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The contribution of endothelial dysfunction in systemic injury subsequent to SARS-Cov-2 infection

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Abstract: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection is associated, alongside with lung infection and respiratory disease, to cardiovascular dysfunction that occurs at any stage of the disease. This includes ischemic heart disease, arrhythmias, and cardiomyopathies. The common pathophysiological link between SARS-CoV-2 infection and the cardiovascular events is represented by coagulation abnormalities and disruption of factors released by endothelial cells which contribute in maintaining the blood vessels into an anti-thrombotic state. Thus, early alteration of the functionality of endothelial cells, which may be found soon after SARS-CoV-2 infection, seems to represent the major target of SARS CoV-2 disease state and accounts for the systemic vascular dysfunction that leads to detrimental effect in terms of hospitalization and death accompanying the disease. In particular, the molecular interaction of SARS-CoV-2 with ACE2 receptor located in endothelial cell surface, either at the pulmonary and systemic level, leads to early impairment of endothelial function which, in turn, is followed by vascular inflammation and thrombosis of peripheral blood vessels. This highlights systemic hypoxia and further aggravates the vicious circle that compromises the development of the disease leading to irreversible tissue damage and death of patients with SARS CoV-2 infection.

The review aims to assess some recent advances to define the crucial role of endothelial dysfunction in the pathogenesis of vascular complications accompanying SARS-CoV-2 infection. In particular, the molecular mechanisms associated to the interaction of SARS CoV-2 with ACE2 receptor located on the endothelial cells are highlighted to support its role in compromising endothelial cell functionality. Finally, the consequences of endothelial dysfunction in enhancing pro-inflammatory and pro-thrombotic effects of SARS-CoV-2

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infection are assessed in order to identify early therapeutic interventions able to reduce the impact of the disease in high-risk patients.

Keywords: SARS-CoV-2; Angiotensin-converting enzyme 2; Endothelium dysfunction; Thrombosis; Vasculitis

1. Introduction

Observational studies carried out in the development of Coronavirus disease 2019 (Covid-19) pandemic revealed that cardiovascular system represents one of the major targets of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) infection. In fact, it has been found that nearly 30% of SARS-CoV-2 patients undergo cardiac injury and that cardiovascular complications including acute cardiac injury, stroke, heart failure, arrhythmias and cardiomyopathies may be detected at any stage of the infection [1]. Furthermore, the prevalence of cardiovascular co-morbidities such as diabetes, hypertension or coronary artery disease, is often associated with an unfavourable prognosis of SARS-CoV-2 infection [2]. On the other hand, a prevalence of hypertension, diabetes and overall cardiovascular diseases has been demonstrated to occur in clinical studies carried out in large number of SARS-Cov-2 patients in China and in Italy, being associated to major complications and death. In particular, these studies showed an elevated case fatality rate in patients with cardiovascular comorbidities, greater than the one found in patients with isolated SARS-CoV-2 infection [3-5].

The pathophysiological mechanisms underlying the higher incidence of cardiovascular complications detected in patients undergoing severe SARS-Cov-2 disease are still to be better clarified. However, the common pathophysiological link between SARS-CoV-2 infection and the cardiovascular events leading to irreversible multi-organ dysfunction is represented by the disruption of factors that maintain the blood vessels into an anti-thrombotic state.

Indeed, the common pathophysiological feature which can be found in patients with irreversible cardio-respiratory complications occurring in SARS-Cov-2 disease is represented by an imbalanced anti-coagulant activity of vascular endothelial cells which is also called “sepsis-induced coagulopathy” (SIC), an effect which leads to an increased risk of thrombotic events [6]. For this reason, although the correlation between SARS-CoV-2 infection and coagulation disorders is still unclear, a tight monitoring of coagulation biomarkers was suggested in high-risk patients [7].

SARS-CoV-2 infection associated coagulopathies are characterized by high levels of D-dimer (a fibrin degradation product detectable in the blood in case of fibrinolysis), fibrinogen, prothrombin time (PT) and thrombocytopenia [8]. Furthermore this condition is accompanied by a micro-thrombosis, systemic inflammatory response and impairment of vascular reactivity [9].

Although the enhanced thrombophilic response represents the major issue in detecting early complications in patients undergoing complicated SARS-Cov-2 disease state, the pathophysiology of SARS-CoV-2-related coagulative impairment is still unkown. Multiple mechanisms have been suggested to approach this phenomenon. In particular, evidence exists that SARS-CoV-2 infection produces an aggressive and systemic pro-inflammatory response, being viral infection associated to consistent release of mediators of inflammation known as the so-called "cytokine storm" [10, 11]. This leads to impressive damage of lung tissue which becomes unable to ensure the due oxygen exchange

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in pulmonary tissue. Moreover, SARS-CoV-2 infection-induced hypoxia is accompanied by an enhanced tendency to develop thrombosis of blood micro-vessels via an increased blood viscosity [12]. This is also related to the general status of hospitalized patients, who are over 60 years old, bedridden for a long time and subjected to invasive treatments; these are risk factors to develop hyper-coagulation or thrombosis [13]. Finally, a systemic impairment of endothelial function seems to occur in the majority of patients undergoing SARS-CoV-2 infection thereby playing a crucial role in the SARS-CoV-2-linked sepsis-related coagulopathy [14]. In particular, emerging evidence suggests that SARS-CoV-2 could damage the endothelial barriers and this event could contribute to the severe and systemic condition generated by pandemic infection.

The present review aims to assess some of the most recent evidence identifying the major targets of SARS-CoV-2 underlying endothelial dysfunction in SARS-Cov-2 disease state. In addition, evidence for the systemic and multi-organ endothelial impairment occurring in SARS-Cov-2 infection will be discussed with the aim to detect potential therapeutic targets to be useful in the course of the disease.

2. Major molecular targets of SARS-CoV-2

Coronaviruses (CoVs) (Nidovirales order, Coronaviridae family, Coronaviridae subfamily) are a comprehensive family of viruses with different phenotypic and genotypic characteristics [15]. There are six known human endemic CoVs, which are called, respectively, HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1. In addition, two further CoVs have detected and characterised over the last twenty years; they are: Severe Acute Respiratory Syndrome (SARS)-CoV (discovered in 2003) and the Middle East Respiratory Syndrome (MERS)-CoV (discovered in 2013) [16]. SARS-CoV and MERS-CoV belong to the β-CoV genus and both have caused very severe lung dysfunction [17]. In December 2019, a new coronavirus called SARS-CoV-2 was discovered and has been identified to be responsible of the ongoing pandemic infection worldwide [18]. SARS-CoV-2 genome consists of a single positive-polarity RNA strand (+ ssRNA) with a number of bases ranging from 27 to 33 kb. The organization of the SARS-CoV-2 genome is polycistronic and RNA is translated to produce a single polyprotein that is later broken down by proteases to obtain 16 non-structural proteins of the virus, making up the viral replication-transcription complex. Moreover, the region near the 3′ end of the viral genome carries information for the main four viral structural proteins: spike (S), membrane (M), envelope (E) and nucleocapsid (N). The homotrimer of the S proteins generates the spikes on the external part of the virus, which are involved in the virus coupling to the receptors of the host cell. M protein binds to the nucleocapsid and favours the curvature of the host cell membrane. E protein takes part both in the assembly and in the release of the virus; finally protein N deals with genome packaging in virions [19]. The first CoV replication step is the ability to penetrate the target cells. To this end, the efficacy of the binding between the S glycoprotein of CoVs and the protein receptor on the cell surface is crucial [20]. SARS-CoV and SARS-CoV-2 use the same receptor, which is angiotensin-converting enzyme 2 (ACE2). Conversely, MERS-CoV uses the Dipeptidyl Peptidase 4 (DPP4) receptor [21]. The binding of the virus spikes with the host receptor leads to the binding of their membranes, the penetration of the virus into the host by endocytosis and the beginning of the life cycle of the virus. The virus releases its viral genome, synthesizes viral structural proteins and genome and assembles mature virions that are released via an exocytosis mechanism [22]. The SARS-

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CoV-2 infection is characterised by various symptoms and may be even lethal: the main symptoms include fever, cough, short breath, pneumonia, fatigue, severe respiratory distress, hepatic and gastrointestinal disorders, lymphopathy and neurological diseases; the symptoms manifest themselves about 14 days after the exposure to the virus [23]. The main mode of transmission of SARS-CoV-2 is through respiratory droplets leading to person-to-person spread with each infected individual on an average causing 2-3 new infections [24]. Main consequences of SARS-CoV-2 penetration are shown in Figure 1.

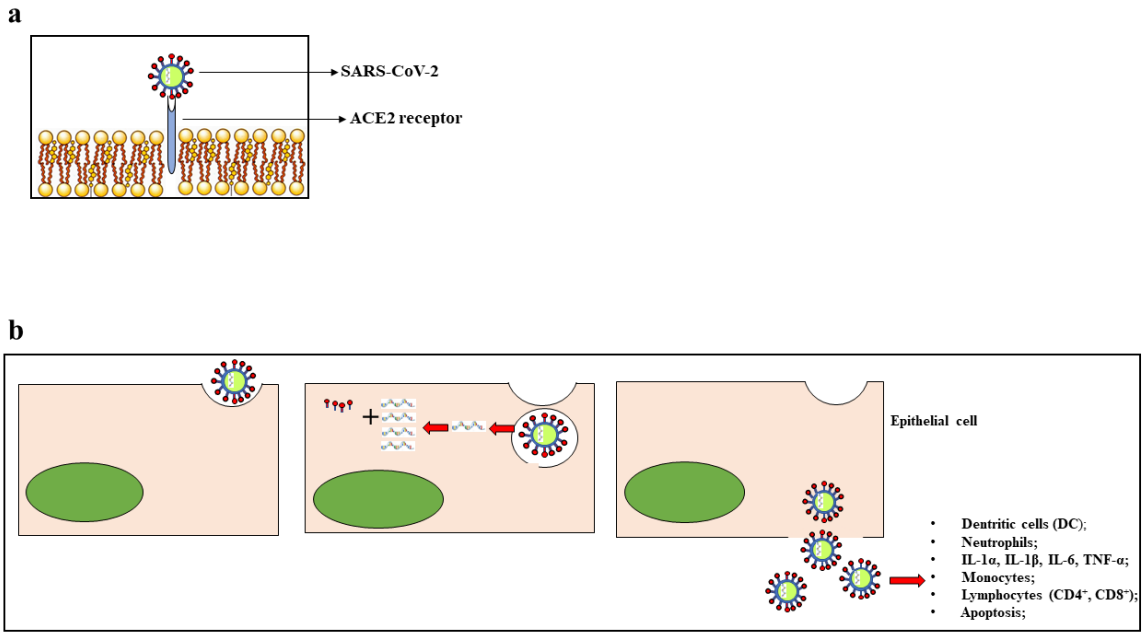

Figure 1. Main consequences of the SARS-CoV-2 penetration. In panel a) the mechanism of SARS-CoV-2 penetration into the cells is represented. Panel b) shows the massive inflammatory response following the cellular introduction of SARS-CoV-2.

3. ACE2 receptor characterization

The renin-angiotensin system (RAS) performs several body functions at the systemic and local level [25]: the systemic RAS is responsible for maintaining proper blood pressure and electrolyte homeostasis whereas local RAS regulates many functions of the heart, kidney and lung. For this reason RAS is the most important regulator of the cardiovascular and renal function and this balanced regulation is guaranteed by proteases that hydrolyze bioactive circulating peptides.

The glycoprotein angiotensinogen is cleaved by enzyme renin, secreted into the circulation in response to numerous stimuli, to produce the decapeptide angiotensin I (Ang I); Ang I can be cleaved to the octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II is the main bioactive component within RAS and can mediate vasoconstrictive or vasodilatory effects depending on the receptor to which it binds. Ang II can further be processed to produce the vaso-dilator heptapeptide Ang 1-7 by angiotensin-converting enzyme 2 (ACE2) [26]. In particular, the peptidase domain of ACE2 cleaves Ang II at the level of amino acid phenylalanine. ACE2 can also

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cleave Ang I, at level of amino acid leucine, creating the biological inactive peptide Ang1-9. Anyway ACE2 shows a greater bond affinity for Ang II than Ang I [27]. To date, cumulative evidences suggest a deleterious role of ACE and a protective role of ACE2 due to their attitude to produce and degrade Ang II respectively [26]. An abnormal activation of RAS leads to diseases such as heart failure, myocardial infarction and renal diseases [28].

The human ACE gene is located on chromosome 17 and encodes a type-I transmembrane glycoprotein anchored to the plasma membrane and consisting of two homologous domains. The human ACE2 gene is located on X chromosome and encodes a type I transmembrane glycoprotein. ACE2's amino-terminal and carboxy-terminal domains show 41,8 and 48% sequence identity with the respective ACE domains [29]. Scientific studies of literature have shown that gene deletion of ACE2 resulted in impaired cardiac contractility and this heart dysfunction was attributed to increased Ang II levels [30]. Both ACE and ACE2 are zinc metallopeptidase angiotensin-converting enzymes and are characterised by a similar intermembrane structure. Nevertheless, ACE1 and ACE2 show many differences:

- Different catalytic activity: ACE is a dipeptidase that hydrolyses bound pairs of amino acids cleaving the C-terminal dipeptide from Ang I to form the octapeptide Ang II. ACE2 is a carboxypeptidase capable of breaking peptide bonds between amino acids at the level of terminal C residue and removing the residue from the decapeptide Ang I to form angiotensin-1–9.
- Several substrates and bond specificity: in particular ACE binds and cleaves Ang I, Ang 1-9 and many bioactive peptides. In contrast ACE2 cleaves Ang I, Ang II, apelin-13, apelin-36 [31].

- A different expression in different tissues of the organism has been evidenced: ACE is more ubiquitous, in fact this enzyme is expressed in heart, lung, kidney, colon, small intestine, ovary, testis, prostate, liver, skeletal muscle, pancreas and thyroid. In contrast, the expression of ACE2 is more specific and is limited in the heart, kidney, endothelial cells and microvasculature [32, 33].
- Inhibitor specificity: The ACE inhibitors act by blocking of the conversion of angiotensin I to angiotensin II and inhibition of the most important step in RAS pathway. For this reason they are widely used as class of antihypertensive drugs. The ACE inhibitors have been linked to cases of hepatotoxicity. ACE2 cannot be inhibited to ACE inhibitors [34].

Since ACE2 decreases levels of the vasoconstrictor Ang II and produces the vasodilator Ang- (1-7), it may protect against cardiovascular and renal disease [35, 36]. ACE2 has two characteristics that allows its characterization:

1. The catalyzed peptides are preferably hydrolysed on the proline residues to the C-terminal group [37]
2. Its enzymatic activity is regulated by chloride ions; the bond with the chloride induces conformational changes of the active site of the enzyme, responsible for modulation of the reactions [38].

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It is important to note that ACE2 performs important biological functions alongside its peptidase role known in the RAS system [39]. For example, it acts as a carrier of amino acids. In particular, evidence exists that the proteins taken with the diet, are digested by hydrolysis reactions carried out by the proteases of the stomach and pancreas and tripeptides, bipeptides and neutral amino acids are absorbed in the intestine by the major small intestine luminal transporter B^0AT1 [40]. Intestinal B^0AT1 expression and function depends on the concomitant presence of the accessory protein ACE2 [41]: the deficiency of ACE2 compromises amino acid absorption in the mouse [42]. Pharmacological inhibition of B^0AT1 reduces protein absorption and increases the elimination of amino acids through the urine [43].

3.1 Molecular mechanisms of ACE-2-Covid 19 interaction

Another biological function performed by the transmembrane domain of ACE2 was recognized in 2003 during the epidemics of Coronavirus SARS. In fact ACE2 was identified as a functional receptor for this pathogenic agent. Structural analyses have been conducted and it has been highlighted that the SARS-Cov spike protein interacts with subdomain I of ACE2 but does not affect the subdomain II nor occludes the peptidase active site [44]. The demonstration of this hypothesis has been provided by experiments in which cells expressing ACE2 catalytic inactive mutants were still permissive for SARS-CoV infection. These results have definitively excluded the involvement of the ACE2 peptidase site in the SARS-CoV penetration in the host cell [45]. After the link between SARS-CoV and ACE2 has been made, the outer portion of ACE2 is split and released while the intramembrane portion is internalized and used to facilitate the fusion of the virus to the host cell [46-48]. As already mentioned, similarly to SARS-CoV also SARS-CoV-2 uses ACE2 as receptor to penetrate the host cell. SARS-CoV-2 consists of a homotrimeric spike protein in which these ends protrude from the viral surface and facilitate the attachment and adhesion of viruses to human target cells [49]. Protein Spike is composed of two subunits S1 and S2: S1consists of four domains named S1A, S1B, S1C and S1D, dealing with receptor association and stabilization of this bond. In particular, S1A engages host sialic acids and S1B recognizes host transmembrane proteins. S2 domain is responsible for membrane fusion [50]. Some experimental structural and biophysical tests have shown that S proteins of SARS-CoV-2 bind to the ACE2 receptor of the host cell with an affinity 10-20 times higher than the one reached by other known members of SARS-CoV family [51].

The characteristics of SARS-CoV-2 to enter the host cell are sufficiently known. To date, much interest has arisen on the correlation between ACE2 receptor and the onset of vascular dysfunction related to SARS-CoV-2 progression. An interesting hypothesis that is currently being evaluated, is the possibility that the entry of the SARS-CoV-2, by the ACE2 receptor, favors a down-regulation of the receptor expression, induces vascular endothelial dysfunction thereby activating a pro-thrombotic cascade. Since ACE2 is an analogue of ACE, a key regulator of RAS system regulating hemodynamic homeostasis in body, a balanced ACE/ACE2 ratio is fundamental for maintenance of endothelial integrity in vessels [52]. On the contrary, dysregulation of this ratio could be associated with vascular thrombosis [53, 54]. This hypothesis is confirmed by *in vitro* studies carried out on lung tissues infected with SARS-CoV; it has been demonstrated that the link between virus and ACE2 regulates the expression of the receptor, induces ACE/ACE2 imbalance and promotes prothrombotic cascades inside the vessels [45]. A low ACE/ACE2 ratio is responsible for a greater degradation of Ang 2 to form Ang 1-7, which plays an anti-thrombotic action preventing the activation of the pro-thrombotic cascade in the vascular endothelium [55]. In contrast, a high ACE/ACE2 ratio will cause an increase

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in Ang 2, the binding of the latter to AT1 receptors and the onset of vasoconstriction, inflammation and thrombosis [56, 57]. Some scientific studies have shown that *ACE2* knockout mice develop a vascular endothelial dysfunction, responsible for pro-inflammatory processes [58], platelet aggregation and thrombosis [59]. At the same time, ACE2 activation has been shown to protect against vascular thrombosis [60]. However, further studies would be needed to confirm this hypothesis.

4. Endothelium dysfunction and SARS-CoV-2

The endothelium can be considered a real organ that constitutes the internal cellular lining of the blood vessels and understands a selectively permeable barrier composed by a layer of endothelial cells. These cells do not perform a passive role; in contrast, they regulate very important physiological functions such as maintaining the homeostatic balance, controlling the vasomotor tone, guaranteeing the correct permeability and managing the reactions of innate immunity [61]. Endothelial permeability allows the physiological transport of a few necessary molecules. Normally endothelial cells can be traversed by water and small solutes while the larger solutes pass through transendothelial channels or transcytosis. Correct permeability of the endothelium is regulated through junction proteins whose function is to maintain endothelial cells closely adjacent. In this way it is impossible to pass unwanted molecules or cells [62, 63]. Junction proteins are made up of tight junctions and adherens junctions; the loss or reduction of these proteins expression leads to disassembly and endothelial dysfunction [64]. The endothelium also constitutes the first defensive barrier against foreign invasion that include mechanical and chemical stimuli. Generally, the integrity of the endothelial barriers depends on the delicate balance between the intracellular contraction and the cell-cell and cell-matrix adhesiveness. Specifically, the cytoskeleton proteins play a key role to ensure the cell adhesions and junctions [65, 66]. At pulmonary level, the respiratory activity takes place in the alveolus-capillary unit that consists of an alveolus supplied by blood capillaries. In particular, the alveolus is covered by an alveolar epithelium that is separated from the capillary by an intermediate space. Eventually, the capillary is surrounded and protected, both internally and externally, by a layer of endothelial cells. Therefore, the pulmonary endothelium acts as a semi-permeable barrier between the blood and the intermediate space. The pulmonary epithelial and endothelial cells are kept close by many tight junction proteins [65]. From the structural point of view, the cells grown together in this unit are enclosed in a small space with an average thickness of about 0.5 μm [66]. On their luminal side, the endothelial cells are covered by a glycocalyx consisting of a network of proteoglycans and glycoproteins involved in cell-cell signalling processes. Moreover, pericyte cells are observed, which adhere to endothelial cells and act as mediators in the various microvascular processes, such as the endothelial cell proliferation and angiogenesis. Pulmonary vascularization is extensive in human beings and would cover a total surface of 90 m^2. The pulmonary endothelium is one of the main components of the alveolus-capillary unit and the safeguard of its integrity is extremely important. In this respiratory system, the endothelium may be subjected to structural changes triggered by both mechanical factors and the invasion of pathogens. Any damage to the endothelial cells leads to the interruption of the barrier, an increased permeability and an inflow of molecules that generate inflammatory responses [67]. Polmonary endothelium is able to generate bioactive molecules and/or to use compounds present in the cell to reduce the effects of toxic

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stimuli and restore its conditions. If the damage is particularly extensive, the endothelium cannot tackle it and its permeability undergoes some alterations. The pulmonary endothelial barrier is totally destroyed in case of chronic lung damages. A typical example of chronic inflammation of the alveolus-capillary unit is represented by virus infections. This process occurs, for example, when the organism comes into contact with the common flu virus [68] In fact, the virus infection impairs both the alveolar epithelium and the pulmonary endothelium: the alveolar epithelium is damaged as a result of the viral entry and the virus replication capacity which can determine the severity of the infection; the impairment of the pulmonary endothelium is caused by the host's adaptive immune response to the virus [69]. Any complication of the seasonal flu, which can lead to severe changes in some patients, cannot be justified exclusively by the destruction and/or apoptotic death of the pulmonary epithelium cells. It is worth considering also the effect of the virus on the other side of the alveolar-capillary membrane, i.e. the pulmonary endothelium. The main change, at the endothelial level, is due to the higher permeability with the internalization of the immune cells (lymphocytes, monocytes and neutrophils) as well as of their inflammatory cytokines. This scenario results in further systemic aggravation [70]. In particular, the pro-inflammatory cytokines produced by leukocytes, pulmonary epithelium and pulmonary endothelium further impair the pulmonary permeability [71, 72]. In short, the flu virus infection is associated with an infiltration of white blood cells in the lungs; neutrophils, in particular, release cytokines, reactive oxygen species, elastases and nucleic acids that contribute to the destruction of the endothelial barrier. Moreover, cytokines and other inflammatory mediators impair the endothelial cell-cell junctions with the following formation of inter-cellular interstices causing the loss of vascular fluid in the intermediate space, resulting in oedemas. The mechanisms underlying the junctional destruction include the reduction of Cadherin 5, type 2 (VE cadherin), a protein that ensures the cohesion of the endothelial cells, and the cytoskeletal rearrangement of the actin filaments [73]. Considering the previous assumptions concerning the endothelium, it would be interesting to imagine a model of the impairment of the alveolus-lung unit resulting from the virus infection caused by SARS-CoV-2. In fact, the cells of the pulmonary endothelium express the ACE2 receptor [63], and it would be argued that the virus, after having attacked and destroyed the pulmonary epithelium, could transmigrate to the underlying endothelium and penetrate the cells [74]. Thus, through the mechanisms already explained, SARS-CoV-2 could damage the endothelium and contribute to the severe and systemic condition generated by this pandemic infection. Post mortem examination of 21 patients diagnosed with SARS-CoV-2 has shown that the primary cause of death was respiratory failure with massive capillary congestion and severe capillarostatis. Nevertheless subsequent findings have highlighted pulmonary embolisms (in four patients), alveolar haemorrhage (in three patients), thrombotic microangiopathy (in three patients) and vasculitis (in one patient). The observation of all patients also highlighted damage of endothelial in the kidneys and intestines, suggesting vascular dysfunction in disease progression [75]. Another important study, carried out with an autoptic examination on 26 patients who dies as a consequence of SARS-CoV-2 infection, demonstrated kidney injuries with glomerular and vascular changes, occlusion of the microvascular lumens and numerous erythrocytes as a consequence of endothelial damage [76]. The damage to the endothelium caused by SARS-CoV-2 is represented in Figure 2.

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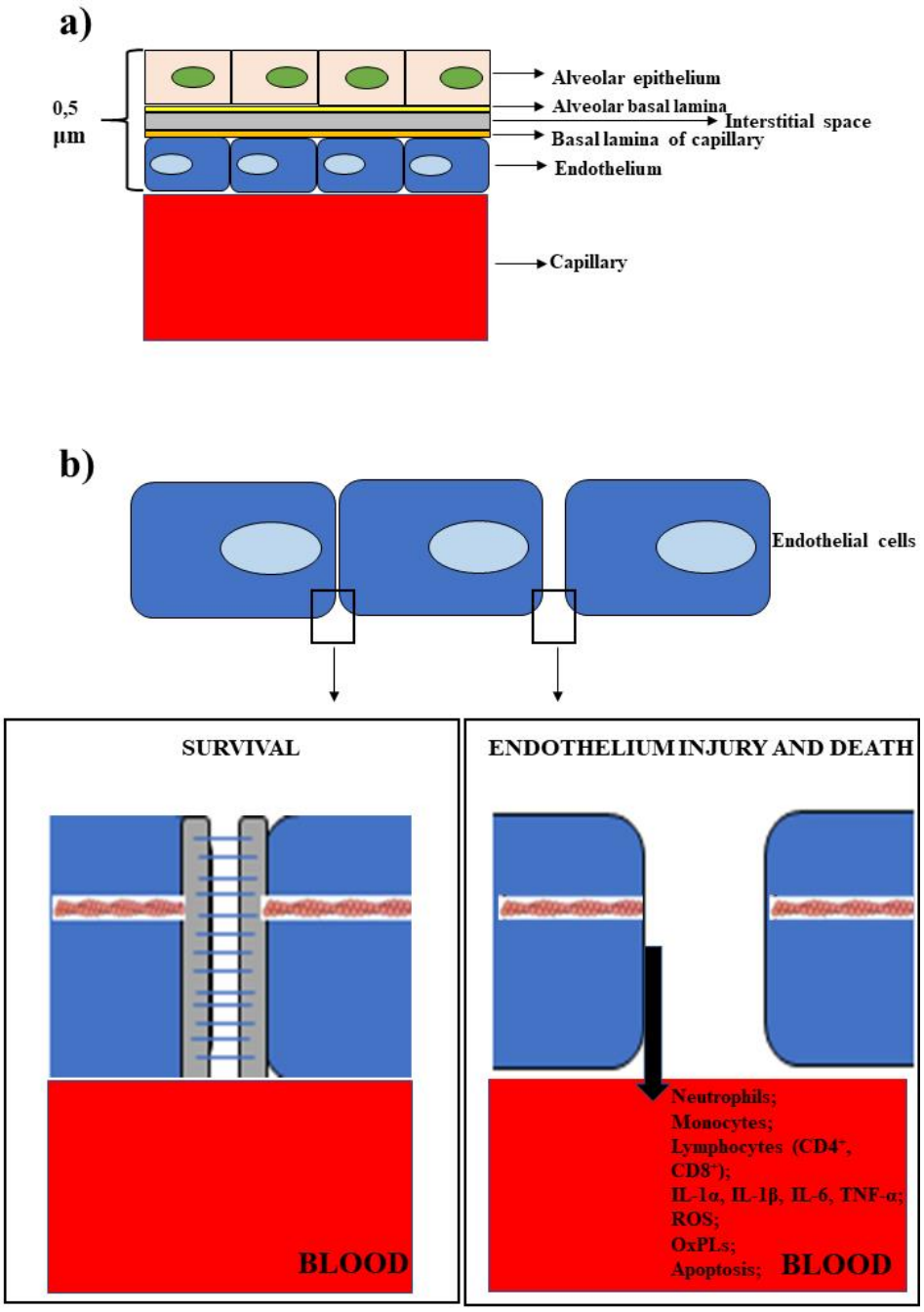

Figure 2. The damage to the endothelium. In panel a) the alveolus-capillary unit at pulmonary level is shown. In panel b) the endothelium damage is represented. In particular any noxious stimulus leads to the interruption of the barrier, increased permeability and inflammatory responses

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5. SARS-CoV-2 related vasculitis

Vasculitis is a specific inflammation of the blood wall and can affect not only the skin but any organs of the body; they are classified according to the size (small, medium or large) of the involved vessel. Most vasculitic lesions are related by immunopathogenic mechanisms classified in: (1) allergic vasculitis, (2) antibody-mediated vasculitis, (3) IC-mediated vasculitis, and (4) T cell–mediated hypersensitivity vasculitis [77]. It has recently been highlighted that there is a direct correlation between SARS-CoV-2 infection and dermatological manifestations such as erythema, rash, urticarial lesions, varicella-like vesicles common to other viral infections. The described lesions appear in a colour ranging from red to purple and can evolve into vesicles similar to chilblains. Moreover the cutaneous vasculitis–like manifestations are considered as a pathognomonic sign of SARS-CoV-2 infection [78]. Some research groups have reported that co-occurring presence of skin manifestations and SARS-CoV-2 symptomatology rules out a reaction to drugs since these patients reported that had no recent history of drug intake before the viral infection [79].

A first study, conducted in Italy (Lecco hospital, Lombardy, Italy) on 88 patients affected with SARS-CoV-2 infection, showed that n=18 (20,4%) developed cutaneous involvement; among these 8 patients experienced symptoms at the onset of the disease, while 10 patients after hospitalization. Cutaneous manifestations were erythematous rash (14 patients), widespread urticaria (3 patients) and chickenpox-like vesicles (1 patient). The most affected region of the body was the trunk and usually lesions healed in few days showing that they are "benign" [80]. Moreover patients with dermatological symptomatology have not always been hospitalized since did not present, at that moment, the typical symptomatology of SARS-CoV-2 infection. This suggested that the patients affected with SARS-CoV-2 might initially present with a skin rash that can be exchanged as another common disease and that may subsequently develop canonical SARS-CoV-2 symptomatology. Therefore dermatological manifestations of SARS-CoV-2 could be considered as a prognostic reference. The number of reports is quickly growing in Italy and in many European countries and seems to overlap the SARS-CoV-2 pandemic propagation [80]. A recent study reported that the cutaneous lesions are preferably shown in asymptomatic or mildly symptomatic pediatric patients with prevalent involvement in the foot and hand [81]. This phenomenon could be due to endothelial cell dysfunction that induces a cytokine storm, recruits macrophages and causes inflammatory reactions, similar to those of vasculitis [82]. Currently there are few papers about the dermatological manifestations of SARS-CoV-2 and we need more knowledge and experience to understand this probable correlation.

6. Conclusion

Similarities between SARS-Cov and SARS-CoV-2 are not only related to symptoms developed during infection or to the receptor mechanism of viral penetration; in fact a common feature to both infections is to develop vascular thrombosis [83-85]. Abnormalities in coagulation response, observed in SARS-CoV-2 infection, are not directly linked to an intrinsic characteristic of the virus but to its ability to trigger an inflammatory cascade [86]. Data reported directly from China, showed that 6% of 99 hospitalized patients affected by SARS-CoV-2 had a high prothrombin time; 36% elevated D-dimer and increased biomarkers of inflammation [87]. Following a viral infection, a physiological

inflammatory response is activated which involves alteration in coagulation process; these events are involved in a process known as "thromboinflammation" or "immunothrombosis" [88, 89]
In most patients who died of severe SARS-CoV-2 infection and who were autopsied, widespread thrombosis and microvascularization were reported. Since thrombosis has also been observed in patients undergoing anticoagulant therapy, it is likely to believe that clotting disorders may be a characterizing factor of this infection [90].
According to this evidence, endothelial dysfunction represents a key mechanism that leads to early impairment of endogenous anti-inflammatory/anti-thrombotic responses of vascular wall able to counteract systemic tissue damage subsequent to SARS CoV-2 infection. Moreover, the tendency to develop thrombotic vascular events associated to SARS CoV-2 disease state must be taken into account when approaching patients with SARS-CoV-2 even asymptomatic. This should be crucial in preventing and treating SARS CoV-2–related systemic damage and to reduce its impact in terms of hospitalization and death that remains an unresolved issue in the course of the disease.

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