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Thromboembolic Manifestations in Hospitalized COVID-19 Patients in India: A Single-Centre Retrospective Study

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ABSTRACT

Backgrounds: This study aimed to evaluate the incidence and clinical profile of thromboembolic disease in COVID-19 patients and analyze its association with D-dimer and Interleukin (IL)-6 levels.

Materials & Methods: This was a retrospective, single-center study conducted by analyzing data obtained from the case records of COVID-19 confirmed patients with thromboembolic manifestations in India during January 2020 to February 2022. Patients with conditions such as malignancy, prothrombotic states, and autoimmune diseases were excluded from the analysis. D-dimer and IL-6 levels and thrombotic events were analyzed along with comorbid conditions like diabetes mellitus (DM), hypertension, and dyslipidemia. Chi-square tests were used to evaluate the association of various thrombotic manifestations with D-dimer and IL-6 levels. A *p*-value of ≤ .05 was considered statistically significant.

Findings: The mean age of 88 COVID-19 confirmed cases with thrombotic manifestations was 61.01±15.23 years, and the majority (62.5%) of the cases were male. D-dimer and IL-6 levels were elevated in 78.41 and 80.68% of the cases, respectively. The predominant thrombotic manifestation was pulmonary thromboembolism (PTE) (48.86%), followed by acute coronary syndrome (ACS) (36.36%), cerebrovascular accident (CVA) (22.73%), etc. There was no significant association between various thrombotic manifestations and D-dimer and IL-6 levels.

Conclusion: PTE was the predominant thromboembolic manifestation in COVID-19 patients in the current cohort. Elevated D-dimer and IL-6 levels though found in the majority of the patients were not associated with thrombotic events. However, early recognition and treatment could reduce morbidity in COVID-19 patients.

Keywords: COVID-19, Thromboembolism, Pulmonary embolism, D-dimer, Interleukin-6.

CITATION LINKS

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Introduction

SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) infection, declared as a pandemic in 2019, has infected over 611 million people and caused 6.5 million deaths worldwide to date. India has witnessed half a million deaths with more than 44 million confirmed cases [1]. Severe acute respiratory infection and resulting acute respiratory distress syndrome (ARDS) confirm the involvement of the lung in coronavirus disease 2019 (COVID-19) [2, 3]. Thrombotic manifestations are frequently reported in critically ill COVID-19 patients, and elevated D-dimer levels are associated with adverse outcomes. Almost 31% of COVID-19 patients requiring intensive care admission are reported to have thrombotic complications [2–7]. In addition to coagulopathies, elevated levels of pro-inflammatory markers like interleukin (IL)-6, cause multi-organ failure and consequently death, indicating grim prognosis [7]. In the present study, the association of thrombotic events with D-dimer and IL-6 levels was analyzed.

Different mechanisms like dysregulated renin-angiotensin-aldosterone system, oxidative stress damage leading to vasoconstriction, endothelial dysfunction and damage, and disseminated intravascular coagulation (DIC) could act synergistically to increase the risk of thrombosis in COVID-19 patients. Pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT) are the most common thrombotic events reported in COVID-19 patients, and the incidence of venous thromboembolism (VTE) is high in hospitalized patients [8, 9]. Extra-pulmonary thrombosis has also been reported in these patients, such as ischemic stroke, and cerebral venous sinus thrombosis (CVT) [9].

Further, COVID-19 patients with coagulopathies are at higher risk of mortality; hence, monitoring of D-dimer levels, thrombocytopenia, and slight prolongation of prothrombin time is necessary [2]. The incidence of thrombotic manifestations has been increasingly reported in Caucasians [2]; however, few studies conducted in North India have reported variable results for the incidence of these events [10–12].

Objectives: This study was conducted in a tertiary care clinic in South India to evaluate the incidence and clinical profile of thromboembolic disease in COVID-19 patients.

Materials and Methods

This was a retrospective observational study conducted after obtaining ethical approval.

Data were obtained from medical records of confirmed COVID-19 patients with thromboembolic manifestations, who visited the tertiary care center between January 2020 and February 2022. Patients with predisposing conditions such as malignancy, prothrombotic states, and autoimmune diseases were excluded from the analysis.

According to patients' medical records, thromboembolic manifestations were diagnosed using various imaging techniques, such as magnetic resonance imaging (MRI) with MR venogram, computed tomography pulmonary angiogram (CTPA), CT of the abdomen, CT peripheral angiogram, and venous Doppler test.

Clinical data collected from patients' medical records included: COVID-19 positive test, disease severity based on D-dimer (Innovance D dimer, Siemens) and IL-6 (Elecsys IL-6, Roche diagnostics) levels, thromboembolic events like DVT, peripheral vascular disease (PVD), and presence of comorbid conditions like diabetes mellitus, systemic hypertension, and dyslipidemia. D-Dimer was reported as fibrinogen equivalent unit (FEU-30kDa).

Statistical analysis: The obtained data were anonymized and analyzed using R software Version 4.2.1 and Microsoft Excel. Categorical variables were represented as frequency

Table 1) Association of different thrombotic manifestations with D-dimer levels in COVID-19 patients in the present study

Thrombotic Manifestations	Sub-Category	D-dimer N (%)		*P*-Value
		Abnormal	Normal	
CVA	No	53 (76.81)	15 (78.95)	1[MC]
	Yes	16 (23.19)	4 (21.05)	
CVT	No	67 (97.1)	19 (100)	1[MC]
	Yes	2 (2.9)	0	
ACS	No	47 (68.12)	9 (47.37)	.096[C]
	Yes	22 (31.88)	10 (52.63)	
PTE	No	33 (47.83)	12 (63.16)	.2365[C]
	Yes	36 (52.17)	7 (36.84)	
DVT	No	65 (94.2)	19 (100)	.5752[MC]
	Yes	4 (5.8)	0	
PVD	No	67 (97.1)	19 (100)	1[MC]
	Yes	2 (2.9)	0	
Portal vein thrombosis	No	67 (97.1)	19 (100)	1[MC]
	Yes	2 (2.9)	0	
Splenic vein thrombosis	No	68 (98.55)	19 (100)	1[MC]
	Yes	1 (1.45)	0	
SMA	No	69 (100)	18 (94.74)	.2284[MC]
	Yes	0	1 (5.26)	
SMV	No	67 (97.1)	19 (100)	1[MC]
	Yes	2 (2.9)	0	

Abbreviation: C: Chi-square test, MC: Chi-square test with Monte Carlo simulation,
SMV: superior mesenteric vein, SMA: superior mesenteric artery, PVD: peripheral vascular disease, DVT: deep vein thrombosis, PTE: pulmonary thromboembolism, ACS: acute coronary syndrome, CVT: cerebral venous thrombosis, CVA: cerebrovascular accident

and percentage, and continuous variables were expressed as mean ± standard deviation (SD) or median (minimum, maximum). Chi-square tests were used to evaluate association of various thrombotic manifestations with D-dimer and IL-6 levels. A *p*-value of less than or equal to 0.05 was considered statistically significant.

Findings

The medical records of 88 COVID-19 confirmed cases with thrombotic manifestations were compiled and analyzed. These patients were diagnosed as positive for COVID-19 using RT-PCR (reverse-transcription polymerase chain reaction) and radiological tests. The mean age of the patients

Table 2) Association of different thrombotic manifestations with IL-6 levels in COVID-19 patients in the present study

Thrombotic Manifestations	Sub-Category	IL-6 N (%)		*P*-Value
		Abnormal	Normal	
CVA	No	54 (81.82)	10 (58.82)	.0675[MC]
	Yes	12 (18.18)	7 (41.18)	
CVT	No	64 (96.97)	17 (100)	1[MC]
	Yes	2 (3.03)	0	
ACS	No	43 (65.15)	10 (58.82)	.6282[C]
	Yes	23 (34.85)	7 (41.18)	
PTE	No	32 (48.48)	10 (58.82)	.4471[C]
	Yes	34 (51.52)	7 (41.18)	
DVT	No	64 (96.97)	16 (94.12)	1[MC]
	Yes	2 (3.03)	1 (5.88)	
PVD	No	64 (96.97)	17 (100)	1[MC]
	Yes	2 (3.03)	0	
Portal vein thrombosis	No	65 (98.48)	17 (100)	1[MC]
	Yes	1 (1.52)	0	
Splenic vein thrombosis	No	65 (98.48)	17 (100)	1[MC]
	Yes	1 (1.52)	0	
SMA	No	65 (98.48)	17 (100)	1[MC]
	Yes	1 (1.52)	0	
SMV	No	65 (98.48)	17 (100)	1[MC]
	Yes	1 (1.52)	0	

Abbreviations: C: Chi-square test, MC: Chi-square test with Monte Carlo simulation, SMV: superior mesenteric vein, SMA: superior mesenteric artery, PVD: peripheral vascular disease, DVT: deep vein thrombosis, PTE: pulmonary thromboembolism, ACS: acute coronary syndrome, CVT: cerebral venous thrombosis, CVA: cerebrovascular accident

was 61.01±15.23 years, ranging from 27 to 88 years. Among the patients, 62.5% (n=55) were male, and 37.5% (n=33) were female. The disease severity and comorbid conditions in the patients are summarized in Figure 1. D-dimer and IL-6 levels were abnormal in 78.41% (n=69) and 80.68% (n=71) of the cases, respectively. The majority of the cases had diabetes mellitus (n=47, 53.41%), while systemic hypertension and dyslipidemia were present only in 38.64% (n=34) and 4.55% (n=4), respectively.

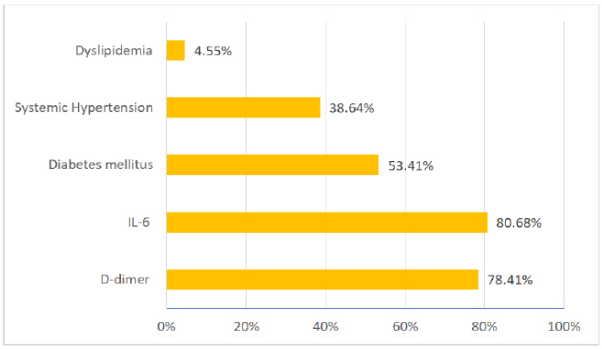

Figure 1) Distribution of clinical variables in COVID-19 patients in the present study
This figure provides percentage distribution of COVID-19 patients with abnormal D-dimer and IL-6 levels and comorbidities.

Figure 2 demonstrates the distribution of thrombotic manifestations in the patients. Among the COVID-19 confirmed cases, predominant thrombotic manifestation was pulmonary thromboembolism (PTE) (48.86%, n=43), followed by acute coronary syndrome (ACS) (36.36%, n=32), cerebrovascular accident (CVA) (22.73%, n=20), etc. There was no statistically significant association between various thrombotic manifestations like CVA (p=1), ACS (p= .096), PTE (p= .2365), and others with D-dimer levels (Table 1). Similarly, these manifestations were not significantly associated with IL-6 levels as well (Table 2).

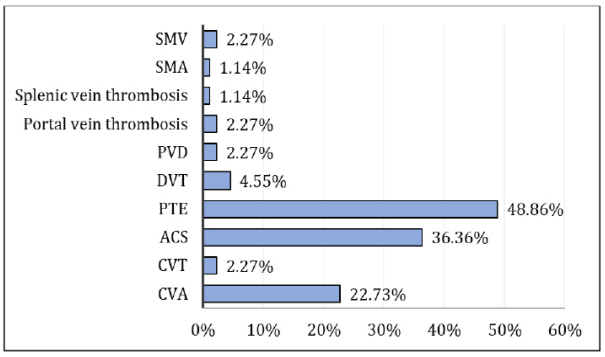

Figure 2) Presence of thrombotic manifestations in COVID-19 confirmed cases in the present study
This figure provides percentage distribution of different thrombotic manifestations among COVID-19 patients.
SMV: superior mesenteric vein, SMA: superior mesenteric artery, PVD: peripheral vascular disease, DVT: deep vein thrombosis, PTE: pulmonary thromboembolism, ACS: acute coronary syndrome, CVT: cerebral venous thrombosis, CVA: cerebrovascular accident

Discussion

The incidence of thrombotic manifestations is frequently reported in critically ill COVID-19 patients, resulting in a poor prognosis [4]. The majority of cases in the present study were male (62.5%), similar to other studies conducted on COVID-19 patients in India [11, 12]. The mean age of the patients in the present study was higher than those reported in other studies [10–12].

The present study gave a glimpse of different thrombotic conditions manifested in COVID-19 patients in a tertiary care center in South India.

PTE was the most common thromboembolic disease observed in the current study. Cytokine storm induced by SARS-CoV-2 leads to endothelial dysfunction, which in turn promotes the formation of thrombi in pulmonary arteries. Additionally, elevated D-dimer levels are indicative of high coagulation due to endothelial dysfunction and a hyper-inflammatory environment [13, 14]. This is corroborated with elevated IL-6 levels, which is one of the cytokines induced by viral infection, as well as D-dimer levels, which indicates intravascular thrombosis, as found in the majority of the patients in the present study. While 48.86% of the cases in the present study manifested PTE, a meta-analysis conducted on studies published between January and June 2020 reported a pooled incidence of 16.5% [15], and another meta-analysis conducted till August 2020 during the peak stages of the pandemic reported a pooled prevalence of 23.4% among patients admitted to the intensive care unit [16]. A meta-analysis of venous thrombolytic events (VTE) in COVID-19 patients reported incidence rates of 2-85% for deep vein thrombosis (DVT) and 2-35% for PTE [17]. The prevalence of DVT in the present study was 4.55%.

Viral infection and subsequent inflammatory environment have been reported to precipi-

tate ACS by elevating cytokine levels that favor thrombosis [18]. ACS was found in 36.36% of the patients in the present study. CVA was also observed in 22.73% of the patients. However, a study conducted on a large sample of COVID-19 patients in Spain reported only a 1.4% incidence rate for CVA [19]. Nevertheless, poor outcomes and increased disease severity have been reported in patients with CVA [20]. The prevalence of other thrombotic events such as splenic vein, portal vein, and cerebral venous thrombosis was minimal in the present study.

Elevated D-dimer levels determined using standard tests have been reported to have 99.5% sensitivity but only 41.0% specificity for pulmonary embolism. Also, elevated D-dimer levels in COVID-19 patients are known predictors of poor outcomes [21, 22]. However, the current study found an unusual result because elevated D-dimer levels were not associated with any thrombotic events. According to the literature, various coagulation-associated diseases could also increase D-dimer levels [22]. This is in contrast to a multicenter retrospective study, where elevated D-dimer level was an indicator of thrombotic complications in hospitalized patients [23]. Another study conducted in North India also reported coagulopathies in severe COVID-19 patients with high D-dimer levels [11].

The present study also found no significant association between IL-6 levels and thrombotic manifestations. This is also inconsistent with the literature reporting the significant role of IL-6 in the manifestation of VTE in COVID-19 patients [24].

In this study, the mortality rate in COVID-19 patients with thrombotic manifestations and the correlation between age and gender with the incidence of thrombotic events were not evaluated. Also, the administration of anticoagulants and their effect on reducing morbidity due to COVID-19 were not assessed. These points need to be considered along with the vaccination status of COVID-19 patients, as few coronavirus vaccines could themselves induce coagulopathies [25, 26].

Conclusion

Among thromboembolic diseases, PTE was predominantly observed in most of the COVID-19 patients in South India, followed by ACS and CVA. D-dimer and IL-6 levels were elevated in the majority of the patients; however, they were not associated with various thrombotic events. Nevertheless, early diagnosis of thromboembolic manifestations and appropriate treatment with anticoagulants could decrease the morbidity and mortality in COVID-19 patients.

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Ethical permissions: Ethical approval was obtained from the Institutional Human Ethics Committee (IHEC) (PSG/IHEC/2022/Appr/Exp/081), dated April 11, 2022.

Conflicts of interests: None declared by authors.

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Data monitoring, project management, final draft and edit- 4 and 5.

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