognosis.

PT, APTT, INR and DD are some of the most often used laboratory coagulation indicators. A high level of DD implies a hypercoagulation state and secondary fibrinolytic state. DD is the product of fibrinolytic solubilization.[19–21] Exogenous and endogenous coagulation system variables, PT and APTT, can be used to diagnose DIC early. The sensitive markers PT, APTT, INR and DD can be utilised to represent different degrees of coagulation dysfunction. This study's objective was to determine whether these markers are associated with COVID-19 patient severity and death.

The findings of this study revealed that D-dimer levels were significantly higher at the time of death, reaching >10000ng/ml, implying that COVID-19 critically ill patients are more susceptible to thrombosis.[22] A higher D-Dimer value when seen at the time of admission implies an unfavorable prognosis.

Furthermore, findings of this study demonstrate a substantial link between coagulating variables and illness prognosis, implying that DD, PT, and APTT, as well as INR, could be used as diagnostic markers for disease progression. 35 of the 50 deceased patients had a higher DD value than usual at the time of admission, and 10 of them had a DD value of more than 10000ng/ml on the day of death, which was an alarming rise.

PT was found to be raised in 19 out of 50 patients on the day of admission, increasing to 43/50 patients on the day of death, while INR was found to be elevated in 22/50 patients on the day of admission, increasing to 44/50 patients on the day of mortality, a 100 percent increase.

5. Conclusion

The steadily rising DD, PT, and INR levels point to a strong link between disease development and these markers. The results showed considerably higher levels of PT, APTT, INR, and DD, suggesting that the dynamic coagulating process in COVID-19 patients is probably a hypercoagulation state followed by fibrinolysis activation. The analysis findings of this study suggested that COVID-19 individuals likely had early hypercoagulation state. The progression of the illness and its clinical effects are also related to hypercoagulation. Coagulation indices including DD, PT, and INR should be evaluated to diagnose thrombotic events. The risk of thromboembolism and DIC caused by coagulation disturbances should be reduced through preventive treatment in order to reduce morbidity

and death in COVID-19-infected people.

6. Conflict of Interest

The authors declare no relevant conflicts of interest.

7. Source of Funding

None.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):723–33. doi:10.1056/NEJMoa2001017.
3. "guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Eng J Med*. 2020;382(18):1708–20.
4. Han W, Quan B, Guo Y, Zhang J, Lu Y, Feng G, et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019. *J Med Virol*. 2020;92(5):461–3. doi:10.1002/jmv.25711.
5. Sun X, Wang T, Cai D, Hu Z, Liao H, Zhi L, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev*. 2020;53:38–42. doi:10.1016/j.cytogfr.2020.04.002.
6. Fogarty H, Townsend L, Cheallaigh CN, Bergin C, Martin-Loeches I, Browne P, et al. COVID19 coagulopathy in Caucasian patients. *Br J Haematol*. 2020;189(6):1044–9. doi:10.1111/bjh.16749.
7. Ranucci M, Ballotta A, Dedda UD, Baryshnikova E, Poli MD, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18(7):1747–51.
8. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844–7.
9. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9–14. doi:10.1016/j.thromres.2020.04.024.
10. Middeldorp S, Coppens M, Van Haaps TF, Foppen M, Vlaar AP, Müller MC, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1995–2002. doi:10.1111/jth.14888.
11. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020;77(2):198–209. doi:10.1111/his.14134.
12. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virology*. 2020;94(7):e00127–20. doi:0.1128/JVI.00127-20.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* . 2020;323(11):1061–9. doi:10.1001/jama.2020.1585.
14. Gates B. Responding to Covid-19-a once-in-a-century pandemic? *N Engl J Med*. 2020;382(18):1677–9. doi:10.1056/NEJMp2003762.
15. Zhou T, Liu Q, Yang Z, Liao J, Yang K, Bai W, et al. Preliminary prediction of the basic reproduction number of the Wuhan novel coronavirus 2019-nCoV. *J Evid Based Med*. 2020;13(1):3–7. doi:10.1111/jebm.12376.
16. Kowalczuk S, Bröer A, Tietze N, Vanslambrouck JM, Rasko JE, Bröer S, et al. A protein complex in the brush-border membrane explains a Hartnup disorder allele. *FASEB J*. 2008;22(8):2880–7.
17. Cohen J. The immunopathogenesis of sepsis. *Nature*. 2002;420(6917):885–91.
18. Giannitsis E, Mair J, Christersson C, Siegbahn A, Huber K, Jaffe AS, et al. How to use D-dimer in acute cardiovascular care. *Eur Heart J Acute Cardiovasc Care*. 2017;6(1):69–80. doi:10.1177/2048872615610870.
19. Ramana CV, Deberge MP, Kumar A, Alia CS, Durbin JE, Enelow RI, et al. Inflammatory impact of IFN-γ in CD8+ T cell-mediated lung injury is mediated by both Stat1-dependent and-independent pathways. *Am J Physiol Lung Cell Mol Physiol*. 2015;308(7):1650–7. doi:10.1152/ajplung.00360.2014.
20. Behrens K, Alexander W. Cytokine control of megakaryopoiesis. *Growth Factors*. 2018;36(3-4):89–103.
21. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*. 2020;27(2):taaa021. doi:10.1093/jtm/taaa021.
22. Available from: https://covid19.who.int.

Author biography

Kunal Gaur, Resident https://orcid.org/0000-0001-7963-8207

Suresh Natarajan, Assistant Professor https://orcid.org/0000-0003-4966-5559

Mohini Gupta, Resident https://orcid.org/0000-0002-6830-2342

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