



HEALTH SCIENCES

Hemostatic abnormalities in COVID-19: A guided review

PLÍNIO C. SATHLER

Abstract: The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already taken on pandemic proportions, affecting over 213 countries in a matter of weeks. In this context, several studies correlating hemostatic disorders with the infection dynamics of the new coronavirus have emerged. These studies have shown that a portion of the patients affected by Coronavirus Disease 2019 (COVID-19) have prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), elevated D-dimer levels and other fibrinolytic products, antithrombin (AT) activity reduced and decrease of platelet count. Based on these hallmarks, this review proposes to present possible pathophysiological mechanisms involved in the hemostatic changes observed in the pathological progression of COVID-19. In this analysis, it is pointed the relationship between the downregulation of angiotensin-converting enzyme 2 (ACE2) and storm cytokines action with the onset of hypercoagulability state, other than the clinical events involved in thrombocytopenia and hyperfibrinolysis progression.

Key words: Hemostasis, Blood coagulation, Hemostatic Disorders, Virus Diseases, Coronavirus Disease 2019, SARS-CoV-2.

INTRODUCTION

Alteration of hemostatic parameters in Covid-19

Since its emergence in Wuhan, Hubei Province, China, in December 2019, the novel coronavirus (SARS-CoV-2) outbreak has spread worldwide, reaching pandemic denomination by WHO in March 2020 (Chen et al. 2020, WHO 2020a). With over 15,000,000 confirmed cases and 600,000 deaths, this pandemic virus follows with wide dissemination around the world. On March 13th, Europe became the epicenter of this pandemic, that previously was in Asia. In continuous expansion, COVID-19 already affects more than 213 countries on five continents, among them, United States, the new global epicenter of the disease and South American countries, such as Brazil (WHO 2020a, b).

SARS-CoV-2 is a positive-sense single-stranded RNA virus with approximately 30,000 nucleotides that was discovered through unbiased sequencing of human airway epithelial cells isolated from a cluster of patients with atypical pneumonia after visiting Wuhan (Cascella et al. 2020). Initially named as 2019-nCov, SARS-CoV-2 was identified as a member of the betacoronavirus genus, the same as SARS-CoV and MERS-CoV. Due to genetic differences with the other coronaviruses, the 2019-nCov was classified as the seventh member of the family of coronaviruses that infect humans (Chan et al. 2020, Zhu et al. 2020).

Despite of not being a descendent of SARS-CoV, and thus a completely independent human pathogen from the SARS-CoV outbreak in 2002-2003, 2019-nCov was found to share 89% identity to bat SARS-like-CovVZXC21 and 82% with

human SARS-CoV. That level of genetic similarity between 2019-nCoV and SARS-CoVs suggests that their characteristics and evolutionary history may be mutually informative. For that reason, the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses designated the 2019-nCoV as SARS-CoV-2 (ICTV-CSG 2020).

Forming a clade with the severe acute respiratory syndrome-related coronavirus, SARS-CoV-2, produces a respiratory and systemic illness that progresses to a severe form of pneumonia with acute respiratory disorders and multiple organ failure as major complications (Mattiuzzi & Lippi 2020). The symptoms of SARS-CoV-2 infection appear after an incubation period of approximately 5.2 days. The period from the onset of COVID-19 symptoms to death average variable 14 days depending on the age and immune system status of the patient (Rothan & Byrareddy 2020).

Given the ongoing pandemic, several studies correlating hemostatic disorders with the dynamics of SARS-CoV-2 infection and lethality are beginning to be developed, aiming at a broader understanding of the pathological aspects of COVID-19 and the identification of new biomarkers and therapeutic targets (Han et al. 2020, Lippi et al. 2020, Liu et al. 2020a, Tang et al. 2020a).

In this context, Tang et al. reported that patients with COVID-19 had a worse prognosis when their blood clotting parameters were abnormal. Those patients were found with evident signs of hypercoagulability, including prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), elevated D-dimer levels, and other fibrin degradation products (FDP), whereas the antithrombin (AT) activity was below normal standards (Tang et al. 2020b). This association between the increase in D-dimer levels with in-hospital deaths of

COVID-19 infected patients was also observed by Zhou and colleagues in a retrospective multicenter cohort study from China (Zhou et al. 2020). Similarly, Lippi et al. (2020) reported the association between systemic thrombocytopenia and increased risk of mortality and prognostic worsening in patients with COVID-19 in a meta-analysis study.

These reports demonstrate that the hemostatic function is significantly altered in patients with SARS-CoV-2 when compared with healthy people, influencing the clinical course of this disease to unfavorable prognostics. However, it is unclear whether these hemostatic disorders are provoked by COVID-19 or are just comorbidities or non-specific complications of infection (Ferrari et al. 2020). Therefore, based on these remarks, this review proposes to present possible pathophysiological mechanisms involved in the hemostasis changes during the COVID-19 progression.

SARS-COV-2 INFECTION AND INFLAMMATORY PROCESS

After respiratory contamination, SARS-CoV-2 accesses the lung by infecting the pulmonary epithelial cells. In the first step of infection SARS-CoV-2 spike (S) glycoprotein binds the angiotensin-converting enzyme 2 (ACE2), enabling the docking of the viral particle to the host cell (Chhikara et al. 2020, Yan et al. 2020) (Figure 1). Zhao et al. (2020) demonstrated that 0.64% of cells in lungs expressed ACE2 and 83% of these cells are type II alveolar epithelial cells, suggesting that these cells can serve as a reservoir for viral invasion.

The infection process also requires cleavage of the viral S protein by host proteases. Similar to the mechanism observed for SARS-CoV, cleavage of SARS-CoV-2 spike protein was shown

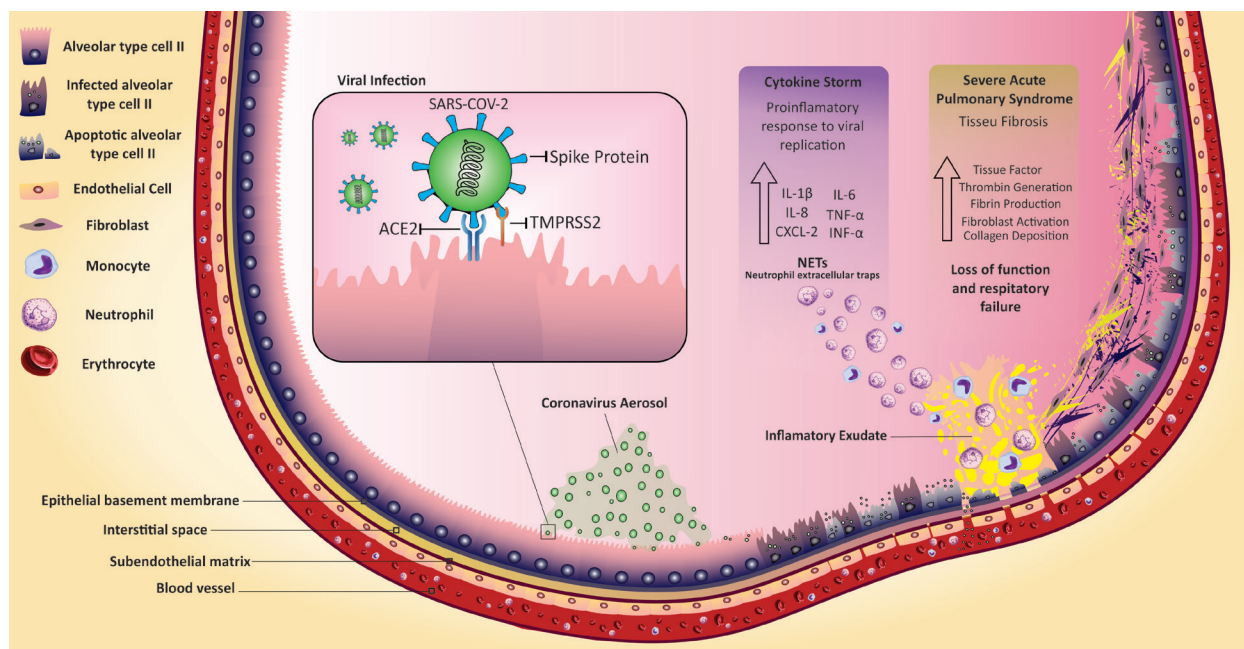


Figure 1. SARS-Cov-2 infection and inflammatory process. The New Coronavirus SARS-CoV-2, in its infection mechanism, binds to angiotensin-converting enzyme 2 (ACE2) via the receptor-binding domain (RBD) of its spike (S) glycoprotein. Proteolytic processing of the viral spike protein assisted by the host protease TMPRSS2 enables viral entry to human airway epithelial cells. The cytopathic effects that follow viral infectivity and replication lead to an intense inflammatory response with increased pro-inflammatory cytokines. These chemical mediator acts by promoting the cytoskeletal reorganization within endothelial cells allow the plasma proteins and leukocytes to leave the circulation producing the inflammatory exudate. Excessive deposit of fibrin in the lungs provides an ideal environment for fibroblast adhesion and proliferation, corroborating to an increase in collagen deposition in the alveolar space and the onset of a fibrotic response that can generate a loss of function and respiratory failure.

to be primarily promoted by TMPRSS2, which is extensively expressed on the human airway epithelial cells (Figure 1). Following proteolytic processing, the viral S protein undergoes irreversible conformational changes that promote viral entry through the fusion of the virus to the host cell membrane (Hoffmann et al. 2020, Wang et al. 2020). Other receptors on the surface of human cells have been suggested to mediate the entry of SARS-CoV-2, including sialic acid receptors, and extracellular matrix metalloproteinase inducer (CD147) (Sardu et al. 2020).

In the absence of exogenous or membrane-bound proteases that enable entry at the plasma membrane surface, the new coronavirus could be internalized via clathrin- and

non-clathrin-mediated endocytosis. As the virus is shuttled along the endocytic pathway towards the cell interior, the pH in the endosome decreases. The low pH environment activates endosomal proteases, such as cathepsins, a family of cysteine proteases (cathepsin B and L), triggering the fusion pathway and releasing the SARS-CoV-2 genome (Tang et al. 2020c).

The release of viral RNA is followed by active transcription and translation of viral proteins by the cellular machinery, ultimately leading to enhanced in situ viral replication with the generation of new viral particles. In response to this infection, the cells produce interferon alpha (INF- α), increasing major histocompatibility complex (MHC) class I expression and presentation of antigens as a

central part of the body's antiviral immunity (Li et al. 2020). The rapid production of virions by the cells induces a cytopathic response in the infected cell, triggering the production of several pro-inflammatory cytokines (Fu et al. 2020).

Interleukin-1 (IL-1) is one of the central cytokines produced in this context, mainly the β isoform (IL-1 β) (Conti et al. 2020, Dhama et al. 2020). This chemical mediator acts by promoting the cytoskeletal reorganization within endothelial cells, causing the opening of intercellular clefts and increasing vascular permeability (Fahey & Doyle 2019). These microcirculation structural changes allow plasma proteins and leukocytes to leave the circulation producing the inflammatory exudate (Zhang et al. 2020a) (Figure 1).

The increase of inflammatory infiltrates in the lungs provides the accumulation of immune cells, mainly monocytes/macrophages, granulocytes. These immune cells increase the local IL-1 β levels in addition to other immune mediators such as Tumor Necrosis Factor α (TNF- α), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Chemokine (CXC motif) Ligand 2 (CXCL2) (Didangelos 2020, Guo et al. 2020a, Huang et al. 2020a, Nikolich-Zugich et al. 2020). These newly released cytokines and chemokines are responsible for the amplifying the activation and recruitment of inflammatory cells to the infection site, respectively, which yields the general inflammatory response characteristic of the severe acute respiratory syndrome (Shi et al. 2020) (Figure 1).

Once cells of the myeloid lineage are activated through viral peptides complexed with MHC class I, expressed by SARS-CoV-2 infected cells or immune mediators, such as cytokines, they can efficiently present viral antigens to the lymphocytes, enabling the cytotoxic response and subsequent antibody production (Ganji et al. 2020, Nikolich-Zugich et al. 2020). In this

context, CD8⁺ T cells can kill viral infected cells, while CD4⁺ T cells activate B cells to promote the production of virus-specific antibody (Yuki et al. 2020).

SARS-CoV-2 induces a robust B cell response, as evidenced by the rapid and near-universal detection of virus-specific IgM, IgG and IgA, and neutralizing IgG antibodies (nAbs) in the days following infection (Huang et al. 2020b). The seroconversion occurs in most COVID-19 patients between 7 and 14 days after the onset of symptoms, and antibody titers persist in the weeks following virus clearance (Vabret et al. 2020). These antibodies can interact with the receptor binding domain (RBD) of the SARS-CoV-2 spike (S) glycoprotein, blocking virus linkage with the host entry receptor (ACE2) (Ju et al. 2020).

Although antibodies are generally protective and beneficial, Zhang et al. reported that patients with severe COVID-19 frequently had an increased IgG response and a higher titre of total antibodies, which was associated with worse outcome. This finding was suggestive of possible antibody-dependent enhancement (ADE) of SARS-CoV-2 infection (Zhang et al. 2020b). This phenomenon can promote cellular uptake of virus particles bound in immune complexes, through their binding to Fc receptors (FcRs) promoting the persistent viral replication and amplification of inflammatory responses that contribute to tissue and organ damage (Felsenstein et al. 2020, Iwasaki & Yang 2020).

During the onset of inflammation in the airways, the presence of abundant exudate containing fibrinogen promotes the generation of persistent intra-alveolar fibrin deposits formed by the proteolytic activity of coagulation factors and, most importantly, local thrombin generation. Excessive deposit of fibrin in the lungs provides an ideal environment for fibroblast adhesion and growth, corroborating

to an increase in collagen deposition in the alveolar space, replacement of functional parenchyma by stromal cells and development of pulmonary fibrosis. Besides, fibrin can also directly impair lung function, inactivating the surfactant, leading to loss of lung compliance causing eventual respiratory failure and subsequent fatality (Gralinski et al. 2013, Hofstra et al. 2008, Kumar et al. 2020) (Figure 1).

PATHOGENIC MECHANISMS OF THE NEW CORONAVIRUS AND THEIR CONSEQUENCES TO NORMAL HEMOSTASIS

ACE2 downregulation and Angiotensin II increased

SARS-CoV-2 can generate hemostatic disorders by several mechanisms impacting the evolution of the disease. One of these mechanisms is directly related to the fusion of the virus to the host cell membrane and involves the Renin-Angiotensin system (RAS), a distinct network for systemic regulation of blood pressure that plays a role in the management of several physiological responses to maintain homeostasis (Guo et al. 2020b).

In the RAS, juxtaglomerular kidney cells secrete the highly specific endopeptidase renin in response to physiological stimuli. Renin then reaches its substrate angiotensinogen in the plasma and hydrolyzes it to generate angiotensin I (Ang I). Subsequently, the exopeptidase angiotensin-converting enzyme (ACE) cleaves Ang I releasing a C-terminal dipeptide His-Leu. This cleavage results in an increase of the vasoconstrictor activity of angiotensin, whose activated form is known as angiotensin II (Ang II). The counter-regulatory carboxypeptidase angiotensin-converting enzyme 2 (ACE2) catalyzes the irreversible conversion of angiotensin I to angiotensin 1-9, a

nine-amino acid peptide with anti-hypertrophic effects in cardiomyocytes (Sotomayor-Flores et al. 2020), and angiotensin II to angiotensin 1-7, which is a potent vasodilator. ACE2 is, therefore, a fundamental regulator of blood volume, vascular resistance, and cardiovascular homeostasis (Jia 2016, Kreutz et al. 2020).

The findings of Hoffmann et al. (2020) reveal how, in a similar mechanism to that of SARS-CoV, the molecular interaction between SARS-CoV-2 spike protein and ACE2 receptors presented on the membrane of the host airway epithelial cells enables viral attachment to target cells, ultimately leading to viral fusion and cell entry. Upon infection, host cells undergo a downregulation of surface-expressed ACE2, which leads to the reduced production of Ang 1-7 and an accumulation of Ang II, promoting a local unbalance of RAS (Kuster et al. 2020, Zhang et al. 2020c) (Figure 2a). The ACE2 downregulation has a positive correlation to the severity of acute lung injury, and according to Kuba et al. (2005) can be directly induced by the *in vivo* administration of recombinant SARS-CoV Spike protein in wild-type mice. Conversely, the severity of lung failure was not affected by the administration of SARS-CoV spike in ACE2-knockout mice, indicating that the effects of the viral spike protein to acute lung injury are specific for ACE2.

Interestingly, the increase on the levels of Angiotensin II is related to the upregulation of tissue factor (TF) expression on the airway-associated endothelial cells that, in turn, initiate the procoagulant response of plasma clotting factors. (Nishimura et al. 1997). The binding of TF to factor VIIa forms a complex with the ability to catalytically convert factors IX and X to their active derivatives IXa and Xa, respectively, thus leading to thrombin generation and the sequential clot formation with the deposition of fibrin protofibrils (D'Alessandro et al. 2018, Fraga-Silva et al. 2010) (Figure 2a).

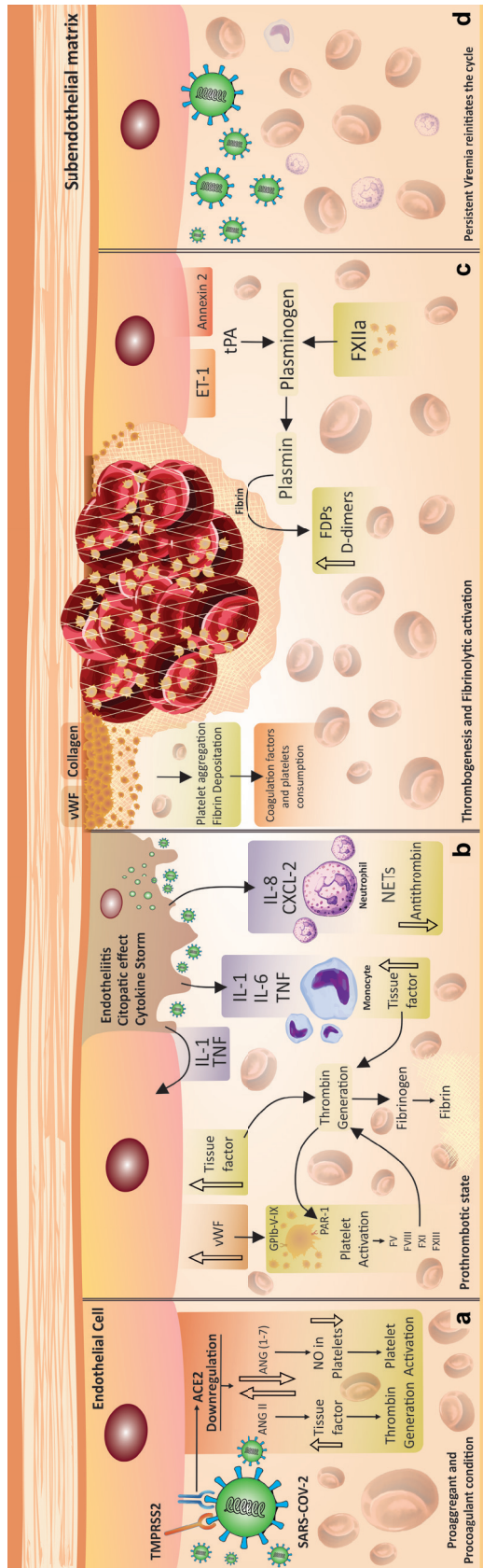


Figure 2. Hemostatic abnormalities in COVID-19: (a) In COVID-19, SARS-CoV-2 can access the bloodstream causing active viremia and subsequent infection of endothelial cells. The downregulation of ACE2 in infected cells produces a state of hypercoagulability marked by thrombin generation. (b) The rapid production of viral particles induces a cytopathic response in the infected cell, triggering the production of several pro-inflammatory cytokines. These inflammatory mediators, in turn, enhance local procoagulant responses by activating neutrophils and promoting the release of neutrophil extracellular traps (NETs). The local increase in cytokine production is also responsible for upregulating TF expression in neighboring endothelial cells, ultimately leading to the initiation phase of plasma coagulation and the increase in local thrombin generation and platelet activation. IL-1, tumor necrosis factor (TNF) and IL-6 further the procoagulant response at sites of infection by activating surveilling monocytes and inducing TF expression in primed cells. As the immunological response progresses, the release of thrombogenic inducers such as factors V, XI, XIII upon platelet activation contributes to the amplification of thrombin production and the propagation phase of the coagulation response in which active clotting factors bind to highly procoagulant membranes of activated platelets. (c) Hypercoagulation promotes the formation of intravascular fibrin-platelet microthrombi that could lead to partial stenosis. The enhanced deposition of fibrin to the inflammation site and the conversion of plasminogen to plasmin lead to the cleavage of fibrin profibrin and the cumulative release of D-dimers. (d) Continuous viral replication on the endothelium contributes to the onset of systemic endotheliitis and the diffusion of thrombotic events in other organs throughout the body.

Thrombin is the central protease in the consolidation of the hypercoagulability seen in COVID-19 because even slow accumulating amounts thrombin can further activate platelets via protease-activated receptor - 1 (PAR-1) (Hsieh et al. 2019) (Figure 2 b). Platelet-derived factor V can also be activated by thrombin into factor Va at the inflammation site, thus amplifying the formation and activity of the prothrombinase complex, generating more active thrombin in a positive feedback loop. Thrombin can also cleave factor VIII into VIIIa, which increases the levels of factor Xa by acting as a co-factor of factor IX on the surface of activated platelets (Levi & Sivapalaratnam 2019).

Concomitantly, Ang 1-7 is a known inducer of nitric oxide (NO) production in thrombocytes, which makes it a potent inhibitor of platelet adhesion and aggregation. Thus, the reduction of Ang 1-7 levels as a consequence of ACE2 downregulation contributes to the onset of a hypercoagulable state due to an impaired physiological control in platelet function (Fraga-Silva et al. 2008) (Figure 2a).

Cytokine storm action

The overproduction of pro-inflammatory cytokines and the overactivation of immune cells during SARS-CoV-2 infection is known as a cytokine storm (Vaninov 2020). This hyper-inflammatory state directly impacts the hemostasis, promoting functional changes that contribute to the worsening of the COVID-19 (Yang & Tang 2016, Yao et al. 2020). The close connection between inflammation and hemostasis is defined as “immunothrombosis” (Engelmann & Massberg 2013, Middleton et al. 2016, Guo & Rondina 2019) (Figure 1 and Figure 2b).

Pro-inflammatory cytokines such as IL-1, tumor necrosis factor (TNF) and IL-6 further enhance local procoagulant responses by

inducing TF expression in monocytes. IL-1 and TNF also promotes the TF upregulation expression in endothelial cell intensifying this process (Grignani & Maiolo 2000, Schouten et al. 2008). Besides, both IL-1 and TNF- α may mobilize von Willebrand factor (vWF) to the endothelial surface during inflammation, inducing higher platelet activation mediated by the binding of vWF to the platelet glycoprotein GPIIb/IIIa (Middleton et al. 2016, Nishimura et al. 2012) (Figure 2b). The joint mobilization of clotting factors and activated platelet to SARS-CoV-2 infected areas is likely linked to a hyper induction of pro-inflammatory cytokine production, which amplifies the generation of thrombin and the likelihood of thrombosis in situ (Van Wissen et al. 2011).

In the progression of COVID-19, the upregulation of IL-8 and CXCL2 can contribute to the recruitment of neutrophils to the sites of infection. One of the ways these polymorphonuclear leukocytes perform their function is through the release of nuclear chromatin, or neutrophil extracellular traps (NETs). NETs disperse cytotoxic mediators that include extracellular histones, myeloperoxidase (MPO) and neutrophil elastase (NE), while strongly stimulating the production of pro-inflammatory cytokines. It is especially noteworthy that NETs can induce macrophages to secrete IL-1 β and this cytokine enhances NET formation. The recognition of NETs as major enhancers of endothelial injury and dysfunction along with their significant contributions to thrombin generation, thrombosis, and organ failure suggests that the activation of NETs in this positive loop could accelerate aberrant immune responses, the formation of microthrombi, and respiratory decompensation (Barnes et al. 2020, Knopf et al. 2019, Monteiro et al. 2019, Narasaraaju et al. 2020) (Figure 1 and Figure 2b).

The severe inflammatory response observed in COVID-19 also promotes an imbalance of the blood coagulation control mechanisms. In this situation, antithrombin (AT) levels are found to be markedly decreased because of impaired synthesis, degradation by NE from activated neutrophils, and cumulative consumption because of ongoing thrombin generation (Levi & van der Poll 2010, Thachil et al. 2020) (Figure 2b).

Endothelial dysfunction

During the course of its infection SARS-Cov-2 can access peripheral blood, causing viremia (Lin et al. 2020a). With the endogenous expression ACE2, TMPRSS2, sialic acid receptor, and CD147 confirmed both by mRNA and protein levels, endothelial cells might provide a possible route of entry for the viral particles (Aimes et al. 2003, Hamming et al. 2004, Sardu et al. 2020, Zhang et al. 2020c) (Figure 2a). In fact, clinical reports have found direct evidence of SARS-CoV-2 infection of endothelial cells with diffuse endothelial inflammation (endotheliitis) and inflammatory cell death (Varga et al. 2020).

The intact endothelium lining the vessel wall represents a barrier separating platelets from adhesive substrates in the subendothelial connective tissue matrix. A potential disruption of the vessel wall integrity due to the cytopathic effect caused by the virus would allow circulating platelets to adhere to the subendothelial matrix through integrin binding to collagen fibrils and recognition of vWF by surface glycoprotein Ib-V-IX, further promoting platelet activation and downstream thrombogenesis (Posch et al. 2018, Ruggeri 2002, Siegel-Axel & Gawaz 2007) (Figure 2c).

The release of thrombogenic inducers such as factors V, XI, XIII upon platelet activation contributes to the propagation phase of the coagulation response in which active clotting factors bind to highly procoagulant membranes

of activated platelets (Hosseinzadegan & Tafti 2017) (Figure 2c). With an enhanced deposition of fibrin to the inflammation site and the conversion of plasminogen to plasmin, lead to the cleavage of fibrin protofibrils and the cumulative release of D-dimers, which are a known marker of COVID-19 associated thrombosis (Ji et al. 2020) (Figure 2b, c).

Continuous evidences emerge in support of the fact that viral replication on the endothelium may be involved with the onset of disseminated intravascular coagulation (DIC) in some COVID-19 patients. In this condition, the formation of fibrin-platelet microthrombi in the pulmonary vasculature contribute to the evolution of progressive respiratory dysfunction and right heart failure. (Thachil et al. 2020, Willyard 2020) (Figure 2c, d).

Thrombocytopenia

Thrombocytopenia is a clinical condition recurrently associated with severe SARS-CoV-2 infections. In COVID-19, the extensive damage caused to the bronchoalveolar tissue and the associated endothelial cells by the viral infection often results in intense platelet recruitment to the lungs and consumption due to intense activation, which lead to the depletion of peripheral platelet count (Lippi et al. 2020, Yang et al. 2005) (Figure 2c).

The reduction of circulating platelets can contribute to the appearance of hemorrhagic disorders mainly as consequences of DIC evolution. Some patients have also been present with skin manifestations of petechiae or tiny bruises, but there is still no report on massive bleeding (Joob & Wiwanitkit 2020, Sai & Wiwanitkit 2020).

Furthermore, the lungs have recently been identified as primary sites for terminal platelet production, with considerable hematopoietic

potential by actively promoting platelet release from mature megakaryocytes (Lefrançois et al. 2017). The inflammation triggered by SARS-CoV-2 can result in morphological changes in the pulmonary capillary bed, impairing the megakaryocytes fragmentation steps and ultimately affecting megakaryocytopoiesis, which contributes to thrombocytopenia (Middleton et al. 2016, Yang et al. 2005).

Other mechanisms have been suggested for thrombocytopenia in COVID-19, including the development of autoantibodies or immune complexes mediating clearance and direct infection of hematopoietic progenitor cells and the megakaryocytic lineage resulting in decreased production of platelets (Amgalan & Othman 2020).

Alteration in fibrinolytic responses

The fibrinolytic system is widely affected in Covid-19. Fibrinolysis is the process of dissolving blood clots, thereby preventing the obstruction of blood vessels. When activated by tissue- or urokinase-type plasminogen activators (tPA or uPA), plasminogen is converted to plasmin, the critical enzyme of this system, whose function is to degrade the deposited fibrin into soluble fibrin degradation products (FDPs) (Figure 2c). The production of plasmin is physiologically modulated by plasminogen activator inhibitors - 1 and - 2 (PAI-1 and PAI-2) (Lin et al. 2020b).

In SARS-CoV2 infection, there is an uncoordinated coexistence of hypercoagulation and hyperfibrinolysis. Although physiological mechanisms provide the generation of antifibrinolytic mediators such as PAI-1, intense fibrinolysis is still a hallmark in about 25% of COVID-19 patients facing venous thromboembolism (VTE) as reported by Cui et al. (2020) in a cohort study with 81 COVID19 patients under severe signs of pneumonia (Gralinski et al. 2013, Ji et al. 2020). In this research, assessment

of fibrinolysis through systematic dosing of D-dimer was recently described as an accurate biomarker of VTE in COVID-19, with a sensitivity of 85%, specificity of 88.5% and negative predictive value of 94.7% (Cui et al. 2020).

A possible explanation for this finding is related to the fact that polyphosphates released from activated platelets and collagen exposed in endothelial injury enable activation of the Hageman factor (Factor XII). The increase in the factor XIIa levels allows the highest conversion of plasminogen to plasmin, stimulating the activation of the fibrinolytic system (Didiasova et al. 2018) (Figure 2c).

Besides, the signaling of IL-1, IL-6 and TNF to the endothelium increases the expression and release of endothelin-1 (ET-1), a vasoconstrictor mediator that contributes to tPA production and plasmin generation (Kahaleh & Fan 1997, Lidbury et al. 1990, Maemura et al. 1992). Newly generated thrombin also promotes the expression of Annexin 2 (tPA receptor) on the endothelial surface, which in turn expands the effectiveness of tPA activation, plasmin production and the systemic increase in D-dimer levels (Dassah et al. 2009, Peterson et al. 2003) (Figure 2c).

ANTITHROMBOTIC THERAPIES IN COVID-19

The propensity of SARS-CoV-2 to cause microvascular, venous and arterial thrombosis, and thereby exacerbating organ injury, combined with the current lack of an effective therapy for this viral infection, has led to significant interest regarding the use of antithrombotics for patients with severe COVID-19 (McFadyen et al. 2020).

In a retrospective study with 449 patients presenting severe COVID-19 in China, 99 of which received low-molecular weight heparin (LMWH) in prophylactic doses for at least 7 days, it was

found that 28-day mortality of patients with elevated D-dimer levels (greater than six-fold at the upper limit of normal) and high sepsis-induced coagulopathy score that used LMWH, was lower than in non-user patients with similar clinical profile. These findings highlight the potential role of anticoagulation in mitigation of clinical complications and mortality reduction in specific COVID-19 patients (Tang et al. 2020a).

Given the potential severity of the SARS-CoV-2 infection the prophylactic dose of LMWH is recommended for hospitalized patients with COVID-19 to prevent venous thromboembolism (VTE) and treatment dose LMWH is contemplated for those with significantly raised D-dimer concentrations due to concerns of thrombi in the pulmonary circulation (Al-Ani et al. 2020).

The anticoagulant activity of heparin is primarily related to its ability to bind AT and accelerate the formation of a molecular complex with activated forms of several coagulation factors, thereby leading to inhibition of secondary hemostasis and consequent thrombotic events (Spadarella et al. 2020). Besides being a potent anticoagulant, heparin also has other potential roles in thromboinflammation and acute lung injury. Based on the immuno-thrombosis model, which highlights a bidirectional relationship between the immune system and thrombin generation, blocking thrombin by heparin may dampen the inflammatory response (Thachil 2020).

Several studies show that heparin is able to decrease production of cytokines markedly elevated in critically ill COVID-19 patients as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF - α) (Atallah et al. 2020). Additionally heparin also protects the endothelium from NETs and histones (Mitchell 2020). There is also data reporting that heparin interacts with spike proteins of several viruses, including the SARS-CoV-2 spike protein receptor binding

domain, suggesting that it may be able to modulate protein's interactions with the endothelium (Mycroft-West et al. 2020). Due to these characteristics, LMWH remains as the best choice of anticoagulant for admitted patients with severe COVID-19.

Although they are alternatives for the treatment of thrombotic disorders evidenced in SARS-CoV-2 infection, both Vitamin K Antagonists (VKA) and Direct Oral Anticoagulants (DOAC) display significant interference with concomitant antiviral treatment to which the COVID-19 patients are subjected (Marietta et al. 2020). The antiviral agents, particularly those that strongly interact with P-glycoprotein and/or cytochrome P450-based metabolic pathways can modify VKA and DOAC pharmacokinetic and pharmacodynamic profiles, consequently changing their plasma anticoagulant activity, increasing risk and bleeding (Testa et al. 2020). Thus, an individualized patient-based approach is recommended, aiming balancing the risk/benefit ratio of various antithrombotic strategies, taking into consideration the underlying hypercoagulable state.

In addition to VTE, there are emerging reports that the rate of arterial thromboembolism is increased in patients with COVID-19. Platelets play a key role in this thrombotic disorder and are a potential target for prevention of the SARS-CoV-2 infection complications (McFadyen et al. 2020). Among the antiplatelet agents, aspirin (ASA) and P2Y₁₂ receptor inhibitors such as clopidogrel are associated with decreased risk of acute respiratory distress syndrome (ARDS) as well as decreased mortality among the critically ill, may representing a valid COVID-19 therapeutic complement (Panka et al. 2017, Reilly & Christie 2015).

However, a number of drugs for the treatment of COVID-19 may have interactions with these oral antiplatelet agents, such as lopinavir/

ritonavir, an antiviral agent that inhibits CYP3A4 metabolism. Although the active metabolite for clopidogrel is mostly formed by CYP2C19, inhibition of CYP3A4 may also lead to reduction in effective dosage of clopidogrel. Therefore, the concomitant use of this agent along with lopinavir/ritonavir should be cautioned (Bikdeli et al. 2020a). Currently, randomized trials evaluating role of aspirin and clopidogrel in COVID-19 patients at increased cardiovascular risk are underway (Bikdeli et al. 2020b).

Vorapaxar and Dipyridamole are also promising antiplatelet agents for adjuvant treatment of the COVID-19. Vorapaxar exerts its antiplatelet activity through antagonism of the protease-activated receptor 1 (PAR-1), which perform an important role in thrombin-induced platelet aggregation and is also related to blood coagulation, inflammation process, and the fibrotic response (Bikdeli et al. 2020a). Nonetheless, its terminal half-life of 8 days renders it difficult to use in patients with severe COVID-19 (Jose & Manuel 2020).

Dipyridamole is a phosphodiesterase inhibitor that inhibits platelet aggregation by increasing intracellular concentrations of cyclic adenosine monophosphate (Liu et al. 2020a). In clinical trial reported by Liu et al., thirty-one patients with COVID-19 were randomized to dipyridamole (150mg three times a day for 7 days) versus control. In this study, those treated with dipyridamole showed trends toward higher cure and hospital discharge rates (Liu et al. 2020b). With respect to SARS-COV-2 infection and antiplatelet agents, there are many unknowns regarding their use, evidencing the need for more clinical trials to guide COVID-19 treatment.

CONCLUSIONS

In summary, in light of the rapid progression of the COVID-19 pandemic around the world, understanding the pathophysiological mechanisms of SARS-CoV-2 is of great importance. The impact of this viral infection on the hemostatic system is broad and can directly influence the management and prognostic of patients. Whether by focal downregulation of ACE2 upon viral entry to infected cells or hyper induction of cytokine production, a significant number of COVID-19 patients develop signs hypercoagulability, thrombocytopenia, and hyperfibrinolysis. The establishment of thrombotic and hemorrhagic complications as a consequence of infection is a noteworthy feature for the worsening of COVID-19 patients. Thus, an overview of the SARS-CoV-2 infection dynamics under the lens and pathophysiology of hemostasis is fundamental to aid the development of improved diagnostic and therapeutic approaches in the management of this ongoing pandemic.

Acknowledgments

I thank Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the financial support and Dr. A.L. Lourenço and Dr. F.A. do Carmo for the scientific assistance and english review. I declare no known conflict of interests to exist regarding this research article.

REFERENCES

- AIMES RT ET AL. 2003. Endothelial cell serine proteases expressed during vascular morphogenesis and angiogenesis. *Thromb Haemost* 89(3): 561-572.
- AL-ANI F, CHEHADE S & LAZO-LANGNER A. 2020. Thrombosis risk associated with COVID-19 infection. A scoping review. *Thromb Res* 192: 152-160.

- AMGALAN A & OTHMAN M. 2020. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered Questions. *J Thromb Haemost* 18(6): 1514-1516.
- ATALLAH B, MALLAH SI & ALMAHMEED W. 2020. Anticoagulation in COVID-19. *Eur Heart J Cardiovasc Pharmacother* 6(4): 260-261.
- BARNES BJ ET AL. 2020. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. *J Exp Med* 217(6): e20200652.
- BIKDELI B ET AL. 2020a. Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research. *Thromb Haemost* 120(7): 1004-1024.
- BIKDELI B ET AL. 2020b. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol* 75(23): 2950-2973.
- CASCELLA M, RAJNIK M, CUOMO A, DULEBOHN SC & DI NAPOLI R. 2020. Features, Evaluation and Treatment Coronavirus (COVID-19). In: *StatPearls*. Treasure Island (FL): StatPearls Publishing. Available at: <<https://www.ncbi.nlm.nih.gov/books/NBK554776>>.
- CHAN JF ET AL. 2020. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* 9(1): 221-236.
- CHEN N ET AL. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395(10223): 507-513.
- CHHIKARA BS, RATHI B, SINGH J & POONAM FNU. 2020. Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics. *Chem Biol Lett* 7(1): 63-72.
- CONTI P ET AL. 2020. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 34(2): 1.
- CUI S, CHEN S, LI X, LIU S & WANG F. 2020. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 18(6): 1421-1424.
- D'ALESSANDRO E, POSMA JIN, SPRONK HMH & TEN CATE H. 2018. Tissue factor (: Factor VIIa) in the heart and vasculature: More than an envelope. *Thromb Res* 168: 130-137.
- DASSAH M, DEORA AB, HE K & HAJJAR KA. 2009. The endothelial cell annexin A2 system and vascular fibrinolysis. *Gen Physiol Biophys* 28 Spec No Focus (SPEC): F20-8.
- DHAMA K ET AL. 2020. An Update on SARS-COV-2/COVID-19 with particular reference on its clinical pathology, pathogenesis, immunopathology and mitigation strategies - A Review. *Travel Med Infect Dis* 101755: DOI 10.1016/j.tmaid.2020.101755.
- DIDANGELOS A. 2020. A Neutrophil Activation Signature in COVID-19. Preprints 2020040363: DOI 10.20944/preprints202004.0363.v1.
- DIDIASOVA M, WUJAK L, SCHAEFER L & WYGRECKA M 2018. Factor XII in coagulation, inflammation and beyond. *Cell Signal* 51: 257-265.
- ENGELMANN B. & MASSBERG S. 2013. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol* 13(1): 34-45.
- FAHEY E & DOYLE SL. 2019. IL-1 family cytokine regulation of vascular permeability and angiogenesis. *Front Immunol* 10: 1426.
- FELSENSTEIN S, HERBERT JA, MCNAMARA PS & HEDRICH CM. 2020. COVID-19: immunology and treatment options. *Clin Immunol* 215: 108448.
- FERRARI R, DI PASQUALE G & RAPEZZI C. 2020. Commentary: What is the relationship between Covid-19 and cardiovascular disease? *Int J Cardiol* 310: 167-168.
- FRAGA-SILVA RA ET AL. 2010. ACE2 activation promotes antithrombotic activity. *Mol Med* 16(5-6): 210-215.
- FRAGA-SILVA RA, PINHEIRO SVB, GONÇALVES ACC, ALENINA N, BADER M & SANTOS RAS. 2008. The antithrombotic effect of angiotensin-(1-7) involves mas-mediated NO release from platelets. *Mol Med* 14(1-2): 28-35.
- FU Y, CHENG Y & WU Y. 2020. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. *Virol Sin* 35(3): 266-271.
- GANJI A, FARAHANI I, KHANSARINEJAD B, GHAZAVI A & MOSAYEBI G. 2020. Increased expression of CD8 marker on T-cells in COVID-19 patients. *Blood Cells Mol Dis* 83: 102437.
- GRALINSKI LE ET AL. 2013. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. *MBio* 4(4): e00271-13.
- GRIGNANI G & MAIOLO A. 2000. Cytokines and hemostasis. *Haematologica* 85(9): 967-972.
- GUO D, LV Y, QI Y & PAN S. 2020a. Increased circulating microparticles and inflammatory factors aggravate

- coronavirus disease 2019 (COVID-19). Research Square: DOI 10.21203/rs.3.rs-19182/v1.
- GUO J, HUANG Z, LIN L & LV J. 2020b. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J Am Heart Assoc* 9(7): e016219.
- GUOL & RONDINAMT. 2019. The era of thromboinflammation: platelets are dynamic sensors and effector cells during infectious diseases. *Front Immunol* 10: 2204.
- HAMMING I, TIMENS W, BULTHUIS MLC, LELY AT, NAVIS GJ & VAN GOOR H. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 203(2): 631-637.
- HAN H ET AL. 2020. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 58(7): 1116-1120.
- HOFFMANN M ET AL. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181(2): 271-280.e8.
- HOFSTRA JJ, HAITSMAN JJ, JUFFERMANS NP, LEVI M & SCHULTZ MJ. 2008. The role of bronchoalveolar hemostasis in the pathogenesis of acute lung injury. *Semin Thromb Hemost* 34(5): 475-484.
- HOSSEINZADEGAN H & TAFTI DK. 2017. Mechanisms of platelet activation, adhesion and aggregation. *Thromb Haemost Res* 1(2): 1008.
- HSIEH CY, SHEU JR, YANG CH, CHEN WL, TSAI JH & CHUNG CL. 2019. Thrombin Upregulates PAI-1 and Mesothelial-Mesenchymal Transition Through PAR-1 and Contributes to Tuberculous Pleural Fibrosis *Int J Mol Sci* 20(20): 5076.
- HUANG AT ET AL. 2020b. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. *medRxiv* 2020.04.14.20065771: DOI 10.1101/2020.04.14.20065771.
- HUANG C ET AL. 2020a. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395(10223): 497-506.
- ICTV-CSG. 2020. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 5(4): 536-544.
- IWASAKI A & YANG Y. 2020. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol* 20(6): 339-341.
- JIA H. 2016. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. *Shock* 46(3): 239-248.
- JI HL, ZHAO R, MATALON S & MATTHAY MA. 2020. Elevated plasmin (ogen) as a common risk factor for COVID-19 susceptibility. *Physiol Rev* 100(3): 1065-1075.
- JOOB B & WIWANITKIT V. 2020. Hemorrhagic Problem Among the Patients With COVID-19: Clinical Summary of 41 Thai Infected Patients. *Clin Appl Thromb Hemost* 26: 1076029620918308. DOI 10.1177/1076029620918308.
- JOSE RJ & MANUEL A. 2020. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 8(6): e46-e47.
- JU B ET AL. 2020. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 10.1038/s41586-020-2380-z.
- KAHALEH MB & FAN PS. 1997. Effect of cytokines on the production of endothelin by endothelial cells. *Clin Exp Rheumatol* 15(2): 163-167.
- KNOPF J, LEPPKES M, SCHEIT G, HERRMANN M & MUÑOZ LE. 2019. Aggregated NETs Sequester and Detoxify Extracellular Histones. *Front Immunol* 10: 2176.
- KREUTZ R, ABD EL-HADY ALGHARABLY E, GANTEN D & MESSERLI F. 2020. Renin-Angiotensin-System (RAS) und COVID-19. *Dtsch Med Wochenschr* 145(10): 682-686.
- KUBA K ET AL. 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 11(8): 875-879.
- KUMAR R ET AL. 2020. Comparative Genomic Analysis of Rapidly Evolving SARS CoV-2 Viruses Reveal Mosaic Pattern of Phylogeographical Distribution. *bioRxiv* 2020.03.25.006213: DOI 10.1101/2020.03.25.006213.
- KUSTER GM ET AL. 2020. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 41(19): 1801-1803.
- LEFRANÇAIS E ET AL. 2017. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. *Nature* 544(7648): 105-109.
- LEVI M & SIVAPALARATNAM S. 2019. Coagulation and anticoagulation in the intraoperative setting. *Transfus Apher Sci* 58(4): 386-391.
- LEVI M & VAN DER POLL T. 2010. Inflammation and coagulation. *Crit Care Med* 38(2 Suppl): S26-34.

- LI X, GENG M, PENG Y, MENG L & LU S. 2020. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal* 10(2): 102-108.
- LIDBURY PS, THIEMERMANN C, KORBUT R & VANE JR. 1990. Endothelins release tissue plasminogen activator and prostanoids. *Eur J Pharmacol* 186(2-3): 205-212.
- LIN L, LU L, CAO W & LI T. 2020a. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* 9(1): 727-732.
- LIN H, XU L, YU S, HONG W, HUANG M & XU P. 2020b. Therapeutics targeting the fibrinolytic system. *Exp Mol Med* 52(3): 367-379.
- LIPPI G, PLEBANI M & HENRY BM. 2020. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta* 506: 145-148.
- LIU X ET AL. 2020a. Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction. medRxiv: DOI 10.1101/2020.02.27.20027557.
- LIU X ET AL. 2020b. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. *Acta Pharm Sin B*: DOI 10.1016/j.apsb.2020.04.008.
- MAEMURA K, KURIHARA H, MORITA T, OH-HASHI Y & YAZAKI Y. 1992. Production of endothelin-1 in vascular endothelial cells is regulated by factors associated with vascular injury. *Gerontology* 38(Suppl 1): 29-35.
- MARIETTA M ET AL. 2020. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus* 18(3): 167-169.
- MATTIUZZI C & LIPPI G. 2020. Which lessons shall we learn from the 2019 novel coronavirus outbreak? *Ann Transl Med* 8(3): 48.
- MCFADYEN JD, STEVENSH & PETER K. 2020. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. *Circ Res*: DOI 10.1161/CIRCRESAHA.120.317447.
- MIDDLETON EA, WEYRICH AS & ZIMMERMAN GA. 2016. Platelets in pulmonary immune responses and inflammatory lung diseases. *Physiol Rev* 96(4): 1211-59.
- MITCHELL WB. 2020. Thromboinflammation in COVID-19 acute lung injury. *Paediatr Respir Ver*: S1526-0542(20)30089-0.
- MONTEIRO RQ ET AL. 2019. IL-1 β blockade attenuates thrombosis in a neutrophil extracellular trap-dependent breast cancer model. *Front Immunol* 10: 2088.
- MYCROFT-WEST CJ ET AL. 2020. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 Receptor Binding Domain undergoes conformational change upon heparin binding. bioRxiv 2020.02.29.971093: DOI 10.1101/2020.02.29.971093.
- NARASARAJU T, TANG BM, HERRMANN M, MULLER S, CHOW VTK & RADIC M. 2020. Neutrophilia and NETopathy as Key Pathologic Drivers of Progressive Lung Impairment in Patients with COVID-19. *Front Pharmacol* 11: 870.
- NIKOLICH-ZUGICH J, KNOX KS, RIOS CT, NATT B, BHATTACHARYA D & FAIN MJ. 2020. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. *Geroscience* 42(2): 505-514.
- NISHIMURA H ET AL. 1997. Angiotensin II increases plasminogen activator inhibitor-1 and tissue factor mRNA expression without changing that of tissue type plasminogen activator or tissue factor pathway inhibitor in cultured rat aortic endothelial cells. *Thromb Haemost* 77(6): 1189-1195.
- NISHIMURA S ET AL. 2012. In vivo imaging visualizes discoid platelet aggregations without endothelium disruption and implicates contribution of inflammatory cytokine and integrin signaling. *Blood* 119(8): e45-56.
- PANKA BA, DE GROOTH HJ, SPOELSTRA-DE MAN AM, LOONEY MR & TUINMAN PR. 2017. Prevention or treatment of ARDS with aspirin: a review of preclinical models and meta-analysis of clinical studies. *Shock* 47(1): 13-21.
- PETERSON EA, SUTHERLAND MR, NESHEIM ME & PRYZDIAL EL. 2003. Thrombin induces endothelial cell-surface exposure of the plasminogen receptor annexin 2. *J Cell Sci* 116(Pt 12): 2399-2408.
- POSCH S, OBSER T, KÖNIG G, SCHNEPPENHEIM R, TAMPÉ R & HINTERDORFER P. 2018. Interaction of von Willebrand factor domains with collagen investigated by single molecule force spectroscopy. *J Chem Phys* 148(12): 123310.
- REILLY JP & CHRISTIE JD. 2015. Linking genetics to ARDS pathogenesis: the role of the platelet. *Chest* 147(3): 585-586.
- ROTHAN HA & BYRAREDDY SN. 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 109: 102433.
- RUGGERI ZM. 2002. Platelets in atherothrombosis. *Nat Med* 8(11): 1227-1234.
- SAI S & WIWANITKIT V. 2020. Uncommon Atypical Presentations of COVID-19: Important and Should Not be Under Recognized! *JHSMR* 38(2): 153-158.

- SARDU C, GAMBARELLA J, MORELLI MB, WANG X, MARFELLA R & SANTULLI G. 2020. Is COVID-19 an Endothelial Disease? Clinical and Basic Evidence. Preprints 2020040204: DOI 10.20944/preprints202004.0204.v.
- SCHOUTEN M, WIERSINGA WJ, LEVI M & VAN DER POLL T. 2008. Inflammation, endothelium, and coagulation in sepsis. *J Leukoc Biol* 83(3): 536-545.
- SHI Y ET AL. 2020. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 27(5): 1451-1454.
- SIEGEL-AXEL DI & GAWAZ M. 2007. Platelets and endothelial cells. *Semin Thromb Hemost* 33(2): 128-135.
- SOTOMAYOR-FLORES C ET AL. 2020. Angiotensin-(1-9) prevents cardiomyocyte hypertrophy by controlling mitochondrial dynamics via miR-129-3p/PKIA pathway. *Cell Death Differ*: DOI 10.1038/s41418-020-0522-3.
- SPADARELLA G, DI MINNO A, DONATI MB, MORMILE M, VENTRE I & DI MINNO G. 2020. From unfractionated heparin to pentasaccharide: Paradigm of rigorous science growing in the understanding of the in vivo thrombin generation. *Blood Rev* 39: 10061.
- TANG N, BAI H, CHEN X, GONG J, LI D & SUN Z. 2020a. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 18(5): 1094-1099.
- TANG N, LI D, WANG X & SUN Z. 2020b. Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 18(4): 844-847.
- TANG T, BIDON M, JAIMES JA, WHITTAKER GR & DANIEL S. 2020c. Coronavirus membrane fusion mechanism offers as a potential target for antiviral development. *Antiviral Res* 178: 104792.
- TESTA S ET AL. 2020. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost* 18(6): 1320-1323.
- THACHIL J. 2020. The versatile heparin in COVID-19. *J Thromb Haemost* 18(5): 1020-1022.
- THACHIL J ET AL. 2020. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 18(5): 1023-1026.
- VABRET N ET AL. 2020. Immunology of COVID-19: current state of the science. *Immunity* 52(6): 910-941.
- VAN WISSEN M ET AL. 2011. Acute respiratory tract infection leads to procoagulant changes in human subjects. *J Thromb Haemost* 9(7): 1432-1434.
- VANINOV N. 2020. In the eye of the COVID-19 cytokine storm. *Nat Rev Immunol* 20(5): 277.
- VARGA Z ET AL. 2020. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395(10234): 1417-1418.
- WANG X ET AL. 2020. Transcriptional Inhibition of Host Viral Entry Proteins as a Therapeutic Strategy for SARS-CoV-2. Preprints 2020030360: DOI 10.20944/preprints202003.0360.v1.
- WHO. 2020a. Rolling updates on coronavirus disease (COVID-19). Available at: <<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>>.
- WHO. 2020b. Novel Coronavirus (2019-nCoV) situation reports - 70. Available at: <<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>>.
- WILLYARD C. 2020. Coronavirus blood-clot mystery intensifies. *Nature* 581(7808): 250.
- YAN R, ZHANG Y, LI Y, XIA L, GUO Y & ZHOU Q. 2020. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 367(6485): 1444-1448.
- YANG M, NG MH & LI CK. 2005. Thrombocytopenia in patients with severe acute respiratory syndrome. *Hematology* 10(2): 101-105.
- YANG Y & TANG H. 2016. Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia. *Cell Mol Immunol* 13(4): 432-442.
- YAO X ET AL. 2020. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* ciaa237: DOI 10.1093/cid/ciaa237.
- YUKI K, FUJIOGI M & KOUTSOGIANNAKI S. 2020. COVID-19 pathophysiology: A review. *Clin Immunol* 215: 108427.
- ZHANG W ET AL. 2020a. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. *Clin Immunol* 214: 108393.
- ZHANG B ET AL. 2020b. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. *medRxiv* 2020.03.12.20035048: DOI 10.1101/2020.03.12.20035048.
- ZHANG H, PENNINGER JM, LI Y, ZHONG N & SLUTSKY AS. 2020c. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med* 46(4): 586-590.

ZHAO Y, ZHAO Z, WANG Y, ZHOU Y, MA Y & ZUO W. 2020. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv 2020.01.26.919985: DOI 10.1101/2020.01.26.919985.

ZHOU F ET AL. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229): 1054-1062.

ZHU N ET AL. 2020. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382(8): 727-733.

How to cite

SATHLER PC. 2020. Hemostatic abnormalities in COVID-19: A guided review. An Acad Bras Cienc 92: e20200834. DOI 10.1590/0001-3765202020200834.

*Manuscript received on May 29, 2020;
accepted for publication on July 20, 2020*

PLÍNIO C. SATHLER

<https://orcid.org/0000-0003-1203-3179>

Universidade Federal do Rio de Janeiro, CCS, Programa de Pós-graduação em Ciências Farmacêuticas, Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, LABHEX, 21941-902 Rio de Janeiro, RJ, Brazil

E-mail: plinio@pharma.ufrj.br

Author contributions

P. C. Sathler performed the literature scientific search and the critical analysis of the content, systematized the article, wrote the manuscript and designed all illustrations.

