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REVIEW

COVID-19: A Disease Driven by Protease/Antiprotease Imbalance? A Specific Review Five Years into the Pandemic

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Abstract: COVID-19, caused by SARS-CoV-2, has profoundly impacted global health since late 2019. Beyond respiratory complications, the disease involves systemic manifestations driven by immune dysregulation, inflammation, and coagulopathy. Among the many mechanisms implicated in severe disease, a growing body of evidence suggests a central role for the imbalance between proteases and antiproteases. This review examines how dysregulated protease activity contributes to viral entry, cytokine activation, vascular injury, and thrombosis. We focus on the integration of proteolytic systems such as the renin-angiotensin system, coagulation cascade, and neutrophil extracellular traps with established pathways like endothelial dysfunction and immune hyperactivation. Furthermore, we highlight therapeutic strategies aimed at restoring proteolytic balance and discuss the potential relevance of this paradigm in the management of long COVID.

Keywords: COVID-19, protease-antiprotease balance, cytokine storm, hypercoagulability, fibrinolysis, serpins, inflammation, imaging, biomarkers

Introduction

The end of 2019 marked the emergence of a novel coronavirus (SARS-CoV-2), responsible for a global outbreak of acute respiratory disease, now universally known as COVID-19. This new virus demonstrated a strong affinity for the human respiratory tract, leading to a disease that rapidly evolved into a worldwide pandemic with high morbidity and mortality rates, particularly in the pre-vaccine era.[1–4]

In the early phase of the pandemic, severe pneumonia was the predominant clinical presentation, often progressing to acute respiratory failure.[5] COVID-19 was also associated with a wide spectrum of complications, including thromboembolic events such as pulmonary embolism (PE), bacterial and fungal co-infections, and cardiovascular dysfunction.[6–9] Among these, the association between COVID-19 and venous thromboembolism (VTE) was particularly alarming and was widely documented across multiple studies.[10]

Additional mechanisms widely discussed in the literature include the cytokine storm, complement activation, viral replication, and endothelial dysfunction.

A less explored but highly relevant mechanism is the imbalance between proteases and their endogenous inhibitors (antiproteases), which appears to play a key role in triggering and amplifying systemic inflammation, endothelial injury, and thrombotic complications. Proteases such as TMPRSS2, furin, and neutrophil elastase facilitate viral entry and replication, but also drive downstream immune activation, microvascular damage, and coagulopathy.

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This review aims to provide a mechanistic overview of how proteolytic systems contribute to the systemic effects of COVID-19, five years after the onset of the pandemic, offering a more integrated understanding of the disease's pathogenesis and potential treatment targets. A schematic representation comparing well-established and underexplored mechanisms, including protease–antiprotease imbalance, is provided in Figure 1.

The Cytokine Network and the Proteolytic Cascade

SARS-CoV-2 gains access to host cells primarily through its interaction with heparan sulphate and the ACE2 receptor on the surface of alveolar epithelial cells.[11–13] Upon entry, viral replication causes cellular damage and destruction of type II pneumocytes, triggering a robust innate immune response.[14]

This immune activation leads to the release of pro-inflammatory cytokines and chemokines (eg, IL-6, IL-10, IFN-γ, CXCL10, CCL2), as well as the recruitment of neutrophils and macrophages, which in turn secrete proteolytic enzymes such as matrix metalloproteinases (MMPs) and elastases.[15–17] The result is a "cytokine storm"—a hyperinflammatory state with systemic repercussions. This phenomenon was particularly evident during the first pandemic waves, where up to 90% of ICU patients exhibited elevated inflammatory markers and multiorgan involvement.[18]

The proteolytic cascade activated during this immune response also involves the complement system and the kallikrein–kinin system (KKS), both of which further amplify inflammation, vascular permeability, and coagulopathy.[19,20] These protease-driven systems generate bioactive peptides such as bradykinin and anaphylatoxins

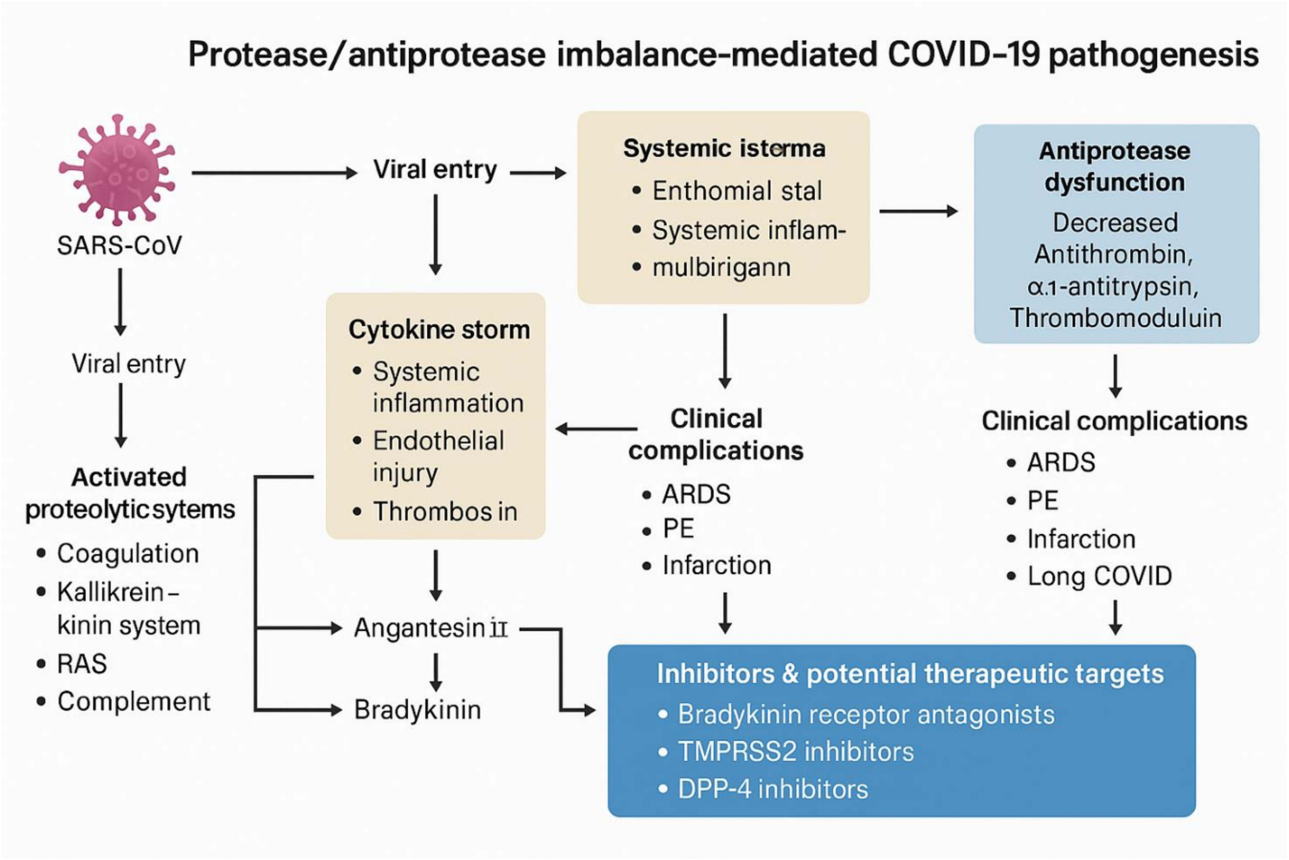

Figure 1 Overview of the protease/antiprotease imbalance in COVID-19 pathogenesis. SARS-CoV-2 entry via ACE2 and heparan sulphate initiates a cascade of inflammatory and proteolytic responses. Activation of multiple protease systems, including the complement cascade, the kallikrein–kinin system (KKS), the renin–angiotensin system (RAS), and the coagulation cascade, leads to cytokine release, endothelial injury, and immunothrombosis. Dysregulation of natural antiprotease mechanisms (eg, antithrombin, α1-antitrypsin, thrombomodulin) contributes to impaired fibrinolysis and promotes a hypercoagulable state. The resulting systemic manifestations include acute respiratory distress syndrome (ARDS), venous thromboembolism (VTE), arterial thrombosis, and multiorgan dysfunction. The diagram also highlights potential therapeutic targets aimed at restoring proteolytic balance.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; KKS, kallikrein–kinin system; PAI-1, plasminogen activator inhibitor-1; RAS, renin–angiotensin system; TAFI, thrombin-activatable fibrinolysis inhibitor; VTE, venous thromboembolism.

(C3a, C5a), contributing to pulmonary oedema, endothelial damage, and progression to multiorgan dysfunction. In addition, proteases such as neutrophil elastase and cathepsin G released from activated immune cells may directly degrade extracellular matrix and tight junction proteins, exacerbating vascular leakage and tissue injury.

In parallel, viral binding to ACE2 results in downregulation of this receptor and an altered ACE/ACE2 ratio, leading to dysregulation of the renin–angiotensin system (RAS).[21] This imbalance has downstream effects on vascular tone, inflammation, and coagulation.

Altogether, the cytokine-driven inflammation and the activation of proteolytic systems form a vicious cycle: tissue injury leads to protease release, which promotes further inflammation, vascular leakage, and hypercoagulability. While some of these pathways are well-established, the precise contribution of protease–antiprotease dysregulation remains under investigation. This interconnection underscores the need to consider protease–antiprotease dysregulation as a central pathogenic mechanism in severe COVID-19.[22]

Protease System Impairment in COVID-19

Once activated by the innate immune system, the complement cascade plays a pivotal role in amplifying inflammation through a proteolytic chain reaction. Complement components are sequentially activated by enzymatic cleavage of zymogens, a process that not only propagates inflammation but also interacts with other proteolytic systems—most notably, the kallikrein–kinin system (KKS), the renin–angiotensin system (RAS), and the coagulation cascade.[23,24]

High-molecular-weight kininogen (HMWK), a precursor of bradykinin, is a central player in the KKS and also serves as a cofactor in intrinsic coagulation. Through the activation of kallikrein, HMWK is cleaved to release bradykinin, a potent vasodilator that increases vascular permeability and contributes to tissue oedema.[25] In COVID-19, excess bradykinin activity (the so-called "bradykinin storm") may exacerbate pulmonary inflammation and gas exchange abnormalities. Recent studies suggest that bradykinin-driven permeability changes may contribute to ARDS in COVID-19, particularly in the setting of high neutrophil activity and low ACE2 expression.

In parallel, SARS-CoV-2–induced ACE2 downregulation leads to an imbalance in the RAS, which in turn enhances bradykinin signalling by reducing its degradation.[11,21,26] This dysregulation affects not only blood pressure and vascular permeability but also enhances the interplay between the RAS and KKS, perpetuating endothelial dysfunction and inflammation. The resulting cross-talk between systems may act as a central driver of organ dysfunction in severe COVID-19.

Importantly, the KKS also serves as a bridge to the coagulation system. Bradykinin-mediated activation of kallikrein promotes the conversion of factor XII (Hageman factor) into its active form, initiating the intrinsic pathway of coagulation.[27] Simultaneously, the innate immune response to viral invasion triggers tissue factor expression, activating the extrinsic pathway via factor VII.[28]

Thus, in COVID-19, multiple protease systems are simultaneously activated—complement, KKS, RAS, and coagulation—creating a self-amplifying proteolytic environment that promotes inflammation, vascular injury, and thrombosis. While many of these pathways are well-characterized, the full extent and sequence of their interplay remains under investigation, and future studies are needed to clarify the temporal dynamics of protease activation in COVID-19.

Antiprotease System Dysfunction and Hypofibrinolysis in COVID-19 (Revised)

The exaggerated inflammatory response in COVID-19 not only activates multiple protease systems but also disrupts the natural counter-regulatory mechanisms mediated by antiproteases. Among these, the serpin (serine protease inhibitor) family is crucial in controlling proteolytic activity and maintaining haemostatic balance.

During systemic inflammation, endothelial injury impairs the release and activity of several key serpins, including plasminogen activator inhibitor-1 (PAI-1), thrombin-activatable fibrinolysis inhibitor (TAFI), and thrombomodulin, all of which are dysregulated in COVID-19. PAI-1 levels are markedly elevated, predominantly due to endothelial release, and inhibit tissue plasminogen activator (tPA), thereby suppressing fibrinolysis and favouring thrombus persistence.[29] Elevated PAI-1 has been correlated with poor prognosis and is increasingly recognized as a marker of severe COVID-19.

TAFI, another antifibrinolytic protein activated by thrombin, requires thrombomodulin as a cofactor for full activity. However, in COVID-19, endothelial damage reduces thrombomodulin expression, leading to impaired protein C activation and dysregulated fibrinolysis.[30] This contributes to resistance to endogenous anticoagulant pathways and may predispose patients to microvascular thrombosis.

Lipoprotein(a) [Lp(a)] also increases during systemic inflammation and exerts antifibrinolytic and pro-inflammatory effects. Elevated Lp(a) levels are associated with impaired fibrinolysis and increased platelet aggregation, contributing to both arterial and venous thrombosis in COVID-19 patients.[31,32] While observational data support these associations, further studies are needed to determine whether Lp(a) directly contributes to COVID-19–associated coagulopathy or reflects a broader inflammatory burden. A simplified visual model of these interrelated mechanisms is presented in Figure 1, summarising the cascade of events from viral entry to systemic inflammation, thrombosis, and organ damage.

The cumulative result of these processes is a profound hypofibrinolytic state. This condition, when combined with excessive activation of clotting factors and endothelial injury, culminates in a highly prothrombotic milieu. Venous thromboembolism (VTE), arterial thrombosis, and disseminated intravascular coagulation (DIC)-like presentations have all been described in severe COVID-19 cases.

Moreover, SARS-CoV-2–induced degradation of heparan sulphate—a key glycosaminoglycan with both anticoagulant and anti-inflammatory functions—further impairs the anticoagulant response. Heparan sulphate facilitates antithrombin binding and enhances its inhibitory activity against thrombin and factor Xa; its loss may thus exacerbate the hypercoagulable state.[11] Given the central role of heparan sulphate in maintaining endothelial integrity, its degradation may also represent a key therapeutic target in future strategies aimed at mitigating vascular injury in COVID-19.

Radiological Findings

The complex systemic inflammation and coagulopathy observed in COVID-19 patients are reflected in imaging studies, which have played a crucial role in diagnosis and disease monitoring throughout the pandemic. Chest radiography was initially used for rapid triage, but it lacked specificity and sensitivity for early or mild disease. As a result, high-resolution computed tomography (HRCT) became the imaging modality of choice for evaluating pulmonary involvement.

HRCT scans typically reveal bilateral ground-glass opacities, “crazy-paving” patterns, consolidations, and peripheral or multilobar distribution of lesions. These findings, while not pathognomonic, are highly suggestive of COVID-19, especially when correlated with clinical and laboratory data.[33,34] In some cases, pleural effusions and halo signs have also been reported.

To quantify pulmonary involvement and facilitate risk stratification, several semi-quantitative CT severity scoring systems were introduced. The most widely used is the Total Severity Score (TSS), which grades the extent of lung involvement in each of the five lobes (from 0 to 4) and yields a global score ranging from 0 to 20.[33] However, while these scores are helpful for diagnosis, their prognostic value remains limited. Moreover, such scoring systems do not account for vascular involvement or thrombotic burden, which may reflect more accurately the systemic consequences of protease/antiprotease dysregulation.

More advanced techniques, such as quantitative CT (QCT), have shown promise in assessing the volume of aerated versus compromised lung tissue, potentially offering a more accurate correlation with oxygenation parameters and clinical outcomes.[35]

Importantly, imaging also plays a critical role in detecting thromboembolic complications. In patients with sudden clinical deterioration, CT pulmonary angiography (CTPA) is the gold standard for diagnosing pulmonary embolism. Severity of PE can be quantified using radiological scores such as the Qanadli index, which assesses clot burden and has prognostic implications.[36–39]

Radiological findings thus reflect the underlying pathophysiological processes of COVID-19, including alveolar injury, vascular inflammation, and thrombosis, correlating with the proposed model of protease/antiprotease imbalance, complement activation, and endothelial injury, and its systemic manifestations.

COVID-19 and Venous Thromboembolism

From the early months of the pandemic, venous thromboembolism (VTE)—particularly pulmonary embolism, emerged as a frequent and often severe complication of COVID-19. The pathogenesis of VTE in these patients is multifactorial,

involving a combination of classical risk factors (immobility, advanced age, comorbidities), endothelial dysfunction, systemic inflammation, and, crucially, protease/antiprotease imbalance.

Numerous observational studies have reported high rates of VTE in hospitalized patients with COVID-19, especially those requiring intensive care. Pulmonary embolism often occurs in the absence of deep vein thrombosis, suggesting in situ pulmonary thrombosis, likely driven by local endothelial injury and inflammation.[40–43] Histopathological analyses have confirmed microvascular fibrin deposition and immune cell infiltration consistent with thromboinflammation rather than embolic events.

Proteolytic activation, cytokine release, and inhibition of fibrinolysis collectively contribute to a hypercoagulable state. Heparan sulphate degradation by viral proteins further impairs natural anticoagulant pathways, while elevated levels of PAI-1, TAFI, and Lp(a) inhibit fibrinolysis and enhance thrombus stability. This aligns with the emerging concept that SARS-CoV-2 promotes a distinct form of immunothrombosis, where inflammatory and proteolytic processes are closely intertwined.

Low-molecular-weight heparins (LMWH) rapidly became the standard of care for thromboprophylaxis due to their dual anticoagulant and anti-inflammatory properties. Several studies have examined their efficacy in preventing VTE and improving survival in COVID-19 patients.[44–46]

The optimal dose and duration of anticoagulation remain under debate. While extended prophylaxis post-discharge has been proposed for selected high-risk patients, consensus is still lacking. Furthermore, the use of direct oral anticoagulants (DOACs) in COVID-19-associated VTE has been explored, but comparative studies with LMWH are limited. Ongoing randomized trials (eg, ACTIV-4 and RAPID) are expected to clarify the therapeutic benefit of various anticoagulation strategies, particularly in non-ICU settings.

Overall, the recognition of VTE as a major complication of COVID-19 has led to important changes in hospital protocols and reinforced the need for early diagnosis, individualized prophylaxis, and a mechanistic understanding of the prothrombotic state induced by SARS-CoV-2. Future research should focus on stratifying patients based on proteolytic and fibrinolytic biomarkers to tailor thromboprophylaxis and treatment approaches more effectively.

COVID-19 and Coronary Heart Disease

In addition to venous thrombosis, SARS-CoV-2 infection has been associated with an increased risk of arterial thrombotic events, including acute coronary syndromes (ACS). This association was particularly evident during the initial waves of the pandemic, before widespread vaccination, and with more virulent viral variants.

Several studies have reported a higher incidence of ST-elevation myocardial infarction (STEMI) among COVID-19 patients, often accompanied by worse outcomes compared to STEMI patients without COVID-19.[47,48] Multiple mechanisms may contribute, including systemic inflammation, endothelial dysfunction, platelet activation, and increased thrombin generation, all downstream effects of cytokine storm, NET formation, and protease system dysregulation.

In addition, delays in care due to prolonged triage, healthcare system overload, or patient reluctance to seek help during lockdowns may have contributed to late diagnosis and increased mortality in patients with ACS.

These findings highlight that COVID-19 creates a dual thrombotic threat, venous and arterial, largely mediated by an inflammatory and proteolytic environment that overwhelms normal vascular homeostasis. This reinforces the importance of early cardiovascular monitoring and raises the question of whether targeted antiprotease therapies might also reduce arterial complications in high-risk patients.

Prognostic Biomarkers in COVID-19-Associated VTE

During the early stages of the pandemic, several laboratory biomarkers were proposed to aid in prognostic stratification of COVID-19 patients, particularly those at risk of VTE and adverse outcomes.

Elevated D-dimer, troponin, proBNP, procalcitonin, and fibrinogen were consistently associated with more severe disease and higher mortality. Among these, D-dimer and IL-6 levels have emerged as the most reliable indicators of hypercoagulability and systemic inflammation.[49,50]

Neutrophil-to-lymphocyte ratio, C-reactive protein (CRP), lactate dehydrogenase (LDH), and neuron-specific enolase (NSE) were also found to correlate with disease severity and risk of complications, particularly in patients requiring ICU

admission. More recently, soluble thrombomodulin and PAI-1 levels have been proposed as additional markers of endothelial injury and hypofibrinolysis, though they are not yet widely used in clinical settings.

These biomarkers reflect the underlying activation of proteolytic cascades, endothelial injury, and inhibition of fibrinolysis, confirming the central role of protease–antiprotease imbalance in COVID-19 pathophysiology. Persistently elevated IL-6 levels have also been linked to long COVID and post-COVID syndromes, reinforcing its prognostic relevance.

Nonetheless, the interpretation of these markers should account for interindividual variability and dynamic changes over time. While biomarkers have helped refine clinical management, integration with imaging findings and individual risk profiles remains essential for optimal therapeutic decisions.

Future Perspectives

A deeper understanding of the molecular mechanisms underpinning COVID-19 reveals multiple potential therapeutic targets. The entry of SARS-CoV-2 via ACE2 and heparan sulphate initiates a cascade of inflammation, protease activation, and endothelial injury. This insight opens avenues for treatments beyond antiviral and corticosteroid therapy.

Anti-cytokine biologics, particularly those targeting IL-1 (eg, anakinra) and IL-6 (eg, tocilizumab), have been tested in various settings with mixed outcomes.[51–60] Timing of administration and patient selection remain critical factors influencing efficacy. More recently, biologics targeting IL-17 or IL-23 have shown theoretical promise, but robust clinical trials are lacking.[61–75]

Heparins remain central not only for thromboprophylaxis but also for their antiprotease and anti-inflammatory properties. Additional strategies aimed at restoring protease/antiprotease balance, either through targeted inhibitors or enhancing natural antiproteases, deserve further investigation. In addition, therapies aimed at inhibiting specific proteolytic pathways, such as TMPRSS2 inhibitors, kallikrein blockers, and complement inhibitors, are under investigation and may offer targeted benefits. Enhancing natural antiproteases like alpha-1 antitrypsin also represents a promising avenue. Preliminary trials exploring these strategies are ongoing, although most remain in early phases.

This proteolytic perspective on COVID-19 may also help elucidate mechanisms underlying post-acute sequelae, such as long COVID, and guide future research in inflammatory and thrombotic complications. The development of diagnostic assays to monitor proteolytic activity could enable patient stratification and individualized therapy, laying the foundation for precision medicine approaches in COVID-19 and beyond.

Conclusions (Revised)

COVID-19 has profoundly impacted global health, particularly during its early waves. While vaccination campaigns have mitigated disease severity and mortality, SARS-CoV-2 remains a significant threat, especially for vulnerable and unvaccinated individuals.

This review highlights the critical role of protease–antiprotease imbalance in driving systemic inflammation, endothelial dysfunction, and hypercoagulability. These interconnected mechanisms, spanning immune activation, complement dysregulation, and impaired fibrinolysis—offer a unified framework to understand the multisystem involvement seen in COVID-19. Recognising COVID-19 as a disease with a strong proteolytic component enhances our understanding of its pathophysiology and supports a more targeted therapeutic approach.

Further research should focus on modulating these proteolytic pathways to reduce complications and improve outcomes in both acute and chronic stages of the disease. Future priorities include: developing reliable biomarkers of protease activity, conducting large-scale clinical trials of targeted antiprotease therapies, and investigating how proteolytic dysregulation contributes to long-term sequelae such as long COVID. Such insights may shift COVID-19 management paradigms and inform broader strategies in infectious and inflammatory diseases.

Data Sharing Statement

Data supporting the reported results can be requested by Email to the corresponding author.

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