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Original Article

Inherited thrombophilia: undetected comorbidity complicating COVID-19 infection

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Abstract: The relation between the severity of COVID-19 and coexisting undiagnosed underlying thrombophilic conditions is not yet established. It may be possible that undiagnosed thrombophilia exaggerates an already pro-thrombotic state in COVID-19 patients and may be responsible for severe disease in absence of any known co-morbidity. The aim was to analyze the association of underlying thrombophilia with the severity of COVID-19 infection in post-COVID patients after a minimum of 6 weeks of recovery and to compare thrombophilia profile in severe versus non-severe COVID-19 patients. Forty severe and 40 non-severe COVID patients at least 6 weeks post recovery were selected for thrombophilia profile and complete blood count evaluation. The data were analyzed using Stata software, USA; version 13. The Chi-square test and Student's t-test were used to compare proportions and mean respectively. A total of 14/80 (17.5%) were positive for the thrombophilia screen. Protein C deficiency was noted in 6/40 (15%) severe COVID patients but not in the non-severe group. The Protein S deficiency was seen in 7/40 (17.5%) severe patients and only 1 patient was deficient in the non-severe group (2.5%). The mean Protein C and Protein S levels of severe and non-severe COVID patients were statistically significant (P-0.002) and (P-0.007) respectively. The difference in mean anti-COVID IgG antibody titer of severe and non-severe COVID patients was also statistically significant (P-0.0001). To Conclude, Protein C & S deficiencies were the commonest abnormalities detected in severe COVID patients. Positive thrombophilia profile and higher titers of anti-IgG COVID-19 antibodies were seen in a significant number of patients who had suffered from Severe COVID-19 than in non-severe infection, even after 6 weeks of recovery. Thereby, suggesting that underlying thrombophilia might have affected the severity of the disease.

Keywords: COVID-19, thrombophilia, protein C, protein S, severe COVID, anti-IgG COVID-19 antibodies

Introduction

Thrombophilia or increased tendency to clot can be due to a variety of factors. Acquired causes top the list but many genetic mutations may lead to thrombophilia. This group of thrombophilia resulting from the inheritance of genetic mutations predisposing to clotting is called 'Inherited thrombophilia'. This may be either due to the overactivity of coagulation factors or deficiency of anticoagulants/fibrinolytic systems. The former group includes Factor V Leiden mutation, prothrombin G20210A mutations, and the rarer ones like factor XIII mutation and familial dysfibrinogenemia. The latter group includes Antithrombin III, Protein C, and Protein S deficiency, elevated levels of various clotting factors, homocysteine levels, and defects in fibrinolytic mechanisms [1].

This undiagnosed and under-recognized thrombophilia increases people's tendency to develop various diseases at an early age like stroke, myocardial infarction, deep vein thrombosis, and intra-abdominal venous/arterial thrombosis. They may remain asymptomatic for a long time but may result in thrombosis in presence of risk factors like hyperestrogenic states (pregnancy and postpartum), oral contraceptive intake, prolonged immobilization, myocardial infarction, etc. Whether COVID-19 is one of the risk factors precipitating thrombosis in patients with undetected thrombophilia and thereby leading them to a severe outcome, is not studied.

COVID-19 is also known to be a hypercoagulable state due to platelet hyperactivation and abnormal clot formation [2, 3]. This is one of the

factors responsible for affecting disease severity and mortality. Up to one-third of patients with COVID-19 manifest more severe disease and increased mortality predominantly due to pulmonary emboli [4, 5]. One study found a strong prevalence of acquired thrombophilia in patients hospitalized for COVID-19 infection, especially a 72% prevalence of antiphospholipid antibodies and a 20% rate of Protein S deficiency [6]. The severity was also influenced by many comorbidities such as older age, male sex, ethnicity, systemic hypertension, diabetes mellitus, chronic lung disease, and any immunocompromised state [7-9]. However, it was noted that many patients without apparent comorbidities also succumbed to severe disease. The reason for it is largely unanswered. The thrombotic complications due to underlying thrombophilia have the potential of exaggerating an already pro-thrombotic state in COVID-19 patients resulting in severe disease. Scant reports hint at the association of underlying thrombophilia with the severity of COVID-19. One study documented a higher risk of COVID-19 venous thrombotic complications in patients with inherited thrombophilia (factor V Leiden and fibrinogen gene mutation) [10]. Another study revealed that even a heterozygous state of Protein C deficiency can lead to a prolonged hospital stay and ICU admission. The patients who had non-severe illnesses were mainly on anticoagulants and therefore did not suffer severe consequences [11]. However, all these sporadic reports are in known cases of thrombophilia.

Hence, the present study aimed at studying the association of previously undiagnosed thrombophilia with the severity of COVID-19 in post-COVID patients after a minimum of 6 weeks of recovery; when the abnormal coagulation parameters resulting from COVID-19 are expected to normalize.

Material and methods

This was a comparative prospective study carried out in the Department of Pathology and the Department of Medicine in a tertiary care hospital from January 2021 to April 2022. A total of 80 COVID-19 (RT-PCR positive) patients were selected for the study after at least 6 weeks post-recovery. The patients were categorized into Severe COVID and Non-severe (Mild and moderate) COVID groups based on severity as per WHO guidelines [12]. Each group consisted of 40 patients.

Inclusion criteria

All consenting consecutive adult patients (18-60 years) with severe/non-severe COVID-19 (RT-PCR positive) after at least 6 weeks post-recovery.

Exclusion criteria

The patients who were transfused with fresh frozen plasma, platelets or red cell concentrates within the last two weeks of being recruited for the study, known co-morbidities like hypertension, diabetes, Coronary artery disease, and those on heparin or any other anticoagulants were excluded from the study.

Sample size calculation

To estimate a difference of 20% between the severe (20%) and non-severe (1%) groups using a Chi-square test with a power of 80% and with an acceptable error of 0.05, a total of 80 patients: 40 severe COVID and 40 non-severe COVID were recruited.

Ethical consideration

The proposal was approved by Institutional Ethical Committee (IEC-HR/2020/46/10-R1). The data was anonymized and coded. Declaration of Helsinki and ICMR guidelines for biomedical research were followed during the conduct of the study.

After taking informed consent, the subjects qualifying the inclusion and exclusion criteria were included in the study, and their relevant past, medication, hospital stay history, and laboratory investigations were recorded. A 7.5 ml blood sample was taken for evaluation of the thrombophilia profile and complete blood count.

Case definition

As per WHO guidelines, a Severe COVID-19 case was defined as “a person who has a fever or lower respiratory tract infection, with $PaO_2 \leq$ 90% on room air at sea level, the ratio of $PaO_2/FiO_2 < 300$ mmHg or has bilateral ground glass

opacities in CT chest or > 50% infiltrates, bilateral seen on chest X-ray" [12].

Mild and moderate COVID also called Non-severe COVID-19, was defined as "a person with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, loss of smell and taste with $PaO_2 \geq 90\%$ at room air at sea level and the ratio of $PaO_2/FiO_2 \geq 300$ mmHg" [12].

Sample collection

A venous sample (2.5 ml) was collected under strict aseptic conditions in a K2-EDTA vial and subjected to Complete blood counts including platelet count on an automated hematology analyzer (MINDRAY BC 6800). For anti-COVID IgG antibody titers, plasma was obtained after centrifugation for 15 minutes. The separated plasma was assessed by Beckman-Coulter Immunoassay Systems (automated analyzer) which detected and reported the titers after comparing them with appropriate quality controls by the principle of chemiluminescence.

Simultaneously 5 ml venous blood was collected in a trisodium citrate vial for coagulation studies and mixed by gentle inversion. The sample was rendered platelet free by centrifugation for 15 minutes at 2000 g and the platelet-poor plasma (PPP) was obtained. The samples were stored at -70°C till further analysis. The samples were thawed at the time of testing. The citrated samples were run on a fully automated coagulometer (STA-Compact Max3, Diagnostica Stago S.A.S, France) to determine Prothrombin Time (PT), Activated Partial Thromboplastin time (APTT), Protein C, Protein S, Antithrombin III, Lupus anticoagulant (DRVVT and APLA antibodies).

A patient was termed thrombophilia profile 'positive' who had any of the above tests as abnormal.

Interpretation of thrombophilia profile

The PT of test plasma was considered to be prolonged if it was greater than the reference range or > 3 seconds from the control. The APTT of test plasma was considered to be prolonged if it was greater than the reference range or > 6 seconds from the control.

The range of antithrombin III was 80%-120% of normal activity, with antigen levels in the range of 17-30 mg/dl. The AT-III levels of less than 80% of activity and less than 17 mg/dl antigen levels suggested type 2 antithrombin or inherited antithrombin deficiency.

The range of Protein C was 60%-130% of normal activity. The values less than 60% activity suggested a deficiency of Protein C. The range of Protein S was 70%-150% of normal activity and values less than 70% activity suggested Protein S deficiency. The normal range of DRVVT was taken as 29-42 seconds. The Screen ratio (test/control) less than 1.20 is considered negative for lupus anticoagulant.

For anti-COVID Ig G antibodies, results were interpreted as non-reactive for less than 0.8 S/CO and reactive - for more than 1.0 S/CO [S/CO is signal to cut-off ratio].

Statistical analysis

The data collected as a part of this study were analyzed using Stata software (Stata Incorporation, USA; version 13). The continuous variables were reported as mean (+ standard deviation) or median (inter-quartile range) as appropriate. The categorical variables were reported as numbers (percentages). The Chi-square test was used to compare proportions between groups while Student's t-test was used to compare means. Multivariate analysis using a logistic regression model was done on variables significantly associated with the outcome of univariate analysis. A *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical parameters

Forty severe and 40 non-severe patients with COVID-19 infection were recruited for the study after a minimum of 6 weeks of recovery. The mean age of severe COVID patients was 35.35 ± 8.97 years whereas the mean age of non-severe COVID patients was 38.70 ± 8.06 years. The majority of the COVID patients were females i.e. 46 (57.5%) among a total of 80 COVID patients whereas followed by 34 (42.5%) males. Among COVID patients with severe infection, the majority of the patients i.e. 21/34 (52.5%) were males followed by 19/46 (47.5%)

Table 1. Vital parameters in severe and non-severe COVID patients post-recovery (N-80)

S.N	Variables	Severity	Mean	Standard Deviation	*P*-value*
1	Pulse Rate	Severe	95.12	8.844	0.916
		Non-Severe	94.92	8.036	
2	Respiratory Rate	Severe	16.62	2.959	0.469
		Non-Severe	17.05	2.207	
3	Systolic Blood pressure (mmHg)	Severe	112.10	11.600	0.486
		Non-Severe	114.10	13.863	
4	Diastolic Blood Pressure (mmHg)	Severe	66.05	8.308	0.810
		Non-Severe	65.60	8.415	
5	SpO_2 Right	Severe	95.68	1.269	0.479
		Non-Severe	95.95	2.087	
6	SpO_2 Left	Severe	96.00	1.396	0.948
		Non-Severe	96.02	1.968	
7	Temperature (°F)	Severe	98.88	1.168	0.855
		Non-Severe	98.93	1.376	

*Significant *P*-value < 0.05. The statistical method applied is the student's t-test.

Table 2. Hematological parameters in COVID patients categorized as severe and non-severe (N-80)

Variables	Severity	Mean	Standard Deviation	*P*-value
Hemoglobin (g/dl)	Severe	12.82	1.48	0.903
	Non-Severe	12.78	1.45	
TLC ($\times 10^6$/l)	Severe	8402.45	3656.67	0.884
	Non-Severe	8277.62	3995.51	
RBC ($\times 10^6$/l)	Severe	4.21	0.59	0.009*
	Non-Severe	4.60	0.73	
MCV (fl)	Severe	81.44	15.89	0.008*
	Non-Severe	92.39	19.90	
MCH (pg)	Severe	25.51	5.16	0.001*
	Non-Severe	32.03	10.47	
Platelet count ($\times 10^9$/l)	Severe	2.47	1.38	0.493
	Non-Severe	26.15	2.93	

Note: TLC-Total Leucocyte Count, RBC-Red Blood Cell Count, MCV-Mean Corpuscular Volume, MCH-Mean Corpuscular Hemoglobin. *Significant *P*-value < 0.05. The statistical method applied is the student's t-test.

Table 3. Protein C and Protein S deficiency in severe and non-severe COVID patients post-recovery (N-80)

COVID-19 Category	Protein C deficiency	Protein S deficiency	Total number of cases positive for thrombophilia screen
Severe (N = 40)	6 (15%)	7 (17.5%)	14
Non-severe (N = 40)	0	1 (2.5%)	

female patients. Among COVID patients with non-severe infection, the majority of the patients were females (67.5%) followed by 32.5% male patients. The hemodynamic parameters like pulse, blood pressure, SpO_2, temperature, and respiratory rates had normalized and were comparable in both categories. The vital parameters in severe and non-severe COVID patients post-recovery were noted (**Table 1**).

Hemodynamic parameters

Routine hematological parameters analyzed such as RBC, MCV, and MCH levels were significantly higher in non-severe COVID patients as compared to severe patients post-COVID recovery (P-0.009, 0.008, and 0.001) respectively (**Table 2**).

Thrombophilia screen

A total of 14/80 (17.5%) were positive for the thrombophilia screen. Of these patients, 13/40 (32.5%) were in a severe category and 1/40 (2.5%) were in the non-severe category. Protein C deficiency was observed in 6/40 (15%) patients in the severe category, however, there were none in the non-severe group. Protein S deficiency was noted in 7/40 (17.5%) severe patients and only 1 patient was deficient in the non-severe group (2.5%) (**Table 3**).

Table 4. Thrombophilia screen among severe and non-severe COVID cases post-recovery (N-80)

Lab Parameters	Severity	Values	Standard Deviation	*P*-value
Prothrombin Time (seconds)	Severe	12.40	1.45	0.721
	Non-Severe	12.50	1.08	
aPTT (seconds)	Severe	25.90	3.57	0.733
	Non-Severe	26.15	2.93	
PROTEIN C (%)	Severe	79.55	34.11	0.002*
	Non-Severe	99.40	17.99	
PROTEIN S (%)	Severe	98.82	27.87	0.007*
	Non-Severe	114.02	20.73	
AT III (%)	Severe	82.42	19.03	0.096
	Non-Severe	89.40	17.99	
LA by DRVVT				
Screen (seconds)	Severe	74.89	26.56	0.110
	Non-Severe	82.95	17.06	
LA by DRVVT				
Confirm (seconds)	Severe	66.62	24.76	0.081
	Non-Severe	74.68	14.72	

Note: aPTT-Activated Partial Thromboplastin Time, AT III-Antithrombin III, LA-Lupus Anticoagulant, DRVVT-Diluted Russel Viper Venom Test. *Significant *P*-value < 0.05. The statistical method applied is the student's t-test.

Table 5. Comparison of anti-COVID IgG antibodies among severe and non-severe COVID patients (N-80)

Parameters	Severity	Mean	Standard Deviation	*P*-value
Anti-COVID IgG Antibody	Severe	82.58	67.73	0.0001*
	Non-Severe	17.50	1.076	

*Significant *P*-value < 0.05. The statistical method applied is the Chi-Square test.

No statistical significance was found in screening coagulation parameters such as platelet count, PT, and aPTT. The Protein C levels of severe COVID patients were 79.55 ± 34.11% whereas the mean Protein C levels of non-severe COVID patients were 99.40 ± 17.99%. This distribution was found statistically significant (P = 0.002). The results for screening coagulation parameters and thrombophilia screen are mentioned (**Table 4**).

The mean Protein S levels of severe COVID patients were 98.82 ± 27.87% whereas the mean Protein S levels of non-severe COVID patients were 114.02 ± 20.73%. This distribution was also found statistically significant (P = 0.007).

The mean AT III levels of severe COVID patients was 82.42 ± 19.03% whereas the mean AT III levels of non-severe COVID patients were 89.40 ± 17.99%. This distribution was found statistically non-significant (*P*-value = 0.096).

Lupus anticoagulant is the most common Acquired Thrombophilia which was screened by DRVVT: Screen & confirm. The DRVVT screen was not significantly different in the two groups (P-0.110). Similarly, DRVVT confirmation was also not significantly different in the two groups (*P*-value = 0.081).

The mean anti-COVID IgG antibody titer of severe COVID patients was 82.58 ± 67.73/SCO whereas; the mean anti-COVID IgG antibody titer of non-severe COVID patients was 17.50 ± 1.07/SCO. This distribution was found statistically significant (*P*-value = 0.0001) (**Table 5**).

Discussion

COVID-19 infection introduced the whole world to thrombophilia as it is one of the complications of this infection. Incidences of thrombotic events were noted especially in severe and moderate COVID infection. Many of those patients were associated with multiple comorbidities like diabetes mellitus and hypertension, however, a significant proportion of patients especially young died without apparent co-morbidities [13]. Hence this study was aimed at identifying cases of inherited thrombophilia in patients who have recovered from severe COVID with the assumption that it could be the possible co-morbidity responsible for causing severity.

In this study, we enrolled 40 severe and 40 non-severe COVID patients who had recovered from COVID. A minimum period of 6 weeks after recovery was taken. Since thrombophilia testing is usually done 6 weeks after an acute

thrombotic event to allow acute phase reactant Proteins of the coagulation cascade to return to baseline, hence this was considered ideal for testing baseline tendency [14]. All these patients were subjected to thrombophilia testing for most common inherited as well acquired disorders mainly because the tests are expensive, not easily available, and subject to extensive standardization. The tests used to detect inherited causes of thrombophilia were limited to the three well-known conditions i.e., deficiencies of Protein C, Protein S, and Antithrombin III.

There is scant data on the prevalence of thrombophilia in the general population. Most of the data on identified inherited thrombophilia is centered on symptomatic patients only. However, few studies have been conducted on asymptomatic individuals with a history of family members diagnosed with inherited thrombophilia [15, 16]. Factor V Leiden mutation is the leading cause of inherited thrombophilia, and its prevalence is highly variable ranging from 2%-14% within the normal population which is attributed to geographical and ethnic variation [17]. Its prevalence is highest (4%-15%) among the European population but rare in Asian, American, or African populations [18-20]. This is followed by a mutation in the Prothrombin gene at G20210A noncoding sequence resulting in increased prothrombin levels. As per an extensive literature review by Dziadosz M et al the prevalence rates of prothrombin G20210A across the globe varies from 0 to 15.9% among ethnic groups [21]. Protein C and Protein S deficiency account for rare inherited disorders. Very rare ones are Fibrinolysis defects and homozygous homocystinuria. The studies regarding the prevalence of thrombophilic disorders in India are scanty. According to a study by Mishra M et al on Indian subjects the prevalence of APC-R, Protein C, and Protein S in controls were 4%, 0%, and 2% in a study of 78 patients with venous thrombosis and 50 age-matched controls [22]. All these studies are not population surveys and are mainly done on symptomatic patients or patients with a family history of thrombophilia. There is no data on general prevalence. So, this data represents only the tip of the iceberg.

A total of 14/80 (17.5%) were positive for the thrombophilia screen. Protein C and Protein S deficiency were the commonest deficiencies found. Out of all the parameters, Protein C and Protein S were significantly deficient in the severe category as compared to non-severe (P-0.002) and (P-0.007) respectively. The mean AT III levels of severe and non-severe COVID patients was not statistically significant (P-0.096). As there are insufficient studies, especially in the Indian population regarding the prevalence of inherited thrombophilia, this could be a significant finding. The presence of 13/40 (32.5%) severe COVID patients compared to 1/40 non-severe COVID patients who tested positive for thrombophilia screening suggests that the prevalence of Inherited thrombophilia may be much more than we know as many severe patients succumbed to illness and also molecular testing for Factor V Leiden mutation and Prothrombin gene mutation was not done in our study.

Moreover, asymptomatic patients with inherited thrombophilia have a greater propensity to develop thrombosis in presence of any inciting agent like COVID-19. Approximately 1/3rd (32.5%) of severe COVID cases were positive for inherited thrombophilia namely Protein C and Protein S deficiency. This is an indicator that if all known defects were tested, a larger proportion of patients with severe COVID, one cause of this exacerbation could be attributed to underlying thrombophilia. This would also possibly explain the increased incidence of stroke and myocardial infarction in patients' post-COVID recovery [23].

Severe COVID-19 is associated with higher antibody production and neutralization titers. The neutralization potency of anti-RBD (anti-receptor binding domain) antibodies predicts disease severity and survival. Immunomodulatory COVID-19-directed therapies may modulate antibody responses in the body against this virus [24]. In our study too, there was a significant difference in severe and non-severe post-COVID patients. However, high titers were also seen in the non-severe category. This could be because in the middle of our study, the vaccination drive for COVID was started and some of our patients had received the vaccination. The mean anti-COVID IgG antibody titer of severe COVID patients was 82.58 ± 67.73 S/CO as compared to 17.50 ± 1.07S/CO in non-severe COVID patients. This distribution was found sta-

tistically significant (0.0001). It is noteworthy that there are significantly larger antibody responses to all SARS-CoV-2 antigens with higher disease severity, yet these antibodies show lower binding affinity in patients with the critical disease. It remains to be elucidated whether this ineffective humoral response is the result of disease severity or an important driver of COVID-19.

Interestingly, acquired thrombophilia as detected by Lupus Anticoagulant is a common cause of thrombophilia and recurrent pregnancy loss; was not seen in our patients [25]. The mean levels of Lupus Antibodies (LA) by DRVVT between severe and non-severe COVID patients were not statistically different in the two groups. The possible reason could be a limited sample size and patient selection, as the presence of LA is more common in patients with recurrent pregnancy loss which was not our study group.

COVID-19 and thrombophilia

The COVID-19 virus induces an imbalance in the coagulation pathway tilting the cascade towards a prothrombotic state due to a systemic inflammatory response. Numerous studies have demonstrated thrombocytopenia, increased fibrinogen, fibrinogen-to-albumin ratio, and D-Dimers in COVID-19 patients, all these parameters were found to be directly associated with a high risk of thrombosis, Acute respiratory distress syndrome, and mortality [26-29]. However, the results regarding Prothrombin Time (PT) in COVID patients yielded highly variable results depending on the severity of the infection [30-32].

In our study, PT & APTT were normal post-recovery in COVID patients. The mean values of platelet count, prothrombin time, and aPTT were comparable and within the normal range in both groups. The patients who were not on anticoagulation were recruited in the study; hence this data represents the true normalization of the screening coagulogram. There are no other studies done on screening coagulogram, post 6 weeks of recovery of the patient. These findings, therefore, need to be validated by a larger number of studies. Usually, hemodynamic and coagulation parameters are altered during COVID infection as stated. However, there is limited data on these parameters post-COVID recovery. In our study, there was complete recovery of hemodynamic and coagulation parameters except in patients with severe COVID who had incomplete recovery of hemoglobin.

The role of underlying thrombophilic conditions in complicating COVID-19 infection is largely unexplored. Various studies have documented thrombosis as the most serious complication of COVID-19. Klok et al detected a remarkably high incidence (31%) of thrombotic complications in COVID-19 patients admitted to the intensive care unit (ICU) complimenting the results of similar studies [4, 33, 34]. In some cases, it has also been reported that Protein C, Protein S, Antithrombin deficiencies, and antiphospholipid antibodies are acquired in COVID [6]. Gardner et al also demonstrated antithrombin deficiency in approximately 26% of 19 patients with COVID-19 [35]. But all these studies are on patients with active COVID-19 infection. Also, patients with inherited thrombophilia have increased thrombin generation which may aggravate already hypercoagulable conditions such as Covid-19 infection. It has been demonstrated that D-Dimer levels increase in patients with inherited thrombophilia [11]. These studies suggest that COVID-19 induces a prothrombotic state which may exacerbate in patients who are already thrombophilic as our study postulates. However, the occurrence of COVID-19 is not related to thrombophilia.

Hence, this study elucidates a strong association of underlying thrombophilia in severe COVID patients, with Protein S & C deficiencies being the commonest abnormalities.

Limitations of the study

This is a novel finding and needs to be explored further with a more extensive thrombophilia profile, as due to cost constraints the number of tests done was limited to testing the three abnormalities only. Other causes of thrombophilia were not studied. Also, the influence of underlying thrombophilia in the patients who succumbed to the disease is unknown and cannot be known in retrospect. However, the extrapolation of the study suggests that it may be an important influence on severity and mortality. A possibly higher incidence of underlying thrombophilia might have been present in

patients who succumbed to thrombotic complications in COVID-19.

Conclusion

To conclude, a positive thrombophilia profile was seen in a significant number of patients who had suffered from Severe COVID-19 infection, even after 6 weeks of recovery. Thereby, suggesting that underlying thrombophilia might have affected the severity of the disease. Protein C & S deficiency was the commonest abnormality detected.

This research suggests that inherited thrombophilia may be a potential killer in unsuspected patients leading to unexplained and sudden mortality as well as the severity of COVID-19. Since COVID-19 is here to stay there is an impending need to recognize this condition so that "Forewarned is forearmed". Hence, population surveys for common genetic abnormalities leading to thrombophilia should be studied.

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Disclosure of conflict of interest

None.

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