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Covid-19 Associated Hemostatic Abnormality for Monitoring Evolution and Complications of Disease

Swati Singh[1], Mayurika S Tyagi[2], Ashi verma[3], Aarthi KB[4]

[1,2] Associate Professor, Department of Pathology, Santosh Medical College, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India.

[3,4] JR 3 Pathology, Department of Pathology, Santosh Medical College, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India.

Email- [1] swati_singh3077@yahoo.com, [2] somyamayuri@hotmail.com, [3] drashiverma@gmail.com, [4] aarthi.balakrishnan1994@gmail.com

ABSTRACT:

Introduction: Coronaviruses are a broad group of viruses that can infect both humans and animals and make them sick. In mid-December 2019, a seafood market in Wuhan, China's Hubei Province, reported an outbreak of the novel coronavirus illness (COVID-19), which later expanded to 214 other nations, territories, and regions. A respiratory tract illness linked to SARS-CoV-2 infection is what the majority of COVID-19 patients primarily experience. A few patients with severe COVID-19 infections also frequently display coagulation problems, which are linked to respiratory decline and death. Additionally, many COVID-19 patients experience thromboembolic issues that appear to be connected to the coagulopathy.

Material and Methods: The site of this study was a tertiary care hospital that was also designated as a Level 3 institution for the care of Covid 19 patients. A semi-automated coagulation analyzer (Coag 2D) was used to perform the following tests: platelet count, Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer tests. The coagulation parameters at admission and later during the hospital stay were compared between the survivors and non-survivors group.

Result: A substantial coagulation disorder appears to be brought on by severe COVID-19 infections. In patients with severe COVID-19, an unusually high D-dimer result is the most obvious coagulation test anomaly. Nearly 40.9% of patients in the current study had D-dimer levels that were noticeably elevated, and 100% of the patients in the severe non-survivor category also had D-dimer levels that were significantly elevated.

Conclusion: Coagulation problems are linked to severe COVID-19 infection. It is important to distinguish the coagulopathy caused by COVID-19 from other types of DIC and to classify it as a distinct kind of prothrombotic intravascular coagulation that may require new diagnostic criteria.

Key words: Covid 19, Coagulopathy, DIC, thromboembolism.

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INTRODUCTION:

Since December 2019, COVID-19, a newly discovered coronavirus disease, has spread throughout China and the rest of the world. A novel encapsulated RNA betacoronavirus with phylogenetic similarities to SARS-CoV and the designation severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) has been discovered as the pathogen.

Background:

Various viruses known as coronaviruses can infect both humans and animals and cause illness. The development of animal coronaviruses, human infection, and subsequent human transmission as occurred with MERS and SARS are highly uncommon. Early in December 2019, in a seafood market in Wuhan, Hubei Province, China, the Novel Coronavirus Disease (COVID-19) outbreak was initially discovered. Later, it was extended to 214 nations, regions, and locations throughout the globe. On January 30, 2020, in compliance with international health laws, the WHO designated the pandemic as a "Public Health Emergency of International Concern" (PHEIC). Following that, on March 11, 2020, WHO declared COVID-19 to be a pandemic [(2)]

Disease Epidemiology:

The best evidence currently available for COVID-19 points to the causal virus (SARS-CoV-2) having a close zoonotic relationship to a coronavirus with a bat origin that is similar to SARS. The virus has been proven to employ the angiotensin-converting enzyme 2 (ACE2) receptor for cell entrance and is an enveloped RNA beta coronavirus similar to the "severe acute respiratory syndrome (SARS)" virus. The main source of infection is people who have already contracted the new coronavirus. Close contact between people allows for direct person-to-person transmission, which primarily happens when respiratory droplets from an infected person's cough, sneeze, or speech are expelled. These droplets might also touch down on surfaces, where the virus is still alive. A person can become infected if they touch a contaminated surface and then touch their eyes, nose, or mouth.

Patho-physiology:

Most COVID-19 patients mostly experience respiratory tract infections linked to SARS-CoV-2 infection. However, in a tiny percentage of instances, they can advance to a more serious, systemic condition marked by "acute respiratory distress syndrome (ARDS)", sepsis and septic shock, multiorgan failure, including acute kidney injury and heart injury, and other symptoms.

The disease's clinical manifestations are extremely diverse and can include anything from mild, non-specific symptoms like fever, dry cough, and diarrhoea to severe pneumonia, lung failure, and even death. 5% of infected individuals experience a decline in respiratory insufficiency requiring mechanical ventilation or multiple organ failure, mostly as a result of age and comorbidities.

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Clinical categorisation is done in mild, moderate and severe categories depending upon the assessment parameters as under

Mild

Mild symptoms, such as a fever, cough, sore throat, nasal congestion, malaise, and headache, might occur in patients with an uncomplicated upper respiratory tract infection.

Moderate

Moderate Pneumonia without symptoms of a serious illness. Adolescent or adult with fever, cough, SpO2 94% (range 90-94%) on room air, and a respiration rate of more than or equal to 24 breaths per minute in addition to other clinical symptoms of dyspnea and/or hypoxia.

Severe

Quite Serious Pneumonia Adolescent or adult: having one of the following symptoms in addition to the clinical signs of pneumonia: respiratory rate >30 breaths per minute, significant respiratory distress, or SpO2 90% on room air.

When a COVID-19 infection is severe, patients typically display coagulation problems that are linked to respiratory decline and death. A significant number of patients who have severe COVID-19 infections also experience thromboembolic consequences, which may be linked to the coagulopathy. Undiagnosed pulmonary embolism may have a role in the abrupt decline in pulmonary oxygen exchange that occasionally occurs in COVID-19 infection patients, according to some research. The coagulation abnormalities linked to COVID-19 mimic other systemic coagulopathies commonly observed after serious infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (TMA).

MATERIAL AND METHODS:

This study was conducted at a Level 3 facility for management of Covid 19 patients, after obtaining approval from Institutional Ethics Committee.

The clinical data was collected and outcomes were monitored for the duration of stay at hospital with a emphasis on a hemostasis-focused laboratory monitoring

The study was conducted on a sample size of 110 patients, during the course of three months. Platelet count, Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer tests were performed using a semi-automated coagulation analyzer (Coag 2D). The samples for coagulation tests were collected in sodium citrate anticoagulant containing vials on admission (Day 1) and during the hospital stay (Day 3). Further samples were collected depending on dynamic changes in coagulation parameters and the clinical status of the patient. The coagulation parameters on admission and thereafter during the hospital stay between survivors and non-survivors group were compared.

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Inclusion Criteria

1. Patients with report of confirmed Covid-19 infection by RT-PCR and admitted in Santosh Medical College Hospital with moderate to severe symptoms.
2. Patients of age >18 years

Exclusion Criteria

1. Patients not giving consent for the study
2. Age <18 years
3. Patients with known history of coagulation disorder

RESULTS:

110 individuals with confirmed Covidium 19 infections were enrolled in the trial, and they all provided the necessary clinical information and laboratory results. Patients were divided into moderate and severe groups based on the clinical data available at the time of admission. The mean age at disease onset in the current research was 53.4 years (range, 20-86 years).

Out of 22 patients in the severe clinical group, 14 (63.6%) were older than 60 years old, and the majority of them had a history of chronic illnesses, such as chronic liver and kidney disease, chronic liver and kidney disease, malignant tumours, respiratory system disease, and other conditions. Table 1 displays the distribution of clinical cases and the severity of symptoms.

Table 1. Distribution of cases according to age and severity of symptoms

Age group	**Moderate**	**Severe**
20-30	09	-
31-40	14	-
41-50	22	02
51-60	22	06
>60	21	14
Total	88	22

The coagulation parameters on admission and thereafter during the hospital stay between different clinical categories and between survivors and non-survivor's patient group were also compared. The samples for coagulation tests were collected on admission (Day 1) and during the hospital stay (Day 3). Further samples were collected on day 5 depending on dynamic changes in coagulation parameters and the clinical status of the patient.

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Table 2. Coagulation parameters of Covid 19 patients on admission

Parameter	**Normal range**	**Moderate (n =88)**	**Severe survivors(n17)**	**Severe Non survivors (n05)**
PT (sec)	12.0-13.5	12-19.1(16.1)	14-18.5(16.1)	14.2-19 (15.3)
APTT (sec)	30-36	30-44 (36.2)	34-41(37.6)	33.4-38 (35.28)
Platelet count	150-400 $x10^3$	69-510 (202.9)	94-523(247.7)	84-111(90))
Fibrinogen (mg/dl)	200-400	110-580 (341)	179-496(345.2)	80-470 (359.8)
D dimer (ug/ml)	<0.5	0.2-1.8 (0.40)	0.21-2.0 (0.64)	2.2-3.9(2.7)

There was only a mild increase in coagulation assays like PT and APTT and with little difference in mean values across different clinical groups. The mean value of PT was 16.1 sec in both moderate and severe survivor groups while the mean value was 15.3 sec in severe non survivor groups.

The average platelet count was mildly reduced in severe non survivor group and range of platelet count in this group was 80-111 $X10^{3/UL}$

The fibrinogen values were predominantly either normal or raised in the study with a few cases especially in severe clinical category showed a drop in fibrinogen levels below 100 mg/dl.

In patients in severe non survivor category the average D Dimer was significantly raised with a mean of 2.7 ug/ml as compared to the average in moderate and severe survivor categories where the average was 0.40 ug/ml and 0.38 ug/ml respectively.

In the present study out of 110 patients 22 patients (20%) were found to be in clinically severe category.

Criteria for disseminated intravascular coagulation (DIC),[6] were evaluated for patients in this category according to the International Society on Thrombosis and Haemostasis (ISTH) diagnostic criteria. (Table 3)

Table 3. Grade of DIC in severe patients (n = 22)

Parameter	No of patients
Platelet count (10/l) 50-100 1 point <50 2 point	 05 -
D dimer (ug/ml) 1.0-3.0 (2 points) >3.0 (3 points)	 04 01

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Fibrinogen (mg/dl) <100 1 point	01
Prolongation of PT (SEC) 3-6 (1 point) >6 (2 points)	04

Abbreviations: DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis

Using the ISTH criteria of DIC in severe non survivor category only 1 patient out of 5 met the criteria of DIC (Total points ≥5) (Table 4). This was associated with a low fibrinogen and a raised D Dimer.

TABLE 4. DIC Score using the ISTH criteria (n=05)

PT (sec)	APTT (sec)	Platelet count ($x10^3$/ul)	Fibrinogen (mg/dl)	DDimer (ug/ml)	DIC Score
19	35	84	420	2.2	04
14.3	34	65	80	3.9	05
15	38	90	409	2.5	03
14.2	33.4	100	420	2.5	03
14.2	36	111	470	3.8	02

DISCUSSION:

As a result of inflammation-induced changes in coagulation and significant endothelial cell injury, severe COVID-19 infections appear to result in a profound coagulation abnormality.

Adult respiratory distress syndrome (ARDS)-related symptoms such as broncho-alveolar fibrin deposition and thromboembolic consequences are all likely caused by this coagulopathy.

In patients with severe COVID-19, an unusually high D-dimer result is the most obvious coagulation test anomaly. (3-6) In the current study, over 40.9% of patients had significantly elevated D-dimer levels, and 100% of patients in the category of severe non-survivors also displayed significantly elevated D-dimer levels.

Fibrinogen is yet another indicator of thrombotic risk and inflammation. It is most likely the result of an acute phase reaction that COVID-19 patients typically have very high mean fibrinogen plasma concentrations. A limited percentage of the most severe COVID-19 patients in China were also associated with a fast reduction in plasma fibrinogen just before they passed away, albeit this was only demonstrated in 1 case in the study's severe non-survivor group [5]

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The most severe patients also have a relatively modest thrombocytopenia, which is another characteristic. (7,8). 40% of the patients in the research had mildly lowered platelet counts, with the majority of these patients having counts between 100 and 150x103/ul; lower platelet counts were only occasionally (5%) observed. In contrast to thrombocytopenia linked to other diseases such viral illness and bacterial sepsis, a low platelet count in COVID-19 was not substantially linked to a poor prognosis.

In the study, patients with the most severe COVID-19 infection only had mildly prolonged prothrombin times (PT), or about 3 seconds, indicating close to normal levels of coagulation factors. Activated partial thromboplastin time (aPTT) prolongation is less obvious and may be hidden by (very) high levels of factor VIII and fibrinogen.

The pattern of coagulation tests seen in DIC is mimicked by thrombocytopenia, increased fibrinogen, increased D-dimer, and modestly extended global coagulation tests. But there do appear to be observable variations from the DIC frequently observed in patients with sepsis, cancer, or other underlying conditions known to be associated with DIC (09).

TABLE 5. Coagulation parameters in COVID 19 and acute DIC compared

Parameters	COVID 19	Acute (decompensated) DIC
Platelet count	Normal or reduced	Reduced
PT	Normal or Prolonged	Prolonged
aPTT	Normal or prolonged	Prolonged
Serum fibrinogen	Elevated	Reduced
D dimer	Elevated	Elevated

The majority of patients with COVID-19 do not exhibit marked thrombocytopenia, whereas more severe thrombocytopenia is typically seen in cases where DIC complicates a serious systemic condition. Additionally, a low platelet count in COVID-19 was not significantly associated with a poor outcome.

Patients with the most severe COVID-19 infection have prothrombin times (PT) that are only marginally prolonged (roughly 3 seconds), which indicates coagulation factor levels that are almost normal.

A hypercoagulable state that at the very least may increase the risk of thromboembolic complications is suggested by the coagulation changes brought on by COVID-19 infection. (10-11) According to several reports, patients with COVID-19 infections may have an abnormally high incidence of venous thromboembolism and possibly arterial thrombosis. These reports include patients with documented pulmonary emboli. [11,12,13]. It can be said that "COVID-19-associated coagulopathy" early in infection reflects abnormalities in tests but does not meet the typical definition of a clinical coagulopathy where impaired ability to clot results in bleeding.

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A type of DIC caused by COVID-19 is typically hypercoagulable in nature. Although the precise pathogenetic mechanism of DIC caused by COVID-19 is unknown, inflammation and cytokine release may be to blame for the observed coagulation impairment that results in thromboembolic complications.

COVID-19–associated coagulopathy

Summary of findings

- In the early stages of infection, coagulopathy shows up as high fibrinogen, elevated D-dimers, and modest changes in PT, aPTT, and platelet count.
- Coagulopathy does not seem to be caused by intrinsic viral activity but rather to the severity of the illness and subsequent thrombo inflammation.
- Increased mortality is linked to elevated D-dimer at admission.
- Multiorgan failure and overt DIC are preceded by rising D-dimer following admission.
- Despite coagulopathy, bleeding symptoms are uncommon.

CONCLUSION:

Conclusion: Severe Infection with the COVID-19 virus is associated with coagulation abnormalities that share traits with both DIC and thrombotic microangiopathy. This coronavirus infection appears to produce a distinct, more localised coagulopathy in contrast to "classic" DIC or thrombotic microangiopathy syndromes. Given the high incidence of thromboembolic consequences in critically sick patients, the unique coagulopathic features of this illness are undoubtedly pertinent and may have a substantial impact on the creation of preventative or therapeutic management measures that may improve clinical outcome.

Given everything, it could be plausible to say that the coagulopathy linked to COVID-19 should be classified as a specific kind of prothrombotic intravascular coagulation that differs dramatically from the DIC that is normally linked to other illnesses and may call for novel diagnostic approaches.

REFERANCES:

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W,et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565- 574.
2. World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int.

ISSN PRINT 2319 1775 Online 2320 7876

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3. 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;395:1054-62

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

5. 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;18:844-7.

6. Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. Thromb Haemost 2020; in press/published online

7. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clinica chimica acta; international journal of clinical chemistry 2020;506:145-8.

8. Brogaard Larsen J, Pasalic L, Hvas AM. Platelets in Coronavirus Disease. Seminars in Thrombosis & Hemostasis 2020; in press/published online

9. Levi M, Scully M. How I treat disseminated intravascular coagulation. Blood 2018;131:845-854..

10. 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; in press/published online

11. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; in press/published online

12. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID19 pneumonia: a random association? Eur Heart J 2020; in press/published online

13. Yuanliang X, Wang X, Yang P, Zhang S. COVID-19 Complicated by Acute Pulmonary Embolism. Images in Cardiothoracic Imaging 2020;Published Online, March 16, 2020.