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A Study Of Thromboembolic Events In Covid-19 Recovered Patients

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Abstract

COVID-19 being an infectious disease caused by SARS COV-2 which remains a global pandemic health burden in present scenario.

Severe disease manifested by fever and pneumonia, leading to acute respiratory distress syndrome (ARDS), has been described in COVID-19 cases. [1, 2]

It is being associated with significant coagulation dysfunction which predisposes patients to an increased risk of both venous and arterial thromboembolic events and potentially leads to an increased mortality risk.

We intended to study thromboembolic events in COVID-19 recovered patients. Also, we intended to study recurrence or new onset thromboembolic events in COVID-19 recovered patient is whether due to incomplete anticoagulant therapy or absence of prophylactic anticoagulation therapy in COVID-19 recovered patient on discharge. We also intended to ascertain type (arterial/venous thrombosis) in COVID-19 recovered patients.

Our study was a cross sectional observational study conducted over a period of 8months.

In our study, total 37 patients were included, mean age group was 64 years, 60% were male. Maximum patients presented with acute coronary event, followed by pulmonary thromboembolism, cerebrovascular event, superior mesenteric artery syndrome and deep venous thrombosis.

We concluded that:

High D-dimer & inflammatory markers must be considered as risk factor for development of thromboembolic events post discharge.

Patients with COVID-19 post recovery require appropriate follow up. Patient at higher risk for thrombosis require prolonged anticoagulation while monitoring for bleeding manifestation.

Keywords: COVID-19, Thromboembolism, D-dimer.

Introduction

COVID-19 being an infectious disease caused by SARS COV-2 which remains a global pandemic health burden in present scenario.

Severe disease manifested as acute respiratory distress syndrome (ARDS), has been described in COVID-19 cases. [1, 2]

COVID-19 caused by the SARS CoV-2, initially the disease manifested with pulmonary involvement. Later it was also found to be associated with significant coagulation dysfunction which predisposes patients to an increased risk of both venous and arterial thromboembolic events [3] and potentially leading to an increased mortality risk.

The thromboembolic complication associated with this disease could either manifest as local or systemic (venous/arterial) thromboembolic event. Deep vein thrombosis (DVT) accounts for approximately 20% of thromboembolic events which is the commonest one. Along with it acute coronary syndrome and

stroke were also noted in these patients with prior history of vascular disease. [4]

The management of thromboses should be carried out according to current guidelines with therapeutic anticoagulation. Post-discharge thromboprophylaxis is a field of dispute, as sufficient data reporting the incidence of Venous thromboembolism (VTE) following hospitalization for COVID-19 is not available. [5]

According to International Society on Thrombosis and Haemostasis recommended that patient with high risk for thromboembolism {advanced age, cardiovascular risk factors, Intensive care unit (ICU admission), prolonged immobilisation, IMPROVE VTE score > 4 or score 2-3 with high D-dimer levels} and low risk of bleeding must be considered to continue thromboprophylaxis post COVID-19 discharge for 4 weeks. They recommended use of low molecular weight heparin (LMWH) or a direct oral Anticoagulant (DOAC) which benefitted with low VTE event and with no major bleeding events. [6, 7, 8, 9]

We intended to study thromboembolic events in COVID-19 recovered patients. Also, we intended to study recurrence or new onset thromboembolic events in COVID-19 recovered patient, whether due to incomplete anticoagulant therapy or absence of prophylactic anticoagulation therapy in COVID-19 recovered patient on discharge. And also intended to ascertain type of thromboembolism (arterial/venous thrombosis).

Materials And Methods

Study design: Cross sectional observational study.

Study place: BVDU and MCH, Sangli, Maharashtra, India.

Study Duration: 8 months.

Study population: All cases of COVID-19 positive recovered admitted or coming to OPD in BVDU and MCH, Sangli, Maharashtra, India during the study period.

Study subjects: All cases of COVID-19 positive recovered above 18 years of age.

Mild cases: - Mild symptoms SPo_2 >94 %, RR <24 /min

Moderate cases: - symptomatic SPo_2 90-94 %, RR >24/ min, Dyspnoea

Severe cases: - severe, extensive pneumonia, SPo_2 90%@ Room Air, RR> 30/min, ARDS

Critically ill: - septic shock, RR > 40/min, SPo_2 < 90%

Inclusion Criteria:

Patients with age above 18 years and COVID-19 positive recovered admitted or coming to OPD in BVDU and MCH, Sangli, Maharashtra, India.

Exclusion criteria:

- Patients who are not willing for test
- Pregnant patients
- Patients with history of recent trauma or surgery
- Chronic liver disease

Methodology:

After the appropriate permission from the institutional heads, each patient were explained about summary of the research conveying the highlights and consent was obtained.

The patients giving the written consent were considered for the study. A detailed clinical history was taken and thorough clinical examination was performed. All the relevant investigations were carried out.

Care was taken to maintain strict confidentiality and also to maximize the level of comfort while doing the clinical examination and evaluation.

Study Variables:

Complete blood count, prothrombin time and activated partial thromboplastin time, fibrinogen, D-dimer, Electrocardiograph (ECG), brain imaging, For DVT: Lower Limb Doppler, For Pulmonary Embolism (PE): Computed tomography with pulmonary angiography (CTPA), Alternative – Ventilation/perfusion scan

Sample Size:

Patient admitted in Bharti Hospital during study period

Sampling Technique:

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Convenient Sampling

Study Tools: Performa and Laboratory Investigations along with Lower limb Doppler and CTPA

Plan For Analysis: Data was analysed using appropriate software.

Results

Table 1: Demographic, Clinical And Laboratory Profile.

	VTE Group (n=17)	ATE Group (n=20)	P Value
Age	56.24±7.75	56.40±7.16	0.94
Sex			
Male	10	12	-
Female	7	8	
Co-morbidity			
DM			
YES	6	12	0.19
NO	11	8	
HTN			
YES	12	17	0.42
NO	5	3	
IHD			
YES	2	8	0.07
NO	15	12	
CKD			
YES	4	8	0.3
NO	13	12	
BMI	31.31±2.83	28.70±2.55	0.0055*
Days of presentation post discharge	24.06±6.88	40.90±9.99	<0.0001***
CTSS (Out of 25)	14±3.06	13.45±2.76	0.56
Duration of hospital stay	11.59±3.45	10.80±2.95	0.45
D-dimer	3.08±1.68	1.79±0.70	0.0034*
CRP	12.29±7.82	11.38±5.33	0.67
LDH	454.2±178.1	358.7±145	0.08

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Anticoagulant taken on follow-up			
YES	15	14	0.24
NO	2	6	
Outcome			
Discharge	16	16	0.34
Mortality	1	4	

In our study total 37 patients were included who were fulfilling the inclusion criteria. Out of which, 20 patients had arterial thromboembolic event and 17 patients had venous thromboembolic event post COVID-19 discharge. Out of 37 patients 22 patients were male and 15 patients were female.

Mean age group in the Arterial thromboembolism (ATE) group was 56.40±7.16 and VTE group was 56.24±7.75 (as seen in Table 1)

In our study we found that out of 20 patients with arterial thromboembolic event, 12 patients were Diabetic and 17 were hypertensive. Out of 17 patients with VTE, 12 patients were also found to have hypertension which shows that hypertension and Diabetes mellitus as the major risk factors for the thromboembolic events in these patients.

31.31 was the mean body mass index (BMI) observed in VTE group where 28.70 was the mean BMI observed in ATE group. VTE group patients had a higher BMI when compared to ATE group. The difference showed statistical significance which could be considered a probable risk factor for VTE.

Table 2: Laboratory Parameters Prior To Discharge

Laboratory Parameters	VTE Group (n=17)	ATE Group (n=20)	P Value
D-dimer	3.08±1.68	1.79±0.70	0.0034*
CRP	12.29±7.82	11.38±5.33	0.67
LDH	454.2±178.1	358.7±145	0.08

Among the VTE group, patients had a high D-dimer levels prior to discharge which was 3.08±1.68mcg/ml which i**s** a significant risk factor for predisposition to thromboembolic event (as seen in Table 2)

Table 3: Days Of Presentation And Duration Of Hospital Stay

During illness	VTE Group (n=17)	ATE Group (n=20)	P Value
Days of presentation post discharge	24.06±6.88	40.90±9.99	<0.0001***
CTSS (Out of 25)	14±3.06	13.45±2.76	0.56
Duration of hospital stay	11.59±3.45	10.80±2.95	0.45

Patient with VTE event presented at 24.06±6.88 day following discharge whereas the patient with ATE event presented at 40.90±9.99 day following discharge (as shown in Table 3), this early venous thromboembolic event could be justified due to prolonged immobilisation adding on to venous stasis leading to an early venous

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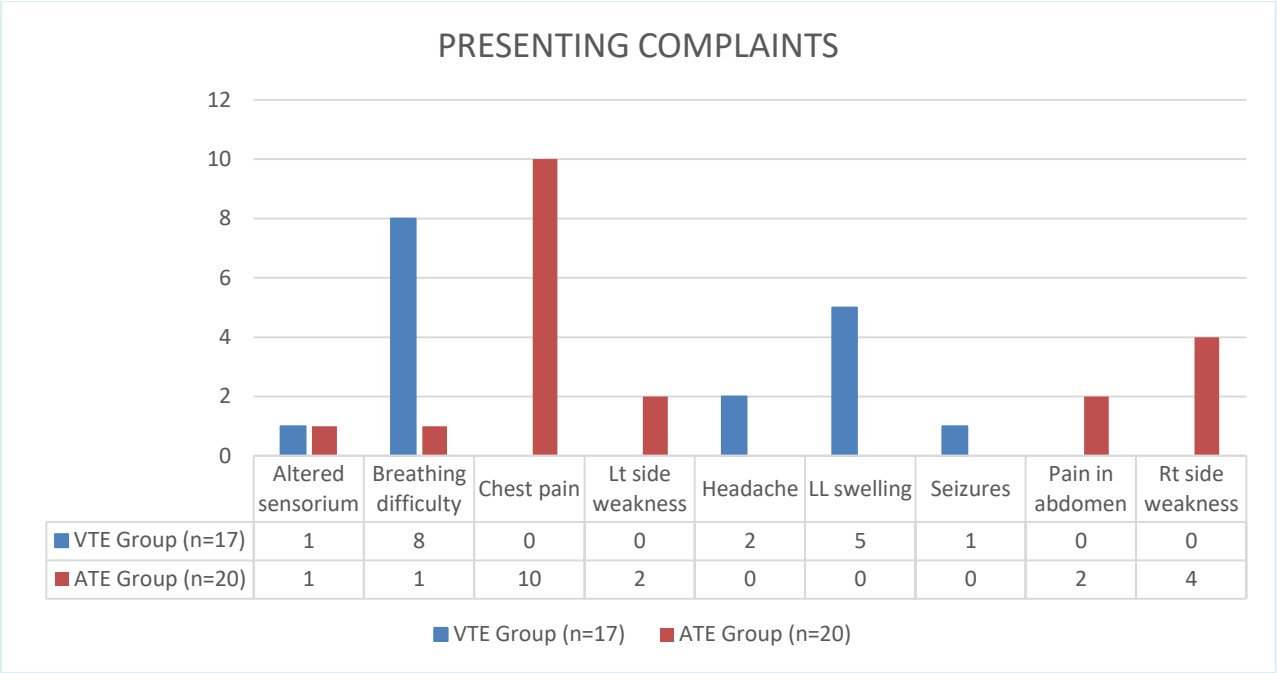
thromboembolic event, whereas arterial thromboembolic event could be a probable result of a systemic sequelae.

In both the groups we found that patients had a CT severity score (CTSS) ranging from moderate to severe score during the admission with COVID-19 (as shown in Table 3).

Figure 1: Presenting Complaints



In our study patients post discharge presented with wide varied symptoms being evaluated accordingly as shown in Figure 1.

Out of 17 cases in VTE group, 8 cases were pulmonary thromboembolism, 5 cases were Deep vein thrombosis and 4 cases were cortical venous sinus thrombosis (as represented in Figure 2).

Out of 20 ATE cases, 11 cases were acute coronary syndrome, 7 cases were Cerebrovascular accident, 2 cases were superior mesenteric artery thrombosis (as represented in Figure 2).

Figure 2: Diagnosis

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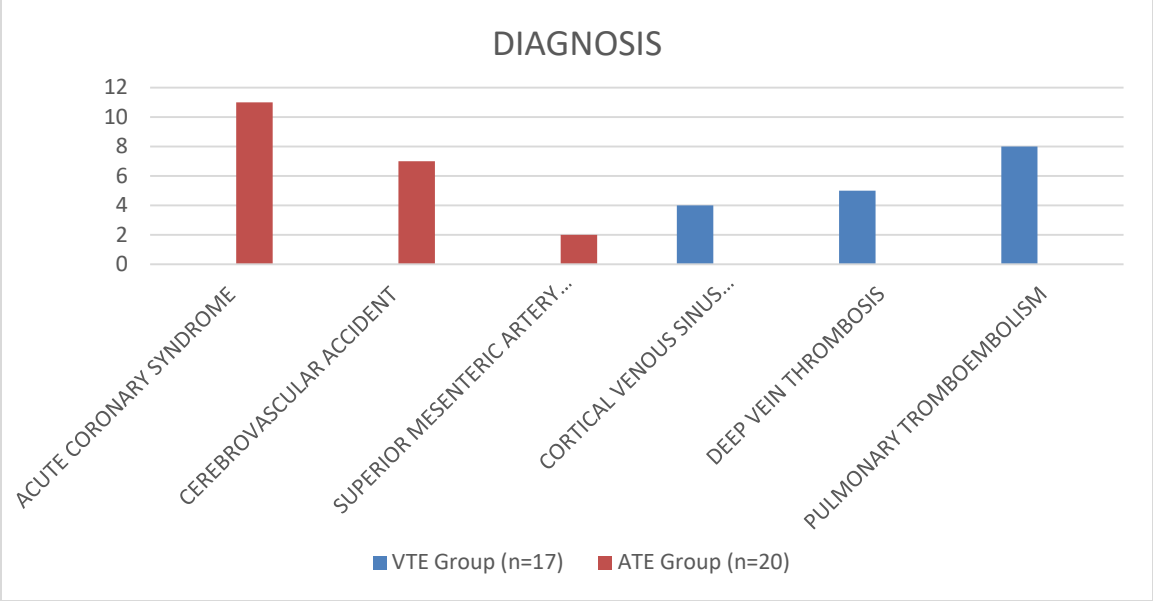
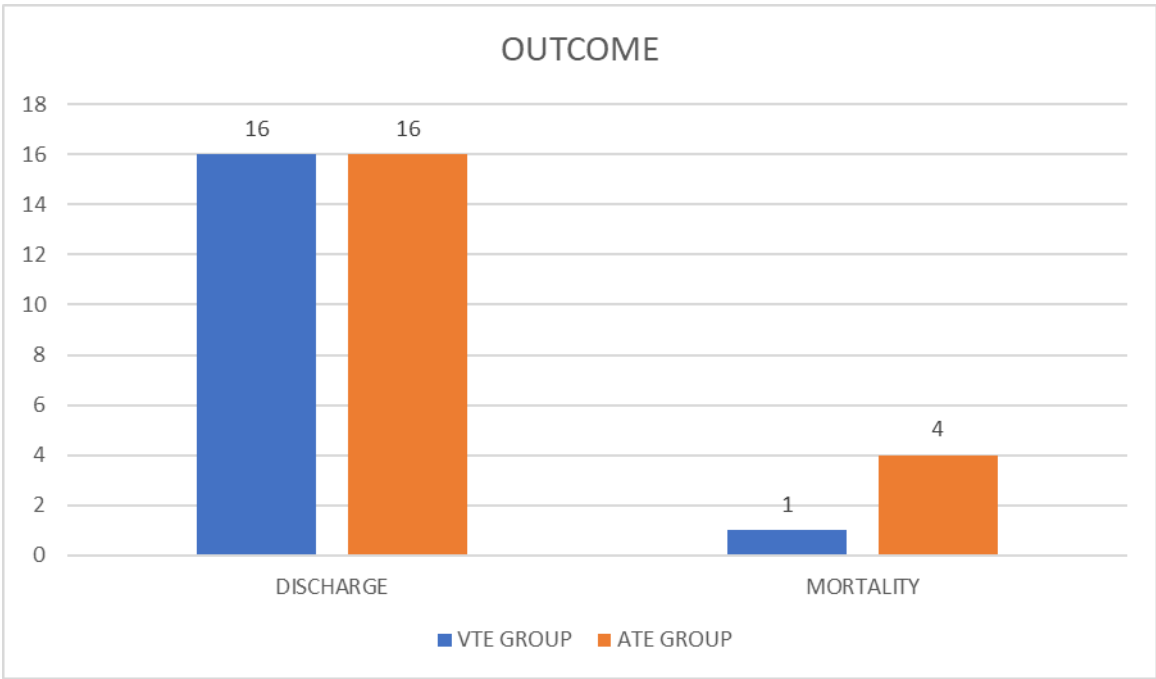


Figure 3: Outcomes



1 mortality was seen in VTE group where 4 cases of mortality were seen in ATE group. No association of outcome between these two groups were observed.

Figure 4: Pathophysiology [12]

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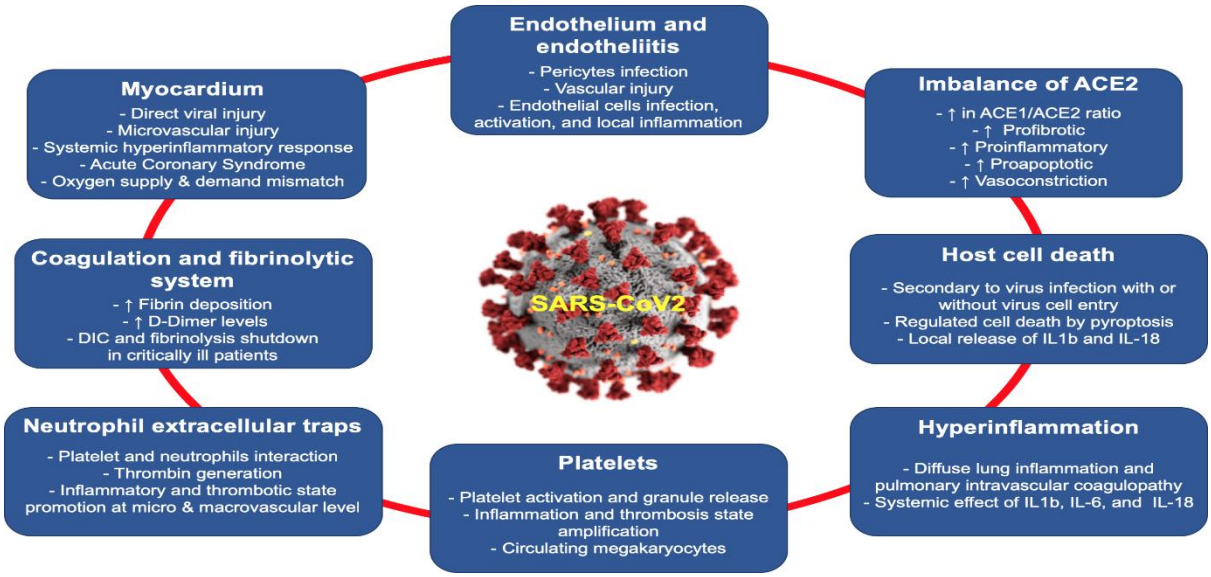
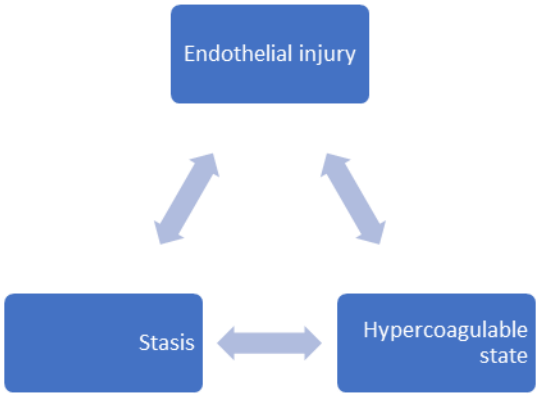


Figure 5: Virchow's Triad



Discussion

Alteration in coagulation parameters and occurrence of arterial and venous thrombosis are well recognized in patients post COVID-19 recovery. [10] This phenomenon is due to endothelial injury and further activation of coagulation cascade. [11] Hence anticoagulation therapy forms the important basis of management during and after COVID-19 illness.

Pathogenesis is incompletely understood.

Virchow's triad(Figure 5): Considered as the major contribution to clot formation in COVID-19

Endothelial injury: Direct invasion of endothelial cells by SARS-COV-2 leads to cell injury.

Stasis: Prolonged hospitalization in critically ill COVID-19 patients can lead to blood stasis

Hypercoagulable state: Changes in circulating prothrombotic factors seen in COVID-19

1. Elevated factor VIII

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2. Elevated fibrinogen
3. Circulating prothrombotic microparticles
4. Neutrophil extracellular traps (NETs)
5. Hyperviscosity

Others

Clotting factors: Increase in clotting factors in COVID-19

Acute inflammatory reaction overdrive with increases in acute phase proteins (Fibrinogen, C-reactive protein) (as shown in Figure 4)

Clinical Features [13]

Wide spectrum of clinical manifestation of thromboembolism is seen in COVID-19:

Venous thromboembolism

Deep venous thrombosis

Pulmonary thromboembolism

Cortical venous sinus thrombosis

Portal vein thrombosis

Splenic infarct

Arterial thromboembolism

Cerebrovascular accident

Acute coronary syndrome

Mesenteric ischemia

Limb ischemia

Renal infarct

Upper extremity arterial thrombosis

Rushad et al in a retrospective study conducted at Beth Israel Deaconess Medical Centre over a period of 3 month to analyse the incidence of thrombosis and haemorrhage at Day 30th post discharge after COVID-19. They found that the incidence of thrombosis was 2.5% and the incidence of haemorrhage was 3.7% with major bleed accounting 0.7%. [14]

Hence the risk of thrombosis and haemorrhage has to be balanced while treating patients with COVID-19.

In patient during admission for COVID-19, not requiring High dependency unit (HDU) or Intensive therapy unit (ITU) - thromboprophylaxis with therapeutic dose has been found to be superior to using prophylactic or intermediate dose.

In patients requiring ITU or HDU, with severe disease – therapeutic dose has been found to be associated with poor prognosis. [15-16]

For patients with active bleeding, HAS-BLED score > 3, severe thrombocytopenia, or underlying bleeding disorder – mechanical thromboprophylaxis must be considered until the contraindication is resolved. [17]

According to International Society on Thrombosis and Haemostasis recommended that patient with high risk for thromboembolism (advanced age, cardiovascular risk factors, ICU admission, prolonged immobilisation and patients with modified IMPROVE-VTE >4 or D-dimer > 2 times the upper limit of normal) must be considered as candidates for thromboprophylaxis for 2-6 weeks post discharge. [8, 18]

Prophylactic anticoagulation with LMWH or DOAC must be considered for 2-6weeks. [19]

Limitation – In our study, incidence was not determined. It was conducted at a single center with a limited number of patients

Conclusion

High D-dimer & inflammatory markers must be considered as risk factor for development of thromboembolic events post discharge. Hence anticoagulation must be considered post discharge in such patients. Our study showed a mortality of 13.5% due to thromboembolic complication post COVID-19.

Patients with COVID-19 post recovery require appropriate follow up. Patient at higher risk for thrombosis require prolonged anticoagulation while monitoring for bleeding manifestation.

Anticoagulant dose must be titrated based on the severity of the patients.

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