A comparative analysis of arterial thrombotic events in post-COVID syndrome and its correlation with a hypercoagulable state

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ABSTRACT

Background: Corona virus disease 2019 can be complicated by post-COVID thrombotic events and need hospitalization. We aimed to discuss the presence of post-COVID thrombotic events and its possible causality in vulnerable patients of COVID-19 to set up an effective preventive and therapeutic strategy for this fatal complication.

Methods: This prospective observational case-control study included a total of 150 admitted patients with COVID-19 after exclusion of chronic medical illness. All patients were closely observed for their demography, clinical profile, disease severity, duration of hospitalization, post-COVID symptoms, and inflammatory markers. All collected data were tabulated, compiled, and analyzed to establish the possible causality of post-COVID thrombotic events.

Results: Among the study sample 20 patients developed post-COVID thrombotic events as cases and the remaining130 had without thrombotic events as a control group. Patients with post-COVID thrombotic events had longer duration of hospitalization (12.6 v/s 9.4 days), higher prevalence of nonspecific post-COVID symptoms (90% v/s 66.15%), and had raised inflammatory markers (CRP 14.04 v/s 10.73; D-dimer 1012.5 v/s 516.4 µg/Ml; IL-6 32.88 v/s 15.07) as compared to control group of without thrombotic events with p-value < 0.05. In our study thrombotic events developed on an average of 10th week from the first positive serology or symptoms onset with mean time duration of thrombotic events was found to be 66.05 days.

Conclusion: Post-COVID thrombotic events after COVID infection can be precipitated by a longer duration of hospitalization with a persistent higher inflammatory state and hypercoagulable state. Incidence of thrombotic events is directly proportional to the severity of the disease.

Keywords: **COVID-19, Hypercoagulable state, inflammatory markers, Post-COVID thrombotic events,**

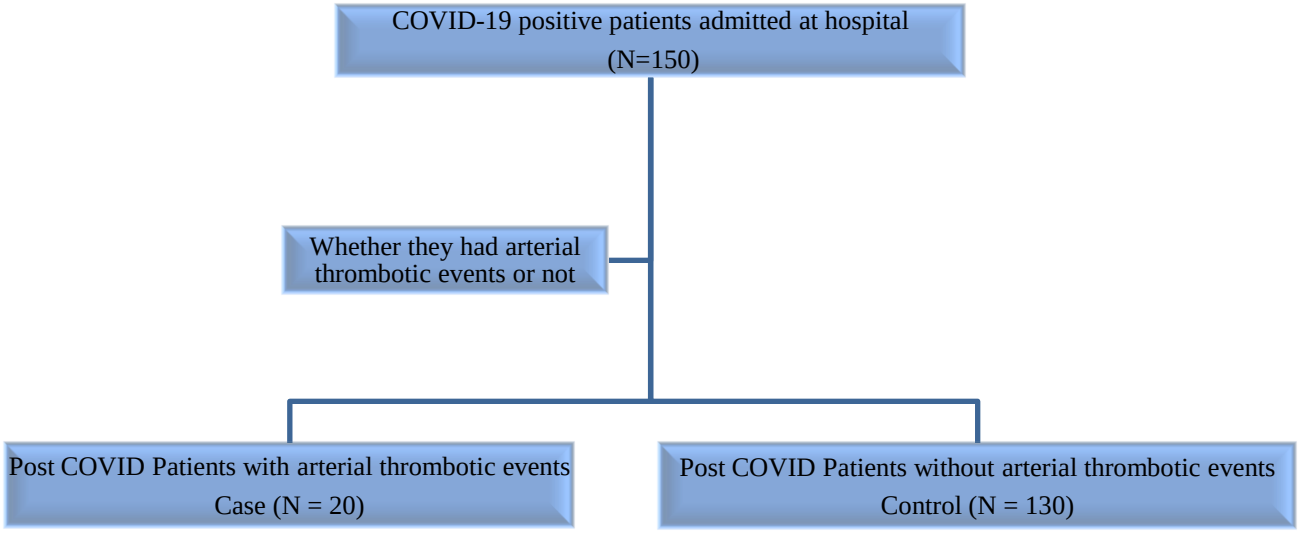
INTRODUCTION:

Severe acute respiratory syndromes are caused by a variety of corona viruses, such as those in the SARS and MERS families. The COVID-19 pandemic did not distinguish between different socioeconomic levels, sex, or age groups [1, 2]. Initially, efforts were focused on controlling the infectious process in order to prevent lung attacks and respiratory insufficiency [3]. In infected individuals, altered levels of oxygenation in arterial blood and the depletion of gases change caused severe deficiencies and losses of pulmonary capacitance, compromising the basic functions of life [3, 4].High levels of endogenous chemical substances produced in response to the inflammation caused by this virus are capable of generating alterations and disturbances in target tissues. Furthermore, during the development of the sepsis process, a high level of pro inflammatory cytokines (IL-6, IL-1 and TNF-Alfa) with pleiotropic abilities has been found to interact with their high-density receptors, immune cells, and vasculature [5]. These cytokines can stimulate a large number of processes involved with the activation of immune cells in response to changes in the vascular environment, promoting greater adhesion and blood pro coagulation [6].Patients with COVID-19 are at increased risk of thrombotic complications, despite the in-hospital use of standard- or escalated-dose thromboprophylaxis [7,8]. As a result, numerous studies have focused on understanding the thrombotic tendency in these patients. Whole-blood viscoelastic tests and thrombin generation assays have demonstrated a hypercoagulable state [9; 10]. In addition, abnormalities in conventional coagulation tests, such as a prolonged prothrombin time (PT), and highly elevated vonWillebrand factor (VWF), D-dimer, and fibrinogen levels have been found[11,12]. Moreover, we have recently shown that the prothrombotic changes found in COVID-19 patients shortly after admission are associated with disease severity and mortality [13]. These data align with the hypothesis that the prothrombotic changes in COVID-19 patients contribute to disease progression, potentially by facilitating pulmonary (micro) thrombosis. [14, 15] Importantly, the persistence of symptoms, such as dispend and fatigue, have been reported in a proportion of hospitalized and non hospitalized COVID-19 patients up to 3 months after primary infection. [16,17] The path physiology of this so-called post–COVID-19syndrome remains largely unknown. We hypothesize that the post–COVID-19 syndrome may involve sustained intrapulmonary activation of coagulation, perhaps driven by residual pulmonary micro vascular injury, with ongoing pulmonary micro thrombosis as a consequence. To the best of our knowledge, the clinical and

laboratory profile of COVID-19 patients after hospital discharge has not yet been assessed. Therefore, we studied the clinical and laboratory profile of patients with a resolved COVID-19 infection. We compared Post COVID-19 patients with arterial thrombotic events from patients without arterial thrombotic events.

METHODS

Study Design: The present prospective observational case-control study was conducted on 150 Post COVID-19 patients, admitted at S.M.S. Medical College and Attached Hospitals, Jaipur, India from 1st June to 15th December 2021. This study was approved by the Institutional Ethics Committee of our institute. In this study we enroll COVID-19 positive patients in the age group of 30 to 60 years without any chronic medical illness. We continuously followed these patients for new onset of symptoms from the date of admission to the end of four months. We define Post COVID as periods after 28 days of onset of symptoms. On observation for various thromboembolic arterial thrombotic events, the study population wills be categorized as Post COVID-19 patients with arterial thrombotic events and without arterial thrombotic events. After categorization of all selected post COVID patients into two groups, we compared clinical and laboratory parameters among both groups. These patients underwent serial observation to collect data till the end of 4 months.



Data Collection: COVID-19 was diagnosed based upon World Health Organization interim guidance [6]. We collect data regarding demography, chronic medical illness, clinical presentation, laboratory investigations, duration of hospital stay, post COVID symptoms and final fibrosis for all patients and followed all patient from date of onset of COVID specific symptoms till 4 months. In this study, the severity of COVID-19 patients was decided as per the Indian Council of Medical Research (ICMR) guidelines. Those patients who lost from follow up were excluded from study sample. Duration of hospital stay was calculated from hospitalization to discharge of COVID-19 patient. Nonspecific post COVID symptoms like malign, fatigue, shortness of breath, chest pain, sick syndrome, headache, vertigo, lack of appetite, generalized weakness, red eyes, etc. were observed in all selected COVID patients. The study population was observed for any arterial thrombotic events like coronary artery disease, cerebral vessels disease, abdominal vessels disease, peripheral vascular disease, and other arterial thrombotic events, and days on which patients developed arterial thrombotic events after the onset of symptoms. We adopt CT angiography to confirm the diagnosis of arterial thrombotic events by an expert radiologist. We collected inflammatory markers like C-reactive protein, D-dimer, and IL-6 at the end of day 28. Data regarding persistent lung fibrosis at the end of the study period were also collected. In this study, we also calculate the incidence of various arterial thrombotic events in cases. The time duration at which the patient developed any arterial thrombotic event was compared among different categories of COVID-19 according to severity. All clinical and laboratory data were compiled, tabulated, interpreted, and compared among both groups.

Statistical analysis: Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as proportions. The parameters were compared among different groups using chi-square test and z-score for significant differences. The level of significance was assigned at p-value less than 0.05. Statistical Package for the Social Sciences (SPSS) and R program was used for statistical analysis.

Results (Table 1, 2& Graph 1):

A total of 150 COVID-19 patients were included in this study out of which 20 patients have post COVID arterial thrombotic events and 130 patients does not develop any arterial thrombotic events. In this study, we try to evaluate precipitating factors for post-COVID arterial thrombotic events especially occur in well-known hypercoagulablestates and cytokine storm. We select the study population without any Comorbid state to avoid the influence of other chronic medical illnesses on arterial thrombotic events. COVID-19 infected patients of the study group were selected in the range of 30 to 60 years of age. The mean age of

those SARS-CoV-2 infected patients who have developed arterial thrombotic events was 45.12 years (45.12 ± 10.85) while in the control group it was 41.14 years (41.14 ± 11.24) without any statistically significant difference (p=0.1665). Male patients have affected more in both cases as well as the control group (p=0.8337). All patients had COVID-19-related major clinical symptoms at hospitalization including fever, cough, and shortness of breath. The severity of disease at hospitalization was not significantly different in patients with arterial thrombotic events and the control group (p>0.05). Meantime duration of hospital stay was found to be significantly higher in those patients who developed post-COVID arterial thrombotic events (12.6 days) as compared to patients without arterial thrombotic events (9.4 days) with a p-value = 0.0153. Patients with post-COVID arterial thrombotic events have a higher incidence (90%) of nonspecific post-COVID symptoms as compared to the control group (66.15%) with P-value = 0.0384.COVID-19-related inflammatory markers especially CRP, D-dimer, and IL-6 were found to be significantly higher in cases of post-COVID-19 patients with arterial thrombotic events as compared to the control group viz. CRP (mg/L) 14.04 ± 5.19 v/s 10.73 ± 4.97 with p=0.0117; D-dimer (µg/mL) 1012.5 ± 312.1 v/s 516.4 ± 251.2 with p<0.001; IL-6 (pg/mL)32.88 ± 10.10 v/s 15.07 ± 7.46 with p<0.001 for cases and controls respectively.

Table 1: A comparative study of demographic, clinical, and laboratory parameters in COVID-19 cases of post-COVID arterial thrombotic events and control group of without post-COVID arterial thrombotic events

Characteristics	Case (N=20) (With arterial thrombotic events)	Control (N=130) (Without Arterial thrombotic events)	P-Value
Age (Year)	45.12 ± 10.85	41.14 ± 11.24	0.1408
Gender			
Male	13 (65.00%)	86 (66.15%)	Z= 0.0952, P=0.9203
Female	7 (35.00%)	44 (33.85%)	
Duration of hospital stay (Days)	12.6 ± 4.9	9.4 ± 5.1	0.0096
The severity of COVID-19 Disease			
Mild	4 (20.00%)	21 (16.15%)	Z=0.4297, P=0.6672
Moderate	14 (70.00%)	101 (77.69%)	Z=0.7572, P=0.4472
Severe	2 (10.00%)	8 (6.15%)	Z=0.6419, P=0.5221
Nonspecific Post-COVID symptoms			
Present	18 (90.00%)	86 (66.15%)	Z=2.071, P=0.0384
Absent	2 (10.00%)	44 (33.85%)	
Laboratory parameters (at the end of 28 days)			
CRP (mg/L)	14.04 ± 5.19	10.73 ± 4.97	0.0066
D-DIMER (µg/mL)	1012.5 ± 312.1	516.4 ± 251.2	<0.001
IL-6 (pg/mL)	32.88 ± 10.10	15.07 ± 7.46	<0.001
Persistent Lung Fibrosis	4 (20.00%)	20 (15.38%)	Z=0.4866, P=0.6241

Table 2: Incidence of various Arterial thrombotic events in Post COVID syndrome

S. No.	Name of Arterial thrombotic events	Number of patients (n)
1	Coronary Artery Disease	12 (60%)
2	Cerebral vascular disease	6 (30%)
3	Abdominal vessels disease	1 (5%)
4	Peripheral artery disease	1 (5%)

Table 3: Average Time duration of arterial thrombotic events in Post COVID syndrome

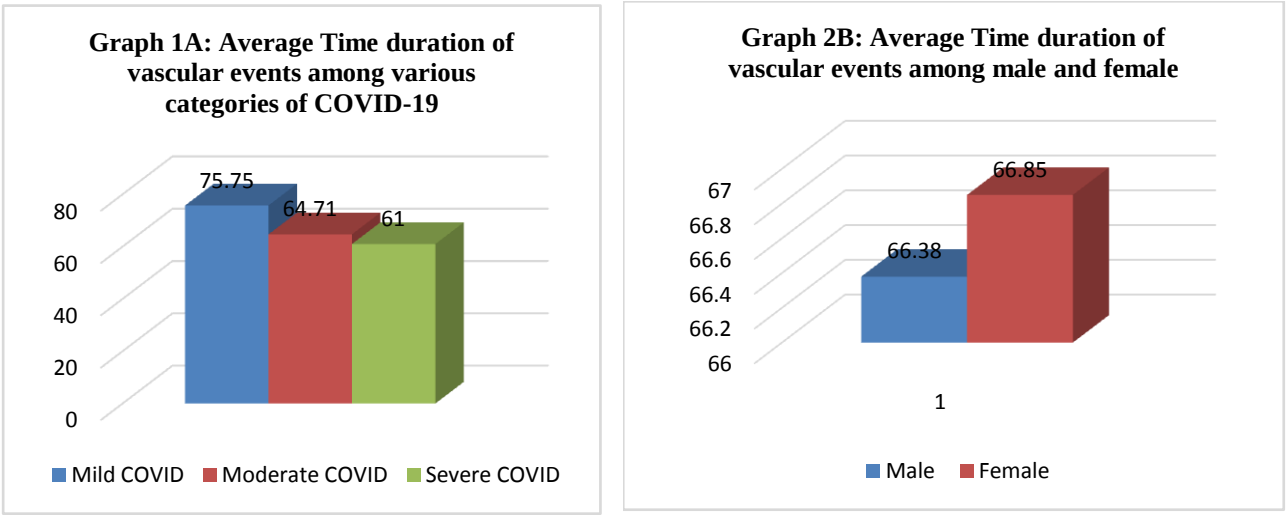
S. No.	Category	Average time duration of the arterial thrombotic event (days)
1	Male	76.38 ± 7.87
2	Female	76.85 ± 9.17
3	Mild COVID	75.75 ± 3.30
4	Moderate COVID	64.71 ± 7.59
5.	Severe COVID	61.0 ± 4.24

Table 4: Comparative differences between time duration for arterial thrombotic events among various categories

S. No.	Categories	Average time duration of the arterial thrombotic event (days)	P-Value
1	Male v/s Female	65.38 ± 7.87 v/s 67.85 ± 9.17	0.2558
2	Mild COVID v/s Moderate COVID	75.75 ± 3.30 v/s 64.71 ± 7.59	0.0132
3	Moderate COVID v/s Severe COVID	64.71 ± 7.59 v/s 61.0 ± 4.24	0.5180
4	Mild COVID v/s Severe COVID	75.75 ± 3.30 v/s 61.0 ± 4.24	0.0087

P values indicate differences between two parameters of case and control. P < .05 was considered statistically significant

Persistent lung fibrosis was also observed slightly higher (20.00%) in patients with arterial thrombotic events as compared to patients without arterial thrombotic events (15.38%) but not statistically significant (P=0.6241).The incidence of various arterial thrombotic events was decreasing order of coronary artery disease (60%), Cerebral vascular disease (30%), Abdominal vessels disease (5%), and Peripheral artery disease (5%).The average time duration on which patients developed post-COVID arterial thrombotic events was found to be 46.55 days (46.55±8.10). In this study, the average time duration of post-COVID arterial thrombotic events did not significantly differ among males and females. The average time duration of arterial thrombotic events among mild, moderate, and severe patients was found to be 55.75 ± 3.30 days, 44.71 ± 7.59, and 41.0 ± 4.24 respectively. The expected time duration on which arterial thrombotic events can occur was inversely proportional to the severity of the disease (*Table 3,4*). In severe COVID -19 patients; there is a higher chance of early arterial thrombotic events, especially in the form of CAD and stroke.



Graph 1: A comparative evaluation of time duration of post-COVID arterial thrombotic events with (A) severity of COVID-19 infection and (B) gender predisposition.

Discussion:

In this study, we evaluate the incidence and precipitating factors of the post-COVID syndrome in hospitalized patients infected with the SARS-CoV-2 virus. We also try to establish an association between the probability of post COVID arterial thrombotic events with severity of disease and inflammatory markers regarding cytokine storm. This is a prospective case-control observational study that includes COVID-19 infected hospitalized patients in the age group of 30 to 60 years after exclusion of underlying chronic medical illness. Critically ill patients who are supposed to be suffering from life-threatening conditions are also excluded from this study. Explaining the exact association between COVID-19 infection and post-COVID arterial thrombotic events is more challenging. While it is known that approximately 30% of myocardial infarctions are preceded by an upper respiratory infection, in particular, influenza; less is known about the thrombotic sequelae in COVID-19 during the convalescent period.7,8 We described 20 cases of COVID-19 recovered patients who presented with acute arterial thrombotic events out of which 60% of patients presented with the acute coronary syndrome. The remarkable differences of these cases included their relatively young age without preexisting risk factors for the hypercoagulable state.

Thrombosis has been classically associated with Virchow's triad of blood stasis, endothelial activation, and hypercoagulable state. However, in the convalescent phase after a COVID-19 infection, studies have described a waning hypercoagulable state with possible persistence of endothelial dysfunction in patients. This has been well described in children during their recovery from COVID-19. Multisystem inflammatory syndrome in children (MIS-C) is a newly defined post-viral myocarditis and inflammatory vasculopathy of children following COVID-19 infection. MIS-C is likely due to the viral tropism of myocardial and endothelial cells by the corona virus. The best evidence supporting MIS-C has been demonstrated in pediatric cases presenting with the self-limited, chilblain-like acral purpuric lesion [18]. Some acute viral infections are associated with transiently elevated lupus

anticoagulant, but they can persist and lead to thromboembolic complications by various mechanisms, including the release of micro particles and exposure of prothrombotic phospholipids [19].Although the significance of these antibodies is not well established yet, COVID-19- induced lupus anticoagulant could favor the occurrence of thromboembolic events in children populations and hence should be systematically tested for. Fibrotic lesions are usually deprived of lipid and inflammatory cells, and hence less likely to rupture and generate embolism. [20]A fibrotic plaque consists mainly of fibrous tissue without a necrotic core or calcium [21].This type of plaque is mostly indolent and stable in comparison with thin cap fibroatheroma, the main culprit in acute coronary syndrome. Interestingly, the current study described, that delayed thrombotic arterial events occurred 28 days from the onset of positive SARS-CoV-2 serology. Further longitudinal studies in patients with "long COVID" should be performed to look for post-COVID-19 associated epitheliopathy and thrombotic squeal, where there may be a role for thromboprophylaxis in high-risk groups.

Our study suggests that post-COVID arterial thrombosis mostly occurred in young male adults ranging from 4^{th} to 6^{th} decades with an average age was found to be 45.12yearsand male to female ratio was 1.86:1. The Control group also had similar mean age and gender ratio without any clinically significant difference. However, patients with arterial thrombotic events have a slightly higher age group as compared to the control group but not statistically significant. A large series of patients with COVID-19 suggest that male patients are more commonly affected by severe forms of the disease, which may account for this observation. This study suggests that patients who require longer hospitalizations are more prone to develop post-COVID arterial thrombotic events as compared to patients discharged from the hospital in the early phase. Hence, longer stays in the hospital also predispose patients to these life-threatening post-COVID arterial thrombotic events. Interestingly, in our study, the severity of COVID-19 during hospitalization did not differ among both groups, hence, post-COVID thrombotic events don't influence by the severity of COVID-19 disease at the time of admission. Nonspecific post-COVID symptoms like malign, fatigue, shortness of breath, chest pain, sick syndrome, headache, vertigo, lack of appetite, generalized weakness, red eyes, etc. were found to be higher among patients who developed post-COVID arterial thrombotic events as compared to those without any thrombotic events. Hence, post-COVID nonspecific symptoms are considered to be an important clue regarding the development of post-COVID arterial thrombotic events.Our study suggests that life-threatening myocardial infarction or stroke can occur unexpectedly in previously healthy patients with even mild to moderate COVID-19 infection. Physicians should have a high index of suspicion in managing patients in the convalescent phase. Screening for and strict management of cardiovascular and cerebrovascular risk factors are of utmost importancepost-COVID-19.

In our study, all patients have raised COVID-19 related inflammatory markers i.e. CRP, D-dimer, and IL-6 which were measured on day 28 of positive serology or onset of symptoms. The mean value of CRP, D-dimer, and IL-6 were much higher in patients who developed post-COVID arterial thrombotic events as compared to the control group. This suggests that increased inflammatory parameters have a major risk factor for the development of post-COVID arterial thrombotic events in patients with COVID-19. However, these inflammatory parameters had been also found to be raised from baseline in patients of the control group but the mean value of the inflammatory markers was found to be much higher in patients with post-COVID arterial thrombotic events as compared to patients without post-COVID arterial thrombotic events. So, we can prevent post-COVID arterial thrombotic events in these vulnerable populations by effective control of the hypercoagulable state in the body. Although direct infection of the lungs with resulting multifocal pneumonia is the major cause of death in patients with COVID-19, inflammatory cytokine syndrome may also be an important cause of morbidity and mortality. Levels of IL-8, IL-6, tumor necrosis factor-α, monocyte chemo attractant protein-1, and regulated upon activation, normal T cell expressed and presumably secreted (RANTES) are significantly elevated in severe COVID-19 cases and IL-6 and IL-8 have been associated with disease progression. It is thought that severely ill patients with COVID-19 are at an increased risk for thromboembolic events, including pulmonary micro thrombi and venous thrombosis perhaps resulting from cytokine storm.

Persistent lung fibrosis was also observed slightly higher (20.00%) in patients with arterial thrombotic events as compared to patients without arterial thrombotic events (15.38%) but not statistically significant (P=0.6241). Arterial thrombotic events associated classically associated with Virchow's triad of blood stasis, endothelial activation, and hypercoagulable state. The combined effect of all events produces a hyper-inflammatory response in lung parenchyma which can lead to persistent lung fibrosis. We observed various arterial thrombotic events in post-COVID patients which were recorded as coronary artery disease (60%), Cerebral vascular disease (30%), Abdominal vessels disease (5%), and Peripheral artery disease (5%) in their decreasing order. The prevalence of coronary artery disease was found to be highest in post-COVID patients who can predispose them for severe lethal cardiovascular disease. The average time duration on which patients developed post-COVID arterial thrombotic events was found to be 66.05 days (66.05±8.10). In this study, the average time duration of post-COVID arterial thrombotic events in male patients was slightly higher than in female patients as per routine genomic structure but did not differ significantly. The average time duration of arterial thrombotic events among mild, moderate, and severe patients was found to be 75.75 ± 3.30 days, 64.71 ± 7.59, and 61.0 ± 4.24 respectively. The expected time duration on which arterial thrombotic events can occur was inversely proportional to the severity of the disease. In severe COVID -19 patients; there is a higher chance of early arterial thrombotic events, especially in the form of CAD and stroke. Initially, during active COVID-19 infection, patients having a higher inflammatory state lead to long-term oxygen support, longer hospital stay, and later on develop early post-COVID arterial thrombotic events. Those patients who required long-term treatment for COVID-19 are the riskiest groups to progress towards thrombotic events. We observed that moderate ill patients have significantly earlier post-COVID thrombotic events than mild ill patients. Similarly, severely ill patients also have significantly earlier post-COVID thrombotic events than mild ill patients.

Conclusion:
Our study highlights post-COVID thrombotic events as a complication of COVID-19 pneumonia in a vulnerable population. Post-COVID thrombotic events may develop in COVID-19 pneumonia due to multiple plausible risk factors including persistent injury of the lung parenchyma, hyper-inflammatory state, and hyper-coagulable state. This study informed about the difference between precipitating factors in patients with post-COVID thrombotic events and without post-COVID thrombotic events. COVID-19 patients will be more prone to post-COVID thrombotic events if the patient has a longer duration of hospitalization, nonspecific symptoms of the post-COVID syndrome, and higher inflammatory states like raised C-reactive protein, IL-6, and hypercoagulable state with raised D-dime. Our study is a reminder that an increase in severity in COVID-19 with a deranged coagulation profile could progress to life-threatening post-COVID thrombotic events. Therefore, clinicians should be aware for post-COVID thrombotic events and must take necessary action to prevent from life-threatening conditions in the form of long-term use of oral anticoagulant medicine.

Limitation: There are several limitations to this study. The number of cases was rather limited and needs to be studied on a larger patient cohort. It was a single-center retrospective observation study and a possibility of bias couldn't be ruled out.

Ethical approval: This study was approved by the ethical and research committee of SMS medical college and Hospital, Jaipur, India.

Author contributions: S. Bhandari, G. Rankawat, and A. Lohmror formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; G. Rankawat and A. Singh collected and analyzed data for the study. G. Rankawat and Shiven Bhandari write the manuscript. S. Bhandari and A. Lohmror conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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