Is It All About Endothelial Dysfunction and Thrombosis Formation? The Secret of COVID-19

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Abstract
The world is in a hard battle against COVID-19. Endothelial cells are among the most critical targets of SARS-CoV-2. Dysfunction of endothelium leads to vascular injury following by coagulopathies and thrombotic conditions in the vital organs increasing the risk of life-threatening events. Growing evidences revealed that endothelial dysfunction and consequent thrombotic conditions are associated with the severity of outcomes. It is not yet fully clear that these devastating sequels originate directly from the virus or a side effect of virus-induced cytokine storm. Due to endothelial dysfunction, plasma levels of some biomarkers are changed and relevant clinical manifestations appear as well. Stabilization of endothelial integrity and supporting its function are among the promising therapeutic strategies. Other than respiratory, COVID-19 could be called a systemic vascular disease and this aspect should be scrutinized in more detail in order to reduce related mortality. In the present investigation, the effects of COVID-19 on endothelial function and thrombosis formation are discussed. In this regard, critical players, laboratory findings, clinical manifestation, and suggestive therapies are presented.

Keywords
COVID19, endothelial dysfunction, thrombosis

Date received: 11 July 2021; revised: 10 August 2021; accepted: 12 August 2021.

Introduction
COVID-19 has been mesmerized the residents of earth. They mobilize all their facilities for fighting against this unexpected enemy. The causative agent, SARS-CoV-2, infects host cells in humans via binding to a zinc-metallopeptidase, angiotensin-converting enzyme-2 (ACE2).¹ Among different host cells throughout the body, those in the respiratory system are at the frontline. Specifically, one-third of the overall cells in the lungs are endothelial cells.² Endothelial cells are directly infected by SARS-CoV-2 substantiating in the presence of viral inclusion bodies in them.³ This phenomenon is further confirmed by the emergence of endotheliitis of the submucosal vessels in histologic examinations.⁴ Although the presence of viral bodies in the target cells imply direct action of SARS-CoV-2 on these cells resulting in diffuse endothelial inflammation, it remains elusive whether endothelial derangement originates from direct infection or it is a side effect of SARS-CoV-2-induced cytokine storm.⁵,⁶

Although increased expression of ACE2 level exacerbates endothelial dysfunction and related inflammation during COVID-19 infection, this receptor possesses an inhibitory effect on the proliferation of endothelial cells which ultimately attenuates endothelial inflammation.²,⁶⁷ As shown in Figure 1, there are some other molecules other than ACE2 like transmembrane serine protease 2,⁸ sialic acid,⁹ and extracellular matrix metalloproteinase inducer (CD147, basigin)¹⁰ that facilitates
the entrance of SARS-CoV-2. Along with ACE2, these three molecules are expressed in arterial and venous endothelial cells as well as arterial smooth muscle cells.\textsuperscript{11}

Comparison of lung tissues among COVID-19 patients, patients with respiratory distress syndrome (ARDS) secondary to influenza A (H1N1), and control group revealed severe endothelial injury and widespread thrombosis along with microangiopathy in the former group. The presence of alveolar microthrombi is significantly higher in COVID-19 than in H1N1 patients.\textsuperscript{12} Invasion of the host cell by SARS-CoV-2 leads to disruption of endothelial cells membrane followed by severe pulmonary injury as reported in a case series study.\textsuperscript{12} It is reasonable that the effects of endothelial dysfunction and thrombosis formation are dependent on the localization of the virus, which is contingent on the distribution of its receptor.\textsuperscript{13} Nonetheless, endotheliitis and systemic disturbances in microcirculatory function in a wide range of vascular beds terminate in apoptosis and pyroptosis of endothelial cells in patients with COVID-19.\textsuperscript{4} The endothelial-related complications substantially contribute to life-threatening outcomes like a venous thromboembolic disease.\textsuperscript{14} This survey tried to scrutinize different aspects of endothelial injury and consequent thrombosis-related outcomes raised by COVID-19.

Is it really all about endothelium?

Endothelium is a dynamic entity with crucial roles in responding to infection, regulating vessels tone, and maintaining vascular homoeostasis.\textsuperscript{15} It secretes several types of cytokines and chemokines guiding leukocytes to the injured site and activating inflammatory responses. These mediators with inherent inflammatory nature in turn activate endothelial cells and provoke injury that eventually promotes prothrombotic conditions.\textsuperscript{14} Accordingly, the inability of the endothelium to maintain vascular homoeostasis, which represents in certain alterations at the glycocalyx, intercellular junctions, and endothelial cells escalate its impairment toward a more severe procoagulant and antifibrinolytic states.\textsuperscript{16} Increased permeability of the endothelium is the underlying reason of almost all endothelial-related destructive sequels.\textsuperscript{2} Tissue edema, inflammation, and organ ischemia result from a loss of vascular homoeostasis and microvascular malfunction.\textsuperscript{4}

Endothelial damage is acutely intensified upon exposure of the pulmonary system to infectious agents, which reduces fibrinolysis capacity leading to the surplus formation of thrombin.\textsuperscript{17-19} Moreover, thrombin itself induces endothelial damage as well.\textsuperscript{2,20} Thrombotic episodes, even short time, and consequent hypoperfusion and hypoxemia not only impose adverse effects

\begin{figure}
\centering
\includegraphics[width=\textwidth]{sars_cov_2_endothelium.png}
\caption{SARS-CoV-2 traverses the endothelium through binding of its S1 glycoprotein to its cognate receptor, ACE2. This receptor is expressed on the surface of endothelial cells. Also, some other molecules like transmembrane serine protease 2 (II), sialic acid (II), and extracellular matrix metalloproteinase inducer (III) facilitate this process. Subsequently, immune cells sense the presence of the virus, and inflammatory responses emerge. This may lead to cytokine storm, increasing the coagulation pathways, thrombin activation, and eventually clot formation and thrombosis. Movement of thrombotic particles in the vessels of vital organs results in the shortage of blood supply representing different though life-threatening clinical manifestations. Abbreviations: ACE2, angiotensin-converting enzyme.}
\end{figure}
on the pulmonary system, but also other organs like the cardiovascular system, kidneys, central nervous system, and skin are being impaired. With this background, the incidence of thrombotic incidents is expected to happen in COVID-19 patients with lung injury.21

Other than respiratory, the cardiovascular system has a determinant role in endothelial dysfunction and severity of COVID-19.22 Endothelial dysfunction substantially contributes to hypertension, diabetes, and obesity, which are traditionally known as cardiovascular risk factors. These are characterized as the most common comorbidities in COVID-19 patients that could predict worse clinical outcomes in such patients.73 Diabetic and obese patients are chronically exposed to adiponectin, which damages the endothelial cells through activation of inflammasome NLRP3 and secretion of IL-1β.24

Presumably, preexisting endothelial dysfunction due to a history of cardiovascular risk factors is an indicator of developing severe forms of COVID-19 and catastrophic endpoints.74 Other factors that determine the complexity of endothelial dysfunction include age, sex hormones, reactive oxygen species, proinflammatory status, generation of circulating endothelial microparticles progenitor cells ratio, and interestingly, lifestyle.25 Cardiovascular disease (CVD) and related risk factors are more seen in aged population. This population usually experiences severe forms of COVID-19 mainly due to endothelial dysfunction and related side effects. Also, the role of sex hormones is evident in this area. Estrogen is decreased with increasing age. This hormone is in close relation with endothelial function through balancing the level of oxidative stress, regulating the renin-angiotensin system, and modulating cellular endothelin.26-30

**Endothelial Dysfunction and Thrombosis**

It is not far from reality assuming COVID-19 as a systemic vascular disease.4 Following infection and hemostatic changes, the incidence of coagulopathies would be common accelerating the progress of disease course especially in those who are vulnerable to thrombotic events.31-34 Injury to the endothelium activates the coagulation system facilitating the formation of thrombi.35 SARS-CoV-2, like other pathogens, activates coagulopathy pathways via inflammatory responses and obviously, there is a strong connection between coagulation pathways and immune system.36 The COVID-19-related coagulopathy is believed to be attributed to the surge of inflammatory response rather than the inherent character of the virus.37 Vessels and the immune system are the potential targets of this virus leading to systemic vasculitis and attenuated immune function.14 Also, diffuse microcirculatory and macrovascular thrombosis were detected in the lung tissue of COVID-19 patients.38 Entry of SARS-CoV-2 via ACE2 on type II alveolar pneumocytes causes cytopathological changes at the interface between alveoli and capillaries which are followed by rapid and progressive alveolar damage, hyperinflammation, and consequent cytokine storm.39 Thrombi make a significant barrier in gas exchange function and result in multisystem organ failure.15,40,41

Hospitalized COVID-19 patients are prone to venous thromboembolism (VTE)32,43 which may be undiagnosed in complex cases.44 In such patients, some factors including immobility, mechanical ventilation, existence of catheters that are being inserted in the veins, nutritional deficiencies, and suboptimum production of coagulation factors due to liver disorders as well as hemostatic changes increase the risk of VTE.45-48 Severe illness and hypoxia additionally exacerbate thrombotic features. In another point of view, patients with a history of coagulopathies may not receive sufficient care in terrible pandemic situations and this put them at a riskier level.44

Thrombotic-related complications like acute pulmonary embolism and emergence of microthrombi in myocardial vessels enhance the risk of disseminated intravascular coagulation (DIC)25,48,49 and fatal outcomes.2,15,36,50 In the following, we discuss some of the prominent factors that affect endothelial function in relation to COVID-19. These include the immune system and its components, oxidative stress, and nitric oxide. Immune system and its components: Hyperinflammatory response COVID-19 often manifests in immunological dysregulation and increased penetration of immune cells into the lung tissues.51,52 In addition, persistent inflammation changes the function of biological anticoagulants, alters the hemostatic balance in favor of increased platelet reactivity, smooths endothelial cell dysfunction, and thrombus formation.53,54 For instance, platelets, which harbor granules of polyphosphates, are activated and released their contents. This triggers a cascade of signaling pathways that totally result in thrombotic conditions.41

Moreover, activation of the complement system, as a part of both innate and acquired immunity, may lead to tissue injuries.53-60 as SARS-CoV-2 has the potential to activate the complement system directly.60 Significant accumulation of the components of the complement system like C5b-9, C4d, and mannann-binding lectin (MBL)-associated MASp261 leads to calamitous microvascular injury and is followed by endotheliitis and thrombotic events.62 C5a is a central component of the complement system that injures a considerable amount of cardiomyocytes63 and involves in the pyroptosis of the immune cells that are infected by SARS-CoV-2.60,64 In addition, C5a behaves like an anaphylatoxin and causes sepsis, acute lung injury,65,66 early proinflammatory responses, and activation of immune cells like neutrophils and macrophages. These activities lead to the release of histones and reactive oxygen species (ROS) that injure the endothelium, facilitates the formation of thrombosis, and causes multiorgan dysfunction.67,68

C3a contributes greatly to lung impairment.69,70 Like C5a, C3a activates endothelial cells and increases endothelial permeability.71,72 This continues with the influx of calcium into the endothelial cells. Hypoxia augments this vicious cycle by releasing more C3a.2,73

Oxidative stress: Oxidative stress raised by COVID-19 imposes impairment in DNA methylation which leads to ACE2 demethylation augmenting and facilitates the
SARS-CoV-2 entry into the bloodstream. In an animal model study, increased oxidative stress caused endothelial dysfunction and lungs vasoconstriction. The resultant hypoxia deteriorated lung perfusion and exacerbated oxygen shortage. Other than oxygen tension, activation of resident cells or inflammatory cells also depletes the antioxidant capacity of the lungs leading to organ injury. 

Another explanation for the occurrence of severe forms of COVID-19 in aged subjects may be related to superoxide dismutase-3 and activating transcription factor-4, the components of the lung antioxidant system, that are not efficacious in old people.

Nitric oxide (NO): As a vasodilator and antithrombotic factor, NO is released from healthy endothelial vessels and its production is decreased by the injured vessels. Consequently, the function of the vasculature system becomes imbalanced, increasing the risk of hypertension and thrombosis formation.

Laboratory Findings

Hemostatic activation indicates endothelial injury in the vascular system, which manifests in some changes such as thrombotic diffuse intravascular coagulation, thrombocytopenia, and decreased activity of anticoagulants. In the first phase of SARS-CoV-2 infection, there is no significant change in coagulation-related factors like antithrombin-III, fibrinogen, and platelet count. Thereby, neither diffuse intravascular coagulopathy, nor evidence of vasculitis was found in most cases.

With developing the disease course, lymphopenia, increased lactate dehydrogenase, increased inflammatory mediators like C-reactive protein, D-dimer, ferritin, and interleukine-6 become common laboratory findings. Lymphopenia along with hyoalbuminemia may be the result of endothelial disintegration of vascular or lymphatic vessels particularly in severe cases of COVID-19. Apoptotic endothelial cells usually release lactate dehydrogenase into the serum. IL-6 levels may have a correlation with COVID-19 severity and coagulation state. Most of the patients with COVID-19 have elevated creatine phosphokinase, myoglobin, creatinine, and uric acid, which in some cases terminates in renal failure.

Elevated D-dimer in the plasma is associated with the activation of coagulation pathways. This facilitates the incidence of thrombotic events increasing the risk of mortality. The survivors showed shortened prothrombin time, decreased levels of D-dimer and fibrin products. Furthermore, non-survivors significantly fulfilled more criteria of DIC. Prothrombin time, thrombin time, and international normalized ratio are associated to disease severity.

Platelet count and fibrinogen also represent the status of coagulopathy in patients with COVID-19. Platelet count is high or at least higher in COVID-19 than other disorders like sepsis or ARDS. It may contribute to pulmonary inflammation and consequent increased levels of thrombopoietin in the serum. However, there are reports of low platelet count in COVID-19 patients, which were associated to mortality. All of this evidence reinforces the higher risk of coagulopathies and thrombotic events in COVID-19.

Changes in the level of biomarkers following endothelial dysfunction could be useful for the early diagnosis of COVID-19. This is especially important for those who are prone to severe complications like older patients and those with underlying disorders. For example, damaged endothelium releases angiopoietin indicating microvascular injury. It could be considered as a prognostic biomarker because of its significant increase in patients with COVID-19.

Clinical Manifestations

Different levels of ACE2 expression in different organs are reflected in a variety of clinical manifestations of COVID-19. Vascular networks, like vehicles, distribute the virus throughout the body from the brain to the heart to the kidneys. Thereby, endothelial dysfunction is expected to occur in these organs that subsequently endanger patients in rapid hazardous coagulopathies. SARS-CoV-2 is able to bring grave fate such as systemic inflammatory response syndrome (SIRS), ARDS, multiorgan failure, and shock in the affected patients. VTE was developed in a considerable portion of patients with severe COVID-19, which did not use any antithrombotic prophylaxis regimen.

Dysfunctional endothelium, by either direct viral infection or as a sequel of chronic prior impairment, does not efficiently play its protection role against SARS-CoV-2 infection resulting in microcirculation disorder, ARDS, or myocardial infarction (MI) substantiating in lung and/or heart failure. Up to now, pulmonary manifestations are the first symptoms of COVID-19 in the majority of patients. Excess production of liquids in the interstitium is owing to the increased generation of hyaluronic acid due to endothelial damage and pulmonary failure. Similar to ARDS, interstitial- and alveolar edema indicating lung injury were reported in COVID-19 patients. For differential diagnosis, diffuse microcirculatory and macrovascular thrombosis are not common in the ARDS.

Similar to other viral diseases such as influenza, there are reports of coronary occlusion in COVID-19 patients because of plaque rupture. This may be the consequence of the combined effect of SIRS and inflammation at the vascular and plaque level. In addition to the involvement of non-fenestrated endothelium such as those present in the lungs and heart, kidneys and liver with fenestrated and sinusoidal endothelium are also potential targets for SARS-CoV-2.

Suggestive Therapies

One of the impactful therapeutic approaches in COVID-19 patients, which significantly improves clinical outcomes, is to
prevent endothelial dysfunction.\textsuperscript{107} It seems that key elements in the treatment and prevention of COVID-19 are stabilization of the endothelial function and inhibition of destructive events of inflammatory origin. This notion becomes therapeutically paramount considering the ability of SARS-CoV-2 to infect endothelial cells directly. Anti-inflammatory anti-cytokine drugs like ACE inhibitors and statins stabilize the endothelium in addition to interference with viral replication.\textsuperscript{108-112} In this way, IL-6 and tumor necrosis factor (TNF)-inhibitors beside antagonists of endothelin receptors, which are anti-inflammatory agents supporting endothelial function, are under current investigation for use in patients with COVID-19.\textsuperscript{108,112-114}

There are drugs like adenosine deaminase and plerixafor that prevent endothelial apoptosis and instigates endothelial proliferation, totally reduce endothelial permeability and improve endothelial function.\textsuperscript{115-117} Prophylactic approaches like trans-fusion of some factors like platelets, fresh frozen plasma, fibrinogen, and prothrombin complex concentrate could also be useful in the COVID-19 treatment plan.\textsuperscript{6} Adrecizumab is a monoclonal antibody that binds to a vasodilator agent secreted from endothelial cells and named adrenomedullin. This binding results in preserving endothelial integrity and reducing vascular leakage.\textsuperscript{92} Inhibitors of the complement system like eculizumab and rukonest have clinically been used for treating COVID-19 patients.\textsuperscript{118} No death was reported in patients treated with eculizumab.\textsuperscript{119}

The risks of contraindications should be considered in the pharmacotherapy of COVID-19 patients as well. Endothelial dysfunction has been reported as secondary to the consumption of some drugs. Propranolol and sirolimus inhibit endothelial proliferation, carteolol and steroids provoke endothelial apoptosis, and ponatinib induces endothelial damage.\textsuperscript{120-122} In the following, some of the nominated treatments against COVID-19 are discussed. These medications maintain endothelial integrity and function. Several clinical trials are under investigation to find the best approach to improve endothelial function and decrease thrombosis formation in COVID-19 patients (Table 1).

Anticoagulations: Rapid emergence of reports on venous and arterial thrombosis in COVID-19 patients makes researchers pursuing the use of anticoagulation drugs.\textsuperscript{96} Prophylactic anticoagulation therapy reduces the risk of VTE in acute cases.\textsuperscript{123,124} In particular, VTE prophylaxis is recommended in hospitalized COVID-19 patients with respiratory failure, active cancer, heart failure, bedridden patients, and generally, those who require intensive care.\textsuperscript{44,125} Although the risk of overt bleeding in COVID-19 patients is low, these types of medications should be discontinued in the case of contraindications and other approaches should be considered.\textsuperscript{44}

Heparin is a valuable medication based on its anti-inflammatory benefits through binding to inflammatory cytokines, neutralization of the complement system components, modulation of acute-phase proteins besides inhibition of neutrophil chemotaxis and migration.\textsuperscript{126} Heparin improves outcomes of COVID-19 patients via hampering IL-6-induced hyperpermeability of alveolar endothelial cells by protecting their tight junctions.\textsuperscript{49,127} Polyanionic nature of heparin interacts with the binding domain of S1 glycoprotein of SARS-CoV-2 probably interfering with the connection between the virus and the host cells.\textsuperscript{2}

World health organization has approved the use of low-molecular-weight heparins (LMWH) and unfractionated heparin as a prophylactic program.\textsuperscript{128} Prophylactic use of LMWH prevents VTE decreases thrombin generation, and totally alters the course of DIC.\textsuperscript{44} All of the VTE prophylactic doses are critical and missing even one single dose increases the risk of worse outcomes.\textsuperscript{44,129} If contraindication existed, intermittent pneumatic compression as mechanical VTE prophylaxis is applied in immobilized patients.\textsuperscript{128,130} However, VTE was seen in a significant amount of severe cases of COVID-19 despite pharmacologic prophylaxis.\textsuperscript{88}

Based on the hemostatic deteriorations caused by SARS-CoV-2 infection,\textsuperscript{131} some clinicians use intermediate- or full-dose, instead of a prophylactic dose of anticoagulative drugs to prevent microvascular thrombosis.\textsuperscript{88} In the case of acute coronary syndrome with risk of plaque rupture, a refined regimen including dual antiplatelet therapy and full-dose anticoagulation are administered.\textsuperscript{132,133} It seems that a combination of prophylactic and therapeutic doses of anticoagulants are beneficial in COVID-19 patients.\textsuperscript{44} However, the optimum dose remains to be elucidated. Different criteria like severity of the disease and existence of comorbidities are critical determinants in this regard.

Among several medications that have been used to manage patients with COVID-19, some of them have adverse interactions with antiplatelet or anticoagulant agents.\textsuperscript{44} Some of these drugs may increase or decrease the risk of thrombotic events or thrombocytopenia. As an example, bevacizumab which is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, and is under investigation for use in COVID-19 patients, increases the risk of adverse outcomes like MI, cerebrovascular events, and VTE.\textsuperscript{134,135} The efficacy of clopidogrel is diminished by lopinavir/ritonavir (treatment options of AIDS). On the contrary, lopinavir/ritonavir augments the effects of ticagrelor, an inhibitor of platelet aggregation. The action of remdesivir and tocilizumab, which are used as anti-COVID-19 drugs, is opposite to that of lopinavir/ritonavir; thereby increases the effects of clopidogrel while reduces the effects of ticagrelor.\textsuperscript{44}

NO: Food and Drug Administration (FDA) issued emergency approval of NO during SARS outbreak to obtain a better lung function. NO was also nominated as a therapeutic agent in the course of COVID-19.\textsuperscript{136} Vasodilative, angiogenic, and anti-thrombotic properties of NO is useful to support endothelium. While endothelial dysfunction causes impairment in endogenous NO availability either by reduced production or increased degradation, exogenous NO inhalation could compensate its shortage providing endothelial improvement by pulmonary vasodilation, direct antiviral activity, inhibition of platelet adhesion, and aggregation.\textsuperscript{15,137,138}

In addition, dietary inorganic nitrate is efficient for its antimicrobial activity, capability to restore endothelial function,
| Identifier       | Complications                                                                 | Study type | Observation/intervention                                                                 | Number of participants |
|------------------|-------------------------------------------------------------------------------|------------|------------------------------------------------------------------------------------------|------------------------|
| NCT04357847      | Endothelial dysfunction                                                        | Obs. Cohort| Assessment of endothelial and homeostatic changes                                          | 100                    |
| NCT04406545      | Endothelial dysfunction                                                        | Obs. Cohort| Changes in systemic microvascular endothelial function in the acute phase of COVID-19 through laser Doppler | 25                     |
| NCT04408365      | Endothelial dysfunction                                                        | Obs. Cohort| Changes in plasma bio-adrenomedullin, proenkephalin, dipeptidyl peptidase-3, renin, and angiotensin II | 82                     |
| NCT04359212      | Thromboembolism, venous                                                        | Obs. Cohort| Thromboprophylaxis with low-molecular-weight heparin or fondaparinux                      | 90                     |
| NCT04335162      | Acute coronary syndrome, myocardial infarction, myocarditis, venous thromboembolism, deep Vein thrombosis, pulmonary embolism | Obs. Cohort| Determine the incidence of cardiomyopathies and venous thromboembolism (time frame: 28 days) | 100                    |
| NCT04405869      | Pulmonary thromboembolism                                                      | Obs. Cohort| Analysis of incidence of thromboembolic events (time frame: 1 month)                      | 300                    |
| NCT04405232      | Thrombosis bleeding anticoagulation                                            | Obs.       | Prevalence and characteristics of coagulation abnormalities and their predictive value for respiratory failure requiring ventilation, multiorgan failure, and death | 5000                   |
| NCT04412473      | Artery thromboses                                                              | Obs.       | Analysis of respiratory distress and anti- thrombolytic therapy                           | 1000                   |
| NCT04423315      | Thrombosis                                                                    | Obs.       | Length of hospital stay                                                                   | 70                     |
| NCT04412304      | Thromboembolic events                                                          | Obs. Cohort| Tinzaparin or dalteparin                                                                  | 166                    |
| NCT04593654      | Thromboembolism                                                                | Obs. Cohort| Tinzaparin or dalteparin                                                                  | 257                    |
| NCT04372589      | Macro- and microvascular thrombosis                                            | Int.       | Heparin                                                                                    | 3000                   |
| NCT04524156      | Endothelial dysfunction                                                        | Int.       | Percutaneous O₂ and CO₂ partial pressures                                                  | 100                    |
| NCT04505774      | Thrombosis                                                                    | Int.       | Therapeutic heparin, prophylactic heparin                                                | 2000                   |
| NCT04409834      | Venous thromboembolism, arterial thrombosis                                    | Int.       | Unfractionated heparin IV, Enoxaparin, clopidogrel, unfractionated heparin                | 750                    |
| NCT04324463      | Thrombosis                                                                    | Int.       | Colchicine, interferon-beta, aspirin, rivaroxaban                                          | 4000                   |
| NCT04593654      | Thromboembolism                                                                | Int.       | Enoxaparin                                                                                 | 300                    |
| NCT04593654      | NO synthesis                                                                   | Int.       | NO delivered through lung fit delivery system                                             | 50                     |
| NCT04397692      | NO synthesis                                                                   | Int.       | NO inhalations of 80 ppm for 40 min 4 times a day                                         | 20                     |
| NCT04312243      | NO synthesis                                                                   | Int.       | Inhaled NO gas, 160 ppm for 15 min                                                        | 470                    |
| NCT04476992      | NO synthesis                                                                   | Int.       | NO- sessions                                                                                | 20                     |
| NCT04650087      | Thrombosis                                                                    | Int.       | Apixaban, 2.5 mg                                                                           | 5320                   |
| NCT04730856      | Thrombosis                                                                    | Int.       | Tinzaparin                                                                                 | 600                    |
| NCT04746339      | Thrombosis                                                                    | Int.       | Apixaban, 2.5 mg                                                                           | 1000                   |
| NCT04345848      | Thrombosis                                                                    | Int.       | Enoxaparin                                                                                 | 200                    |
| NCT04498273      | Thrombosis                                                                    | Int.       | Apixaban, 2.5 mg; apixaban, 5 mg; aspirin                                                  | 7000                   |
| NCT04662584      | Venous thromboembolism                                                         | Int.       | Rivaroxaban, 10 mg                                                                         | 320                    |
| NCT04367831      | Venous thromboses, Arterial thrombosis                                         | Int.       | Enoxaparin prophylactic dose, heparin infusion, heparin SC, enoxaparin/lovenox intermediate dose | 100                    |
| NCT04400799      | Pulmonary embolism, deep vein thrombosis                                       | Int.       | Enoxaparin 40 mg/0.4 mL injection                                                          | 1000                   |
| NCT04373707      | Pulmonary embolism, deep vein thrombosis                                       | Int.       | Enoxaparin                                                                                 | 602                    |
| NCT04368377      | Pneumonia, viral coronavirus infection, respiratory failure, embolism, and thrombosis | Int.       | Tirofiban injection, clopidogrel, acetylsalicylic acid, fondaparinux                       | 5                      |
| NCT04508439      | Pneumonia, coagulation Disorder, pulmonary embolism                            | Int.       | Enoxaparin                                                                                 | 130                    |

(continued)
and decreasing hypertension in pulmonary and arterial vessels.\textsuperscript{139} Tongue microflora change dietary inorganic nitrate to nitrite followed by another step that produces NO in different organs such as lung and bloodstream.\textsuperscript{140} COVID-19 patients, similar to chronic obstructive pulmonary disease or ARDS, commonly experienced acidosis and hypoxemia in their pulmonary vasculature. These conditions augment the generation of NO from inorganic nitrite.\textsuperscript{141,142} Also, NO has direct anti-COVID-19 activity through interference with the binding of S glycoprotein to its receptor, ACE2. Indeed, two critical components in viral entry to the host cell, viral cysteine proteases, and host serine proteases, are vulnerable to NO.\textsuperscript{137,143} Thus, providing NO with its beneficial properties could have therapeutic effects especially for the prevention of endotheliitis and improving thrombotic status.\textsuperscript{139}

## Conclusion

Endothelial dysfunction and consequent thrombosis formation may be responsible for all the clinical and paraclinical manifestations of COVID-19. Stabilization and supporting endothelial function are the key elements toward effective preventive and therapeutic strategies.

Zahra Elyaspour is submitting the paper in their own personal professional capacity and is not an employee of any US-sanctioned government.

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## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Shiraz University of Medical Sciences (grant number 21964).

## Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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