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Coagulation Disorders and Thrombotic Events in Patients with COVID-19: A Narrative Review

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Abstract

Background: This review explores the coagulation disorders and thrombotic events observed in COVID-19 patients, highlighting the underlying pathophysiological mechanisms and current management strategies.

Pathophysiology and clinical impact: Important mechanisms contributing to thrombosis include cytokine storm-induced thrombosis, antiphospholipid antibody syndrome, macrophage activation syndrome, complement cascade activation, and renin-angiotensin system dysregulation. Thrombotic complications significantly impact mortality and morbidity, with pulmonary emboli frequently observed in autopsy studies. Notably, this prothrombotic state may persist for weeks post-hospitalization.

Management: Effective management of COVID-19-associated coagulopathy requires prompt treatment of underlying infections and comprehensive assessment of co-infections in critically ill patients. While heparin and its derivatives remain the cornerstone for managing venous
thromboembolism, their efficacy for COVID-19-associated coagulopathy remains to be a subject of investigation.

Conclusion: Understanding the complex interplay between inflammation and thrombosis in COVID-19 is crucial for developing targeted therapeutic strategies that address coagulation disorders and the underlying infection.

Keywords: COVID-19, Coagulopathy, Thrombosis, Immunothrombosis, D-dimer, Anticoagulation

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Introduction

The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and subsequently characterized the outbreak as a pandemic on March 11, 2020 (1). While the PHEIC status has been lifted, the disease remains a significant global health burden worldwide (2). Although primarily, COVID-19 is a respiratory tract infection, some individuals progress to more severe manifestations, including refractory fever, acute lung injury leading to acute respiratory distress syndrome (ARDS), shock, and multi-organ dysfunction leading to a high mortality rate (3). A hallmark of severe COVID-19 is the development of coagulopathy, resembling disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (3).

Epidemiological data indicate that coagulopathy occurs in up to 50% of severe cases, with venous thromboembolism (VTE) prevalence ranging from 20% to over 40% in critically ill patients (4, 5), significantly escalating mortality rates (6). However, COVID-associated coagulopathy (CAC) exhibits unique characteristics that distinguish it from other infectious- induced coagulopathy (7). Understanding these differences is critical for developing effective treatment strategies and improving patient outcomes. Specifically, CAC is characterized by a profound hypercoagulable state, with a high incidence of arterial and venous thromboembolic complications (2, 3).

Thrombotic complications in hospitalized COVID-19

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Key Messages:

↑What is "already known" in this topic:

COVID-19 is associated with a hypercoagulable state characterized by elevated D-dimer levels, endothelial injury, platelet activation, and NETosis.

→What this article adds:

This review study shows that the complex interplay between inflammation and thrombosis in COVID-19 is crucial for developing targeted therapeutic strategies that address coagulation disorders and the underlying infection.

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patients are approximately 14.7%, rising sharply to 23.2% in intensive care unit (ICU) settings (8), illustrating a clear correlation between disease severity and thrombotic risk (9). In contrast, coagulopathy in other infections can manifest as either hypo- or hypercoagulable states, with varying complications including bleeding risk or thrombotic events (2, 3, 7). A key driver of this state is Neutrophil extracellular traps (NETosis), a special neutrophil process in which neutrophils release web-like structures promoting tissue damage and creating a hypercoagulable state, which is called immunothrombosis (2, 3). The ongoing pandemic has prompted a surge in studies aimed at understanding the mechanisms underlying COVID-19-associated coagulopathy, yet inconsistencies in therapeutic approaches persist. Furthermore, as vaccination efforts expanded, there is a growing concern regarding post-vaccination coagulation issues (10).

This systematic review aims to synthesize current knowledge on the pathophysiological mechanisms of CAC and inform clinical guidelines to optimize patients' management.

Methods

Study Design and Search Strategy

This study is a narrative review focusing on the pathophysiology of COVID-19-associated coagulopathy.

A comprehensive search was conducted across PubMed, Scopus, and Google Scholar using keywords such as "COVID-19", "Immunothrombosis", and "Coagulopathy". The search period spanned from December 2019 to May 2026 to incorporate the most recent clinical and mechanistic findings.

Selection Criteria

Peer-reviewed articles, clinical trials, and autopsy studies published in English were included based on their relevance to systemic thrombosis and molecular mechanisms. Data were synthesized narratively to provide an up-to-date overview of the disease's systemic nature.

Results

Epidemiology

The systematic analysis of the included studies reveals a significant prevalence of coagulopathy among hospitalized patients with COVID-19.

Epidemiological data indicate that coagulation abnormalities occur in approximately 20% to 50% of hospitalized patients with severe COVID19 infections (4, 11).

Specifically, the incidence of Venous Thromboembolism (VTE) varies significantly by clinical setting; while it remains at a low incidence in non-hospitalized/mild cases, it occurs around 5-15% in general wards, and escalates sharply to 25-45% in Intensive Care Unit (ICU) patients, despite standard thromboprophylaxis (5, 12). Furthermore, patients presenting with coagulopathy at admission demonstrate a significantly higher mortality rate (Hazard Ratio 1.5–4.0) compared to those with normal hemostatic profiles (13).

Pathophysiology and Laboratory Findings

The most prevalent coagulation disorder observed in patients with COVID-19 is an elevation in D-dimer levels, accompanied by a relative decrease in platelet count and prolonged prothrombin time (6, 14, 15).

D-dimer

In a study involving 1,099 COVID-19 patients from China, elevated D-dimer levels (greater than 0.5 mg/L) were noted in 260 out of 560 patients with coagulation disorders, representing 46% of this subgroup. Another study conducted on 183 COVID-19 patients reported that the mean D-dimer concentration was significantly higher in deceased patients (2.12 mg/L, range 0.77-5.27) compared to recovered patients (0.61 mg/L, range 0.35-1.29). Furthermore, patients admitted to intensive care units (ICUs) exhibited markedly higher mean D-dimer concentrations (2.4 mg/L) compared to those not requiring ICU care (0.5 mg/L). A separate analysis indicated that a D-dimer level exceeding 1 mg/L at the time of admission was associated with an 18-fold increase in the risk of death (odds ratio = 18.42, 95% confidence interval: 2.6-128.6, $P = 0.0033$) (6). These findings underscore the significance of monitoring D-dimer levels as a prognostic indicator in COVID-19 patients, particularly in assessing the risk of thromboembolic complications and mortality (1).

Prothrombin

Coagulation abnormalities in patients with COVID-19 present distinct characteristics compared to bacterial infections. The average prothrombin time in deceased patients has been reported at 15.5 seconds (range 14.4-16.3), while recovered patients exhibited a mean prothrombin time of 13.6 seconds (range 13.0-14.3). These values, expressed as the International Normalized Ratio (INR), indicate that subtle changes may not always be detected (14).

Platelet Count

Mild thrombocytopenia, defined as a platelet count under 150 x 10^9 cells per liter, occurs in 70% to 95% of patients with severe COVID-19; however, this condition has not been identified as a significant predictor of disease progression or adverse outcomes (15, 16).

Fibrinogen Levels

Fibrinogen levels are typically elevated in COVID-19 patients, as fibrinogen is classified as an acute phase protein. Nevertheless, a marked decrease in plasma fibrinogen concentration to below 1 g/L has been observed shortly before death in some cases. Additionally, plasma antithrombin levels are lower in patients who succumb to COVID-19 (84% of normal) compared to those who recover (91% of normal), although values rarely fall below 80% of the normal limit (17).

Other Laboratory Abnormalities

Other laboratory abnormalities associated with CAC include elevated lactate dehydrogenase and, in some instances, significantly high ferritin concentrations, resem-

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bling findings in thrombotic microangiopathy. Postmortem examinations have revealed platelet-rich thrombotic deposits in the small vessels of the lungs and other organs, without signs of hemolysis or schistocytosis in peripheral blood smears, and platelet counts generally higher than those observed in thrombotic microangiopathy, representing a combination of low-grade DIC and localized thrombotic pulmonary microangiopathy that leads to organ dysfunction in severely affected patients (18).

The virus's affinity for ACE2 receptors on endothelial cells triggers widespread endotheliitis—a direct vascular injury that, combined with the "cytokine storm" (marked by high IL-6 levels), leads to the massive release of von Willebrand factor and the formation of Neutrophil Extracellular Traps (NETs) (19) resulting in the trapping of platelets and fibrin.

TNF-α and IL-1 suppress endogenous anticoagulant pathways. In a subset of severe COVID-19 cases, a cytokine storm profile emerges, characterized by elevated levels of pro-inflammatory cytokines and chemokines (20).

These systemic inflammatory responses, as part of innate immunity, lead to subsequent coagulation and thrombin production as critical components of humoral and cellular enhancement pathways, termed thromboinflammation or immunothrombosis. In sepsis, this can progress from adaptive hemostasis to DIC and multi-organ failure, driven by inflammatory procoagulant pathways (21-23).

Coronaviruses also significantly activate the fibrinolytic system. In SARS-CoV-1, t-PA levels were six times higher than in healthy controls. Similarly, inflammation-induced endothelial damage in COVID-19 leads to a massive release of plasminogen activators, explaining the markedly elevated D-dimer and fibrin degradation products (3).

Furthermore, disrupted endothelial cells release large von Willebrand factor multimers, which may cause thrombotic microangiopathy if not cleaved by ADAMTS13**.** Secondary ADAMTS13 deficiency can occur during severe inflammatory conditions associated with systemic infections; however, data on ADAMTS13 concentrations specifically in severe COVID-19 infections are limited (7).

Disseminated Intravascular Coagulation (DIC)

The combination of thrombocytopenia, prolonged prothrombin time, and elevated D-dimer levels may suggest disseminated intravascular coagulation (DIC), though the pattern differs from classic sepsis. In COVID-19, thrombocytopenia is less severe, yet D-dimer levels are significantly higher. Consequently, most COVID-19 patients do not meet the standard International Society on Thrombosis and Hemostasis (ISTH) scoring criteria for DIC (3, 4).

In Table 1, all of these laboratory findings are listed briefly.

Clinical Manifestations

Microvascular and macrovascular thromboembolic complications, as well as in-situ thrombosis, have been observed in various vascular beds, including the lungs, spleen, brain, intestines, and peripheral circulation in patients with COVID-19. Asymptomatic thrombotic events have also been identified among hospitalized patients.

Thrombosis in COVID-19 can persist for weeks post-hospitalization, reflecting a prolonged prothrombotic state similar to those observed in SARS (severe acute respiratory syndrome) and MERS (Middle East Respiratory Syndrome (3, 24).

Pulmonary Thrombotic Complications

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are the most prevalent thrombotic events in COVID-19, occurring in 20% to 30% of critically ill patients, often involving segmental and subsegmental pulmonary arteries. Those experiencing thrombotic events face a fivefold increase in mortality risk, suggesting a uniquely aggressive prothrombotic profile compared to other viral pneumonias (25).

These disseminated pulmonary microthrombi are thought to contribute to the unique pathophysiology of COVID-19-associated acute respiratory distress syndrome (ARDS), which may exhibit relatively normal pulmonary adaptations and necessitate different ventilatory strategies compared to ARDS caused by other etiologies. In patients with COVID-19, alveolar capillary microthrombi were found to be nine times more frequent than in influenza patients. Severe endothelial damage and intracellular viral presence were also documented in areas associated with

Table 1. Summary of coagulation laboratory findings in COVID19

Number	Parameter	Laboratory Pattern	Clinical Significance & Mechanism
1	D-dimer	Marked Elevation (often >1 mg/L)	Prognostic indicator; reflects massive activation of the fibrinolytic system (t-PA release) (6)
2	Platelet Count	Mild Thrombocytopenia	Observed in 70–95% of severe cases; unlike classic sepsis, it is not a primary predictor of adverse outcomes (16)
3	Prothrombin Time (PT)	Mild Prolongation	Mean ~15.5s in non-survivors; indicates subtle extrinsic pathway disruption (14)
4	Fibrinogen	Initial Elevation (Acute Phase)	Acts as an acute-phase reactant; a terminal drop (<1 g/L) indicates severe consumption prior to death (17)
5	VWF & ADAMTS13	High VWF / Relative ADAMTS13 Deficiency	Massive release of VWF multimers from damaged endothelium; drives localized thrombotic microangiopathy (7)
6	DIC Pattern Atypical DIC	High D-dimer with relatively preserved platelet counts	Most patients do not meet standard ISTH criteria for classic DIC (3)
7	Ancillary Markers	Elevated LDH & Ferritin	Reflects systemic inflammation and tissue injury, resembling thrombotic microangiopathy (18)

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microthrombus formation, suggesting that endothelial injury and inflammation may directly facilitate thrombus development (26).

Extrapulmonary and Cardiac Thrombotic Complications

While pulmonary thrombosis is commonly detected in COVID-19 patients, there is also an increase in extrapulmonary thrombotic events. These may represent de novo thrombosis or exacerbation of pre-existing atherosclerotic disease and endothelial dysfunction, including acute ischemic strokes, notably in patients under 50 with few risk factors. The incidence of stroke among ICU patients has been reported at approximately 2.5% across several cohorts. Other reported complications include mesenteric ischemia, peripheral artery occlusion, obstructive atherosclerosis, and cerebral venous sinus thrombosis (27).

Cardiac involvement is equally critical; myocardial infarction, in-stent thrombosis, and sudden left ventricular dysfunction are reported. Non-thrombotic mechanisms may also contribute to cardiac pathophysiology. In a study involving 416 hospitalized COVID-19 patients, cardiac injury identified by high-sensitivity troponin I (TnI) was associated with a significantly higher risk of mortality (51.2% mortality with cardiac injury versus 4.5% without). Furthermore, mortality risk was proportional to TnI levels (28).

Management

Hospitalized COVID-19 patients should undergo coagulation screening (D-dimer, PT, aPTT, fibrinogen, and platelet count) upon admission for prognostic assessment. Elevated D-dimer correlates with increased mortality, while a rapid fibrinogen decline may signal DIC—typically occurring 7–11 days after symptom onset. Although most coagulation shifts coincide with hospitalization duration (starting days 7–10), D-dimer elevations can emerge as early as day 4 (4, 21, 29).

In critically ill patients, progressive coagulation changes may signal the development of DIC. These changes can arise independently of COVID-19 due to factors such as prolonged hospitalization, mechanical ventilation, superinfection, and other common ICU-related complications. Based on current evidence, monitoring PT, platelet count, and D-dimer every 2–3 days is recommended in patients with severe COVID-19 (4, 30).

All hospitalized patients should receive prophylactic doses of LMWH unless contraindicated. If unavailable, unfractionated heparin or Fondaparinux are alternatives; however, LMWH's potential anti-inflammatory benefits compared to heparin remain uncertain (21, 31).

In non-critically ill hospitalized patients, therapeutic-dose heparin may reduce the need for organ support. (Extended prophylaxis update). whereas in ICU patients, standard prophylaxis remains the safer approach to avoid major bleeding (16).

Extended thromboprophylaxis (14–35 days) is recommended for high-risk survivors after discharge (32-35).

While early trials like ATTACC and INSPIRATION established the foundation of care, the 2025 Global Task Force guidelines now emphasize a more nuanced, biomarker-driven approach to anticoagulation, especially in the context of post-hospitalization recovery (36, 37).

Discussion

The present review highlights the unique and aggressive nature of COVID-19-associated coagulopathy (CAC), distinguishing it from conventional hemostatic disorders. Our findings underscore a profound prothrombotic state that correlates directly with disease severity and mortality.

The cytokine storm associated with severe COVID-19 promotes tissue factor expression, suppresses endogenous anticoagulant pathways, and amplifies thrombin generation, a process described as immunothrombosis which is the most striking aspect of CAC and shows the synergy between the immune system and the coagulation cascade (2), Recent analyses in 2025 have further confirmed this synergy by showing how next-generation anti-inflammatory drugs can simultaneously reduce thrombin generation (38).

Autopsy studies have demonstrated extensive pulmonary endothelial injury and platelet-rich microthrombi, supporting the concept of localized pulmonary thrombotic microangiopathy rather than systemic DIC (26). Extrapulmonary thrombotic events, including ischemic stroke and cardiac injury, further highlight the systemic nature of COVID-19-associated coagulopathy and its contribution to increased mortality (2, 27, 28)

Severe infections promote the release of Neutrophil Extracellular Traps (NETs), especially in the lungs, which provide a physical scaffold for platelet aggregation and fibrin deposition (Figure 1) and explain why microthrombi in the lungs are nine times more prevalent in COVID-19 than in other viral infections like Influenza, contributing to the severe ventilation-perfusion (V/Q) mismatch observed in these patients (19, 26, 39).

Our analysis confirms that D-dimer is the most potent prognostic marker. However, the "D-dimer paradox" in COVID-19—where extremely high levels coexist with normal platelet counts and fibrinogen levels in early stages—suggests that the process is initially driven by fibrinolysis shutdown rather than consumptive coagulopathy. This necessitates a shift in diagnostic focus; clinicians should not wait for traditional DIC markers to initiate aggressive thromboprophylaxis (4, 6, 40).

Thrombocytopenia in COVID-19 is typically mild and does not independently predict poor outcomes, suggesting that platelet consumption is localized rather than systemic (15, 16). Similarly, prolongation of prothrombin time is generally subtle and may not be fully captured by INR measurements, particularly in comparison with bacterial sepsis (14).

Elevated fibrinogen levels observed in most patients reflect an acute-phase response (3, 20).

Routine monitoring of coagulation parameters, especially D-dimer, platelet count, prothrombin time, and fibrinogen levels, can help to predict patients' condition (4, 40).

One of the most debated findings in our review is the optimal dosing of anticoagulants. While prophylactic LMWH is universally accepted as survival-beneficial, the

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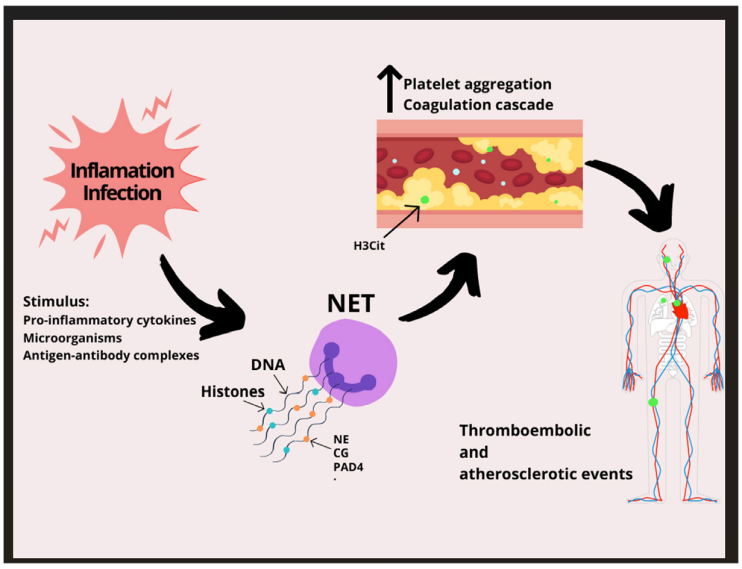

Figure 1. Mechanisms of NET-mediated thromboinflammation *:* This figure has been adapted from Reference 23. Infectious and inflammatory signals induce the release of NETs, which act as procoagulant scaffolds. Through their DNA strands, histones, and associated enzymes, NETs promote platelet aggregation and activate coagulation pathways, leading to clinical manifestations like DVT, PE, and arterial thrombosis (23).

role of therapeutic-dose anticoagulation in ICU patients remains controversial (32). Our synthesized data suggest that while higher doses may reduce macrovascular events, they do not always translate to a mortality benefit and significantly increase major bleeding risks. This highlights the need for a personalized medicine approach, where anticoagulation intensity is tailored to individual risk factors, D-dimer trajectories, and bleeding scores (32, 34).

The marked disparity in thrombotic risk between outpatients and hospitalized patients underscores that COVID-19-associated coagulopathy (CAC) is fundamentally driven by the intensity of the systemic inflammatory response (36, 37).

In outpatients with mild disease, the localized viral containment within the upper respiratory tract typically fails to trigger a systemic hemostatic breakdown. In contrast, severe and critical cases are characterized by a ″Cytokine Storm—″a massive release of pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β (36, 37).

This review is limited by the heterogeneity of the included studies, particularly regarding the timing of laboratory measurements and the lack of standardized anticoagulation protocols in early 2020. Future research should focus on the "Long-COVID" thrombotic risk and the potential role of antiplatelet agents or specific cytokine inhibitors in preventing microvascular occlusion.

Conclusion

COVID-19-associated coagulopathy (CAC) is fundamentally a thrombo-inflammatory phenomenon where the intensity of the systemic inflammatory response dictates thrombotic risk. While localized viral containment protects outpatients, the "cytokine storm" in severe cases triggers systemic hemostatic breakdown.

Evidence from major 2025–2026 trials confirms that while prophylactic anticoagulation is vital, universal therapeutic dosing in ICU patients fails to improve survival and significantly increases major bleeding risks. Consequently, clinical practice must shift from a "one-size-fits-all" model to personalized medicine, tailoring anticoagulation intensity to individual D-dimer trajectories and inflammatory phenotypes to balance thrombotic prevention with patient safety.

Acknowledgment

None.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

Dr. Marziyeh Ghalamkari and Dr.Mahdi Khatuni collected the majority of the data. Dr.Behnaz Varaminian and Dr. Maryamolsadat Ghoreyshi collaborated in the study drafting.

Ethical Considerations

Since this study is a review of previously published literature and does not involve human or animal subjects, ethical approval was not required.

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Data Availability

Not applicable.

AI Use Statement

AI-assisted technologies were used in the Grammer editing of the manuscript.

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