

Thrombotic risk in patients with COVID-19

Edoardo Pancaldi^{1,†}, Greta Pascariello^{1,†}, Giuliana Cimino¹, Angelica Cersosimo¹, Ludovica Amore¹, Fabio Alghisi¹, Nicola Bernardi¹, Emiliano Calvi¹, Carlo Mario Lombardi¹, Enrico Vizzardi^{1,*}, Marco Metra¹

¹Cardiology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, 23123 Brescia, Italy

*Correspondence: vizzardi72@gmail.com (Enrico Vizzardi)

† These authors contributed equally.

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Emerging evidences prove that the ongoing pandemic of coronavirus disease 2019 (COVID-19) is strictly linked to coagulopathy even if pneumonia appears as the major clinical manifestation. The exact incidence of thromboembolic events is largely unknown, so that a relative significant number of studies have been performed in order to explore thrombotic risk in COVID-19 patients. Cytokine storm, mediated by pro-inflammatory interleukins, tumor necrosis factor α and elevated acute phase reactants, is primarily responsible for COVID-19-associated hypercoagulopathy. Also comorbidities, promoting endothelial dysfunction, contribute to a higher thromboembolic risk. In this review we aim to investigate epidemiology and clarify the pathophysiological pathways underlying hypercoagulability in COVID-19 patients, providing indications on the prevention of thromboembolic events in COVID-19. Furthermore we aim to reassume the pathophysiological paths involved in COVID-19 infection.

Keywords

Thrombosis; COVID-19; Pulmonary embolism; Endothelitis; Coagulopathy

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread rapidly around the world, with high morbidity and mortality.

The World Health Organization (WHO) has declared COVID-19 a public health emergency of international concern, and, as of 26 April 2021, with 146,689,258 global estimate laboratory confirmed cases and 3,102,410 deaths (<https://www.who.int>) [1].

In view of the rapid increase in the number of patients suffering from this unpredictable disease, the aim of physicians working on first line should be to know in depth its pathophysiology, clinical evolution and short and long-term consequences. Today, pneumonia remains the major clinical manifestation of COVID-19 [2] but, however, the onset of the disease have highlighted severe features previously unthinkable in patients, even in young patients with no previous pathology [3, 4].

In addition, hospitalized COVID-19 patients frequently develop laboratory abnormalities compatible with hypercoagulability and clinically high prevalence of thromboembolic events [5]. Indeed, pulmonary embolism (PE) is one of the most important parts of the spectrum of clinical manifestations of these patients [6], but left ventricular thrombosis as

a rare complication of Takotsubo syndrome has also been reported [7], and extracorporeal circuits and arterial thrombosis [8].

These events appear to be a response to COVID-19 with an exuberant cytokine storm [9]. Immunological studies have also shown that pro-inflammatory cytokines interleukin (IL)-6, IL-17A and tumor necrosis factor α were elevated in most patients with severe outcomes [10].

Pro-inflammatory cytokines are known to be critically involved in abnormal blood clot formation and platelet hyperactivation and also play an important role in the downregulation of important anticoagulant physiological pathways [11].

The purpose of this review is to clarify the pathophysiological mechanism underlying hypercoagulability in COVID-19 patients and to provide indications on the correct prevention of thromboembolic events to reduce the morbidity and mortality rate.

Furthermore we aim to reassume the pathophysiological paths involved in COVID-19 infection.

2. Methodology

In this review we analyze the most recent research article, reviews and case reports about COVID-19, found on PubMed and published in several scientific journals.

2.1 Epidemiology

Since we are witnessing a novel and still ongoing COVID-19 pandemic, there is yet lack of a clear awareness of thrombotic risk. To date, several studies attempted to examine the epidemiology of venous thromboembolism (VTE), PE, deep venous thrombosis (DVT), arterial thrombosis and bleeding in COVID-19.

In literature, a substantial risk of VTE in COVID-19 patients is described especially with regard to Intensive Care Unit (ICU), where PE may emerge in up to one-third of severely ill patients [12]. Bompard *et al.* [13] stated a 24% cumulative incidence of PE, 50% in ICU patients and 18% in other patients despite receiving prophylactic anticoagulation. Interestingly, Poissy *et al.* [14] compared patients with COVID-19, admitted in ICU from February to March 2020, and patients with Influenza, admitted in ICU for respiratory fail-

ure during the same time interval in 2019; the frequency of PE in COVID-19 cases was doubly as high as the frequency observed in patients suffering from Influenza in 2019 (20.6% versus 7.5%).

In a single-centre cohort study of 198 patients admitted for COVID-19 and treated with thrombosis prophylaxis, VTE was observed in 39 of 198 patients (20%) [6.6% of PE and 13% of DVT]. In the ICU, the cumulative incidence of VTE was even higher, reaching 47% [15]. The analysis of different risk factors among this cohort revealed that a higher white blood cell count, higher D-dimer level and higher neutrophil-to-lymphocyte ratio was independently associated with VTE, underlining the tight relationship between coagulation and inflammatory pathways.

Also comorbidities, such as diabetes, hypertension and acute kidney injury, play a role promoting endothelial damage and may be, consequently, linked to COVID-19-related complications [16]. Noteworthy, an Italian study compared clinical characteristics and outcomes between COVID-19 patients with concomitant cardiac disease and subjects not affected by cardiac diseases. They noted a high proportion of mortality, septic shock and thromboembolic events in cardiac patients (23% versus 6%) [17].

Llitjos *et al.* [18] carried out a backward looking study in two French ICU, finding a surprisingly significant percentage of thromboembolic events (around 56%) in COVID-19 patients who were receiving therapeutic anticoagulation, suggesting to consider an early therapeutic anticoagulation in critically ill COVID-19 patients.

In a cohort of 184 ICU patients affected by COVID-19 pneumonia and admitted in three hospitals in the Netherlands, a radiographically confirmed VTE was reported in 27% of the patients, with PE as the most recurring thrombotic complication (13.6%), and arterial events occurred in 3.7% of the patients. All the above events took place despite the usage of standard doses thromboprophylaxis [19].

A 21% cumulative rate of VTE events (corresponding to a rate of 7.7% among closed cases) was reported in an Italian single-centre retrospective cohort study, ranging from a cumulative rate of 27.6% in ICU and 6.6% in patients on the general ward [20], comparable to the incidence of VTE (25%) reported in a ICU in Wuhan, China where patients were, however, not on anticoagulant therapy [21]. Conversely, a lower rate of radiographically confirmed VTE was reported in an American multicentre retrospective study of 400 COVID-19 hospitalized patients and mainly treated with standard-dose prophylactic anticoagulation (4.8% confirmed VTE, with a VTE rate of 3.1% in non critically ill patients and 7.6% in ICU). Arterial thrombosis rate was 2.8% (1.2% in non critically ill patients and 5.6% in ICU) while, interestingly, bleeding rate was 4.8% (3.1% in non critically ill patients and 7.6% in ICU), pointing out the urgent need of randomized trials to establish the best anticoagulant treatment in this pathology. Interestingly, the group affected by thrombotic complications had systematically higher D-dimer, fibrinogen, C-

reactive protein (CRP), ferritin and procalcitonin, whereas the bleeding complications group had higher procalcitonin and peak D-dimer and lower platelet counts [22].

A multicentre registry (CORONA-VTE), composed of 1114 COVID-19 patients, was filled in to estimate the frequency of arterial or venous thromboembolic disease and major adverse cardiovascular events. It showed a higher occurrence of the above events over 30 days in patients admitted in ICU, in spite of a nearly 90% use of thromboprophylaxis. They observed a rate of 35.3% regarding major arterial or venous thromboembolic event and a rate of 45.9% regarding major cardiovascular events in ICU patients, followed by the hospitalized non-intensive care cohort, with a rate of 2.6% regarding major arterial or venous thromboembolic event and a rate of 6.1% regarding major cardiovascular events, and the outpatients, with a rate of 0% for both [23].

To assess the burden of asymptomatic DVT in COVID-19 patients with elevated D-dimer levels, an observational study, performed in Madrid, described a high incidence (14.7%) of asymptomatic DVT [24].

In conclusion, given the retrospective nature of the studies and the relatively short follow-up, which may underestimate the real incidence of thromboembolic disease in COVID-19 patients, we can reasonably assert that an accurate incidence is difficult to establish. Several reviews and meta-analysis tried to evaluate the incidence of VTE in COVID-19 showing that VTE incidence, among hospitalized COVID-19 patients, is significant, even in patients undergoing anticoagulant therapy [12, 25–29] (Tables 1,2,3,4).

In agreement with this assumption, randomized trials are needed to determine the realistic picture of an eventual life-threatening complication of COVID-19.

In this perspective, VTE-COVID is an ongoing trial evaluating the augmented risk of VTE in patients recovered in ICU and in general ward for COVID-19.

2.2 Pathophysiology of hypercoagulability in COVID-19

The main entry point into cells for SARS-CoV-2 is angiotensin converting enzyme 2 (ACE-2), which is attached to the outer surface of cells in lungs, arteries, heart, kidney and intestines. The binding of spike S1 protein to ACE-2 causes endocytosis. Furthermore, some studies demonstrated that SARS-CoV-2 can not only infect cells through ACE-2 receptors, but there are also other pathways. In fact, some authors report that there might be another pathway on the surface of red blood cells (RBC) that interact with S1 spike protein. In particular, they demonstrated that S1 spikes interact with RBC Band3 protein, similarly to the interaction of S1 spikes and ACE-2 receptors. This can determine a capture of oxygen, causing low levels of oxygen in blood: hypoxia.

In patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a key role is played by inflammatory response, signalling the progression of COVID-19, as proved in a Chinese retrospective study in which the plasmatic levels of IL-6 (the paramount trigger of the so called 'cytokine storm') and C-reactive protein (CRP) have been found

Table 1. Published studies describing the epidemiology of thrombotic risk in COVID-19 patients.

References	Date	Number of patients	Venous thromboembolism	Major arterial or venous thromboembolic event	Pulmonary embolism	Deep venous thrombosis	Arterial thrombosis	Bleeding events
Al-Samkari <i>et al.</i> [22]	2020.03–2020.04	400 (144 critically ill)	4.8% (7.6% in critically ill patients)	-	-	-	2.8% (1.2% non critically ill; 5.6% critically ill)	4.8% (3.1% non critically ill; 7.6% critically ill)
Piazza <i>et al.</i> [23]	2020.03–2020.04	1114 (170 critically ill)	4.6% (27% in critically ill patients)	5.9% (35.3% in critically ill patients)	0.7% (1.8% in critically ill patients)	3.5% (22.9% in critically ill patients)	-	-
Lodigiani <i>et al.</i> [20]	2020.02–2020.04	362 (48 critically ill)	4.4% (8.3% in critically ill patients)	7.7% (16.7% in critically ill patients)	2.8% (4.2% in critically ill patients)	1.7% (4.2% in critically ill patients)	-	-
Klok <i>et al.</i> [19]	2020.03–2020.04	184 critically ill	27%	-	13.6%	-	3.7%	-
Middeldorp <i>et al.</i> [15]	2020.03–2020.04	198 (75 critically ill)	20% (47% in critically ill patients)	-	6.6% (15% in critically ill patients)	13% (32% in critically ill patients)	-	-
Poissy <i>et al.</i> [14]	2020.02–2020.03	107 critically ill	-	-	20.6%	4.7%	-	-
Bompard <i>et al.</i> [13]	2020.03–2020.04	135 (24 critically ill)	-	-	24% (50% in critically ill patients)	-	-	-
Cui <i>et al.</i> [21]	2020.01–2020.03	81 critically ill	25%	-	-	-	-	-
Demelo Rodriguez <i>et al.</i> [24]	2020.04	156 critically ill	-	-	-	14.7%	-	-
Llitjos <i>et al.</i> [18]	2020.03–2020.04	26 critically ill (18 on therapeutic anticoagulation)	69% (56% on therapeutic anticoagulation)	-	23% (33% on therapeutic anticoagulation)	-	-	-
Inciardi <i>et al.</i> [17]	2020.03	99 (43 patients with cardiac history)	12% (17% in cardiac patients)	-	-	-	3% (6% in cardiac patients)	-

Table 2. Reviews and Meta-Analysis describing epidemiology of thrombotic risk in COVID-19 patients.

References	Number of studies	Venous thromboembolism	Pulmonary embolism	Deep vein thrombosis
Sakr <i>et al.</i> [12]	17 studies (5884 patients)	-	2.6–8.9%	-
Lu <i>et al.</i> [25]	23 studies (2747 patients)	21%	15%	27%
Zhang <i>et al.</i> [26]	17 studies (1913 patients)	25%	19%	7%
Desai <i>et al.</i> [27]	9 studies (3066 patients)	-	15.8%	-
Porfidia <i>et al.</i> [28]	30 studies (3487 patients)	26%	12%	14%
Di Minno <i>et al.</i> [29]	20 studies (1988 patients)	31.3%	18.9%	19.8%

Table 3. Percentage of anticoagulation therapy reported in reviews analyzed.

References	Percentage of patients on anticoagulation therapy
Sakr <i>et al.</i> [12]	-
Lu <i>et al.</i> [25]	33.8%
Zhang <i>et al.</i> [26]	-
Desai <i>et al.</i> [27]	-
	73.2% prophylactic doses
Porfidia <i>et al.</i> [28]	81% intermediate doses
	16.8% therapeutic doses
Di Minno <i>et al.</i> [29]	78.4%

to be independent predictive factors of the disease severity in COVID-19 patients [30]. Inflammatory response leads to severe complications and contribute to COVID-19-associated hypercoagulability. Coagulation disorders frequently occur in COVID-19 patients. In the first American autopsy series of COVID-19-related deaths, the main pulmonary findings included thrombosis and microangiopathy in the small pulmonary vessels and capillaries, whereas cardiac involvement did not show lymphocytic myocarditis but only individual cell necrosis [31].

During hospitalization time, in fact, elevated fibrinogen, ferritin, prothrombin time (PT) and D-dimer levels (a fibrin catabolite, released when plasmin cleaves cross-linked fibrin) were noted [32], outlining an hypercoagulable state. Moreover, plasma D-dimer measurement is considered as a direct prognostic marker in SARS-CoV-2 disease and appears to be higher in patients with severe SARS-CoV-2 compared to patients without severe disease [33].

Most of the available D-dimers assays have also been developed to have the best reproducibility around the threshold value used for excluding deep vein thrombosis and/or pulmonary embolism, which is usually around 500 ng/mL. Therefore, their performance at higher values, such as those proposed for initiating high dose anticoagulation in COVID-19 patients (i.e., over 3000 ng/mL), is probably suboptimal and would need to be assessed in order to avoid the use of inaccurate results in these patients [34].

Methods used to assess thrombin generation and fibrinolysis have also significant limitations that should be considered [34].

Interestingly, novel surveys emphasize the emerging role of endothelial cells damage in COVID-19 patients. Guervilly and coworkers first provide *in vivo* evidence of endothelial injury. Among ninety-nine patients with COVID-19, they measure circulating endothelial cells (CEC) detached from damaged vessels. Noteworthy, higher levels of CEC positively correlated with admission in ICU, length of hospitalization, disease severity and inflammatory cytokines whereas they inversely correlated with platelet and lymphocyte counts [35]. Interestingly, CEC can be considered non-invasive biomarkers of disease severity in COVID-19 and get the chance for therapies targeting the endothelium.

The pathogenesis of the disease is the following: SARS-

Table 4. Percentage of anticoagulation therapy reported in studies analyzed.

References	Use of anticoagulation therapy
	None (mechanical thromboprophylaxis):
	3.5% in patients not critically ill
	1.4% in critically ill
	Standard prophylactic anticoagulation:
Al-Samkari <i>et al.</i> [22]	89.9 % in not critically ill
	86.1% in critically ill
	Intermediate or full-dose anticoagulation:
	6.6% in not critically ill
	12.5% in critically ill
	Thromboprophylaxis:
	84.8% in not critically ill
	89.4% in critically ill
Piazza <i>et al.</i> [23]	Therapeutic anticoagulation:
	11.5% in not critically ill
	25.3% in critically ill

CoV-2 can directly invade the vascular endothelium expressing ACE-2; infected cells undergo pyroptosis contributing to the release of danger-associated molecular patterns (DAMPs) and initiate the release of cytokines and chemokines. The activated endothelium upregulates the expression of Von Willebrand factor (VWH) and adhesion molecules including intercellular adhesion molecule (ICAM)-1, $\alpha v\beta 3$, P-selectin and E-selectin, involving platelets and leukocytes and complement activation [35]. Neutrophils release neutrophil extracellular traps (NETs), a part of DNA with neutrophils granule proteins, such as myeloperoxidase (MPO), cathepsin G, and neutrophil elastase, causing direct activation of the contact pathway [36, 37]. NETs, in fact, is the primary defensive mechanism leading to invasion of pathogens. They are also involved in the pathogenesis of arterial and venous thrombosis in addition to sepsis, disseminated intravascular coagulation, systemic lupus erythematosus, preeclampsia and vasculitis [38]. In a picture of thrombosis, the release of the highly negatively charged NETs can trap erythrocytes and activate platelets [39]. Moreover, NETs are the trigger of coagulation through inhibition of tissue factor pathway, increasing endothelial and monocyte tissue factor and degrading the anticoagulant protein. However, histones activate platelets throughout Toll-like receptors 2 and 4 and facilitate fibrin formation, while the contact activation system, via FXII activation, is started off by negatively charged DNA and activated platelets by the release of inorganic polyphosphate (PolyP) from platelet dense granules [38, 39]. The activation of factor XII has important proinflammatory features as its ability to liberate the generation of bradykinin, to up-regulate neutrophil function, to generate monocyte-derived proinflammatory chemokines (IL-1 β , CXCL4, CXCL7, and CCL5), growth factor, and cytokines (IL-1, IL-8, RANTES, IL-6, and MCP-1) [40, 41], but, above all, it initiates coagulation too. These mechanisms have the consequence in excess thrombin generation, which improve the activation of

platelets, leukocytes, and endothelium by protease-activated receptors (PARs) and result in the formation of a fibrin clot [36, 42]. The role of complement in thrombosis and inflammation in COVID-19 was investigated by Skendros *et al.* providing the proof that complement activation potentiates the platelet/NETs/tissue factor/thrombin axis in SARS-CoV-2 infection. The above findings lay the groundwork for a wider use of the C3-targeted therapeutic AMY-101 (now available as compassionate use and objective of an ongoing trial assessing its impact in severe COVID-19 patients) in critically ill patients [43].

Nougier *et al.* [44] assessed the fibrinolytic activity and thrombin generation in 78 COVID-19 patients and observed a high thrombin generation capacity which remained within normal values despite anticoagulation therapy and a hypofibrinolysis state associated with increased PAI-1 levels.

Critical patients could have a slightly longer PT than patients with more favorable prognosis. APTT is less prolonged than PT, probably due to an increased concentration of factor VIII, which is an acute phase reactant [45, 46].

Therefore we can summarize the prothrombotic effect of SARS-CoV-2 infection in:

- (1) Facilitation of extensive deposition of the terminal complement components, membrane attack complex C5b-9 and C4d, in addition to the mannose-binding lectin-associated serine protease (MASP-2) within the microvasculature resulting in a release of endothelial cytokines, such as IL-1, IL-8, RANTES, IL-6, and MCP-1, and in an up regulation of the expression of endothelial adhesion molecules, such as VWF and P-selectin [47].

- (2) Excessive formation NETs by neutrophils' release [36, 48].

- (3) Directly interaction with platelets' TLR-7 and the fragment crystallisable gamma receptor IIa (FcγRIIA) [42] which can translate into:

- Thromboinflammatory response throughout thrombin that activates endothelial cells by endothelial PAR-1, leading to up regulation of platelet-activating factor (PAF), IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1 in addition to the adhesion molecules E-selectin, P-selectin, and intercellular adhesion molecule (ICAM)-1 [36].

- Increasing of B-cell immunoglobulin (Ig) G1, IgG2, and IgG production [49] with potentially development of anti-phospholipid antibodies, such as anti-β2 glycoprotein IgG antibodies [50].

- Facilitating the recruitment of T lymphocytes to sites of vascular injury or infection [51].

All of the above explains that:

- (1) VTE in patients with SARS-CoV-2 infection appears highly expanded. Indeed, the cumulative incidence of VTE is reported to be between 25% and 49% of patients with severe SARS-CoV-2 infection with PE being the most common thrombotic complication [23].

- (2) Arterial thromboembolism is increased [36].

- (3) Acute myocardial injury and myocarditis usually com-

plicates the clinical course of severe SARS-CoV-2 infection and it is linked in up to 20% of hospital presentations with an adverse impact on mortality [52, 53].

- (4) Increased microvascular thrombosis, especially pulmonary microvascular thrombosis has been previously described in autopsies as a complication of severe acute respiratory distress syndrome (ARDS) [33, 54].

- (5) Thrombocytopenia is present in severe cases, caused by direct infection of bone marrow cells with inhibition of platelet synthesis, platelet destruction by the immune system and aggregation in the lungs, resulting in blood clot and platelet consumption [55].

In Fig. 1 coagulation cascade is illustrated and in Fig. 2 the cytokine storm, involved in thrombus generation, is resumed.

2.3 Therapeutic anticoagulation

As described before, COVID-19 is a viral infection that, resulting in cytokine storm and systemic inflammatory response, can determine a thrombotic risk and coagulopathy (Table 5). Different reports in the literature of elevated risk of thrombosis during COVID-19 infection have determined the empiric use of anticoagulant drugs for hospitalized patients [56].

A study of the Hubei province in China demonstrates that, without anticoagulation, 25% of COVID-19 patients developed lower extremity DVT as assessed by doppler ultrasound of lower extremities [23].

We must consider that acutely ill patients, with or without COVID-19, poses several risk factor for thromboembolism. Moreover, there can be additional risk factors for VTE such as age, cancer, obesity, pregnancy, diabetes, congestive heart failure, and history of prior VTE.

In some early studies conducted in acutely ill medical patients, a prophylaxis anticoagulation reduced the incidence of venous thromboembolism up to 60%, without increasing major bleeding risk [57].

An Italian study described thromboembolic events in 7.7% of patients admitted with COVID-19, estimating a cumulative rate of 21% [21].

The study by Klok *et al.* [21] described 25 symptomatic VTE events in 184 adult patients affected by COVID-19, all of whom was receiving VTE prophylaxis. VTE was reported in 27% of patients, arterial thrombotic events in 3.7%, PE was the most frequent thrombotic complication in 81%. Thus, this study demonstrates that critically ill adults with COVID-19 on standard pharmacologic VTE prophylaxis may develop a thromboembolic event.

Another French study conducted among 150 patients with COVID-19 and ARDS receiving prophylactic or empiric treatment dose anticoagulation described that 16.7% of patients developed pulmonary embolism [58].

For acute COVID-19 patients over age 50 or with medical problems an early treatment regimen with anti-thrombotic agents should be started the first day of illness [59].

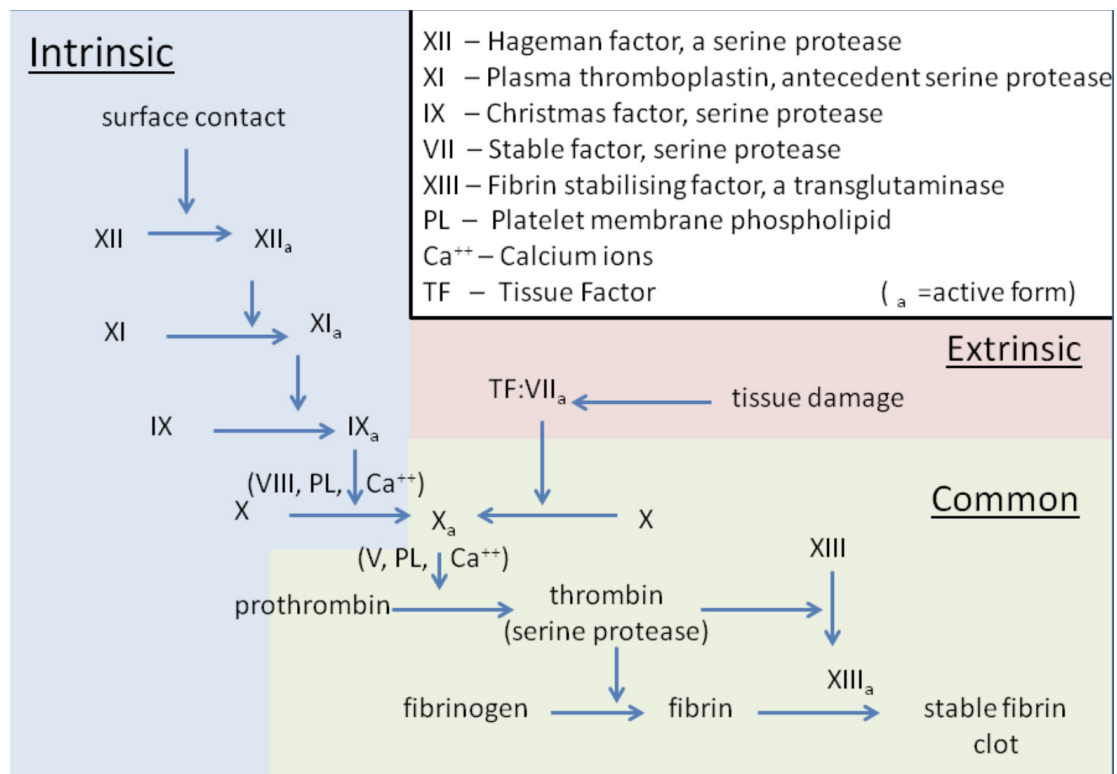


Fig. 1. Coagulation cascade. This figure represents the coagulation cascade: in the intrinsic way the surface contact activates the XII factor, which transforms the XI factor to the X factor; in the extrinsic way a tissue damage activates the VII factor which activates the X factor which transforms the prothrombin into thrombin and the fibrinogen into fibrin and creates a stable fibrin clot.

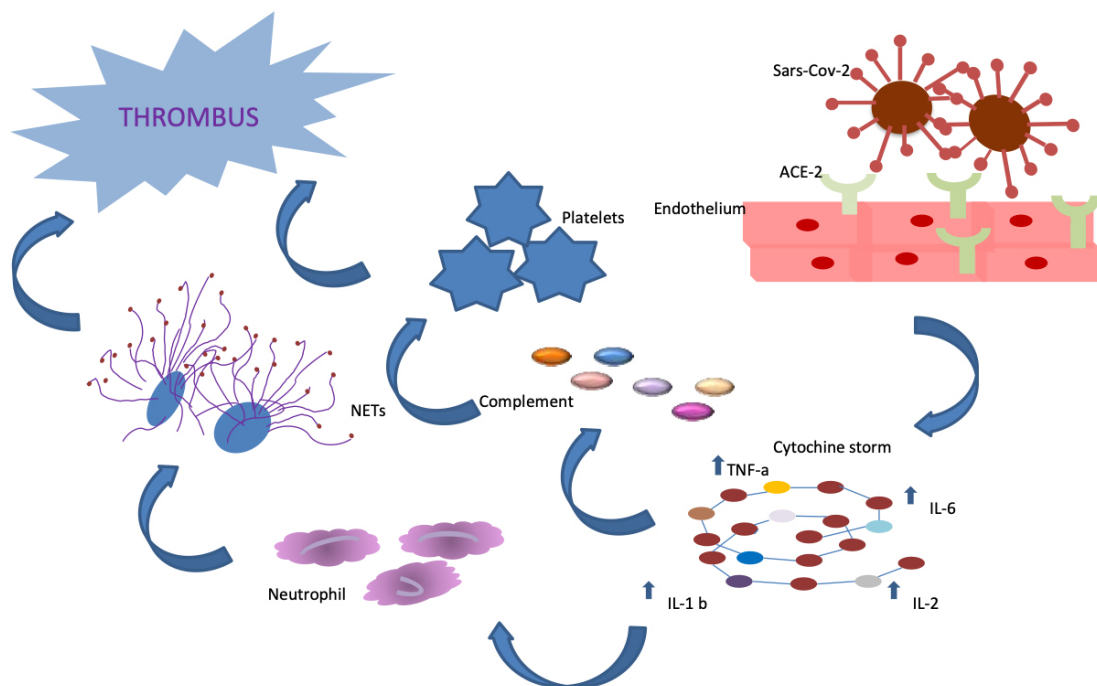


Fig. 2. Cytokine storm involved in thrombus generation. This figure represents the cytokine storm involved in thrombus generation: the SARS-CoV 2, through ACE-2 receptor, induces a cytokine storm, releasing TNF-α, IL-6, IL-2, IL-1b. These factors induce an activation of complement and neutrophils, causing the platelets aggregation and the thrombus generation.

Table 5. COVID-19 associated Coagulopathy (CAC).

COVID-19 associated Coagulopathy (CAC)
Coagulopathy is characterized by elevated levels of fibrinogen, D-dimer and low variations in the value of PT, aPTT and platelets count
Levels of IL-6 is correlated with levels of fibrinogen
Coagulopathy seems to be correlated to the severity of infection
Elevated levels of D-dimer at the time of hospitalization is associated to an increased mortality
The increasing of D-dimer levels precedes multi-organ failure and DIC
Bleeding events are not common

Thus, in critically ill patients with COVID-19 an intensified prophylaxis regimen may be safer and there is no evidence for use of biomarkers such as D-dimer or fibrinogen to guide the intensity and duration of anticoagulant therapy [60].

The European Society of Cardiology described an anticoagulation algorithm: for high thrombotic risk patients, as those with dyspnea, respiratory rate >24 , oxygen saturation $<90\%$, elevated CRP, high D-dimer levels and elevated fibrinogen levels anticoagulation strategies should be considered [61].

A recent study by Ruocco *et al.* [62] conducted among Italian patients hospitalized for COVID-19 infection, showed that CHA(2)DS(2)-VASc risk score for thromboembolic events can be used for risk stratification for complications and death. In particular, patients with higher CHA(2)DS(2)-VASc scores had a higher rates of mechanical ventilation or death and should be considered for anticoagulant treatment.

Tang *et al.* [63] described 449 patients with severe COVID-19 infection and reported a reduction in mortality with anticoagulant therapy in patients with high D-dimer and/or high sepsis-induced coagulopathy (SIC) score. Another study in New York conducted among 2773 COVID-19 patients reported an improvement of median survival with anticoagulant therapy, especially in mechanically ventilated patients [64].

On 11 April 2020, the Swiss Society of Hematology published recommendations that all in-hospital COVID-19 patients should receive thromboprophylaxis, which echoed the International Society of Thrombosis and Haemostasis (ISTH) guidelines [65]. The ISTH proposed a new method for identify an earlier phase of sepsis-associated disseminated intravascular coagulation (DIC), called SIC. The factors included in this ISTH scoring system are: platelets count, INR, SOFA score.

During hospitalization it is suggested to use low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for the treatment of confirmed or suspected VTE, in order to avoid laboratory monitoring, minimize nursing and phlebotomy exposure.

The WHO interim guidance statement recommends prophylactic daily LMWH or twice daily UFH [66]. The use of UFH is recommended in patients with creatinine clearance <15 mL/min. A gradual decline of D-dimer levels suggests the response to therapy [23]. An increased plasma D-dimer con-

centration during thromboprophylaxis should guide in the administration of higher doses of anticoagulants.

Hermans *et al.* [67] suggested that it would be appropriate to shift patients on vitamin K antagonist (VKA) to a direct-acting oral anticoagulant (DOAC) to reduce the number of needed laboratory testing. This cannot be applied to patients with mechanical valve or anti phospholipid syndrome.

Furthermore, it is important to pay attention to DOACs interactions with antiretroviral drugs and to patients unstable kidney function.

Consideration for risk of VTE in pregnant patients with COVID-19 deserves a great attention. The risk of VTE during pregnancy and postpartum period is increased [68]. Although limited data are available, pregnant women with COVID-19 infection have an high risk of VTE.

There is no evidence for extended VTE prophylaxis in COVID-19 patients after hospital discharge: Barnes *et al.* [56] suggested that extended VTE prophylaxis is not necessary for all patients with COVID-19 being discharged from hospital. However, a multidisciplinary discussion may be necessary at discharge for patients with multiple VTE risk factors. After hospital discharge from an acute illness, extended prophylaxis with LMWH or DOAC can reduce the risk of VTE, at the cost of increasing bleeding events [69–71].

Spyropoulos *et al.* applied the modified IMPROVE VTE score to the MAGELLAN subpopulation to investigate whether an elevated D-dimer level could identify a high VTE risk subgroup. This study showed that the modified IMPROVE VTE score with an elevated D-dimer identifies a threshold higher VTE risk subpopulation where benefits are achieved from anticoagulation with rivaroxaban [72].

It is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic risk. It has been reported that patients with high bleeding risk can have also an high ischemic risk [73].

The role of thromboprophylaxis for patients in quarantine with mild COVID-19 but with important comorbidities or for patients is uncertain.

Cohen *et al.* demonstrated that in acutely ill medical patients, rivaroxaban was non-inferior to enoxaparin for standard-duration thromboprophylaxis. In an extended-duration thromboprophylaxis rivaroxaban reduced the risk of venous thromboembolism, but it was associated with an increased risk of bleeding [74].

APEX trial found that among acutely ill medical patients with high D-dimer levels, there was no significant difference between extended-duration betrixaban and a standard regimen of enoxaparin in asymptomatic proximal DVT and symptomatic VTE [74]. Thus, if post discharge prophylaxis seems to be reasonable, approved agents as betrixaban or rivaroxaban or enoxaparin can be used. The duration of anticoagulant therapy is the one indicated in the clinical trials (enoxaparin 40 mg OD for 6–14 days; rivaroxaban 10 mg OD for 31–39 days; betrixaban 160 mg OD for 35–42 days).

In the clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patient with COVID-19, Spyropoulos *et al.* [75] suggested that, for those who are at low bleeding risk and with VTE risk (advanced age, cancer, prior history of VTE, thrombophilia, immobility, D-dimer >2 times ULN) and IMPROVE VTE score >4, an extended thromboprophylaxis with LMWH or DOACs for at least 2 weeks up to 6 weeks post-hospital discharge can be reasonable.

Relatively to the use of thrombolytic therapy, the case of some patients with COVID-19 and ARDS treated with Alteplase 50 mg has been reported and has demonstrated an improvement in oxygenation [76]. However Chatterjee *et al.* [77] demonstrated that systemic administration of thrombolytic therapy increased major bleeding and intracranial hemorrhage rates.

Recent studies have investigated the effect of inhibition of complement, which is a key player of protective immunity against pathogens, but its excessive or deregulated activation may result in collateral tissue injury [78]. So far, complement inhibitors are currently only used in rare human diseases.

In conclusion, for not hospitalized patients affected by obesity, previous VTE, tumors, with asymptomatic COVID-19, the use of prophylactic dose of LMWH must be considered, using validate risk scores for hospitalized patients (Padua Score >4). The most recent consensus documents underline the recommendation for a prophylactic dose of LMWH in all hospitalized patients with COVID-19, with the exception of the presence of severe low platelets count (inferior to 25.000/4 μ L) or active bleeding.

3. Conclusions

Data reported in our review are derived from prospective, multinational and multicenter studies and could help clarify similarities and differences in the presentation and outcomes of COVID-19 disease, especially in the presence of thromboembolic disease, also helping to identify strategies for better management in these patients.

We have provided a brief guide to thrombotic disease and antithrombotic therapy during the COVID-19 pandemic, and it could support clinical decision making.

Important considerations for the preventive and therapeutic use of antithrombotic agents must be kept in mind to mitigate thrombotic and haemorrhagic events in these high-risk patients.

All doctors and investigators should work together to create a diagnostic and therapeutic process aimed at early identification of patients with VTE high risk.

This would allow to avoid fatal complications causing a drastic clinical worsening of patients with COVID-19.

Author contributions

EV, CML, MM designed the research study. EP, GP performed the research. AC, LA provided help and advice on the table and figures; GC, FA, NB, EC analyzed the literature data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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