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Review

The Role of Platelet Molecules in Risk Stratification of Patients with COVID-19

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Abstract: The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China and is responsible for Coronavirus disease (COVID-19). Despite being well tolerated by most patients, a fraction of cases evolve into a potentially fatal condition requiring intensive care. In addition to respiratory complications, several studies have reported cases of patients who developed intense thrombosis, including acute myocardial infarction and ischemic stroke, as well as the presence of elevated coagulation markers. Evidence has shown that the virus can interact directly with platelets and modulate their thrombotic and inflammatory functions, with significant prognostic implications. It is important to highlight that the emerging literature shows that when hyperactive these cells can act as pro-viral infections both in transporting their particles and in increasing inflammation, leading to a hyperinflammatory state and consequent clinical worsening. In this review, we searched for studies available in public databases and discussed the interaction of platelet biomarkers in the pathogenesis of COVID-19. In this context, understanding the mechanism of SARS-CoV-2 and these cells in different clinical conditions could help us to understand the coagulation and inflammation profiles of critically ill patients with the disease, guiding faster clinical management and enabling the reuse and targeting of more efficient therapies.

Keywords: COVID-19; SARS-CoV-2; platelets; biomarkers; inflammation

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1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, an enveloped positive-sense single-stranded RNA virus belonging to the Coronaviridae family which has in common with others of the same species the presence of four proteins—Spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N)—which are closely related to the toxicity and infectivity of these coronaviruses and are responsible for viral maintenance and replication [1–4].

The S protein has a vital role in the infection and pathogenesis of COVID-19, in addition to being the glycoprotein that determines the fusion of the virus in cells. This protein is further subdivided, where the ectodomain is divided into subunits: S1, which helps in binding to the ACE-2 receptor on the surface of the host cell, and the second, S2, which is responsible for membrane fusion (Figure 1) [5,6].

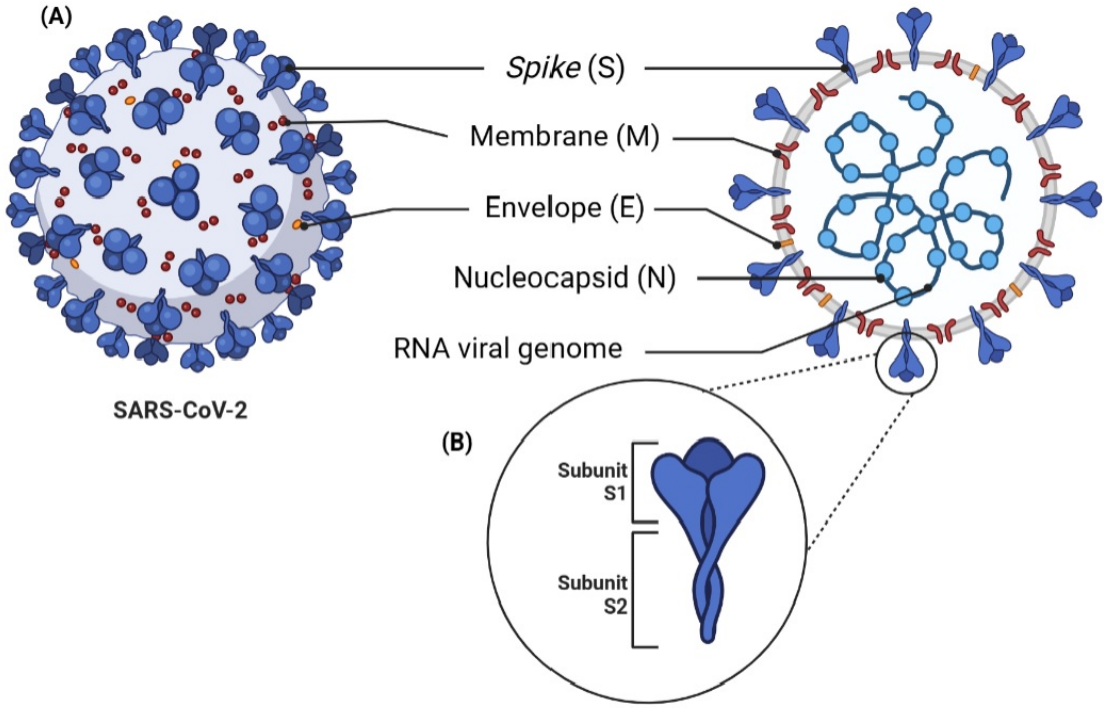

Figure 1. Structure and genomic organization of SARS-CoV-2. Adapted from Ref. [7]. (**A**) schematic representation of the structure of the SARS-CoV-2 virus and the positions of the Spike glycoproteins, envelope, membrane, nucleocapsid and viral genome. (**B**) enlarged schematic representation showing the S1 and S2 subunits of the SARS-CoV-2 spike glycoprotein. Created with BioRender.com, accessed on 17 August 2023.

SARS-CoV-2 became known for its mutagenesis, and despite being less pathogenic when compared to other coronaviruses, a high transmission rate was observed due to its rapid spread from person to person [8]. Through the transmembrane protease serine 2 (TMPRSS2), a serine protease that acts in the proteolytic cleavage and activation of the Spike protein, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE-2) in order to contribute to the fusion of the virus to the host's cell membrane and then entry of the viral genome into the cell [6,8,9].

Even though infection by this virus presents tropism for respiratory endothelial cells, studies indicate cases of patients who developed intense thrombosis, including myocardial infarction and ischemic stroke [5,10]. Despite being considered the main effector cells of hemostasis and playing an important role in thrombus formation, platelets are also responsible for mediating inflammatory and immunological responses [11,12].

Since platelet activation occurs through inflammatory or infectious events, these are commonly associated with a prothrombotic response and, consequently, with platelet hyperactivity, as is observed in several viral infections [2], including the human immunodeficiency virus (HIV) [13,14], influenza virus [15], dengue virus [16,17] and human cytomegalovirus [18]. Similar to the process of thrombocytopathy, coagulopathy and inflammation are observed in patients infected by SARS-CoV-2, leading to a significant increase in thrombotic and embolic events [4,9].

Therefore, a systematic understanding of the thrombotic effects of SARS-CoV-2 represents a promising strategy for redirecting and developing therapies capable of minimizing the damage associated with this disease [19].

2. Pathophysiology and Pathogenesis of SARS-CoV-2

SARS-CoV-2 infection begins when the Spike protein binds to its receptor on the host cell membrane, with ACE-2 being considered the main enzyme responsible for the virus's entry into the cell. In addition, the high expression of ACE-2 in the nasal and oral mucosa

makes its entry via inhalation possible. After binding to ACE-2, the TMPRSS2 protease cleaves and activates the spike protein to favor the fusion of the viral envelope with the cell membrane [20–22].

Depending on the availability of proteases on the surface of the host cell, the Spike protein enables virus entry by endocytosis or via direct fusion. Within the alveoli, due to considerable expression of ACE-2 and TMPRSS2, epithelial cells lining the lower airways are the primary target. From then on, the structural proteins move along the secretory pathway to the Golgi complex, where the viral progeny will be assembled and then released from the host cell by exocytosis [8,23] (Figure 2).

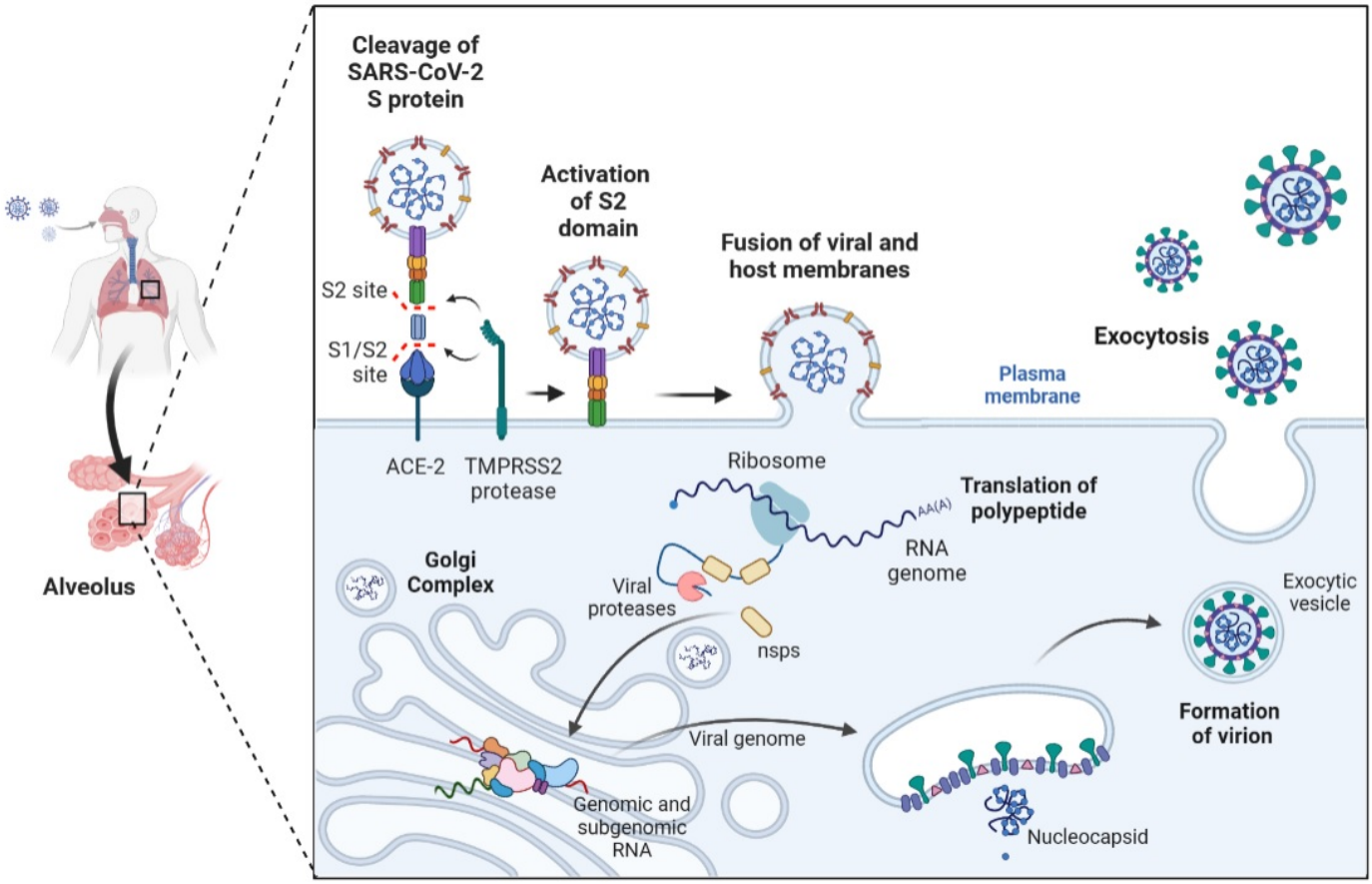

Figure 2. Schematic representation of the entry mechanism and replication cycle of SARS-CoV-2. Adapted from Ref. [1]. The S protein of SARS-CoV-2 binds to ACE-2 and cleaves the S1/S2 subunits through TMPRSS2, enabling the entry of the virus into the host's cells and the consequent translation of the viral genome. Transcription and replication occur in the Golgi complex, where subgenomic RNA is translated into structural and accessory proteins that are inserted into the genomic RNA in the nucleocapsid. Then, the virion is formed and released by exocytosis. ACE-2, Angiotensin Converting Enzyme 2; TMPRSS2, Transmembrane Protease Serine 2; nsps, Non-structural Proteins. Created with BioRender.com, accessed on 17 August 2023.

As epithelial cells are infected, the virus induces apoptosis as part of the replication cycle, which is related to the vascular leakage that initiates local infection and the recruitment of immune cells in an attempt to contain the infection. In this context, the increase in cytokines in the lungs can aggravate this inflammatory response and lead to pneumonia [24,25].

Even though most patients have mild symptoms and a good prognosis, a fraction of these individuals may develop severe COVID-19 [26,27], with the occurrence of thrombosis and abnormal platelet parameters such as decreased platelet count as well as changes in

the coagulation profile, including decreased prothrombin time (PT) and increased activated partial thromboplastin time (aPTT), D-dimer and fibrinogen, which are associated with the severity and prognosis of the disease [28–31].

Abnormalities range from coagulopathies commonly associated with serious infections, such as disseminated intravascular coagulation (DIC) [32,33], to deep venous and arterial thrombosis—which can cause ischemic stroke, systemic arterial embolism, acute coronary syndrome and limb ischemia [34]—and pulmonary embolism [35], with prevalences in patients in intensive treatment units (ITU) [36].

Although its pathophysiology has not been completely explained, an uninterrupted and disproportionate immune-inflammatory response is observed, mainly from platelet-derived signaling proteins that mediate and regulate the immune response [37].

3. Immunothrombosis and SARS-CoV-2 Infection

Platelet activation generally occurs in response to inflammatory and/or infectious diseases. The infection stimulates a systemic inflammatory response in which activation of the host's defense systems results in the activation of coagulation pathways, leading to the formation of thrombin as a component of communication between humoral and cellular immunity, called immunothrombosis [38].

Once the pathogen is recognized by platelets, they increase the immune response through the release of cytokines and antimicrobial peptides and through the platelet–leukocyte interaction [4,39,40]. During this process, a type of physical barrier is formed by platelets and immune cells with the aim of preventing the spread and survival of the pathogen [4,38,41]. However, the accumulation of immune cells, mainly monocytes and neutrophils, can lead to adverse immunological and hemostatic responses, contributing to a worse clinical context, with the development of thrombosis and organ failure [4].

The platelet–leukocyte interaction plays a role in the pathophysiology of different viral infections [42–44], being seen as a driver of vascular disease, and is considered the main factor responsible for thromboinflammatory responses during COVID-19, associated with serious disease and elevation of coagulation markers, such as fibrinogen and D-dimer, where its increase was described in patients in need of ventilatory support and in those who died in hospital [40].

When in contact with the respiratory system, the virus increases inflammation, triggering a storm of cytokines that are responsible for recruiting immune cells, establishing the cycle of inflammation of the lung epithelium and thrombotic events [10]. Polyphosphates derived from microorganisms activate platelets, mast cells and factor XII (FXII), while the exacerbated release of cytokines increases the recruitment of leukocytes to the site of injury, promoting the formation of neutrophil extracellular traps (NETs) which, together with FXII, stimulate the formation of thrombin and induce a thromboinflammatory state. As vascular endothelial damage increases, the passage of fluids to the lung cavity is made possible, leading to respiratory failure (Figure 3) [4,10,44].

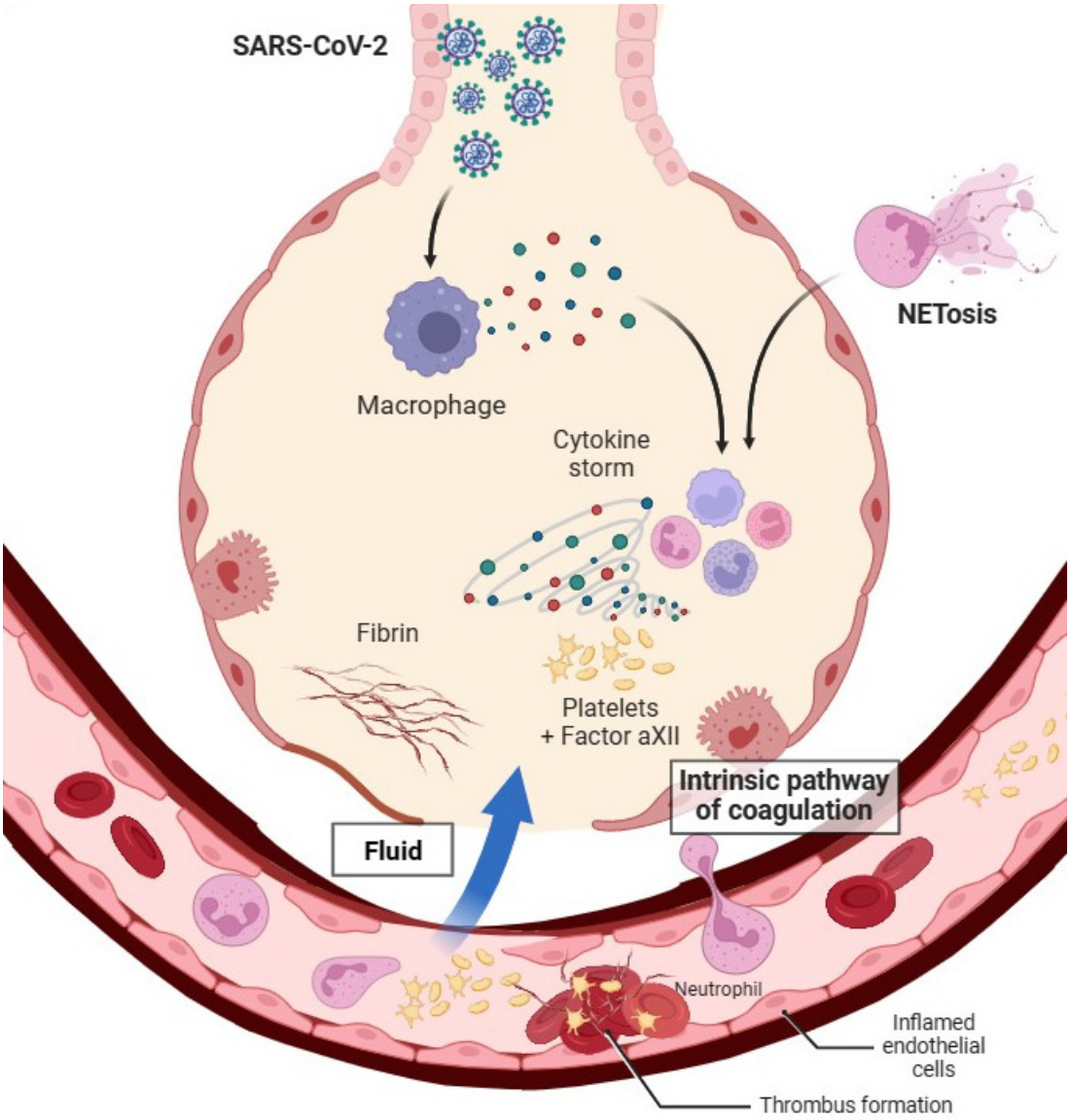

Figure 3. Schematic representation of the immunothrobosis mechanism triggered by SARS-CoV-2. Adapted from Ref. [7]. When immune cells recognize the virus, inflammatory cytokines are produced that attract defense cells in an attempt to contain the pathogen. In the presence of a deregulated immune response and the exacerbated production of these cytokines, the cycle of inflammation is established, mediated by the platelet–leukocyte interaction and the consequent thrombus formation. Compromising the vessel wall and resulting in the accumulation of fluids in the bronchioles and vasoconstriction via platelet activation, the oxygen exchange capacity is reduced. Created with BioRender.com, accessed on 25 October 2023.

4. Viral Infections, including SARS-CoV-2 and Its Interaction with Platelets

Platelets are widely known for their contributions to thrombosis and hemostasis and for having a broad expression of immune and adhesion receptors [12]. However, their interaction and favorability with viral infections have aroused increasing interest among researchers [12,16].

The involvement of these cells in viral defenses occurs through their direct activity, where specific receptors are released. Also, the virus can be phagocytosed through the formation of complexes with the virus and platelets, leading to thrombocytopenia. Through indirect routes, the virus is neutralized through the formation of aggregates with leukocytes, platelet apoptosis and/or activation of the vascular endothelium [45].

Platelets play an important role in the host's immune defense against viruses; they engulf viral particles and thus reduce viremia. However, they can also contribute to increased inflammation and tissue damage in these infections [46], such as influenza [15,43], HIV [14,15], hepatitis C [47,48], dengue [16,17], HSV-1 (herpes simplex virus A) [49] and cytomegalovirus [18], acting on the internalization of virions, platelet activation and contributing to the transport of these particles [50,51].

Additionally, the interaction of platelets in the pathogenesis of COVID-19 has been discussed. One study identified the presence of viral particles in the lungs and in megakaryocytes morphologically active in the production of platelets in bone marrow in patients who died from the disease. The same particles were also observed in circulating platelets, suggesting that SARS-CoV-2 is transferred from megakaryocytes to platelets or phagocytized by them when circulating [19].

Another two studies described platelet activation in patients with severe COVID-19, demonstrating increased levels of platelet aggregates and immune cells [4,51]. In addition, one of them showed that the platelets of these patients contained viral RNA, suggesting that these cells can absorb SARS-CoV-2 mRNA as well as present changes in the expression of platelet genes, similar to those observed in patients infected with the H1N1 virus [4].

In this context, understanding the mechanistic role of SARS-CoV-2 with platelets and its development of a cascade of pro-coagulatory events proves to be a key tool for early diagnostic screening and therapeutic targeting of thrombotic complications of severe COVID-19 [19,43].

5. Platelet Markers and COVID-19

Platelets are small cellular fragments derived from megakaryocytes which, in addition to acting in the establishment of hemostasis, play important roles in the immune response. When activated, platelets release substances responsible for recruiting defense cells to the site of injury/inflammation and promote their adhesion to platelet thrombi, thus modulating the functional response of leukocytes [12,52].

Although it is considered an effective way to help protect the body, its critical contributions to thrombosis are already known. During various infections—viral or bacterial—activated platelets adhere to the subendothelium and their hyperactivity results in the formation of thrombi, leading to arterial ischemia and even pulmonary embolisms [4,12,41].

The cytoplasm of platelets contains three main types of granules: α, dense and lysosomes. Alpha granules are larger and more abundant and store a wide variety of proteins. Dense granules are smaller and less present [53]. Lambda granules are sparse and composed of glycohydrolases and lysosomal enzymes. When stimulated, the granules undergo exocytosis and release their contents into the extracellular environment, contributing to platelet activation and thrombus formation [54,55]. Also, many of these mediators participate in the recruitment of leukocytes and inflammatory cells, which help in the establishment of the hyperinflammatory state [55,56].

As knowledge about severe COVID-19 advances, hypercoagulability is identified as the central pathological characteristic of clinical complications since evidence shows that the virus can interact directly with platelets and modulate their thrombotic and inflammatory functions [4,57]. In addition to the severity of the disease, thrombotic events associated with increased levels of coagulation markers have been shown to be important in determining the prognosis of patients with COVID-19 [58,59]. The identification of new platelet markers, in addition to enabling a better understanding of the thrombotic complications caused by SARS-CoV-2, during evaluation of these molecules during hospital admission would indicate sick patients with a predisposition to thrombosis and optimize therapeutic management [60].

Table 1 is made up of a series of platelet molecules acting in thromboinflammatory processes in the clinical context of COVID-19, followed by their methods of detection. And, although they have not been sufficiently tested in clinical practice, different studies have

highlighted the influence of these markers on the risk stratification of the disease, providing sustainable data for future research.

Table 1. Main Platelet Molecules associated with thromboinflammation in severe COVID-19.

Molecule	Biological Function	Methods	Pro-Infection Mechanism	Clinical Complications	Ref.
P-Selectin	Platelet activation; adhesion and modulation of platelet–leukocyte interaction.	Flowcytometry	Increased surface expression.	Platelet–leukocyte aggregates; increased platelet aggregation, adhesion and spread.	[39,61–63]
VWF	Recruitment of circulating platelets to the site of injury; platelet activation and aggregation.	LIA, ELISA, immunohistology	Increased plasma levels in patients on ITU support.	Thrombosis; vasculopathy; greater severity and in-hospital mortality.	[64–72]
PAI-1	Fibrinolytic regulation.	ELISA	Significantly higher levels in ITU patients.	Predisposition to thrombotic events; associated with worse respiratory status and unfavorable clinical outcome.	[73–78]
PF4	Coagulation; regulating angiogenesis and inflammatory and infectious responses.	ELISA	High expression in plasma and tracheal aspirate.	Platelet hyperactivation associated with immunothrombosis and the formation of PF4/heparin immune complexes.	[39,79–91]
TGF-β	Inflammatory regulation; coagulation; wound healing.	ELISA	High serum levels are associated with greater disease severity.	Increased coagulation; immune dysregulation; pulmonary fibrosis.	[92–97]
PAF	Leukocyte chemotaxis; platelet aggregation; inflammatory mediator in infectious processes.	ELISA	Increased levels were described in patients with moderate COVID-19.	Increased inflammation; interstitial edema; immunothrombosis.	[98–107]
MMP-2, MMP-9	Degradation of extracellular matrix proteins; embryonic development and fibrinolysis.	Zymography, ELISA	Elevated levels of MMP-2 and MMP-9 in severe COVID-19 patients.	Increased mortality; respiratory complications; neurological syndrome.	[108–116]
PDGF	Cell differentiation, proliferation and chemotaxis.	ELISA	High levels were associated with greater disease severity.	Platelet activation; formation of platelet–leukocyte aggregates; lung damage.	[4,39,117–119]
RANTES (CCL5)	Monocyte recruitment; activation and differentiation of T cells.	ELISA	Increased plasma levels and activity in critically ill patients.	Lung damage; NETs; immunothrombosis.	[85,120–127]
Glutamate	Regulation of platelet production and activation.	Chromatography, mass spectrometry	Lower glutamine levels and higher glutamate levels in severe COVID-19.	Lung damage; hypoxia; neurological disability; thrombosis risk.	[128–136]
Serotonin	Vasoconstriction; T cell activation and differentiation; platelet aggregation.	ELISA	High serum levels in severe COVID-19.	Serotonergic toxicity; platelet degranulation; vascular injury.	[137–147]
CLEC-2	Hemostasis; healing; maintenance of vascular integrity; platelet adhesion.	CLEIA	Elevated plasma levels in severe and critical COVID-19.	Platelet activation; thrombotic syndrome.	[13,148–160]
MPs	Regulation of inflammation; coagulation; cell proliferation and differentiation.	Flowcytometry, ELISA	High levels of circulating MPs in ITU patients.	Lung injury; increase in plateletleukocyte aggregates; worse clinical outcome.	[161–172]

Legend: VWF, Von Willebrand Factor; ITU, Intensive Treatment Unit; PAI-1, Plasminogen Activator Inhibitor-1; PF4, Platelet Factor 4; TGF, Transforming Growth Factor; PAF, Platelet-Activating Factor; MMP, Metalloproteinase; PDGF, Platelet-derived Growth Factor; RANTES, Regulated on Activation Normal T cell expressed and secreted; CLEC-2, C-Type Lectin-Like Receptor; MPs, Microparticles; NETs, Neutrophil Extracellular Traps; LIA, Latex Immunoturbidimetric Assay; ELISA, Enzyme-linked Immunosorbent Assay; CLEIA, Chemiluminescent Enzyme Immunoassay.

5.1. P-Selectin

The study by Manne et al. described changes in the expression profile of circulating platelets in patients with COVID-19. Despite the normal morphology of these cells, they were hyperreactive and an increase in the expression of basal P-selectin and a greater formation of circulating platelet–leukocyte aggregates were also evidenced [4]. Therefore, P-selectin may play a crucial role in endotheliopathy and platelet hyperactivation in SARS-CoV-2 infection [29].

P-selectin is an inflammatory marker of coagulation which is present in the alpha granules of platelets, the Weibel–Palade bodies of the endothelium and the platelet membrane, acting as an adhesion receptor to support the rolling and emigration of leukocytes to the site of inflammation. In its soluble form (sP-selectin), it is responsible for modulating blood cell and endothelial cell interactions [61,62].

In agreement, other authors also demonstrate increased expression of surface P-selectin in patients with severe COVID-19 [39], as well as being correlated with higher levels of platelet–monocyte aggregates in infected individuals admitted to the ITU [63]. In addition, the levels of soluble selectins have been identified as a predictor of thrombosis in patients with the disease and in identifying the need for therapeutic intervention with prophylactic anticoagulants [39].

5.2. Von Willebrand Factor (VWF)

Von Willebrand factor (VWF) is an essential glycoprotein regulating thrombosis and hemostasis, found in both endothelial cells and platelets [64]. During vascular injury, VWF assists in the recruitment of platelets to the site, promoting their adhesion and aggregation [64,65]. Elevated plasma concentrations of this factor are associated with an increased risk of venous thromboembolism [66] and its deficiency with bleeding disorders [67].

Different studies have described increased plasma levels of VWF in patients with COVID-19 [68–70], pointing out a strong correlation with disease severity and mortality, suggesting an important role in the pathogenesis of thrombosis in COVID-19 [69]. Furthermore, a French study carried out with adult hospitalized and outpatient patients described, through immunohistochemistry, an increase in the reaction to VWF in the pulmonary endothelium when the disease duration was longer than 10 days [68].

In addition to other authors describing the presence of higher levels of VWF in patients who died [71], in those admitted to the ITU and when compared to non-ITU patients [29], they were also associated with a greater severity of the disease [72].

5.3. Plasminogen Activator Inhibitor (PAI-1)

Plasminogen Activator Inhibitor-1 plays an important role in the fibrinolysis regulation process. This mechanism is regulated by plasminogen activators and inhibitors, in which a fibrin-rich thrombus is degraded and remodeled by proteases responsible for converting plasminogen into plasmin as the final product [73]. In patients with COVID-19, reduced clot lysis was evidenced, suggesting impaired fibrinolytic activity and an increased risk of thrombotic complications [74].

In inflammatory conditions, the release of PAI-1 through endothelial cells and activated platelets is stimulated, promoting a high concentration of it at the site, in which, persistent fibrin deposition in the lung parenchyma establishes the hypofibrinolytic state, which is a risk factor for venous thrombosis in severe COVID-19 [75].

Furthermore, some studies carried out with hospitalized patients demonstrated elevations in PAI-1 in critically ill patients [76,77], as well as being associated with a worse respiratory status and an unfavorable clinical outcome [76]. These high plasma levels were also highlighted as a possible explanation for the high incidence of serious infection in obese patients since adipose tissue contributes to the production of PAI-1 [78].

5.4. Platelet Factor 4 (PF4)

PF4 is a chemokine that is mostly present in platelet alpha granules and is released during platelet activation [79], playing an important role in coagulation, regulation of angiogenesis and inflammatory and infectious responses [80]. Due to its negative charge at physiological pH, PF4 binds to endogenous herapan sulfate, neutralizing the side chains of this glycosaminoglycan, promoting blood clotting and facilitating aggregation and thrombus formation [79].

Different studies performed in vitro [81,82] and in vivo [83] demonstrated that this chemokine can also affect hemostasis and thrombosis through inflammatory and vascular pathways. After pathogen recognition, platelets mediate and propagate the immune response, activating mechanisms such as the release of inflammatory cytokines and modulation of leukocyte migration to the site of inflammation/infection, inducing the formation of NETs, which are important mediators in the process of coagulopathy associated with COVID-19 [84,85], in addition to the increased formation of platelet–leukocyte aggregates that favor the triggering of immunothrombosis [39].

As an example, circulating PF4 levels were highly elevated in patients with the disease when compared to the control group, supporting the hypothesis of greater platelet activation [86]. In addition, its presence was quantified in tracheal aspirates from a patient with COVID-19 under mechanical ventilation, suggesting that platelet activation products can infiltrate the airways of patients with severe COVID-19 [39].

Furthermore, the formation of anti-PF4 autoantibodies by binding of PF4 to heparin has been reported in thrombotic patients with COVID-19 [87,88]. In cases of heparin-induced thrombocytopenia (HIT), the formation of PF4/heparin immune complexes occurs, which have the ability to bind to platelet receptors and induce platelet activation and aggregation, as well as the activation of coagulation pathways that lead to severe thrombotic syndrome [88–90]. High titers of anti-PF4 antibodies were observed in ITU patients treated with heparin and in those without prior exposure, suggesting that spontaneous HIT may occur during viral infection [91].

5.5. Transforming Growth Factor-Beta (TGF-β)

TGF-β is a pleiotropic cytokine stored in its latent form in platelet alpha granules, known for its participation in the regulation of inflammation, tissue healing and platelet aggregation [92–94]. However, its continuous stimulation during infectious processes triggers increased coagulation and immune dysregulation which can lead to tissue fibrosis, which is common in the inflammatory phase of COVID-19 [92].

Increasing evidence suggests that TGF-β signaling disorder is a feature of the microvascular coagulation and inflammatory injury observed in SARS-CoV-2 infection and such events could contribute to acute respiratory distress syndrome (ARDS), microthrombosis and pulmonary fibrosis seen in critically ill patients [92,95]. Furthermore, high serum levels of this cytokine have been correlated with increased severity of the disease [94,96], and it has also been shown that serum from these patients can inhibit the function of NK cells and early control of the virus [97].

5.6. Platelet-Activating Factor (PAF)

Another important effective mediator of inflammation in infectious processes is platelet-activating factor (PAF), expressed mainly on the surface of leukocytes, endothelial cells, mast cells and platelets [98,99]. Within platelet cells, PAF promotes aggregation and clot formation [99], which are linked to a variety of clinical conditions, such as heart failure, asthma, cancer, atherosclerosis and viral diseases [100,101].

Although PAF promotes a natural inflammatory response, its effect can become pathogenic in the presence of excessive or unregulated activity, resulting from changes in its synthesis and termination cycles as a result of diseases or genetic variations [99,102].

The similarities between the physiological effects of PAF and the clinical context of severe COVID-19 are discussed in different studies [102–104]. PAF release from platelets

has been reported to stimulate mast cell activation and inflammation [105], and mast cell degranulation associated with interstitial edema and immunothrobosis has been observed in the alveoli of deceased COVID-19 patients [106] and increased levels of PAF have been found in the blood of patients with moderate COVID-19 [107].

5.7. MMP-2, MMP-9

Metalloproteinases (MMPs) are zinc- and calcium-dependent proteinases which have the ability to degrade extracellular matrix proteins. In their latent form, MMP-2 and MMP-9 are stored mainly in the cytoplasm of platelets, where they mediate inflammatory responses through the migration of immune cells to the site of infection [108,109], as well as inducing platelet–leukocyte aggregation [110].

MMPs participate in several physiological processes including embryonic development, coagulation cascade and fibrinolysis, as well as in pathological processes such as lung diseases, vascular changes, obesity, inflammation, cancer and atherosclerosis [108–113]. More recently, these enzymes were also associated with clinical manifestations during coronavirus infection [114–116].

In view of the known role of MMPs in the lung physiology and respiratory symptoms of severe COVID-19, a study carried out in patients admitted to the Intensive Care Unit (ICU) demonstrated higher MMP-9 levels in the COVID-19 group compared to the control. Also, hypertensive COVID-19 patients had higher levels of MMP-2 compared to the normotensive COVID-19 group. In addition, a survival analysis had associated greater mortality with increased levels of MMP-2 and MMP-9 [114].

Another study described higher plasma levels of MMP-9 and greater plasma activity of MMP-9 and MMP-2 in COVID-19 patients with ARDS compared to those without ARDS. Furthermore, increased levels of these enzymes were identified in the cerebrospinal fluid of COVID-19 patients, being associated with the neurological complications of the disease [116].

5.8. Platelet-Derived Growth Factor (PDGF)

PDGF is a protein responsible for regulating cell differentiation, proliferation and chemotaxis, as well as acting in the healing and fibrosis processes [117,118]. Present in platelet α-granules, under biological conditions this peptide is released from platelet activation during blood clotting. However, PDGF dysregulation is associated with different pathological contexts, such as atherosclerosis, pulmonary hypertension, diabetes and cancer [117].

In the context of viral infections, different authors have currently associated increased levels of PDGF with a more severe clinical condition of COVID-19 [4,39,119]. Furthermore, significant elevation of PDGF was detected in diabetic and obese COVID-19 patients compared to the control group [118]. In addition to the presence of this factor in tracheal aspirates from COVID-19 patients under mechanical ventilation, it is suggested that the secretory products of platelet activation have access to the airways in severe disease [39].

5.9. RANTES (CCL5)

Regulated on activation, normal T cell-expressed and -secreted (RANTES) is a chemokine abundantly stored in platelet α-granules and secreted after platelet activation [120]. The ability to induce monocyte recruitment [121] and T-cell activation and differentiation are well-defined characteristics of RANTES [122]. However, increased production is associated with a variety of diseases, such as asthma [123] and respiratory syncytial virus (RSV) infection [124]. Furthermore, it has been demonstrated that mutations in RANTES can attenuate aggregation induced by this chemokine [125].

Highly expressed during the inflammatory state, different studies have described an increased activity of CCL5 in COVID-19 patients, being mentioned as an aggravating factor in the lung damage observed in these patients [85,126]. Furthermore, the increase in its

production has been described as influencing the release of neutrophil extracellular traps (NETs), which can lead to immunothrombosis [85].

Furthermore, another study carried out with ten critically ill patients with COVID-19 demonstrated that blocking its receptor (CCR5) with an antagonist resulted in the restoration of lymphopenia and a reduction in inflammation and plasma viremia, suggesting that this treatment route may be beneficial not only for its immunomodulatory effects on inflammation but also in establishing hemostasis in these patients [127].

5.10. Glutamate

The glutaminase enzyme is responsible for converting glutamine into glutamate, an important neurotransmitter released in large concentrations by platelet dense granules after their activation [128,129], in which the expression of ionotropic glutamate receptors in these cells, including N-methyl-D-aspartate (NMDA), has the function of regulating production and inhibiting platelet activation [128].

Despite the relatively high concentrations of this neurotransmitter in the central nervous system, studies aimed at using peripheral markers for neurological diseases demonstrate that increased stroke plasma glutamate levels that remain elevated for up to 2 weeks may contribute to a greater risk of thrombotic events [130,131]. Furthermore, different authors have demonstrated the involvement of altered glutamine metabolism in viral infections, as well as its role in viral proliferation and virus assembly [132,133].

More recently, changes in this metabolic pathway have been associated with the appearance of adverse effects due to SARS-CoV-2 infection such as lung damage, hypoxia and neurological impairment and, consequently, with more severe disease [134,135]. A metabolic analysis performed in African populations identified glutamine/glutamate metabolism as the most significant pathway associated with severe COVID-19 [134]. In addition, the metabotropic glutamate receptor subtype 2 (mGluR2) has been indicated as a facilitator for the internalization of SARS-CoV-2 into cells [136].

5.11. Serotonin (5-HT)

Among neurotransmitters, serotonin plays an important role in the immune system and in the regulation of inflammatory responses [137]. In the periphery, a large part of 5-HT is stored in the platelet dense granules and is mainly involved in the mechanisms of vasoconstriction, activation and differentiation of T-cells and platelet aggregation [138–140].

Some studies point to the involvement of serotonin and its receptors in the pathogenesis of chronic inflammatory conditions [141] and in the induction of systemic shock dependent on the release of 5-HT from platelets [142].

In the context of COVID-19, due to reports of neurological dysfunction in these patients, from encephalopathy to thromboembolic diseases, elevated plasma 5-HT levels have come to be seen as a possible indicator of disease severity [143,144], being associated with serotonergic toxicity [145] and increased platelet degranulation during SARS-CoV-2 infection [146]. It can also directly affect the integrity of vessels and promote the recruitment of leukocytes and the release of inflammatory cytokines [142,147].

5.12. C-Type Lectin-like Receptor 2 (CLEC-2)

CLEC-2 is an important platelet-activating receptor that is expressed on the membrane of these cells [148–150] and plays an important role in normal hemostasis, wound healing, maintenance of vascular integrity and platelet adhesion [151]. The soluble C-type lectin-like receptor 2 (sCLEC-2) has been introduced due to its potential as a marker for platelet activation and thrombotic complications [148,152–154].

Elevated plasma levels of sCLEC-2 have been reported in cases of cardiovascular diseases [154,155], ischemic stroke [156,157], traumatic brain injury [158] and in thrombotic microangiopathy [153,159]. In addition, CLEC-2 has been implicated as a facilitator of the spread of HIV-1 in infected patients [13]. In the current context, elevated levels of soluble CLEC-2 have been described in patients hospitalized with severe and critical COVID-19

and have been noted as a useful tool in assessing disease severity [160] and for the early diagnosis of sepsis-induced coagulopathy [148].

5.13. Microparticles (MPs)

MPs are a type of extracellular vesicles of phosphatidylserine, which is a phospholipid that stimulates the activation of the coagulation cascade. Their formation occurs in response to cell activation or apoptosis [161] and, although most MPs are of platelet origin, they can also be released by leukocytes, erythrocytes, macrophages or endothelial cells, being considered sensitive markers for vascular damage [162,163]. Evidence points to the role of these molecules in regulating inflammation, coagulation and cell proliferation and differentiation [164–166]. However, high levels have been associated with thrombotic disorders and systemic inflammatory conditions [167].

MPs derived from platelets and containing tissue factor are strong procoagulants, and due to abnormalities in coagulation markers in SARS-CoV-2 infection, detailed investigation of platelets in these patients is indicated [168–170]. One study reported higher levels of platelet-derived microvesicles and platelet–leukocyte aggregates in the circulation of COVID-19 ITU patients [170], in individuals with the disease associated with acute pulmonary embolism [171] and in cases with a fatal outcome, correlating with the severity and being indicated as a possible risk marker for the disease [172].

6. Treatment and Thromboprophylaxis in COVID-19

Hypercoagulopathy is a common and deadly consequence of SARS-CoV-2 infection in hospitalized patients and was frequently associated with increased levels of the molecules discussed in this review. Although there are controversies in both the prevention and treatment of thromboinflammatory complications, some consensus statements and expert opinions are available on the prophylaxis and clinical management of these patients [173–175].

The International Society on Thrombosis and Hemostasis (ISTH) gathered evidence in an international panel and released recommendations on anticoagulants and antiplatelet agents for patients with COVID-19 in different clinical conditions. The guidelines suggest a weak recommendation for antiplatelet and anticoagulant therapy in non-hospitalized patients and strong recommendations for the use of prophylactic doses of low-molecular-weight heparin or unfractionated heparin (LMWH/UFH), for the preferable use of a therapeutic dose of LMWH/UFH, to the prophylactic dose, and against the addition of antiplatelets. For hospitalized critical patients, recommendations remain unclear [175]. In a severe COVID-19 patient population with non-invasive respiratory support, a full-dose prophylactic strategy reduced thrombotic complications without serious bleeding events [176], while thromboprophylaxis was not beneficial in patients with mild to moderate COVID-19 without requiring hospitalization [177].

Anticoagulation in hospitalized COVID-19 patients has been associated with improved survival; however, the ideal thrombosis prophylaxis strategy has not yet been defined [174,178]. Due to the common use of prophylactic doses of LMWH in hospitalized patients, for greater safety, factors such as renal function and body weight must be considered and its administration is contraindicated in individuals with a platelet count $<50 \times 10^9$/L, hemoglobin < 8 g/dL, bleeding in the last 30 days and history of bleeding disorders [177].

And although to date there is no consensus on the ideal medication, start, duration and dosage of treatment [174,177,179], detailed study of these molecules would help in understanding the pathophysiology of the disease and could help expand therapeutic options. The markers discussed here suggest possible therapeutic targets for the treatment and thromboprophylaxis of patients hospitalized with COVID-19 and perhaps for other viral infections. However, more research is needed to clarify the scope of antithrombotic prophylaxis and examine the potential benefits of new prophylactic and therapeutic agents.

7. Conclusions

In the pandemic context, SARS-CoV-2 infection presented a variable clinical course of the disease, where severe cases were frequently associated with thrombotic changes and elevated coagulation parameters. Platelets are widely known for their role in hemostasis; however, their role as an enhancer in viral infections is well discussed. In this review, we highlight important platelet molecules associated with thromboinflammation and their possible role in the risk stratification of COVID-19, contributing to the early identification of serious disease as well as enabling drug reuse.

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