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REVIEW ARTICLE

Oxidative Stress Induced Thrombosis and Hypercholesterolemic Condition in COVID-19 Infection

Ashfaq Ahmed[1], Hrishik Iqbal[2*], Md Shaki Mostaid[3], Afroza Zannat[4], Srikumar Chakravarthi[5], Nikolaos Syrmos[6]

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Abstract

The COVID-19 pandemic, caused by SARS-CoV-2, has emerged as a global health crisis, with severe disease and mortality disproportionately affecting individuals with comorbidities such as cardiovascular disease, diabetes, obesity, and immunosuppression. These conditions are associated with elevated basal reactive oxygen species (ROS) levels, predisposing patients to oxidative stress, systemic inflammation, endothelial dysfunction, and thrombotic complications. SARS-CoV-2 infection further exacerbates ROS generation via dysregulation of the renin–angiotensin system, NADPH oxidase activation, and immune-mediated neutrophil and macrophage responses, contributing to vascular injury, cytokine storm, and acute respiratory distress syndrome (ARDS). Hypercholesterolemic patients are particularly vulnerable, as oxidized LDL (OxLDL) enhances ROS production, promotes neutrophil extracellular trap formation, and accelerates thrombosis, further compounding COVID-19 severity. COVID-19–associated coagulopathy is characterized by elevated D-dimer, von Willebrand factor, and platelet activation, reflecting systemic hypercoagulability and multiorgan involvement. Therapeutically, targeting oxidative stress represents a promising strategy. Statins exhibit cholesterol-lowering and immunomodulatory effects, potentially reducing thrombotic risk. Nrf2 activators, glutathione, and N-acetylcysteine enhance endogenous antioxidant defenses, mitigate inflammation, and preserve endothelial integrity. Micronutrients such as vitamins C, D, E, and selenium further support redox homeostasis and immune function. Collectively, in this narrative review we have shown that understanding the interplay between oxidative stress, thrombosis, hypercholesterolemia, and immune dysregulation may inform preventive and therapeutic strategies to improve outcomes in high-risk COVID-19 patients. Clinical trials are warranted to validate the efficacy of these interventions.

Keywords: COVID-19; ROS; thrombosis; von Willebrand Factor; hypercholesterolemia; OxLDL

INTRODUCTION

The outbreak of the novel coronavirus disease (COVID-19), initially reported in Wuhan, China, on 8 December 2019, rapidly evolved into a global health crisis. The World Health Organization (WHO) declared the situation a Public Health Emergency of International Concern on 30 January 2020 and subsequently characterized it as a pandemic on 11 March 2020. Within six months, the infection had extended to more than 216 countries, with over 32 million confirmed cases worldwide by 25 September 2020, including nearly 16 million cases in the United States alone (Zhou, et al., 2020b). Although most infected individuals experience mild or asymptomatic disease, approximately 14% develop severe illness and about 5% progress to critical conditions, among whom mortality may reach up to 50%. The risk of severe outcomes and death is markedly higher in individuals with pre-existing comorbidities, including cardiovascular diseases, diabetes mellitus, obesity, and immunosuppressive disorders (Chan et al., 2020). These conditions are commonly associated with elevated basal levels of reactive oxygen species (ROS), which predispose patients to heightened oxidative stress and subsequent complications. Accumulating evidence indicates that oxidative stress significantly contributes to disease progression and mortality in COVID-19. Clinically, patients may present with sputum production, myalgia or arthralgia, chills, vomiting, and nasal congestion, alongside marked elevations in acute-phase reactants, reflecting dysregulation of the host inflammatory response (Guan et

[1] Department of Pharmacy, Brac University, Bangladesh
[2*] QUEST Bangladesh Biomedical Research Center, Bangladesh
[3] Department of Pharmaceutical Sciences, North South University
[4] Assistant Professor, European University of Bangladesh
[5] Faculty of Medicine, Nursing and Health Sciences, SEGi University, Selangor, Malaysia.
[6] Aristotle University of Thessaloniki, Thesaaloniki, Macedonia, Greece
*) corresponding author

Hrishik Iqbal
Dhaka, Bangladesh
Email: hrishik.iqbal@gmail.com

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al., 2020). This imbalance between pro-inflammatory and anti-inflammatory mediators promotes leukocyte recruitment and infiltration into tissues, particularly the lungs, culminating in acute respiratory distress syndrome (ARDS) (Laforge et al., 2020).

Oxidative stress represents a pathological state characterized by an imbalance between ROS generation and antioxidant defense mechanisms. Under physiological conditions, ROS are produced as by-products of cellular oxygen metabolism and function in redox signaling pathways (Ntyonga et al., 2020). However, during SARS-CoV-2 infection and in metabolic disorders such as hypertension, diabetes, and obesity, excessive ROS production leads to structural and functional cellular damage, thereby exacerbating disease severity and increasing mortality risk (Dey et al., 2021).

A critical and life-threatening manifestation observed in a subset of patients is cytokine storm syndrome, a hyperinflammatory state marked by excessive neutrophil activation and elevated concentrations of pro-inflammatory cytokines, frequently resulting in respiratory failure. Severe cases are characterized by neutrophilia, lymphopenia, and increased levels of D-dimer, interleukin-6 (IL-6), and C-reactive protein (CRP), all of which correlate strongly with poor clinical outcomes and higher mortality (Mahedi et al., 2024). Prospective data suggest that each 10% rise in IL-6 or D-dimer levels is associated with a corresponding 10% increase in mortality risk. Critically ill patients also demonstrate markedly elevated ROS levels, which initiate a cascade of pathological events, including endothelial dysfunction, hypercoagulability, thrombosis, and enhanced platelet aggregation that key contributors to severe COVID-19 manifestations (Baqi et al., 2020). Collectively, oxidative stress and inflammation are now recognized as central drivers of COVID-19 pathogenesis (Cummings et al., 2020). This review therefore examines the molecular and cellular mechanisms by which SARS-CoV-2 induces oxidative stress, leading to systemic inflammation, endothelial injury, and vascular thrombosis (Terpos et al., 2020; Tang et al., 2020). Furthermore, we also discuss the immune-pathological consequences of Thrombosis and Hypercholesterolemic Condition potential impact of preventive therapeutic opportunities to address oxidative stress.

Searching Strategy

A comprehensive literature search was conducted using the PubMed database. Relevant publications were identified using keywords such as oxidative stress, SARS-CoV-2, thrombosis, hypercholesterolemia, cholesterol, COVID-19, coagulopathy, glutathione (GSH), Nrf2 activators, vitamins, and minerals. The search covered studies published between 2001 and 2026.

Problem Statement

Notwithstanding the extensive clinical and epidemiological research, the underlying mechanism of COVID-19-related thrombosis has not been fully clarified. Severe SARS-CoV-2 infection is always associated with endothelial dysfunction, hypercoagulability, and multi-organ thrombotic events, but the underlying molecular mechanisms by which SARS-CoV-2 infection triggers systemic coagulopathy have not been fully elucidated. Recent evidence suggests that oxidative stress plays a pivotal role, especially through the abnormal regulation of the renin-angiotensin system, overactivation of NADPH oxidase, and defective antioxidant mechanisms.

Moreover, despite the established role of hypercholesterolemia as a risk factor for vascular diseases, its role in the pathogenesis of COVID-19 and thrombosis has not been properly defined. Moreover, the relationship between high LDL cholesterol levels, the formation of oxidized LDL (OxLDL), the increase in reactive oxygen species (ROS) production, neutrophil extracellular trap (NET) formation, and endothelial damage in SARS-CoV-2 infection has not been adequately explored. Thus, the most important issue that this paper aims to address is the absence of a comprehensive mechanistic model that defines the role of SARS-CoV-2-induced oxidative stress, combined with the presence of hypercholesterolemia, in the pathogenesis of endothelial dysfunction, thrombus formation, and the clinical outcome of COVID-19 patients. This review therefore aims to elucidate how oxidative stress, oxidized LDL, and NET formation collectively contribute to thrombotic complications, addressing a critical gap in the current mechanistic understanding of COVID-19 pathogenesis.

Oxidative stress

Oxidative stress arises when the generation of reactive oxygen species (ROS) surpasses the capacity of endogenous antioxidant defense mechanisms. The principal intracellular ROS include superoxide anion ($O_2\bullet^-$), hydroxyl radical ($\bullet OH$), and hydrogen peroxide (H_2O_2). Under physiological conditions, ROS homeostasis is tightly regulated by key antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Excessive ROS accumulation disrupts cellular redox balance, leading to structural damage of essential organelles and dysregulation of gene expression pathways implicated in heart failure, ischemia–reperfusion injury, diabetes, obesity, and aging (Fukai et al., 2020).

Among multiple ROS-generating systems, NADPH oxidases represent a major vascular source. These enzymes catalyze the transfer of electrons from NADPH to molecular oxygen, producing superoxide anion. SOD rapidly dismutates superoxide into molecular oxygen and hydrogen peroxide. Three isoforms of SOD have been characterized: SOD1 (Cu/Zn-SOD) localized primarily in the cytosol, SOD2 (Mn-SOD) within mitochondria (Abouhashem et al., 2020), and SOD3 (extracellular Cu/Zn-SOD) in the extracellular matrix. Hydrogen peroxide, a comparatively stable ROS, is subsequently detoxified into water and oxygen by catalase in peroxisomes through an iron-dependent reaction. Alternatively, GPx reduces H_2O_2 to water, utilizing reduced glutathione (GSH) as an electron donor (Polonikov, 2020). During this process, GSH is oxidized to glutathione disulfide (GSSG), which is then regenerated to its reduced form by glutathione reductase (GSR). Adequate intracellular GSH levels are therefore critical for maintaining GPx and GSR activity. In addition to its role in enzymatic antioxidant cycles, GSH directly scavenges ROS via its reactive sulfhydryl group, contributing to cellular redox buffering (Muhammad et al., 2021).

These enzymatic antioxidant systems are essential for preserving redox equilibrium. Impairment of these pathways has been documented in metabolic disorders such as diabetes, hypertension, obesity, and during aging. Although comprehensive clinical evidence regarding antioxidant status in SARS-CoV-2 infection remains limited, increased oxidative stress associated with metabolic dysfunction and aging has been proposed as a key contributor to COVID-19 severity and mortality. Reduced pulmonary SOD activity has been reported in

elderly patients with severe COVID-19, potentially exacerbating disease progression. Similarly, diminished endogenous GSH levels have been associated with heightened oxidative stress, severe clinical manifestations, and increased mortality. Comparative analyses have further demonstrated significantly lower levels of antioxidant enzymes (SOD, CAT, GPx) and essential trace elements including selenium, zinc, magnesium, and copper in infected individuals relative to healthy controls. Moreover, elevated NADPH oxidase–mediated oxidative stress has been correlated with greater disease severity and thrombotic complications in SARS-CoV-2–infected patients (Violi et al., 2020).

SARS-CoV-2 infection triggers oxidative stress

Physiological concentrations of reactive oxygen species (ROS) are essential for normal immune regulation. For example, neutrophils generate ROS via NADPH oxidase to eliminate invading microorganisms. However, upregulation of NADPH oxidase activity markedly enhances ROS production, particularly superoxide anion ($O_2\bullet^-$). NADPH oxidase is widely expressed in neutrophils, macrophages, endothelial cells, vascular smooth muscle cells, and cardiomyocytes (Hoffmann et al., 2020). Both in vivo and in vitro investigations have demonstrated that excessive $O_2\bullet^-$ accumulation induces oxidative stress and contributes significantly to vascular pathologies, including atherosclerosis and microthrombosis. In addition to NADPH oxidase, other major intracellular sources of ROS include xanthine oxidase, enzymes of the mitochondrial electron transport chain, and uncoupled endothelial nitric oxide synthase (eNOS).

The renin–angiotensin system (RAS) represents a central regulator of ROS generation. This cascade is initiated by hepatic release of angiotensinogen into the circulation, followed by renal secretion of renin, which cleaves angiotensinogen to form angiotensin I (Ang I). As Ang I traverses the pulmonary circulation, angiotensin-converting enzyme 1 (ACE1) converts it into angiotensin II (Ang II), a potent effector peptide responsible for vasoconstriction and blood pressure homeostasis (Verdecchia et al., 2020). Angiotensin-converting enzyme 2 (ACE2) subsequently metabolizes Ang II to angiotensin 1–7 (Ang 1–7), which, through activation of the Mas receptor, counteracts the molecular and cellular effects of Ang II. Functionally, Ang II stimulates NADPH oxidase and enhances superoxide production, whereas Ang 1–7 suppresses $O_2\bullet^-$ generation. Thus, a dynamic equilibrium between Ang II and Ang 1–7 is critical for maintaining vascular integrity and organ protection (Simadibrata et al., 2020).

Although the precise molecular mechanisms underlying SARS-CoV-2–associated oxidative stress remain incompletely characterized, current evidence indicates that viral binding reduces the availability of membrane-bound ACE2 due to receptor engagement and internalization. The consequent reduction in ACE2 activity limits the conversion of Ang II to Ang 1–7, leading to Ang II accumulation. Elevated Ang II levels activate angiotensin receptors and stimulate NADPH oxidase, thereby amplifying ROS production. Experimental studies in rat vascular smooth muscle cells have confirmed the Ang II–dependent activation of NADPH oxidase, and ACE2-deficient animal models exhibit increased NADPH-mediated oxidative stress, particularly in renal tissue. Clinically, enhanced NADPH oxidase activity and oxidative stress have been observed in patients with COVID-19. Impaired eNOS function following SARS-CoV-2 infection further exacerbates redox imbalance. Moreover, elevated neutrophil-to-lymphocyte (N/L) ratios, frequently reported in COVID-19 that are associated with increased oxidative stress, greater disease severity, and higher mortality, underscoring the pathogenic link between immune dysregulation, redox imbalance, and adverse clinical outcomes (Man et al., 2021).

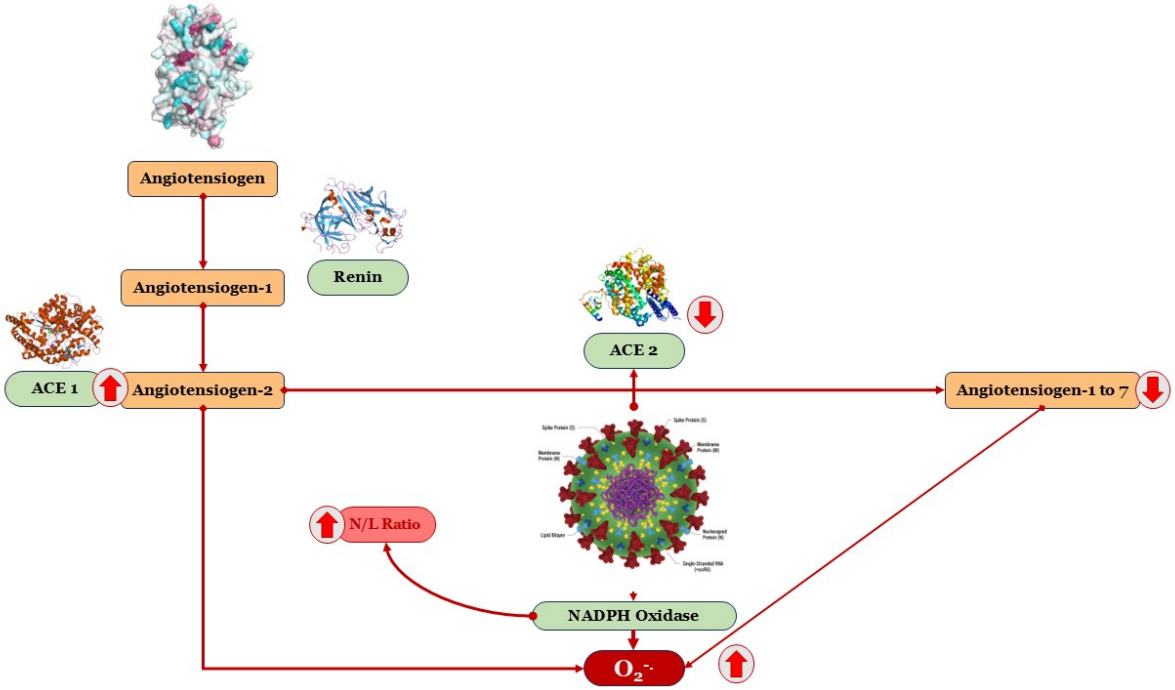

Figure 1: Potential mechanism through which SARS-CoV-2 infection elevates oxidative stress involves the virus impairing ACE2′s ability to convert Ang II to Ang 1–7, thereby enhancing $O_2\bullet^-$ production. In addition, SARS-CoV-2 infection directly stimulates the generation of $O_2\bullet^-$ and other •OH radicals by increasing the neutrophil-to-lymphocyte ratio, primarily via activation of the NADPH oxidase pathway.

Accordingly, in individuals with COVID-19 and underlying comorbid conditions, SARS-CoV-2 infection may potentiate oxidative stress through two principal mechanisms (Fig. 3). First, viral engagement with angiotensin-converting enzyme 2 (ACE2) impairs the conversion of angiotensin II (Ang II) to angiotensin 1–7 (Ang 1–7), thereby favoring Ang II accumulation and enhanced generation of superoxide anion ($O_2\bullet^-$). Second, infection-associated immune dysregulation, characterized by an elevated neutrophil-to-lymphocyte ratio, contributes to increased production of superoxide and hydroxyl (•OH) radicals (Imran et al., 2021). These mechanisms may operate systemically across multiple tissues, collectively amplifying overall oxidative stress burden

Thrombosis

Blood clotting is a crucial physiological process that occurs when there is vascular damage, preventing excessive bleeding through the aggregation of platelets in fibrin at the injury site (Nguyen & Coull, 2017). However, excessive clotting can lead to thrombosis, a condition characterized by abnormal clot formation that disrupts normal blood flow (Furie & Furie, 2008; D. Nguyen & Coull, 2017). Factors such as severe injury, certain medications, genetic defects, and autoimmune disorders can contribute to thrombosis (Johns Hopkins Medicine, n.d.). Common types of thrombosis include deep vein thrombosis (DVT) (Thachil, 2014), pulmonary embolism (PE) (Di Nisio, van Es, & Büller, 2016), portal vein thrombosis (Intagliata, Caldwell, & Tripodi, 2019), renal vein thrombosis (Asghar et al., 2007), and atherothrombosis (Sloop, Weidman, & St. Cyr, 2017). Thrombosis is a leading cause of death in developed countries and is particularly significant in patients with cancer or cardiovascular issues (Mackman, 2008; Furie & Furie, 2008).

DVT typically manifests in the leg veins, causing swelling, pain, and changes in skin color (Thachil, 2014). An embolism, which may consist of a blood clot, fat particle, or tumor, can obstruct blood flow, leading to conditions like PE when it occurs in lung arteries (Essien, Rali, & Mathai, 2019). Symptoms of PE include shortness of breath, coughing, and severe chest pain (Aurora Health Care, n.d.). Both DVT and PE are categorized as venous thromboembolism (VTE) (Essien et al., 2019).

Conversely, atherothrombosis involves the rupture of atherosclerotic plaques in arteries, potentially leading to coronary artery disease, stroke, and peripheral arterial disease (Viles-Gonzalez, Fuster, & Badimon, 2004). A noted case linked PE with myocardial infarction (MI) through a paradoxical embolism, where a venous thrombus reached the arterial system via a cardiac or pulmonary shunt (Kikuni, Silance, Debbas, & Unger, 2019). However, the Centers for Disease Control and Prevention clarified that DVT does not typically cause MI (Centers for Disease Control and Prevention, 2020).

Physiology of Thrombus Formation

Thrombus formation in blood vessels requires both platelet activation and fibrin formation, involving intrinsic and extrinsic coagulation pathways that activate factor X to factor Xa, subsequently transforming prothrombin (factor II) into thrombin (factor IIa). Thrombin then facilitates platelet activation and converts fibrinogen into fibrin, which forms a mesh-like structure that traps platelets and other blood cells, crucial for clot stability (Swieringa, Spronk, Heemskerk, & van der Meijden, 2018; Chaudhry & Babiker, 2018).

Collagen, located in the subendothelial region, is pivotal for initiating platelet activation upon vascular injury. Platelet receptors, such as glycoprotein VI, bind to exposed collagen, and glycoprotein Ib-V-IX interacts with von Willebrand factor embedded in the collagen, further promoting platelet activation (Furie & Furie, 2008; Xu & Shi, 2014). This activation process involves shape change, release of ADP, and thromboxane A2, which bind to P2Y12 and TP receptors on other platelets respectively, amplifying the activation process (Dorsam & Kunapuli, 2004).

Atherothrombosis involves thrombus formation triggered by atherosclerotic plaque disruption and erosion, where tissue factor (TF) expressed in the plaque interacts with factor VII, initiating the coagulation cascade leading to fibrin formation and thrombus development (Yamashita & Asada, 2015; Furie & Furie, 2008).

Moreover, oxidative stress plays a role in platelet activation through the production of reactive oxygen species (ROS), resulting from an imbalance in the antioxidant system and increased expression of NADPH oxidase in platelets. This oxidative stress leads to vascular endothelial dysfunction, further exposing collagen and enhancing interactions with von Willebrand factor and platelet glycoprotein Ib-V-IX, which promotes platelet aggregation and thrombus formation (Fuentes et al, 2018; Incalza et al., 2018). Notably, elevated levels of von Willebrand factor have been observed in patients with acute myocardial infarction, suggesting a significant role in atherothrombosis following plaque rupture (Yamashita et al., 2006).

Oxidative stress as a potential cause of thrombosis

COVID-19 has traditionally been classified as a respiratory illness based on its predominant clinical presentation (Zhou et al., 2020a; Wu et al., 2020). Although the lungs serve as the principal portal of entry for SARS-CoV-2, increasing evidence indicates that the vascular system represents a central target in the progression to severe disease. The infection is now widely regarded as a systemic vascular disorder characterized by endothelial injury, arrhythmogenesis, coagulopathy, and thromboembolic complications (Madjid et al., 2020). Similar to cerebrovascular and cardiovascular events where vascular pathology within the brain or heart manifests as stroke or myocardial infarction that vascular injury within the pulmonary circulation is commonly interpreted as a respiratory condition. The susceptibility of the vasculature may be attributed to the abundant expression of angiotensin-converting enzyme 2 (ACE2) on endothelial cells in the lungs, gastrointestinal tract, heart, blood vessels, kidneys, and brain (Clerkin et al., 2020).

Endothelial dysfunction in severe COVID-19 arises through multiple interrelated mechanisms (Fig. 4). First, viral interaction with ACE2 impairs its physiological role in converting angiotensin II (Ang II) to angiotensin 1–7 (Ang 1–7), thereby favoring Ang II–mediated reactive oxygen species (ROS) generation (Zheng et al., 2020). Second, SARS-CoV-2 infection promotes neutrophil activation and expansion, enhancing ROS production via the NADPH oxidase pathway (Rapkiewicz et al., 2020). The resulting oxidative stress contributes to endothelial injury and localized tissue damage at inflammatory sites (Shen et al., 2020). Moreover, endotheliitis further amplifies oxidative stress through AMPK inhibition and upregulation of MDM2 (Varga et al., 2020). Third, the viral spike protein itself has been shown to directly impair endothelial integrity, inducing mitochondrial fusion and suppressing endothelial nitric oxide synthase (eNOS) activity, thereby exacerbating

vascular dysfunction. Finally, direct viral invasion of endothelial cells has been documented in multiple organs of affected patients (Ackermann et al., 2020), where widespread endotheliitis is characterized by endothelial swelling, apoptosis, and functional impairment.

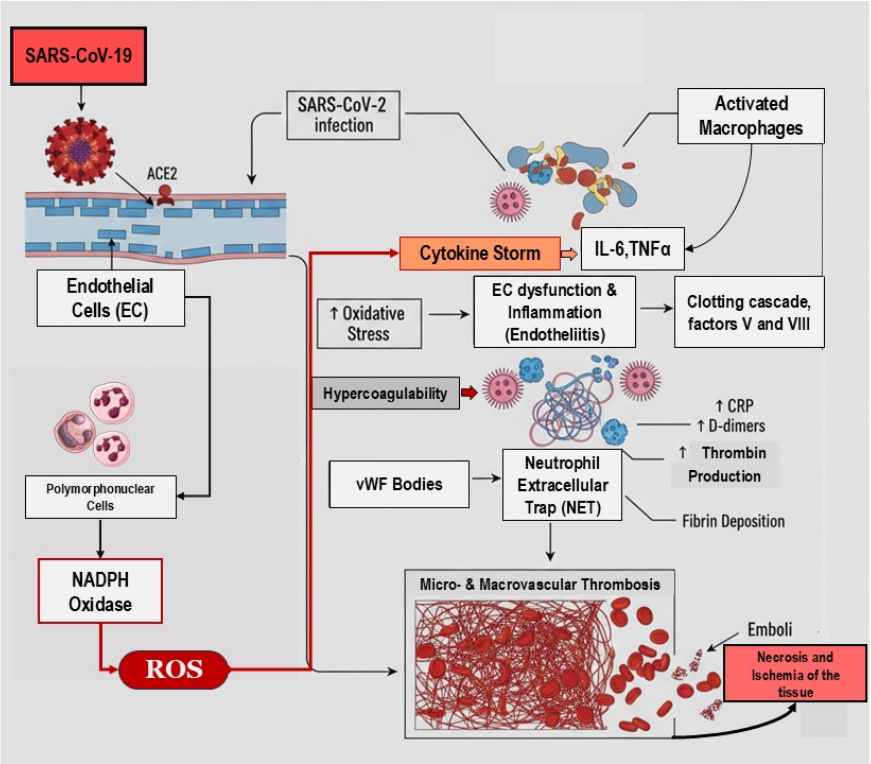

Figure 2: Proposed mechanisms of SARS-CoV-2–induced vascular thrombosis. SARS-CoV-2 enters endothelial cells (ECs) via ACE2 receptors, potentially leading to ACE2 downregulation and a consequent increase in angiotensin II (Ang II) levels, which promotes oxidative stress. In addition, the virus activates polymorphonuclear cells, primarily neutrophils, enhancing reactive oxygen species (ROS) production through the NADPH oxidase pathway. In severe COVID-19 cases, activated macrophages contribute to a cytokine storm by releasing proinflammatory cytokines such as IL-6 and TNF-α. The combined effects of oxidative stress and the cytokine storm cause endothelial dysfunction and inflammation (endotheliitis), characterized by EC swelling and apoptosis. Endotheliitis triggers the coagulation cascade, activates clotting factors V and VIII, and stimulates the release of von Willebrand factor (vWF) from Weibel-Palade bodies in ECs. Elevated levels of C-reactive protein (CRP) and D-dimers further enhance hypercoagulability. Cytokine-mediated platelet activation promotes interactions with neutrophils, inducing the formation of neutrophil extracellular traps (NETs), which in turn stimulate thrombin generation and fibrin deposition, ultimately leading to microvascular and macrovascular thrombosis. Fragmentation of thrombi can produce emboli that travel downstream, occluding smaller vessels and causing tissue ischemia and necrosis.

Histopathological examination of lung tissue from individuals with COVID-19 consistently demonstrates extensive vascular thrombosis. Alveolar capillary microthrombi have been reported at markedly higher frequencies, approximately nine times greater than those observed in patients with influenza (Ladikou et al., 2020). Autopsy-based investigations further indicate that thrombotic lesions are not confined to pulmonary structures but are distributed across multiple organ systems, underscoring the systemic nature of the coagulopathy (Oxley et al., 2020). Clinically, thromboembolic complications such as ischemic stroke, including cases among younger adults, have reinforced concerns regarding coagulation abnormalities as a central contributor to COVID-19–related mortality. Thrombocytopenia has emerged as a common hematological finding in infected individuals and has been proposed as a prognostic indicator, with meta-analytic data confirming its association with disease severity (Giannis et al. 2020). Notably, apoptotic platelets exhibit a dramatically enhanced procoagulant capacity, generating clots at rates substantially exceeding those of physiologically intact platelets. Beyond their traditional hemostatic role, platelets are now recognized as key mediators of thrombo-inflammation. Vascular wall inflammation combined with reduced platelet counts promotes thrombus formation, and subsequent embolization may result in downstream vessel occlusion, tissue ischemia, and necrosis. Cerebral emboli may precipitate stroke, whereas coronary obstruction can culminate in myocardial infarction (Levi et al., 2020).

At the molecular level, accumulating evidence supports a pivotal role for endothelial dysfunction in COVID-19–associated thrombosis. Analyses of critically ill patients have demonstrated elevated circulating concentrations of endothelial and platelet activation markers, including von Willebrand factor (vWF), soluble thrombomodulin, and soluble P-selectin, with higher levels observed in intensive care settings and strong correlations with mortality (Lippi et al., 2020). Oxidative stress, driven in part by reduced superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity, diminishes nitric oxide bioavailability, thereby impairing endothelial integrity and promoting apoptosis. This endothelial injury facilitates the release of procoagulant mediators and accelerates clot formation (Escher et al., 2020). Severe cases are characterized by marked elevations of vWF and increased factor VIII activity, both of which potentiate a hypercoagulable state. vWF is stored in Weibel–Palade bodies within endothelial cells and is rapidly secreted into

the circulation following endothelial activation or damage, where it mediates platelet adhesion and forms high-molecular-weight multimers associated with pathological thrombosis (Lodigiani et al., 2020). Endotheliitis, a defining feature of severe disease, amplifies vWF release, and elevated plasma levels serve both as an early indicator of endothelial injury and as a predictor of adverse outcomes. The observed surge in vWF may arise from increased basal secretion or exaggerated release from dysfunctional endothelium (Zhang et al., 2020). Collectively, these findings suggest that COVID-19–associated coagulopathy represents a form of endotheliopathy characterized by excessive vWF release, thrombocytopenia, and systemic hypercoagulability, culminating in venous, arterial, and microvascular thrombosis and ultimately multi-organ failure, particularly in patients with underlying comorbid conditions (Goshua et al., 2020). The convergence of inflammation, oxidative stress, and endothelial activation thus provides a coherent mechanistic framework linking SARS-CoV-2 infection to widespread thrombotic complications (Klok et al., 2020).

Hypercholesterolemia

Hypercholesterolemia is a condition characterized by abnormally high cholesterol levels in the blood. It is a significant risk factor for atherosclerosis and its associated complications. The American Heart Association defines hypercholesterolemia as having high levels of LDL (Low-Density Lipoprotein) cholesterol in the blood. Cholesterol is categorized into two types: HDL (High-Density Lipoprotein) and LDL. HDL is considered "good" cholesterol because it is processed by the liver and does not contribute to plaque formation. In contrast, LDL, often referred to as "bad" cholesterol, circulates through the bloodstream and can form plaques, leading to atherosclerosis and cardiovascular complications. The risk of developing atherosclerosis increases with the concentration of LDL cholesterol in the blood. Individuals with LDL cholesterol levels above 190 mg/dl and HDL levels below 40 mg/dl are considered at high risk.

Cholesterol Generation

Cholesterol biosynthesis in the body occurs via the mevalonate pathway. Initially, three acetyl-CoA molecules combine to form HMG-CoA (3-hydroxy-3-methylglutaryl-CoA). Subsequently, HMG-CoA is reduced to mevalonate by the enzyme HMG-CoA reductase, which is a crucial target for inhibiting cholesterol production in the body. Following the synthesis of mevalonate, sterol and nonsterol isoprenoids are produced. Among these, the sterol isoprenoids include cholesterol, while nonsterol isoprenoids encompass compounds such as dolichols and ubiquinone.

Viral Entry and Cholesterol Levels

Viruses such as human immunodeficiency virus (HIV), transmissible gastroenteritis virus (TGEV), flavivirus, rubella virus, and borna disease virus (BDV) have shown increased cellular entry in the presence of high cholesterol. Research on SARS-CoV found that it also exhibits high affinity for cholesterol-rich membranes, enhancing viral binding to host cells. Additionally, a study on porcine delta coronavirus (PDCoV) demonstrated that low membrane cholesterol levels reduce viral infection, while high cholesterol levels increase it.

Given this evidence, and considering the observed reduction of cholesterol in COVID-19 patients, we can hypothesize that elevated cholesterol levels may facilitate COVID-19 entry into host cells, similar to other viruses. This could suggest that cholesterol plays a role in enhancing the susceptibility to SARS-CoV-2 infection.

Hypercholesterolemic Patients with COVID-19

Patients with hypercholesterolemia, characterized by elevated levels of total and LDL cholesterol, may face increased risks when infected with COVID-19. During COVID-19 infection, reactive oxygen species (ROS) are generated (Ntyonga-Pono, 2020), and LDL cholesterol can be oxidized by these free radicals, producing oxidized LDL (OxLDL). Hypercholesterolemic patients are thus more likely to develop higher OxLDL levels following infection. Fan et al. and X. Wei et al. emphasized the importance of measuring OxLDL in their studies (Fan et al., 2020; X. Wei et al., 2020).

COVID-19 patients often exhibit increased neutrophils and macrophages due to the innate immune response (Prompetchara, Ketloy, & Palaga, 2020). Research shows that OxLDL in the presence of neutrophils and macrophages generates additional ROS and leads to the formation of neutrophil extracellular traps (NETs), fiber-like structures composed of histones and DNA. In vitro studies demonstrated that OxLDL accelerates NET formation compared to non-oxidized LDL. In vivo studies on human aortic endothelial cell cultures confirmed a similar pattern, with OxLDL significantly increasing NET formation.

Further studies revealed that OxLDL-induced NET formation is driven by the NADPH oxidase enzyme, with its inhibition significantly reducing NET formation. Macrophages exposed to OxLDL in mice were shown to generate high levels of ROS and NETs, leading to the development of atherosclerosis. Macrophages treated with OxLDL also upregulated the expression of p47phox, a regulatory subunit that activates NADPH oxidase, further increasing ROS production.

Given this, hypercholesterolemic patients with COVID-19 are likely to experience elevated ROS and OxLDL levels, leading to increased oxidative stress and NET formation. Moreover, COVID-19 reduces angiotensin 1-7, which typically inhibits NADPH oxidase activity, thus further contributing to ROS production. Consequently, patients with hypercholesterolemia may be more vulnerable to severe outcomes, including thrombotic events and organ failure, such as liver damage, which could explain the observed reduction in cholesterol levels.

In conclusion, the increased generation of ROS and oxidative stress in hypercholesterolemic patients infected with COVID-19 significantly heightens their risk of thrombus formation and organ failure, making them more susceptible to severe complications.

Association of Thrombosis and Hypercholesterolemia with COVID-19

Upon interaction with ACE-II receptors, there is a noted downregulation of angiotensin 1-7 (Alexandre et al., 2020). Angiotensin 1-7, known for its vasodilatory, anti-inflammatory, and antioxidant properties, contrasts the effects of angiotensin II, which stimulates reactive oxygen species (ROS) production primarily through the activation of NADPH oxidase enzymes such as Nox1, Nox2, and Nox4. These enzymes are integral to the conversion of oxygen molecules into superoxide, contributing to the formation of

various ROS including superoxide, hydrogen peroxide, and hydroxy free radicals within the mitochondria.

Interestingly, angiotensin 1-7 inhibits the activity of NADPH oxidase, reducing ROS production by decreasing the expression of components like p22phox. However, the binding of SARS-CoV-2 to ACE-II receptors leads to an increase in angiotensin II levels, concurrently decreasing angiotensin 1-7. This alteration potentially contributes to an overproduction of ROS in COVID-19 patients, aggravating oxidative stress (Alexandre et al., 2020).

Following viral entry, the body's innate immune response activates, releasing various cytokines and chemokines such as IL-1β, IL-1RA, IL-7, IL-8, IL-10, IFN-γ, MCP-1, MIP-1A, MIP-1B, G-CSF, and TNF-α (C. Huang et al., 2020). These inflammatory mediators attract neutrophils to the infection site, which also produce ROS via NADPH oxidase to combat pathogens (Barnes et al., 2020; Didangelos, 2020; Hemmat et al., 2020; Y. Zhao et al., 2020). Elevated neutrophil levels, therefore, might further heighten ROS production in COVID-19 infections, contributing to the disease's severe manifestations. Cholesterol Levels of COVID-19 Patients

Several studies have observed a decrease in cholesterol levels among COVID-19-infected patients. A retrospective longitudinal analysis involving 21 COVID-19 patients showed that LDL, HDL, and total cholesterol (TC) levels dropped during infection, with LDL and TC levels increasing after recovery, while HDL levels remained low (Fan et al., 2020). Similarly, a study on 597 COVID-19 patients found decreased LDL and TC levels across mild, severe, and critical cases, with HDL levels particularly reduced in critical patients (X. Wei et al., 2020). Another study of 2,629 confirmed cases also noted low LDL and HDL levels (W. Huang et al., 2020).

In a cohort of 97 hospitalized COVID-19 patients, HDL levels were found to decrease as the disease progressed, alongside reductions in ApoA1, CD3+ T cells, and CD8+ T cells (Nie et al., 2020). A comparative study involving 861 COVID-19 patients and 1,108 healthy controls revealed lower HDL and triglyceride levels in COVID-19 patients (C. Wei et al., 2020). Additionally, a study of 71 COVID-19 patients in Wenzhou, China, compared to 80 controls, found significantly lower HDL, LDL, and TC levels in the infected group (Hu et al., 2020).

Both Fan et al. and C. Wei et al. hypothesized that liver damage could explain the reduced cholesterol levels, as liver function plays a key role in lipid metabolism (Fan et al., 2020; X. Wei et al., 2020). This hypothesis is supported by another study involving 19 COVID-19 pneumonia patients and 15 non-COVID pneumonia patients, which found elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), suggesting liver impairment (D. Zhao et al., 2020). The liver damage could be attributed to the oxidative stress induced by COVID-19, which may reduce cholesterol synthesis.

Epidemiological Studies on CAC (COVID-19 Associated Coagulopathy)

Infections, including COVID-19, can induce thrombosis by increasing the expression of tissue factors on immune cells (Connors & Levy, 2020). Reports have consistently shown altered coagulation patterns in patients with COVID-19, termed COVID-19 associated coagulopathy (CAC). Early data from China indicated significant coagulopathy among COVID-19 patients, with 36% showing elevated D-dimer levels, and smaller percentages exhibiting prolonged activated partial thromboplastin time and elevated prothrombin levels (Chen et al., 2020). Additional reports include cases of severe pulmonary embolism in ICU patients (Pishgahi et al., 2020) and high levels of prothrombin among 138 patients in a Wuhan hospital, with 26% of ICU patients displaying high D-dimer levels (D. Wang et al., 2020).

A broader study involving 191 hospitalized patients linked high D-dimer levels at admission to increased mortality rates (Ramanathan et al., 2020). Another investigation highlighted that deceased patients exhibited markedly high D-dimer and fibrin degradation product levels, increased prothrombin time, and widespread dissemination of intravascular coagulation, suggesting a strong connection between COVID-19 and coagulation disorders (Tang, Li, Wang, & Sun, 2020).

Comparative studies of lung autopsies from COVID-19 and influenza patients showed significantly higher levels of CD4 positive T cells and a greater expression of inflammation-related genes in COVID-19 affected lungs. Notably, microthrombi were markedly more prevalent in COVID-19 than in influenza samples, suggesting unique pathophysiological mechanisms at play (Ackermann et al., 2020). Another study indicated that 40% of COVID-19 patients were at high risk of venous thromboembolism (T. Wang et al., 2020), and a different analysis found that 31% of ICU patients with COVID-19 pneumonia developed thrombotic complications, highlighting the necessity of antithrombotic treatment in severely affected patients (Klok et al., 2020).

Further research has identified potential mechanisms contributing to COVID-19-related thrombosis, such as microbial-induced polyphosphate generation causing platelet activation, complement system activation leading to fibrin deposition, and the formation of thrombin via neutrophil extracellular traps. An investigation into 24 ICU patients confirmed that hypercoagulability in COVID-19 is associated with severe inflammatory states (Panigada et al., 2020). These findings collectively underscore the complex interplay between infection, inflammation, and thrombosis in COVID-19 patients, necessitating ongoing research to clarify these mechanisms and improve patient outcomes.

Oxidative stress as a potential therapeutic target

Statins

HMG-CoA reductase inhibitors, commonly known as statins, are a class of drugs used to reduce cholesterol production. Statins have been on the market for many years and are highly effective in treating hypercholesterolemia, significantly reducing cardiovascular complications associated with elevated cholesterol levels. Statin monotherapy is generally well tolerated by patients. However, combining statins with other medications can often lead to side effects. One of the most frequently reported side effects is statin-associated muscle symptoms (SAMS), which is the primary reason for discontinuing statin therapy. In the UK, five statin drugs are currently available: atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin.

In addition to their cholesterol-lowering effects, statins also exhibit immunomodulatory properties. Research indicates that statins possess immunosuppressive effects by inhibiting the mevalonate pathway. This immunosuppressive capability has led to the proposal that statins could be a potential adjunct in the treatment of COVID-19 infection (Castiglione et al., 2020).

Toll-like receptors (TLRs), a class of proteins involved in pathogen recognition, have been shown in animal studies to interact with SARS-CoV-1, resulting in the

upregulation of MyD88 (Myeloid differentiation primary response 88), which triggers the production of the pro-inflammatory factor NF-κB. Another study demonstrated that inhibiting NF-κB significantly improved survival rates in mice infected with SARS-CoV-1. Atorvastatin has shown the ability to mitigate NF-κB activation.

In COVID-19 patients, it has been suggested that the infection induces endotheliitis, an inflammation of the endothelial cells (Varga et al., 2020). During the Ebola outbreak in West Africa, a combination of statins and angiotensin receptor blockers (ARBs) was used to prevent endotheliitis. Based on this, a similar treatment approach has been proposed for managing COVID-19 patients to address endothelial inflammation (Fedson, Opal, & Rordam, 2020).

Statins like lovastatin, simvastatin, and atorvastatin are metabolized in the liver via the cytochrome P450 enzyme CYP3A4. On the other hand, drugs such as cobicistat and ritonavir, which are used in the treatment of COVID-19, inhibit CYP3A. As a result, the concurrent use of cobicistat or ritonavir with these statins could lead to increased plasma concentrations of the statins, raising the risk of statin-associated muscle symptoms (SAMS) and liver toxicity. Therefore, it is recommended that statins such as lovastatin, simvastatin, and atorvastatin should not be taken alongside cobicistat or ritonavir (Castiglione et al., 2020).

The use of statins as a sole treatment for COVID-19 infection is not yet established, and evidence from clinical trials is necessary to determine their actual benefits and safety in COVID-19 patients (K. C. H. Lee, Sewa, & Phua, 2020). An observational study involving 8,910 patients across 11 countries suggested a potential relationship between statin use and reduced COVID-19-related mortality, but the authors emphasized the need for randomized control trials to confirm this association (Mehra et al., 2020). Current guidance recommends against using statins specifically for treating COVID-19, but advises that patients already on statin therapy should continue their medication (European Society of Cardiology, 2020).

A retrospective cohort study conducted in South Korea showed that statin use was associated with a reduction in COVID-19-related mortality, with a hazard ratio (HR) of 0.637 and a 95% confidence interval of 0.425-0.953 (P=0.0283), indicating a significant reduction in mortality for statin users (H.-Y. Lee et al., 2021). Another study by Rossi, Talarico, Coppi, and Boriani found that simvastatin and atorvastatin use was linked to lower mortality in COVID-19 patients (Rossi et al., 2020).

Given statins' well-established cholesterol-lowering and anti-inflammatory effects, they could be beneficial for hypercholesterolemic patients with COVID-19. Several clinical trials are currently underway to further investigate the potential role of statins in COVID-19 treatment.

Nrf2 activators

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a pivotal redox-sensitive transcription factor that maintains intracellular oxidative balance. Under basal physiological conditions, Nrf2 is sequestered in the cytoplasm through its interaction with Kelch-like ECH-associated protein 1 (Keap1), which facilitates Nrf2 ubiquitination and subsequent proteasomal degradation (Olagnier et al., 2020). Exposure to reactive oxygen species (ROS) or electrophilic stress induces structural modifications in Keap1, leading to disruption of the Keap1–Nrf2 complex (Lou et al., 2021). Freed Nrf2 translocates into the nucleus, where it binds to antioxidant response element (ARE) sequences within the promoter regions of cytoprotective genes, thereby enhancing their transcription (Sardu et al., 2020). The coordinated upregulation of these antioxidant and detoxifying enzymes mitigates oxidative stress, attenuates excessive inflammatory responses, and preserves endothelial integrity.

Emerging evidence indicates that impaired Nrf2 signaling is associated with several comorbidities linked to severe COVID-19 outcomes. Advancing age is characterized by diminished Nrf2 activity, resulting in elevated ROS accumulation and heightened vulnerability to oxidative injury (Bhandari et al., 2021). Similarly, obesity is associated with reduced Nrf2 activation, while suppression of the Keap1/Nrf2 axis has been implicated in the pathogenesis of diabetes mellitus through increased oxidative damage in pancreatic β-cells (Mohiuddin & Kasahara, 2021). Endothelial dysfunction and thrombotic complications—hallmarks of critical COVID-19—are exacerbated by oxidative stress, whereas Nrf2 activation confers endothelial protection and limits inflammatory cytokine amplification (Bousquet et al., 2020). Notably, experimental findings suggest that females exhibit relatively higher Nrf2 activity than males, which may partly account for observed sex-based differences in disease severity (Liskova et al., 2021). Furthermore, Nrf2 has been shown to suppress cytokine storm by negatively regulating the NF-κB signaling pathway. Collectively, these findings underscore the therapeutic potential of targeting the Keap1/Nrf2 pathway to attenuate COVID-19 severity.

Numerous natural and synthetic Nrf2 activators have been identified, and their relevance in SARS-CoV-2 management continues to gain attention. Bioactive compounds derived from fermented foods, fruits, vegetables, and plant secondary metabolites particularly flavonoids that have demonstrated the capacity to stimulate Nrf2 signaling and may contribute to reducing disease severity (Izadi et al., 2021). In addition, modalities such as controlled ionizing radiation and ozone therapy have been reported to exert beneficial effects in COVID-19 pneumonia, potentially through activation of the Nrf2 pathway (Calabrese et al., 2021).

Glutathione (GSH)

Glutathione (GSH) is a water-soluble intracellular antioxidant that plays a central role in cellular redox homeostasis by facilitating the detoxification of hydrogen peroxide (H_2O_2) and supporting the functional activity of major antioxidant enzymes, including glutathione peroxidases, peroxiredoxins, and thioredoxins. Clinical observations have indicated that diminished GSH levels may contribute to heightened vulnerability to SARS-CoV-2 infection, particularly among elderly individuals with underlying conditions such as hypertension, diabetes mellitus, and obesity [67]. Furthermore, GSH has been reported to reduce viral replication and viral load, attenuate oxidative stress, suppress the release of pro-inflammatory cytokines (e.g., IL-6, IL-8, and TNF-α), and limit thrombotic complications, while also exerting immunomodulatory effects [67]. A recent case report demonstrated that administration of 2 g GSH, either orally or intravenously, significantly improved dyspnoea in patients with COVID-19 (*Horowitz et al., 2020*), highlighting the potential therapeutic value of restoring depleted GSH levels.

N-acetyl cysteine (NAC)

N-acetylcysteine (NAC), an FDA-approved mucolytic agent widely used in the management of chronic obstructive pulmonary disease, is currently being evaluated in multiple clinical trials involving patients with

COVID-19. As a precursor of glutathione (GSH), NAC plays a central role in cellular redox homeostasis by serving as an electron donor in reactive oxygen species (ROS) detoxification. Preclinical investigations in rodent models have demonstrated that NAC mitigates the harmful effects of angiotensin II, partly through modulation of ACE2-related pathways. In addition, in vivo studies in influenza and respiratory syncytial virus models have shown that NAC suppresses NF-κB activation, highlighting its anti-inflammatory potential (Poe & Corn, 2020).

Beyond its antioxidant and anti-inflammatory properties, NAC also exhibits anticoagulant and thrombolytic activities. It reduces disulfide (-S–S-) bonds within large von Willebrand factor (vWF) multimers to sulfhydryl (-SH) groups, promoting their fragmentation and subsequent platelet disaggregation. Supporting these findings, experimental models indicate that NAC attenuates oxidant generation and decreases the production of coagulation factors. Collectively, both experimental and clinical evidence suggest that NAC, when used alongside standard therapy, may represent a promising adjunctive treatment strategy in COVID-19, particularly among high-risk populations (de Alencar et al., 2021). The proposed mechanisms underlying its beneficial effects during SARS-CoV-2 infection are illustrated in Figure.

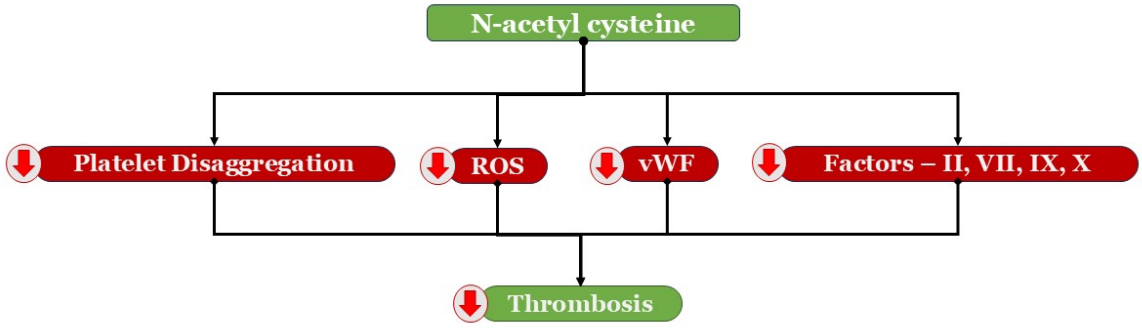

Figure 3: Pharmacological targets of NAC in COVID-19 patients

Vitamin C (ascorbic acid)

Vitamin C is a water-soluble essential micronutrient required for redox homeostasis, immune competence, and inflammatory regulation. Inadequate status promotes oxidative stress, heightened inflammatory responses, and impaired host defense (Arvinte et al., 2020). European dietary recommendations suggest approximately 90 mg/day for men and 80 mg/day for women to maintain plasma concentrations near 50 µmol/L. Circulating levels around 23 µmol/L indicate hypovitaminosis, whereas concentrations below 11 µmol/L reflect overt deficiency. Pharmacokinetic evidence from healthy individuals demonstrates that an intake of about 200 mg/day achieves plasma concentrations of 70–90 µmol/L, while doses near 400 mg/day may be warranted during acute infectious conditions (Chiscano-Camón et al., 2020). Individuals with suboptimal vitamin C status appear more susceptible to pneumonia and other respiratory tract infections, and may benefit from increased intake. Long-term prospective data involving over 19,000 participants followed for two decades revealed that those within the highest quartiles of plasma vitamin C exhibited approximately a 30% lower incidence of pneumonia. Consistently, meta-analytic findings indicate reduced pneumonia risk among individuals receiving oral supplementation, particularly in those with baseline deficiency (J. Zhang et al., 2020).

Emerging evidence further links inadequate vitamin C status with increased severity of COVID-19, including a higher risk of acute respiratory distress syndrome (ARDS) and mortality. In critically ill patients with COVID-19, survivors have been reported to possess higher plasma concentrations compared with non-survivors (Ma et al., 2021). Observational data from patients with COVID-19–associated ARDS have also demonstrated profoundly reduced or undetectable vitamin C levels in most cases. Therapeutic investigations suggest potential benefit of high-dose intravenous administration (e.g., 24 g/day) in critically ill patients (Colunga et al., 2020), with reported improvements in oxygenation parameters. A plausible explanation is that critical illness accelerates metabolic consumption and turnover of vitamin C, thereby increasing physiological requirements and predisposing to rapid depletion (Blanco et al. 2020).

Several biological mechanisms may underlie the protective role of vitamin C in severe viral infections. It may attenuate viral entry by modulating ACE2 receptor expression on endothelial cells, enhance antiviral defense through upregulation of interferon production, and suppress pro-inflammatory signaling via inhibition of the NF-κB pathway. Additionally, vitamin C may limit neutrophil extracellular trap formation, thereby reducing endothelial injury and thrombotic complications. It also contributes to preservation of endothelial barrier integrity, supports tissue repair and wound healing, mitigates oxidative damage, and may consequently reduce the development and progression of ARDS (Kashiouris et al., 2020).

Vitamin D

Vitamin D, a fat-soluble vitamin, is obtained through sunlight exposure or dietary supplementation. Optimal serum levels of vitamin D, around 30 ng/mL, are essential for proper immune system modulation, whereas levels below 20 ng/mL indicate deficiency and 21–29 ng/mL are considered insufficient (Zhang et al., 2020). Recent randomized clinical trials have highlighted the therapeutic potential of vitamin D against SARS-CoV-2 infection, and reviews have corroborated its role in reducing COVID-19 severity and mortality. This protective effect is partly attributed to vitamin D's enhancement of innate immunity, which can lower viral load and prevent overactivation of the adaptive immune system and cytokine storms (Kieliszek & Lipinski, 2020), thereby mitigating disease progression. Additionally, vitamin D exhibits antioxidant properties in the context of SARS-CoV-2 infection. Notably, combined supplementation with

vitamin D and L-cysteine has been shown to more effectively reduce oxidative stress and inflammation than either compound alone. Magnesium deficiency, which impairs immune function and increases inflammation, can further compromise host defense; supplementation with magnesium alongside vitamin D has been observed to enhance immune responses. Similarly, co-supplementation of vitamin D with N-acetylcysteine (NAC) shows promise in alleviating oxidative stress during SARS-CoV-2 infection. Certain populations, including individuals with comorbidities such as hypertension, diabetes, obesity, or advanced age, as well as Black and dark-skinned individuals, due to reduced UVB-mediated vitamin D synthesis, are at higher risk of deficiency. Overall, accumulating evidence supports the significant benefits of vitamin D supplementation, particularly for vulnerable groups, in mitigating COVID-19 outcomes.

Zinc

Zinc is recognized for its potent antioxidant properties. It enhances respiratory epithelial function and inhibits caspase activation and apoptosis, further supporting its antioxidant effects. Zinc may also prevent SARS-CoV-2 entry into host cells by inhibiting RNA-dependent RNA polymerase (RdRp) and reducing ACE-2 expression. Concurrently, it boosts immune responses by promoting IFNα production and suppressing the NF-κB signaling pathway, thereby lowering pro-inflammatory cytokine levels. Additionally, zinc enhances the activity of NK cells, CD8+ T cells, and B cells, increases antibody production, and modulates regulatory T (Treg) cell function to prevent hyperinflammation. Clinical studies have demonstrated its potential efficacy in COVID-19, with zinc supplementation improving respiratory outcomes and oxygen saturation in infected patients (Shakoor et al., 2021).

Vitamin E (α-tocopherol) and selenium

Vitamin E and selenium are well-recognized as potent antioxidants. A retrospective analysis in China revealed a positive correlation between selenium levels and COVID-19 recovery rates. Epidemiological and observational studies further indicate that deficiencies in these nutrients compromise immune responses and enhance viral pathogenicity. Conversely, supplementation with vitamin E and selenium has been shown to improve resistance to respiratory infections. Combined administration of these nutrients enhances CD4+ and CD8+ T cell activity and promotes IL-2 secretion, thereby reducing the risk of infections. Their antioxidant properties also help inhibit reactive oxygen species (ROS) production. While α-tocopherol is the most biologically active form of vitamin E, mixed tocopherols exhibit greater efficacy than α-tocopherol alone, likely due to the diversity of cellular receptors they engage. Despite their potential in supporting immunity and antioxidant defenses against SARS-CoV-2, rigorous clinical trials are still required to confirm their effectiveness (Derwand & Scholz, 2021).

PROPOSED SOLUTION & RESULTS ACHIEVED

Extensive investigations since the emergence of COVID-19 have established that infection with SARS-CoV-2 is strongly associated with endothelial dysfunction, hyperinflammation, and coagulopathy. Prior research has demonstrated:

- Elevated D-dimer, von Willebrand factor (vWF), IL-6, and CRP levels in severe cases.
- Increased incidence of venous and arterial thromboembolic events in critically ill patients.
- Downregulation of ACE2 following viral binding, leading to imbalance in the renin–angiotensin system (RAS).
- Reduced antioxidant enzyme activity (SOD, CAT, GPx) and glutathione depletion in severe disease.
- Decreased LDL, HDL, and total cholesterol levels during acute infection, possibly linked to hepatic dysfunction and systemic inflammation.
- Observational associations between statin therapy and reduced mortality, though randomized evidence remains limited.

While these findings independently implicate oxidative stress, thrombosis, and lipid dysregulation, previous literature has largely addressed these components in isolation rather than within a unified mechanistic framework.

The present updated paper proposes an integrated Oxidative Stress–Hypercholesterolemia–Thrombosis Axis as a central pathogenic mechanism in COVID-19–associated coagulopathy. The novelty of this work lies in:

(A) Mechanistic Integration

We propose that SARS-CoV-2–mediated ACE2 downregulation increases Ang II accumulation, which stimulates NADPH oxidase–dependent ROS production. In hypercholesterolemic individuals, elevated LDL becomes oxidized (OxLDL) under high oxidative stress conditions. OxLDL further:

- Activates macrophages and neutrophils
- Enhances NET formation
- Amplifies ROS generation
- Promotes endothelial injury and vWF release

This establishes a self-amplifying redox–inflammatory loop, directly linking metabolic comorbidity with thrombotic severity.

(B) Biomarker-Driven Validation Strategy

We propose systematic clinical measurement of:

- Circulating ROS and oxidative stress markers (e.g., MDA, 8-isoprostane)
- OxLDL levels
- Antioxidant enzyme activity (SOD, GPx, CAT)
- vWF multimers and NET markers
- Lipid profile dynamics across disease stages

This structured approach allows validation of oxidative stress as a measurable driver of COVID-19–associated thrombosis.

(C) Targeted Therapeutic Modulation

- Based on the integrated model, we propose a multi-target adjunct strategy:
- Redox Restoration – Glutathione, NAC, Nrf2 activators
- Endothelial Protection – Statins, ACE2/Ang 1–7 pathway modulation
- Antithrombotic Support – Standard anticoagulation with adjunct antioxidant therapy
- Metabolic Risk Optimization – Early lipid profile monitoring and OxLDL assessment

This approach differs from prior symptom-directed management by addressing upstream redox imbalance. Although the current study is conceptual and mechanistic in its approach and not an interventional clinical trial, there are a number of key advances that the revised synthesis offers. Firstly, it provides a comprehensive pathophysiological model that integrates oxidative stress, hypercholesterolemia, neutrophil extracellular trap (NET)

formation, endothelial dysfunction, and thrombosis into a cohesive model of COVID-19. Secondly, it hypothesizes a potential high-risk group, suggesting that hypercholesterolemic patients with high reactive oxygen species (ROS) and oxidized LDL (OxLDL) are a high-risk group who are predisposed to developing severe thrombotic complications. Thirdly, it provides a prioritized list of therapeutic targets by suggesting that antioxidant and redox modulation approaches, such as N-acetylcysteine (NAC), glutathione (GSH), and Nrf2 activators, are mechanistically sound and therefore adjunctive therapies rather than supplements that are administered empirically. Additionally, the review provides a research roadmap by developing three testable hypotheses: (i) ROS levels are directly correlated with thrombotic events in COVID-19, (ii) OxLDL levels are increased in hypercholesterolemic patients with severe disease outcomes, and (iii) redox balance restoration reduces vWF release and NET-mediated thrombosis.

In contrast to prior studies that evaluated oxidative stress, thrombosis, or lipid alterations separately, this updated work introduces a comprehensive redox-metabolic-thrombotic axis as a unifying explanation for severe COVID-19 outcomes. The proposed solution emphasizes mechanistic integration, biomarker validation, and targeted adjunctive therapy aimed at oxidative stress modulation.

CONCLUSION

This review highlights recent evidence supporting the hypothesis that oxidative stress is strongly implicated in the etiology of thrombosis in COVID-19 infection. Emerging studies point to the increased production of reactive oxygen species (ROS) via disruption of the renin-angiotensin-aldosterone system (RAAS) as one of the mechanisms causing endothelial dysfunction. Endothelial dysfunction leads to the secretion of pro-thrombotic factors, including von Willebrand factor (vWF), which increases the incidence of thrombotic complications in severe cases of COVID-19.

Furthermore, high cholesterol appears to be another pathway that amplifies the disease process. High concentrations of LDL molecules and the formation of oxLDL increase oxidative stress and inflammation, and the binding of oxLDL to neutrophils and the development of NETs could create a positive feedback loop that escalates thrombotic events and multiple organ damage in critical cases. In summary, this review highlights a possible mechanistic connection between oxidative stress, endothelial dysfunction, and thrombosis associated with COVID-19, emphasizing the role of hypercholesterolemia in this relationship. More research is highly required to prove the validity of this mechanism in practice. Specifically, the following studies should be conducted:

1. Direct measurement and correlation of redox biomarkers (e.g., ROS levels) with thrombotic outcomes in COVID-19 patients
2. Quantification of OxLDL levels and their association with disease severity and coagulopathy
3. Investigation of NET formation and its contribution to thrombosis in clinical settings
4. Evaluation of circulating vWF as a marker of endothelial dysfunction and thrombotic risk.

In conclusion, while our review offers critical insights into the potential mechanisms of thrombosis in COVID-19 and the role of hypercholesterolemia, future research is essential to establish these hypotheses and develop effective therapeutic strategies.

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DECRALATION

Ethics approval and consent to participate

Not Applicable

Artificial Intelligence-Assisted Technology

Artificial intelligence–assisted technology was used to improve language clarity during manuscript preparation. All substantive content, analyses, interpretations, and conclusions are the sole responsibility of the author.

Consent for publication

Not Applicable

Availability of data and materials

The data used in this study are publicly available from the UNICEF MICS program upon reasonable request and subject to standard data access procedures. Details on how to obtain the data are available on the data provider's official website.

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Authors' contributions

Ashfaq Ahmed, Hrishik Iqbal, Md Shaki Mostaid: Web-Survey Design, Supervised the Data Collection Process, And Checked Writing, Approved Methodology, Manuscript Editing and Supervised All Steps;
Afroza Zannat, Srikumar Chakravarthi, Nikolaos Syrmos: Final Editing, Reviewing, And Supervising the Steps.

AUTHORS INFORMATION

Hrishik Iqbal completed his Master of Science in Biotechnology and Bachelor of Pharmacy from BRAC University, Dhaka, Bangladesh. He began his research career with pharmaceutical formulation studies, where his undergraduate work focused on improving the biopharmaceutical characteristics of poorly soluble drugs. Following his undergrad, he gained experience in clinical research through internships and collaborative studies at Renata PLC, Bangladesh. As a clinical research coordinator and product manager within the Onco-hematology portfolio, his responsibilities included clinical trial coordination, oncology product strategy, and cancer care. His research work includes studies in infectious diseases, oncology, and pharmacogenomics, with a particular focus on the impact of genetic polymorphisms. He has contributed to multiple peer-reviewed publications and clinical research projects, as well as promoting skin cancer

awareness in Bangladesh through his postgraduate thesis. His research interests center on clinical trials, molecular oncology, and pharmacogenomics, with an emphasis on translational applications.

Dr. Md. Shaki Mostaid joined the Department of Pharmaceutical Sciences, North South University in January, 2021. Prior to that he served as an Assistant Professor at the Department of Pharmacy, Brac University. He completed his PhD from the Department of Psychiatry, University of Melbourne, Australia in 2018. His doctoral studies involved identifying suitable blood biomarkers for treatment-resistant schizophrenia using genomic, transcriptomic, and proteomic analysis tools. Following this he was awarded the Harley Hotchkiss Samuel Weiss Postdoctoral Research Fellowship to pursue postdoctoral training at the Department of Medical Genetics, University of Calgary, Canada. His doctoral and postdoctoral works led to several internal publications among which 5 are in nature research journal group. His research area focuses on genomic, transcriptomic and proteomic analysis of candidate genes for suitable biomarkers in various mental health disorders specially schizophrenia and depression. Prior to the doctoral studies, Dr. Mostaid completed his Bachelor of Pharmacy (Honors) and Masters of Pharmacy from the Department of Pharmacy, University of Dhaka. He also worked as a lecturer at the Department of Pharmacy, Northern University Bangladesh.

Prof. Dr. Nikolaos Syrmos, MD, MSc, PhD, is a board-certified Consultant Neurosurgeon and Paediatric Neurosurgeon from Thessaloniki, Greece. Trained in Verona, Italy, and Aristotle University of Thessaloniki, he completed residencies in Crete and AXEPA University Hospital. His PhD thesis focused on the endoscopic anatomy of the fourth ventricle. He has broad research interests spanning paediatric neurosurgery, vascular neurosurgery, endoscopic procedures, and experimental medicine.

Srikumar Chakravarthi serves as Deputy Vice Chancellor (Academic, Research and Innovation) at SEGi University & Colleges, with 28 years in academic leadership, research administration, and medical education. Previously, he was Director for Research, Innovation, Enterprise, and Postgraduate Studies at MAHSA University, Dean of the Graduate School of Medicine at Perdana University, and Dean at International Medical University. A prolific researcher, he has published 300+ papers in peer-reviewed journals (H-index 48, 12,000+ citations), secured numerous patents in biotechnology, AI, healthcare and more, and earned numerous international awards

Afroza Zannat is a Lecturer in the Department of Chemistry under the Faculty of Science and Engineering at European University of Bangladesh. She has been serving in this role since 2017. Afroza obtained both her BSc and MSc degrees in Applied Chemistry and Chemical Engineering from Noakhali Science and Technology University. Her teaching expertise includes courses such as Polymer Science, Chemistry of Materials, General Chemistry, and Environmental Chemistry. Afroza is actively involved in research, focusing particularly on computational chemistry, and has contributed several notable publications. Her works include theoretical investigations into thermophysical properties, chemical reactivity, and biological indicators of substances such as cannabinoids and ionic liquids. Her commitment to continuous learning and mentorship shapes her academic journey. She views teaching as a vocation marked by the meaningful exchange of knowledge, collaborative growth, and the inspiration of future scholars.

Ashfaq Ahmed completed his Master of Pharmacy in Pharmacology and Clinical Pharmacy from North South University, Dhaka. His thesis focused on genetic polymorphism and the risk of multiple sclerosis. His research interest encompasses the impact of genetic polymorphism on change of drug activity, psychosis, and autoimmune diseases.

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Correspondence All inquiries and requests for additional materials should be directed to the Corresponding Author.

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