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ORIGINAL ARTICLE

# Venous Thromboembolism and COVID-19—an Epidemiological Perspective

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## Abstract

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as pandemic by World Health Organization (WHO) in March 2020. The outbreak has caused 5,232,562 deaths worldwide until December 3rd, 2021. Though primarily affecting the respiratory system, involvement of other organ systems have been reported in severe disease. Venous thromboembolism (VTE) has been recognized as an important complication. Previous studies have reported the prevalence of VTE in intensive care unit (ICU) patients between 7 and 85% and in non-ICU patients between 0 and 19%. COVID-19 patients that are at high risk for VTE are also at increased risk for bleeding. In such cases, anticoagulation may potentially be harmful. Thereby, it is important to understand the risk factors for VTE predisposition in the COVID-19 patients, timing of VTE, and the rate of occurrence of VTE in hospitalized patients post-discharge. Comparison of the rate of occurrence of VTE in COVID-19 patients with the non-COVID-19 patients with similar disease severity is required to truly interpret the reportedly high rates of VTE in COVID-19 patients. Several pathophysiological mechanisms have been reported for the development of VTE in COVID-19. Autopsy-based studies have contributed to the existing knowledge. D-dimer, presently, seems to be the most suitable investigation for risk-identification of VTE supported by Doppler studies and overall clinical context. Further, prospective studies and clinical trials are essentially required to fill the gaps in evidence for occurrence, risk prediction and management of VTE in COVID-19 patients.

**Keywords** Epidemiology · COVID-19 · Coronavirus · D-dimer · Thrombosis · Venous thromboembolism

## Introduction

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in approximately 1 out of 1000 individuals in the general population and is often secondary to associated clinical conditions [1]. Most VTE events are asymptomatic but a good number of cases are associated with morbidity in form of post-phlebitis syndrome, pulmonary hypertension and mortality [2, 3].

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as a pandemic by World Health Organization (WHO) in March 2020.[4]. The outbreak has killed 5,232,562 patients worldwide until December 3rd, 2021 [5]. It affects primarily the respiratory system; however, involvement of other organ systems has been reported with the increasing severity of the disease [6].

During the COVID-19 pandemic, a high reported prevalence of DVT was observed in severe/hospitalized COVID-19 patients, especially in the intensive care unit (ICU). Many studies have reported a high prevalence of incident thrombosis in small and mid-sized pulmonary arteries, despite thromboprophylaxis [2]. Over the period with an increased understanding of COVID-19 and its clinical course, VTE has been recognized as a particular complication of the disease. Initial epidemiological studies have found alarmingly

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high rates of PE in patients with severe COVID-19 treated at ICUs, reporting VTE incidences as high as 50% [7].

COVID-19 patients at high risk for VTE are also at increased risk for bleeding, making them prone to devastating intracranial bleed. In such cases anticoagulation may potentially be harmful, thereby it will be important to identify the risk factors for thrombosis among those hospitalized COVID-19 patients. Early studies have reported coagulation abnormalities and coagulopathy in COVID-19 patients with pro-thrombotic characteristics [8, 9].

In response to the clinical challenges and lack of high-quality evidence, guidelines were laid down by expert groups and scientific societies concerning diagnosis, prevention, and treatment of VTE in patients with COVID-19, which suggest the broad application of thromboprophylaxis in patients with severe COVID-19 in the absence of contraindications [10].

With this background, we present a narrative review to describe the epidemiology of VTE in COVID-19 infection and associated risk factors.

## Prevalence and Incidence of VTE in COVID-19 Patients

The annual incidence of the first symptomatic DVT event in the adult population ranges from 50 to 100 per 100,000 population, with the overall incidence of VTE around 25% higher on adding the PE events. The rate of recurrent VTE is around 10% in the first year and 30% after 5 years for patients with unprovoked DVT and with an unidentified precipitating factor [11].

VTE events were first reported in 30% of the COVID-19 patients admitted in intensive care units (ICUs) in Netherland and China [12]. A multi-centric retrospective study on 2779 COVID-19 patients with VTE events from China was compared with 23,434 non-COVID-19 medical inpatients for VTE occurrence. The reported odds for developing symptomatic VTE in severe and non-severe hospitalized COVID-19 patients were 5.94 and 2.79 times higher than the non- COVID-19 patients respectively, after adjusting for age and gender [2].

Doppler ultrasound (DUS) is the common method of screening for thrombosis in patients with COVID-19 [13]. A scoping review has reported incidence of VTE ranging from 9 to 65% when screened by routine ultrasound on patients in the Intensive Care Unit (ICU) [14]. However, a study on 23 patients with mild/moderate COVID-19 pneumonia who underwent computed tomography pulmonary angiography (CPTA) and computed tomography venography (CTV) scans of the lungs and extremity veins reported that only one of the VTE patients was positive when screened by DUS while the other VTE patients were screened negative by DUS. They concluded that through the usage of CTV screening for DVT, the incidence of thrombosis in patients with mild/moderate COVID-19 markedly increased to 82.6% (19/23) and found CTV more sensitive than DUS for thrombosis detection [15].

A study from Amsterdam medical center on 198 hospitalized patients with COVID-19 reported the cumulative incidences of VTE on days 7, 14, and 21 as 16%, 33%, and 42% respectively. They reported an association of mortality with VTE (adjusted HR, 2.4; 95% CI, 1.02–5.5). The observed cumulative incidence of VTE for ICU patients was 26%, 47%, and 59% on days 7, 14, and 21 respectively. While for the patients admitted in the wards the observed cumulative incidence of VTE was 5.8%, 9.2%, and 9.2% on days 7, 14, and 21 respectively. Similar observations have been reported from COVID-19 ICU patients in Italy and France [16].

One of the early systematic review and meta-analysis studies conducted on 42 studies (8271 patients) on COVID-19 patients reported an overall VTE rate of 21% and 31% in ICU admitted patients [17]. Another systematic review on 91 studies (35,017 patients with COVID-19) reported the proportion of VTE in all patients, ICU and non-ICU as 12.8%, 24.1%, and 7.7% respectively. ICU patients had almost three times higher relative risk of developing VTE when compared with non-ICU patients. The rate of DVT was more than double in studies that used systematic screening (13.5%) compared to the studies that performed ultrasound only when symptomatic (6.2%) [18]. A similar finding was reported in another meta-analysis conducted on 86 studies that were mainly from Europe (66.3%), North America (19.8%), and Asia (9.3%). The pooled prevalence estimate of all reported VTE events (VTE, DVT, and PE) was 14.1%. In the 52 studies in which no ultrasound screening was performed, the estimated rate of VTE was 9.5% while in the 14 studies with ultrasound screening performed the estimated prevalence of VTE was as high as 40.3%. Rates of VTE in studies with screening strategies in the ICU cohorts were 45.6% and in those without screening strategy was 18.7% [7].

One of the latest reviews found that the prevalence of VTE (DVT/PE) in ICU patients ranges between 7 and 85% and in non-ICU patients between 0 and 19% [19]. In a meta-analysis from non-ICU hospitalized COVID-19 patients (20,886 patients from 43 studies), the overall prevalence estimates of VTE were 7.9% [7]. The reported incidence of VTE findings from various published epidemiological studies (mostly retrospective cohorts) varies widely (4.1% to 85.4%). The reason for such large variations in the reported incidence of VTE in COVID-19 hospitalized patients can be attributed to the different characteristics of the study population, varying study designs and sample size, different diagnostic methods, the timing of the tests, influx of COVID

patients, and various thrombo-prophylaxis modalities used [2].

## Timing of VTE Event in COVID-19 Patients

The timing of the VTE was assessed through a large retrospective cohort study on 54,354 COVID-19 patients between 1st March and 31st December 31, 2020. A 29-fold increased rate of VTE was reported during the first week following the diagnosis of COVID-19 infection when compared to the pre-COVID-19 period. The rate of VTE steadily declined and returned to baseline by the 6th week [20]. The rate of VTE during post-discharge of COVID-19 hospitalized patients was found to be 1.3% in a cohort study on 2832 adult hospitalized COVID-19 patients [21].

## Incidence of VTE in Non-Hospitalized COVID-19 Patients

Majority of the studies on COVID-19 and VTE have focused on hospitalized patients. A retrospective cohort followed 715 COVID-19 outpatients from a health care network in the Greater Boston area for their cardiovascular outcomes. On average, these participants were young (mean age of 45 years), had a low prevalence of the previous coronary artery disease (3%), VTE (3%), and moderate prevalence of hypertension (25%) and diabetes (10%). Just one participant received thromboprophylaxis. Though they reported 6% lost to follow up, there were no symptomatic PE or DVT at 30 days in this cohort [22, 23]. A second even larger retrospective cohort of 24,746 COVID-19 patients of health management organization in California, either in the outpatient setting or the emergency department, reported117 patients developing a VTE after 30 days (risk of 0.5%). When the analysis was restricted to those who were not admitted to the hospital during the 30 days, the risk was even lower (0.1%). [23, 24]

## Incidence of VTE in Post-Discharge COVID-19 Patients

There are limited and conflicting data on VTE occurrence rates in the post-discharge period of hospitalized COVID-19 patients with varying sample sizes, study designs, and non-standardized follow-up protocol. A prospective registry reported the VTE rate as 1.55% within 90 days of hospital discharge. Post-discharge anticoagulation reduced risk by 46% [25].

One of the cohort studies on 2832 adult patients hospitalized with COVID-19 reported that patients with a history of venous thromboembolism have three times the odds of developing VTE after discharge. Similarly raised D-dimer greater than 3 µg/mL and pre-discharge C-reactive protein level greater than 10 mg/dL also raises the odds of VTE post-discharge by three times [21]. The recently updated British Thoracic Society guidance mentioned low incidences of acute VTE following hospital discharge between 0 and 0.6% in observational studies, which is comparable to that in non-Covid-19 patients [26].

## Limitations in Studies Reporting Epidemiological Parameters for VTE in COVID-19 Patients

The main limitation discussed in most systematic reviews was the high heterogeneity of included studies concerning study design, clinical setting, and locally adopted thromboprophylaxis strategies. The majority of the studies enrolled critically ill patients from ICUs and used screening strategy through ultrasonography. Asymptomatic VTE events were also commonly included, which accounted for 65.2% to 87.8% of total VTE events [2]. Thus, markedly high rates of VTE in hospitalized COVID-19 patients were reported. Thereby, the true underlying burden of VTE in patients with COVID-19 is still not fully understood. In the light of the ever-growing infection rates worldwide, the introduction of new variants of varying virulence in the population and clinical challenges in patient management, understanding of the true frequency of VTE in COVID-19 is essentially important which may help to support clinical decision-making.

Most of the initial epidemiological studies have reported higher rates of VTE events when compared to VTE rates observed in trials validating thromboprophylaxis in hospitalized patients for acute medical conditions, like sepsis or cardiac and/or respiratory failure. Based on clinical and autopsy-based observations in the patients with VTE in COVID-19 patients, many clinicians and subsequently many scientific societies proposed empirical modifications to the usual thromboprophylaxis strategies [23]. This could be a reason the decreasing incidence of VTE as observed in later epidemiological studies.

## Pathogenesis of VTE in COVID-19 Patients

Large observational cohorts and clinical trials in critically ill patients with various underlying diseases have reported elevated rates of VTE in the ICU setting ranging from 5.1 to 15.5% [7, 27–31]. Thus the higher VTE reported rates in COVID-19 patients admitted in ICU setting cannot be solely explained as a complication hospitalization. The high VTE rates in COVID-19 patient supports the hypothesis of

direct involvement of the viral infection with the vascular and hemostatic system leading to a prothrombotic state.

A previous study on critically ill patients with severe acute respiratory syndrome coronavirus from the early 2000s reported similarly high VTE rates (14 of 46 patients suffered from VTE). VTE events were observed less frequently in other respiratory viruses such as the Middle East respiratory syndrome coronavirus and influenza [7]. Due to lack of evidence, one can only speculate common underlying pathophysiology which is causing higher VTE events in COVID-19 infected patients.

Various patho-physiological developments linked to VTE in COVID-19 infection have been reported in the previous studies: [26, 32–36].

1. Direct viral invasion of endothelial cells via angiotensin-converting enzyme-2 (ACE2), or as a result of the subsequent marked inflammatory response and tissue hypoxia.
2. Increased markers of complement activation such as C5b-9 in COVID-19 hospitalized individuals compared to controls, in severe cases compared to moderate disease and those requiring mechanical ventilation to those who did not. An in vitro study found SARS-CoV-2 spike protein responsible for activation of the alternative complement pathway leading to endothelial injury.
3. COVID-19 induces a prothrombotic state with an increase in factors V, VII, VIII, X, fibrinogen, circulating prothrombotic microparticles, von Willebrand factor, platelet activation.
4. Other important sources of endothelial injury include the intravascular catheterization, stasis of blood flow due to prolonged immobilization, activation of the acute systemic inflammatory response mediators such as cytokines (interleukin (IL)-6), and other acute phase reactants.
5. Release of neutrophil extracellular traps (NETs) from decondensed chromatin of dead neutrophils fighting to immobilize pathogens induces a prothrombotic state in COVID-19.

Previous autopsy studies have provided some essential insights into this pro-thrombotic state in COVID-19. An autopsy study has also revealed that systematically almost all organs in the body show signs of thrombosis. Irrespective of the anticoagulation status, significant macro and microvascular thrombosis was found in multiple organs [37, 38].

## Risk Factors for VTE in COVID-19 Patients

Several studies have been conducted to assess the important risk factor for the development of VTE like age, gender, ethnicity, seasonal pattern, associated co-morbidities such as obesity, hypertension, cardiac ailments, diabetes mellitus, cancer, the need for hospitalization for severe COVID-19 disease management, and biochemical parameters reflecting a state of hypercoagulability.

In the general population, the lifetime risk of developing VTE is at least one in 12 middle-aged adults. The incidence of DVT is slightly greater in women aged 20–45 years, but men aged between 45 and 60 years have a higher incidence. The incidence is higher for men in all age groups if women-specific risk factors like oral contraceptives and pregnancy are excluded. The incidence increases two-fold per 10 year age increase. Sixty percent of all VTE events occur in patients aged more than 65 years. Certain ethnicity such as African-Americans has reported a higher incidence of DVT than Caucasians and Native Americans. While, Asians overall have a lower incidence. Seasonal variations, especially winters (peak in February), have reported a higher incidence of VTE [11].

Though most of the patients completely recover from the infection, men with increasing age, associated co-morbidities, previous history of VTE, prolonged ambulation, longer ICU stay, requiring invasive procedures like mechanical ventilation, receiving anti-cancer therapy, abnormal baseline biochemical, and hematological parameters are at increased risk of VTE. The risk factors can be summarized broadly in three categories: (1) Socio-demographic factors, (2) associated co-morbidities, (3) biochemical markers at baseline and during COVID-19 management, (4) status of thromboprophylaxis, and (5) ICU-specific risk factors (Table 1) [2, 7, 11, 12, 37, 39–42].

Though the annual incidence of VTE has not changed in the last two to three decades, the prevalence of cancer, major surgery, trauma, and obesity has increased, and so does the widespread availability of improved diagnostic modalities with computed tomography (CT) and magnetic resonance imaging (MRI) leading to increased detection of incidental VTE in patients and better thromboprophylaxis strategies [43].

One of the largest multicentre studies from China reported cancer as an independent risk factor for VTE. Both active cancer and anti-cancer therapies are well-known risk factors for thrombotic events [2]. Certain neoplasms with the primary site as pancreas, esophagus, and stomach carry the highest risk. Cancer Consortium registry (CCC19) cohort study assessed the incidence of VTE within 90 days of COVID-19-associated hospitalization and reported an elevated risk of VTE (7.6%) among hospitalized patients with both active cancer and COVID-19 [39].

One of the initial autopsy studies on 12 consecutive patients, who died of COVID-19, found a high incidence of deep venous thrombosis (58%) in obese patients. All deceased patients had pre-existing chronic medical conditions such as obesity, coronary heart disease, asthma or chronic obstructive

**Table 1** Risk factors for venous thromboembolism (VTE) [2, 7, 11, 12, 37, 39–42]

| COVID-19 related risk factors | Variables |
|---|---|
| **Socio-demographic factors** | |
| Age | ≥ 70 years |
| Gender | Male > Female |
| Ethnicity | Hispanic > White |
| Female specific factors | Pregnancy, Oral contraceptives, Hormone therapy |
| **Associated co-morbidities** | Obesity (BMI ≥ 40), Active Cancer, Hypertension, CVD, Diabetes, Stroke, CKD, Sepsis, Trauma, Recent Surgery/Trauma, personal/ familial VTE, familial hypercholestrolemia |
| **Biochemical and hematological markers at baseline and during COVID-19 management** | Raised D-dimer levels, D-dimer increment in first week of hospitalization, low fibrinogen levels, raised white blood counts, pre-discharge raised C-reactive protein |
| **Status of thromboprophylaxis** | No prophylaxis > therapeutic/prophylactic medication |
| **ICU-specific risk factors** | Immobilization, sedation, vasopressors, catheterization |

pulmonary disease, peripheral artery disease, and diabetes mellitus type 2 [37].

A genome-wide association study (GWAS) of patients with severe COVID-19 identified genetic associations for the chromosome 3 locus (3p21.31) and with chromosome 9 locus (9q34.2). The association signal at locus 9q34.2 coincided with the *ABO* blood group locus showed a 1.45 times higher risk in blood group A than in other blood groups and a protective effect in blood group O (OR, 0.65; 95% CI: 0.53 to 0.79) [44].

Whether COVID-19 infection is directly contributing to higher VTE rates when compared to VTE rates in patients hospitalized for other reasons is subject to debate. Unfortunately, to date, there is a lack of studies that compare the VTE rates in COVID-19 hospitalized patients and patients hospitalized for other reasons using the same assessment methodology.

A recent meta-analysis found that the rate of VTE between COVID-19 cohorts was comparable with non-COVID-19 cohorts with similar disease severity. However, they also reported that the ICU patients with COVID-19 are at a significantly higher risk of developing VTE than the non-COVID-19 ICU patients. Severe COVID-19 requiring ICU admission may thus be a risk factor for developing VTE [45]. In line with this, another systematic review also observed that a high-risk difference between COVID-19 and non-COVID-19 patients for VTE (6% more risk as compared with non-COVID-19) and PE, in particular in patients admitted to the ICU [46].

## D-Dimer as a Predictor for VTE in COVID-19 Patients

The limited availability of duplex ultrasound or computer tomography pulmonary angiography (CTPA) and ICU equipment for COVID-19 patients due to lack of resources in the developing countries, an overwhelming load of the existing resources and strict quarantine warrants a novel predictor of VTE events.

Raised D-dimer (prevalence up to 46.4%) with increased severity and complications of COVID-19 has been correlated in several previous studies. Patients with D-dimer > 1000 ng/mL present a 20-fold higher mortality risk compared to those with lower D-dimer values [2]. D-dimer was largely considered as a potential screening tool for VTE in COVID-19 patients and for also monitoring the therapeutic and thromboprophylaxis dosages [47]. However, it was observed that many patients did not develop asymptomatic VTE despite a high D-dimer level reflecting a low specificity. A recent meta-analysis also points that though D-dimer has high sensitivity (90%) for diagnosing VTE related to COVID-19 but has low specificity (60%) [48].

One of the largest multicentre studies from China observed that D-dimer increment ≥ 1.5-fold had the most significant association, followed by D-dimer level at the time of admission, and lower fibrinogen level at the time of admission. They observed a sharp rise in D-dimer level in the first week of hospitalization among COVID-19 patients who are likely to develop asymptomatic VTE. Thus the investigators recommended monitoring of D-dimer level for an increment of ≥ 1.5-fold, from day 1–3 to day 4–6 following hospitalization [2].

Validation for these proposed thresholds through prospective studies is required before their routine adoption can be recommended. The recent guidance update based on current data does not support the routine use of elevated D-dimer levels in isolation for decision making regarding the investigation and anticoagulation. Markedly elevated D-dimer levels with the overall clinical suspicion should prompt investigations to exclude VTE [26]. The American Society of Hematology has recently (February 14, 2022) mentioned

that the D-dimer levels are higher in COVID-19 patients especially with increasing severity irrespective of presence or absence of VTE/PE and thus higher D-dimer levels generally cannot be implicated as a diagnostic marker of VTE/PE. However, elevated levels have been utilized in trials to risk stratify the patients [49]. The recently (February 24, 2022) updated NIH COVID-19 guideline panel has recommended therapeutic-dose heparin for patients with elevated levels of D-dimer, requiring low-flow oxygen and have no increased risk of bleeding [50].

Several registries, multi-centric cohort studies, and clinical trials are ongoing which will be addressing epidemiological perspective for thromboembolic outcomes in patients with COVID-19 and guide several unanswered questions with regards to risk models, timing, dosage, and duration of anticoagulation [51].

## Conclusion

Incidence of venous thromboembolism is more prevalent in patients with COVID-19 especially in the patients admitted in intensive care but the exact incidence is still not known and may vary from 5 to 89% with an average of 50%. The problem is that it is also associated with bleeding so one has to be judicious in using the anticoagulants. The risk persists even after the discharge from the hospital. D-dimer is an important investigation along with Doppler studies and overall clinical condition for identification and risk stratification of venous thromboembolism. Further, prospective studies and clinical trials are essentially required to fill the gaps in evidence for venous thromboembolism occurrence, risk prediction, and management in COVID-19 patients.

## Declarations

**Competing Interests** The authors declare no competing interests.

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