A STUDY ON COAGULATION ABNORMALITIES AND LONG-TERM PULMONARY OUTCOMES AMONG COVID 19 PATIENTS

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Abstract
Background: The coronavirus strain SARS-COV2, also known as COVID-19, is responsible for the recent coronavirus sickness with various pathological conditions like coagulation abnormalities, mainly thrombotic complications, inflammation, and long-term pulmonary outcome**s**.
Material methods: An observational, cross-sectional study was conducted in Department of Respiratory Medicine, National Institute of Medical Science and Research, Jaipur among COVID-19 patients. Patients of age 21-60 years who have suffered with COVID-19 diseases in past 18 months have been evaluated. All statistical analysis was performed in SPSS (statistical package for social sciences) version23.
Results: From the results, elevated D-dimer and Factor VIII levels above normal ranges were noted in 27% and 48% of patients respectively, the results also showed that COVID-19 vaccination preceding SARS-CoV-2 infection show statistically significant differences in the outcome of the disease.
Conclusion: The study findings among COVID-19 patients showed that hypercoagulability, endotheliopathy, and inflammation extend well beyond acute SARS-CoV-2 infection, where recovered COVID-19 patients may develop long-term thrombotic and cardiovascular complications. Hence the need for robust public health measures and sound primary prevention policies in preventing SARS-CoV-2 infection as well as appropriate follow-up strategies for recovered patients.
Keywords: COVID-19, endotheliopathy, thrombotic complications

1. INTRODUCTION

The coronavirus strain SARS-COV2, also known as COVID-19, is responsible for the recent coronavirus sickness with various pathological conditions like coagulation abnormalities, mainly thrombotic complications, inflammation, and long-term pulmonary outcomes.

Even though many patients with severe COVID-19 present with lung function abnormalities, a proportion of patients with severe COVID 19 also present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy, but COVID-19 has distinct features. Coagulopathy in patients with COVID-19 is associated with an increased risk of death.

The most typical finding in patients with COVID-19 and coagulopathy is an increased D-dimer concentration, a relatively modest decrease in platelet count, and a prolongation of the prothrombin time.

Abnormal coagulation parameters in COVID-19 patients are important prognostic factors of disease severity.

The combination of thrombocytopenia, prolonged prothrombin time, and increased D-dimer is suggestive of DIC, although the pattern is distinctively different to DIC seen in sepsis.

In sepsis, thrombocytopenia is usually more profound, and D-dimer concentrations do not reach the high values seen in patients with COVID-19.

Severe COVID-19 is also associated with increased concentrations of pro inflammatory cytokines, such as

- Tumor necrosis factor-α (TNF-α)
- Interleukins (IL), including IL-1 and IL-6. IL-6 can induce tissue factor expression on mononuclear cells, which subsequently initiates coagulation activation and thrombin generation.
- TNF-α and IL-1 are the main mediators driving a suppression of endogenous anticoagulant pathways.

In a subset of patients most severely affected by COVID-19, a cytokine storm can be found, characterized by high concentrations of pro inflammatory cytokines and chemokines.

- Up to 20%−30% of patients hospitalized with coronavirus disease 2019 (COVID-19) have evidence of myocardial involvement.
- Acute cardiac injury in patients hospitalized with COVID-19 is associated with higher morbidity and mortality.
- This study was aimed to summarize coagulation profile and long-term pulmonary outcome among COVID 19 affected patients.

2. MATERIALS AND METHODS

STUDY TYPE AND AREA:
An observational, cross-sectional study was conducted in Department of Respiratory Medicine, National Institute of Medical Science and Research, Jaipur. Ethical clearance was obtained and approved by National Institute of Medical Science and Research, Jaipur.

STUDY POPULATION:
In this study, we have included 106 patients upto age of 65 years who have suffered with COVID-19 disease in past 18 months diagnosed with RT-PCR.

COAGULATION PROFILE AND CLINICAL DATA:

Clinical details, laboratory investigations and coagulation profile was collected and the coagulation parameters were compared with the manufacturer cut off of normal range of PT = 11.7-15 seconds, APTT = 23.8-37.9 seconds, INR = 1.0-1.2 and PLT = 159-386/μl.

The coagulation parameters above the cut off value were considered as a prolonged and thrombocytopenia in the case of lower than cut off value for platelets.

Data compilation and segregation was done in MS Excel. Statistical Package for the Social Sciences (SPSS) software version 23.0 (SPSS1 Inc., Chicago, IL, USA) was used for statistical analysis.

Chi-square test was used to determine association among categorical variables. The quantitative data were expressed as Mean ± SD. P value < 0.05 was considered as statistically significant.

OBSERVATIONS & RESULTS

- Total 106 Covid-19 patients at NIMS Hospital, Jaipur were included.
- Among the study participants, 67 (63.21%) were males and mostly above 55 years of age (38.7%) followed by middle age group, 36-55 years (34.9%) and young age, 18-35 years (22.6%).

Tables 1: Sociodemographic characteristics of study participants

Variables		Frequency	Percent
Gender	Male	67	63.2%
	Female	39	36.8%%
Age group	0-18 years	04	3.8%
	18-35 years	24	22.6%
	36-55 years	37	34.9%
	>55 years	41	38.7%
Disease severity	Moderate	69	65.1%
	Severe	21	19.8%
	Critical	16	15.1%

Only 3.8% of patients belonged to age less than 18 years. Based on disease severity of COVID-19, out of total, 69 (65.1%) cases were moderate, 21 (19.8%) were severe, and 16 (15.1%) were critically ill.
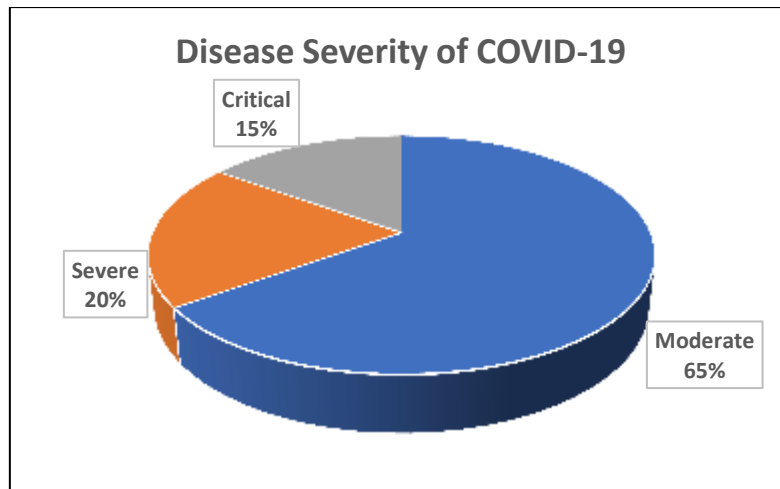
Figure 1: Severity of COVID-19 among Study Subjects

Prolonged PT, APTT and INR was found among 54(50.9%), 55(51.8%) and 50(40.2%) of COVID-19 patients respectively. Prolonged PT, APTT and INR were more frequently seen among severely (14/21, 66.6%) and critically ill cases (12/16,75%).

Tables 2: Coagulation parameters of study participants with severity of COVID-19

Variables		Disease severity		
		Moderate (69)	*Severe (21)*	*Critical (16)*
PT	*High (54)*	28	14	12
	Normal (47)	38	6	3
	Low (5)	3	1	1
APTT	*High (55)*	34	11	10
	Normal (36)	25	7	4
	Low (15)	10	3	2
INR	*High (50)*	30	11	9
	Normal (51)	36	9	6

Thrombocytopenia was detected in 24(22.6%) of COVID-19 cases and half of them were older than 55 years. 11(45.8%) severely ill and 9(37.5%) critically ill patients were more frequently found with thrombocytopenia.

Elevated D-dimer and Factor VIII levels were found above normal ranges among 35 (33.01%) and 50 (47.2%) of patients respectively.

3. DISCUSSION

The COVID-19 pandemic had a major impact on health care globally. COVID-19 has already caused >1.2 million deaths worldwide as of October 30, 2020 according to WHO report.

Coagulation abnormalities are frequent in COVID-19 patients and are associated with poor prognosis and reduced survival.

Teimury A et. al. (2022) has reviewed the most commonly reported problems of COVID-19 patients, such as venous thromboembolism, pulmonary embolism, disseminated intravascular coagulation, etc. and investigated the causes in these patients.

Coagulation and inflammatory markers, such as platelets and fibrinogen, C-reactive protein, lactate dehydrogenase, d-dimer, prothrombin time, etc., were also discussed, and the treatment options were briefly reviewed and its dysfunction and dysregulation is considered as poor prognostic markers.

Previous studies indicated that the coagulopathy in patients hospitalized with COVID-19 is characterized by **increase in coagulation parameters** such as PT, APTT and INR. In this recent study, prolonged PT, APTT and INR were more frequent among severe and critical COVID-19 patients. Similarly, studies also reported that thrombotic complications are common among COVID-19 patients admitted to intensive care unit (ICU).

Published studies indicate that COVID-19 is associated with a hyper-coagulable state. Venous thromboembolism (VTE) and arterial thrombosis ranging from **15% to 30% were found in critically ill patients** with COVID-19 and about 7% in those admitted to medical wards.

In the current study, thrombocytopenia was detected in 24(22.6%) of COVID-19 cases and half of them were older than 55 years. **45.8% severely ill and 37.5% critically ill patients more frequently found with thrombocytopenia** and this was in line with studies conducted in different countries.

Many studies reported that coagulopathy associated with COVID-19 as similarly found in our study, characterized by thrombocytopenia, prolongation of the prothrombin time, high levels of D-dimer, and elevated levels of fibrinogen, factor VIII, and von Willebrand factor.

Although, there is much to be known about the pathogenesis of COVID-associated coagulopathy; however, the mechanisms overlap with thrombotic microangiopathy, haemophagocytic syndrome and antiphospholipid syndrome compounded by the diffuse endothelial damage.

The recommendations regarding the treatment are still evolving, but **antithrombotic therapy has a definite role in positive outcomes of sick patients**.

4. CONCLUSION

- Elevated D-dimers and fibrinogen in the early stage of the disease with minimally deranged prothrombin time and platelet counts are prominent and distinguishing features.
- The study findings among COVID-19 patients showed that hypercoagulability, endotheliopathy, and inflammation extend well beyond acute SARS-CoV-2 infection, where recovered COVID-19 patients may develop long-term thrombotic and cardiovascular complications.

RECOMMENDATIONS:
- Screening for residual cardiac involvement in the convalescent phase for patients recovered from COVID-19 associated cardiac injury is needed.

- Hence the need for robust public health measures and sound primary prevention policies in preventing SARS-CoV-2 infection as well as appropriate follow-up strategies for recovered patients.

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