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– REVIEW –

Hypercoagulability and COVID-19 Infection

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Abstract

COVID-19 is a relatively recent and clinically heterogeneous infection, with a broad spectrum of complications, including significant hematologic involvement. Since 2020, COVID-19-associated coagulopathy has been investigated both biologically and clinically through single-center and multicenter studies—initially in China and subsequently across all continents. These investigations have consistently reported elevated D-dimer levels, disseminated intravascular coagulation (DIC), impaired fibrinolysis, disruptions in coagulation factors, endotheliopathy linked to thrombopathy, antiphospholipid syndrome, and complex alterations involving genetic dysfunction and neutrophil extracellular traps (NETs).

Research has encompassed patients in the acute phase, as well as those experiencing long COVID or post-acute sequelae, with follow-up extending beyond one year. Notably, a prothrombotic state has been observed to persist even in the post-acute phase.

More recent investigations have examined vaccine-related effects, particularly those associated with adenoviral vector-based vaccines such as ChAdOx1 and Ad26.COV2.S, where thromboembolic adverse events have been documented.

In conclusion, the pathogenesis of COVID-19-related coagulopathy is multifactorial, and the elevated risk of thromboembolic events may persist for up to one year following the acute phase. This underscores the critical need for continuous clinical and laboratory monitoring of affected patients.

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Introduction

The emergence of the SARS-CoV-2 virus, responsible for COVID-19, caught both Romania and the global community unprepared in 2020. On March 11, 2020, the World Health Organization officially declared the outbreak a pandemic. COVID-19 was associated with notably high morbidity and mortality rates, particularly during the initial two years of the global crisis. To date, a total of 7,095,536 confirmed deaths have been reported worldwide.[1]

Owing to the severity of illness caused by the initial circulating variants of SARS-CoV-2, the majority of patients required hospitalization, allowing for comprehensive inpatient evaluations. This context enabled the detailed assessment of hematological, biochemical, immunological, and imaging alterations associated with SARS-CoV-2 infection.

The clinical manifestations and complications of COVID-19 are highly heterogeneous and appear to vary depending on the predominant viral variant. Respiratory and

gastrointestinal symptoms are most frequently reported; however, cardiac, hepatic, neurological, renal, immunological, and hematological complications have also been widely documented.

The diverse spectrum of acute and post-acute manifestations observed in COVID-19 is thought to arise from a dysregulated immune response, involving elevated levels of proinflammatory mediators, endothelial dysfunction, coagulation abnormalities, and organ infiltration by inflammatory cells. The determinants of disease severity and the mechanisms underlying its variability remain incompletely understood.[2]

The objective of this literature review is to provide an analytical perspective on hematological complications related to hemostasis. From the broad range of observed alterations, this study focuses on the presentation of thromboembolic complications occurring during acute infection, as well as in post-acute and post-vaccination phases.

Material and methods

This review was conducted by systematically analyzing the scientific literature published between January 2020 and May 2025, focusing on thromboembolic complications associated with SARS-CoV-2 infection. The search strategy included databases such as PubMed, Scopus, Web of Science, and Google Scholar. The following keywords and MeSH terms were used in various combinations: “COVID-19”, “SARS-CoV-2”, “coagulopathy”, “thromboembolism”, “hemostasis”, “D-dimer”, “vaccine-induced thrombotic events”, “long COVID” and “post-acute COVID-19 syndrome”.

Results and discussions

To date, numerous studies have documented the hematological complications associated with COVID-19 across different phases of the pandemic, starting in 2020. While some investigations have focused on direct hematological alterations, others have sought to identify hematological markers predictive of disease progression. These studies have consistently reported abnormalities in complete blood count parameters—particularly leukocyte differentials—as well as disruptions in primary and secondary hemostasis. COVID-19-associated coagulopathy has been characterized as an immunothrombotic state, predominantly favoring a prothrombotic profile rather than hemorrhagic manifestations.

Although SARS-CoV-2 primarily transmits via the respiratory tract, viral replication and immune modulation also occur within tissues and the bloodstream, facilitated by receptor-mediated endocytosis of virions into host cells. This infection elicits unique immunological responses, reflected in altered leukocyte and erythrocyte biomarkers when compared to typical viral infections.[3]

The earliest hematological studies published in 2020 included evaluations of coagulation disturbances. These initial investigations predominantly involved patients in the acute disease phase, generally those with severe illness.[4] Notably, elevated blood D-dimer concentrations (≥0.5 mg/L) were among the first observations, with significantly higher levels detected in severe cases (59.6%) compared to non-severe ones (43.2%).[5] Furthermore, Wang et al demonstrated that patients requiring Intensive Care Unit (ICU) care exhibited markedly elevated D-dimer levels relative to those with less severe clinical presentations ($P < 0.001$).[6]

Coagulation abnormalities in COVID-19 patients were marked by thrombocytopenia, prolonged prothrombin time (PT), elevated fibrinogen levels, increased D-dimer and fibrin degradation products (FDP), alongside reduced antithrombin III (AT-III) activity (all $p < 0.001$), indicative of a consumptive coagulopathy driven by the inflammatory response. Although D-dimer levels significantly decreased at three months post-infection ($p = 0.001$), 66.96% of patients continued to exhibit abnormal D-dimer values at 12 months, reflecting persistent microthrombotic activity and hyperfibrinolysis. Platelet counts also remained reduced beyond 12 months, suggestive of sustained platelet consumption.[7] Hasanefendic et al reported significant positive correlations between D-dimer and inflammatory markers such as lactate dehydrogenase (LDH), fibrinogen, and ferritin, underscoring the utility of D-dimer as a key biomarker for monitoring COVID-19 patients. Furthermore, a positive correlation was noted between C-reactive protein (CRP) and activated partial thromboplastin time (aPTT).[8] In a prospective cohort study, levels of D-dimer, FDP, and fibrinogen were significantly elevated in COVID-19 patients relative to healthy controls ($p < 0.001$), with procoagulant changes characterized by increased fibrinogen and D-dimer levels. Elevated D-dimer was also associated with increased mortality risk.[4] Ennas (2022) similarly documented laboratory evidence of coagulopathy, including elevated D-dimer, mild thrombocytopenia, prolonged PT, and decreased fibrinogen levels.[9] Sonnweber et al.’s

retrospective study of 150 patients found elevated D-dimer in 25.3% of convalescent patients at a mean of 80.5 days (range 44–155) post-SARS-CoV-2 infection.[10] A meta-analysis encompassing 22 studies from China with 4,889 COVID-19 patients reported mean values for D-dimer at 0.67 µg/mL (95% CI: 0.56–0.78), platelet count at 186.34 × 10⁹/L (95% CI: 175.84–196.85), PT at 12.20 seconds (95% CI: 11.52–12.84), and fibrinogen at 4.24 g/L (95% CI: 3.40–5.15). Patients with severe disease exhibited longer PT (MD = 0.65 s; 95% CI: 0.36–0.95; $p < 0.05$), shorter aPTT (MD = –0.01 s; 95% CI: –2.58 to 2.56; $p = 0.99$), higher D-dimer levels (MD = 0.44 µg/mL; 95% CI: 0.23–0.66; $p < 0.05$), and lower platelet counts (MD = –14.47 × 10⁹/L; 95% CI: –33.0 to 4.06; $p = 0.126$) compared to those with less severe disease.[11]

COVID-19-associated coagulopathy meets the criteria for sepsis-induced coagulopathy or disseminated intravascular coagulation (DIC), according to the scoring system published by the International Society on Thrombosis and Haemostasis (ISTH) in 2009.[12]

During the cytokine storm, the host immune response to infection precipitates an excessive production of proinflammatory cytokines, which in turn activate the coagulation cascade. Subsequently, the tightly regulated mechanisms governing thrombin generation become disrupted. This dysregulation, coupled with decreased synthesis and increased consumption of anticoagulant factors, results in microvascular thrombosis, overt DIC, and multiorgan dysfunction. Elevated D-dimer levels serve as an adverse prognostic marker, and DIC is frequently observed in patients who do not survive.[13] Contrastingly, Yao et al demonstrated that the elevated D-dimer concentrations observed in COVID-19 patients do not consistently fulfill DIC criteria, as prothrombin time (PT), fibrinogen levels, and platelet counts remain within normal ranges.[14]

Several studies have explored the relationship between hemostatic abnormalities and clinical complications. Notably, patients with COVID-19-associated cardiac injury exhibit a higher propensity for coagulation disorders compared to those without cardiac involvement ($P = 0.02$). Disseminated intravascular coagulation in SARS-CoV-2-infected patients has been identified as an independent cause of mortality, distinct from the multiorgan failure commonly encountered. Furthermore, D-dimer levels progressively increased over time in non-survivors relative to survivors ($P < 0.05$).[6] Willems et al reported an elevated thrombin: antithrombin (AT) ratio in 48.3% of studied patients. Markers indicative of contact system activation were elevated in 16–30% of cases, with increased ratios of FVIIa:AT (35%) and von Willebrand factor antigen (vWF:Ag) detected in 80.8%.[15] Elevated inflammatory cytokines persisted in most patients up to three months post-infection. Supporting this, Henderson et al highlighted the contributory role of the intrinsic/contact coagulation pathway in the pathogenesis of COVID-19-associated prothrombotic states.[16]

Recent studies have detailed abnormalities in clot resistance and fibrinolysis. ROTEM lysis tests revealed elevated levels, indicating reduced fibrinolytic activity. Scanning electron microscopy (SEM) images showed temporal alterations in the structure of the fibrin network and clot morphology, while initial fibrinogen P levels indicated a hypercoagulable state. Whole blood rotational thromboelastometry (ROTEM) demonstrated significant procoagulant profiles, reflected by a faster clot activation rate (clot formation time) and increased clot firmness (maximum clot firmness, MCF).[17]

Similarly, Lee et al found that COVID-19 patients exhibit increased fibrin generation (global coagulation potential and global haemostatic potential) and altered fibrinolysis (global fibrinolytic potential), which are associated with poor prognosis and increased morbidity.[18]

Confocal microscopy studies conducted by Whyte et al revealed a denser and more highly branched fibrin network in COVID-19 patients, while Boknäs et al demonstrated impaired fibrinolysis in COVID-19 through analysis of fibrin clot structure.[19] Szekely et al demonstrated that in the majority of fatal cases, fibrin coagulation occurs within the intra-alveolar space rather than within blood vessels. They also showed that thromboembolic events may be caused by increased platelet aggregation rather than by the intravascular coagulation mechanism.[20]

Elevated levels of fibrinogen molecule components have been demonstrated in patients with severe COVID-19 at the time of diagnosis, and they remained elevated in those with severe forms who did not survive, suggesting a potential contribution to disease severity.[21]

Other significantly elevated markers in patients with acute SARS-CoV-2 infection were those associated with platelet activation. These proteins include GP1BB (platelet glycoprotein Ib beta subunit) and glycoprotein IX (GPIX), both of which have been linked to poorer outcomes in COVID-19. These proteomic changes indicate dysregulation of coagulation, complement activation, and platelet activation as hallmark features of viral sepsis.[22]

SARS-CoV-2 directly invades vascular endothelial cells and creates a permissive environment for immune cell migration and aggregation by downregulating ACE-2 receptor activity and promoting angiotensin II accumulation.[23] The release of proinflammatory and procoagulant cytokines, along with endothelial injury, leads to subsequent activation of the coagulation cascade, impairment of fibrinolysis and thrombin generation, and alteration of the hemostatic environment. Mild endothelial activation and downstream signalling of prothrombotic pathways, along with low-grade inflammation, have been shown to persist beyond the acute phase of the disease.[24]

Immune dysregulation and endothelial dysfunction may play an active role in the underlying pathophysiology[25], which remains to be elucidated in future studies.

The possibility of endothelial cell activation or damage due to the binding of the virus to the ACE2 receptor may further increase the risk of deep vein thrombosis (DVT). The release of large amounts of inflammatory mediators and the therapies administered to patients with severe forms of the disease can lead to increased blood viscosity. Additionally, central venous catheterization may cause vascular endothelial injury.[26] For these reasons, thromboprophylaxis and anticoagulant therapy have been considered appropriate for patients with COVID-19.[27] Moreover, monitoring D-dimer levels is advisable even in patients with moderate or mild forms of the disease, to identify those at increased thrombotic risk.[28,29]

Studies have also detected the presence of lupus anticoagulant and antiphospholipid antibodies in the blood of COVID-19 patients, further contributing to the hypercoagulable state.[30,11] Antiphospholipid antibodies were detected in 52% of patients (24% IgG anti-phosphatidylserine/prothrombin, 18% IgG anti-phosphatidylserine/prothrombin, and 23% IgM anti-cardiolipin) in a cohort of hospitalized patients.[31]

The contribution of von Willebrand factor (vWF) to thromboinflammation has also been studied. Several mechanisms are involved, primarily endothelial dysfunction.[32] In patients with severe COVID-19, a marked increase in von Willebrand factor (vWF) and factor VIIIc levels has been observed, similar to that seen in patients with severe sepsis without COVID-19 who were admitted to the ICU. As the disease progresses, and in the absence of anticoagulant treatment, vWF and fibrinogen levels decline, while D-dimer and P-selectin levels remain persistently elevated, indicating a poor prognosis.[33]

Homocysteine levels have been found to be significantly elevated in patients with COVID-19, with a mean value of 27.5 µmol/L. Elevated homocysteine levels may serve as a potential marker for predicting the risk of disease severity and progression. Hyperhomocysteinemia is detrimental to the endothelium, as it promotes the proliferation of vascular smooth muscle cells, increases platelet aggregation, and disrupts the coagulation and fibrinolytic cascades, either by directly inducing a prothrombotic state or by acting synergistically with other cardiovascular risk factors.[34]

Understanding the interaction between the host's genetic profile and the SARS-CoV-2 virus, specifically COVID-19, has become a major focus of research since the onset of the pandemic. When the recombinant spike protein (S1) of SARS-CoV-2 is absorbed, HPMEC liver cells release PAI-1. A zinc metalloproteinase known as ZPMSTE24 and a transcription factor called KLF2 are the two upstream regulators of PAI-1 expression in HPMEC liver cells infected with SARS-CoV-2-S1.[35] It is known that KLF2 overexpression reduces PAI-1 synthesis and has previously been identified as a critical regulator of thrombin-mediated endothelial activation.[36] There is evidence linking the ACE1 I/D polymorphism (rs1799752) on chromosome 17 to a range of clinical conditions caused by SARS-CoV-2 infections, including ischemic stroke, pneumonia, kidney injury, and immunological responses such as the cytokine storm.[37]

Mutations in the ACE-2, ACE I/D, and ACE2 T/A genes may predispose COVID-19 patients to acute myocardial infarction or ischemic stroke.[38]

The high prevalence of thromboembolic events, as demonstrated by postmortem findings, indicates a significant role for COVID-19-induced coagulopathy, which may arise through a vicious cycle of self-amplifying neutrophil extracellular trap (NET) formation, ultimately resembling an autoimmune-like condition.[39]

Endothelial cell (EC) activation, thrombin generation, and NETosis components were assessed in a cohort of post-COVID-19 patients up to 65 days after the acute phase. Thrombin generation tests revealed shorter lag times combined with increased endogenous thrombin potential and peak thrombin levels. EC biomarkers such as VWF: Ag, von Willebrand factor propeptide (VWFpp), and factor VIII (FVIII:C) were significantly elevated in the plasma of COVID-19 convalescent individuals. Plasma levels of soluble thrombomodulin (sTM) were also significantly elevated, all indicating infection-induced endotheliopathy.[40,41]

Another theory related to the pathogenesis of thrombosis in COVID-19 involves the impairment of hematopoietic stem cells (HSC). Viral particles within affected CD34+ HSCs are associated with the highest risk of severe thrombosis related to SARS-CoV-2 infection.[42]

Studies have shown not only laboratory abnormalities but also an increased rate of thrombotic events in COVID-19 patients. The rate of symptomatic deep vein thrombosis (DVT) in hospitalized patients during the acute phase reaches up to 10%.[43]

The occurrence of thromboembolic complications in critically ill patients can be attributed to a combination of factors: immobilization, systemic inflammation induced by critical illnesses such as sepsis or acute pancreatitis, dehydration, endothelial dysfunction, and stasis. Additionally, the presence of metabolic syndrome (including hypertension, diabetes, and obesity), coronary artery disease, peripheral arterial disease, a history of deep vein thrombosis (DVT), and inherited thrombophilia are some of the patient-related risk factors that predispose to thromboembolic complications.[44] Nevertheless, even in patients without other thrombophilic risk factors, COVID-19 is an independent risk factor for acute myocardial infarction and ischemic stroke, particularly within the first two weeks after symptom onset, according to the authors of a study conducted on 86,472 subjects.[45]

Klok et al reported a 31% incidence of thrombotic complications among ICU patients with COVID-19, despite thromboprophylaxis.[46]

In the early phase of the pandemic (2020–2021), most studies showed that patients with COVID-19 had a high risk of thrombosis (arterial or venous, 11.5%), particularly among those admitted to the ICU (29.4%).[47]

The risk of venous thromboembolism was particularly high in the ICU, with a cumulative incidence rate of 27% according to a meta-analysis of studies from 2020–2021.[48]

The correlation between hypercoagulability and poorer prognosis may be explained by the progression to disseminated intravascular coagulation (DIC) and/or microvascular thrombosis, which leads to hypoxemic respiratory failure.[49]

COVID-19 patients who exhibited cardiac injury and elevated troponin T levels were more likely to develop coagulation disorders compared to those without cardiac involvement.[50]

Coagulopathy is further complicated by venous thromboembolism in 24%, deep vein thrombosis in 7%, and pulmonary embolism in 19% of critically ill COVID-19 patients.[51] Independent predictive parameters for thromboembolism have been shown to include pneumonia, advanced age, spontaneous prolongation of PT by more than 3 seconds, and aPTT by more than 5 seconds.[46]

Arterial thrombosis, in the form of acute myocardial infarction, acute limb ischemia, and stroke, has also been reported in patients with COVID-19.[52]

Al-Saadi et al have demonstrated that altered coagulation markers are poor prognostic indicators in COVID-19. Other markers evaluated for prognosis include low platelet count, prolonged prothrombin time (PT), and hypofibrinogenemia.[9]

Studies from 2020–2021 have shown that patients with an unfavourable disease outcome exhibit hypercoagulable states and alterations in platelet, leukocyte, and erythrocyte counts, indicating a poor prognosis; these parameters should be closely monitored in patients with COVID-19.[53]

Regarding stroke, no statistically significant differences in incidence were found between COVID-19 patients and other patient groups.[54]

The rate of a major arterial or venous thromboembolic event was 16.5% among hospitalized COVID-19 patients. This study was conducted on a cohort of 1,114 patients, including those hospitalized, treated on an outpatient basis, or post-discharge.[55]

The question has been raised whether the risk of thromboembolic events is related to the circulating Sars-CoV-2 variant. Kaptein et al, showed that, compared to the first wave of COVID-19 (February 24 – April 26, 2020), the incidence of DVT and arterial thrombotic events remained comparable among hospitalized COVID-19 patients during the second wave.[56]

However, Roubinian observed that patients with COVID-19 had a higher incidence of venous thromboembolism during the Delta variant period compared to the pre-Delta or Omicron periods.[57]

Studies have also shown that COVID-19 patients who received prophylactic anticoagulant therapy, whether at low or high doses, had a significantly reduced incidence of pulmonary embolism.[58]

The assessment of thromboembolic complications and thrombotic risk has also been carried out in patients with long COVID. Although long COVID symptoms vary, abnormalities in hematologic markers related to COVID-19 infection—particularly coagulation parameters—are believed to play a role in the pathogenesis of long COVID symptoms.[59]

Patients with more than six concurrent long COVID symptoms had higher leukocyte counts, lower PT values, and increased PT activity compared to those with fewer than six concurrent long COVID symptoms (study up to 985 days post-acute phase).[60]

Observations on acute patients were later complemented by studies on patients in the post-acute phase, even several months after the acute episode. These assessments became increasingly important as thromboembolic phenomena were observed in post-COVID-19 patients, both young and elderly. Patell et al., in a retrospective observational study, noted that thromboembolic events such as a pulmonary embolism can occur up to 23 days (median duration) after discharge of a COVID-19 patient.[61] Roberts et al reported thrombotic complications, specifically deep vein thrombosis (DVT), occurring between 3 and 33 days after the acute phase of infection.[62]

It is important for clinicians to be aware of this information to follow the patients and prevent thromboembolic events. Engelen et al reported the occurrence of venous thromboembolism up to 6 weeks after the acute episode.[63] Other authors have reported thrombotic events such as pulmonary embolism, deep vein thrombosis (DVT), splanchnic vein thrombosis, and stroke occurring up to 90 days after hospital discharge.[64]

The risk of thrombotic complications in the post-acute phase of COVID-19 is likely related to the duration and severity of the hyperinflammatory state.[65]

The risk of thrombotic complications in the post-acute phase of COVID-19 correlates with infection severity, including ICU admission and length of hospitalization, as well as established thrombosis risk factors.[66] Contrastingly, Roubinian et al reported that the 30-day incidence of venous thromboembolism (VTE) among outpatients with COVID-19 (1.8%) was not significantly different from that of non-COVID-19 patients (2.2%).[67] Implementation of standardized thromboembolic risk assessment tools is essential to identify patients at higher risk for thrombosis during the post-acute period.[68] At 90 days post-infection, data from a cohort of 89,877 patients demonstrated a significantly increased risk of thromboembolism, specifically deep vein thrombosis (DVT), among COVID-19 patients relative to those without SARS-CoV-2 infection.[69]

With the availability of the SARS-CoV-2 vaccine, studies have stratified patients based on thromboembolic risk according to their vaccination status. At the 6-month follow-up of vaccinated patients with recent episodic infection, higher rates of cardiovascular complications were observed compared to a control group (RR: 1.74, 95% CI: 1.66–1.83). Conversely, lower rates of cardiovascular complications were noted among recently infected vaccinated patients compared to unvaccinated individuals (RR: 0.87, 95% CI: 0.78–0.96).[70]

Complete vaccination status is associated with a reduced rate of acute myocardial infarction (RR: 0.48, 95% CI: 0.25–0.94) and ischemic stroke (RR: 0.40, 95% CI: 0.26–0.63) following episodic COVID-19 infection, compared to unvaccinated patients, as reported in the study coordinated by Kim in 2022.[71]

A sustained prothrombotic state, marked by elevated plasma concentrations of factor VIII and plasminogen activator inhibitor-1 (PAI-1), has been observed to persist up to four months following hospital discharge, as evidenced by a longitudinal follow-up study of 52 COVID-19 survivors.[72] Furthermore, the 2022 study by Xie et al tracked post-COVID-19 patients for up to one year, revealing significantly increased one-year incidences of ischemic heart disease, pericarditis, myocarditis, deep vein thrombosis (DVT), and arrhythmias in COVID-19 survivors compared to non-infected controls.[73]

Patients positive for SARS-CoV-2 infection exhibited an increased risk of deep vein thrombosis (DVT) up to three months post-diagnosis and pulmonary embolism up to six months, compared to COVID-19-negative patients.[74]

Longitudinal studies beyond three months post-acute infection, such as those by Giannis et al., reported similar findings for 2021 and 2022.With an average follow-up of 92 days, venous thromboembolism was identified in 1.55% of discharged COVID-19 patients. Post-discharge anticoagulation therapy was associated with a 46% reduction in this risk.[64]

Many of the existing studies conducted between 2020 and 2022 were single-center or had small sample sizes, limiting both the power to detect relevant signals and the external validity of the results. There is limited high-quality data regarding the associations between prior vaccination status, the use of anti-inflammatory therapies or antiviral agents, and the incidence and types of cardiovascular events.

These shortcomings have been addressed by the multicenter CORONA-VTE-Network study[75], which plans to include 10,000 patients from the USA, both hospitalized and outpatient. This study aims to incorporate as many clinical manifestations of thromboembolic syndrome as possible, both in the acute phase and in early and late post-infection phases, thus

applying homogeneous evaluation criteria for the proposed objectives. Additionally, event rates will be assessed based on vaccination status, use of antiviral and anti-inflammatory therapies, and within vulnerable subgroups such as pregnant or breastfeeding women, the elderly, and patients with end-stage renal disease. Trends over time in the incidence of cardiovascular and thrombotic events will also be evaluated. The results are expected to be published in the coming years.

Administration of the AstraZeneca/Oxford and Johnson & Johnson/Janssen COVID-19 vaccines, which use an adenoviral vector for DNA delivery, has been associated with very rare thromboembolic complications linked to an immune response against platelet factor 4 (PF4). The thromboembolic events are caused by impaired binding of coagulation factor X to the viral capsid.[76]

Vaccine-induced immune thrombocytopenia and thrombosis emerged as an unexpected complication following the first dose of adenoviral vector vaccines, ChAdOx1 and Ad26.COV2.S.Initial mortality rates exceeded 50%, later decreasing to 22% with increased awareness and prompt disease management.[77] It is mediated by antibodies against platelet factor 4 (PF4).The thrombosis is rapid, often extensive, and most frequently involves the cerebral venous system, with secondary intracranial hemorrhage occurring in one-third of cases. Cases of thrombotic thrombocytopenic purpura have also been observed following the first dose of ChAdOx1; whether these are coincidental or caused by the vaccine remains unclear.[78] Additionally, another Brazilian study associates thrombotic complications following first exposure to adenoviral vector vaccines in patients under 50 years old.[79]

Figure 1 illustrates the multifactorial pathophysiology of COVID-19-associated coagulopathy, highlighting the interplay between endothelial dysfunction, immune dysregulation, and coagulation cascade disruption that contributes to thromboembolic events during and after SARS-CoV-2 infection.

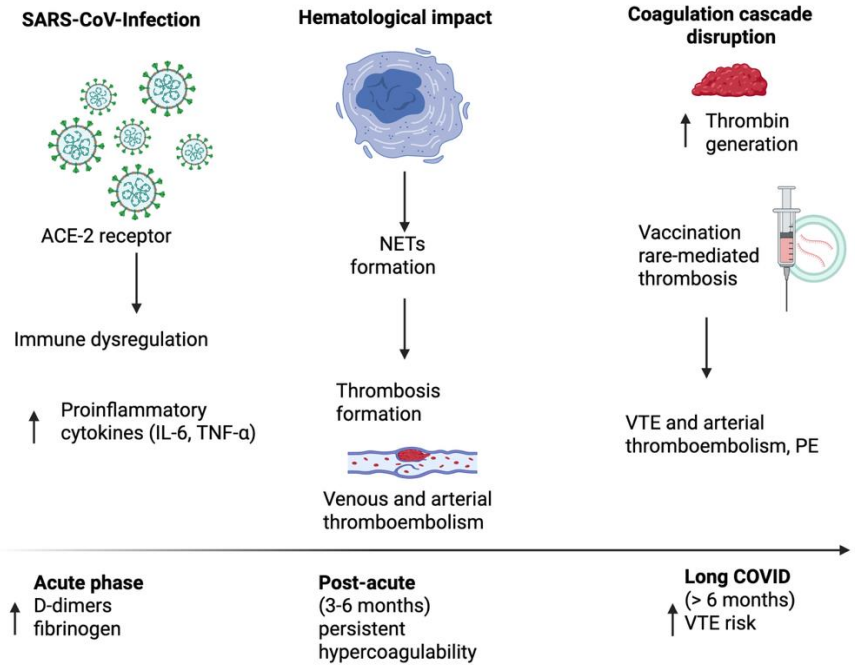

***Figure 1**.Pathophysiology of COVID-19 associated coagulopathy and thrombolitic events. Created with Biorender.com*

Conclusion

The present analysis highlights the significant and ongoing scientific interest in elucidating the hematological complications associated with COVID-19, spanning from the acute infection phase to extended post-infectious periods. Hypercoagulability has emerged as a hallmark of COVID-19 pathogenesis, evidenced by extensive clinical, biochemical, and molecular studies.

The coagulation abnormalities observed include a DIC-like syndrome, persistent elevation of D-dimer levels independent of the full DIC profile, platelet dysfunction, antiphospholipid antibody positivity, and both quantitative and qualitative alterations of coagulation factors. These hemostatic perturbations markedly exacerbate the clinical severity and complexity of SARS-CoV-2 infection, underscoring the importance of integrated multi-level investigations to better understand and manage COVID-19-associated coagulopathy.

References

1. https://data.who.int/dashboards/covid19/deaths
2. T.Mokhtari, F.Hassani, N.Ghaffari, B.Ebrahimi, A.Yarahmadi, G.Hassanzadeh, COVID-19 and multiorgan failure: a narrative review on potential mechanisms, J. Mol. Histol., 51 (6) (2020), pp.613-628
3. AlJame M, Imtiaz A, Ahmad I, Mohammed A.Deep forest model for diagnosing COVID19 from routine blood tests, Sci Rep.2021;11(1): 1-12.doi:10.1038/s41598-021-95957-w
4. Zhou F, Yu T, Du R, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study., Lancet 2020.28; 395(10229):1054–1062.[DOI] [PMC free article] [PubMed] [Google Scholar]
5. Guan WJ, Ni ZY, Hu Y, et al., Clinical characteristics of coronavirus disease 2019 in China., N EnglJMed.2020;382(18):1708-1720.10.1056/NEJMoa2002032. [DOI] [PMC free article] [PubMed] [Google Scholar] [Ref list]
6. Wang D, Hu B, Hu C, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China.JAMA.2020;323(11):1061-1069.10.1001/jama.2020.1585.[DOI] [PMC free article] [PubMed] [Google Scholar] [Ref list]
7. Yucan Li, Zhengqi Jiang, Fengjiao Han, Qiuyu Guo, Qi Feng, Tichao Shan, Jun Peng, Miao Xu, Coagulation Abnormalities in Post-Acute COVID-19 Syndrome: A Cross-Sectional Study, Blood, Volume 144, supplement 1, 2024, Page 1232, ISSN 0006-4971, https://doi.org/10.1182/blood-2024-207215.
8. B.Hasanefendic A.Husic-Selimovic, E. Sehercehajic, L.Halilovic, S.Tihic-Kapidzic, J.Foco-Solak, V.Smajlbegovic, L.Ibricevic-Balic, Correlation of specific inflammatory and coagulation parameters among COVID-19 patients, Clinica Chimica Acta, Volume 558, Supplement 1, 2024, 119119, ISSN 0009-8981, https://doi.org/10.1016/j.cca.2024.119119.
9. Enass Abdul Kareem Dagher Al-Saadi, Marwa Ali Abdulnabi, Hematological changes associated with COVID-19 infection, Journal of Clinical Laboratory Analysis, Volume36, Issue1, January 2022, e24064, first published November 2021, https://doi.org/10.1002/jcla.24064
10. Sonnweber T, Sahanic S, Pizzini A, et al., Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial., Eur Respir J.2021;57(4):2003481.[DOI] [PMC free article] [PubMed] [Google Scholar] [Ref list]
11. Jin S, Jin Y, Xu B, Hong J, Yang X., Prevalence and impact of coagulation dysfunction in COVID-19 in China: a meta-analysis., Thromb Haemost.2020; 120: 1524-1535.
12. Levi M, Toh CH, Thachil J, Watson HG (2009) Guidelines for the diagnosis and management of disseminated intravascular coagulation., British Committee for Standards in Haematology.Br J Haematol 145(1):24–33.https://doi.org/10.1111/j.1365-2141.2009.07600.x
13. Jose RJ, Manuel A.COVID-19 cytokine storm: the interplay between inflammation and coagulation., Lancet Respir Med.2020; 8: e46-e47.
14. Yao, Y.; Cao, J.; Wang, Q.; Shi, Q.; Liu, K.; Luo, Z.; Chen, X.; Chen, S.; Yu, K.; Huang, Z.; et al., D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study., J.Intensive Care 2020, 8, 49.[CrossRef] [PubMed]
15. L.H.Willems, M.Nagy, H.ten Cate, H.M.H.Spronk, L.A.Groh, J.Leentjens, N.A.F.Janssen, M.G.Netea, D.H.J.Thijssen, G.Hannink, A.S.van Petersen, M.C.Warlé, Sustained inflammation, coagulation activation and elevated endothelin-1 levels without macrovascular dysfunction at 3 months after COVID-19, Thrombosis Research, Volume 209, 2022, Pages 106-114, ISSN 0049-3848, https://doi.org/10.1016/j.thromres.2021.11.027.
16. Michael W.Henderson et al., Contact and intrinsic coagulation pathways are activated and associated with adverse clinical outcomes in COVID-19, Blood Advances, Volume 6, Issue 11, 2022, Pages 3367-3377, ISSN 2473-9529, https://doi.org/10.1182/bloodadvances.2021006620.

17. Elaa, C.Syrine, M.Haifa, N.Walid, B.Amene, S.Houyem, et al., Assessment of coagulation profiles by rotational thromboelastometry in COVID 19 patients, Clin Lab [Internet].(2022), Available from: http://www.clin-lab-publications.com/article/4205
18. N.Lee, J.Wang, R.Brook, P.Monagle, G.Donnan, H.Nandurkar, et al., The evaluation of overall hemostatic potential assay in patients with COVID -19 infection, Int J Lab Hematol [Internet], 44 (5) (Oct 2022), Available from: https://1g10a41eg-y-https-onlinelibrary-wiley-com.z.e-nformation.ro/doi/10.1111/ijlh.13881
19. C.S.Whyte, M.Simpson, G.B.Morrow, C.A.Wallace, A.J.Mentzer, J.C.Knight, et al., The suboptimal fibrinolytic response in COVID-19 is dictated by high PAI-1, J.Thromb.Haemost., 20 (10) (Oct 2022), p.2394-2406
20. Laszlo Szekely, si colab, Pulmonary stromal expansion and intra-alveolar coagulation are primary causes of COVID-19 death, Heliyon, Volume 7, Issue 5, 2021, e07134, ISSN 2405-8440, https://doi.org/10.1016/j.heliyon.2021.e07134.
21. N.Tang, D.Li, X.Wang, Z.Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J.Thromb.Haemost., 18 (2020), pp.844-847
22. D.Bongiovanni, M.Klug, O.Lazareva, S.Weidlich, M.Biasi, S.Ursu, S.Warth, C.Buske, M.Lukas, C.D.Spinner, et al., SARS-CoV-2 infection is associated with a pro-thrombotic platelet phenotype, Cell Death Dis., 12 (2021), p.50
23. Varga Z, Flammer AJ, Steiger P, et al.Endothelial cell infection and endotheliitis in COVID-19., Lancet.2020;395(10234):1417-1418.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
24. Dalan R, Boehm BO., The implications of COVID-19 infection on the endothelium: a metabolic vascular perspective., Diabetes Metab Res Rev.2021;37(3):e3402.[DOI] [PubMed] [Google Scholar][Ref list]
25. Lillicrap D., Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia., J Thromb Haemost.2020;4:786-787.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
26. Witt DM, Nieuwlaat R, Clark NP, et al., American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy., Blood Adv.2018;2(22):3257-3291.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
27. E Terpos, I Ntanasis-Stathopoulos, I Elalamy, E Kastritis, TN Sergentanis, M Politou, et al., Hematological findings and complications of COVID-19, Am J Hematol, 95 (7) (2020), pp.834-847
28. Chen J, Wang X, Zhang S, et al., Findings of acute pulmonary embolism in COVID-19 patients (in review)., Lancet Infect Dis.2020..[Google Scholar][Ref list]
29. Mafalda Urbano, Elísio Costa, Catarina Geraldes, Hematological changes in SARS-COV-2 positive patients, Hematology, Transfusion and Cell Therapy, Volume 44, Issue 2, 2022, Pages 218-224, ISSN 2531-1379, https://doi.org/10.1016/j.htct.2021.12.001.
30. Khandait H, Gandotra G, Sachdeva S, et al., COVID-19 and hematology—what do we know so far?, SN Compr Clin Med.2020; 2(12): 2631-2636.
31. Zuo Y, Estes SK, Ali RA, et al., Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19., Sci Transl Med.2020;12(570):eabd3876.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
32. Delrue M, Siguret V, Neuwirth M, et al., von Willebrand factor/ADAMTS13 axis and venous thromboembolism in moderate-to-severe COVID-19 patients., Br J Haematol.2020; 192(6): 1097-1100.
33. Grobler C, Maphumulo SC, Grobbelaar LM, Bredenkamp JC, Laubscher GJ, Lourens PJ, Steenkamp J, Kell DB, Pretorius E., Covid-19: The Rollercoaster of Fibrin(Ogen), D-Dimer, Von Willebrand Factor, P-Selectin and Their Interactions with Endothelial Cells, Platelets and Erythrocytes., International Journal of Molecular Sciences.2020; 21(14): 5168.http://dx.doi.org/10.3390/ijms21145168
34. P.Kaplan, Z.Tatarkova, M.K.Sivonova, P.Racay, J.Lehotsky, Homocysteine and mitochondria in cardiovascular and cerebrovascular systems, Int.J.Mol.Sci., 21 (20) (2020), p.7698
35. M.Han, D.Pandey, ZMPSTE24 regulates SARS-CoV-2 spike protein–enhanced expression of endothelial PAI-1, Am.J.Respir.Cell Mol.Biol.(2021), pp.65300-65308
36. D.E.Vaughan, R.Rai, S.S.Khan, M.Eren, A.K.Ghosh, Plasminogen activator inhibitor-1 is a marker and a mediator of senescence, Arterioscler.Thromb.Vasc.Biol., 37 (2017), pp.1446-1452

37. A.S.Yehualashet, T.F.Belachew, ACEIs and ARBs and their correlation with COVID-19: a review, Infect.Drug Resist., 13 (2020), p.3217
38. T.Alhogbani, Acute myocarditis associated with novel Middle east respiratory syndrome coronavirus, Ann.Saudi Med., 36 (1) (2016), pp.78-80
39. S.Sharma, A.Mishra, Z.Ashraf, COVID-19 induced coagulopathy (CIC): thrombotic manifestations of viral infection, TH Open, 6 (1) (2022), pp.e70-e79
40. Fogarty H, Townsend L, Morrin H, et al., Persistent endotheliopathy in the pathogenesis of long COVID syndrome., J Thromb Haemost.2021;19(10):2546-2553.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
41. S.L.Cohen, E.Gianos, M.A.Barish, S.Chatterjee, N.Kohn, M.Lesser, et al., Prevalence and predictors of venous thromboembolism or mortality in hospitalized COVID-19 patients, Thromb Haemost., 121 (08) (Aug 2021), pp.1043-1053
42. Balzanelli MG, Distratis P, Dipalma G, et al.Sars-CoV-2 virus infection may interfere CD34+ hematopoietic stem cells and megakaryocyte-Erythroid progenitors differentiation contributing to platelet defection towards insurgence of thrombocytopenia and thrombophilia.Microorganisms.2021;9(8):1632.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
43. Kahn SR, Lim W, Dunn AS, et al., Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.Chest.2012;141(suppl 4):e195S-e226S.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
44. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I (2011), Risk factors for venous and arterial thrombosis. Blood Transfus 9(2):120–138.https://doi.org/10.2450/2010.0066-10
45. Katsoularis I., Fonseca-Rodriguez O., Farrington P., Lindmark K., Fors Connolly A.M., Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study.Lancet.2021;398(10300):599–607.doi: 10.1016/S0140-6736(21)00896-5.Aug 14.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
46. Klok F.A., Kruip M., van der Meer N.J.M., et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19.Thromb.Res.2020;191:145–147.doi: 10.1016/j.thromres.2020.04.013.Jul.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
47. Bilaloglu S., Aphinyanaphongs Y., Jones S., Iturrate E., Hochman J., Berger J.S., Thrombosis in hospitalized patients with COVID-19 in a new York City health system.JAMA.2020;324(8):799–801.doi: 10.1001/jama.2020.13372.Aug 25.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
48. Jiménez D., García-Sanchez A., Rali P., et al., Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and Meta-analysis.Chest.2021;159(3):1182–1196.doi: 10.1016/j.chest.2020.11.005.Mar.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
49. JM Connors, JH.Levy, Thromboinflammation and the hypercoagulability of COVID-19, J Thromb Haemost, 18 (7) (2020 Jul), pp.1559-1561
50. Shi S, Qin MU, Shen BO, et al., Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan.China.2020; 5: 802-810.
51. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M., Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis.Thromb Res.2020; 196: 67-74.
52. Helms J, Tacquard C, Severac F, et al., High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study.Intensive Care Med.2020; 46: 1089-1098.
53. Al-Aly, Z.; Xie, Y.; Bowe, B., High-dimensional characterization of post-acute sequelae of COVID-19., Nature 2021, 594, 259–264.[CrossRef]
54. Qureshi A.I., Baskett W.I., Huang W., et al., Acute ischemic stroke and COVID-19: an analysis of 27 676 patients., Stroke.2021;52(3):905–912.doi: 10.1161/STROKEAHA.120.031786.Mar.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
55. Piazza G., Campia U., Hurwitz S., et al., Registry of arterial and venous thromboembolic complications in patients with COVID-19., J.Am.Coll.Cardiol.2020;76(18):2060–2072.doi: 10.1016/j.jacc.2020.08.070.Nov 3.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
56. Dutch C., Thrombosis C., Kaptein F.H.J., et al., Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave., Thromb.Res.2021;199:143–148.doi: 10.1016/j.thromres.2020.12.019.Mar.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
57. Roubinian N.H., Vinson D.R., Knudson-Fitzpatrick T., et al., Risk of posthospital venous

thromboembolism in patients with COVID-19 varies by SARS-CoV-2 period and vaccination status., Blood Adv.2023;7(1):141–144.doi: 10.1182/bloodadvances.2022008984.Jan 10.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

58. Fauvel C., Weizman O., Trimaille A., et al., Pulmonary embolism in COVID-19 patients: a French multicentre cohort study., Eur.Heart J.2020;41(32):3058–3068.doi: 10.1093/eurheartj/ehaa500.Jul 1.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

59. Kell, D.B.; Laubscher, G.J.; Pretorius, E., A central role for amyloid fibrin microclots in long COVID/PASC: Origins and therapeutic implications.Biochem.J.2022, 479, 537–559.[CrossRef] [PubMed]

60. Galúcio VCA, Menezes DC, Lima PDL, Palácios VRDCM, Vasconcelos PFDC, Quaresma JAS, Falcão LFM., Evaluation of the Hematological Patterns from Up to 985 Days of Long COVID: A Cross-Sectional Study., Viruses.2023 Mar 29;15(4):879.doi: 10.3390/v15040879.PMID: 37112859; PMCID: PMC10142608.

61. Patell R, Bogue T, Koshy A, et al., Postdischarge thrombosis and hemorrhage in patients with COVID-19., Blood.2020;136(11):1342-1346.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

62. Roberts LN, Whyte MB, Georgiou L, et al., Postdischarge venous thromboembolism following hospital admission with COVID-19., Blood.2020;136(11):1347-1350.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

63. Engelen MM, Vandenbriele C, Balthazar T, et al., Venous thromboembolism in patients discharged after COVID-19 hospitalization., Semin Thromb Hemost.2021;47(4):362-371.[DOI] [PubMed] [Google Scholar][Ref list]

64. Giannis D, Allen SL, Tsang J, et al., Postdischarge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: the CORE-19 registry., Blood.2021;137(20):2838-2847.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

65. Yong SJ., Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments., Infect Dis (Lond).2021;53(10):737-754.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

66. Bikdeli B, Madhavan MV, Jimenez D, et al., COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review., J Am Coll Cardiol.2020;75(23):2950-2973.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

67. Oubinian N.H., Dusendang J.R., Mark D.G., et al., Incidence of 30-day venous thromboembolism in adults tested for SARS-CoV-2 infection in an integrated health care system in northern California., JAMA Intern.Med.2021;181(7):997–1000.doi: 10.1001/jamainternmed.2021.0488.Jul 1.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

68. Korompoki E, Gavriatopoulou M, Fotiou D, Ntanasis-Stathopoulos I, Dimopoulos MA, Terpos E., Late-onset hematological complications post COVID-19: An emerging medical problem for the hematologist., Am J Hematol.2022 Jan 1;97(1):119-128.doi: 10.1002/ajh.26384.Epub 2021 Nov 8.PMID: 34687462; PMCID: PMC8646944.

69. Lund L.C., Hallas J., Nielsen H., et al., Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study., Lancet Infect.Dis.2021;21(10):1373–1382.doi: 10.1016/S1473-3099(21)00211-5.Oct.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

70. Al-Aly Z., Bowe B., Xie Y., Long COVID after breakthrough SARS CoV2 infection., Nat.Med.2022;28(7):1461–1467.doi:10.1038/s41591-022-01840-0.Jul.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

71. Kim Y.E., Huh K., Park Y.J., Peck K.R., Jung J., Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19 infection., JAMA.2022;328(9):887–889.doi: 10.1001/jama.2022.12992.Sep 6.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

72. Von Meijenfeldt FA, Havervall S, Adelmeijer J, et al., Sustained prothrombotic changes in COVID-19 patients 4 months after hospital discharge., Blood Adv.2021;5(3):756-759.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

73. Xie Y., Xu E., Bowe B., Al-Aly Z., Long-term cardiovascular outcomes of COVID-19., Nat.Med.2022;28(3):583–590.doi: 10.1038/s41591-022-01689-3.Mar.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

74. Katsoularis I., Fonseca-Rodriguez O., Farrington P., et al., Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study.,

BMJ.2022;377:e069590.doi: 10.1136/bmj-2021-069590.Apr 6.[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]

75. Bikdeli B, Khairani CD, Krishnathasan D, Bejjani A, Armero A, Tristani A, Davies J, Porio N, Assi AA, Nauffal V, Campia U, Almarzooq Z, Wei E, Achanta A, Jesudasen SJ, Tiu BC, Merli GJ, Leiva O, Fanikos J, Sharma A, Vishnevsky A, Hsia J, Nehler MR, Welker J, Bonaca MP, Carroll BJ, Lan Z, Goldhaber SZ, Piazza G; CORONA-VTE-Network Investigators. Major cardiovascular events after COVID-19, event rates post-vaccination, antiviral or anti-inflammatory therapy, and temporal trends: Rationale and methodology of the CORONA-VTE-Network study. Thromb Res.2023 Aug;228:94104.doi:10.1016/j.thromres.2023.05.019.Epub2023May29.PMID:37302267; PMCID: PMC10226776.

76. Peter A.Feldman, Proposed mechanism for rare thrombotic events after use of some Covid-19 vaccines, Medical Hypotheses, Volume 159, 2022, 110756, ISSN 0306-9877, https://doi.org/10.1016/j.mehy.2021.110756.

77. S.Pavord, M.Scully, B.J.Hunt, et al., Clinical features of vaccine-induced immune thrombocytopenia and thrombosis, N Engl J Med, 385 (2021), pp.1680-1689

78. Sue Pavord, Will Lester, Reassurance on bleeding and thrombotic events following second dose BNT162b2 and ChAdOx1 COVID-19 vaccines, The Lancet Regional Health - Europe, Volume 32, 2023, 100708, ISSN2666-7762, https://doi.org/10.1016/j.lanepe.2023.100708.

79. Daniela P.Mendes-de-Almeida, et al., Vaccine-induced immune thrombotic thrombocytopenia post COVID-19 booster vaccination in Brazil: a case series, Research and Practice in Thrombosis and Haemostasis, Volume 7, Issue 8, 2023, 102243, ISSN 2475-0379, https://doi.org/10.1016/j.rpth.2023.102243.