


# Unpuzzling COVID-19 Prothrombotic State: Are Preexisting Thrombophilic Risk Profiles Responsible for Heterogenous Thrombotic Events?

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## Keywords

COVID-19, thrombophilia, thrombosis, gene polymorphisms

The purpose of this Editorial is 2-fold: to raise the alarm about certain thrombophilic patterns that would predispose to thrombosis in the context of COVID-19 infection, and to explore and propose new ways of research in this regard, with the obvious aim of optimizing treatment and limiting thrombotic complications in the context of SARS-CoV-2 infection.

Our assumption is advocated by a theory validated in a reasonably related condition such as sepsis, according to which thrombophilic mutations in patients with sepsis can affect their clinical response.<sup>1</sup> The similarity between these 2 conditions is sustained by autopsy studies findings, documented immune pathogenesis, and microcirculation dysfunctions, the ability of SARS-CoV-2 to disseminate the infection in other organs and by the fact that many critically ill COVID-19 patients developed clinical symptoms of shock following a process called “viral sepsis.”<sup>2</sup>

A recent paper dealing with SARS-CoV-2 and “viral sepsis” raised alarm signals that despite the huge percentage of 71,4% of non-survivors of COVID-19 who matched the grade of overt disseminated intravascular coagulation, the concrete mechanisms of vascular thrombosis are not yet known.<sup>2</sup> Far fewer studies have addressed the matter of identifying non-viral, predisposing factors (genetic, environmental) for thrombotic events in COVID-19, despite the crucial impact this could have on risk stratification, more precise therapies, and less adverse events.

The issue of thrombosis (both arterial and venous) in COVID-19 is intensely debated due to its deleterious and often fatal consequences. The International Society on Thrombosis and Haemostasis guidance issued at the end of May 2020 recommended that all hospitalized patients with COVID-19, including non-critically ill, should be considered for thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin unless they have contraindications,<sup>3</sup> although no level of evidence was stated. Although thromboprophylaxis for any

hospitalized COVID-19 patient is generally accepted, there is an ongoing debate about the exact dosage to be administered.<sup>4,5</sup> Furthermore, the World Health Organization advises for a pharmacological prophylaxis of thromboembolism in hospitalized COVID-19 patients but warns on carefully considering the significant side-effects and drug-drug interactions that may affect COVID-19 symptomatology.<sup>6</sup>

Especially among critically ill patients or patients developing acute respiratory distress syndrome (ARDS) shortly after COVID-19 onset, the need for anticoagulation is justified by the mechanism and the consequences of the alveolar injuries that occur during the viral attack when characteristically neutrophil-platelet aggregates are formed. Aside from increasing the pulmonary vascular permeability to proteins, these aggregates emerge from the endothelial cell activation. This process increases the vascular permeability furthermore in a positive-feedback loop.<sup>7</sup> The pathophysiology of the thrombotic events during viral aggression begins with the increased expression of the tissue factor (TF), induced by proinflammatory cytokines in the alveolar macrophages and alveolar epithelial cells<sup>8,9</sup> which is a membrane protein of the fibroblasts present in the lungs that become exposed to the bloodstream during the endothelial

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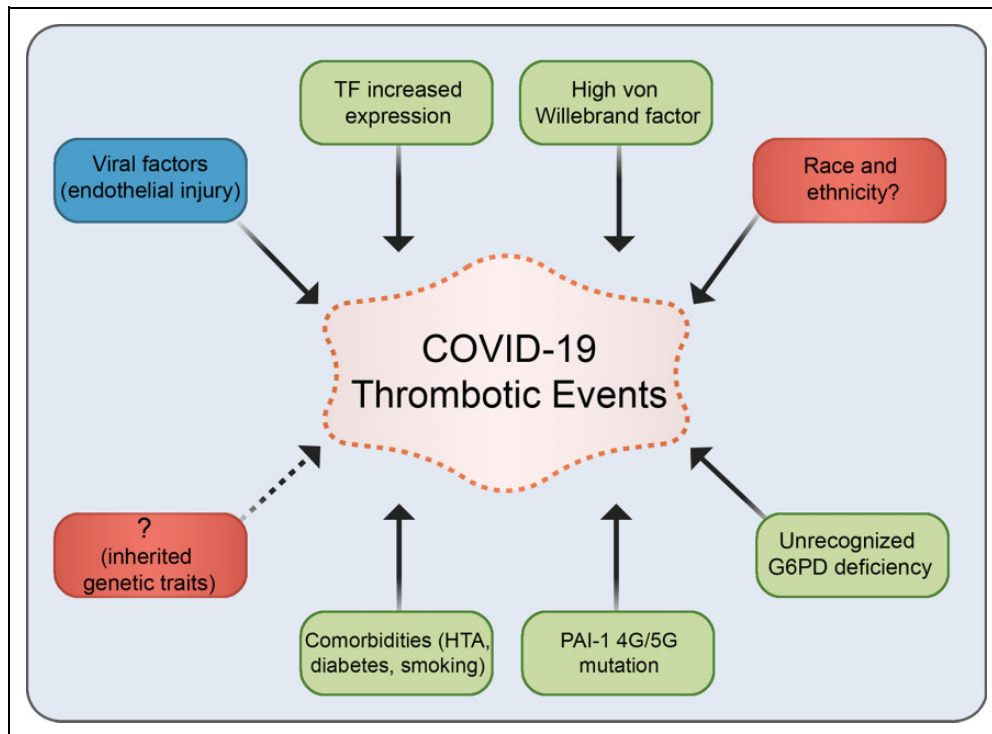
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**Figure 1.** Various etiologies involved in thrombotic complications during SARS-CoV-2 infection.

damage.<sup>10</sup> TF binds to the circulating Factor VIIa's serine protease, thus initiating the coagulation cascade.<sup>11</sup>

It seems that a documented procoagulant state characterizes ARDS due to the immunothrombosis mechanisms and the apparent links between inflammation and coagulation.<sup>10</sup> However, there are particularities regarding COVID-19 ARDS that require higher anticoagulation targets due to the patients developing life-threatening thrombotic complications despite anticoagulation treatment.<sup>12</sup>

These findings suggest that either SARS-COV-2 acts with a particular form of aggression that sustains the thrombotic state or COVID-19 patients developing severe ARDS have a typical preexisting bio-molecular particularity. A third variant consists of combinations of the previous 2 in different proportions.

In a recent study targeting COVID-19 autopsies, 58% of patients who died with COVID-19 had deep venous thrombosis—a condition unknown before their death. Pulmonary embolism was the cause of death for 30% of patients.<sup>13</sup> More alike, studies confirmed that most COVID-19 deaths were associated with pulmonary embolism despite the use of prophylactic anticoagulation.<sup>14,15</sup>

Although anticoagulation proved its beneficial effects on a subset of critically ill patients, the strategy of thromboprophylaxis for all hospitalized COVID-19 cases might expose some patients to unnecessary anticoagulation and its inherent side effects.<sup>16,17</sup> A study on 81 severe COVID-19 patients from Wuhan, with no preventive anticoagulant administration, found an incidence of venous thromboembolism of 25%,<sup>18</sup> leaving a remaining of 75% of patients with no thrombotic events and, subsequently, no apparent need for anticoagulation therapy. However, the number of thrombotic events with or without anticoagulation is

inconsistent between studies, probably due to important data heterogeneity regarding study endpoints and disease severity.

Numerous studies have suggested the intrinsic potential of SARS-CoV-2 infection to generate blood clots, mainly causing endothelial damage. Indeed, SARS-CoV-2 was discovered inside endothelial cells,<sup>19</sup> probably due to their broad expression of angiotensin-converting enzyme 2 (ACE2) receptor.

A major question remains to be addressed, though: **why only a percentage of severe COVID-19 patients develop thrombosis, despite the disease's proven hypercoagulable state?** We strongly believe that unexplored preexisting individual thrombophilic profiles predisposing patients to thrombotic complications during SARS-CoV-2 infection represent notable elements that must be taken into account (see Figure 1).

Thereby, recent evidence pointed that higher levels of von Willebrand coagulation factor (vWF) might be tightly linked to COVID-19 severity,<sup>20</sup> while high vWF levels were shown to increase thrombosis risk.<sup>21</sup> Given racial and ethnic genetic differences, Chinese patients showed a 3–4-fold lower thrombotic risk in SARS-CoV-2 infection than Caucasians, and, conversely, African-Americans showed significantly higher risk compared to Caucasians.<sup>22</sup> Additionally, unrecognized glucose-6-phosphate dehydrogenase genetic deficiency may impact venous thrombosis risk in COVID-19 patients.<sup>23</sup> Ultimately, there was only 1 attempt to evaluate the impact of a prothrombotic inherited mutation, namely plasminogen activator inhibitor (PAI)-1 4G/5G, in coronavirus infections. This endeavor revealed a relationship between PAI-1 4G/5G gene polymorphism and post-SARS osteonecrosis mediated by the mechanisms of intravascular coagulation-induced thrombosis

**Table 1.** Ongoing Randomized Controlled Trials Assessing the Usefulness and Safety of Anticoagulant Therapy in COVID-19 Hospitalized Patients.

	Randomized controlled trials	Trial number
<b>High vs. low/standard doses of heparin</b>	Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care	NCT04362085
	Full Dose Heparin Vs. Prophylactic Or Intermediate Dose Heparin in High-Risk COVID-19 Patients	NCT04401293
	Anticoagulation in Critically Ill Patients With COVID-19 (The IMPACT Trial) (IMPACT)	NCT04406389
	Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes in Hospitalized Patients With COVID-19	NCT04377997
	Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-COVID 19)	NCT04366960
<b>Heparin + antiplatelets vs. heparin alone</b>	High Versus Low LMWH Dosages in Hospitalized Patients With Severe COVID-19 Pneumonia and Coagulopathy (COVID-19 HD)	NCT04408235
	Prevention of Arteriovenous Thrombotic Events in Critically Ill COVID-19 Patients Trial (COVID-PACT)	NCT04409834
	Prasugrel in Severe COVID-19 Pneumonia (PARTISAN)	NCT04445623

and resulting fibrin thrombi in the area of osteonecrosis.<sup>24</sup> In support of our assumptions, PAI-1, vWF, and factor VIII were revealed to be increased in all 4 studied patients with severe and deleterious COVID-19 associated pneumonia.<sup>25</sup>

All these findings put forward that patients' underlining genetic variations might be responsible for different thrombotic events risks in the novel coronavirus disease. To objectively assess this hypothesis's factuality, we advocate a thorough study on possible preexisting thrombophilic genotypes in SARS-CoV-2 infected patients, considering that no study has yet been conducted. These associated factors are also linked to a more severe COVID-19 disease course and have been cited as independent risk factors for thrombosis. The above correlations require that well-designed studies be conducted to avoid confounding for a more accurate assessment of thrombosis risk levels.

Few papers suggested a higher risk of thrombosis in COVID-19 patients with a history of cardiovascular diseases (pulmonary thromboembolism, deep vein thrombosis)<sup>26</sup> or patients with risk factors for endothelial damage (high blood pressure, male sex, smoking, diabetes).<sup>27</sup> In particular, COVID-19 appeared to be an independent stroke predictor.<sup>28</sup> An increase in stroke incidence has also been reported in young patients with COVID-19, without essential risk factors.<sup>29</sup> These could be important elements in favor of the fact that a genetic predisposition could contribute to increase the thrombotic and thromboembolic risk.

Remarkably, several studies reported severe thrombotic complications in patients infected by SARS-CoV-2 occurring despite the use of antiplatelet or anticoagulant therapy and also, only patients with markedly elevated D-dimer were found to benefit from anticoagulant treatment.<sup>30</sup> The latter findings emphasize, even more, the inappropriateness of large-scale use of thromboprophylaxis and the existence of hidden mechanisms and unknown individual factors that might substantially contribute to coagulation unpredictability in COVID-19.

Several randomized controlled trials have been designed and are undergoing the usefulness and safety of anticoagulant

therapy in patients hospitalized for COVID-19 disease, as shown in Table 1. [**High vs. low/standard doses of heparin:** Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care, NCT04362085; Full Dose Heparin Vs. Prophylactic Or Intermediate Dose Heparin in High-Risk COVID-19 Patients, NCT04401293; Anticoagulation in Critically Ill Patients With COVID-19 (The IMPACT Trial) (IMPACT). NCT04406389; Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes in Hospitalized Patients With COVID-19, NCT04377997; Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-COVID 19), NCT04366960; High Versus Low LMWH Dosages in Hospitalized Patients With Severe COVID-19 Pneumonia and Coagulopathy (COVID-19 HD), NCT04408235. **Heparin + antiplatelets vs. heparin alone:** Prevention of Arteriovenous Thrombotic Events in Critically Ill COVID-19 Patients Trial (COVID-PACT), NCT04409834; Prasugrel in Severe COVID-19 Pneumonia (PARTISAN), NCT04445623]. However, none of these trials has considered the possibility that there may be a different genetic predisposition to the development of thrombotic phenomena in patients to be enrolled.

In the spirit of academical correctness we are bound to emphasize the fact that, at this point of the COVID-19 understanding, considering the evolution of the pandemic and the considerable heterogeneity of clinical forms (from asymptomatic patients to severely-ill and rapid degradations patients), there are still unclaimed issues and unanswered questions regarding the in-depth pathophysiology of the viral attack and its consequences. Hence the lack of a consensus on an efficient, worldwide therapeutic approach based on procedures. The hypercoagulation state consequent to SARS-COV-2 infection seems to manifest not only as pulmonary embolism, but also as other thrombotic events such as deep vein thrombosis, myocardial infarction, or ischemic stroke,<sup>31</sup> suggesting that the most plausible explanation has to be a pattern concerning either the patients or the virus. We strongly recommend genetic studies to

explore the genetic profile of proteins involved in thrombophilia (e.g., MTHFR C677 T, MTHFR A1298C, Factor XIII V34 L, Factor V G1691A (Leiden), Factor V H1299 R (R2), Factor II prothrombin G20210A, Factor XIII V34 L,  $\beta$ -fibrinogen-455 G-A, Plasminogen activator inhibitor-1 4G/5G) in patients who have had COVID-19 and thrombotic events. The more data is gathered on the matter, and the more this pattern will lead to a unitary approach not only in successfully treating COVID-19 related ARDS but also in preventing COVID-19 deaths or treatment-related complications.

### Author Contribution

Alexandru Burlacu and Simonetta Genovesi Both Authors contributed equally.


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